University of Southampton

Faculty of Medicine

School of Primary Care, Population Sciences and Medical Education

Examining maternal and early life risk associations with childhood overweight and obesity

by

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Thesis for the degree of Doctor of Philosophy

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Abstract

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In England, 1 in 10 children aged 4-5 years and 1 in 5 aged 10-11 years are obese, with the prevalence in the most deprived areas being more than twice as that in the least deprived. There is no system-based early identification of childhood obesity risk at the pregnancy stage and onwards. The aim of this project was to examine the associations between risk factors for childhood obesity (including maternal obesity and size at birth) and to develop and validate prediction models on childhood overweight/obesity utilising prospectively collected routine healthcare data at pregnancy, birth and early life. A population-based anonymised cohort of maternal antenatal and birth records for all births registered with University Hospital Southampton, between 2003 to 2018, was linked to child health records including information on postnatal growth, type of feeding and childhood body mass index (BMI) up to the age of 14 years. A systematic review was conducted as part of this work identifying eight prediction models for childhood overweight and obesity. It highlighted methodological limitations in model development, validation and non-standard reporting limiting usability of the published models.

In terms of risk factor associations, a large proportion of women (47.7%) gained weight (≥1 kg/m^2) between pregnancies. An interpregnancy interval of 12-23 months was associated with the lowest risk of starting the second pregnancy with a higher body weight as well as a lower risk of small for gestational age (SGA) birth in the second pregnancy. Overweight women were at lower risk of recurrent large for gestational age (LGA) birth in the second pregnancy if they lost weight between pregnancies, whereas normal weight and overweight women who gained weight were at increased risk of 'new' LGA after having a non-LGA birth in their first pregnancy. In terms of prediction models, these were developed in stages, incorporating data collected at first antenatal booking appointment, birth and early life predictors. Maternal predictors included BMI, highest educational attainment, partnership status, smoking at booking, ethnicity, first language and intake of folic acid supplements. Early life predictors included birthweight and gestational age, sex and weight at 1 and 2 years. Most maternal predictors remained consistent across models indicating that risk could be identified at pregnancy, with more precise estimation at birth/in early-years. Maternal BMI was a key predictor and the high proportion of women gaining weight after pregnancy indicates that preventing weight gain between pregnancies is an important measure to achieve better maternal and offspring outcomes.

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Research Thesis: Declaration of Authorship

Print name:	Nida Ziauddeen

Title of thesis:	Examining maternal and early life risk associations with childhood overweight and obesity

I declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;
2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;
3. Where I have consulted the published work of others, this is always clearly attributed;
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   - **N. Ziauddeen, P.J. Roderick, N.S. Macklon, N.A. Alwan. Predicting childhood overweight and obesity using maternal and early life risk factors: a systematic review. *Obesity* Reviews 2018,19(3):302-312**
     NZ carried out the literature search and drafted the first version of the manuscript. All authors have contributed to the study concept and design and have reviewed and approved the final draft of the manuscript.

- **N. Ziauddeen, P.J. Roderick, N.S. Macklon, N.A. Alwan. The duration of the interpregnancy interval in multiparous women and maternal weight gain between pregnancies: findings from a UK population-based cohort. *Scientific Reports* 2019; 9(1):9175**

  NZ designed the study, undertook statistical analysis, acquired and interpreted data and drafted the manuscript. NAA assisted with study design, data acquisition and interpretation. PJR and NSM assisted with study design. All authors reviewed and approved the final manuscript.

- **N. Ziauddeen, S. Wilding, P.J. Roderick, N.S. Macklon, N.A. Alwan. Is maternal weight gain between pregnancies associated with risk of large-for-gestational age birth? Analysis of a UK population-based cohort. *BMJ Open* 2019;9:e026220**

  NZ designed the study, undertook statistical analysis, acquired and interpreted data and drafted the manuscript. SW assisted with statistical analysis. NAA assisted with study design, data acquisition and interpretation. PJR and NSM assisted with study design. All authors reviewed and approved the final manuscript.

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- **N. Ziauddeen, P.J. Roderick, N.S. Macklon, N.A. Alwan. Use of maternal and early life risk factors to predict childhood overweight and obesity: a systematic review. (abstract) The Lancet 2017; 390,S100**

  NZ carried out the literature search and drafted the first version of the abstract. All authors have contributed to the study concept and design and have reviewed and approved the final draft of the abstract.

- **N. Ziauddeen, P.J. Roderick, N.S. Macklon, N.A. Alwan. Length of inter-pregnancy interval and subsequent preconception adiposity: findings from a population-based cohort in the South of England. (abstract) Revue d'Épidémiologie et de Santé Publique; 66(supplement 5), S374**

  NZ designed the study, undertook statistical analysis, acquired and interpreted data and drafted the manuscript. NAA assisted with study design, data acquisition and interpretation. PJR and NSM assisted with study design. All authors reviewed and approved the final abstract.

- **N. Ziauddeen, P.J. Roderick, N.S. Macklon, N.A. Alwan. LB5 Is the duration of the preceding inter-pregnancy interval associated with offspring's size at birth? – analysis of a UK population-based cohort. (abstract) *Journal of Epidemiology and Community Health* 2018;72:A43-A44**

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  NZ designed the study, undertook statistical analysis, acquired and interpreted data and drafted the manuscript. NAA assisted with study design, data acquisition and interpretation. PJR and NSM assisted with study design. All authors reviewed and approved the final abstract.
- **N. Ziauddeen, S. Wilding, P.J. Roderick, N.S. Macklon, N.A. Alwan. OP38 Predicting the risk of childhood overweight and obesity at 4-5 years using pregnancy and early life healthcare data. (abstract)** ***Journal of Epidemiology and Community Health*** **2019;73(Suppl 1) A17**
  NZ designed the study, undertook statistical analysis, acquired and interpreted data and drafted the manuscript. SW assisted with statistical analysis. NAA assisted with study design, data acquisition and interpretation. PJR and NSM assisted with study design. All authors reviewed and approved the final abstract.

Signature:		Date:	

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Abbreviations

aRR	Adjusted relative risk
ADRN	Administrative Data Research Network
AIC	Akaike information criterion
ALSPAC	Avon Longitudinal Study of Parents and Children
AUC	Area under the curve
BiB	Born in Bradford cohort study
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CHARMS	**CH**ecklist for critical **A**ppraisal and data extraction for systematic **R**eviews of prediction **M**odelling **S**tudies
CHIE	Care and Health Information Exchange
CHIS	Child Health Information System
CI	Confidence intervals
CPRD	Clinical Practice Research Datalink
CSU	Commissioning Support Unit
CVD	Cardiovascular disease
DM	Diabetes mellitus
DOHaD	Developmental origins of health and disease
eDRIS	electronic Data Research and Innovation Service
EPV	Events per variable
ERGO	Ethics and Research Governance Online
GCSE	General Certificate of Secondary Education
GDM	Gestational diabetes mellitus
GP	General Practitioner
GWG	Gestational weight gain

Abbreviations

HbA1c	Haemoglobin A1c
HICSS	Hospital Integrated Clinical Support System
HHR	Hampshire Health Record
HRA	Health Research Authority
HSE	Health Survey for England
IRAS	Integrated Research Approval System
IOM	Institute of Medicine
IOTF	International Obesity Task Force
IQR	Interquartile range
LBW	Low birth weight
LGA	Large for gestational age
MDAU	Maternity Day Assessment Unit
MFP	Multivariable fractional polynomial
MICE	Multiple imputation by chained equations
MRH	Maternal resources hypothesis
NICE	National Institute for Health and Care Excellence
NCMP	National Child Measurement Programme
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NPV	Negative predictive value
NWIS	NHS Wales Informatics Service
PIA	Privacy Information Assessment
Pmm	Predictive mean matching
PPV	Positive predictive value
R&D	Research and Development
REC	Research Ethics Committee
RR	Relative risk

SAIL	Secure Anonymised Information Linkage
SCW	South, Central and West
SD	Standard deviation
SGA	Small-for-gestational age
SLOPE	Studying Lifecourse Obesity PrEdictors
TRIPOD	Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
TTP	Trusted Third Party
UHS	University Hospital Southampton
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Chapter 1 Rationale and overview of thesis

1.1 Rationale of thesis

Overweight and obesity is defined as excessive fat accumulation that could impair health (World Health Organization, 2018). The rate of obesity has nearly tripled worldwide in four decades between 1975 and 2016 with a higher rate of increase in children compared to adults. The increase in prevalence has been accompanied by an increase in associated disease burden. Globally, high body mass index (BMI) contributed to 7.1% of deaths, 4.9% of disability-adjusted life years and 3.6% of years lived with disability from any cause among adults in 2015. The leading causes of death and disability-adjusted life years due to high BMI were cardiovascular disease (CVD), diabetes, chronic kidney disease and cancer (The GBD 2015 Obesity Collaborators, 2017).

The World Health Organisation (WHO) has identified childhood overweight and obesity as one of the most serious public health challenges of the 21st century with 41 million children aged under 5 years estimated as overweight globally in 2016 (World Health Organization, 2018). A further 340 million children and adolescents aged 5 to 19 years are obese worldwide. Data from the National Child Measurement Programme (NCMP) in England showed that in 2016/17, 23% of children in Reception (aged 4 to 5 years) and 34% in Year 6 (aged 10 to 11 years) were classified as overweight or obese (NHS Digital, 2017). Children living in the most deprived areas in England were twice as likely to be obese than children in the least deprived areas. This deprivation gap has shown an increase over time from the 2006/07 to the 2016/17 academic year. These high rates of obesity in children are of concern due to the increased risk of persistence of weight status into adulthood (Guo and Chumlea, 1999; Power *et al.*, 1999; Singh *et al.*, 2008; Han *et al.*, 2010). This risk is higher in children with two overweight/obese parents (Lake *et al.*, 1997; Schaefer-Graf *et al.*, 2005; Brisbois *et al.*, 2012; Durmus *et al.*, 2013).

Obesity is a complex disorder governed by many genes and their interactions with each other in addition to physiological and environmental factors (Parsons *et al.*, 1999; Berenson, 2005). High or persistently increasing levels of BMI in childhood and adolescence lead to a predisposition to high body fat levels in adulthood (Cronk *et al.*, 1982). A meta-analysis of 48 studies concluded that there was a high degree of BMI tracking over time and a low probability of weight

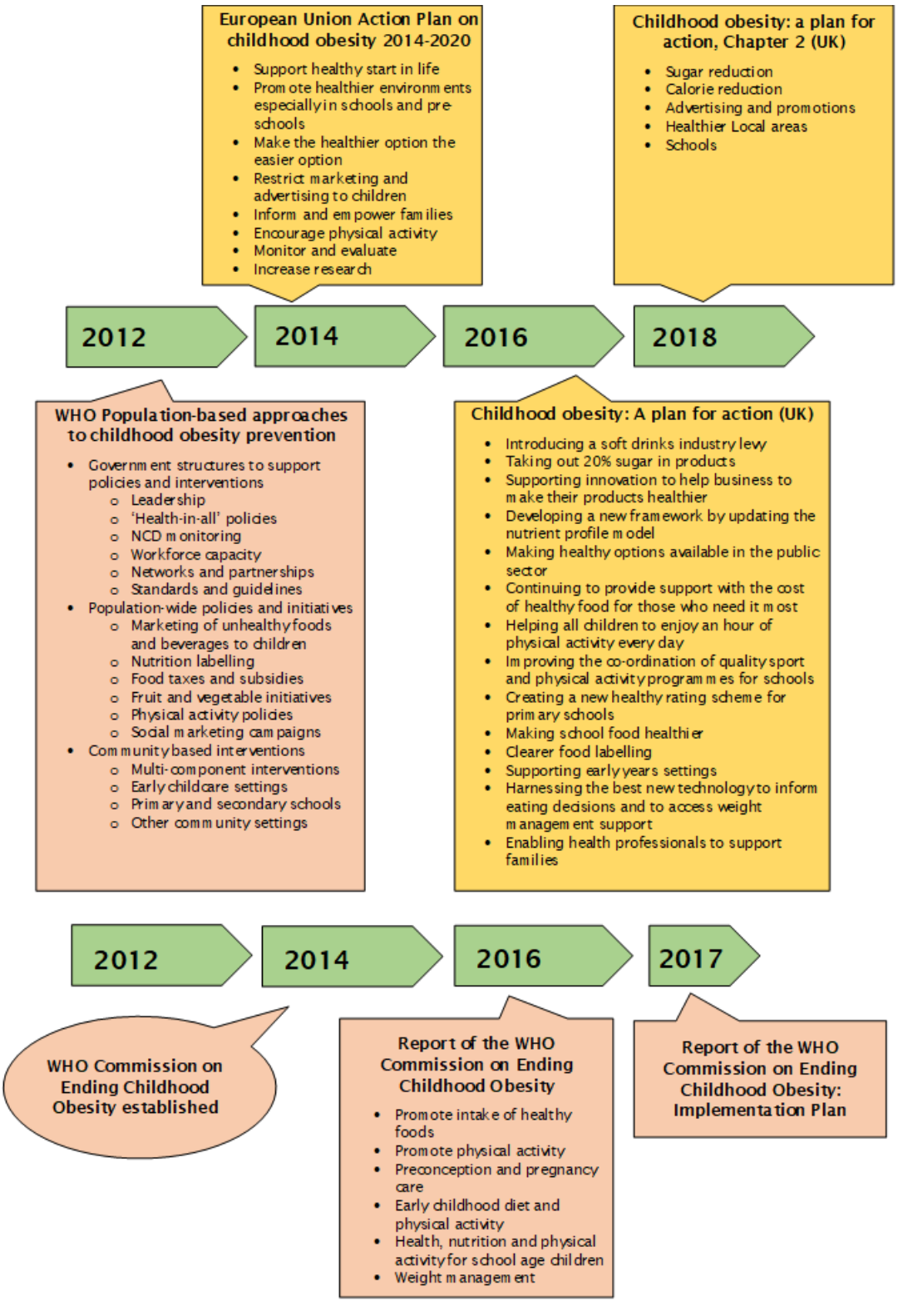
change without weight loss treatment (Bayer *et al.*, 2011). BMI tracking started from as young as two years of age (Brisbois *et al.*, 2012) and decreased gradually over time. A high degree of tracking remained after ten years, regardless of whether BMI was measured in childhood, adolescence or adulthood and was strongest in adulthood and the pubertal period (10 to 14 years) (Bayer *et al.*, 2011). A decrease in adiposity into adulthood has been associated with markedly reduced and similar risks to those who had a consistently normal BMI through childhood (Juonala *et al.*, 2011). Pre-adolescent children of a healthy weight remained of a healthy weight during adolescence but few obese or overweight children reduced to a healthy weight. There was little evidence of new cases of overweight or obesity emerging during adolescence, further supporting the case that obesity prevention should be targeted in early years as persistent obesity could be established before 11 years of age (Wardle *et al.*, 2006).

Childhood obesity is also associated with increased risk of CVD and type 2 diabetes (Csábi *et al.*, 2000; Juonala *et al.*, 2011). This is in part due to metabolic comorbidities associated with obesity such as elevated blood pressure, insulin resistance and dyslipidaemia (Berenson, 2005; Litwin, 2014), with insulin resistance having been identified in overweight and obese children as young as 5 years of age (Young-Hyman *et al.*, 2001). Prolonged exposure to such pathology could contribute to premature CVD in the young adult population (Berenson, 2005; Litwin, 2014). Thus, obesity affects the immediate and long-term health of a child and their overall quality of life.

In 2012, the WHO published a report on population-based approaches to childhood obesity prevention, which identified improved government structures to support policy and intervention as well as population-based and community based interventions as actions to prevent childhood obesity (World Health Organization, 2012). In 2014, The WHO Commission on ending childhood obesity was established to review, build upon and address gaps in existing strategies. The report of the Commission was published in 2016 (World Health Organization, 2016b) followed by an implementation plan in 2017. Between 2014 and 2018, the European Union (EU) and the United Kingdom (UK) Government have published action plans on childhood obesity (European Commission, 2014; HM Government, 2016; Department of Health and Social Care, 2018). The key areas of action identified under these reports and plans are outlined in Figure 1.1. The goal of the 2014 EU Action Plan was to contribute to halting the rise in overweight and obesity in children aged 0 to 18 years by 2020. The aim of the UK

Government's 2016 Action Plan was to significantly reduce rates of childhood obesity within the next ten years. This was followed by a second instalment in 2018 that set the national ambition as halving childhood obesity while also significantly reducing the gap in obesity between the most and least deprived areas by 2030.

Figure 1.1: Areas covered under the childhood obesity action plans



The WHO Commission considered it essential to address critical time periods in development including pre-conception and pregnancy as well as treating children identified as obese (World Health Organization, 2016b). This is due to the increasing prevalence of obesity in women of reproductive age which affects both the health of the mother and puts the offspring at risk of developing childhood obesity and its consequences (Hanson *et al.*, 2016). There is evidence that the *in-utero* environment induces a response in the foetus which could lead to enhanced susceptibility for diseases in later life (Galjaard *et al.*, 2013). This concept is described as the "developmental origins of health and disease (DOHaD)". This has been studied extensively in relation to maternal undernutrition and later risk of coronary heart disease (Barker, 1995). Developing foetuses adapt to an adverse (undernourished) *in-utero* environment by downregulation of growth leading to permanent structural, physiological and hormonal changes (predictive adaptive responses) (Gluckman and Hanson, 2004a) which are beneficial for short term survival (Godfrey and Barker, 2000). However, there is a cost to future health as the foetus is left to cope with the consequences that are dependent on the nutritional status of the postnatal environment. This phenomenon has been termed the "thrifty phenotype hypothesis" (Hales and Barker, 1992). Additionally, non-genetic evolution has led to a competitive dominance of adipocytes over other cell types in the acquisition and sequestering of energy in the body. This is maintained by the co-existence of excess maternal resources and sedentary behaviour during pregnancy leading to continued dysfunction in foetal metabolism. This hypothesis has been termed as the "maternal resources hypothesis (MRH)" (Archer, 2015). Behavioural patterns are transmitted between generations through socially mediated learning (Jablonka and Lamb, 2007) and the postnatal environment could affect the behaviour of infants and young children based on that of the primary caregiver (Archer, 2015). Thus, it has been suggested that DOHaD should include all aspects of environment and all sensitive windows (preconception, pregnancy, early childhood and any others yet to be identified) (Heindel *et al.*, 2015).

Routine data are data collected routinely as part of healthcare or population health monitoring. This is a unique and valuable source of information on a large group of individuals collected over many years. Through the health visiting service in the UK, all families with children up to 5 years of age have regular contact with trained health professionals aimed to enhance health and reduce health inequalities with targeted programmes for vulnerable populations. Thus, utilising routine data for this project provides an understanding of the data that

are recorded as part of the healthcare process during this key stage of development. The findings can support health visitors in the conversations with families around healthy weight and reducing obesity which is one of the impact areas that health visitors focus on.

1.2 Aims and objectives

The aim of this PhD is to examine risk associations between maternal, early life factors and childhood overweight and obesity utilising routinely collected and recorded population data for the purpose of identifying windows of opportunities for prevention. Maternal factors also include a focus on the interpregnancy period and maternal weight change during this period to examine risk in subsequent children. It also aimed to develop and internally validate a childhood overweight/obesity risk score that would inform population risk stratification and intervention development at an early preventive stage tackling the combination of maternal and early life risk factors.

In addition to the research findings, this project explored the feasibility of utilising and linking routine National Health Service (NHS) and local government data for research and practice including the ethics and governance around data access and linkage.

The thesis objectives by chapter are:

Chapter 3: Systematic review of risk prediction scores

- To carry out a systematic review of existing prediction models for childhood overweight and obesity
- To critically assess the development and reporting of the methodology used to develop these models

Chapter 4: Methods (data access and linkage including governance)

- To identify the data holders of the relevant routine data sources necessary for this project
- To explore the ethics and governance requirements for accessing these data for research

Chapter 5: Interpregnancy interval, maternal interpregnancy weight change and size at birth

- To investigate the change in maternal BMI between pregnancies and examine its association with length of the interpregnancy interval.

Chapter 1

- To examine the association between length of the interpregnancy interval and size at birth

Chapter 6: Maternal interpregnancy weight change and size at birth

- To examine the association between interpregnancy weight change and size at birth

Chapter 7: Development of prediction model of childhood overweight and obesity at 4-5 and 10-11 years

- To develop a prediction model for the risk of childhood overweight and obesity at 4-5 years and 10-11 years using maternal and early life routinely recorded data

Chapter 8: Development of prediction model of childhood obesity at 4-5 years incorporating interpregnancy change

- To develop a prediction model for the risk of childhood overweight and obesity at 4-5 years in the second born offspring using maternal and early life risk factors taking into account interpregnancy change

1.3 Overview of thesis

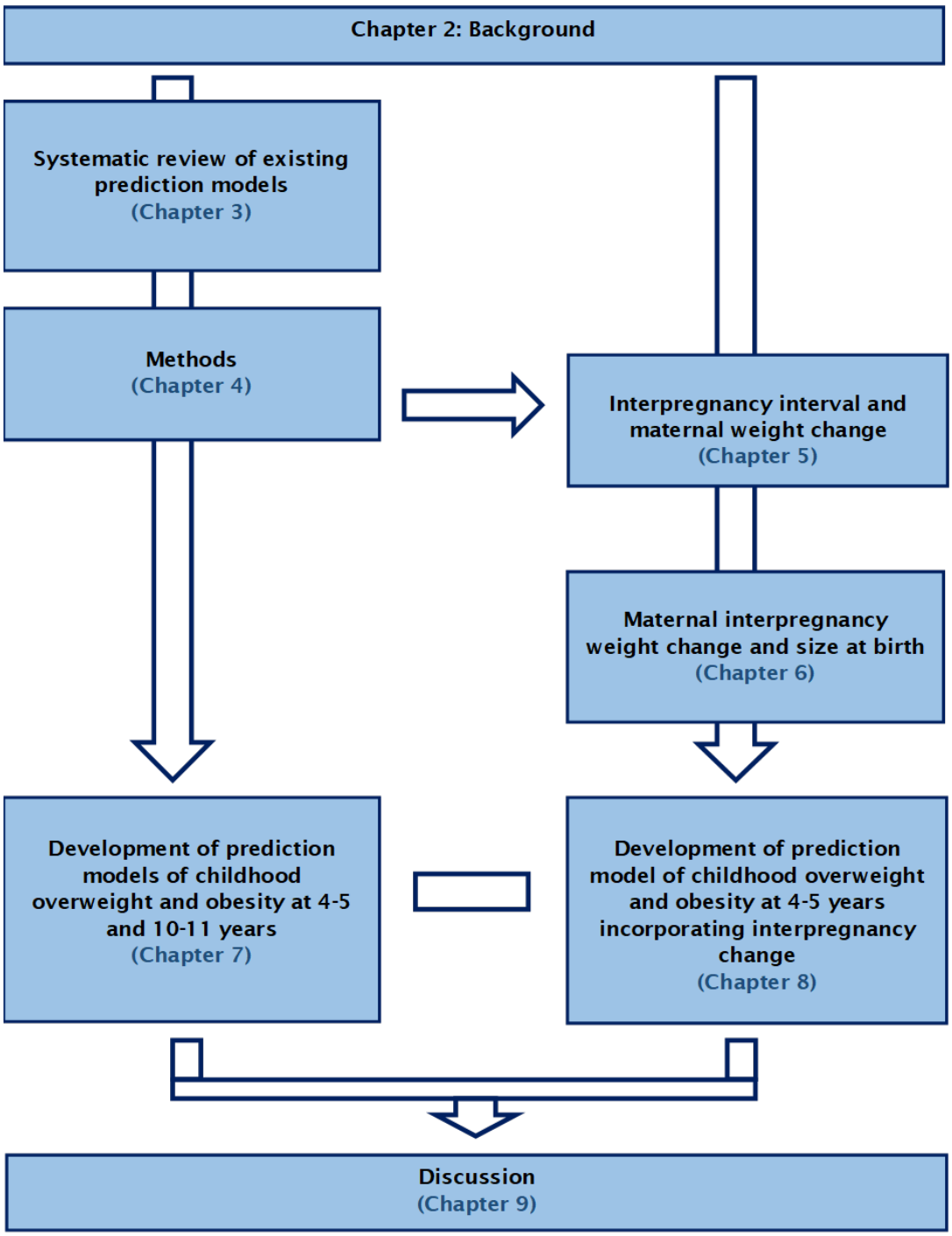
This section provides an overview of the thesis structure by chapter (Figure 1.2). Chapter 2 provides a detailed background on the maternal and early life risk factors for childhood overweight and obesity which is supplemented by the systematic review of prediction models in Chapter 3 to set the scene for the analysis included in this thesis. As this PhD utilises linked routinely recorded data, the process of accessing and linking the data was slow. As maternal antenatal and birth record data was accessed first, I decided to embark on the inter-pregnancy analysis while waiting to access and link the childhood data. This was to utilise a key strength of this dataset (records on more than one pregnancy per mother) and to carry out novel analysis on the interpregnancy interval and maternal weight change.

There are five results chapters (including the systematic review). Chapter 4 presents the methods and considerations of accessing and linking routinely recorded data utilised to meet the objectives of this thesis. Statistical methods used in each analysis are outlined in the respective results chapter. Chapters 5 and 6 presents results on the interpregnancy interval and maternal interpregnancy weight change mentioned in the paragraph above. Chapter 7 presents the development of the risk prediction model for the risk of childhood overweight and obesity in the full sample. Chapter 8 ties in the interpregnancy

analysis with childhood overweight and obesity by developing a prediction model using interpregnancy factors in the subsample with two consecutive live birth pregnancies.

Each results chapter presents a discussion section focussed specifically on the analysis included in that chapter. Chapter 9 synthesises and discusses all the findings. Areas for future research as well as considerations for implementing the risk prediction tool are presented.

Figure 1.2: Overview of thesis structure



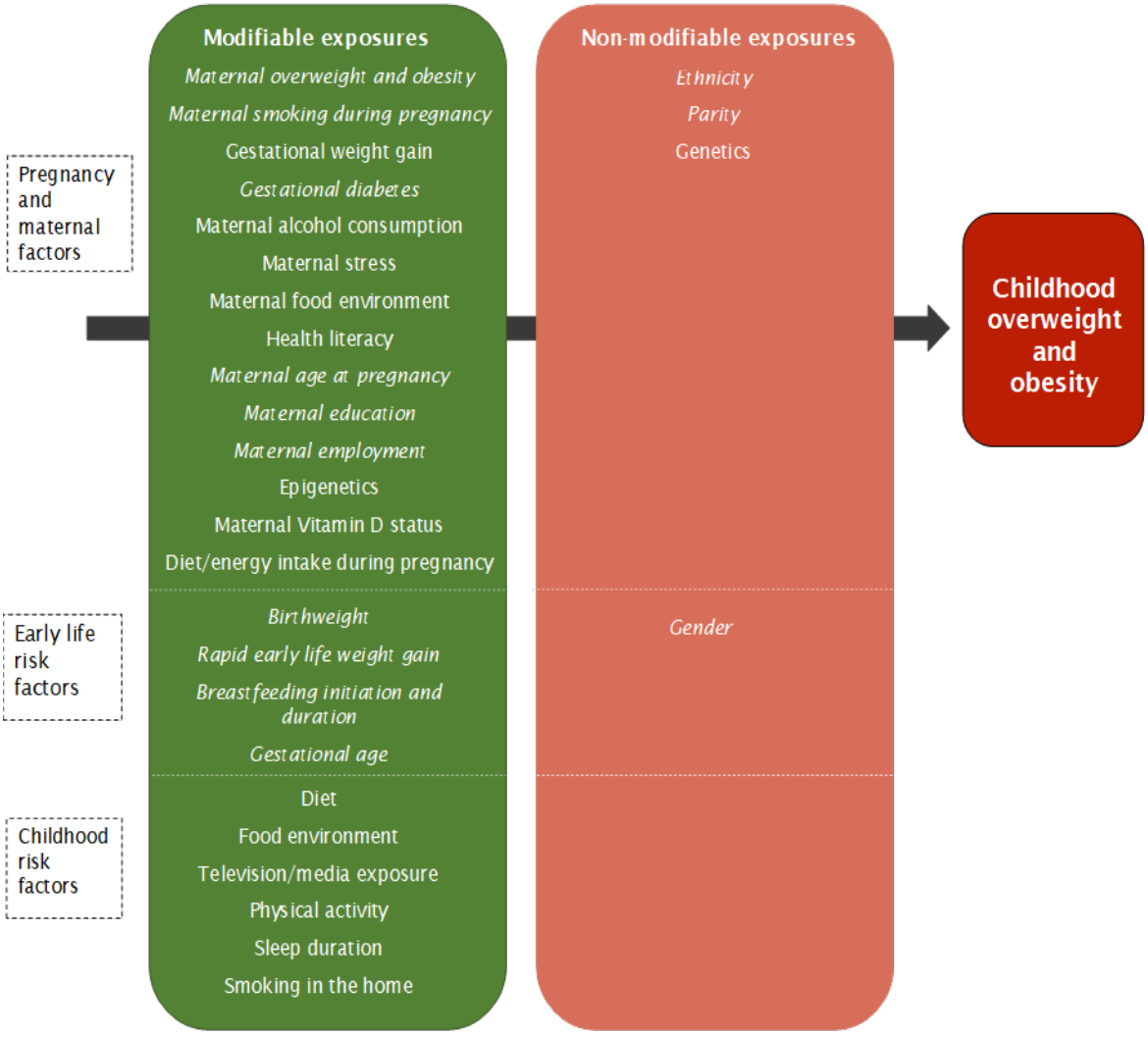
1.4 Conclusion

This chapter has provided a brief rationale for the study including the aims and objectives as well as the thesis structure. The next chapter provides a general background to the research questions posed by this thesis.

Chapter 2 Background

The developmental influences on obesity outlined in Chapter 1 include maternal factors, both pre- and during pregnancy, and early life factors which are described in detail below. Several risk factors for childhood overweight and obesity have been identified through previous research in this area as outlined in Figure 2.1. Due to the planned design of this project, this review has focussed only on risk factors that are collected through routine care during pregnancy and early life in the UK (in italics in the figure) and thus does not cover all the previously identified risk factors. Additionally, this review does not cover an exhaustive list of all the risk factors considered in prediction as predictive factors do not have to be causal (Riley *et al.*, 2013).

Figure 2.1: Modifiable and non-modifiable risk factors of childhood overweight and obesity as identified in the literature*



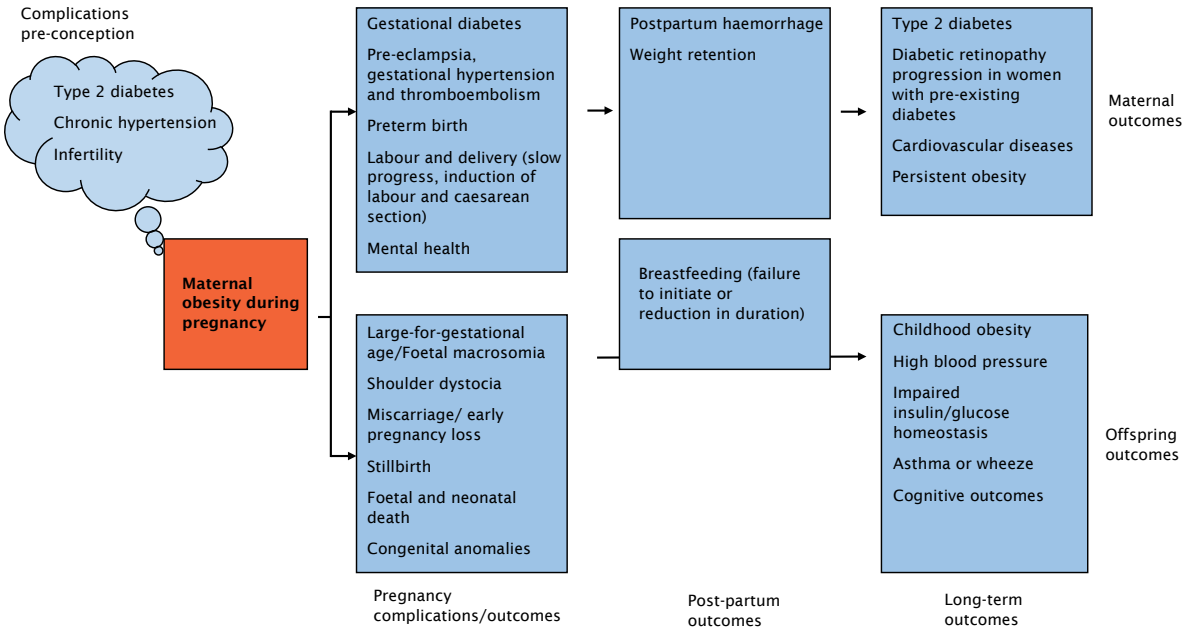
*Exposures in italics are those that collected during routine care in the UK and thus included in this project.

2.1 Pregnancy and maternal risk factors for childhood obesity

2.1.1 Maternal overweight and obesity

The rate of obesity is rising worldwide which implies that the prevalence in women of reproductive age is also rising and is seen in all populations regardless of income status (Hanson *et al.*, 2016). Data from the Health Survey for England (HSE) 2015 indicate that an average of 52.1% of women aged 16 to 54 years are overweight or obese (Moody, 2016). Similarly, data from the United States of America's (USA) National Health and Nutrition Examination Survey (NHANES) (1999 to 2004) and the 2002 USA National Survey of Family Growth indicated that nearly half of women of childbearing age in USA are either overweight or obese (Ogden *et al.*, 2006; Vahratian, 2009). Maternal obesity (during pregnancy) in England has shown a significant increase over time, having more than doubled between 1989 to 2007 (7.5% to 15.6%), with the rate of normal weight pregnancies showing a 12% decrease from 66% to 54% (Heslehurst *et al.*, 2010). Super-obesity, defined as BMI ≥ 50 kg/m^2, was reported in 2.1 per 1000 women giving birth in Australia (Sullivan *et al.*, 2015). Maternal overweight and obesity is associated with increased risks during pregnancy for both the mother and child as summarised in Figure 2.2.

Figure 2.2: Maternal and offspring outcomes associated with maternal obesity*



*Shoulder dystocia is when the baby's head has been born but one of the shoulders becomes stuck behind the mother's pubic bone delaying the birth of the body and usually requires extra help to release the baby's shoulder.

Maternal obesity increases the mother's risk of gestational diabetes mellitus (GDM), longer term type 2 diabetes and cardiovascular risk while putting her offspring at risk particularly of childhood obesity (Hanson *et al.*, 2016). Compared with normal weight women, the estimated risk of developing GDM is increased two-fold in overweight, four-fold in obese and eight-fold in severely obese (Chu *et al.*, 2007). Other risks include development of pre-eclampsia (Sebire *et al.*, 2001; Anderson *et al.*, 2012) and gestational hypertension (Poston *et al.*, 2016).

Overweight and obese women also have an increased risk of preterm birth before 32 weeks as well as induced and overall preterm birth before 37 weeks (Baeten *et al.*, 2001; McDonald *et al.*, 2010). However, a population-based cohort comparing super obese women (BMI >50 kg/m^2) with the general population of women giving birth in Australia (BMI ≤50 kg/m^2) reported no difference in preterm birth between groups but higher rates of caesarean section, pre-eclampsia, GDM in super obese women and high birth weight ≥ 4500g in their offspring (Sullivan *et al.*, 2015). Similarly, retrospective database analysis of 287,213 pregnancies in London between 1989 and 1997 found that delivery before 32 weeks gestation was significantly less likely in the overweight and obese groups as was breastfeeding at discharge (Sebire *et al.*, 2001). Given that the control group in the Australian cohort included obese women and analysis was stratified by BMI group in the London cohort, the findings are indicative that the risk of adverse outcomes increases with increasing BMI.

Compared to infants of normal weight women, infants of overweight or obese women have higher birth weight, specifically higher fat mass (Sewell *et al.*, 2006; Hull *et al.*, 2008). Infants of overweight or obese women are at higher risk of large-for-gestational age (LGA) and foetal macrosomia (significantly large birth weight usually 4kg or greater regardless of gestational age) (Weiss *et al.*, 2004). In addition to high birth weight, infants of overweight and obese women are more likely to require resuscitation at birth and have Apgar score <7 at five minutes (Dodd *et al.*, 2011). The risk of infant death within one year of birth was found to be significantly higher in obese than lean women in a population based cohort in Washington (Baeten *et al.*, 2001). A recent systematic review and meta-analysis of 79 studies identified higher risk of childhood obesity with increasing maternal pre-pregnancy BMI with maternal overweight increasing the odds by 89% and maternal obesity by 264% (Heslehurst *et al.*, 2019).

Thus, maternal obesity during pregnancy increases the risk of adverse pregnancy outcomes for both mother and child. It also increases the risk of long-term health problems in the child including obesity, cardiovascular disease, diabetes and cognitive and behavioural disorders (Poston, 2012). Maternal obesity is the strongest known risk factor for childhood overweight and obesity, the burden of which is growing, and a need to focus on the pre-conception period has been highlighted by the WHO to attempt to reverse the cycle and trans-generational effect of maternal obesity. The interpregnancy period between two pregnancies is also a preconception intervention opportunity for subsequent pregnancies as women and their families have intensive contact with health-care professionals after birth of a child.

2.1.2 Maternal smoking

According to national figures for England in 2018/19, 10.6% of pregnant women were smokers at the time of delivery but rates across the country showed wide variation from 1.6% to 25.7% (NHS Digital, 2019). The higher prevalence was observed in more deprived areas and is indicative of the socioeconomic gradient in smoking during pregnancy. The rates of smoking in pregnancy has shown a gradual decrease over time from 15.1% in 2006/07 to 10.5% in 2016/17 meeting the national ambition laid out in the Tobacco Control Plan for England published in 2011 which aimed to reduce smoking rates in pregnancy to 11% or less by the end of 2015 (Department of Health, 2011). Based on this progress, the 2017 Tobacco Control plan has set the national ambition to reduce pregnancy smoking rates to 6% or less by the end of 2022 (Department of Health, 2017). However, despite the decline in smoking rates, approximately 70,000 babies are still being born every year in the UK to women who smoke during pregnancy.

Smoking in pregnancy may cause growth retardation which becomes evident during the second half (week 17 onwards) of the pregnancy with offspring of smokers exhibiting catch-up growth in early life resulting in greater BMI at five years of age (Vik *et al.*, 1996). Maternal smoking during pregnancy was found to be negatively correlated with birth weight although smoking data in this study were collected retrospectively when the offspring were aged 12 to 32 years and thus subject to recall bias (Agrawal *et al.*, 2010). A longitudinal study found that LBW associated with maternal smoking was reversed with age where children of smokers exhibited catch-up growth between two and four years of age such that they weighed more by six years of age and tended to be more obese by early

adolescence than children of non-smokers. This catch-up growth was found to be higher in males than females and a protective effect of longer duration of breastfeeding was observed (Fried *et al.*, 1999).

A questionnaire based cross-sectional study in Germany found that children of women who smoked in the first trimester only or throughout pregnancy were at increased risk of overweight and obesity compared to those of women who never smoked (Toschke, 2003). However, the analysis was restricted to German children aged five to seven years with complete information on maternal smoking and potential confounding factors thus increasing the possibility of selection bias. Maternal smoking during early pregnancy has been associated with childhood adiposity (using BMI and skinfold measurements) (Widerøe *et al.*, 2003; Oken *et al.*, 2005; Suzuki *et al.*, 2009) but there was no association with smoking prior to pregnancy (Oken *et al.*, 2005). However, children of women in a prospective population based cohort in Norway who stopped smoking early in pregnancy did not have an increased risk of being overweight at age four years whereas those of women who continued smoking throughout pregnancy did (Fasting *et al.*, 2009). Maternal smoking during pregnancy was associated with increased overweight and obesity in offspring at adolescence compared to offspring of mothers who had never smoked or quit smoking during pregnancy (Al Mamun *et al.*, 2006).

Data from the 1958 British birth cohort showed that children of women who smoked past the fourth month of pregnancy had higher BMI and waist circumference at 45 years of age than those who were not exposed to tobacco prenatally. A dose-response relationship was identified with smoking such that BMI and waist circumference in adult offspring increased with increase in number of cigarettes smoked during pregnancy (Power *et al.*, 2010). Maternal smoking both before and during pregnancy was also associated with elevated systolic blood pressure in the offspring at 3 years of age (Oken *et al.*, 2005). A few studies have shown that smoking cessation early in pregnancy is associated with similar offspring outcomes as those of non-smoking mothers though the mechanism is not entirely clear. Foetal growth retardation related to smoking can be prevented or reduced if the mother quits smoking in early pregnancy (Ahlsten *et al.*, 1993) and thus timing, duration and amount of cigarette exposure could be important. Lifestyle habits and socioeconomic status of women who do not smoke or are able to quit smoking when pregnant may be different to that of women who choose not to or were unable to quit.

Passive maternal smoking through paternal or household smoking were also found to be associated with increased risk of childhood overweight and obesity however effect estimates remained higher for maternal smoking during pregnancy (Riedel *et al.*, 2014). Higher risk of childhood overweight at seven years of age was observed with maternal smoking during both pregnancy and the postnatal period compared to smoking during pregnancy alone with risk increasing with each additional cigarette smoked. Although the prevalence of LBW was low in this cohort, mothers who smoked during pregnancy were more likely to have LBW babies who were at higher risk of childhood overweight than LBW babies whose mothers did not smoke (Moller *et al.*, 2014).

Thus, offspring of mothers who smoke during pregnancy or are exposed to passive smoke are at higher risk of childhood overweight and obesity. Smoking cessation early in pregnancy reduces the risk of adverse outcomes for the offspring.

2.1.3 Impaired glucose tolerance, type II diabetes and gestational diabetes

Hyperglycaemia first identified at any time during pregnancy is classified as GDM. GDM usually disappears after giving birth but women who are diagnosed with GDM are at increased risk of developing type 2 diabetes. The diagnosis is based on meeting one or more of the criteria outlined in Table 2.1 based on the 2006 and 2011 WHO criteria for diabetes mellitus (DM) (World Health Organization and International Diabetes Federation, 2006; World Health Organization, 2011) and the 2013 WHO recommendations for GDM (World Health Organization, 2014).

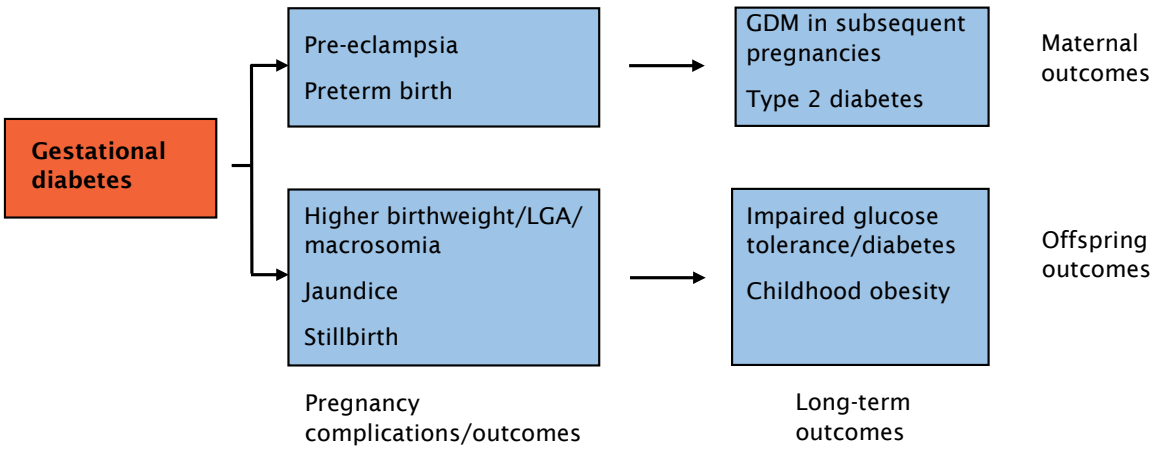
Table 2.1: Criteria for diagnosis of diabetes mellitus and gestational diabetes mellitus

Diagnosis criteria	Diabetes Mellitus (DM)	Gestational diabetes mellitus (GDM)
Fasting plasma glucose	≥7.0 mmol/l (126 mg/dl)	5.1-6.9 mmol/l (92-125 mg/dl)
1-hour plasma glucose following a 75g oral glucose load	-	≥10 mmol/l (180 mg/dl)
2-hour plasma glucose following a 75g oral glucose load	≥11.1 mmol/l (200 mg/dl)	8.5-11.0 mmol/l (153-199 mg/dl)
Random plasma glucose in the presence of diabetes symptoms	≥11.1 mmol/l (200 mg/dl)	-
Haemoglobin A1c (HbA1c)	≥48 mmol/mol (6.5%)	-

The global age-standardised prevalence of type 1 and type 2 DM in women has risen from 5.0% in 1980 to 7.9% in 2014 (NCD Risk Factor Collaboration (NCD-RisC), 2016). This rise in prevalence combined with the existence of a large number of undiagnosed cases of DM, means that there is a need to detect pre-existing DM in pregnancy. This has been identified in guidelines from WHO, UK, Europe and USA due to increased risk of pregnancy complications and adverse foetal outcomes (American College of Obstetricians and Gynecologists, 2013; World Health Organization, 2014; Benhalima *et al.*, 2015; National Institute for Health Care and Excellence, 2015). Between 1994 and 2004, the rates of pre-existing Type 2 DM in pregnant women in USA increased more than fourfold and in 2003 surpassed the rate of Type 1 DM (Albrecht *et al.*, 2010). This striking increase in the pre-existing cases of type 2 diabetes among pregnant women is considered to be due to the rise in obesity.

Infants of GDM women including those born average weight-for-gestational age have higher fat mass compared with infants of women with normal glucose tolerance (Catalano *et al.*, 2003). High rate of weight gain in early- and mid-pregnancy was associated with increased risk of impaired glucose tolerance (Herring *et al.*, 2009). A sex-specific interaction was observed where only male offspring of mothers with GDM (and not intermediate glucose intolerance) and female offspring of mothers with intermediate glucose intolerance (and not GDM) had higher adiposity at mean age of 8 years (Regnault *et al.*, 2013). Male offspring of women that were treated for GDM (dietary intervention, blood glucose self-monitoring and insulin therapy if necessary) had significantly lower birth weight, fat mass > 90th percentile and frequency of large-for-gestational age (LGA) compared to women who received usual prenatal care (Landon *et al.*, 2015).

Figure 2.3: Maternal and offspring outcomes associated with gestational diabetes



Maternal hyperglycaemia during pregnancy was associated with adiposity in offspring at 5 to 7 years but this effect was attenuated when adjusted for maternal BMI indicating that this was not a dependent association (Thaware *et al.*, 2015). Conversely, increasing levels of hyperglycaemia during pregnancy was found to be associated with offspring adiposity at age 5 to 7 years in a diverse US population. However risk was attenuated on multivariate adjustment (maternal age, parity, ethnicity, GWG, macrosomia and offspring sex) when GDM was treated with diet or diet/insulin suggesting the modifiable nature of this risk (Hillier *et al.*, 2007). Children exposed to GDM *in-utero* were found to have higher adiposity (assessed using skinfold measurements) and systolic blood pressure at three years of age (Wright *et al.*, 2009). Offspring of diabetic mothers tended to gain weight faster than children not exposed to diabetes *in-utero* with rapid weight gain observed from 5 years of age such that approximately half the children of diabetic mothers had weights above the 90th percentile (Silverman *et al.*, 1991). Although GDM is associated with overweight in adolescence, adjusting for birth weight attenuated this association suggesting that GDM might not be on the causal pathway for offspring obesity but instead could be a marker by programming the foetus for postnatal influences (Gillman *et al.*, 2003). However, another study in Caucasian women in Germany found that offspring of GDM mothers had consistently higher BMI measured at several time points up to eight years of age compared with the average German population with maternal, paternal and birth BMI identified as independent predictors (Schaefer-Graf *et al.*, 2005). Similarly, an increased risk of overweight and obesity at age 3 years was found in children exposed *in-utero* to maternal glucose concentration ≥ 130 mg/dL in the absence of pre-existing diabetes and GDM (Deierlein *et al.*, 2011).

Maternal diabetes induces foetal hyperinsulinemia through foetal hyperglycaemia resulting in macrosomia. Foetal hyperinsulinemia during critical development periods could lead to insulin and leptin resistance and fat cell overgrowth thus increasing obesity risk (Wright *et al.*, 2009). Macrosomia is a consequence of an increased fuel environment associated with neonatal morbidities as well as potential *in-utero* programming leading to long-term consequences such as obesity, hypertension and hyperglycaemia (Vohr and Boney, 2008). However, foetal outcomes are similar regardless of type of diabetes in the mother thus suggesting that the metabolic effects of the diabetic environment *in-utero* are dependent on the level of exposure to hyperglycaemia rather than the diabetes type.

2.1.4 Maternal age

Maternal age at first pregnancy has increased over time (Nabukera *et al.*, 2009) with data from 1969-2006 in Switzerland showing that maternal age at first pregnancy had increased from 25.0 to 30.1 years (Kalberer *et al.*, 2009). In England and Wales, 54% of all live births in 2016 were to mothers aged 30 years and over compared to 41% in 1996 with mean age at first pregnancy having risen to 28.8 years compared to 26.8 years in 1997 (Office for National Statistics, 1998, 2017b). Thus, there is a clear trend of increased delaying of childbearing, particularly in high-income countries.

Maternal age of 35 years or more has been associated with increased risk of GDM and caesarean delivery with maternal age of 40 years and over additionally associated with increased risk of macrosomia, preterm delivery and LBW (Cleary-Goldman *et al.*, 2005). Analysis of a population-based cohort in Sweden showed an increased risk of very low (<1500g) and moderately low (1500 to 2499g) birth weight, preterm birth (less than or equal to 32 weeks and less than 37 weeks) and SGA infants in mothers aged 30 to 34 years compared to those aged 20 to 24 years. The risk increased in mothers aged 40 years and over (Cnattingius *et al.*, 1992). Similarly, analysis of a population-based cohort in the North of England showed that mothers aged 30 years and over had increased risk of LGA and preterm delivery with risk increasing with age group (30 to 34, 35 to 39 and 40 years and over) compared to mothers aged 20 to 29 years (Kenny *et al.*, 2013). This risk was higher in older women of higher social deprivation.

Maternal age has mainly been examined in relation to birth outcomes. It is treated as a confounder and controlled for in analysis of risk factors and childhood obesity. There is insufficient evidence on whether maternal age is a risk factor or a confounder.

2.1.5 Socio-demographic factors

2.1.5.1 Maternal educational attainment

Educational attainment is the highest degree of education completed and is one of the factors encompassed within socio-economic status. A cross-European cohort comprised of 11 birth cohorts found an association with low maternal education and increased risk of childhood overweight and obesity with gender differences observed in some cohorts but without a consistent pattern (Ruiz *et al.*, 2016). Data from the Millennium Birth Cohort in the UK (included in the cross-

European cohort above) analysed separately showed increased risk of overweight at 11 years of age in children of mothers with low educational attainment. Relative risks were calculated for maternal education status and then additional risk factors were added that showed that maternal pre-pregnancy overweight status and smoking during pregnancy contributed to approximately 40% risk attenuation in the lowest maternal qualifications group suggesting that these two factors explain a considerable amount of the social inequalities in weight status (Massion *et al.*, 2016).

Analysis of data from a nationally representative Danish cohort showed that Danish mothers tended to have a higher education level than fathers and maternal education level was inversely associated with risk of childhood overweight and obesity, particularly in boys. When highest parental education level (highest education level of mother or father) was taken into account, combined parental education was found to the more influential than maternal or paternal education separately (Matthiessen *et al.*, 2014). A cross-sectional cohort in Germany also found significantly increased risk of childhood overweight and obesity in children of parents with low educational attainment (Lamerz *et al.*, 2005). Both studies recruited school-age children and collected information on parental education level through questionnaire/interview so educational attainment of some parents may be higher than at birth of the child.

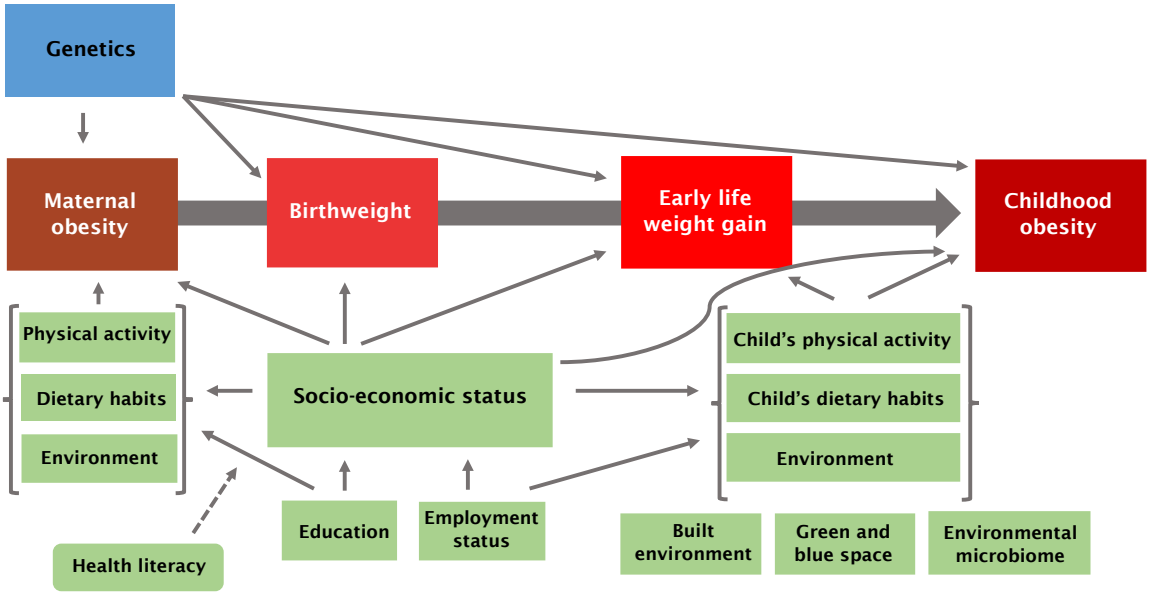
2.1.5.2 Maternal employment

The rate of employment of mothers in England has increased from 61.9% in 1996 to 74.0% in 2018. Since 2010, the rate of employment of mothers (74.0%) has been higher than that of women with no dependent children (69.7%) (Office for National Statistics, 2017c). Mothers with children aged 1 to 11 years were more likely to work part-time. It is important to assess the impact of the increase in maternal employment rates on child outcomes.

Data from a birth cohort in the UK showed that children were more likely to be overweight if the mother had held any employment since the birth of the child and the risk increased with increasing hours worked by the mother in high-income families only (Hawkins *et al.*, 2008). This suggests that long hours of maternal employment may impede children's access to healthy foods and physical activity due to parental time constraints. The increased risk with increasing number of hours worked was also demonstrated in USA (Anderson *et al.*, 2003) and Canada (Phipps *et al.*, 2006). Conversely, children aged 2 to 6

years of working mothers in a rural town of Japan were found to have lower risk of childhood overweight compared to children of non-working mothers and the risk was lowest in children of mothers who worked less than eight hours per day (Mitsuhashi *et al.*, 2012). This was a cross-sectional study with data collected through postal questionnaires and thus employment status and weight and height measurements were self-reported by the parent.

Figure 2.4: Influence of socio-demographic factors on maternal and offspring obesity



Results from an Irish cohort indicate that the key drivers of socioeconomic inequalities in childhood overweight and obesity are parental BMI (particularly maternal), smoking and alcohol consumption, parental occupation and parental educational attainment. Smoking and alcohol consumption may be an indicator of constrained food budgets and thus consumption of foods of low nutritive value (Walsh and Cullinan, 2015) but may also be an indicator of less healthy lifestyle choices. High fat and high carbohydrate intake during pregnancy has been associated with increased neonatal adiposity (Chen *et al.*, 2016; Crume *et al.*, 2016) and early childhood BMI (Chen *et al.*, 2017). Better-educated parents may be more aware of the child's weight status as well as the importance of healthy eating and physical activity. Educational attainment and occupation could be reflective of higher socioeconomic status and thus ability to afford healthier lifestyle choices. Thirty percent of children in the UK in 2017/18 are living in poverty (Department for Work and Pensions, 2019). Socio-economic factors are determinants of the environment that children are exposed to which could influence choices, for example, a weak positive association has been found

between fast food outlet exposure around home and body weight in girls using cross-sectional data (Williams *et al.*, 2015). A beneficial effect of access to green space on childhood BMI emerged in boys as they got older (followed from 6 to 13 years of age). A similar association was observed in girls but this was attenuated on adjusting for socio-economic confounders (Sanders *et al.*, 2015).

2.1.6 Parity and interpregnancy changes

Birth registration data from England and Wales show that 36% of women have no or one child (18% each) and 64% have two or more children (27% have two, 17% have three and 10% have four or more). This is based on a cohort of women born in 1972 who were 45 years of age in 2017 when these data was analysed and assumed to have completed childbearing (Office for National Statistics, 2018).

Pregnancy is a period of metabolic and behavioural changes, the effects of which last beyond the immediate pregnancy for both mother and child (Gilmore *et al.*, 2015) thus affecting subsequent children. Various changes follow the pregnancy and birth of the first child. Interpregnancy change can be biological (weight change and continuing impact of gestational diabetes or other obstetric complications), socioeconomic (employment issues, child care and income, lone parenthood), psychological (stress, mental illness) and lifestyle (diet, physical activity, smoking). The number and extent of these changes can vary between women and between pregnancies and thus maternal exposures can differ from the first to subsequent pregnancies. However, epidemiological research has primarily focussed on studying exposures and outcomes in one pregnancy per mother longitudinally. Parity of women is evaluated and accounted for through adjustment or stratification. But an adjustment for parity may not fully account for the differential circumstances (Wilding *et al.*, 2019a) and effects of factors such as baseline BMI and weight change, pregnancy number, length of the interval from previous pregnancy and breastfeeding.

Pregnancy can alter a woman's weight trajectory due to the risk of weight gain on childbearing due to biological and behavioural reasons (Schmitt *et al.*, 2007). Weight gained during pregnancy is not always lost after delivery and thus pregnancy is a risk factor for overweight and obesity in women which increases with additional pregnancies (Davis *et al.*, 2009). Post-pregnancy weight retention is variable with women on average retaining 0.5 to 3kg, however a substantial number (12-20%) retain a considerable amount of weight (Gore *et al.*, 2003). Analysis of data from the Danish Medical Birth Registry between 2004 and 2012

showed an increase in maternal BMI with each additional parity (Iversen *et al.*, 2018). Similarly, childbearing has been found to have a persistent long-term effect on adiposity in women in the UK with a progressive BMI increase observed from nulliparous women to multiparous women with four or more births. This effect was further modified by breastfeeding initiation and duration (Bobrow *et al.*, 2013).

Interpregnancy interval is the interval between a birth and the conception of the next pregnancy. Short (<18 months) and long (>59 months) intervals between pregnancies have been associated with increased risk of adverse perinatal outcomes (Conde-Agudelo *et al.*, 2006). The interval between pregnancies could also affect the observed increase in BMI with consecutive pregnancies and warrants consideration. The WHO technical consultation on birth spacing in 2005 recommended an interval of 2 years or more (World Health Organization, 2005) but there is no national guidance on the optimal interval between pregnancies.

2.2 Early life risk factors for childhood obesity

2.2.1 Birth weight

The first indicator found to be associated with later non-communicable disease within DOHaD was birth weight (Barker *et al.*, 1989). Birth weight is considered an indicator of the foetal environment and thus indicative of foetal growth restriction (through undernutrition) or growth enhancement (through over-nutrition).

Increasing birth weight has been found to be associated with obesity prevalence at age 7 years (Danielzik *et al.*, 2004; Reilly *et al.*, 2005) and into adulthood (Curhan *et al.*, 1996a; Curhan *et al.*, 1996b; Phillips and Young, 2000). A systematic review identified seven studies that considered high birth weight as a potential risk factor of which six studies found a positive association and one study found no association (Weng *et al.*, 2012). Birth weight is positively associated with BMI in adolescence with each 1kg increment in birth weight leading to approximately 30% increase in overweight prevalence (Gillman *et al.*, 2003). Analysis of overweight and obesity risk stratified by gender and birth weight (low birth weight (LBW) <2500g, normal 2500-4000g and high birth weight >4000g) in children aged 4 to 5 years born at term in a national Australian cohort showed that the risk was higher in high birth weight children particularly boys. LBW, on the other hand, was found to be associated with reduced risk of overweight and obesity significantly so in girls (Oldroyd *et al.*, 2011). The models

were adjusted for ethnicity and sociodemographic variables including child age and gestational age. These findings are supported by similar findings from a cross-sectional cohort of low socioeconomic status in Argentina of the risk of overweight and obesity at age 5 to 13 years (Hirschler *et al.*, 2008). However, these studies may inadequately adjust for known confounders.

Birth weight is an important predictor of childhood overweight and obesity and thus a useful intermediate outcome to examine.

2.2.2 Breastfeeding initiation and duration

Benefits of breastfeeding include fewer infections partly through passive transmission of maternal antibodies and possible protection against diabetes; and it also plays a role in birth spacing (Victora *et al.*, 2016). Breastfeeding rates are generally higher in low- and middle-income countries than high-income countries (Victora *et al.*, 2016). The breastfeeding rate at six to eight weeks after birth in England for 2016/17 was 44.4% (30% exclusive and 14.4% partial breastfeeding) (Public Health England, 2017). The evidence on the protective effect of breastfeeding on childhood overweight and obesity is conflicting to date.

Using random effects meta-analysis on ten studies, a systematic review concluded that breastfeeding (exclusive, ever or mixture of formula and breast milk) in the first year of life decreased the risk of childhood overweight by 15% (Weng *et al.*, 2012). An inverse and linear relationship was found between duration of breastfeeding and risk of overweight that reduced with every additional month of breastfeeding up to nine months (Harder *et al.*, 2005). A reduced risk of overweight at age two years was observed with increased duration of exclusive breastfeeding (six months or more) compared to exclusively breastfeeding for less than three months (Weyermann *et al.*, 2006). A systematic review of published and unpublished studies examining the relationship between breastfeeding and BMI throughout life found lower BMI in those who had been breastfed in infancy however; the effect size was halved on adjustment for maternal BMI and abolished on meta-analysis of 11 studies adjusted for maternal BMI, maternal smoking and maternal socioeconomic status (Owen *et al.*, 2005).

Analysis of a nationally representative cohort of children aged 9 years in the Republic of Ireland showed a reduced risk of obesity in breastfed children with a dose-response pattern such that children breastfed for longer had lower risk. Information on breastfeeding and maternal smoking during pregnancy was

collected retrospectively when the child was aged 9 years and could be subject to bias. The analysis controlled for measured parental weight status at age of outcome which does not necessarily account for the effect of maternal weight status during pregnancy. Gestational age at birth was also adjusted for and although very preterm infants may not be able to initiate breastfeeding at birth it is unlikely to be directly related to the outcome (McCrory and Layte, 2012). Breastfeeding until six months was found to be associated with lower BMI z-score and lower odds of obesity at three years of age however infant weight gain was found to be a strong independent predictor of both BMI z-score and obesity and fully mediated the associations with BMI but only partially for obesity (van Rossem *et al.*, 2011). Infants who were predominantly breast fed for the first six months of life had lower prevalence of overweight at 9 to 14 years of age with an estimated 22% risk reduction compared to predominantly formula fed infants and larger protective effects observed with increasing breastfeeding duration (Gillman *et al.*, 2001).

2.2.3 Weight gain in early life

A large variation in weight gain is seen in the first two years of life where babies can exhibit significant "catch-up" or "catch-down" growth to compensate for intrauterine restriction or enhancement. Change in standard deviation (SD) scores of greater or less than 0.67 SD score has been taken to indicate significant catch-up and catch-down growth respectively (Ong *et al.*, 2000). Catch-up growth is an example of the thrifty phenotype hypothesis as children exhibiting catch-up growth are assumed to be compensating for a poor nutritional environment as a foetus and their genes are maladapted to an environment with abundant nutrition.

Children born small-for-gestational age (SGA) exhibited catch-up growth in the first two years of life followed by transition to higher adiposity and abdominal fat between 2 and 4 years of age compared to children born with normal weight (Ibanez *et al.*, 2006). Rapid weight gain in infants as early as at six weeks to six months of age was found to be related to overweight and obesity in childhood (Eid, 1970; Stettler *et al.*, 2002; Taveras *et al.*, 2009) and young adulthood (Stettler *et al.*, 2003). Lower birth weight infants are more likely to gain weight more rapidly than higher birth weight infants (Druet *et al.*, 2012). Conversely, regardless of weight gain patterns between birth and 3 years of age, smaller infants did not have higher fat mass or percentage body fat at mid-childhood (6

to 10 years) (Perng *et al.*, 2016). This suggests that weight gain during early life may have differential effects on fat and fat free mass acquisition.

Children have an increased risk of overweight by 12 years of age if they are in >50th BMI percentile with a detectable increase in risk if they enter into the ≥75th BMI percentile at any previous age from 24 months onwards (Nader *et al.*, 2006). A meta-analysis of individual data from ten cohort studies found a consistent association of rapid infant weight gain in the first year of life and risk of obesity with a larger effect size for childhood compared to adult obesity. Three of these studies had data on weight gain to two years of life, which was found to be more strongly linked to childhood obesity than weight gain in first year of life. No effect modification by birthweight was observed (Druet *et al.*, 2012).

2.3 Combination of risk factors for childhood obesity

Several risk factors have been identified for childhood obesity as discussed above and initial research using birth cohort data from the Southampton Women's Survey in the UK has shown that having a greater number of pregnancy and early life risk factors increases the risk of childhood obesity (Robinson *et al.*, 2015). Studies that have analysed the presence of a combination of risk factors have examined a variety of combinations and this sections aims to provide an overview of these. A summary of the combined risk factors considered is provided in Table 2.2. This section has been subdivided into sections of two risk factors, three or more risk factors and classification tree analysis. The reason for this distinction is because four combinations of two risk factors have been identified in more than one study in the literature whereas studies that have examined three or more risk factors have not considered the same combination of risk factors and thus cannot be directly compared. Risk factor identification through classification tree analysis is a data driven method and again cannot be directly compared to the other findings presented in this section.

2.3.1 Two risk factors

2.3.1.1 Maternal pre-pregnancy BMI and gestational weight gain (GWG)

Offspring infancy weight gain (Li *et al.*, 2013; Jin *et al.*, 2016) and BMI (Stuebe *et al.*, 2009; Hinkle *et al.*, 2012; Stamnes Kopp *et al.*, 2012) increased with increasing maternal pre-pregnancy BMI and GWG. Offspring of women with

excessive pre-pregnancy BMI and GWG were at highest risk of overweight and obesity from birth to 18 months of age, however offspring of women with excessive pre-pregnancy BMI but non-excessive GWG were at highest risk from 24 to 36 months of age despite being low risk at birth (Jin *et al.*, 2016). Although offspring BMI increased with maternal pre-pregnancy BMI and GWG, offspring of overweight and obese women with excessive and extreme GWG were at similar risk indicating that there was a plateauing of risk in the extreme categories (Stamnes Kopp *et al.*, 2012). GWG of 15-19 pounds (6.8-8.6kg) was associated with lowest offspring BMI at age 18 years and in adulthood in all categories of maternal pre-pregnancy BMI. However, this study only included mother-daughter dyads as data from the Nurses Health Study was used which only recruited female nurses with maternal BMI and GWG collected through recall when the offspring was aged 38 to 56 years (Stuebe *et al.*, 2009). Results from these studies indicate that excessive GWG strengthens the effect of high pre-pregnancy BMI on offspring risk of overweight and obesity.

2.3.1.2 Maternal pre-pregnancy BMI and breastfeeding

The prevalence of overweight in a national longitudinal survey of children aged 2 to 14 years in 1996 in USA ranged from 6.0% in normal weight women who breastfed for 4 months or more to 31.5% in obese women who never breastfed. Offspring of women with BMI ≥ 30 who never breastfed were at highest risk of overweight with evidence of significant interaction on the additive scale (Li *et al.*, 2005). Of interest is overweight was defined as ≥ 95th percentile which is the definition for obesity in USA with overweight defined as ≥ 85th percentile (Flores and Lin, 2013a; Li *et al.*, 2013; Wen *et al.*, 2013). Another study in USA also reported similar findings with a protective effect observed with increasing duration of breastfeeding although even <1 month of breastfeeding was associated with reduced risk in offspring of normal weight women. In comparison to exclusive formula feeding, exclusive breastfeeding or equal formula and breastfeeding was associated with lower risk of childhood obesity in offspring of women with BMI <25 whereas in offspring of women with BMI ≥25 lower risk was observed with exclusive or predominant breastfeeding (Mayer-Davis *et al.*, 2006). Hence, the evidence thus far indicates that breastfeeding attenuates the risk associated with increased maternal pre-pregnancy BMI but the extent of risk attenuation is dependent on the number of months of breastfeeding.

Table 2.2: Summary of studies that examined a combination of risk factors

Author name and year	n	Study design	Country	Risk factors	Outcome	Effect
(Li *et al.*, 2013)	38,539 mother-child pairs	Population cohort using health care records (routine data)	China	• Maternal BMI • Gestational weight gain (GWG) (Institute of Medicine (IOM) guidelines)	Offspring weight, length and weight –for-length (overweight/obesity) from birth to 12 months measured at 3 month intervals	Increased risk of overweight and obesity: • Normal weight + excessive GWG • Overweight + inadequate or excessive GWG or for childhood obesity only - adequate GWG • Obese + adequate or excessive GWG
(Jin *et al.*, 2016)	826 mothers and child pairs	Prospective cohort	China	• Maternal BMI • GWG (IOM guidelines)	Offspring overweight/obesity (0-3 years)	Increased risk of overweight and obesity: • Excessive pre-pregnancy BMI + non-excessive GWG • Non-excessive pre-pregnancy BMI + excessive GWG • Excessive pre-pregnancy BMI + excessive GWG
(Hinkle *et al.*, 2012)	3600 singleton full term infants born in 2001 to	Prospective cohort (Early Childhood Longitudinal Study- Birth cohort) -	USA	• Maternal BMI • GWG (IOM guidelines)	BMI z-score at 5 years	Increase in child BMI z-score with adequate to excessive GWG in normal

Author name and year	n	Study design	Country	Risk factors	Outcome	Effect
	nondiabetic mothers	retrospective pregnancy/birth data				weight and overweight women
(Stamnes Kopp *et al.*, 2012)	31169 pairs enrolled 2000 to 2009	Prospective population cohort (Norwegian Mother and Child Cohort study (MoBa))	Norway	• Maternal BMI • GWG (IOM guidelines) • Paternal BMI (subset of 5898)	Offspring BMI at 3 years	Interaction between maternal BMI and GWG and highest risk of increased offspring BMI in women with high BMI and high GWG
(Li *et al.*, 2005)	2636 pairs with children born at ≥32 weeks gestation and birthweight 0.5-6kg	Prospective cohort (National Longitudinal Survey of Youth, Child and Young Adult) - retrospective pregnancy/birth data	USA	• Maternal BMI • Breastfeeding	Overweight in children 2 to 14 years	Additive interaction between maternal BMI and lack of breastfeeding Increased risk in offspring of: • overweight and obese women in all categories of breastfeeding (never, 1 to 3 months and ≥4 months) • Normal weight women who never breastfed
(Mayer-Davis *et al.*, 2006)	15253 mother-child pairs	Prospective cohort (Growing Up Today Study (GUTS)) – retrospective pregnancy/birth data	USA	• Maternal BMI in nondiabetic mothers or diabetes • Breastfeeding	Childhood overweight and obesity at 9 to 14 years	Increased risk in offspring of overweight women with short duration of breastfeeding (<3 months) and diabetic women (<1 month)

Author name and year	n	Study design	Country	Risk factors	Outcome	Effect
(Kubo *et al*., 2014)	421 mother-daughter pairs	Prospective cohort (Cohort Study of Young Girls' Nutrition, Environment, and Transitions (CYGNET)) – retrospective or routine pregnancy data	USA	• Maternal BMI • Gestational diabetes	Overweight and obesity at 9 to 14 years	Increased risk in overweight and obese women with gestational diabetes
(Crume *et al*., 2011)	89 pairs + 379 control pairs	Retrospective cohort (Exploring Perinatal Outcomes among Children (EPOCH))	USA	• Breastfeeding • Gestational diabetes	• BMI • Waist circumference • Subcutaneous adipose tissue (SAT) • Visceral adipose tissue (VAT) and • Subscapular-to-triceps skinfold ratio (STR) at 6 to 13 years	Higher BMI in offspring exposed to diabetes and breastfed for <6 months Same pattern for other outcome measures
(Shearrer *et al*., 2015)	2295 pairs	Women, Infants and Children programme (WIC) survey – retrospective exposure data	USA	• Breastfeeding • Gestational diabetes	Obesity (≥95th percentile for age) at 2 to 4 years	Higher risk of obesity in all categories of breastfeeding (none, <6 months, 6-12 months and ≥12months) in GDM mothers Risk decreased with increasing duration of breastfeeding
(Wen *et al*., 2013)	21063 singletons born appropriate-for-	Prospective cohort (Collaborative Perinatal Project (CPP))	USA	• Maternal smoking during pregnancy and lactation • Breastfeeding	Overweight (≥85th percentile) at 7 years	Increased risk in offspring of breastfeeding smoking mothers

Author name and year	n	Study design	Country	Risk factors	Outcome	Effect
	gestational age at term Complete data Multiple imputation of missing data on confounders					Risk increased with increasing cigarette smoking (1-9, 10-19 and 20+ cigarettes/day) Positive interaction between heavy maternal smoking and breastfeeding for BMI and overweight risk in offspring
(Robinson *et al.*, 2015)	991 mother-child pairs	Prospective birth cohort (The Southampton Women's Survey)	UK	• Maternal obesity • Excessive gestational weight gain • Smoking during pregnancy • Low maternal vitamin D status • Short duration of breastfeeding (no or <1month)	BMI, dual-energy X-ray absorptiometry–assessed fat mass, overweight and obesity (International Obesity Task Force categorisation) at 4 and 6 years	Increase in BMI and fat mass with increasing number of risk factors Four-fold difference in relative risk in children with 4 or 5 risk factors compared to children with 0 risk factors
(Gillman *et al.*, 2008)	1110 Singleton pregnancy	Prospective pre-birth cohort (Project Viva)	USA	• Maternal smoking during pregnancy • Gestational weight gain • Breastfeeding duration • Infant sleep duration	Overweight (≥95th percentile) at 3 years	Risk of 6% in children with favourable levels of all four risk factors to 29% with adverse levels of all four risk factors
(Shi *et al.*, 2013)	968 Term birth Birthweight ≥1500g	Cross-sectional with retrospective data collection (Canadian Health Measures Survey	Canada	• Maternal smoking during pregnancy • Birthweight • Breastfeeding (obesity) • Sleep duration (obesity)	Overweight and obesity at 6 to 11 years	54% obesity attributable to four risk factors combined

Author name and year	n	Study design	Country	Risk factors	Outcome	Effect
		(CHMS)) – retrospective pregnancy/birth data		• Physical activity (overweight)		22% overweight attributable to three risk factors combined
(Plachta-Danielzik *et al.*, 2012)	34240	Pooled data from 4 population-based cross-sectional cohorts	Germany	• Maternal BMI • Paternal BMI • Highest parental educational attainment • Single parenthood • Current smoking status • Maternal smoking status in pregnancy • Weight gain during pregnancy • Birthweight (adjusted for gestational age) • Gestational age (preterm/term) • Breastfeeding (ever, never) • Media time	Overweight (at 3 to 18 years)	Combined attributable risk of 78% of overweight prevalence
(Toschke *et al.*, 2007)	5472 Complete cases	Cross-sectional at school entry	Germany	• Parental obesity • Low parental educational attainment • Maternal smoking during pregnancy • Breastfeeding • Low meal frequency in child • Decreased physical activity • Television >1 hour/day	Overweight and obesity at 5 to 6 years	Calculated as population attributable fractions – increased with each additional risk factor 62.8% for overweight and 84.6% for obesity

2.3.1.3 Maternal pre-pregnancy BMI and GDM

Compared to offspring of women with BMI < 25 and no GDM, offspring of GDM women with BMI ≥ 25 were at highest risk of overweight whereas those of GDM women with BMI < 25 were at reduced risk at 10-12 years of age. However, only mother-daughter dyads were included and the sample size in both GDM groups was very small (11 each) leading to large confidence intervals (CI) (Kubo *et al.*, 2014). Thus, further research into this interaction including a possible gender difference is needed.

2.3.1.4 Breastfeeding and GDM

Breastfeeding for greater than six months attenuated the effect of GDM in a multi-ethnic population whereas offspring of women with GDM who breastfed for less than six months were at increased risk compared to offspring of women with normal glycaemic levels breastfed for the same duration (Crume et al., 2011). Another study found that offspring of normal glycaemic women who breastfed for three months or more and those of GDM women who breastfed for six months were at reduced risk of obesity with highest risk reduction observed with breastfeeding for 12 months or longer in both groups in a predominantly Hispanic low income sample. The prevalence of obesity was higher in offspring of GDM women in every category of breastfeeding (none, 1-3 months, 3-6 months, 6-12 months and ≥12months) indicating that although breastfeeding had a positive effect on risk reduction it did not completely attenuate the effect of GDM (Shearrer et al., 2015).

2.3.1.5 Breastfeeding and maternal smoking

Exclusively breastfed offspring of maternal smokers at all categories of smoking (1-9, 10-19 and 20+ cigarettes per day) were at increased risk of overweight at 7 years of age compared to exclusively formula fed children (Wen *et al.*, 2013). Smoking and breastfeeding was reported in 3.8% of the sample (796 of 21063 women). Third trimester smoking status was used as proxy for lactation smoking status. Validation in a subset of the sample in a second pregnancy less than two years apart found that 92% and 90% of women who reported smoking and not smoking respectively in the third trimester of the first pregnancy retained the same status at the same time point in the second pregnancy. Feeding status was assessed during postpartum hospital stay of an average of 5 days. The authors considered this a reasonable extrapolation based on evidence from the 1950's in

the UK which suggested that >60% of women who breastfed in hospital continued to breastfeed for 3 months. Thus, although this study suggests a positive interaction between maternal smoking and breastfeeding, further research into this interaction is needed with robust data on exposure and consideration that key differences exist in delivery system, physiological barriers and development period with smoking exposure both *in-utero* and in breast milk.

2.3.2 Three or more risk factors

Birth cohort data from USA examined the association between overweight at 3 years with the presence and combination of four risk factors (maternal smoking during pregnancy, breastfeeding duration, excessive GWG and daily infancy sleep duration). The probability of overweight ranged from 6% (absence of all four factors) to 29% (presence of all four factors) (Gillman *et al.*, 2008).

Data from a cross-sectional survey in Canada was used to examine birthweight, child sleep duration (<8 hours) and physical activity at age 6 to 11 years in addition to maternal smoking and breastfeeding (duration/exclusiveness) as risk factors for childhood overweight and obesity at 6 to 11 years. Maternal smoking in pregnancy and large birthweight (>4000g) were found to have similar influence on risk of both overweight and obesity. However, non-exclusive breastfeeding and less than eight hours child sleep duration additionally attributed to obesity risk alone whereas child physical inactivity additionally was attributed to overweight risk. These were all considered preventable risk factors, the modification of which could result in the prevention of 53.9% of obesity and 21.5% of overweight (Shi *et al.*, 2013). As this was a cross-sectional survey with retrospective data collection, the limitations of the cross-sectional design need to be considered in interpretation.

Pooled analysis of one cross-sectional, one cohort and two intervention studies in Germany found that 31.4% of overweight risk was attributable to early life and lifestyle preventable factors identified as maternal smoking during pregnancy, GWG, birthweight, breastfeeding status and media time at age 3 to 18 years. The inclusion of parental overweight, parental education determined by highest level attained by either parent, current parental smoking and single parenthood with early life factors raised the attributable risk proportion to 77.7% (Plachta-Danielzik *et al.*, 2012). Another cross-sectional survey in children aged 5 to 6 years in Germany in 2001/02 identified preventable risk factors attributable to 42.5% and 48.2% of overweight and obesity respectively. The risk factors that

contributed substantially to this percentage were lifestyle factors (watching television for more than one hour per day, less than five meals per day and decreased physical activity) with formula feeding and smoking during pregnancy providing small contributions to the risk. Although parental obesity and low educational level were associated with 20.4% and 36.2% attributable risk to childhood overweight and obesity respectively, these were considered non-modifiable risk factors in the study. The observed prevalence of overweight and obesity in this study was 11.3% and 3.2% respectively. The maximum achievable reduction of prevalence was calculated in the study by multiplying adjusted population attributable fractions by the respective prevalence and this was 4.8% for overweight and 1.5% for obesity based on preventable risk factors (Toschke *et al.*, 2007). The variability in risk fractions indicates that quantitative results may not be directly applicable to populations other than those under consideration. However, the combination of preventable risk factors contribute a substantial proportion to the prevalence of overweight and obesity.

Although various combinations of risk factors have been considered, there was no consistency in the combinations considered across studies. Maternal smoking during pregnancy, breastfeeding and birthweight were the most commonly considered factors. Parental obesity was considered as a risk factor in two studies but pre-pregnancy/pregnancy maternal obesity was not included as a risk factor in the studies that considered three or more risk factors. Most studies that examined two or more risk factors did so by stratification or grouping of the risk factors to identify all possible combinations of the risk factors under consideration and used the most favourable combination of all risk factors as the reference group. Only three studies tested for interaction between the risk factor combinations examined. With the exception of one study which used routine data, all the studies used cohort or survey data. Some of the risk factor combinations considered information that is not routinely collected in the UK such as GWG, paternal BMI, child sleep duration, child physical activity, media time and meal frequency. Pregnancy and birth data were collected retrospectively through self-report in half the studies and thus could be subject to recall bias.

2.3.3 Risk factor identification through classification tree analysis

Classification tree analysis is a method of partitioning data into binary predictors and fitting a simple regression prediction model within each partition that can be presented as a decision tree (Loh, 2011). This method of analysis is usually well

suited when there is little *a priori* knowledge or a clear relationship between all the variables of interest. This is a data dependent method and is presented as a separate section due to the differences in methodology (and interpretation) to the other studies examining the association between risk factors and childhood overweight and obesity.

In a cross-sectional survey of 8981 children in Germany, the prevalence of overweight was highest in children aged 3 to 17 years if they had one or more obese parent. Additional risk factors varied by age group, in children aged 3 to 6 years if they had a migrant parent; in children aged 7 to 10 years if they were born LGA; and in children aged 11 to 17 years if they were born LGA and not breastfed. Other factors such as smoking in pregnancy, socio-economic status, GDM and older siblings were considered but combinations with these were associated with lower risk (Beyerlein *et al.*, 2014).

A retrospective cohort in Germany found the highest prevalence in overweight at 5 to 7 years of age if the child gained ≥ 10kg in weight during the first two years of life, BMI of both parents were <30 and <25, <10 years parental education and ≥ 3.8kg birthweight. On the other hand, the lowest prevalence was observed in children who gained less than 10kg in the first two years of life, BMI of both parents were <30 and <25, German nationality and breastfed (Toschke *et al.*, 2005). However, some predictors in this study are difficult to interpret as non-obese parents contribute to the lowest and highest risk group and thus further understanding of the interaction is required.

In a longitudinal birth cohort in the USA, the highest prevalence of overweight at age 4 years was if the child had been overweight at 2 years. Other risk groups included normal weight at 2 years in the child and overweight/obese mother of Hispanic descent; and normal child BMI at 2 years, normal maternal BMI, low or middle socioeconomic status and high birth weight (≥4kg) but risk was substantially reduced if birthweight was low or normal (Kitsantas and Gaffney, 2010). This analysis achieved 62.2% sensitivity and 76.7% specificity in prediction but was the only study that used this method and assessed model performance. In the same cohort, 100% of children in BMI percentile ≥ 85th at 2 years, white and exposed to GDM was overweight at 5 to 6 years of age as were 89% of non-white, less than 2695.5g birthweight and pulled to stand at less than 7.5 months of the same BMI percentile at 2 years (Flores and Lin, 2013a). Children in the same cohort in ≥85th BMI percentile at 3 to 4 years and at 9 months, high school or less as highest household educational attainment and maternal age ≥ 29.5 years

had 78.6% of severe obesity (≥99th centile) at 5 to 6 years if they did not have rules about bedtime at 3 to 4 years of age. This increased to 80% prevalence if born by vaginal delivery, had rules about bedtime at 3 to 4 years of age and went out to play few times a month or less (Flores and Lin, 2013b). Although data from the same cohort was used, few consistent factors were identified despite two of the three studies using the same definition for the outcome (≥85th centile) but at slightly different ages (4 years and 5-6 years).

As this is a data dependent method, it would be useful to cross-validate the findings in another sample which has not been done by any of the studies that have used this method. A limitation of classification trees is instability and small modifications in the data can lead to a very different classification tree. Additionally, depending on how many times the data is split, the issue of overfitting needs to be considered. However, it adds to the evidence base which supports an increased risk of childhood overweight and obesity with the presence of a combination of two or more risk factors despite various combinations of risk factors having been examined in the literature with some combinations more than others. There is a need to comprehensively examine combined risk factors and review prediction models to identify the most powerful combination of risk factors for identifying children at risk.

2.4 Summary of risk factors

There is increasing evidence and focus on the role of maternal obesity as a determinant for childhood obesity (Godfrey *et al.*, 2016) but further research is needed on underlying mechanisms and other aspects of the maternal lifestyle. Birthweight is another key predictor of later obesity. Rapid reversal of maternal obesity does not seem plausible at present and thus the first step would be breaking the cycle of maternal and offspring obesity (Godfrey *et al.*, 2016). Additionally, there is some evidence of the persistence and progression of maternal overweight and obesity with additional pregnancies which needs further examination.

This chapter has demonstrated the evidence for the effect of maternal and early life exposures on long-term health and disease risk of the offspring. The underlying mechanisms are thought to be through epigenetic changes in non-imprinted genes, which modify gene expression but do not alter DNA sequences (Godfrey *et al.*, 2007). The altered embryonic gene expression profile persists

through subsequent cell cycles leading to life-long alterations. The environment triggers the developmental pathway which determines the vulnerability of individuals to disease. Two classes of pathways are suggested - the mismatch or thrifty pathway and the early-life hypernutrition pathway (Gluckman and Hanson, 2008).

Every organ and system has a critical period of development during which it has to grow and mature during which it is sensitive to the environment. These periods mostly occur in utero and are brief (Barker and Thornburg, 2013). Developmental plasticity provides the ability to modify structure and function in response to the environmental conditions during this period (Gluckman and Hanson, 2004b). Few systems have the ability to adapt or respond to physiological challenges after the first 1000 days from fertilization (Oestreich and Moley, 2017). A range of phenotypes can develop from a single genotype due to this plasticity in response to the environment. The resulting phenotype is best suited to the predicted later environment (Gluckman and Hanson, 2004b). Epigenetic changes are inspired by cues from the developmental environment and play a role in determining the phenotype. There is a decline in developmental plasticity and increase in exposure to environmental challenges with age.

Adaptive responses are made in early development to better match the future predicted environment. The placenta regulates the transfer of nutrients to the foetus depending on the ability of the mother to deliver and the foetus's demand (Jansson and Powell, 2007). Variations in placental size and shape reflect variations from the normal process of development which are accompanied by variations in foetal nutrient delivery. The availability of nutrients to the foetus is influenced by maternal nutrient stores and metabolism (James, 1997) as well as maternal diet during pregnancy. Nutrient imbalance or constraint through maternal metabolism means that foetal nutrition may be impaired. This impaired nutrition through maternal, environmental and placental factors is reflected in birthweight. This could lead to a mismatch between the predicted and actual environment affecting the ability to respond to environmental challenges and increase the risk of disease (Godfrey *et al.*, 2007).

The second developmental pathway reflects the effects of hypernutrition in foetal or early life. These create conditions for the pathphysiological effects of an obesogenic diet through mediation of modifications in adipogenesis and/or appetite control mechanism. An example of the foetal hypernutrition pathway is offspring of women with diabetes or those who develop GDM. The pathway is

believed to be that maternal hyperglycaemia leads to increased transfer of glucose across the placenta to the foetus which in late gestation leads to increased foetal insulin release and greater adipogenesis. This is because insulin is adipogenic in late foetal and infant life (Wu *et al.*, 1999). The association between rapid weight gain during early life and risk of overweight and obesity in childhood implies that the window for hypernutrition could extend further in postnatal life (Gluckman and Hanson, 2008). Energy allocation to rapid weight gain leads to reduction in energy allocation to other developmental activity (Barker and Thornburg, 2013).

As obesity is a complex disorder with interactions between several factors (genes, physiological and environmental), it is important to understand the risk in the presence of a combination of factors. The number of risk factors may not necessarily amplify risk by the same degree and further investigation is needed to identify the extent of risk amplification and to identify if a risk 'saturation point' can be reached. Identifying these risk factors not only allows intervening to individually tackle modifiable factors in order to modify the risk of later childhood obesity, but also refines the targeting of interventions when they are used collectively as a tool for risk stratification in routine health and social care. Some risk factors are non-modifiable such as ethnicity and genetics whereas others are modifiable such as maternal age at pregnancy, maternal educational attainment and employment, overweight and obesity, breastfeeding, media exposure and environmental factors. Modifiable risk factors require intervention, advice and support to modify but intervening will help reduce the risk of childhood overweight and obesity in the at risk population. Prediction models aid in stratification and targeted intervention but the intervention does not need to include a direct focus on all or any of the factors in the prediction model.

2.5 Risk prediction

In 2012, the WHO published a report on population-based approaches to childhood obesity prevention, which identified improved government structures to support policy and intervention as well as population-based and community based interventions as actions to prevent childhood obesity (World Health Organization, 2012). However, there is a lack of evidence on effective long term treatments which implies that the focus of reducing childhood obesity rates should be on prevention (Oude Luttikhuis *et al.*, 2009). Key to an effective prevention strategy is the ability to identify individuals at high risk but no defined

criteria exist to identify children at risk despite the detrimental effects of overweight and obesity (Nader *et al.*, 2006). High-risk individuals could be targeted for an intervention and the advantages of this include a favourable benefit-to-risk ratio, cost-effective use of resources and intervention that is appropriate/tailored to the individual/group at risk. However, it also has some key disadvantages, one of which is the repeated need for screening and its associated costs. Weight gain leading to overweight and obesity can occur at any age and thus to target high-risk individuals, a repeated process of identification needs to be in place. Conversely, a population-based approach is more equitable but with the disadvantage that it has small benefit to individual and thus low motivation. This leads to the prevention paradox which is that a measure that benefits the population offers little benefit to each participating individual (Rose, 2001). Additionally, disease events occur in both high and low risk individuals and so targeting just the high risk population would mean that that there would still be a large number of events. Thus, a whole population prevention approach such as taxation and town/environment planning to tackle the obesogenic environment could be combined with targeting interventions in high-risk families through routine health services and public health initiatives as a supplement to help boost effectiveness of the intervention.

2.6 Significance of the proposed research

2.6.1 How is this novel?

Research into maternal and early life risk associations with childhood overweight and obesity have primarily been carried out for individual risk factors. Research into risk modification by the presence of a combination of risk factors has been limited to specific combinations of two risk factors. Research that examined three or more risk factors have not focused on the same combinations of risk factors. This project examines association between interpregnancy interval, maternal weight changes and size and birth as well as develops a prediction model for the risk of childhood overweight and obesity. This contributes to the evidence base of risk factors for childhood obesity identifiable during antenatal care and early life with a particular focus on the presence of a combination of risk factors.

The interpregnancy analysis aims to provide a better understanding of some of the changes between pregnancies that may not be captured by adjustment or

stratification for parity in analysis. Birth spacing and change in maternal BMI has not been previously investigated in the UK.

A systematic review on prediction models for childhood obesity has not been carried out previously. A prediction model was then developed as part of this study utilising routinely available data. Routine healthcare data in pregnancy and early life are collected by different organisations in the UK and the information for the mother and child is held separately. There is a need to integrate maternal and childhood factors to understand and predict risk. This study was the first time that routine data from several different sources were linked to develop a risk prediction model for childhood obesity. Additionally in the UK, data from mother and child are usually only linked for antenatal care and all records are maintained separately post-birth and discharge from hospital so linking pregnancy data from the mother to child data will also be novel. The feasibility of access and linkage of data for the same individuals from different organizations within the UK was also explored.

2.6.2 Recent developments and public health relevance

During recent years, there has been increased focus on pre-conception health and prevention. The Lancet has published a series on preconception health that highlights the importance, summarises the evidence for future health and suggests interventions (Barker *et al.*, 2018; Fleming *et al.*, 2018; Stephenson *et al.*, 2018). The action areas for intervention identified to improve preconception health progress from children and adolescents, adults with no immediate intention to become pregnant, adults with intention to become pregnant to adults with intention to become pregnant again. The inter-pregnancy analysis in Chapter 5 and Chapter 6 of this thesis provides evidence towards the importance of maintaining or improving preconception health before the second pregnancy.

The long-term plan for the National Health Service (NHS) includes prevention as a central theme (National Health Service, 2019). Key to effective prevention is identifying individuals at risk alongside whole population-based approaches. The prediction model using routine data developed as part of this thesis which will be made available to health professionals in the form of a toolkit to aid in the decision of appropriate level of intervention or preventive care. It can also be used as an aid to parents for the quantification of risk to encourage behaviour change. The predictive model would assist in targeting high-risk groups for preventive initiatives.

The next chapter will present the findings of a systematic review to identify existing prediction models for the risk of childhood overweight and/or obesity.

Chapter 3 Predicting childhood overweight and obesity using maternal and early life risk factors: a systematic review

This chapter is a systematic review with the aim to identify existing prediction models of childhood overweight and obesity using maternal and early life factors and critically assess the development and reporting of the methodology used to develop these models. This was the first piece of analysis carried out as part of this PhD to examine the need for a new prediction model as planned for this PhD and inform modelling processes and predictive variables as identified by previous research. The aim was to systematically review studies of prediction models for childhood overweight and obesity using maternal and/or early life risk factors and critically assess the development and reporting of the methodology used to develop these models.

Work from this chapter has been published as a peer reviewed conference abstract and peer-reviewed paper in the journal Obesity Reviews. This work has also been presented at three conferences (Southampton Medical and Health Research Conference 2017, Lancet Public Health Science 2017 and Wessex Public Health Conference 2018).

3.1 Background

There is a lack of evidence on effective long term treatments for childhood obesity and so the focus of reducing childhood obesity rates should be on prevention (Oude Luttikhuis *et al.*, 2009). The increased risk of persistence of childhood weight status into adulthood makes it essential to intervene early. Although this tracking of childhood BMI to adulthood was weaker in late adulthood (Aarestrup *et al.*, 2016), there is an increased risk of adult morbidity and mortality associated with overweight and obesity in childhood and adolescence (Reilly and Kelly, 2011). Thus, the identification of high-risk populations and intervening as early as possible to prevent the development of overweight and obesity should be a priority (World Health Organization, 2016a).

3.2 Methods

Medline and Embase were searched from their start dates to December 2016 using recommended filters and the bibliographies and citations of all included studies were hand searched (using Web of Science Core Collection). The following search strategy was used:

{Pediatric Obesity/ OR Fetal Macrosomia/ OR

[(child or childhood or children or p#ediatric* or infant* or toddler or embry* or prenatal* or neonat*).mp. AND (obes*.mp. OR overnutrition/ or obesity/ or overweight/ OR overweight.mp. OR overweight.mp.)]} AND

[exp causality/ OR ((Reinforc* or Enabl* or predispos*) and factor*).mp. OR (risk* or predict* or causal* or prognos* or causation).mp.] AND

[exp Maternal Behavior/ OR maternal.mp. OR mother*.mp. OR early life.mp.]

3.2.1 Eligibility criteria

The inclusion criteria for the systematic review are outlined in Table 3.1. All studies that reported on one or more multivariable prediction models or scores that have been developed for individual risk estimation of future risk of childhood overweight and obesity were included. The outcome considered was overweight and obesity between 1 and 13 years of age. No criteria were defined for overweight and obesity as different criteria can be considered given the age

under consideration. Studies that only developed, developed and validated or just validated a risk score were not differentiated. The review was limited to studies conducted in humans and published in English. No limits were imposed on study timing or setting.

Table 3.1: Inclusion criteria for papers

Study type	Studies that developed; developed or validated or just validated a prediction model or score for childhood overweight and obesity Published studies Published in English Any setting
Participant data	Maternal preconception/pregnancy data and Child early life data
Outcome measure	Overweight and obesity between 1 and 13 years of age. No set criteria for measurement of overweight and obesity as different criteria can be used for this age group

3.2.2 Data extraction and critical appraisal

The list of data extraction was based on the **CH**ecklist for critical **A**ppraisal and data extraction for systematic **R**eviews of prediction **M**odelling **S**tudies (CHARMS) published by the Cochrane Prognosis Methods Group (Moons *et al.*, 2014). The Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement was used to assess transparency in reporting (Collins *et al.*, 2015). I assessed all articles and extracted the data. Items extracted from studies describing model development included study design, study population and location, number of study participants, outcome and age of outcome if available, method of modelling, method of internal validation (random split of data, bootstrapping or cross-validation), number of predictors considered and included in the final model, model presentation and predictive performance including measures of discrimination and calibration where available.

For studies describing external model validation alone, items extracted included study design, study population and location, number of study participants and

model performance. Predictors were checked to confirm that these were the same as the original model.

I critically assessed the conduct and reporting of the methods used to develop these risk prediction models. However, a quantitative synthesis of the prediction models' results was not performed as formal methods for meta-analysis of models are not yet fully developed and are beyond the scope of this review.

3.3 Results

From the 11867 articles identified by the search strategy, 143 full articles were reviewed of which nine articles were selected for inclusion in this review (Figure 3.1). An additional study was identified through hand searching the citations of the included studies.

Eight of the studies developed a risk score, seven of which were internally (six) and/or externally (two) validated in the same publication, and two were external validation studies of two of the eight existing prediction models (Table 3.1).

Figure 3.1: Literature search flow chart

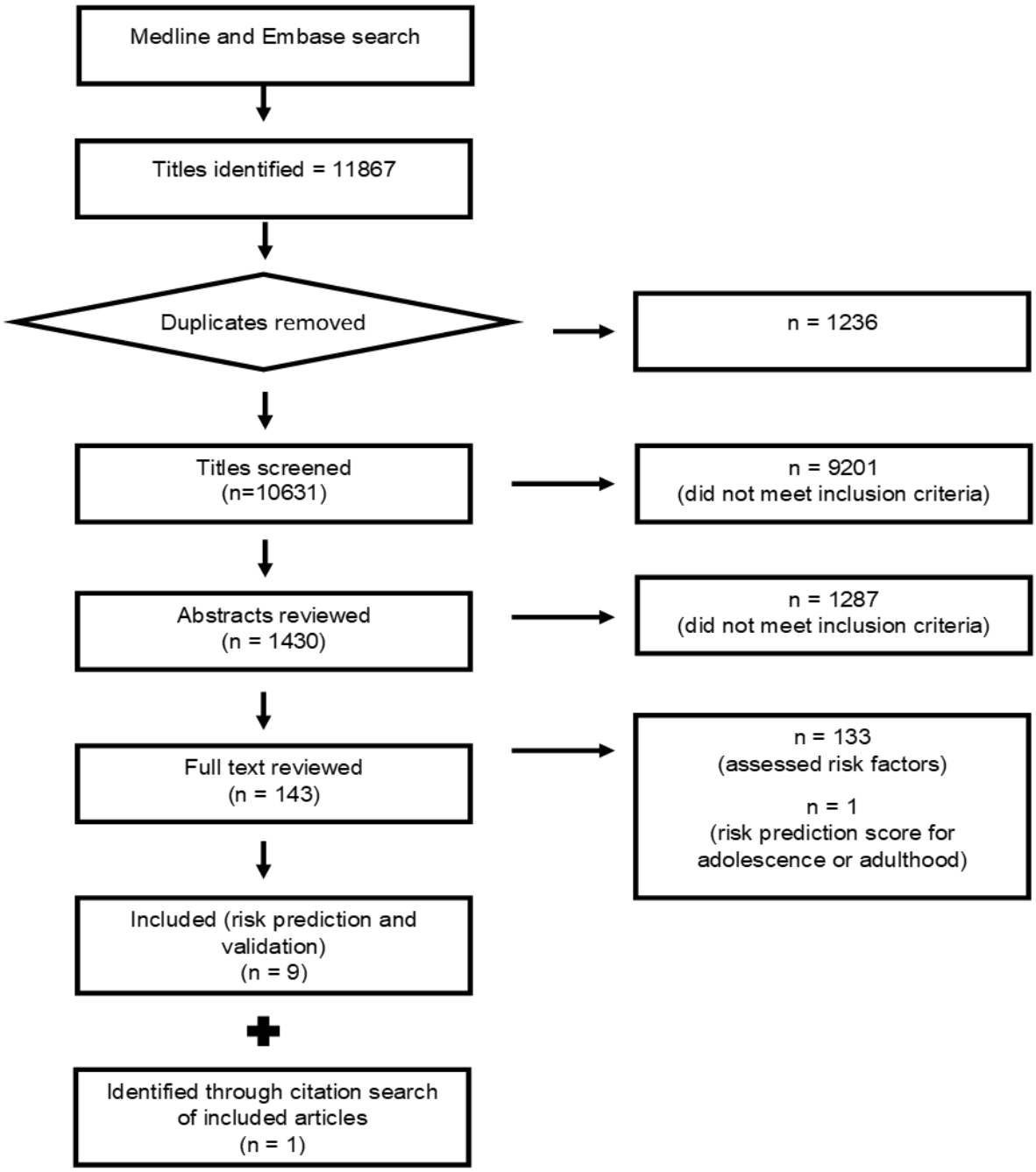


Table 3.2: Summary of prediction models in the included studies

Author, year	Druet 2012	Manios 2013	Manios 2016	Morandi 2012	Pei 2013	Redsell 2016	Robson 2016	Santorelli 2013	Steur 2011	Weng 2013
N, derivation	8236	2294	-	4032	1515	-	166	1868	1687	10810
N, validation	8236	-	5946	1503	757	980		867-880	-	2703
Country	UK, Europe, America, Seychelles	Greece	Greece	Finland Validation – Italy, USA	Germany	UK	USA (Latino cohort)	UK	The Netherlands	UK
Design	Meta-analysis of three birth cohorts	Cross-sectional with retrospective data collection	Cross-sectional with retrospective data collection	Prospective birth cohort (Finland, USA) Retrospective cohort (Italy)	Prospective birth cohorts	Prospective birth cohort	Birth cohort	Prospective birth cohorts	Prospective birth cohort	Prospective birth cohort
Outcome	Childhood obesity	Childhood obesity (9-13 years)	Childhood obesity (6-15 years)	Obesity and overweight at 7 years	Overweight at age 10 years	Obesity at age 5 years	Obesity at 5 years	Obesity at age 1 year	Overweight at age 8 years	Overweight at age 3 years

Author, year	Druet 2012	Manios 2013	Manios 2016	Morandi 2012	Pei 2013	Redsell 2016	Robson 2016	Santorelli 2013	Steur 2011	Weng 2013
Variables included	4	5	5	6	5	7	10 (full model) 5 (reduced model)	4	6	7
Derivation area under the curve (AUC)	-	0.64	-	0.67 (overweight-obesity) 0.78 (obesity)	-	-	0.84 (full model) 0.82 (reduced model)	0.91	-	0.72
Validation AUC	0.77	-	0.64	0.70, 0.73	-	0.67 (original model) 0.93 (recalibrated)	-	0.89	-	0.76
TRIPOD	21	19	20	28	23	23	24	29	24	23

3.3.1 Study reporting

Using the TRIPOD (Collins *et al.*, 2015) reporting recommendation, a median of 23 (interquartile range (IQR), 22 to 24) items out of 37 (31 for derivation or validation alone) were reported suggesting some shortcomings (Table 3.2). One study was reported as a brief communication, which by nature is restrictive for information that can be provided (Manios *et al.*, 2016). As this review assessed the extent of reporting, authors were not contacted to seek further information.

Table 3.3: TRIPOD items reported in the ten studies

Section/Topic		TRIPOD item description	Reported
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	8
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	10
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	9
	3b	Specify the objectives, including whether the study describes the development or validation of the model, or both.	10
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation datasets, if applicable.	10
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	10
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	10
	5b	Describe eligibility criteria for participants.	10
	5c	Give details of treatments received, if relevant.	-
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	10
	6b	Report any actions to blind assessment of the outcome to be predicted.	0
Predictors	7a	Clearly define all predictors used in developing the multivariable prediction model; including how and when they were measured.	8
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	0
Sample size	8	Explain how the study size was arrived at.	10
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	4
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	9
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	8

Section/Topic		TRIPOD item description	Reported
	10c	For validation, describe how the predictions were calculated.	8
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	8
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	3
Risk groups	11	Provide details on how risk groups were created, if done.	0
Development vs validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	2
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	6
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	7
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors, and outcome).	1
Model development	14a	Specify the number of participants and outcome events in each analysis.	4
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	1
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	6
	15b	Explain how to use the prediction model.	6
Model performance	16	Report performance measures (with CIs) for the prediction model.	7
Model updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	1
Discussion			
Limitations	18	Discuss any limitations of the study (such as non-representative sample, few events per predictor, missing data).	10
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	3
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	10
Implications	20	Discuss the potential clinical use of the model and implications for future research.	10
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and datasets.	6
Funding	22	Give the source of funding and the role of the funders for the present study.	9

3.3.2 Study designs, population and sample size

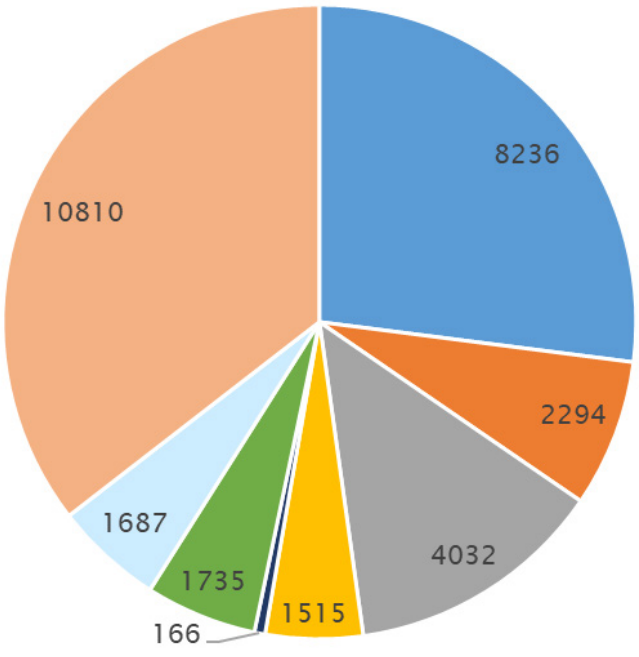
Most of the studies used data from prospective birth cohorts (seven plus one that pooled individual data from three birth cohorts) and two studies used cross-sectional studies in childhood with retrospective data collection of maternal and early life factors. All the studies were in high income countries with the exception of data from Seychelles in the study that pooled cohort data from three studies.

3.3.3 Outcomes, number of patients and events

The outcome was overweight (three studies) (Steur *et al.*, 2011; Pei *et al.*, 2013; Weng *et al.*, 2013), obesity (three) (Manios *et al.*, 2013; Santorelli *et al.*, 2013; Robson *et al.*, 2016) or both (two) (Druet *et al.*, 2012; Morandi *et al.*, 2012) in the eight included studies that developed a score. The age at which this was predicted varied from one to ten years of age in children. Sex- and age- specific BMI was calculated using the International Obesity Task Force (IOTF) (Steur *et al.*, 2011; Druet *et al.*, 2012; Morandi *et al.*, 2012; Manios *et al.*, 2013; Weng *et al.*, 2013), Centers for Disease Control (CDC) (Robson *et al.*, 2016), WHO (Pei *et al.*, 2013) and UK90 growth chart (Santorelli *et al.*, 2013) criteria and appropriate thresholds for overweight or obesity applied.

The number of participants used to develop the prediction models was reported in all studies (Figure 3.2). The number of participants was 30475 from all studies and the median number was 2015 (IQR 1644 to 5083) across the studies.

Figure 3.2: Number of participants in each of the eight included models



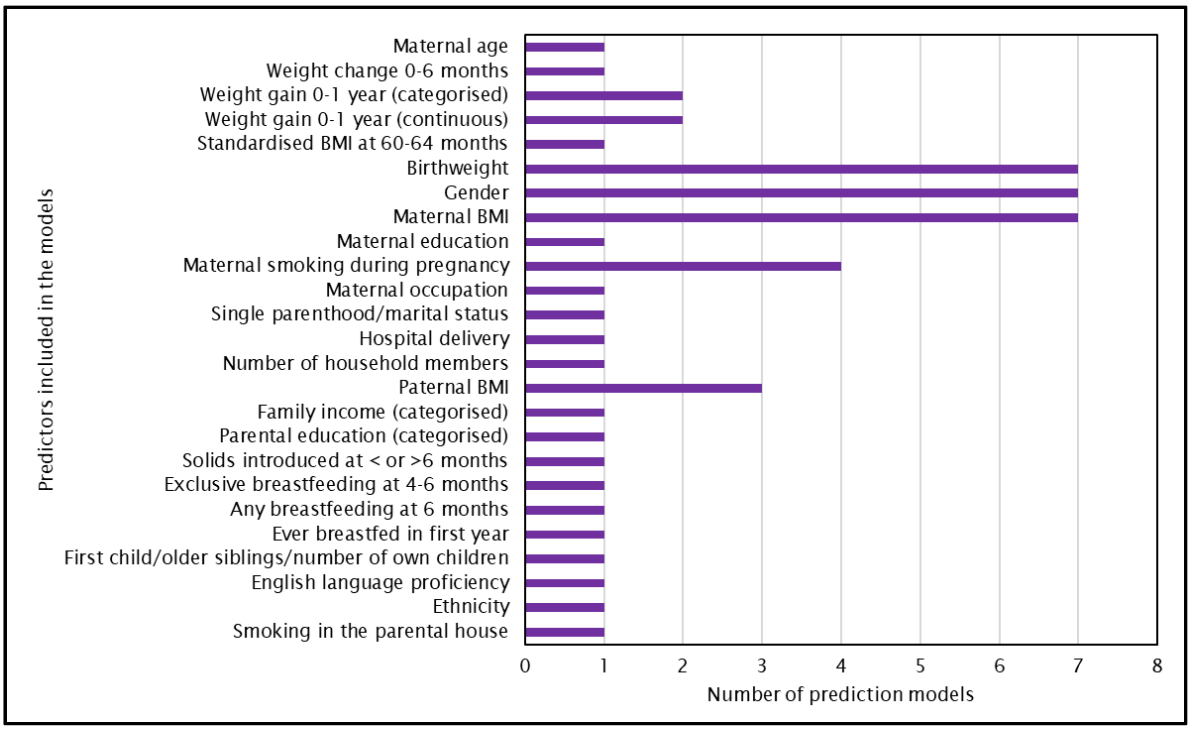
Six (Steur *et al.*, 2011; Druet *et al.*, 2012; Morandi *et al.*, 2012; Santorelli *et al.*, 2013; Weng *et al.*, 2013; Robson *et al.*, 2016) out of eight studies reported the prevalence of the outcome in the study population of which two reported the prevalence of both overweight and obesity (12-23% overweight and 3-32% obesity). Where recorded, the median number of events that were used in model development was 821 (IQR 549 to 1374) for overweight and 133 (IQR 104 to 170) for obesity. The prevalence of overweight was lower in children born in 1996/97 in Netherlands (14%) and 1993 in Finland (16%) at 7 and 8 years respectively compared to those born in 2000/01 in the UK at 3 years (23%). Similarly, the prevalence of obesity was lower in children born in 1985/86 in Finland at 8 years of age (3%) (Morandi *et al.*, 2012) compared to those born in 2007-10 in the UK (8%) (Santorelli *et al.*, 2013) and 2006/07 in USA (32%) at 1 and 5 years respectively (Robson *et al.*, 2016).

3.3.4 Risk predictors

Across the studies analysed, 57 putative predictors were derived from literature review (Table 3.3). A median of 11 risk predictors (IQR 8 to 19) were considered in the development models. These were defined a priori in six studies (Steur *et al.*, 2011; Druet *et al.*, 2012; Morandi *et al.*, 2012; Santorelli *et al.*, 2013; Weng *et al.*, 2013; Robson *et al.*, 2016), identified through previous multivariable regression (Manios *et al.*, 2013) or defined a priori for maternal predictors and through univariable regression for child predictors (Pei *et al.*, 2013). Only four of the six studies that defined predictors a priori provided the rationale or references for including these predictors.

Twenty-five predictors were included in the final risk prediction models. However, eighteen of these predictors were only included in one risk score model (Figure 3.3). The final reported prediction models included a median of six (IQR 5 to 6) predictors with maternal pre-pregnancy BMI, birthweight and infant gender included in seven out of eight scores (Table 3.3).

Figure 3.3: Predictors included in the prediction models



Two studies assessed risk at birth (using preconception, antenatal and birth factors) (Steur *et al.*, 2011; Morandi *et al.*, 2012) whereas other scores incorporated weight gain in the first year of life (Druet *et al.*, 2012; Manios *et al.*, 2013; Santorelli *et al.*, 2013; Weng *et al.*, 2013; Robson *et al.*, 2016) predicting risk from the age of 12 months and over or childhood age- and sex- adjusted BMI at 5 years of age (Pei *et al.*, 2013) to predict risk at 10 years of age. Two studies also included models that predicted risk before 12 months (Steur et al., 2011) or during adolescence (Morandi et al., 2012) but these were not included as before 12 months was considered too early whereas adolescence was older than our age group of interest.

3.3.5 Treatment of continuous risk predictors

Four (50%) risk prediction models retained continuous predictors as continuous (Steur *et al.*, 2011; Morandi *et al.*, 2012; Pei *et al.*, 2013; Robson *et al.*, 2016), two (25%) categorised or dichotomised all continuous predictors and one (12.5%) retained some continuous predictors as continuous and categorised some predictors (Santorelli *et al.*, 2013). It was unclear how continuous risk predictors were treated in one study but a categorical score chart was developed so it is likely that all continuous variables were categorised or dichotomised (Weng *et al.*, 2013).

Table 3.4: Predictor variables assessed (-) and included (+) in the models

Author, year	Druet 2012	Manios 2013	Morandi 2012	Pei 2013	Robson 2016[a]	Santorelli 2013	Steur 2011	Weng 2013
Gender	+	+	-	+	+	+	+	+
Gestational age	-					-		
Weight change 0-6 months					'+'			
Weight gain 0-1 year (categorised)	-	+						+
Weight gain 0-1 year (continuous)	+					+		
Weight gain 0-5 years (categorised)				-				
Standardised BMI at 60-64 months				+				
Birthweight	+		+	+	'+'	+	+	+
Maternal age					'+'			-
Maternal BMI	+	+	+		'+'	+	+	+
Maternal education		+					-	-
Pre-pregnancy maternal smoking			-					
Maternal smoking during pregnancy		+	+	+		-	-	+
Maternal occupation			+					
Maternal employment							-	-
Employment in pregnancy								-
Single parenthood/marital status			-					+
Gestational weight gain			-					
Maternal alcohol consumption								-
Maternal feelings of depression								-
Maternal health								-
Maternal diabetes								-
Gestational diabetes						-		
Hospital delivery							+	
Delivery type							-	-
Number of household members			+					
Obesity predisposing single-nucleotide polymorphisms			-					
Paternal BMI			+				+	+
Paternal education							-	

Author, year	Druet 2012	Manios 2013	Morandi 2012	Pei 2013	Robson 2016[a]	Santorelli 2013	Steur 2011	Weng 2013
Paternal employment							-	
Family income (categorised)				+				-
Parental education (categorised)				+				
Solids introduced at < or >6 months					+			-
Exclusive breastfeeding at 4-6 weeks					'+'			
Any breastfeeding at 6 months					+		-	
Ever breastfed in first year								+
Breastfeeding duration								-
Ever formula fed								-
First child/older siblings/number of own children					+		-	-
English language proficiency					+			
Ethnicity						-	-	+
Smoking in the parental house							+	
Living in a highly urbanized environment (≥2500 address/km^2)							-	
Maternal vegetable consumption during pregnancy							-	
Premature birth of child							-	
Region of birth							-	
Financial status								-
Child care arrangements								-
Unhappy when feeding interrupted								-
Makes a fuss going to sleep								-
Makes a fuss after waking								-
Upset when not getting things								-
Does the infant sit up?								-
Does the infant stand?								-
Does the infant grab objects?								-
Does the infant hold objects?								-
Can the infant walk?								-

A – '+' indicates predictors retained in the reduced model, + indicates predictors retained in the full model

3.3.6 Missing data

Four studies only included cases with complete data in model development (Steur *et al.*, 2011; Druet *et al.*, 2012; Pei *et al.*, 2013; Santorelli *et al.*, 2013), two studies carried out multiple imputation (Morandi *et al.*, 2012; Robson *et al.*, 2016) and one study did not report the presence or handling of missing data (Manios *et al.*, 2013). The remaining study included participants with full anthropometric data at follow-up when outcome was assessed but it is unclear if there were missing data at previous data collection points and how this was handled (Weng *et al.*, 2013). Of the two studies that carried out multiple imputation, one study included participants with missing values for one predictor variable and carried out multiple imputation for the remaining missing values.

One of the studies that carried out multiple imputation had on average 1.7% (range 0 to 11.4%) (Morandi *et al.*, 2012) missing data for each predictor whereas 17% of the other study (Robson *et al.*, 2016) participants had missing data for at least one predictor. Two of the studies that carried out complete case analysis, 23.8% (Steur *et al.*, 2011) and 27.2% (Pei *et al.*, 2013) of the sample were excluded due to the missing data but it is unclear what percentage of sample was excluded for missing data alone in the other studies (Druet *et al.*, 2012; Santorelli *et al.*, 2013).

3.3.7 Model building

Six (75%) studies used automated variable selection (stepwise, backward deletion) to derive the final predictive model (Steur *et al.*, 2011; Druet *et al.*, 2012; Morandi *et al.*, 2012; Santorelli *et al.*, 2013; Weng *et al.*, 2013; Robson *et al.*, 2016). One of these studies used their own guiding principles described as concerns of infrequent inclusion in routine medical care, time burden to document, low prevalence in study cohort or collinearity with other selected variables to create the predictive model (Robson *et al.*, 2016). It then went on to create an alternate or reduced model using stepwise backward deletion and variable importance rankings from a nonparametric conditional random forest classifier both of which identified the same five variables from the initial ten variables.

All studies were clear on the method used to develop the prediction model - logistic regression was used in seven studies (Steur *et al.*, 2011; Druet *et al.*, 2012; Morandi *et al.*, 2012; Manios *et al.*, 2013; Santorelli *et al.*, 2013; Weng *et al.*, 2013; Robson

et al., 2016) whereas linear regression was used in one study (Pei *et al.*, 2013). One study had selected predictor variables based on previous multivariable logistic regression analysis and only carried out univariable logistic regression to assign integer values to the categories of risk predictor variables without any further modelling (Manios *et al.*, 2013). Two models (Steur *et al.*, 2011; Santorelli *et al.*, 2013) included interaction terms while modelling whereas there was no mention of interaction terms while modelling in the other studies.

3.3.8 Predictive performance

Model performance was assessed in all studies, seven of which used AUC in either the derivation, validation or both cohorts. The other study tested for specificity and predictive value alone (Pei *et al.*, 2013). Although model performance was assessed and validated in all studies, only one study reported change in regression co-efficient post validation and updating the model (Steur *et al.*, 2011). Two studies from the UK used data from the same birth cohort (Avon Longitudinal Study of Parents and Children ALSPAC) for validation of the same outcome but at different ages (two (Santorelli *et al.*, 2013) and five (Redsell *et al.*, 2016b) years). Model development AUC ranged from 0.64 to 0.91 (median 0.78, IQR 0.70 to 0.81). The AUC of 0.91 was replicated in internal validation using bootstrapping and only decreased to 0.89 on external validation (Santorelli *et al.*, 2013).

Three studies (Steur *et al.*, 2011; Morandi *et al.*, 2012; Robson *et al.*, 2016) carried out Hosmer-Lemeshow tests to test calibration, two of which did so during model development both achieving $p>0.5$. All studies assessed model classification (sensitivity and specificity) though one study (Manios *et al.*, 2013) did not present positive and negative predictive values.

3.3.9 Internal Validation

With the exception of two, all studies internally validated the models by random split of data (Druet *et al.*, 2012; Weng *et al.*, 2013), random split followed by cross-validation (Pei *et al.*, 2013) or bootstrapping (Steur *et al.*, 2011; Santorelli *et al.*, 2013; Robson *et al.*, 2016). Of the studies that did not internally validate the model, one validated the model externally in two separate cohorts (Morandi *et al.*, 2012) whereas the other was externally validated in a subsequent publication with overlapping authors in the development and validation papers (Manios *et al.*, 2013;

Manios *et al.*, 2016). Additionally one of the studies that internally validated the model using random split was also externally validated in a subsequent publication by the same authors (Weng *et al.*, 2013; Redsell *et al.*, 2016b). Model validation AUC ranging from 0.75 to 0.91 (median 0.78, IQR 0.77 to 0.81) was achieved and the original model was updated in one study only (Steur *et al.*, 2011). Of the studies that carried out the Hosmer-Lemeshow test for calibration, one did not report the exact p-value but that p>0.5 was achieved (Robson *et al.*, 2016) whereas the other achieved p=0.30 on recalibration post validation (Steur *et al.*, 2011).

3.3.10 External validation

Only four of eight models have been externally validated - once for three models all of which used data from the same country for validation (Santorelli *et al.*, 2013; Manios *et al.*, 2016; Redsell *et al.*, 2016b) and twice for one model that was developed in Finland and validated in Italy and USA (Morandi *et al.*, 2012). Of the models validated using data from the same country, two studies calculated AUC, which were 0.89 (Santorelli *et al.*, 2013) and 0.67 (Redsell *et al.*, 2016b). The only study that externally validated the model in two countries other than that in which it was developed (Morandi *et al.*, 2012) found that AUC (0.70, confidence intervals 0.63 to 0.77) and calibration (Hosmer-Lemeshow p=0.12) was satisfactory in one population but although AUC (0.73, confidence intervals 0.67 to 0.80) was satisfactory in the other, calibration (Hosmer-Lemeshow p=0.02) was not. The predictors and model were then tailored to these populations by carrying out a replication analysis using stepwise logistic regression such that calibration achieved satisfactory levels. The initial model developed in Finland included six risk factors and reduced to three and five for the Italian and USA cohort respectively with only two factors remaining consistent across all three models (maternal and paternal BMI). Ethnicity was introduced in the risk prediction score for USA and this was primarily because the birth cohort in Finland had high ethnic homogeneity. One of the external validation studies (Redsell *et al.*, 2016b) also developed a recalibrated model using multivariable logistic regression to apply a recalibrated algorithm reflecting the characteristics of the validation cohort, imputed model for missing risk factor prediction and a recalibrated imputed model which incorporated the two. This led to an increase in discrimination compared to the original model from 2% in the recalibrated to 25% in the recalibrated imputed model.

3.3.11 Model presentation

The complete regression formula (including all regression coefficients) was presented in six studies (Steur *et al.*, 2011; Druet *et al.*, 2012; Morandi *et al.*, 2012; Santorelli *et al.*, 2013; Weng *et al.*, 2013; Robson *et al.*, 2016) and two of these studies provided a decision rule/score chart or risk score algorithm (Steur *et al.*, 2011; Weng *et al.*, 2013). Of the remaining two studies, one provided the regression coefficients (Pei *et al.*, 2013) whereas the other only provided a score chart (Manios *et al.*, 2013). Two studies that created a score chart did so by assigning an integer value to each risk predictor category. One study either based the integer value on the odds ratio such that an odds ratio of 2.15 was assigned a value of 2 or based on categories whereby underweight/normal weight pre-pregnancy weight status was assigned 0 and obese was assigned 3. The other study divided the β-coefficient in the fully adjusted model by the β with the smallest values to obtain relative strength of each category which was rounded to the nearest whole number and assigned. Reference categories were assigned zero in both studies.

3.4 Discussion

To my knowledge, this is the first systematic review to examine prediction models for childhood overweight and obesity. Eight studies that modelled the prediction of childhood overweight and obesity were identified, however four of these prediction scores have been externally validated once or twice and there is no evidence of further validation or validation in populations outside of those in which they were developed (except for the Finnish one) to assess applicability. Additionally new models have been developed with no evidence of comparison with already existing models and none of the models have been compared with each other to assess predictive performance. There is no evidence of implementation of the risk scores in the population in which they were developed. There were inadequacies identified in reporting of the methodology of development of risk prediction models.

Whilst there is clear overlap between risk factors included in the prediction models, no single risk factor has been included in all prediction models with maternal pre-pregnancy BMI, infant gender and birthweight being the most commonly included. For risk factors that were included in seven studies, no association was seen during univariable analysis for infant gender in the eighth study, which was considered and

then excluded. The other risk factors included in seven studies, maternal pre-pregnancy BMI and birthweight, were not considered for inclusion in the eighth model. Thus, it is difficult to recommend the use of any one score, as there are no consistent predictors, no comparison of predictive ability between models and the outcome has been variable and predicted at different ages through childhood up to 13 years of age. The question of predictors considered for inclusion in the model also needs to be considered. Although not retained in the final prediction model, several predictors around infant temperament were considered. These are self-reported by parents and highly likely to be subjective. Additionally, these factors were identified a priori based on a previous systematic review but the conclusion of the review was that the evidence was inconclusive due to limited number of studies (Weng *et al.*, 2012).

On examination of the risk factors included in the prediction models, three each include factors up to and including birth or one year and one each at six months and five years. Thirteen of the 25 risk factors identified were preconception and thus some of these could prove impactful in planned pregnancies such as maternal and paternal BMI whereas others are non-modifiable such as ethnicity. Although factors such as maternal education, occupation and income are modifiable, it is difficult to modify possibly even more so than maternal and paternal BMI. English language proficiency was identified as a factor in a Latino cohort in USA but this is likely to be linked to access to care, advice and support. Maternal smoking during pregnancy and hospital delivery were the only two antenatal risk factors identified and included in risk prediction. Hospital delivery was identified as a predictor in a study in the Netherlands where it is common to have a home delivery in non-complicated pregnancies, which may not be possible in other countries. Additionally, it is likely that hospital delivery is a proxy for one or more of several factors including primiparity, maternal age, low socio-economic status and non-Dutch ethnicity, all of which have been associated with place of delivery in the Netherlands (Steur *et al.*, 2011). Eight of the ten early life risk factors identified can be broadly classified into weight gain particularly in first year of life and breastfeeding including weaning, both of which are modifiable. The other two risk factors were gender and birthweight, of which gender is non-modifiable but birthweight can be monitored and is considered modifiable by factors known to affect foetal growth (Barker, 1995). In the UK, most risk factors identified thus far are available as part of routine healthcare however preconception and antenatal

information for the mother is not linked to the early life information for the child (such as birthweight and gender). It is also collected and held by different organisations within the NHS (hospital and general practice/community) and thus risk prediction in early life could be dependent on maternal recall of preconception and antenatal factors.

Some key aspects of multivariable model development and validation need to be considered. These include handling missing data, overfitting, method of treatment of continuous variables, selecting variables for inclusion in the model and methods of validation including assessing discrimination and calibration (Harrell Jr *et al.*, 1996). Missing data, a common issue in population studies, was identified in most studies included in this review. If inappropriately handled, missing data can introduce bias thus impeding the construction of a valid prediction model (Burton and Altman, 2004). Multiple imputation minimises the effect of missing data, providing data is missing at random (Spratt *et al.*, 2010) and enables the use of all available data but was only done in 25% of studies included in this review. All other studies excluded participants with missing data which is an acceptable approach only if the amount of missing data is small (Little, 1992) however, these studies did not provide any indication of how much data was missing per individual and per variable to enable readers to reach their own judgement of the validity of the prediction.

It is recommended that models are developed when the number of events is at least 10 to 20 per predictor variable to avoid overfitting (Peduzzi *et al.*, 1996). Also, as the smaller category of the binary outcome predominantly determines statistical power of logistic regression coefficients, it is recommended that the number of variables considered and the number of events of outcome is reasonably balanced (Harrell Jr *et al.*, 1996). Six studies reported the prevalence of the outcome and thus the number of events could be calculated which was sufficient in five studies. The sixth study developed a full model with 10 predictor variables and a reduced model with five predictor variables but only had 53 cases of the outcome and thus the number of events for the full and reduced model was five and 10 cases respectively implying overfitting in the full model. Overfitted models fail to replicate performance in other independent samples exhibiting poor calibration and thus usability is limited (Steyerberg *et al.*, 2000; Babyak, 2004).

At least three prediction models categorised some or all continuous variables for inclusion in the model. However, discarding information through categorisation of continuous variables to estimate a continuous relationship between a predictor variable and risk has been shown to lead to a substantial loss of power and precision (Faraggi and Simon, 1996), thus reducing the efficiency of the analysis with increased probability of biased estimates (Becher, 1992). An inflation in Type 1 error has been demonstrated on the testing of a continuous predictor using multivariable analysis and this inflation increases on categorisation of the continuous confounding variable particularly when categorised into a small number of categories (Austin and Brunner, 2004). In addition, a model that categorises continuous variables is unrealistic as individuals close to but on opposite side of the category cut-point will be characterised as having very different outcome when a very similar outcome is more likely (Royston *et al.*, 2006). It is recommended that continuous predictors are retained as continuous and suitable functions such as fractional polynomial are used (Royston and Altman, 1994; Royston *et al.*, 2006). Although this is true from a methodological point of view, the clinical practice in terms of implementation of any score needs to be considered. For example, NICE in the UK recommends action before, during and after pregnancy in women with BMI greater than 30 (National Institute of Health and Care Excellence, 2010). Thus, including this categorisation could make the prediction rule easier to incorporate into clinical practice.

Although predictors shown to have little effect on the outcome should not be included in the prediction, the method of selection of predictor variables for inclusion is crucial. The majority of studies (75%) used an automated variable selection method however there was no acknowledgment of the limitations of this method. The use of automated selection methods increases the likelihood that variables that do not truly predict the outcome will be identified as a predictor (Austin and Tu, 2004). This is because it is a data-driven approach that cannot account for clinical relevance leading to biased regression estimates and poor predictions as true predictors could be excluded due to lack of power (Steyerberg *et al.*, 1999; Collins *et al.*, 2011). It also leads to loss of information due to inclusion of variables based on a binary decision. It has been suggested that a more reasonable reduction of variables using automated selection procedures could be achieved by using a liberal selection criteria such as $p = 0.50$ (Steyerberg *et al.*, 1999) instead of 0.05 which is more commonly used and has been used in the

prediction models included in this review that used this procedure. It could also be important to retain predictors which are known to be important from the literature but do not achieve statistical significance in the model development dataset (Collins *et al.*, 2011). Two studies carried out univariable analysis to identify predictors for inclusion in the final model. However, the use of univariable analysis for pre-screening predictor variables has been critiqued as inappropriate due to the possibility of rejection of potentially important variables when the relationship is confounded by a confounder that hasn't been controlled for (Sun et al., 1996).

Once developed, the performance of a model needs to be evaluated to demonstrate usability. Although a biased model could provide useful clinical separation into groups if the predictor information entered into the model is strong (Altman and Royston, 2000), evidence is needed that the model performs well in populations other than that in which it was developed (Altman *et al.*, 2009). Validation can be internal (through random split, cross-validation or bootstrapping) or external using a completely different sample thus also examining the generalisability of the model (Altman *et al.*, 2009). Six studies (75%) internally validated the model through random split of the dataset (two), random split and cross-validation (one) or bootstrapping (three). Four studies (50%) externally validated the model, only one of which externally validated the model in cohorts from different countries. This was followed by replication analysis to rebuild the model in these two cohorts resulting in only two predictors being retained across all three models in this study (maternal and paternal BMI). As the use of random split sample decreases the precision of estimates and increases the frequency of missing important independent variable (Hirsch, 1991), there is limited value in doing so unless the sample size is particularly large (Collins *et al.*, 2011). A non-random or chronological split has been suggested as a more precise approach but internal methods such as bootstrapping and cross-validation remain more informative (Altman and Royston, 2000).

This review has been carried out with a systematic approach thus identifying all studies that have developed and/or validated a risk prediction model for childhood overweight and obesity but the limitations need to be considered. Systematic reviews are subject to publication bias. As this review assessed the development and reporting of prediction models, we did not contact authors for further information and therefore did not identify unpublished analysis. A need for methodological work to investigate potential bias has been identified in the area of

prognosis reviews (Hayden *et al.*, 2009). Prospective registration of protocols has also been recommended as an option to reduce publication bias in prognosis factor research (Riley *et al.*, 2013), though the extent to which this is done is unclear. Another limitation is that screening was carried out by one reviewer instead of the recommended double screening by two reviewers with a third resolving any disagreements. This could lead to more studies being missed than if two reviewers carried out screening. However, bibliography and citation searching of included studies only yielded one additional validation article and so we are confident that no relevant studies were excluded. Heterogeneity exists at many levels in the included studies particularly the outcome (overweight, obesity or both) under consideration and age at which outcome is predicted. This heterogeneity combined with the deficiency of external validation limits the applicability of these scores. Additionally, poor reporting in aspects of development of the prediction models was observed with insufficient detail on steps involved in model building. Risk prediction models have nearly all been developed or validated in high-income countries but almost half and one quarter of the estimated 42 million overweight children under the age of five years live in Asia and Africa respectively (World Health Organization, 2004). Models tailored to these countries are important, as associations are known to vary between ethnic groups. Ethnicity was considered in three and included in one model so the applicability of these risk scores to ethnically diverse populations living in developed countries should also be assessed.

3.5 Conclusion

Despite the existence of several models for the prediction of childhood overweight and obesity, most have not been externally validated or compared to existing models to assess predictive performance. Moreover as the outcome of childhood obesity has been predicted at different ages, it may not be possible to combine or compare all models against each other. This review also highlights methodological limitations in model development and validation combined with non-standard reporting thus limiting the usability of these prediction models.

There remains a need to develop new methods for combining findings from existing prediction models and develop prediction models for childhood obesity using robust methods of development followed by external validation and recalibrating to

populations, which would then enable assessment of impact of the implementation of the score.

This chapter has identified the need for a new prediction model based on the limited usability of the existing models as outlined in the chapter. All the prediction models were developed using cohort data and thus some include variables that are not available in routine data further limiting usability. The next chapter will present the methods of accessing and linked data used for the analysis in this thesis. Following this, analysis on the interpregnancy interval and maternal interpregnancy weight change will be presented before returning to the development of the prediction models in Chapter 7 and Chapter 8.

Chapter 4 Methods

The systematic review reported in Chapter 3 confirmed the need for further work in developing a prediction model for childhood overweight and obesity. This chapter outlines the data that will be used as part of this project to achieve the objectives outlined on page 5. It also outlines the project design including the process of data linkage and summarises the data linkage process including the journey of navigating data access and information governance issues.

This study is a population-based cohort study. The cohort is defined as all women who have received antenatal care by the University Hospital Southampton (UHS) Midwifery Service between January 2003 and April 2018. Antenatal care and birth outcomes data were linked to early life and childhood obesity data at age 4-5 and/or 10-11 years as outlined in section 4.1 below. The linkage to childhood obesity data were only possible for children who were born on or before 31 August 2013 (at 4-5 years) and those born before 31 August 2006 (at 4-5 and 10-11 years).

This PhD forms part of a larger project; Studying Lifecourse Obesity PrEdictors (SLOPE). An example of the other main areas of research in the overall project is to explore areal-place data (area of residence of mother during pregnancy and of child during early life) reflective of social and environmental circumstances and to examine if these factors will improve the predictive power of the childhood overweight and obesity model.

4.1 Data sources

To achieve the objectives of this project as outlined on page 5, three main sources of data (Figure 4.1) have been identified:

4.1.1 UHS Hospital Integrated Clinical Support System (HICSS) database

Antenatal care and birth outcomes data are recorded on the HICSS maternity database for all women receiving care and giving birth at UHS. This database has been in place since 2002 but cases from 2002 were not included as the database was in the implementation phase during this period. Cases between January 2003 and April 2018 were included in this study.

A record is created on the HICSS database when the midwifery team receive a referral from the general practitioner (GP). This record is then updated at the first antenatal (booking) appointment, which is recommended to occur around 10 weeks of pregnancy in the UK (National Institute for Health Care and Excellence, 2008a). The midwifery team aims to hold the booking appointment at UHS so that all the information is recorded directly onto the electronic database. In a minority of cases where it is not possible to have the appointment at UHS, the midwife can access the database on a laptop or use a paper version and then transfer the information onto the

electronic database when back at the office. Although women may have previous appointment/s at general practice, booking appointments are always carried out by the midwifery team at UHS.

The booking appointment is arranged for an hour and information is collected through a series of questions. Information is collected through self-report on age, ethnicity, employment status, educational attainment, previous illness and family history in both parents-to-be, previous obstetric history, infertility treatment, current smoking behaviour, current diet and alcohol and supplement intake. BMI is calculated using self-reported height and weight measured at the appointment. Blood pressure is also measured and blood samples are taken for screening tests. During the appointment, the midwife also provides information on the baby's development during pregnancy, nutrition and diet during pregnancy including foods to avoid, exercise, screening tests, maternal benefits and outline of care during pregnancy. The information is printed out and provided to the mother as a handheld record. With the exception of the dating and ultrasound scanning appointments, the remainder of midwifery appointments are usually held in the community. Information from the scans is recorded on the database but not information from community appointments.

Obstetric complications such as GDM, pre-eclampsia and gestational hypertension are usually diagnosed during the second half of the pregnancy. Once diagnosed, these are recorded in the women's handheld notes. If a women attends the Maternity Day Assessment Unit (MDAU) to be assessed by a midwife for concerns or problems in the pregnancy which needs monitoring, the database is then updated with obstetric complications. Otherwise, these are recorded in the database as part of the birthing record.

This record is then updated when the woman goes into labour with information on labour, mode of birth and birth outcomes of the child including gestational age, birthweight, gender, Apgar score and breastfeeding at discharge. Maternal smoking status at end of pregnancy is also recorded. This information is filled out in handheld records first and the midwives aim to update the record with labour and birth information as soon as possible after their duties in the labour ward.

4.1.2 Child Health Information System (CHIS) (NHS England, 2013)

CHIS are patient administration systems that provide a clinical record for individual children and support a variety of child health care including immunisation, child screening and support for children with special educational needs. The Solent NHS Trust CHIS creates and maintains child health records for children aged 0 to 19 years in Portsmouth and Southampton. In other parts of Hampshire (excluding Portsmouth and Southampton), this is carried out by Southern Health NHS Foundation Trust. The data are provided by midwifes, GPs, paediatricians, health visitors and school nurses. Every child in the UK is offered five statutory heath visitor checks (also called health and development reviews) until the age of 2 years. These checks occur shortly after birth and when the child is aged 1-2 weeks, 6-8 weeks, 9 months-1 year and 2-2.5 years. These are usually carried out by a member of the health visiting team with the information from the reviews recorded on the child record and in the Personal Child Health Record or the 'red book' that is given to parents at the child's birth and filled out by a healthcare worker every time the child is seen in a healthcare setting.

4.1.3 National Child Measurement Programme (NCMP) (NHS Digital, 2020)

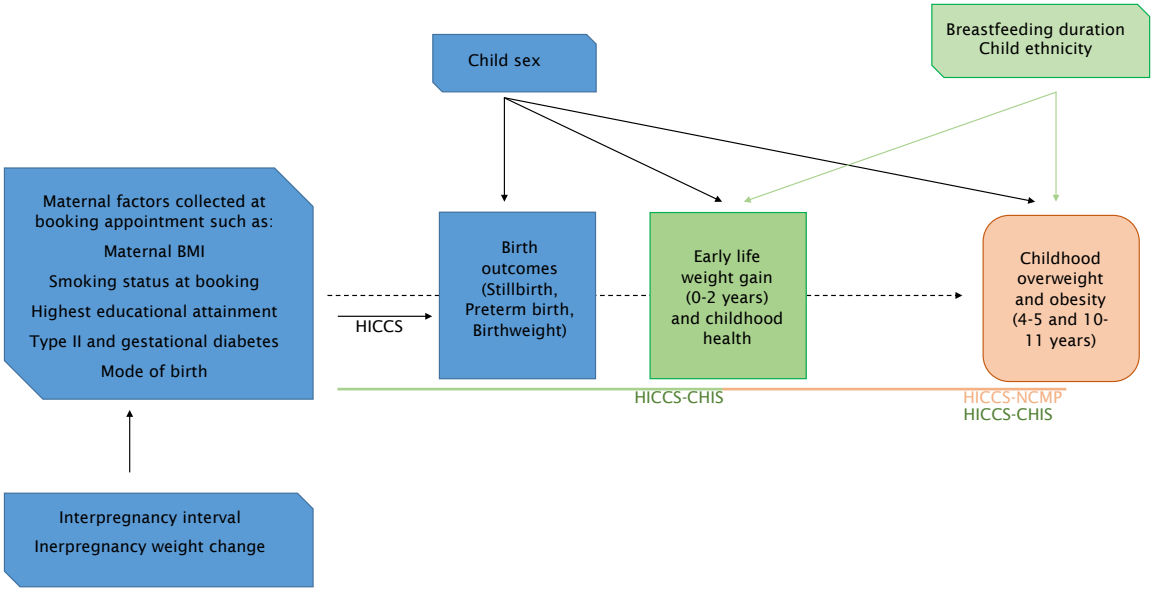
The NCMP is an annual surveillance programme that collects data on the height and weight of children in Reception (aged 4 to 5 years) and Year 6 (aged 10 to 11 years) within all state maintained schools in England. The programme was established in 2006 and it was the responsibility of primary care trusts to gather data but was moved to local government in 2013 at which point recording of NHS number also commenced. Data collected also include child's name, sex, address, postcode, ethnicity and date of birth.

NCMP data required for this project are held by Southampton City Council and Hampshire County Council. However, community trusts (Southern Health NHS Foundation Trust for Hampshire excluding Portsmouth and Southampton, and Solent NHS Trust for Southampton) are commissioned by the local authorities to collect NCMP data through the School Nursing service and thus hold this information in CHIS. Accessing these data through the local council would limit the data to the period in which NHS number was recorded as the NHS number is the common identifier across

the datasets for linkage. But if this data can be accessed through CHIS, then these limits would not apply and thus data from a larger cohort may be available for linkage.

The data linkage process is outlined in detail in section 4.6 on page 70.

Figure 4.1: Data sources and example variables from each source (the colours in the graph indicate the data that are available from each source)



4.2 Inclusion/exclusion criteria

Only women who have received antenatal care and delivered at UHS were included. No exclusion criteria were defined for accessing the sample however for the purposes of analysis only singleton births will be included.

4.3 Sampling

The estimated number of women giving birth at UHS is 6000 per annum. The required variables were extracted from the antenatal care records for appointments between January 2003 and April 2018. This was provided to the research team by the data holder (UHS) following the removal of all personal identifiers as assessed by a UHS Privacy Information Assessment (PIA) and scrutinised by the data holder's Caldicott Guardian. All babies identified by UHS were linked if they were identified in CHIS. Details of the linkage process is described in section 4.6 below.

4.4 Consent

Participant consent was not sought for this research for the following reasons:

1. The anonymised linked research dataset does not contain any personal identifiers and cannot be linked back to any individuals by the research team
2. The timeline of the data included in this study leads to a large number of individuals, many of whom are likely to be uncontactable which could lead to selection bias.
3. There is no direct effect or feedback to the individual.

4.5 Ethics

University of Southampton Faculty of Medicine ethics approval (Ethics and Research Governance Online ((ERGO) 24433 and 25508) and Health Research Authority (HRA) approval (Integrated Research Approval System (IRAS) id 242031) has been granted for the SLOPE project.

4.6 Data handling and linkage

The data from the data sources (UHS and CHIS) listed in section 4.1 on page 66 was linked using child NHS number with the maternity dataset acting as the primary dataset. This dataset was provided to the research team as separate anonymised datasets with no personal identifiers and linked using a common anonymised identifier.

The data informatics team at UHS as the primary dataset holder generated a link between child NHS number and an anonymised identifier. UHS then provided this link directly to the other data holders (Southern Health NHS Foundation and Solent NHS Trusts). NCMP data was accessed through CHIS and thus this link was not shared with the local authorities who also hold NCMP data. No other individual-level data was shared between any of the data holders. The only information shared between the data holders was a table with two columns: one with the child NHS number and the other with the anonymised identifier. The community NHS Trusts used this information to select their study samples and then anonymise the required data variables from their datasets using the same anonymised identifier and sent the data directly to me. I linked the study variables from the three datasets using the anonymised identifier. This way, the

individual-level data holders listed in section 4.1 did not have access to any data other than that which they already hold, and all research study data was received in an anonymised format by the research team at the University of Southampton, who do not have access to the identifier link.

This method of linking anonymised datasets was selected as this was the most straightforward way of satisfying data holders regarding data access and for the research team to maintain a degree of control and understanding of the linkage process. However, before settling on this approach, other options of access and linkage were explored as outlined in section 4.9 below.

Child weight, height, BMI, head circumference, feeding status and postcode were linked to the HICSS data using NHS number. Children born on or after 31 August 2013 were not old enough to start school and children born in 2018 were unlikely to have had more than one (if any) of the development reviews offered by the NHS however all identified records in CHIS were linked. This ensured that no records were excluded unintentionally during the data extraction and psuedonymisation process which was carried out by different data holders.

Date of birth and postcode information was not shared with the researchers to maintain confidentiality. Date of birth was converted to age (for the mother) and month and year (for the child). Postcode was converted to lower layer super output area (LSOA) which covers approximately 1500 residents/650 households and thus is a summary measure sufficient to examine environment exposures but cannot be used to identify individuals.

4.7 Data checks and exclusion

Checks were carried out to ensure successful linking and to identify extreme cases. One common variable (child sex) was checked across the datasets to ensure these matched. Maternal ethnicity was recorded in the maternity dataset and child ethnicity was recorded in the community trust dataset. Although maternal and child ethnicity do not have to be identical, a high proportion will be identical or part similar (mixed race) so unfeasible ethnicity records were checked. Additionally, feasibility of recorded weight and height measurements based on child age and pattern recorded were also checked. Extreme outliers for childhood BMI or unrealistic data points in the weight gain trajectory were excluded as there is no mechanism for validating back to the original data.

UHS provides standard and specialist antenatal care and it is likely that the women booking late have previously booked elsewhere and were then transferred to UHS for specialist care thus not capturing the early booking information. Children with a gestational age at birth of 43 weeks or greater were excluded. This is because pregnancies do not usually progress to/beyond this point however the maternity system continues to count the days till the record is closed. This has been checked and amended to the correct gestational age in more recent years but was not always done when the database was first set up.

Table 4.1: Number of records excluded based on unfeasible records by outcome

	Interpregnancy birth outcomes (1st to 2nd livebirth pregnancies)	Year R BMI	Year 6 BMI
Total n after exclusions	15940	29060	13482
Gestational age at booking < 0 days	3	1	0
Gestational age at booking > 168 days	5376	1207	686
Gestational age at birth > 301 days	577	266	250
Maternal weight <= 30 kg	10	5	6
Maternal height >2m	10	3	2

4.8 Sample size

The dataset received from UHS contained 96489 records of which 84219 had a pregnancy outcome with the remainder having booked but not yet delivered or having delivered elsewhere. Of these 84219 records, 738 records ended in stillbirth, miscarriage or termination and thus the final sample size was 83481 pregnancies ending in live births with birth information recorded. Of these, data for 74770 children were successfully linked to their CHIS records (40% from Solent NHS Trust, 49% from Southern Health NHS Foundation Trust and 11% from both at different time points).

Before study-related exclusions:

- 55925 children had at least one measurement of weight before the age of 2.5 years
- 30958 had BMI measurement 4-5 years
    - 21412 had one weight measurement before 2.5 years
    - 416 records of twins/triplets
- 14611 had BMI measurement 10-11 years
    - 5340 with weight measurement <2.5 years
    - 185 record of twins/triplets
- 7062 had both
    - 3736 with weight measurement <2.5 years

The actual sample size for outcome at age 4-5 years was around half and at age 10-11 years was around 61% of the expected sample size. Migration could be a contributing factor as only children who were born and going to school in this area was included but is unlikely to explain such a large difference from the estimated sample. It was assumed that all records on the community trust systems would have NHS number linked to the child measurement even before the responsibility of recording moved to local authorities and the recording of NHS number became a requirement. Based on the final sample size, we can assume that NHS number was recorded for some records while recording was the responsibility of the primary care trust but was not done routinely which could explain the lower sample size than expected.

A formal sample size calculation was not carried out as this study used existing prospectively collected data. Sample size requirements for developing a prediction model are based on the number of predictors under consideration and the number of outcome cases in the dataset and are thus considered as part of the analysis.

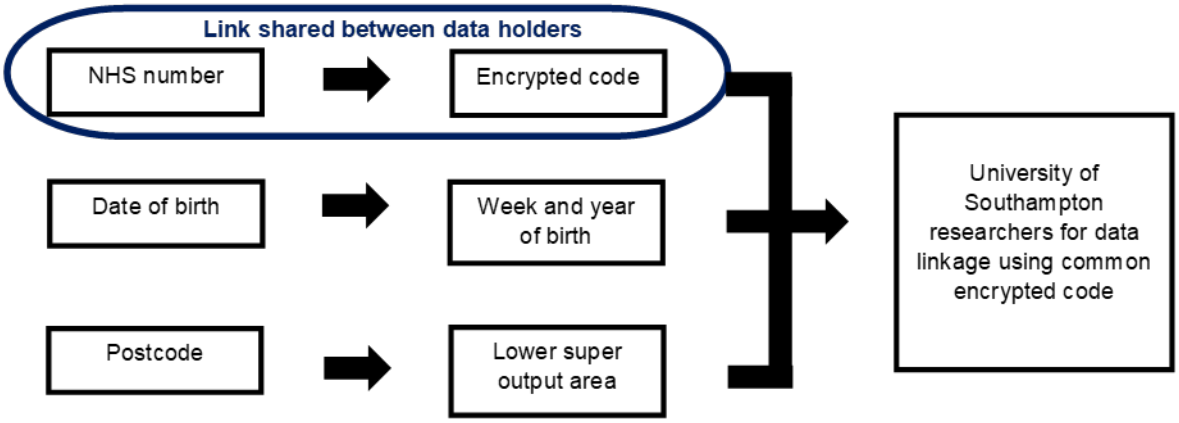
4.9 Reflections on the data retrieval and linkage process

When we (my primary supervisor and I) initially started exploring the possibility of accessing and linking data, the plan was to apply for data considered identifiable by the NHS such as NHS number to link across the datasets. This would require NHS ethics review and a secure data environment to link and access the data. On seeking advice from the Administrative Data Resource Network (ADRN) team based in Southampton, we were told that the linkage process in data linkage

projects are usually dictated by the data holders. At this time, we were looking into accessing NCMP data from NHS Digital who hold the national data although local data are collected and held by local councils. NHS Digital also provide services that receive and link external datasets. On further exploration, we decided to approach the local councils for accessing the NCMP data as suggested by NHS Digital who have their own application process for data access and we were advised that a linkage project involving data from children was unlikely to be approved by NHS Digital. Furthermore, as we only needed local data for this project, this was likely to be a faster process. As NHS Digital was no longer a data holder for this project, we looked into the process of linking and accessing the linked dataset at the ADRN centre in Southampton. We were informed that we could either link the datasets or hold the linked datasets at the centre but both functions could not be carried out in the same place and thus were recommended to explore the option of linkage by a trusted third party (TTP) followed by holding the dataset at ADRN Southampton. TTP linkage is a process in which all data holders would securely transfer identification data and serial ids to a TTP who would create a linkage id for each record and send these back to the data holders who would use this linkage id in the dataset to be provided to the researchers. A common factor across data holders was a willingness to receive data accompanied by a lack of willingness to share data with other data holders and thus we needed a process of linkage that did not require data holders to share identifiable data.

At a conference, my primary supervisor attended a talk about the Secure Anonymised Information Linkage (SAIL) Databank, which holds anonymised routine healthcare data about the population of Wales for research purposes (Swansea University, 2016). After exploring the process of anonymising data used by SAIL databank, we adapted the workflow outlined in Figure 4.2 to link data without access to identifiable information. The SAIL databank utilises TTP linkage for their linkage but the TTP is the NHS Wales Informatics Service (NWIS), who as an organisation, deliver technology and digital services for patient care in Wales and thus is part of the clinical system and are experienced in handling such data.

Figure 4.2: Workflow of data anonymization for linkage



Once we had decided on the method of linkage, we looked into the process of ethical approval. Research using anonymised data does not require approval by the NHS Research Ethics Committee (REC) and thus we applied for ethics approval from the Faculty of Medicine ethics committee at the University of Southampton. HRA approval was a modification of an existing system within NHS ethics that was introduced in March 2016 and the guidance has continued to evolve since it was introduced. The community trusts required HRA approval to send the anonymised data. I contacted a member of staff at HRA to seek advice and found that approval was required when using NHS facilities, patients, data or staff. We then applied for HRA approval for the overall project which was granted within a month from application.

Accessing anonymised data from UHS was relatively straightforward. My supervisory team had already been in contact with the midwifery team who then put us in touch with the data informatics team. We provided the informatics team with study information and ethics approval, filled out a privacy impact assessment for review by the information governance team at the hospital who approved the project and discussed with the Caldicott guardian for Caldicott approval. The process was slow as the data informatics team are involved in maintaining the hospital systems and were implementing service upgrades at the time which was a higher priority. However, being a teaching hospital and heavily involved in research meant that the staff were more aware of the benefits of using healthcare data in research and thus supportive of the project. The data extraction costs were covered by a grant related to the project from the Academy of Medical Sciences.

As UHS provides antenatal care to women living in areas under the jurisdiction of Southampton City and Hampshire County councils, we approached both councils to request access to NCMP data. The process was again slow at both councils but moved faster with Southampton City Council's Public Health team who reviewed the protocol, discussed with their legal team and met with our research team (my primary supervisor, project research fellow and I) to discuss queries raised and identify a way forward for the research. Hampshire County Council also reviewed the protocol and raised some queries that we responded to but we were then recommended to approach Southern Health NHS Foundation Trust to try to access the data through CHIS first. The team from Southampton City Council drafted a data sharing agreement and it was agreed that we could access the data once this was signed. However, this access was conditional on anonymised identifiers being deleted once the data were linked and only analysis stated in the protocol being carried out. While this was a reasonable request, it would not allow us to carry out any future analysis in the existing linked dataset around additional research questions. Since we discovered that most of the relevant variables that the council holds are also recorded in CHIS, we opted to use CHIS outcome data for both Hampshire and Southampton.

By this stage, we had made progress on accessing exposure (antenatal) data and outcome (childhood overweight and obesity) data. However, we were also interested in early life data, which is collected by the health visitor through a series of regular health and development checks until the child is two years of age. This information is usually filled in the Personal Child Health Record or the 'red book' that is given to parents at the child's birth and filled out by a healthcare worker every time the child is seen in a healthcare setting. It was not clear from online searches if this data is held electronically in the record held by general practice or community trusts. Therefore, we approached data analysts at the University of Southampton working on the Hampshire Health Record (HHR) (now called the Care and Health Information Exchange CHIE). This is a computer system, which safely shares information about a patient with those treating them (with patient's consent) and contains information from hospital, general practice, community care and social services. This system is managed by the South, Central and West (SCW) Commissioning Support Unit (CSU) and the information held on the system can be accessed for research in an anonymised format. All research proposals using CHIE data are reviewed by the CSU and if approved, data analysts at the University of Southampton extract and provide the data to the researchers. This process was further complicated for my project as only CSU

have access to the NHS number and the University data analysts only have access to psuedonymised identifiers. This meant that CSU would have to convert the NHS number-anonymised identifier link provided by UHS (outlined in section 4.6) to CSU psuedonymised-anonymised identifier link that could then be used by the University data analyst to extract the data. The preferred approach for CSU would have been for the other data holders to send data to them and then they would provide us with a linked dataset. However, other data holders were not willing to share data with CSU. Although we continued to explore the possibility of accessing health visitor data through HHR/CHIE further, this was soon abandoned when it was difficult to identify a clear path forward due to cost and staffing.

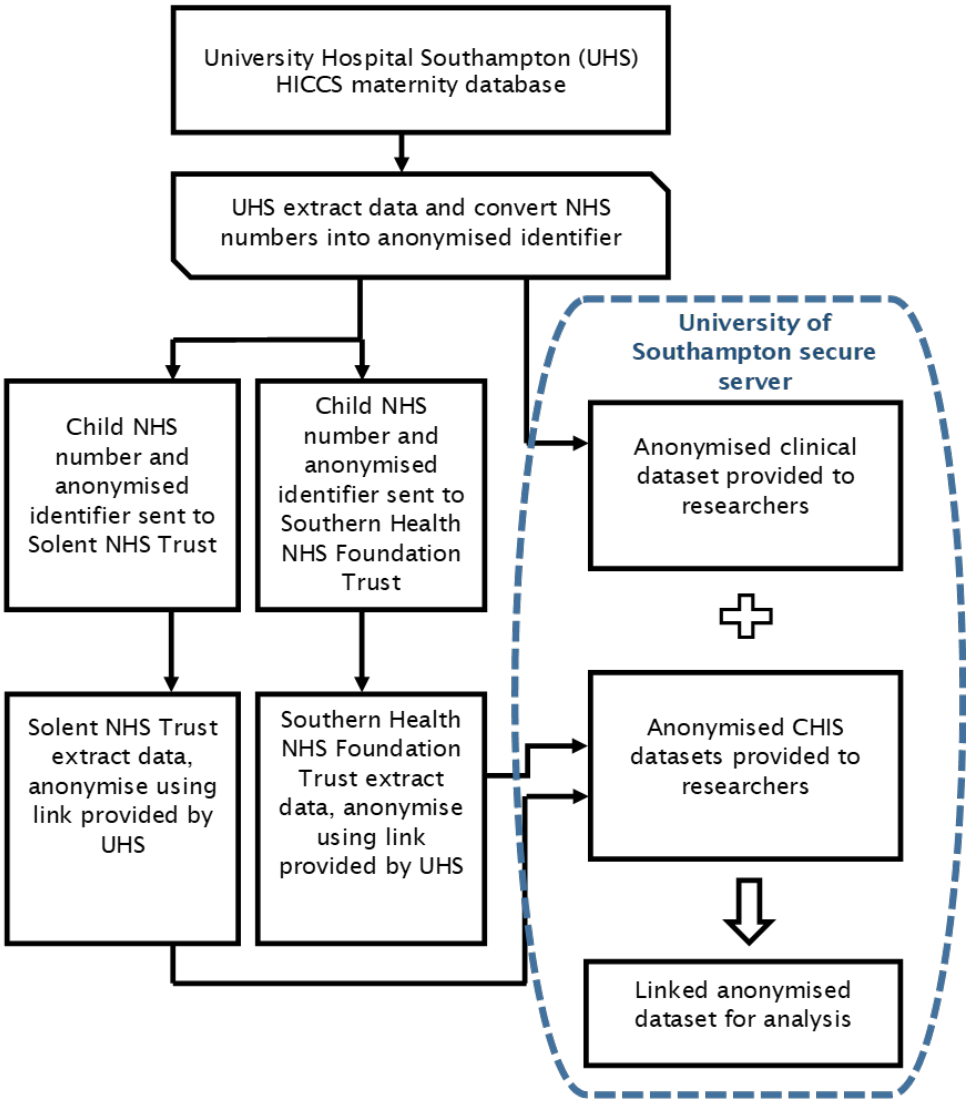
At the same time, we were also exploring the possibility of accessing the health visitor data through the community trusts – Southern Health NHS Foundation Trust (for Hampshire excluding Portsmouth and Southampton) and Solent NHS Trust (for Southampton) who create and maintain CHIS (see section 4.1.2). Once HRA approval was received, Solent NHS Trust quickly confirmed their capacity to provide data for the study but the process was slower at Southern Health NHS foundation trust as data requirements and staff time to provide the data was only considered after the approval.

We received several extracts of the antenatal care and birth data. This was because the first extract received in September 2017 (for records between 2003 and September 2017) was missing some of the variables we requested. We were provided with an updated extract shortly after with the additional variables. UHS then provided us with an updated extract in April 2018 (for records between 2003 and April 2018) with the identifier key as requested to ensure successful linkage. As the interpregnancy analysis was carried out in this interim period, the dataset with records between 2003 and September 2017 was used for the analysis presented in Chapter 5 and Chapter 6.

Another issue that was considered was the increased risk of identification from linking together information from the mother and child even though there was no identifiable information. This is partly because the more data that is available on an individual the more likely is the possibility of identification but linking a mother-child could make it a unique pair particularly if there was any information about the mother outside of pregnancy. However, no information was available on the mother outside of pregnancy and although this was raised during discussions with data holders, it did not prove a barrier to the project. The data is

stored on a secure server within the Faculty of Medicine at the University of Southampton. Figure 4.3 illustrates the process of data linkage for this study.

Figure 4.3: Flow of data access and linkage



4.9.1 Lessons learnt to date and discussion

The findings are that accessing data from existing sources takes time and can be a costly process. These factors have previously been identified as the two main barriers to accessing and linking healthcare data (cost and slow rigid time-consuming application processes) (Dattani *et al.*, 2013; Gilbert *et al.*, 2015). For example, a one-off dataset with bespoke linkage from NHS Digital can cost a minimum of £3,300 to cover costs of processing and delivering the service (NHS Digital, 2016). Costs of up to £7,000 per data source depending on complexity and linkage was identified by other researchers (Dattani *et al.*, 2013). A medium size linked dataset from the electronic Data Research and Innovation Service

(eDRIS) in Scotland was costed at around £15,000 (electronic Data Research and Innovation Service, 2017). These costs are not large in comparison to the cost of carrying out observational cohort or intervention studies but this cost is incurred by every data user. Infrastructure funding to increase capacity and innovation and reduce rigid rulings could make healthcare data affordable to all researchers (Gilbert *et al.*, 2015). Other barriers include lack of transparency on what data is used for research and by whom and the impact of this on health including care and society (Gilbert *et al.*, 2015). Dattani *et al.* also found that availability of some datasets are not advertised or public knowledge and they only knew of the existence of the datasets through contacts within the institutions that held the data (Dattani *et al.*, 2013). This is similar to the issues I faced in trying to identify if and where health visitor data is held. Additionally the lack of data dictionaries for routine data means that even when researchers know that data is available, they are not aware of exactly what is included in the dataset. However, identifying the right people and working effectively together helps navigate the data availability and access requirements.

Routine healthcare data are a rich information source about a large number of patients although completeness and accuracy can be variable. Data linkage creates the possibility of new areas of research that were previously not possible. Linked hospital and general practice/community health records can be used for research and then findings implemented to stratify risk and target patient groups for intervention (Grath-Lone *et al.*, 2015). There have been examples of population-based linked anonymised health and administrative datasets such as the SAIL Databank in Wales (Swansea University, 2016), eDRIS in Scotland (electronic Data Research and Innovation Service, 2017) and Clinical Practice Research Datalink (CPRD) (NHS National Institute for Health Research and Medicines and Healthcare products Regulatory Agency, 2018). Access to and analysis of such data sources has important policy implications (Gilbert *et al.*, 2015) but there are still a lot of data that has not yet been used for research. In the UK, maternal and child health data with the exception of birth outcomes is held separately and there is huge untapped potential in linking these together which to my knowledge has only been done in Scotland to date (ISD Scotland, 2018). The Maternity and Children's Data Sets project (MCDS) was developed in 2015 to help achieve better care outcomes for mothers and children nationally. It incorporates the Maternity Services Data Set (MSDS), Children and Young People's Health Services Data Set (CYPHS) and the Child and Adolescent Mental Health Services Data Set (CAMHS) (NHS Digital, 2015). Information from this data set will

be made available to commissioners, providers, clinicians and service users however it is not clear if this will be made available for research and if there would be a cost attached to it.

This chapter covered the methods related to accessing the dataset utilised in this thesis. Statistical methods specific to each analysis are outlined in the methods section of each chapter. The process of linking the dataset took place over a period of two years from starting discussions to receiving all the datasets and having a linked dataset. The datasets were received in stages starting with the maternity dataset following which the first child dataset was received approximately eight months later. I utilised this period to clean and familiarise myself with the maternity dataset but also to carry out the interpregnancy weight change analysis as outlined in section 1.2. Analysis are presented in the chronological order they were carried out so the focus of the next two chapters move to the interpregnancy analysis. Following this, I will return to the development of the prediction models in Chapter 7.

Chapter 5 Interpregnancy interval and maternal interpregnancy weight change

Maternal obesity is a strong predictor of childhood obesity and weight gained during pregnancy is not always lost after delivery. This chapter presents findings from an analysis in women with consecutive pregnancies investigating the length of the interpregnancy interval and examining its association with the change in maternal BMI between pregnancies, and size at birth. This has not previously been explored in the UK and as this analysis only uses the antenatal care dataset, I carried out this analysis while waiting for the linked child data as outlined in section 4.6 on page 70.

Work from this chapter has been published as conference abstracts and part of the work has been published as a peer-reviewed paper in the journal Scientific Reports. Elements of the work from this chapter has been presented at three conferences (Public Health Research and Science Conference 2018, Southampton Medical and Health Research Conference 2018 and European Congress of Epidemiology 2018).

5.1 Background

5.1.1 Interpregnancy interval

Interpregnancy interval is defined as the timing between a live birth and the conception of the next pregnancy. The WHO technical consultation on birth spacing in 2005 recommended an interval of 2 years or more however the only maternal outcomes considered were mortality and morbidity (World Health Organization, 2005). This is consistent with the WHO recommendation on breastfeeding that recommends exclusively breastfeeding for the first six months of life followed by breastfeeding with complementary foods up to two years of age or beyond (World Health Organization, 2002). This is because one of the major concerns with a short interval is maternal nutritional depletion because of inadequate time to recover from one pregnancy before entering the next (Conde-Agudelo *et al.*, 2012).

The length of the interpregnancy interval has been found to be dependent on various factors of which maternal age, social class and outcome of the previous pregnancy have been identified as most influential (Fedrick and Adelstein, 1973). In the USA, nearly a third of second or higher order births were conceived within 18 months of the previous with 5% conceived within six months (Thoma *et al.*, 2016). The interpregnancy interval was found to be shorter as maternal age at first pregnancy increased with women who delay the start of childbearing to ≥35 years having increased odds of intervals less than six months (Nabukera *et al.*, 2009). Data from 1969-2006 in Switzerland showed that maternal age at first pregnancy had increased from 25.0 to 30.1 years with shorter intervals between pregnancies (Kalberer *et al.*, 2009).

5.1.2 Interpregnancy weight change

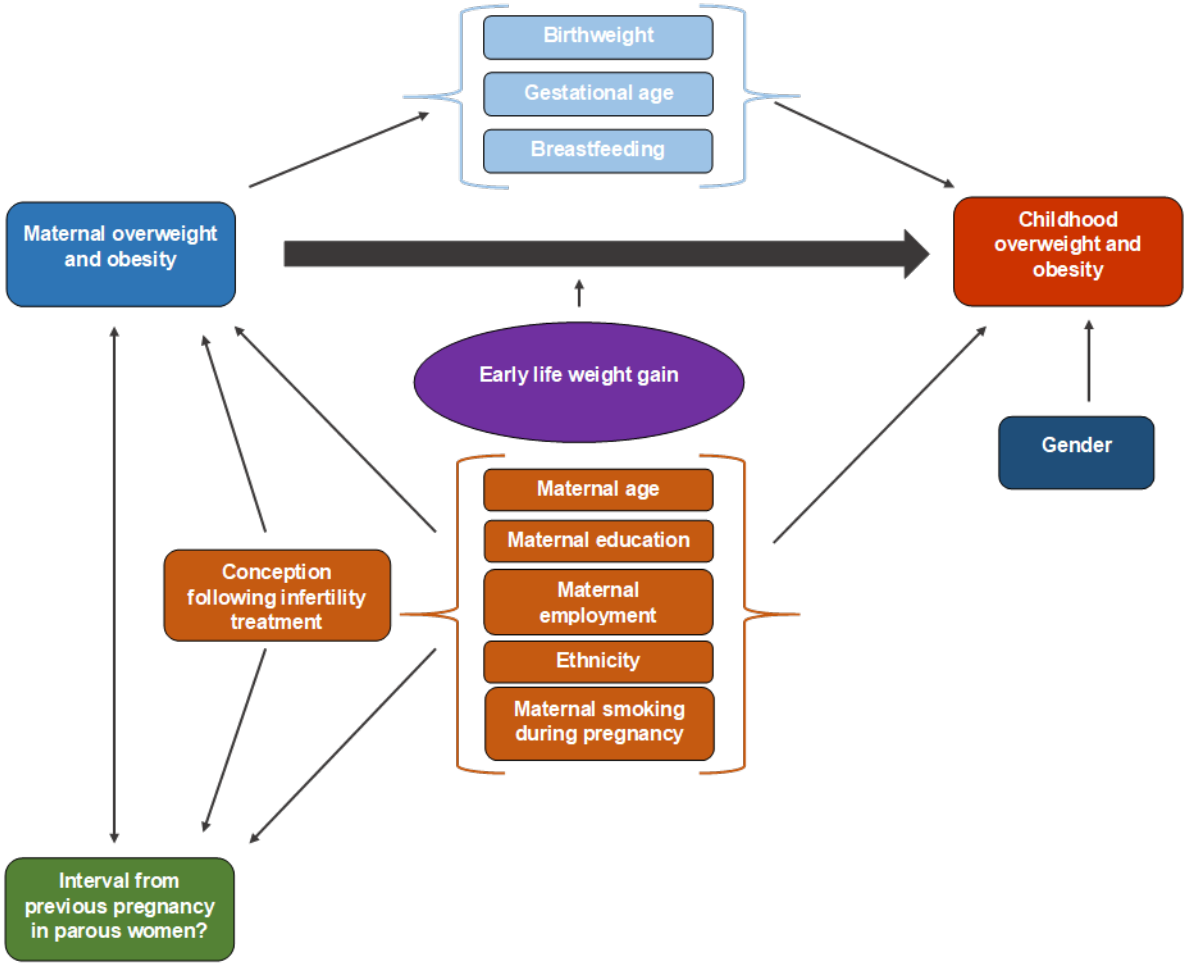
As mentioned in section 2.1.1 on page 10, maternal obesity is a key predictor of maternal and fetal pregnancy outcomes as well as long-term health outcomes (such as obesity, diabetes and cardiovascular disease) in the mother, child and subsequent children (Hanson *et al.*, 2016). The rise in obesity in women of childbearing age and its associated effects on maternal health and offspring risk of obesity (Hanson *et al.*, 2016) make maternal weight change between pregnancies an important consideration as this could modify risk of subsequent offspring.

Women who have given birth are at higher risk of developing obesity than women who have not (Davis *et al.*, 2009). Additionally, women with excess gestational weight gain who failed to lose pregnancy weight by six months postpartum were at increased risk of subsequent obesity (Rooney and Schauberger, 2002). Although overweight and obesity in nulliparous women is associated with increased risk of adverse outcomes (Baeten *et al.*, 2001), evidence on association with increased risk of postpartum weight retention is conflicting (Harris *et al.*, 1997; Linné and Rössner, 2003; Abebe *et al.*, 2015). A meta-analysis of 17 studies concluded that GWG rather than pre-pregnancy BMI determines weight retention (Rong *et al.*, 2015) but only one of the studies included adjusted for potential confounding factors and there were a limited number of studies with long-term follow-up. A systematic review reported that postpartum, weight follows a steep decrease in the first three months followed by a continuous decrease until 12 months following which an increase in weight was reported. However, this was only assessed in two cohorts (Schmitt *et al.*, 2007). Post-partum weight retention is variable with women on average retaining 0.5 to 3kg, however a substantial number (12-20%) retain a considerable amount of weight (Gore *et al.*, 2003). Approximately two-thirds of women presenting for antenatal care for a second pregnancy in Ireland an average of 18 months after delivery had gained weight with 20% in a higher compared to 5.8% in a lower BMI category than the first pregnancy (Crosby *et al.*, 2015).

Weight retention is highest after the first pregnancy (Gunderson *et al.*, 2004), and gestational weight gain and retention postpartum in subsequent pregnancies follow a similar pattern to the first (Linné and Rössner, 2003). Analysis of a retrospective cohort of 37178 women with three pregnancies in Canada found that women with short interpregnancy intervals (<12 months compared to 18 to 23months) were more likely to enter the subsequent pregnancy obese (Hanley *et al.*, 2017). However, BMI at the start of the previous pregnancy and socioeconomic status was not taken into account.

Weight gain between pregnancies was found to be strongly associated with increased risk of maternal and perinatal complications, independent of maternal BMI (Villamor and Cnattingius, 2006). A conceptual diagram of how this affects childhood obesity is shown in Figure 5.1.

Figure 5.1: Conceptual diagram of the link between interpregnancy interval with childhood overweight and obesity



5.1.3 Interpregnancy interval and size at birth

Both interpregnancy weight change and interpregnancy interval can be linked to birthweight, which is a key early life risk factor for long-term health outcomes such as obesity and cardiovascular disease. Birthweight can be monitored and is considered modifiable by factors known to affect foetal growth (Barker, 1995). This is because birth weight is an indicator of the in-utero environment.

Birthweight, on average, increases with parity such that the first-born infant on average has the lowest birthweight and the birthweight of subsequent infants increases up to the fourth pregnancy. However, birthweight was found to decrease with parity for women who had short intervals between pregnancies and the increase in birthweight with parity was higher in women with long intervals (Hinkle *et al.*, 2014). Conversely, analysis of birthweight in families with five or more singleton births using data from the Medical Birth Registry in Norway found an increase in birthweight with maternal age, parity and time since last pregnancy

up to five years. All the variables were correlated and although the time between pregnancies had an impact on birthweight, this was considered relatively small compared to other factors over the timescale in which families are completed (Beaty *et al.*, 1997). Another study in the United States examined the association of maternal age and birth order on birthweight and found that birth order had a greater influence with the incremental increase in birthweight highest from first to second pregnancy (Swamy *et al.*, 2012). A systematic review of 41 studies assessing parity and pregnancy outcome identified increased risk of LBW and SGA among nulliparous women with birthweight lower in nulliparous women compared to those of multiparous women (Shah and Knowledge Synthesis Group on Determinants of LBW/PT births, 2010).

Birth certificate data from Utah between 1989 and 1996 was used to examine the association between interpregnancy interval and LBW (<2500g) and SGA (<10th percentile). The reference interval of 18 to 23 months was associated with lower risk of both outcomes with increased risk at intervals of 0 to 5, 60 to 119 and ≥120 months (Zhu *et al.*, 1999). Similarly, a study in Michigan used birth certificate data between 1993 and 1998 to identify singleton infants born to women who had previously had at least one live birth to examine the effect of the interpregnancy interval on perinatal outcomes including LBW and SGA. The analysis was stratified by race and showed that an interval of 12 to 17 months was associated with similar risk of LBW and SGA as the reference group of 18 to 23 months in both White and Black women and these were the intervals associated with lowest risk. Additionally, an interval of 24 to 59 months was not associated with increased risk of LBW in Black women only (Zhu *et al.*, 2001). A population-based cohort in Brazil found that an interval of 18 to 23 months was associated with the least risk of LBW and SGA and risk was highest with an interval less than six months (Cecatti *et al.*, 2008). Both analyses adjusted for confounders including parity but women with any number of previous pregnancies were included and thus the effect could be further confounded by the number of and interval between previous pregnancies. Additionally, there was no evidence of adjustment of gestational age in the analysis of LBW and thus the effect could be overestimated. Analysis of a 5% random sample of women who had at least two pregnancies between 1980 and 1992 from the Danish Birth Registry found an increased risk of LBW at an interval of more than 36 months compared to 24 to 36 months but little difference in risk with shorter intervals (Basso *et al.*, 1998). This analysis adjusted for gestational age at birth but as a categorical variable of < or ≥ 37 weeks.

5.1.4 Summary

To my knowledge, no previous epidemiological studies have examined gain in maternal BMI in relation to the interval between pregnancies. There is little evidence to support an optimal birth spacing in terms of changes in maternal BMI for subsequent pregnancies. Although previous studies have examined the risk of SGA and LGA in relation to the interpregnancy interval, only one study has done this stratified by pregnancy order.

5.2 Aim

- To describe the change in maternal BMI between pregnancies
- To examine the association of maternal interpregnancy BMI change with length of the interpregnancy interval
- To examine the association of the length of the interpregnancy interval with size at birth (SGA and LGA)

5.3 Methods

This analysis utilises the prospectively collected routine antenatal care and birth records data between January 2003 and September 2017 at University Hospital Southampton, Hampshire, UK as outlined in section 4.1.1 on page 66. Records of women with two or more consecutive singleton live birth pregnancies were included in this analysis. Women with more than five previous births (due to small numbers) were excluded. Only singleton pregnancies were included. Analysis was carried out by pregnancy order by using information on parity to categorise the pregnancies as first to second, second to third, third to fourth and fourth to fifth, even if the previous live births were not recorded in the analysed dataset (for example, if the women had received antenatal care elsewhere). The size at birth analysis was restricted to first to second consecutive live birth pregnancies as low or high birthweight are an outcome of 7-11% of pregnancies in England and Wales (Office for National Statistics, 2017a), and thus the sample size for subsequent pregnancies was insufficient.

5.3.1 Exposure assessment

The difference in days between two consecutive births was calculated and gestational age of the latter birth subtracted from this to derive the

interpregnancy interval (World Health Organization, 2005). For multiparous women, no information was available on the interval from previous pregnancy if delivery was before the start of the study period (2003) or at another hospital. Only women whose first pregnancy resulted in a live birth were included as other pregnancy outcomes (stillbirth, miscarriage) could affect the interpregnancy interval (Sholapurkar, 2010). Two categorical variables were created – one based on the WHO guideline (0-23 months and 24 months or more) and the other with more detailed categories (0-11, 12-23, 24-35 and 36 months or more). Within the detailed categories, 24-35 months was used as the reference category as this was in line with the WHO guideline of at least 2 years.

5.3.2 Outcome assessment

5.3.2.1 Interpregnancy weight change

With the exception of weight, all data were self-reported to a trained midwife at the first antenatal (booking) appointment, which is recommended to take place ideally by 10 weeks of pregnancy in the UK (National Institute for Health Care and Excellence, 2008a). The booking appointment is booked by midwives once pregnancy is confirmed by general practice. Women are prioritised by gestational age with the aim of booking the appointment during the recommended period. Maternal weight in kilograms was measured at this appointment and thus any woman who had a booking at or after 24 weeks of pregnancy was excluded. BMI was calculated as weight (in kg) divided by height (in metres) squared. BMI was analysed as both a continuous (kg/m^2) and categorical variable. The categorical variable was defined as underweight (BMI <18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) and obese (≥30 kg/m^2). Change in BMI was calculated as the difference in BMI at booking appointment between two consecutive live birth pregnancies. Weight gain was calculated as any gain in weight that led to a change in BMI. Baseline BMI was defined as the BMI at the first pregnancy that information was available for.

Gestational age (date of last menstrual period) is ascertained and recorded at the booking appointment.

5.3.2.2 Size at birth

Birth weight is measured and recorded at delivery by the midwife for every birth. Gestational age was based on a dating ultrasound scan which routinely takes place between 10 and 13 weeks gestation (National Institute for Health Care and

Excellence, 2008a). Age- and gender- specific birthweight centiles were calculated using reference values for England and Wales provided in the most recently released national data (Norris *et al.*, 2017). SGA was defined as <10th percentile weight and LGA was defined as >90th percentile weight for gestational age. This was only defined for babies born between 24 to 42 weeks gestation as reference values only exist for these gestational ages.

5.3.3 Covariables

Maternal date of birth is recorded at the booking appointment and converted to age on extraction of the dataset to maintain anonymity. Highest maternal educational attainment was self-reported and categorised as primary, secondary, college, undergraduate, postgraduate, graduate and none. For the purposes of this analysis, this was condensed to three categories - secondary (GCSE) and under, college (A levels) and university degree or above. Self-reported ethnicity was recorded under 16 categories and condensed to White, Mixed, Asian, Black/African/Caribbean and Other. Categories of not asked and not stated were coded as missing. Smoking was self-reported as current smoking or non-smoking. Non-smokers were further asked if they had ever smoked or had previously smoked and quit. This was categorised as stopped more than 12 months before conception, stopped less than 12 months before conception or stopped when pregnancy confirmed. Employment was self-reported at booking appointment and categorised as employed, unemployed, in education and not specified. Infertility treatment was categorised as no/investigations only and yes (hormonal only, in-vitro fertilisation, gamete intrafallopian transfer and other surgical) in either one or both pregnancies. Breastfeeding was recorded at discharge from the hospital as exclusive, partial or no breastfeeding.

The size at birth analysis also included pre-eclampsia (SGA) or GDM (LGA) as an additional covariable. Pre-eclampsia is usually diagnosed during routine pregnancy checks and is reported in the database if diagnosed. In this population, an oral glucose tolerance test was used for screening for GDM in women with one or more risk factors (BMI > 30kg/m^2; GDM in previous pregnancy; previous baby weighing ≥4.5kg; diabetes in parents or siblings and of Asian, African-Caribbean or Middle Eastern ethnicity) (National Institute for Health Care and Excellence, 2015). GDM diagnosis was then reported in the database.

5.3.4 Statistical analysis

All analysis was performed using Stata 15 (StataCorp., 2017).

5.3.4.1 Interpregnancy weight change

Characteristics of women with an interpregnancy interval less than 2 years were compared to those with an interval of 2 years or more using two-sample t-test for continuous and chi-squared test for categorical variables. Results using the categorical variable based on the WHO guideline are presented in Appendix C.

Linear regression was used to examine the association of maternal change in BMI between pregnancies (assessed as a continuous variable in kg/m^2) with interpregnancy interval (assessed as a continuous variable in years). Generalised linear regression with log link and robust variance estimator (Cummings, 2009) was then used to examine the same association (maternal change in BMI with interpregnancy interval) but by categorising maternal change in BMI into gained weight compared with no change or lost weight using the detailed categorisation of interpregnancy interval described above. This method of analysis was chosen to calculate relative risk (RR) due to the high prevalence of the outcome (>10%) in which instance odds ratios can substantially overestimate RR.

Initial univariable analysis was followed by multi-variable models adjusting for potential confounding factors – timing of booking appointment (as this is when BMI is measured), maternal age, ethnicity, highest educational attainment, whether or not undergone infertility treatment, employment status, smoking behaviour and baseline maternal BMI. Finally, the role of a potential mediating factor (breastfeeding behaviour at hospital discharge) was examined in the subgroup in which this data was available.

A statistical significance level of 0.01 with 99% confidence intervals was used in the regression models to reduce the risk of Type I error due to multiple testing. A lower significance level was set for this analysis compared to the size at birth analysis below due to the additional testing of a different classification of the interval as well as the analysis of higher order pregnancies.

5.3.4.2 Size at birth

Generalised linear regression with log link and robust variance estimator (Cummings, 2009) was used to examine the association of SGA and LGA separately with interpregnancy interval. Initial univariable analysis was followed

by multi-variable models adjusting for potential confounding factors – maternal age, ethnicity, highest educational attainment, conception following infertility treatment, employment status, smoking status at second booking appointment, baseline maternal BMI and change in maternal BMI between pregnancies. Sensitivity analysis was carried out adjusting for SGA or LGA in previous pregnancy.

A statistical significance level of 0.05 with 95% confidence intervals was used in the regression models.

5.4 Results

5.4.1 Interpregnancy weight change

The main sample consisted of 19,362 women with at least two consecutive live birth pregnancies (Figure 5.2). Of the 15,940 women who had their first two pregnancies in the dataset, 12,636 women only had first two, 2,654 had three, 530 had four and 120 had five consecutive pregnancies. A further 1,884 women had their second to third, 430 second to fourth, 136 second to fifth, 758 third to fourth, 207 third to fifth and seven fourth to fifth pregnancies. A description of the sample characteristics by pregnancy order is shown in Table 5.1. Mean maternal BMI at first pregnancy was 24.6 kg/m^2 (standard deviation 5.0) and increased with pregnancy order. Overweight and obesity in the sample increased with higher order pregnancies with 13.0% obese at first pregnancy to 31.6% obese at fifth pregnancy. The proportion of women who stopped smoking when pregnancy was confirmed was highest in the first pregnancy and decreased in subsequent pregnancies. The proportion of women who continued smoking through pregnancy was highest in later pregnancies. Women with secondary school education or lower tended to have a higher number of pregnancies. There was a slight shift in ethnic distribution from first to higher order pregnancies with a decrease in White women and an increase in Asian and Black/African/Caribbean women.

Figure 5.2: Flow diagram showing the data preparation process

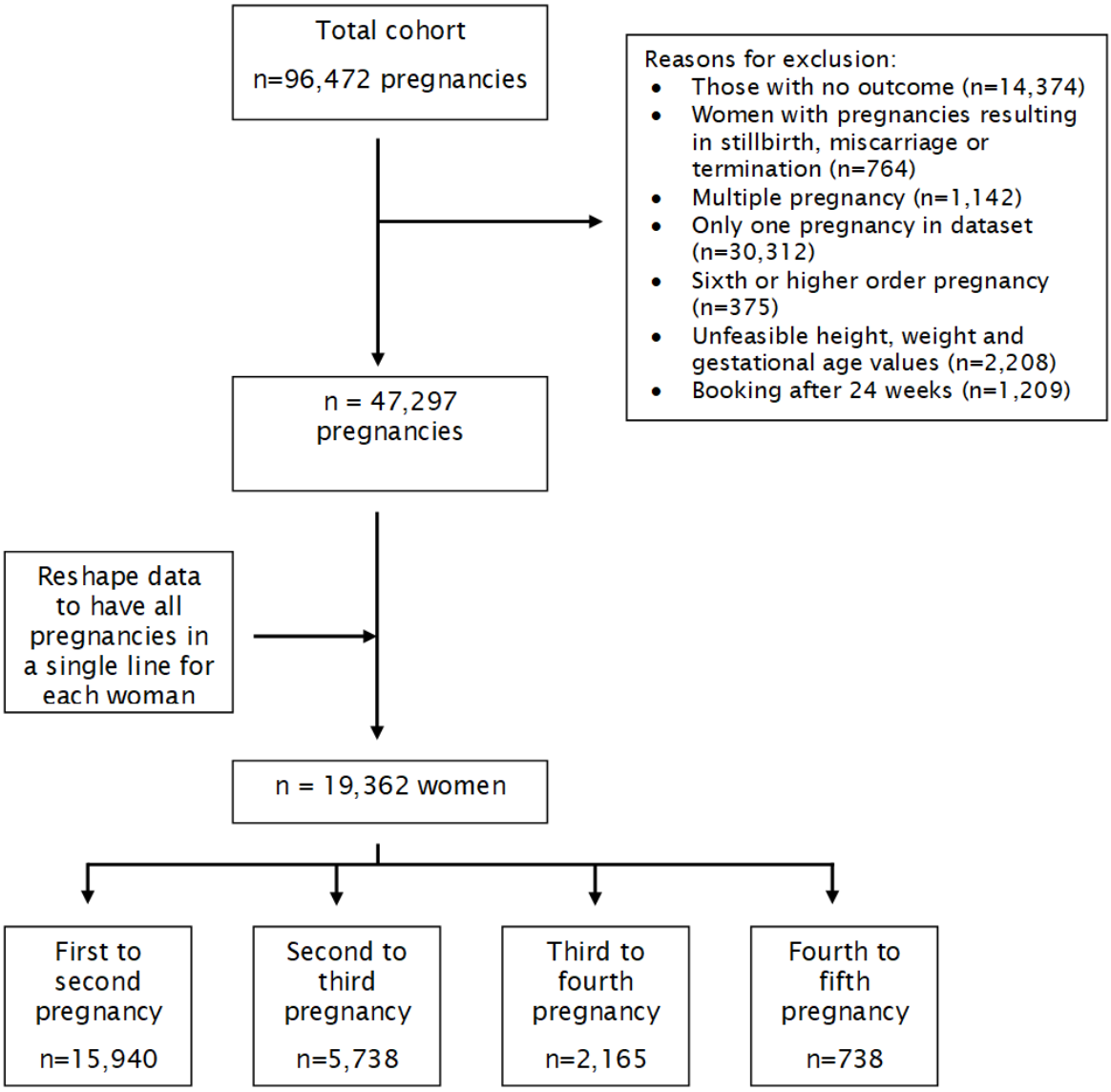


Table 5.2 summarizes the interpregnancy interval and change in maternal BMI between consecutive pregnancies. Median interpregnancy interval followed a u-shaped pattern and was shortest from first to second pregnancy, increased from second to third pregnancy but decreased for subsequent pregnancies and was similar to the interval between first to second pregnancy. However, the proportion of women with an interval of 0-11 months between pregnancies increased from 17.5% in the first to second pregnancy to 28.5% in the fourth to fifth pregnancy. Eighteen percent of second pregnancies were conceived within 12 months of the first, 35% within 12-23 months, 23% within 24-35 months and 24% after 36 months or more (up to 12 years).

Table 5.1: Pregnancy characteristics by gestational order for period of January 2003 - September 2017, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, England

	First pregnancy	Second pregnancy	Third pregnancy	Fourth pregnancy	Fifth pregnancy
N	15,940	18,954	6,844	2,533	738
Maternal age (mean ± SD)	25.9 ± 5.5	28.6 ± 5.4	29.3 ± 5.0	30.3 ± 4.9	31.6 ± 4.8
Timing of first booking appointment, weeks (mean ± SD)	11.3 ± 2.7	11.2 ± 2.5	11.5 ± 2.8	11.8 ± 3.1	12.0 ± 3.3
Maternal BMI (mean ± SD)	24.6 ± 5.0	25.8 ± 5.6	26.5 ± 6.0	27.3 ± 6.2	28.2 ± 6.6
Maternal BMI (%, 99% CI)					
Underweight (< 18.5)	3.9 (3.5 to 4.3)	2.9 (2.6 to 3.2)	2.5 (2.0 to 3.0)	2.1 (1.5 to 3.0)	1.5 (0.6 to 3.1)
Normal weight (18.5 to 24.9)	59.2 (58.2 to 60.2)	51.6 (50.6 to 52.5)	46.1 (44.5 to 47.7)	41.1 (38.6 to 43.7)	36.2 (31.7 to 40.9)
Overweight (25.0 to 29.9)	23.9 (23.0 to 24.7)	26.6 (25.8 to 27.5)	28.7 (27.3 to 30.2)	28.4 (26.1 to 30.8)	30.8 (26.5 to 35.3)
Obese (≥30.0)	13.0 (12.4 to 13.7)	18.9 (18.2 to 19.7)	22.7 (21.4 to 24.0)	28.3 (26.0 to 30.7)	31.6 (27.2 to 36.2)
Maternal smoking status (%, 99% CI)					
Never smoked/quit	53.3 (52.3 to 54.4)	57.5 (56.5 to 58.4)	50.8 (49.3 to 52.4)	47.6 (45.0 to 50.2)	45.3 (40.5 to 50.1)
Stopped >1 year before conceiving	12.0 (11.4 to 12.7)	16.2 (15.5 to 16.9)	14.7 (13.6 to 15.8)	12.7 (11.1 to 14.5)	11.1 (8.3 to 14.4)
Stopped <1 year prior to conceiving	7.3 (6.8 to 7.8)	4.1 (3.8 to 4.5)	4.2 (3.6 to 4.8)	3.2 (2.4 to 4.2)	5.4 (3.5 to 7.9)
Stopped when pregnancy confirmed	12.1 (11.4 to 12.7)	7.4 (6.9 to 7.9)	7.5 (6.7 to 8.3)	7.6 (6.3 to 9.1)	6.4 (4.3 to 9.0)
Continued smoking	15.3 (14.6 to 16.0)	14.8 (14.2 to 15.5)	22.8 (21.5 to 24.2)	28.9 (26.6 to 31.3)	31.8 (27.5 to 36.4)
Educational attainment (%, 99% CI)					
Secondary (GCSE) or under	23.7 (22.9 to 24.6)	24.9 (24.1 to 25.7)	36.3 (34.8 to 37.8)	45.9 (43.3 to 48.5)	51.8 (47.0 to 56.5)
College (A levels)	43.0 (42.0 to 44.0)	43.2 (42.3 to 44.1)	44.0 (42.5 to 45.6)	41.8 (39.3 to 44.4)	41.7 (37.1 to 46.5)
University degree or above	33.3 (32.3 to 34.3)	31.9 (31.0 to 32.8)	19.7 (18.5 to 21.0)	12.3 (10.7 to 14.1)	6.5 (4.4 to 9.2)
Maternal employment (%, 99% CI)					
Employed	80.0 (79.1 to 80.8)	64.0 (63.1 to 64.9)	45.4 (43.8 to 46.9)	28.8 (26.5 to 31.2)	20.5 (16.8 to 24.5)
Unemployed	15.7 (14.9 to 16.4)	34.3 (33.4 to 35.1)	52.3 (50.7 to 53.9)	68.7 (66.3 to 71.1)	77.5 (73.3 to 81.3)
In education	4.0 (3.6 to 4.4)	1.1 (0.9 to 1.3)	1.3 (1.0 to 1.7)	1.3 (0.8 to 2.0)	1.1 (0.3 to 2.5)
Not specified	0.4 (0.3 to 0.6)	0.7 (0.5 to 0.9)	1.0 (0.7 to 1.4)	1.2 (0.7 to 1.9)	0.9 (0.3 to 2.3)

	First pregnancy	Second pregnancy	Third pregnancy	Fourth pregnancy	Fifth pregnancy
Ethnicity (%, 99% CI)					
White	86.9 (86.1 to 87.5)	85.7 (85.0 to 86.3)	82.6 (81.4 to 83.7)	81.2 (79.1 to 83.1)	81.7 (77.8 to 85.2)
Mixed	1.2 (1.0 to 1.4)	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.6)	1.4 (0.9 to 2.1)	1.9 (0.8 to 3.6)
Asian	6.3 (5.9 to 6.9)	6.8 (6.4 to 7.3)	9.7 (8.8 to 10.6)	10.3 (8.8 to 12.0)	9.8 (7.1 to 12.9)
Black/African/Caribbean	1.4 (1.2 to 1.7)	1.7 (1.5 to 1.9)	2.5 (2.1 to 3.1)	3.4 (2.5 to 4.4)	3.4 (1.9 to 5.5)
Other	1.0 (0.8 to 1.2)	1.2 (1.0 to 1.4)	1.4 (1.1 to 1.8)	1.5 (0.9 to 2.2)	1.8 (0.8 to 3.4)
Not specified	3.2 (2.9 to 3.6)	3.4 (3.1 to 3.8)	2.6 (2.1 to 3.1)	2.3 (1.6 to 3.2)	1.5 (0.6 to 3.1)

Table 5.2: Change in maternal body mass index (BMI) measured at the first antenatal visit between consecutive pregnancies by gestational order

	First to second pregnancy	Second to third pregnancy	Third to fourth pregnancy	Fourth to fifth pregnancy
N	15,940	5,738	2,165	738
Interpregnancy interval, months (median, IQR)	22.9 (14.6 to 35.5)	25.0 (14.0 to 43.1)	22.6 (12.3 to 40.7)	22.9 (10.8 to 41.1)
Interpregnancy interval, categorised (%, 99% CI)				
0-11 months	17.5 (16.8 to 18.3)	19.7 (18.4 to 21.1)	24.7 (22.3 to 27.1)	28.5 (24.3 to 32.9)
12-23 months	35.3 (34.3 to 36.3)	28.2 (26.7 to 29.8)	28.5 (26.0 to 31.0)	23.8 (19.9 to 28.1)
24-35 months	23.1 (22.2 to 23.9)	18.7 (17.4 to 20.0)	16.7 (14.7 to 18.9)	18.0 (14.5 to 21.9)
36 months or more	24.1 (23.3 to 25.0)	33.4 (31.8 to 35.0)	30.2 (27.6 to 32.8)	29.7 (25.4 to 34.2)
Direction of change of maternal BMI (%, 99% CI)				
No change	2.9 (2.6 to 3.3)	2.9 (2.3 to 3.5)	3.2 (2.3 to 4.3)	3.5 (2.0 to 5.7)
Lost BMI units	31.3 (30.3 to 32.2)	31.8 (30.2 to 33.4)	31.7 (29.1 to 34.3)	27.4 (23.2 to 31.8)
Gained BMI units	65.8 (64.9 to 66.8)	65.3 (63.7 to 66.9)	65.1 (62.4 to 67.8)	69.1 (64.5 to 73.4)
Change in maternal BMI (median, IQR)	0.9 (-0.4 to 2.4)	0.9 (-0.4 to 2.5)	0.9 (-0.4 to 2.8)	1.3 (-0.2 to 2.8)
Change in maternal BMI in women who lost weight	-1.0 (-1.9 to -0.5)	-1.2 (-2.2 to -0.5)	-1.3 (-2.4 to -0.6)	-1.1 (-2.3 to -0.6)
Change in maternal BMI in women who gained weight	1.8 (0.9 to 3.4)	1.9 (0.9 to 3.4)	2.1 (1.0 to 3.8)	2.2 (1.1 to 3.6)

	First to second pregnancy	Second to third pregnancy	Third to fourth pregnancy	Fourth to fifth pregnancy
Weight gained by interpregnancy interval (%, 99% CI)				
0-11 months	65.3 (62.9 to 67.6)	61.7 (57.9 to 65.4)	62.4 (56.8 to 67.7)	61.0 (51.9 to 69.5)
12-23 months	60.3 (58.6 to 61.9)	60.3 (57.1 to 63.4)	62.8 (57.6 to 67.8)	63.1 (53.2 to 72.3)
24-35 months	66.2 (64.2 to 68.2)	64.5 (60.7 to 68.3)	60.8 (53.9 to 67.3)	73.7 (62.7 to 82.9)
36 months or more	74.0 (72.1 to 75.8)	72.2 (69.5 to 74.8)	72.0 (67.2 to 76.4)	79.0 (71.1 to 85.6)
Change in maternal BMI category (%, 99% CI)				
No change in BMI category	71.6 (70.7 to 72.5)	71.2 (69.6 to 72.7)	69.6 (66.9 to 72.1)	69.4 (64.8 to 73.7)
Underweight (< 18.5)	1.5 (1.3 to 1.8)	1.4 (1.0 to 1.8)	1.0 (0.5 to 1.7)	1.4 (0.5 to 2.9)
Normal weight (18.5 to 24.9)	45.1 (44.1 to 46.1)	39.1 (37.5 to 40.8)	34.0 (31.4 to 36.7)	30.4 (26.1 to 34.9)
Overweight (25.0 to 29.9)	13.6 (12.9 to 14.3)	15.2 (14.0 to 16.5)	15.7 (13.7 to 17.8)	15.7 (12.4 to 19.5)
Obese (≥30.0)	11.4 (10.9 to 11.9)	15.5 (14.3 to 16.7)	18.8 (16.7 to 21.1)	22.0 (18.2 to 26.1)
% decreased to normal weight	3.7 (3.3 to 4.1)	3.7 (3.1 to 4.4)	4.2 (3.2 to 5.5)	3.9 (2.3 to 6.2)
% decreased to overweight	1.5 (1.2 to 1.7)	2.5 (2.0 to 3.1)	2.2 (1.5 to 3.2)	2.6 (1.3 to 4.5)
% increased to overweight	11.7 (11.0 to 12.3)	11.5 (10.5 to 12.7)	11.2 (9.5 to 13.1)	12.5 (9.5 to 15.9)
% increased to obese	7.9 (7.4 to 8.5)	7.7 (6.8 to 8.6)	9.9 (8.3 to 11.6)	9.6 (7.0 to 12.8)

Between 47-52% of women had intervals of 2 years or more between pregnancies. The median overall change in maternal BMI from first to second pregnancy was 0.9 kg/m^2 (interquartile range IQR -0.4 to 2.4) however the change in women who lost weight was 1.0 kg/m^2 (IQR -1.9 to -0.5) and that in women who gained weight was 1.8 kg/m^2 (IQR 0.9 to 3.4). The change remained similar across pregnancies with approximately two-thirds of women having gained weight when presenting for antenatal care for the subsequent pregnancy. Over a fifth were in a higher BMI category by start of the next pregnancy with 1-2% having moved two BMI categories (for example normal weight to obese).

Figure 5.3 shows the percentage of women gaining weight by BMI category and interpregnancy interval from first to second pregnancy. A substantial proportion of women within each BMI category gained weight across all intervals however, the lowest proportion of women gaining weight and changing BMI category across all BMI categories was in the 12-23 months interval. A similar pattern was observed across all pregnancies (Appendix C).

Figure 5.3: The percentage of weight gain by interpregnancy interval and maternal body mass index (BMI category) between first to second pregnancy

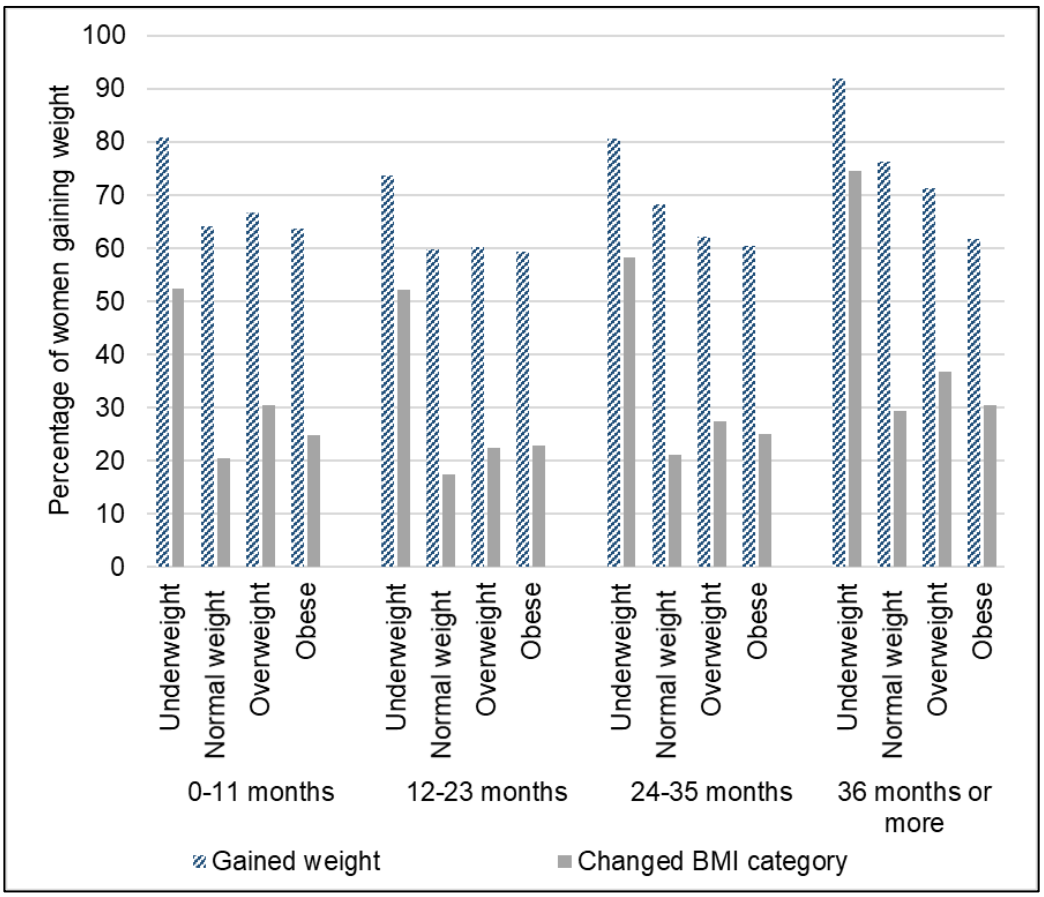
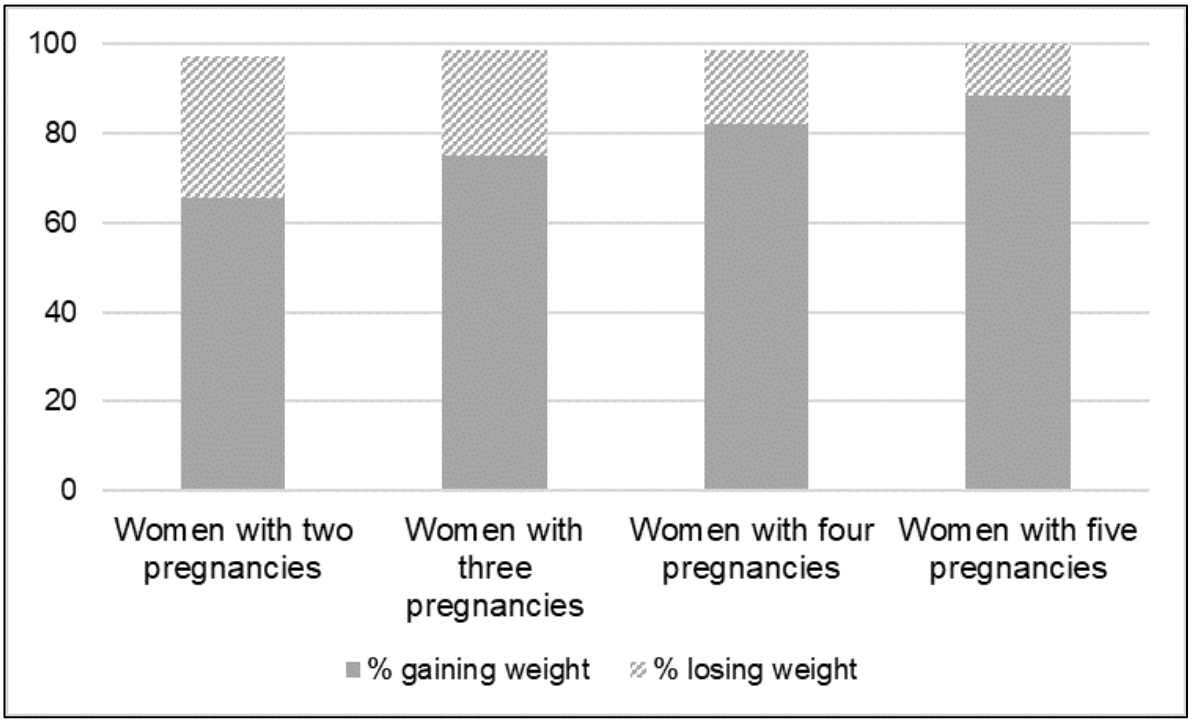


Figure 5.4 summarizes the longer-term change in maternal BMI between pregnancies defined as the change in maternal BMI during the course of all her pregnancies in the dataset. The proportion of women who gained weight increased from 65.7% by second pregnancy in women who had their first two to 88.5% by fifth pregnancy in women who had their first five pregnancies.

Figure 5.4: The percentage of weight gain and loss in women with two and more pregnancies across all their pregnancies



In both unadjusted and adjusted linear regression analyses, there was a significant positive association between change in maternal BMI with each year of interpregnancy interval (adjusted increase in maternal BMI per year of interpregnancy interval 0.25 kg/m^2, 99% CI 0.21 to 0.28) for first to second pregnancy. The coefficient remained similar across pregnancies and increased for the fourth to fifth pregnancy (adjusted increase in maternal BMI per year of interpregnancy interval 0.36 kg/m^2, 99% CI 0.22 to 0.50) (Table 5.3).

Table 5.3: Linear regression estimates for association between change in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy and the length of the interpregnancy interval (in years)

	First to second pregnancy			Second to third pregnancy			Third to fourth pregnancy			Fourth to fifth pregnancy		
	n	Maternal BMI (kg/m^2) per year (99% CI)	p	n	Maternal BMI (kg/m^2) per year (99% CI)	p	n	Maternal BMI (kg/m^2) per year (99% CI)	p	n	Maternal BMI (kg/m^2) per year (99% CI)	p
Unadjusted	15,940	0.27 0.23 to 0.30	<0.001	5,738	0.22 0.17 to 0.27	<0.001	2,165	0.24 0.16 to 0.32	<0.001	738	0.34 0.21 to 0.48	<0.001
Model 1	15,940	0.27 0.24 to 0.31	<0.001	5,738	0.22 0.18 to 0.27	<0.001	2,165	0.25 0.17 to 0.33	<0.001	738	0.33 0.20 to 0.47	<0.001
Model 2	15,259	0.25 0.21 to 0.28	<0.001	5,498	0.24 0.19 to 0.29	<0.001	2,081	0.25 0.16 to 0.33	<0.001	711	0.36 0.22 to 0.50	<0.001
Model 3	15,259	0.25 0.21 to 0.28	<0.001	5,498	0.24 0.19 to 0.29	<0.001	2,081	0.25 0.16 to 0.33	<0.001	711	0.36 0.22 to 0.50	<0.001
Model 4	4,667	0.17 0.07 to 0.26	<0.001	1,608	0.19 0.04 to 0.33	0.001	617	0.07 -0.19 to 0.32	0.51	213	0.32 -0.06 to 0.71	0.03

Model 1 is adjusted for: timing of first (booking) antenatal appointments (as this is when maternal BMI is measured)
Model 2 is adjusted for: timing of first (booking) antenatal appointments, maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking and employment status
Model 3 is adjusted for: first (booking) antenatal appointment, maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking, employment status and baseline maternal BMI (for the first pregnancy in the dataset)
Model 4 is adjusted for: first (booking) antenatal appointments, maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking, employment status, baseline maternal BMI and breastfeeding or not at hospital discharge

Table 5.4: Logistic regression models testing the association between interpregnancy gain in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy and the length of the interpregnancy interval (categorised)

		Gain in maternal BMI: First to second pregnancy			Gain in maternal BMI: Second to third pregnancy			Gain in maternal BMI: Third to fourth pregnancy			Gain in maternal BMI: Fourth to fifth pregnancy		
		Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p
Total n, n of cases		15,940; 10,493			5,738; 3,748			2,165; 1,410			738; 510		
Unadjusted	0-11m	2,793; 1,824	0.99 0.94 to 1.03	0.45	1,132; 698	0.96 0.88 to 1.04	0.16	534; 333	1.03 0.89 to 1.18	0.63	210; 128	0.83 0.68 to 1.01	0.01
	12-23m	5,624; 3,389	0.91 0.87 to 0.95	<0.001	1,618; 975	0.93 0.86 to 1.01	0.02	616; 387	1.03 0.90 to 1.18	0.53	176; 111	0.86 0.70 to 1.05	0.05
	24-35m	3,675; 2,433	(reference)		1,074; 693	(reference)		362; 220	(reference)		133; 98	(reference)	
	>=36m	3,848; 2,847	1.12 1.07 to 1.16	<0.001	1,914; 1382	1.12 1.04 to 1.20	<0.001	653; 470	1.18 1.04 to 1.34	<0.001	219; 173	1.07 0.91 to 1.26	0.26
Model 1	0-11m	2,793; 1,824	0.98 0.93 to 1.02	0.22	1,132; 698	0.95 0.87 to 1.03	0.13	534; 333	1.01 0.88 to 1.17	0.79	210; 128	0.84 0.69 to 1.02	0.02
	12-23m	5,624; 3,389	0.91 0.87 to 0.95	<0.001	1,618; 975	0.93 0.86 to 1.01	0.02	616; 387	1.02 0.89 to 1.17	0.69	176; 111	0.85 0.70 to 1.04	0.04
	24-35m	3,675; 2,433	(reference)		1,074; 693	(reference)		362; 220	(reference)		133; 98	(reference)	
	>=36m	3,848; 2,847	1.12 1.08 to 1.16	<0.001	1,914; 1,382	1.12 1.05 to 1.21	<0.001	653; 470	1.19 1.05 to 1.34	<0.001	219; 173	1.08 0.92 to 1.27	0.22

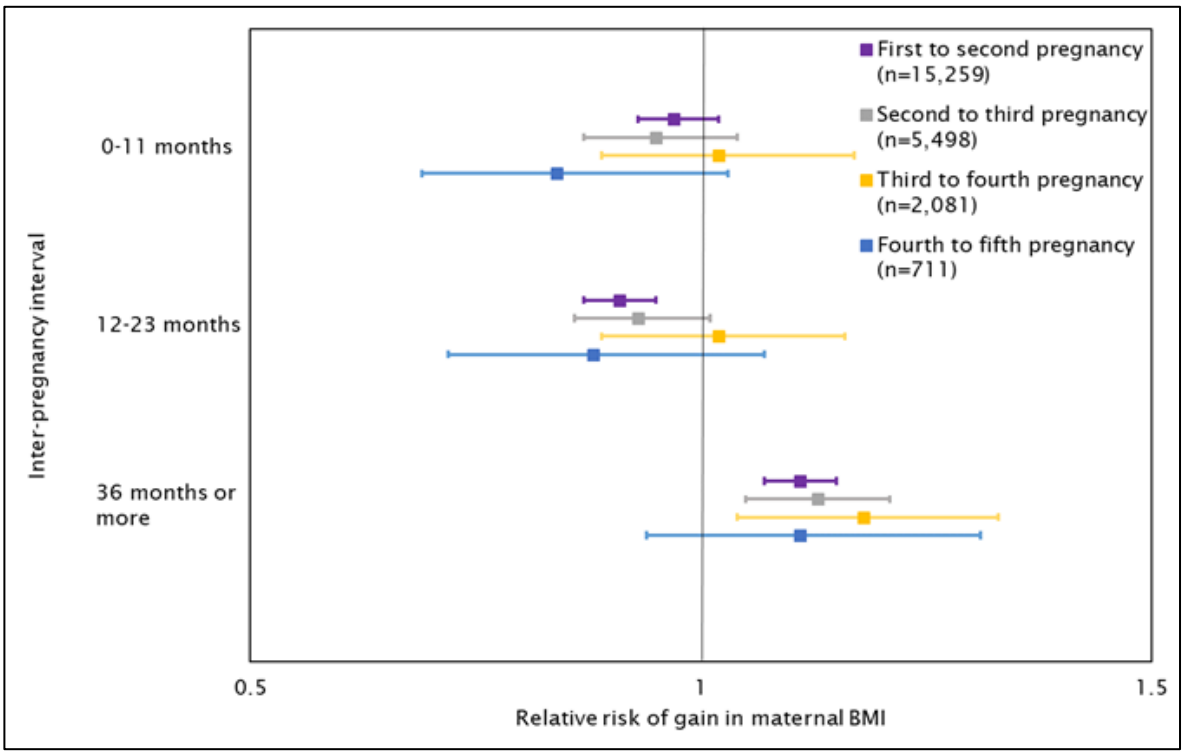
		Gain in maternal BMI: First to second pregnancy			Gain in maternal BMI: Second to third pregnancy			Gain in maternal BMI: Third to fourth pregnancy			Gain in maternal BMI: Fourth to fifth pregnancy		
		Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p
Model 2		15259; 10042			5,498; 3,598			2,081; 1,361			711; 491		
	0-11m	2634; 1722	0.97 0.93 to 1.02	0.15	1,071; 656	0.95 0.87 to 1.04	0.13	511; 321	1.02 0.89 to 1.18	0.79	202; 122	0.85 0.69 to 1.04	0.03
	12-23m	5383; 3234	0.91 0.88 to 0.95	<0.001	1,551; 934	0.93 0.86 to 1.01	0.03	588; 369	1.02 0.89 to 1.17	0.80	170; 108	0.88 0.72 to 1.08	0.12
	24-35m	3521; 2326	(reference)		1,027; 663	(reference)		349; 215	(reference)		125; 91	(reference)	
	>=36m	3721; 2760	1.11 1.06 to 1.15	<0.001	1,849; 1,345	1.14 1.06 to 1.21	<0.001	633; 456	1.18 1.04 to 1.34	0.001	214, 170	1.11 0.94 to 1.31	0.11
Model 3	0-11m	2634; 1722	0.97 0.93 to 1.02	0.14	1,071; 656	0.95 0.87 to 1.04	0.14	511; 321	1.02 0.89 to 1.17	0.70	202; 122	0.84 0.69 to 1.03	0.03
	12-23m	5383; 3234	0.91 0.87 to 0.95	<0.001	1,551; 934	0.93 0.86 to 1.01	0.02	588; 369	1.02 0.89 to 1.16	0.76	170; 108	0.88 0.72 to 1.07	0.09
	24-35m	3521; 2326	(reference)		1,027; 663	(reference)		349; 215	(reference)		125; 91	(reference)	
	>=36m	3721; 2760	1.11 1.07 to 1.15	<0.001	1,849; 1,345	1.13 1.05 to 1.21	<0.001	633; 456	1.18 1.04 to 1.33	0.001	214; 170	1.11 0.94 to 1.31	0.12

		Gain in maternal BMI: First to second pregnancy			Gain in maternal BMI: Second to third pregnancy			Gain in maternal BMI: Third to fourth pregnancy			Gain in maternal BMI: Fourth to fifth pregnancy		
		Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p	Total n; n of cases	Relative risk (RR)* (99% CI)	p
Model 4		4,667; 3,011			1,608; 1,039			617, 382			213, 153		
	0-11m	970, 645	0.99 0.92 to 1.08	0.83	419, 262	0.93 0.81 to 1.07	0.17	198, 119	0.96 0.76 to 1.22	0.68	78, 52	0.78 0.60 to 1.03	0.02
	12-23m	1,948, 1,163	0.91 0.85 to 0.98	0.001	575, 353	0.92 0.81 to 1.04	0.09	217, 133	0.96 0.75 to 1.21	0.62	59, 39	0.80 0.60 to 1.08	0.06
	24-35m	1,152, 757	(reference)		343, 227	(reference)		108, 70	(reference)		41, 33	(reference)	
	>=36m	597, 446	1.12 1.03 to 1.21	0.001	271, 197	1.08 0.95 to 1.24	0.13	94, 60	0.99 0.76 to 1.31	0.96	35, 29	1.00 0.77 to 1.31	0.97

*Generalised linear model with log link and robust variance estimator used to derive RR
Model 1 is adjusted for: timing of first (booking) antenatal appointments (as this is when maternal BMI is measured)
Model 2 is adjusted for: timing of first (booking) antenatal appointments, maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking and employment status
Model 3 is adjusted for: first (booking) antenatal appointment, maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking, employment status and baseline maternal BMI (for the first pregnancy in the dataset)
Model 4 is adjusted for: first (booking) antenatal appointments, maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking, employment status, baseline maternal BMI and breastfeeding or not at hospital discharge

The logistic regression models show that there is a significantly increased risk of starting the next pregnancy with a higher weight compared to the previous one with an interval of 36 months or more (adjusted RR (aRR) 1.11, 99% CI 1.07 to 1.15 for first to second; aRR 1.13, 99% CI 1.05 to 1.21 for second to third; aRR 1.18, 99% CI 1.04 to 1.33 for third to fourth pregnancy) (Table 5.4, Figure 5.5). In contrast, there was a decreased risk of weight gain between pregnancies in those with an interval of 12 to 23 months (aRR 0.91, 99% CI 0.87 to 0.95 for first to second; aRR 0.93, 99% CI 0.86 to 1.01 for second to third; aRR 1.02, 99% CI 0.89 to 1.16 for third to fourth pregnancy). The only exception was in women with five pregnancies where birth spacing was not significantly associated with interpregnancy weight gain in the period between their fourth and fifth pregnancies.

Figure 5.5: Adjusted association between interpregnancy gain in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy and the length of the interpregnancy interval (categorised)*



*The reference category is an interval of 24-35 months

5.4.2 Size at birth

Twelve percent of first pregnancy and 7% of second pregnancy births were SGA (Table 5.5). Seven percent of first pregnancy and 13% of second pregnancy births

were LGA. Three percent of women each had SGA and LGA babies in both pregnancies.

Table 5.5: Birth characteristics by gestational order for period of January 2003 - September 2017, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, England

	First pregnancy	Second pregnancy
Birthweight, grams (mean ± SD)	3357 ± 538	3490 ± 541
Size at birth		
Small-for-gestational age	12.4 (11.9 to 12.9)	7.0 (6.6 to 7.4)
Appropriate-for-gestational age	80.6 (80.0 to 81.3)	79.8 (79.2 to 80.4)
Large-for-gestational age	7.0 (6.6 to 7.4)	13.2 (12.7 to 13.8)

Compared to an interval of 24-35 months, there was a lower risk of SGA birth in second pregnancy with an interval of 12-23 months (aRR 0.83, 95% CI 0.68 to 1.00). The association remained after adjusting for previous outcome of SGA in sensitivity analysis (aRR 0.83, 95% CI 0.69 to 1.00). No association was observed between risk of SGA with intervals of <12 or ≥36 months (Table 5.6).

No association was observed between risk of LGA and interpregnancy interval both in the main and sensitivity analyses (Table 5.6).

5.1 Discussion

This analysis examined the association of change in maternal BMI between pregnancies with birth spacing in 19,362 women. The rate of obesity increased from 13.0% at first pregnancy to 31.6% at fifth pregnancy, with approximately two thirds of the study sample gaining weight by the start of their subsequent pregnancy compared to the start of their previous one. Eighteen percent of second pregnancies were conceived within 12 months of the first, 35% within 12-23 months, 23% within 24-35 months and 24% after 36 months or more (up to 12 years). An interval of 12 to 23 months between the first and second pregnancy was found to confer the lowest risk of weight gain, and hence of starting the next pregnancy with a higher weight. This association remained statistically significant after adjusting for maternal age and starting maternal BMI. This interval of 12-23 months was also associated with lower risk of SGA; however, the duration of the interval was not found to be associated with LGA risk.

Table 5.6: Associations between risk of SGA and LGA birth in the second pregnancy and interpregnancy interval in the full sample

Interpregnancy interval (categorised)		SGA			SGA (sensitivity analysis)*			LGA			LGA (sensitivity analysis)*		
		Total n, cases n	Relative risk, (RR)**	95% CI	Total n; cases n	RR**	95% CI	Total n; cases n	RR**	95% CI	Total n; cases n	RR**	95% CI
Unadjusted n, n of cases		15,922; 1,112			15,897; 1,110			15,922; 2,106			15,897; 2,103		
0-11 months	Unadjusted*	2,787; 220	1.13	0.95 to 1.34	2,781; 220	1.08	0.89 to 1.31	2,787; 353	0.94	0.83 to 1.07	2,781; 352	0.96	0.84 to 1.10
	Adjusted***	2,640; 213	1.09	0.90 to 1.34	2,634; 213	1.01	0.83 to 1.23	2,640; 329	0.97	0.84 to 1.11	2,634; 328	0.94	0.82 to 1.08
12-23 months	Unadjusted*	5,618; 328	**0.83**	**0.71 to 0.98**	5,608; 326	0.89	0.74 to 1.06	5,618; 788	1.04	0.94 to 1.15	5,608; 787	1.04	0.93 to 1.16
	Adjusted***	5,394, 319	**0.83**	**0.68 to 1.00**	5,386; 318	**0.83**	**0.69 to 1.00**	5,394; 750	1.04	0.93 to 1.16	5,386; 749	1.03	0.93 to 1.15
24-35 months	Unadjusted*	3,671; 257	Ref		3,667; 257	Ref		3,671; 495	Ref		3,667; 495	Ref	
	Adjusted***	3,537; 251	Ref		3,533; 251	Ref		3,537; 475	Ref		3,533; 475	Ref	
≥36 months	Unadjusted*	3,846; 307	1.14	0.97 to 1.34	3,841; 307	1.01	0.84 to 1.21	3,846; 470	0.91	0.81 to 1.02	3,841; 469	0.96	0.85 to 1.09
	Adjusted***	3,733; 297	1.04	0.86 to 1.25	3,728; 297	0.92	0.76 to 1.12	3,733; 458	0.90	0.79 to 1.02	3,728; 457	0.89	0.77 to 1.04

*Sensitivity analysis was carried out adjusting for previous outcome of SGA or LGA respectively in both unadjusted and adjusted analyses
**Generalised linear model with log link and robust variance estimator used to derive RR
***Adjusted for: maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking status, employment status, baseline BMI, inter-pregnancy interval and pre-eclampsia (SGA) or gestational diabetes (LGA) in current pregnancy and inter-pregnancy interval and in the sensitivity analysis additionally for outcome of SGA or LGA respectively in the first pregnancy

About 22% of women presented to antenatal care for their subsequent pregnancy in a higher BMI category, compared to 4-6% in a lower BMI category than the previous pregnancy. These findings are comparable to those from a previous study of a longitudinal cohort in Dublin (Crosby *et al.*, 2015). Only two percent of women in a higher BMI category at the start of a subsequent pregnancy were underweight at the previous pregnancy and so had moved up into the healthier category of normal weight. An additional eight percent of women were obese at the start of a subsequent pregnancy with this rising to 10% in higher order (fourth and fifth) pregnancies. This pattern of weight gain was seen across pregnancies and thus we additionally show that this persists through subsequent pregnancies and not just from the first to second.

Relatively small BMI gains (1-2 kg/m^2) increase the risk of perinatal complications in the subsequent pregnancy even if the woman remains normal weight (Villamor and Cnattingius, 2006). In this sample, women changed 1 kg/m^2 between pregnancies on average whereas in the two-thirds that gained weight the average gain was 2 kg/m^2 with some women gaining substantially more. The proportions of overweight and obesity in this sample were higher in subsequent pregnancies compared to the first. It is not possible to attribute weight change between pregnancies purely to pregnancy-related factors but with two-thirds of the women in this cohort gaining weight and under a third losing weight, the likelihood is that pregnancy (including lifestyle change postpartum) plays an influential role in this weight change, particularly given the small percentage (2.5%) whose weight did not change.

To my knowledge, this is the first cohort study investigating the association between birth spacing and maternal weight change between pregnancies. The study sample is based on a relatively large population-based cohort and thus representative of the local population. One city is unlikely to be representative of the general population of the country and according to the UK Department of Communities and Local Government English indices of deprivation report, Southampton is more deprived than average with the situation having worsened between 2010 and 2015 (Department for Communities and Local Government, 2015). However, about half of the women included in this analysis reside in surrounding areas to Southampton in Hampshire, many of which are much less deprived. The sample was 87% White comparable to the 2011 England and Wales population census of 86% White (Office for National Statistics, 2012). The analysis

was adjusted for several key confounders that were reasonably complete (96% complete for ethnicity and employment status).

An important limitation was the lack of information on GWG during pregnancy, which is a key factor influencing post-partum weight. Women who had their first booking appointment later into the pregnancy (more than 24 weeks) were excluded from the analysis in order to ensure comparability of weight measurements between pregnancies. BMI was measured in early pregnancy at the booking appointment at a mean of 11 weeks, however 13-21% of women across the pregnancies were measured between 14 to 24 weeks of pregnancy and thus weight could be slightly overestimated which is why timing of booking appointment was adjusted for in all analyses. Breastfeeding initiation and duration can also influence post-partum weight. No information was available on breastfeeding duration and although breastfeeding initiation (at discharge) was available, this was only recorded in a little over a third of the pregnancies included. Another limitation is that this study is based on observational data so inferences about causation cannot be drawn and the risk of residual confounding influencing the results needs to be considered. However, it is not feasible or ethical to conduct a randomised trial to address the aim of this study. Ageing-related non-pregnancy weight gain was not controlled for as it is not possible to predict if women would have gained weight had they not become pregnant. Additionally, sensitivity analysis showed that a lower proportion of older women in this sample gained weight and changed BMI category by their second pregnancy as compared to younger women. The risk of starting the second pregnancy with a higher weight was slightly higher in older women with an interval of 36 months or more but the risk was also slightly lower with an interval of 12 to 23 months compared to younger women.

To my knowledge, the only guideline on birth spacing is the 2005 WHO technical consultation published in 2007 which recommends waiting at least 24 months after a previous live birth (World Health Organization, 2005). This was based on evidence on maternal, perinatal, infant and child health outcomes from a wide range of countries. However, in light of the rising rates of maternal obesity and its consequences on pregnancy outcomes and maternal and offspring health, updated recommendations on the optimal interpregnancy interval would benefit from incorporating evidence around this such as that generated by this study. A shorter optimal interval is further supported by the findings of a meta-analysis of 62 studies that an interpregnancy interval of 18 to 23 months was associated

with the lowest risk of adverse perinatal outcomes in the offspring with both shorter (<18 months) and longer (>59 months) intervals being associated with increased risk (Conde-Agudelo *et al.*, 2006). The included studies were classified as being carried out in developed (28 cohort and 1 case-control) or developing (24 cohort and 14 case-control) countries.

A qualitative study in Sweden in women who had retained ≥10kg postpartum found that the first year postpartum is a neglected year in women with the focus of care being on the baby with little or no weight loss support. The main areas identified related to weight retention were a lack of knowledge, misconceptions, eating for relief, lack of support and barriers to physical activity including tiredness and competing responsibilities (Christenson *et al.*, 2016). Another study reported that women considered their personal health was not top priority during the early postpartum period and identified childcare, time management and lack of support as barriers to adopting healthier lifestyles (Carter-Edwards *et al.*, 2009). Lifestyle changes were motivated by the child's health in women diagnosed with gestational diabetes during pregnancy with vague understanding and low levels of concern of increased future risk of Type 2 diabetes (Eades *et al.*, 2018). Another study in Sweden also found that a healthier lifestyle adopted during pregnancy and in early parenthood was motivated by supporting a health-promoting environment for the child (Edvardsson *et al.*, 2011) and thus weight retention in the context of the health of future children could be a motivator to promoting weight loss.

Stabilizing interpregnancy weight and promoting weight loss in overweight and obese women before the next pregnancy could be important steps in reducing adverse outcomes in subsequent pregnancies. The use of the six to eight week postnatal check to discuss the women's weight and treatment strategies particularly in overweight and obese women as well as in women that have concerns about their weight is part of the NICE guidelines (National Institute of Health and Care Excellence, 2010). However, only women with a pre-pregnancy BMI of 30kg/m^2 or more are recommended to have a discussion with their health professional about the increased risk of being obese and encouraged to lose weight, particularly that gained during pregnancy. Additionally, the interpregnancy interval is not discussed as there are no UK guidelines on interval and thus advice is based on losing weight gained during pregnancy, preventing women from becoming overweight or obese and weight loss in obese women. The health and wellbeing of the mother needs to be considered with an equal

focus as the health of the baby for any preventive measures during the period between pregnancies. Providing information to women planning to have more children on the potential link between birth spacing and maternal outcomes, including overweight and obesity, which could affect subsequent children, would help them make an informed choice on the desired timing of their next gestation. Although women may not be completely in control of birth spacing, awareness of weight change patterns in the late postpartum period and support to regain pre-pregnancy weight or further weight loss could be conducive to starting their next pregnancy at a healthier weight. More research is needed, considering other short and long-term maternal and offspring outcomes, to investigate the optimal interpregnancy interval in high-income countries.

5.2 Conclusion

Most women do not maintain their weight across pregnancies, with substantially more gaining than losing weight. An interpregnancy interval of 12-23 months was associated with the lowest risk of starting the second pregnancy with a higher body weight as well as a lower risk of SGA birth in the second pregnancy compared with intervals of 24-35 months and 36 months or more. Preventing weight gain and continuing to promote weight loss in overweight and obese women between pregnancies are important preventive measures of subsequent adverse maternal and offspring health outcomes. Further research investigating optimal birth spacing in relation to important public health risk factors such as maternal and childhood obesity is needed. Also, the potential advantages of shorter optimal interval between pregnancies than that recommended by WHO should be considered in high-income countries.

Chapter 6 Maternal interpregnancy weight change and size at birth

This chapter examines the association between maternal interpregnancy weight and size at birth categorised as SGA and LGA. The first step was to examine the association between the risk of SGA or LGA and interpregnancy weight change followed by stratification by maternal baseline (first pregnancy) BMI category.

Part of this work has been published as a peer reviewed paper in the journal BMJ Open and presented at two conferences (Lancet Public Health Science 2018 and Wessex Public Health Conference 2018).

6.1 Background

The analysis on interpregnancy weight change reported in Chapter 5 showed that the majority of women gain weight between pregnancies. This change in maternal BMI between pregnancies could modify risk in the subsequent pregnancy.

The incidence of large-for-gestational age (LGA) birth, defined as >90th percentile weight for gestational age, has increased over time in high-income countries (Kramer *et al.*, 2002; Surkan *et al.*, 2004). A key risk factor for LGA birth is gestational diabetes mellitus (Casey et al., 1997), the incidence of which has also increased over time (Hunt and Schuller, 2007; Ignell et al., 2014). Offspring of mothers with gestational diabetes have increased risk of childhood overweight and obesity (Baptiste-Roberts *et al.*, 2012; Zhu *et al.*, 2016). Maternal obesity is an established risk factor for both GDM and LGA birth (Marchi *et al.*, 2015). Change in maternal body mass index (BMI) between pregnancies could modify the risk of LGA birth in the subsequent pregnancy. Increased birthweight is associated with increased risk of childhood overweight and obesity (Weng *et al.*, 2012).

Birthweight, on average, increases with parity. Women who returned to their pre-pregnancy weight before the next conception had subsequent born infants who weighed less than infants of women who retained or gained weight between pregnancies (Hinkle *et al.*, 2014). Also, maternal weight change between pregnancies was found to modify the relationship between parity and birthweight. In a UK-based study, women who lost at least six kilograms between their first and second pregnancy had a smaller average increase in birthweight of the second baby compared to women who gained ten kilograms or more (in a 1.60m tall woman, 6 kg equates to approximately 2.3 kg/m^2 and 10 kg to approximately 3.8 kg/m^2) (Wilcox *et al.*, 1996). However, between-pregnancy decrease in BMI was associated with increased risk of SGA in the second pregnancy in a population-based case control study (Cheng *et al.*, 2004).

In a population-based cohort in the USA, women were found to be at an increased risk of LGA in the second pregnancy if pre-pregnancy BMI category increased towards overweight or obese between their first and second pregnancies. This applied to all first pregnancy BMI categories, except underweight women who became normal weight by the start of their second pregnancy. Overweight and obese women who dropped BMI category by their second pregnancy remained at

an increased risk of LGA birth, but had a lower risk compared to women whose BMI category increased between pregnancies (Getahun *et al.*, 2007).

Analysis of interpregnancy weight change between first and second pregnancies in 12,740 women in Aberdeen, Scotland found an increased risk of SGA and decreased risk of LGA with between pregnancy weight loss of >1 BMI unit and an increased risk of LGA with modest (1-3 BMI units) and large (≥3 BMI units) weight gain. The effect remained in both categories on stratification by BMI (< or ≥25) (Wallace *et al.*, 2014). In a population-based cohort of 151,080 women in Sweden, 5943 women had an LGA birth in the second pregnancy after excluding 2,847 women who had an LGA birth in the first pregnancy. The risk of LGA in second pregnancy showed an increase with weight gain of 1-2 BMI units and progressive increase in risk with increase in BMI. The association between weight change and outcome of LGA in the second pregnancy was stronger in women with a healthy first pregnancy BMI (<25kg/m^2) (Villamor and Cnattingius, 2006). In 10,444 obese women in the USA, interpregnancy weight gain of 2 or more BMI units was associated with increased risk of LGA and a weight loss of 2 or more BMI units was associated with decreased risk compared to the reference group of weight maintained between 2 BMI units. The analysis was adjusted for LGA birth in previous pregnancy in addition to other confounders. Association between interpregnancy weight change and SGA risk in this sample of obese women was only found with weight loss of ≥8 kg/m^2 which was found to be associated with increased risk of SGA (Jain *et al.*, 2013).

To my knowledge, only one study has examined the risk of recurrent SGA and LGA (occurring in both first and second pregnancies) in relation to maternal weight change between pregnancies (Wallace *et al.*, 2016). The study, conducted in Aberdeen, Scotland, included 24,520 women of which 706 women had SGA births and 813 women had LGA births in both pregnancies. Inter-pregnancy weight loss (≥2 kg/m^2) was associated with increased risk of recurrent SGA, while weight gain (≥2 kg/m^2) was protective in women with BMI <25kg/m^2 at first pregnancy. Inter-pregnancy weight gain (≥2 kg/m^2) was associated with increased risk of recurrent LGA, while weight loss (≥2 kg/m^2) was protective. Women with BMI <25kg/m^2 were at increased risk of recurrent LGA on gaining weight whereas women with BMI ≥25kg/m^2 were at reduced risk of recurrent LGA on losing weight (Wallace *et al.*, 2016).

6.2 Aim

- To investigate the association between the incidence of SGA, recurrent SGA and 'new' SGA births in the second pregnancy and maternal change in BMI between the first and second pregnancies, stratifying by maternal BMI category in the first pregnancy
- To investigate the association between the incidence of LGA, recurrent LGA and 'new' LGA births in the second pregnancy and maternal change in BMI between the first and second pregnancies, stratifying by maternal BMI category in the first pregnancy

6.3 Methods

This analysis utilises the antenatal care and birth outcomes dataset outlined in section 4.1.1 and used in Chapter 5. As with the size at birth analysis in Chapter 5, only records of women with their first two consecutive singleton pregnancies were included.

6.3.1 Exposure assessment

Maternal weight was measured at the booking appointment and height was self-reported. Any woman who had a booking appointment at or after 24 weeks of pregnancy was excluded. BMI was calculated as weight (in kg) divided by height (in metres) squared.

Baseline BMI was defined as the BMI at the first pregnancy. Change in BMI was calculated as the difference in BMI at booking appointment of the first two consecutive live birth pregnancies. Change in BMI was categorised as weight loss (≥1 kg/m^2), weight stable (>-1 to <1 kg/m^2) and two categories of weight gain (1-3 kg/m^2 and ≥3 kg/m^2). These categories were chosen based on other studies which have used similar categories to facilitate comparison. There is no consensus in the literature as to appropriate categories for this type of analysis. Some studies have used change in BMI categories (Getahun *et al.*, 2007) whilst others have used change in BMI value split into various categories ranging from 1 kg/m^2 to ≥3 kg/m^2 (Villamor and Cnattingius, 2006; Wallace *et al.*, 2014; Wallace *et al.*, 2016). It was felt that these categories would be discriminating enough to differentiate between those who gained or lost a relatively small amount of weight and those who were stable or experienced large changes in weight, while allowing the study to maintain power in the analyses.

6.3.2 Outcome assessment

Birthweight (grams) is measured and recorded at delivery by healthcare professionals for every birth. Gestational age was based on a dating ultrasound scan which routinely takes place between 10 and 13 weeks gestation (National Institute for Health Care and Excellence, 2008a). SGA was defined as <10th percentile weight and LGA was defined as >90th percentile weight for gestational age (Norris *et al.*, 2017). This was only defined for babies born between 24 to 42 weeks gestation as reference values only exist for these gestational ages and with determinate gender.

6.3.3 Covariables

Covariables for this analysis were the same as those reported for the previous analysis in section 5.3.3 on page 88 with the exception of breastfeeding at discharge. The only additional covariable in this analysis was inter-pregnancy interval which was the exposure in the previous analysis described in section 5.3.1 on page 86.

6.3.4 Statistical analysis

Univariable comparisons were carried out using ANOVA for continuous variables and chi square test for categorical variables. Generalised linear regression with log link (Cummings, 2009) was used to examine the association between the categorised variable of maternal change in BMI between pregnancies with risk of SGA and LGA separately in the second pregnancy. This was analysed first in the whole sample and then stratified by 'baseline' maternal BMI category as calculated in the first antenatal appointment of the first pregnancy.

Risk of SGA and LGA in the second pregnancy was explored in the whole sample adjusting for previous pregnancy outcome of SGA and LGA respectively. The risk of 'new' SGA/LGA in second pregnancy after having a non-SGA/LGA baby in the first pregnancy was explored in the sub-sample of women who had non-SGA/LGA births respectively in the first pregnancy. The risk of recurrent SGA/LGA (SGA/LGA in both pregnancies) was explored in a sub-sample of women who had SGA/LGA births in the first pregnancy.

Initial univariable analysis was followed by multivariable models adjusting for potential confounding factors – maternal age, ethnicity, highest educational attainment, whether or not undergone infertility treatment, employment status,

smoking behaviour in second pregnancy, baseline BMI, pre-eclampsia (SGA) or GDM (LGA) in second pregnancy and inter-pregnancy interval. Sensitivity analysis was conducted adding gestational age at booking in the second pregnancy to the models.

A statistical significance level of 0.05 with 95% confidence intervals was used in the regression models.

6.4 Results

The first and second pregnancies of 15,940 women were included. Of these, size at birth could be defined at first pregnancy in 15,914 women and at second pregnancy in 15,922 women who had delivered between 24 and 42 weeks gestation.

Figure 6.1 shows the percentage of women in each BMI category in the first and second pregnancy and the weight gain over time. There has been a decline in normal weight women at first pregnancy and a slight increase in overweight and obese women over time. There also was a slight decline in the percentage of women gaining ≥3 kg/m^2 and a slight increase in those gaining 1–3 kg/m^2.

Figure 6.1: The percentage of women in each body mass index (BMI) category in the first and second pregnancy and weight gain over time in the cohort (2003-2017)

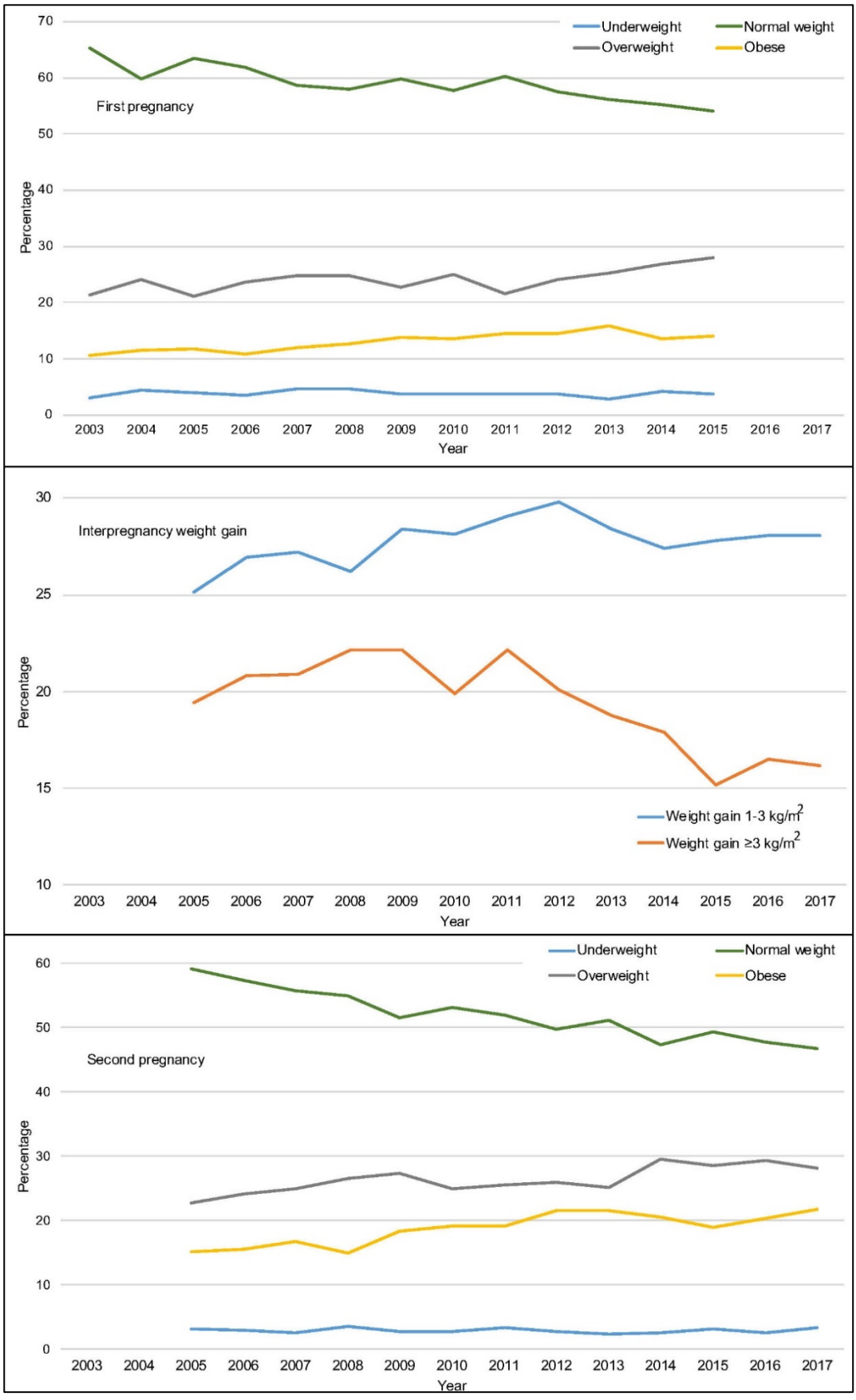


Table 6.1: Maternal and birth characteristics in second live birth pregnancy categorised by weight loss/no change and weight gain from previous pregnancy for the period of January 2003 - September 2017, University Hospital Southampton NHS Foundation Trust

	Lost ≥1 kg/m² from previous pregnancy	Weight stable (>-1 to <1 kg/m²)	Gained 1-3 kg/m² from previous pregnancy	Gained ≥3 kg/m² from previous pregnancy	p*
N	2,548	5,785	4,446	3,161	
Maternal age, years (mean ± SD)	28.7 ± 5.4	29.8 ± 5.3	29.2 ± 5.4	27.3 ± 5.5	<0.001
Timing of first booking appointment, weeks (mean ± SD)	10.8 ± 2.3	11.0 ± 2.3	11.1 ± 2.4	11.0 ± 2.6	<0.001
Maternal BMI at booking, kg/m2 (mean ± SD)	24.1 ± 5.1	23.8 ± 4.4	25.9 ± 4.7	30.8 ± 5.9	<0.001
Maternal BMI at booking in first pregnancy (%, 95% CI)					
Underweight (< 18.5)	0.8 (0.5 to 1.2)	4.3 (3.8 to 4.8)	5.3 (4.7 to 6.0)	3.7 (3.1 to 4.4)	<0.001
Normal weight (18.5 to 24.9)	47.6 (45.6 to 49.5)	67.4 (66.2 to 68.6)	62.5 (61.0 to 63.9)	49.0 (47.2 to 50.7)	
Overweight (25.0 to 29.9)	30.1 (28.3 to 31.9)	19.4 (18.4 to 20.5)	22.0 (20.8 to 23.3)	29.5 (28.0 to 31.2)	
Obese (≥30.0)	21.5 (19.9 to 23.2)	8.9 (8.2 to 9.7)	10.2 (9.3 to 11.1)	17.8 (16.5 to 19.2)	
Maternal BMI at booking in second pregnancy (%, 95% CI)					
Underweight (< 18.5)	6.9 (5.9 to 7.9)	4.3 (3.8 to 4.8)	0.6 (0.4 to 0.9)	0.0 (0.0 to 0.2)	<0.001
Normal weight (18.5 to 24.9)	61.1 (59.2 to 63.0)	66.8 (65.6 to 68.1)	50.7 (49.2 to 52.1)	14.9 (13.7 to 16.2)	
Overweight (25.0 to 29.9)	20.1 (18.6 to 21.7)	19.7 (18.7 to 20.7)	32.6 (31.2 to 34.0)	36.7 (35.0 to 38.4)	
Obese (≥30.0)	11.9 (10.7 to 13.3)	9.2 (8.5 to 10.0)	16.1 (15.0 to 17.2)	48.3 (46.6 to 50.1)	
Maternal education (%, 95% CI)					
Secondary (GCSE) or under	30.7 (28.9 to 32.5)	24.0 (22.9 to 25.2)	29.4 (28.1 to 30.8)	36.3 (34.6 to 38.0)	<0.001
College (A levels)	40.4 (38.5 to 42.3)	38.8 (37.6 to 40.1)	39.5 (38.1 to 41.0)	45.8 (44.0 to 47.5)	
University degree or above	28.9 (27.2 to 30.7)	37.1 (35.9 to 38.4)	31.1 (29.7 to 32.5)	17.9 (16.6 to 19.3)	

	Lost ≥1 kg/m² from previous pregnancy	Weight stable (>-1 to <1 kg/m²)	Gained 1-3 kg/m² from previous pregnancy	Gained ≥3 kg/m² from previous pregnancy	p*
Maternal smoking status at booking (%, 95% CI)					
Never smoked/quit	57.2 (55.3 to 59.2)	63.0 (61.8 to 64.3)	60.5 (59.0 to 62.0)	50.7 (48.9 to 52.4)	<0.001
Stopped >1 year before conceiving	16.1 (14.6 to 17.5)	17.2 (16.3 to 18.2)	17.7 (16.5 to 18.8)	14.9 (13.7 to 16.2)	
Stopped <1 year prior to conceiving	4.0 (3.3 to 4.8)	2.8 (2.4 to 3.2)	3.5 (3.0 to 4.1)	4.9 (4.2 to 5.7)	
Stopped when pregnancy confirmed	6.8 (5.8 to 7.8)	5.9 (5.3 to 6.6)	6.9 (6.2 to 7.7)	10.3 (9.3 to 11.4)	
Continued smoking	15.9 (14.5 to 17.4)	11.0 (10.2 to 11.8)	11.4 (10.5 to 12.4)	19.1 (17.8 to 20.6)	
Maternal employment (%, 95% CI)					
Employed	66.2 (64.3 to 68.0)	71.7 (70.5 to 72.9)	67.2 (65.8 to 68.5)	56.5 (54.8 to 58.2)	<0.001
Unemployed	31.8 (30.0 to 33.7)	26.9 (25.8 to 28.1)	31.1 (29.7 to 32.5)	41.6 (39.8 to 43.3)	
In education	0.9 (0.6 to 1.4)	0.8 (0.6 to 1.1)	1.1 (0.8 to 1.4)	1.3 (0.9 to 1.8)	
Not specified	1.0 (0.7 to 1.5)	0.6 (0.4 to 0.8)	0.7 (0.5 to 1.0)	0.6 (0.4 to 1.0)	
Ethnicity (%, 95% CI)					
White	89.9 (88.7 to 91.1)	88.0 (87.1 to 88.8)	85.1 (84.0 to 86.1)	84.8 (83.5 to 86.1)	<0.001
Mixed	0.8 (0.5 to 1.3)	0.9 (0.7 to 1.2)	1.4 (1.1 to 1.8)	1.6 (1.1 to 2.0)	
Asian	4.8 (4.0 to 5.7)	5.6 (5.0 to 6.0)	7.2 (6.5 to 8.0)	7.7 (6.8 to 8.7)	
Black/African/Caribbean	0.6 (0.4 to 1.0)	1.0 (0.8 to 1.3)	1.6 (1.3 to 2.1)	2.4 (1.9 to 3.0)	
Other	0.7 (0.4 to 1.1)	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.4)	1.3 (0.9 to 1.7)	
Not specified	3.1 (2.5 to 3.9)	3.5 (3.0 to 4.0)	3.6 (3.1 to 4.2)	2.2 (1.8 to 2.8)	
Interpregnancy interval (median, IQR)	21.7 (14.4 to 32.7)	21.6 (14.1 to 32.0)	23.7 (14.4 to 35.6)	27.7 (16.0 to 45.6)	<0.001
Interpregnancy interval (%, 95% CI)					
0-11 months	17.4 (15.9 to 18.9)	17.6 (16.6 to 18.6)	18.1 (17.0 to 19.3)	16.6 (15.4 to 17.9)	<0.001
12-23 months	39.8 (37.8 to 41.7)	39.9 (38.6 to 41.1)	33.1 (31.7 to 34.5)	26.3 (24.8 to 27.9)	
24-35 months	22.6 (21.0 to 24.2)	23.6 (22.5 to 24.7)	24.4 (23.2 to 25.7)	20.5 (19.1 to 21.9)	
36 months or more	20.3 (18.7 to 21.9)	18.9 (17.9 to 20.0)	24.3 (23.1 to 25.6)	36.5 (34.9 to 38.2)	

	Lost ≥1 kg/m² from previous pregnancy	Weight stable (>-1 to <1 kg/m²)	Gained 1-3 kg/m² from previous pregnancy	Gained ≥3 kg/m² from previous pregnancy	p*
Birthweight, grams (mean ± SD)	3463 ± 563	3467 ± 523	3507 ± 536	3531 ± 558	
Previous size at birth (first pregnancy)					
Small-for-gestational age	13.1 (11.8 to 14.4)	12.6 (11.8 to 13.5)	11.7 (10.8 to 12.7)	12.4 (11.3 to 13.6)	0.11
Appropriate-for-gestational age	79.6 (77.9 to 81.1)	81.1 (80.0 to 82.1)	81.2 (80.1 to 82.4)	79.9 (78.4 to 81.3)	
Large-for-gestational age	7.4 (6.4 to 8.5)	6.3 (5.7 to 7.0)	7.1 (6.3 to 7.8)	7.7 (6.8 to 8.7)	
Size at birth (second pregnancy)					
Small-for-gestational age	8.7 (7.6 to 9.8)	7.0 (6.4 to 7.7)	6.2 (5.5 to 6.9)	6.7 (5.9 to 7.6)	<0.001
Appropriate-for-gestational age	79.0 (77.3 to 80.5)	81.1 (80.0 to 82.1)	80.3 (79.1 to 81.5)	77.4 (75.9 to 78.9)	
Large-for-gestational age	12.4 (11.1 to 13.7)	11.9 (11.1 to 12.8)	13.5 (12.5 to 14.5)	15.9 (14.6 to 17.2)	

*p values calculated using ANOVA for continuous and chi square test for categorical variables

Between the first and second live birth pregnancies, sixteen percent of women lost ≥1 kg/m^2, 36.3% remained weight stable (-1 to 1 kg/m^2), 27.9% gained 1-3 kg/m^2 and 19.8% gained ≥3 kg/m^2 between their first and second live birth pregnancies. Weight loss of >2 kg/m^2 was observed in 7.3% of women whereas 30.5% gained >2 kg/m^2. Mean BMI at second pregnancy booking was 30.8 kg/m^2 (standard deviation (SD) 5.9) in women who gained ≥3 kg/m^2, 25.9 kg/m^2 (SD 4.7) in women who gained 1-3kg/m^2 , 24.1 kg/m^2 (SD 5.1) in women who lost weight, and 23.8 kg/m^2 (SD 4.4) in women whose weight remained stable between pregnancies (p<0.001) (Table 6.1).

Women who gained ≥3 kg/m^2 by the start of their second pregnancy were more likely to be smokers, unemployed, with lower educational attainment and to have a longer inter-pregnancy interval, compared to those who maintained a stable weight between pregnancies. Mean maternal age was lowest in the women who gained ≥3 kg/m^2 (27.3 years, SD 5.5) and highest in the women who remained weight stable (29.8 years, SD 5.3). Mean maternal age in women who lost weight was 28.7 years (SD 5.4). Mothers who gained ≥3 kg/m^2 were more likely to be obese (48.3%) at the start of the second pregnancy compared to 16.1% in women who gained 1-3 kg/m^2, 9.2% in women who remained weight stable and 11.9% in women who lost ≥1 kg/m^2.

6.4.1 SGA

The percentage of SGA births were higher in first pregnancy in all BMI categories (Figure 6.2). A higher proportion of babies born to women who lost weight (8.7%) between pregnancies were SGA compared with 7.0% in women who remained weight stable, 6.2% in women who gained 1–3 kg/m^2 and 6.7% in women who gained ≥3 kg/m^2 (p<0.001) (Table 6.1, Figure 6.3). The proportion of SGA births decreased with increasing first pregnancy maternal BMI and interpregnancy change in maternal BMI so the highest proportion of SGA was in underweight women who lost weight (28.6%) and the lowest was in obese women who lost weight (5.1%). Recurrent SGA was highest in underweight women who lost weight.

The logistic regression models in the full sample show that there was a significantly increased risk of SGA birth in the second pregnancy in women who lost ≥1 BMI kg/m^2 (aRR 1.23, 95% CI 1.06 to 1.45) compared to the reference group of women who remained weight stable (Figure 6.3).

Figure 6.2: The percentage of small-for-gestational age (SGA) births in first and second pregnancy by maternal body mass index category

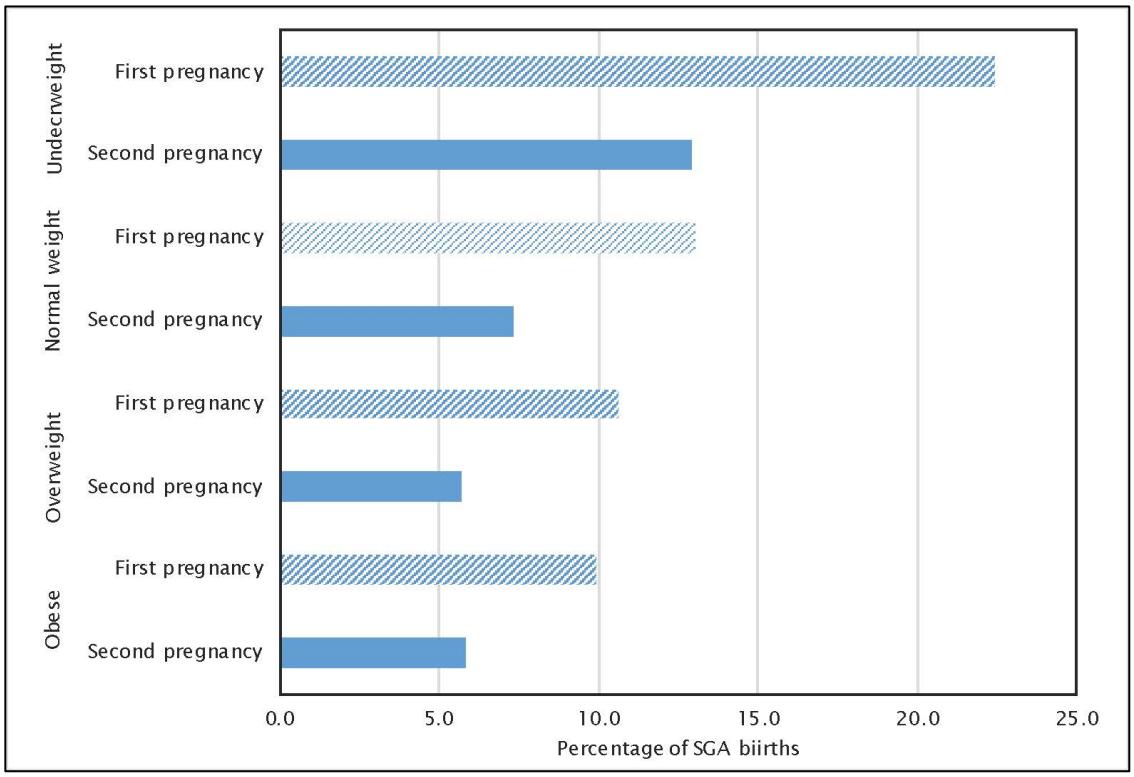
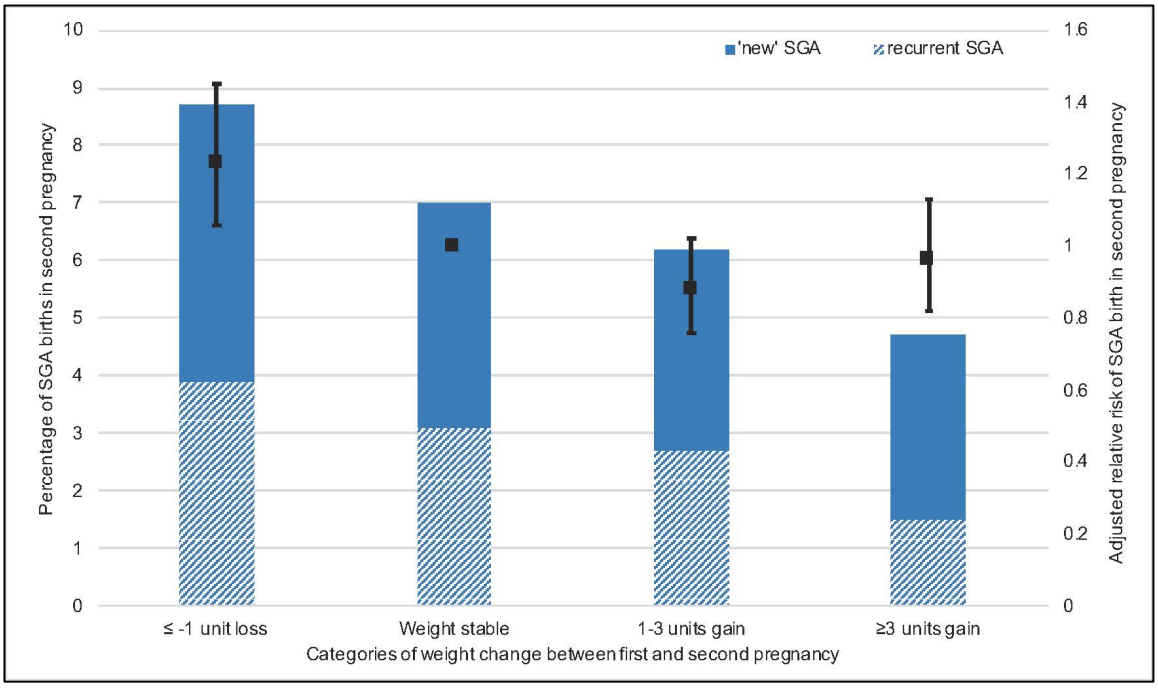


Figure 6.3: The percentage and risk* of small-for-gestational age (SGA) births in second pregnancy stratified by maternal interpregnancy weight change categories



*Relative risk adjusted for maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking status, employment status, baseline BMI, pre-eclampsia in current pregnancy and inter-pregnancy interval

Table 6.2: Associations between risk of recurrent small-for-gestational age (SGA) birth in the second pregnancy and change in maternal body mass index (BMI) between pregnancies as measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Underweight			Normal weight			Overweight			Obese		
		Total n; n of cases	Relative risk, (RR)*	95% CI	Total n; n of cases	Relative risk, (RR)*	95% CI	Total n; n of cases	Relative risk, (RR)*	95% CI	Total n; n of cases	Relative risk, (RR)*	95% CI	Total n; n of cases	Relative risk, (RR)*	95% CI
Unadjusted n, n of cases		1,969; 468			138; 41			1,222; 303			403; 87			206; 37		
Lost ≥1 kg/m² from previous pregnancy	Unadjusted	331; 98	1.18	0.96 to 1.46	7; 4	1.85	0.87 to 3.94	169; 56	**1.30**	**1.00 to 1.69**	94; 27	1.22	0.76 to 1.95	61; 11	1.06	0.48 to 2.37
	Adjusted**	323; 96	1.19	0.96 to 1.47	7; 4	**2.49**	**1.43 to 4.36**	164; 54	1.14	0.86 to 1.49	92; 27	1.04	0.57 to 1.92	60; 11	1.26	0.41 to 3.97
Weight stable (>-1 to <1 kg/m²)	Unadjusted	728; 182	Ref		55; 17	Ref		514; 131	Ref		106; 25	Ref		53; 9	Ref	
	Adjusted**	699; 176	Ref		53; 17	Ref		494; 126	Ref		100; 24	Ref		52; 9	Ref	
Gained 1-3 kg/m² from previous pregnancy	Unadjusted	520; 120	0.92	0.75 to 1.13	51; 15	0.95	0.53 to 1.70	323; 76	0.92	0.72 to 1.18	103; 21	0.86	0.52 to 1.44	43; 8	1.10	0.46 to 2.60
	Adjusted**	502; 118	0.89	0.72 to 1.09	50; 15	1.07	0.49 to 2.33	310; 74	0.88	0.68 to 1.14	100; 21	0.83	0.42 to 1.61	42; 8	1.54	0.40 to 5.92
Gained ≥3 kg/m² from previous pregnancy	Unadjusted	390; 68	**0.70**	**0.54 to 0.90**	25; 5	0.65	0.27 to 1.56	216; 40	**0.73**	**0.53 to 1.00**	100; 14	0.59	0.33 to 1.08	49; 9	1.08	0.47 to 2.51
	Adjusted**	376; 67	**0.58**	**0.43 to 0.77**	22; 5	0.54	0.25 to 1.14	210; 39	**0.59**	**0.41 to 0.85**	96; 14	0.50	0.24 to 1.02	48; 9	1.23	0.42 to 3.62

**Adjusted for: maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking status, employment status, baseline BMI, pre-eclampsia in current pregnancy and inter-pregnancy interval

Table 6.3: Associations between the risk of 'new' small-for-gestational age (SGA) birth in the second pregnancy following a non-SGA birth in the first pregnancy and change in maternal body mass index (BMI) between pregnancies measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Underweight			Normal weight			Overweight			Obese		
		N; n of cases	RR*	95% CI	N; n of cases	RR*	95% CI	n; n of cases	RR*	95% CI	n; n of cases	RR*	95% CI	n; n of cases	RR*	95% CI
Unadjusted n, n of cases		13,928; 642			482; 39			8,187; 391			3,393; 128			1,866; 84		
Lost ≥1 kg/m² from previous pregnancy	Unadjusted	2208; 121	**1.24**	**1.00 to 1.54**	14; 2	-	-	1,039; 75	**1.72**	**1.31 to 2.25**	670; 27	1.11	0.68 to 1.80	485; 17	0.62	0.34 to 1.13
	Adjusted**	2,113; 116	**1.34**	**1.00 to 1.80**	14; 2	-	-	988; 72	**1.71**	**1.19 to 2.46**	639; 25	1.14	0.41 to 3.21	472; 17	0.79	0.16 to 3.94
Weight stable (>-1 to <1 kg/m²)	Unadjusted	5,048; 223	Ref		193; 18	Ref		3,378; 142	Ref		1,016; 37	Ref		461; 26	Ref	
	Adjusted**	4,845; 216	Ref		184; 18	Ref		3,229; 137	Ref		982; 35	Ref		450; 26	Ref	
Gained 1-3 kg/m² from previous pregnancy	Unadjusted	3,915; 154	0.89	0.73 to 1.09	185; 8	0.46	0.21 to 1.04	2,445; 101	0.98	0.77 to 1.26	875; 25	0.78	0.48 to 1.29	410; 20	0.86	0.49 to 1.53
	Adjusted**	3,743; 148	0.87	0.68 to 1.12	178; 8	0.12	0.00 to 3.64	2,343; 95	0.92	0.67 to 1.25	825; 25	0.79	0.25 to 2.50	397; 20	0.75	0.21 to 2.70
Gained ≥3 kg/m² from previous pregnancy	Unadjusted	2,757; 144	1.18	0.96 to 1.45	90; 11	1.31	0.65 to 2.66	1,325; 73	**1.31**	**1.00 to 1.73**	832; 39	1.29	0.83 to 2.00	510; 21	0.73	0.42 to 1.28
	Adjusted**	2,680; 142	0.97	0.73 to 1.28	86; 10	0.29	0.04 to 1.88	1,275; 72	0.94	0.66 to 1.36	816; 39	1.03	0.43 to 2.44	503; 21	0.59	0.33 to 1.06

**Adjusted for: maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking status, employment status, baseline BMI, pre-eclampsia in current pregnancy and inter-pregnancy interval

There was a significantly reduced risk of recurrent SGA birth in the second pregnancy in normal weight women who had a SGA infant in the first pregnancy and gained ≥3 kg/m^2 in weight (aRR 0.59, 95% CI 0.41 to 0.86) (Table 6.2). Underweight women who lost weight were at increased risk of recurrent SGA (aRR 2.49, 95% CI 1.43 to 4.36) but the sample size in this subgroup was very small. No association was observed between risk of recurrent SGA and maternal BMI change between pregnancies in overweight and obese women.
There was an increased risk of 'new' SGA birth in the second pregnancy after having a non-SGA infant in the first pregnancy in normal weight women who lost ≥1 kg/m^2 (aRR 1.71, 95% CI 1.19 to 2.46) (Table 6.3). No association was observed between the risk of 'new' SGA in the second pregnancy and maternal BMI interpregnancy change in obese women.

6.4.2 LGA

The proportion of LGA births was higher in all BMI categories in the second pregnancy (Figure 6.4). A lower proportion of babies born to women who lost weight (12.4%) or remained weight stable (11.9%) between pregnancies were LGA compared with 13.5% in women who gained 1–3 kg/m^2 and 15.9% in women who gained ≥3 kg/m^2 (p<0.001) (Table 6.1, Figure 6.5). Compared with normal weight women, overweight and obese women were at increased risk of LGA births in both pregnancies with risk highest in obese women (unadjusted RR 2.06, 95% CI 1.78 to 2.38 and 1.86, 95% CI 1.69 to 2.05 in first and second pregnancy, respectively). The lowest proportion of LGA births in the second pregnancy was in underweight women in the first pregnancy who remained weight stable (2.8%), while the highest was in obese women who gained ≥3 kg/m^2 (21.2%). Within BMI categories, recurrent LGA was lowest in normal weight and overweight women who lost weight and highest in obese women who gained 1–3 kg/m^2.

Women who gained ≥3 kg/m^2 were at increased risk of LGA in the second pregnancy in the full sample compared with remaining weight stable (aRR 1.28, 95% CI 1.14 to 1.44) (Figure 6.5).

Figure 6.4: The percentage of large-for-gestational age (LGA) births in first and second pregnancy by maternal body mass index category

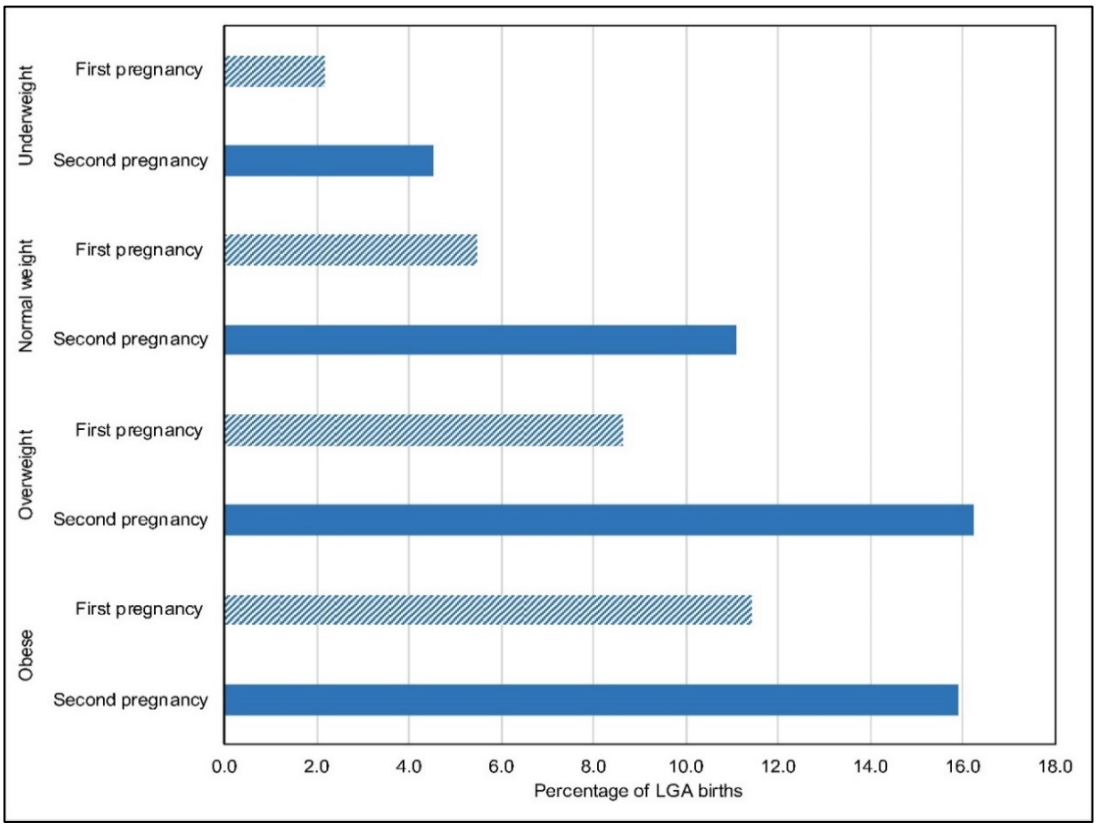
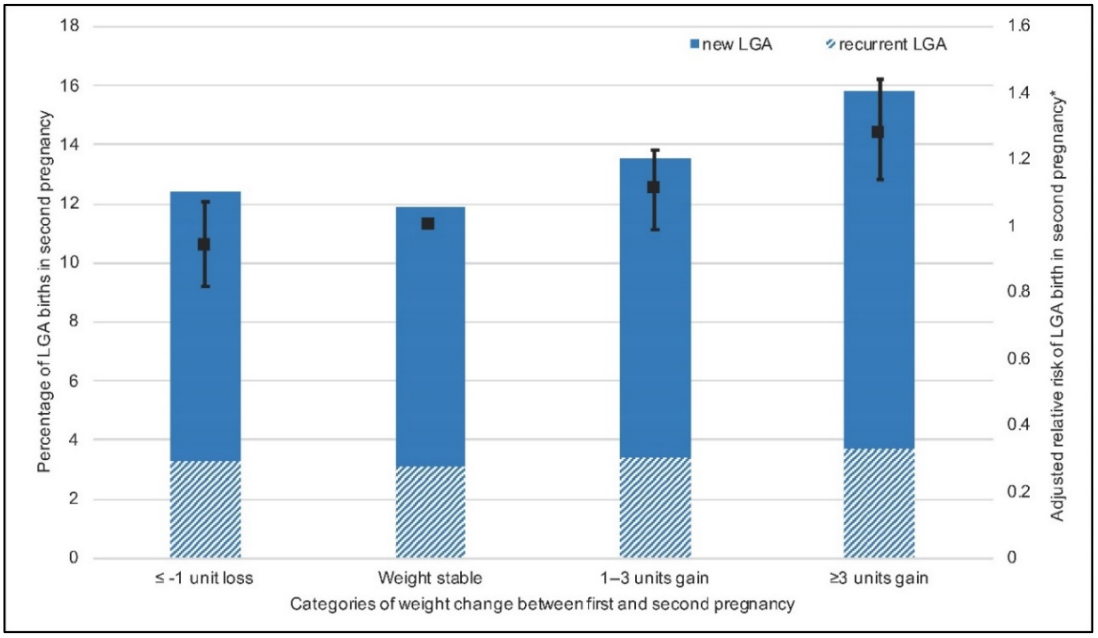


Figure 6.5: The percentage and risk* of large-for-gestational age (LGA) births in second pregnancy stratified by maternal interpregnancy weight change categories



*Relative risk adjusted for maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and interpregnancy interval. BMI, body mass index.

Table 6.4: Associations between risk of recurrent large-for-gestational age (LGA) birth in the second pregnancy and change in maternal body mass index (BMI) between pregnancies as measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		Total n; n of cases	Relative risk, (RR)*	95% CI	Total n; n of cases	RR*	95% CI	Total n; n of cases	RR*	95% CI	Total n; n of cases	RR*	95% CI
Total unadjusted n, n of cases		1,109; 530			521; 234			338; 170			236; 122		
Lost ≤ -1 kg/m^2 from previous pregnancy	Unadjusted	188; 83	0.89	0.74 to 1.08	45; 17	0.80	0.54 to 1.20	74; 30	**0.68**	**0.50 to 0.94**	69; 36	1.16	0.79 to 1.69
	Adjusted**	178; 78	0.88	0.72 to 1.07	44; 16	0.79	0.54 to 1.17	68; 27	**0.69**	**0.48 to 0.97**	66; 35	1.21	0.79 to 1.83
Weight stable (>-1 to <1 kg/m^2)	Unadjusted	365; 181	Ref		212; 100	Ref		98; 58	Ref		51; 23	Ref	
	Adjusted**	353; 176	Ref		204; 96	Ref		97; 57	Ref		49; 23	Ref	
Gained 1-3 kg/m^2 from previous pregnancy	Unadjusted	313; 150	0.97	0.83 to 1.13	162; 74	0.97	0.78 to 1.21	90; 43	0.81	0.62 to 1.06	55; 31	1.25	0.85 to 1.83
	Adjusted**	301; 142	0.98	0.84 to 1.15	156; 70	1.02	0.83 to 1.27	86; 40	0.81	0.61 to 1.08	53; 30	1.28	0.86 to 1.91
Gained ≥3 kg/m^2 from previous pregnancy	Unadjusted	243; 116	0.96	0.81 to 1.14	102; 43	0.89	0.68 to 1.17	76; 39	0.87	0.66 to 1.14	61; 32	1.16	0.79 to 1.71
	Adjusted**	234; 111	1.00	0.83 to 1.20	96; 39	0.91	0.68 to 1.21	73; 38	0.91	0.67 to 1.25	61; 32	1.28	0.84 to 1.94

*Generalised linear model with log link and robust variance estimator used to derive RR

**Adjusted for: maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

Table 6.5: Associations between the risk of 'new' large-for-gestational age (LGA) birth in the second pregnancy following a non-LGA birth in the first pregnancy and change in maternal body mass index (BMI) between pregnancies measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Underweight			Normal weight			Overweight			Obese		
		n; n of cases	RR*	95% CI	n; n of cases	RR*	95% CI	n; n of cases	RR*	95% CI	n; n of cases	RR*	95% CI	n; n of cases	RR*	95% CI
Unadjusted n, n of cases		14,788; 1,573			606; 24			8,888; 812			3,458; 454			1,836; 283		
Lost ≤ -1 kg/m² from previous pregnancy	Unadjusted	2,351; 232	1.05	0.91 to 1.22		-	-	1,163; 85	0.88	0.68 to 1.14	690; 79	0.95	0.73 to 1.24	477; 68	0.90	0.67 to 1.23
	Adjusted**	2,258; 222	0.94	0.80 to 1.10	-	-	-	1,108; 81	0.87	0.68 to 1.12	663; 76	0.96	0.72 to 1.29	466; 65	0.95	0.67 to 1.34
Weight stable (>-1 to <1 kg/m²)	Unadjusted	5,411; 508	Ref		244; 7	Ref		3,680; 305	Ref		1,024; 123	Ref		463; 73	Ref	
	Adjusted**	5,191; 489	Ref		234; 7	Ref		3,519; 292	Ref		985; 118	Ref		453; 72	Ref	
Gained 1-3 kg/m² from previous pregnancy	Unadjusted	4,122; 450	**1.16**	**1.03 to 1.31**	230; 8	1.21	0.45 to 3.29	2,606; 259	**1.20**	**1.02 to 1.40**	888; 127	1.19	0.94 to 1.50	398; 56	0.89	0.65 to 1.23
	Adjusted**	3,944; 427	1.13	0.99 to 1.28	222; 7	1.04	0.36 to 3.04	2,497; 251	**1.26**	**1.06 to 1.50**	839; 115	1.16	0.89 to 1.50	386; 54	0.86	0.61 to 1.22
Gained ≥3 kg/m² from previous pregnancy	Unadjusted	2,904; 383	**1.40**	**1.24 to 1.59**	111; 9	**2.83**	**1.08 to 7.40**	1,439; 163	**1.37**	**1.14 to 1.64**	856; 125	1.22	0.96 to 1.53	498; 86	1.10	0.82 to 1.46
	Adjusted**	2,822; 364	**1.34**	**1.17 to 1.54**	104; 6	2.08	0.67 to 6.51	1,389; 151	**1.34**	**1.09 to 1.65**	839; 123	**1.35**	**1.05 to 1.75**	490; 84	1.21	0.89 to 1.65

*Generalised linear model with log link and robust variance estimator used to derive RR

**Adjusted for: maternal age, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and inter-pregnancy interval

There was a significantly reduced risk of recurrent LGA birth in the second pregnancy in overweight women who had a LGA infant in the first pregnancy and lost ≥1 kg/m^2 in weight (aRR 0.69, 95% CI 0.48 to 0.97) (Table 6.4). No association was observed between risk of recurrent LGA and maternal BMI change between pregnancies in underweight, normal weight and obese women.

There was an increased risk of new LGA birth in the second pregnancy after having a non-LGA infant in the first pregnancy in normal weight women who gained 1-3 kg/m^2 (aRR 1.26, 95% CI 1.06 to 1.50) and in normal weight and overweight women who had gained ≥3 kg/m^2 weight (aRR 1.34, 95% CI 1.09 to 1.65, aRR 1.35, 95% CI 1.05 to 1.75, respectively) (Table 6.5). No association was observed between the risk of new LGA in the second pregnancy and maternal BMI interpregnancy change in obese women.

6.5 Discussion

This analysis examined the association between change in women's BMI between their first and second live birth pregnancies and risk of SGA and LGA birth in the second pregnancy in a population-based cohort of 15,940 women in the South of England. Almost half of the sample (48%) of women gained ≥1 kg/m^2 in the time between the first antenatal care visits of their first and second pregnancies. The proportion of SGA birth was significantly higher in women who lost weight (8.7%) compared to women who remained weight stable (7.0%) and women who gained weight (6.2-6.7%). Normal weight women who lost ≥1 kg/m^2 were at increased risk of 'new' SGA. The proportion of LGA births was significantly higher in women with an inter-pregnancy weight gain of ≥3 kg/m^2 (16%) compared to women who lost weight (12%) and those who remained weight stable (12%) between pregnancies. Overweight women who lost ≥1 kg/m^2 had a reduced risk of recurrent LGA. Normal weight women who gained 1-3 kg/m^2 and both normal weight and overweight women who gained ≥3 kg/m^2 between pregnancies had an increased risk of LGA birth in their second pregnancy after a non-LGA birth in the first.

Compared to the population-based Swedish cohort which carried out a similar analysis for LGA and other outcomes in 151,025 women, a lower proportion of women remained weight stable in this cohort (46% compared to 36%) and a

higher proportion lost (11% compared to 16%) or gained (43% compared to 48%) weight. Amongst women who gained weight, a higher proportion gained 3 or more BMI units in this cohort (20%) compared to the Swedish cohort (11%) (Villamor and Cnattingius, 2006). Similarly, in comparison to a population-based cohort of 24,520 women in Aberdeen, Scotland; a larger proportion of women in this study lost (4.8% compared to 7.3%) or gained (25.6% compared to 30.5%) weight (>2 BMI units) (Wallace *et al.*, 2016). The Swedish cohort used data from 1992 to 2001 and the Scottish cohort from 1986 to 2013. The differences could reflect the increase in the prevalence of maternal overweight and obesity over time since this dataset is more recent.

In the adjusted model utilising the full sample, there was an increased risk of LGA in the second pregnancy for interpregnancy weight gain compared to remaining weight stable. In a population-based cohort in the USA, women were found to be at increased risk of LGA in the second pregnancy if their pre-pregnancy BMI category changed towards overweight or obese from first to second pregnancy regardless of their BMI category in first pregnancy except in underweight women who increased to normal weight (Getahun *et al.*, 2007). This study is different to ours in that it only examined risk in second pregnancy without adjustment for LGA outcome in first pregnancy. It also considered weight change as change in BMI category only, while we studied change in maternal BMI regardless of whether BMI category has changed or not in the second pregnancy.

In obese women in the USA, interpregnancy weight gain of ≥2 kg/m^2 was associated with increased risk of LGA and a weight loss of ≥2 kg/m^2 was associated with decreased risk compared to the reference group of weight maintained (between >-2 kg/m^2 and <2 kg/m^2) (Jain *et al.*, 2013). We found no association between weight change and risk of second pregnancy LGA in women who were obese at the start of their first pregnancy. This may be because obese women are already at increased risk of LGA births, and the average inter-pregnancy BMI change in this subgroup was not large enough to detect a further increase in risk. Greater efforts are needed for primary prevention of obesity in women of child bearing age and obese women need more effective weight loss strategies in the inter-partum period to assess impact on LGA and other outcomes.

Risk of recurrent LGA was analysed in one previous study in Scotland which found that interpregnancy weight gain (≥2 kg/m^2) was associated with increased risk of recurrent LGA and weight loss (≥2 kg/m^2) was found to be protective. Stratification by BMI showed that women with BMI <25 kg/m^2 were at increased risk of recurrent LGA on gaining ≥2 kg/m^2 whereas women with BMI ≥25kg/m^2 were at reduced risk of recurrent LGA on losing ≥2 kg/m^2 weight (Wallace *et al.*, 2016). We showed a similar reduction in risk in overweight women who lost ≥1 BMI kg/m^2 between pregnancies, but found no association in normal weight women. This difference in findings may be because the <25 kg/m^2 group in the previous Scottish study included underweight women whereas our stratified analysis examined normal weight women separately to underweight women. This study also showed that interpregnancy weight loss (≥2 kg/m^2) was associated with increased risk of recurrent SGA, while weight gain (≥2 kg/m^2) was protective in women with BMI <25kg/m^2 at first pregnancy. We showed a similar protective effect of weight gain (≥3 kg/m^2) on recurrent SGA but no effect with weight loss.

There was an increased risk of 'new' SGA on weight loss ≥1 kg/m^2 and decreased risk on weight gain ≥3kg/m^2 in normal weight women. This is in line with findings from the study in Scotland (Wallace *et al.*, 2014) which also reported similar findings but additionally found the same effect in women with BMI ≥25kg/m^2. This could be because we further stratified the ≥25kg/m^2 category as well as the low number of cases in this group.

We showed an increased risk of new LGA in the second pregnancy (after a non-LGA birth in the first pregnancy) on weight gain compared to remaining weight stable. After stratification by BMI, we found that this association between interpregnancy weight gain and new LGA remained only in normal-weight and overweight women. The findings from this study are in line with findings with other studies in Scotland (Wallace *et al.*, 2014) and Sweden (Villamor and Cnattingius, 2006) which found increased risk of new LGA with modest (1-3 kg/m^2) and large (≥3 kg/m^2) weight gain. Both studies also found a decreased risk with interpregnancy weight loss of >1 kg/m^2 which was not found in our study. Both studies stratified BMI as < and ≥25kg/m^2, while we further stratified the ≥25kg/m^2 category as overweight (BMI 25-29.9kg/m^2) and obese (≥30kg/m^2) and found an increased risk of 'new' LGA in overweight, but not in obese women. We carried out sensitivity analysis merging overweight and obese categories and

found increased risk in this category (data not shown) suggesting that the results are comparable to previous studies.

Women included in this analysis had a range of interpregnancy interval of less than 1 to up to 12 years and thus weight change could be due to postpartum weight retention or late postpartum weight gain. A study looking at the effects of pregnancy on long-term weight gain concluded that women who had not lost pregnancy weight at one year postpartum were more likely to retain weight longer term (Linné *et al.*, 2004). In this analysis, we have adjusted for the length of the interpregnancy interval in the models.

The DOHaD hypothesis suggests that adverse exposures during development could lead to enhanced susceptibility in the foetus thus increasing the risk of non-communicable diseases in later life. Although the focus has previously been on exposures during pregnancy, the importance of the preconception period is now recognised (Barker *et al.*, 2018; Fleming *et al.*, 2018; Stephenson *et al.*, 2018). Efforts to systematically identify women in the preconception period to improve health and lifestyle during conception are underway (Stephenson *et al.*, 2018). Promoting health of all women of child-bearing age with targeting of women and partners planning a pregnancy has been identified as an effective approach to improving preconception health (Barker *et al.*, 2018). It is difficult to identify all women who are planning a pregnancy but as the inter-conception period is also the preconception period for the next pregnancy, it is important to engage with women during this period to optimise their and their children's health.

Future research that characterises the predictors of postpartum weight change would help design interventions to support postpartum weight loss and prevent weight gain. Key to this is an understanding of the pattern of weight change during this period as well as identifying the optimal setting and delivery of the intervention. Support with healthy eating and physical activity is more commonly received during pregnancy than after birth. Even when lifestyle advice is received postpartum, it was found not to be associated with healthy diet or physical activity behaviours (van der Pligt *et al.*, 2016). Most interventions that have been successful in limiting and promoting weight loss were combined diet and physical activity interventions with self-monitoring (van der Pligt *et al.*, 2013). However, the timing of engaging women and length of intervention or engagement are

important with one study showing that an intervention from 16 weeks pregnancy to six months postpartum was more effective than the same intervention from birth to six months postpartum intervention (Huang *et al.*, 2011).

As pregnancy and early postpartum is a period of major change for women and their families, interventions need to be carefully designed to be attractive, flexible, affordable and feasible for women at this stage with competing priorities and time demands. Focus during the postpartum period in the UK healthcare system is mostly on child health and development. The feasibility and effectiveness of better utilising contact time with health professionals during the two years after birth to engage and support maternal health needs to be explored. There may also be a role for mutual support groups for mothers. There is additionally a need to recognise that weight management issues are greater in more disadvantaged mothers so there is also the issue of identifying the most effective weight management strategies for such mothers to reduce social inequity in subsequent birth and maternal outcomes. Weight gain does not occur in isolation and is usually combined with other risk factors particularly in socioeconomically disadvantaged groups and hence a holistic approach taking into account priority setting for these families should be considered.

The strengths and limitations of this analysis are the same as those reported for the analysis in Chapter 5. In addition to lack of information on gestational weight gain during pregnancy which was previously reported, information was also lacking on other potential confounders (breastfeeding duration/exclusivity and paternal characteristics/behaviour) in the association between maternal inter-pregnancy weight gain and LGA birth (Nohr *et al.*, 2008). We adjusted for first feed was breast milk as a proxy for breastfeeding initiation in sensitivity analysis and the results remained unchanged (not shown). We also adjusted for gestational age at booking, as this was the point when maternal BMI was measured, in sensitivity analysis and the estimates remained similar.

6.6 Conclusion

Gaining weight after SGA birth in normal weight women reduces the risk of subsequent SGA, while losing weight increases its risk in normal weight women with no previous history of SGA. Conversely, losing weight after LGA birth in overweight women reduces the risk of subsequent LGA, while gaining weight

increases its risk in women with no previous history of LGA. Supporting women achieve and maintain a healthy weight and preventing weight gain between pregnancies is an important preventive measure to achieve better maternal and offspring outcomes.

A large proportion of women gained weight between their first and second pregnancy, and a higher proportion of these women had a LGA birth in their second pregnancy compared to their first in this English cohort. Overall, weight gain between pregnancies was associated with an increased risk of LGA in the second pregnancy. Risk of new LGA was higher in normal weight and overweight women who gained weight after a non-LGA birth in their first pregnancy compared who remained weight stable. Overweight women who had a LGA birth in their first pregnancy were at a lower risk of a recurrent LGA birth in their second pregnancy if they lost weight between pregnancies. Supporting efforts to lose weight in overweight and obese women between pregnancies, and stop weight gain in all women planning to have further children (except those who are underweight) are important preventive measures of subsequent adverse maternal and offspring health outcomes.

In the next chapter, I will focus on the development of prediction models for the risk of childhood overweight and obesity in the full sample. Following this, I will develop a prediction model incorporating the findings from the interpregnancy change analysis in Chapter 8.

Chapter 7 Development of prediction models of childhood overweight and obesity at 4-5 and 10-11 years

Having focused on the interpregnancy analysis and outcome in the second or higher order pregnancy in the last two chapters, this chapter now returns the focus on all live births/children and presents the prediction models developed for the risk of childhood overweight and obesity using routine data.

Work from this chapter has been published as an abstract and has been presented at two conferences (Southampton Medical and Health Research Conference 2019 and the Society for Social Medicine & Population Health and International Epidemiology Association European Congress Joint Annual Scientific Meeting 2019).

7.1 Background

With high rates of overweight and obesity and evidence of tracking of weight status from childhood to adolescence to adulthood, a higher proportion of the population is being exposed to obesity for longer. Obesity was a factor (primary or secondary diagnosis) in 617,000 hospital admissions in England in 2016/17, an 18% increase from the year before (2015/16) (NHS Digital, 2018b). A survey conducted by the All-party Parliamentary Group on Obesity to inform a report on the current landscape of obesity services in the UK found that 42% of people with obesity did not feel comfortable discussing it with their GP. About a third of people with obesity had not accessed lifestyle or prevention services with about 40% of those who had accessed services finding it difficult to do so (All-party parliamentary group on obesity, 2018).

After weight and height are measured in schools as part of NCMP, parents receive a feedback letter informing them of the child's weight status which includes resources to encourage healthy eating, physical activity and wellbeing. Proactive follow-up which involves offering personalised advice, follow-up measurement and services to support healthier weight is recommended as a minimum in children in the extreme centiles (<0.4 or ≥99.6). However, proactive follow-up in underweight or overweight children not falling into the extreme centiles is dependent on the local authorities and varies across the country (Public Health England, 2018).

A recent systematic review on global childhood overweight and obesity prevention interventions concluded that combined diet and physical activity interventions in a school setting have the greatest effectiveness. However, the paucity of studies and design heterogeneity limited the evidence on preschool-, community- and home-based interventions (Bleich *et al.*, 2018). The majority of interventions in childhood target children aged 6-12 years but intervening early to prevent childhood obesity is gaining importance (World Health Organization, 2016b). There is some evidence on effective early interventions however the focus is on infant feeding (including increasing breastfeeding rates), preventing GDM and maternal diet and physical activity (which indirectly addresses maternal BMI) but key maternal risk factors (maternal BMI, prenatal exposure to smoking, socioeconomic status) are not directly addressed in existing interventions (Blake-Lamb *et al.*, 2016). Prevention is a central theme of the UK government's vision

for the nation's health (Department of Health and Social Care, 2018, 2019; National Health Service, 2019). Key to effective prevention is identifying individuals at risk as presented in section 2.5 on page 37 to complement population-based prevention. So this chapter addresses the issue of risk prediction to identify and enable early intervention in those at high risk of childhood overweight and obesity.

7.1.1 Predictive modelling of health outcomes

Risk prediction based on one predictive factor tends to be poor and the use of multiple predictive factors combined in a prediction model improves the prediction (Riley *et al.*, 2013). Predictive factors do not have to be causal and are often associated with the true casual factors which may or may not be known (Riley *et al.*, 2013). A predictive model uses the combination of predictor values to estimate the risk of the outcome within or at a specific time-period (Steyerberg *et al.*, 2013). The requirement for the usability of a prediction model is that it is feasible to collect information on the predictors, clinically meaningful, accurate (well calibrated and good discrimination) and generalizable within the intended population. This can then be utilised to identify children who are likely to become overweight or obese by the age or ages that they are routinely measured. Better predictive information is beneficial due to the ability to identify children at risk early thus providing the ability to target interventions and support earlier and more effectively.

7.1.2 Existing prediction models

Chapter 3 of this thesis reported on a systematic review of existing prediction models for the risk of overweight and obesity. Instead of developing a model, it is possible to combine existing models or update or recalibrate an existing model. Although this approach was considered, it was decided to develop new models. This is because only two of the existing eight prediction models identified could be applied to a routine antenatal care dataset in the UK. The other six models included predictors related to the father (such as paternal BMI or employment) or household (such as parental education, smoking in the household, number of siblings, income) which are not routinely collected and some of which may be complex to measure routinely. Both models that could be applied to the routine dataset included the same predictors – maternal BMI, birthweight (z-score),

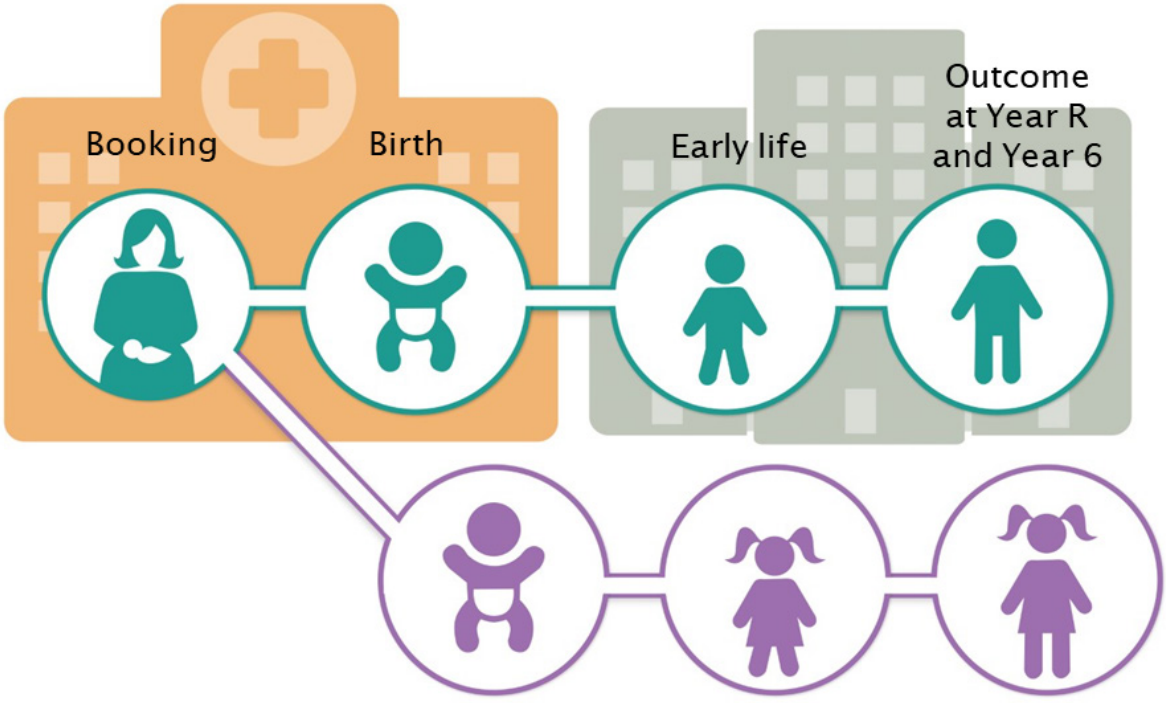
weight gain (z-score) and infant gender. The use of z-scores in both these models complicates the application of prediction score in practice as this is calculated using reference values and thus these calculations need to be incorporated into an online programme or application and cannot be easily carried out manually or incorporated into a paper tool. Hence, there remains a need to develop a model using routinely collected data.

7.2 Methods

7.2.1 Data source

The linked dataset described in Chapter 4 was used for this analysis. Briefly, maternal antenatal care and birth records for all women registered for maternity care at University Hospital Southampton between January 2003 and April 2018 were linked to child health records. Only singleton pregnancies were included in this analysis. Figure 7.1 shows the stages that data are available.

Figure 7.1: Stages that data are available for analysis



7.2.2 Summary of data

Baseline characteristics were summarised by outcome. Mean and SD were reported for continuous variables. Total numbers and proportions were reported for categorical variables.

7.2.3 Data considerations

Clustering by mother was adjusted for as some women had more than one pregnancy in the dataset.

7.2.4 Dealing with missing data

Both complete case and multiple imputation analysis was carried out (White *et al.*, 2011). This was to enable comparison between the two approaches. Additionally, due to the high percentage of missing data particularly in the early life model, the uncertainty introduced by multiple imputation could outweigh the benefits of the approach.

Multiple imputation by chained equations (MICE) can be used when several variables have missing values. MICE uses a set of imputation models to impute values for each variable in turn using information from the other variables including the outcome in the regression model. It is restricted to individuals that have an observed value for the variable being imputed and is then used to predict values for the individuals who are missing values for that variable. The imputed values for the first variable in the imputation model are included when imputing missing values for the next variable in the imputation model. The missing values are imputed in turn for each variable until all missing values have been imputed. This is called a cycle and several cycles are run to stabilize the results in one imputed dataset. This procedure is run multiple times resulting in several imputed datasets. Each imputed dataset is analysed separately and overall estimates are obtained by combining the estimates across the datasets using Rubin's rules (White *et al.*, 2011). The uncertainty in the parameter estimate itself and the uncertainty due to missing data is reflected in the total variance for an estimate as it includes the within- and between- imputation variance. MICE was carried out using the mi impute chained function in Stata using the options *truncreg* for continuous variables and predictive mean matching (*pmm*) for categorical variables.

The sample was limited to those with the outcome of interest and only missing predictor values were imputed. The number and percentage of missing data is outlined in Table 7.1. Given the high percentage of missing data during early life, I carried out 70 imputations of the Year R sample and 85 imputations of the Year 6 sample. This was based on the recommendation that the number of imputations equal the percentage of missing data in the dataset.

Table 7.1: Number of missing observations by variable and outcome

Variable	Number (%) missing for outcome at Year R (n= 29,060)	Number (%) missing for outcome at Year 6 (n=13,482)
Maternal age at booking	0	0
Gestational age at booking	0	0
Maternal BMI at booking	32 (0.11)	14 (0.10)
Maternal smoking at booking	30 (0.10)	13 (0.10)
Maternal education at booking	14 (0.05)	10 (0.07)
Maternal employment status at booking	215 (0.74)	85 (0.63)
Maternal ethnicity	1331(4.58)	1289 (9.56)
Maternal intake of folic acid supplements	30 (0.10)	14 (0.10)
First language English (yes/no)	0	0
Partnership status at booking	7 (0.02)	1 (0.00)
Infertility treatment	30 (0.10)	14 (0.10)
History of mental health	0	0
Previous stillbirth	0	0
Parity	0	0
Previous caesarean section	0	0
Maternal diet	669 (2.30)	778 (5.77)
Maternal disability status	0	0
Maternal substance use	0	0
Obstetric history of gestational diabetes	0	0
Obstetric history of pre-eclampsia	0	0
Family history of diabetes	0	0
Family history of hypertensive disorder	0	0
Family history of mental health conditions	0	0
Birthweight	0	0
Gestational age at birth	0	0

Variable	Number (%) missing for outcome at Year R (n= 29,060)	Number (%) missing for outcome at Year 6 (n=13,482)
Gender	0	0
Delivery method	252 (0.87)	101(0.75)
Gestational diabetes in current pregnancy	0	0
Pre-eclampsia in current pregnancy	0	0
Breastfeeding status and duration	20067 (69.05)	13389 (99.31)
Weight at 1 year	20555 (70.73)	11407 (84.61)
Weight at 2 years	19435 (66.88)	11090 (82.26)

Summary statistics are presented for the data available for each variable as well as for complete case analysis and multiply imputed data (Table 7.2). The statistics are very similar in all four settings for the continuous variables but the proportions of minority ethnic groups and overweight and obesity is slightly higher in the complete cases only. This suggests that there could be some bias due to the missingness of these variables particularly in the complete case sample at ~2 years. The estimates from the multiply imputed data are closer than the complete case estimates when compared to all available data.

Table 7.2: Summary statistics for all available data, complete case and multiply imputed data

Variables	Year R				Year 6			
	All available data	Complete case at booking	Complete case at ~2 years	Multiply imputed data	All available data	Complete case at booking	Complete case at ~2 years	Multiply imputed data
Age at booking, years	28.4 ± 5.9	28.4 ± 5.8	28.4 ± 5.7	28.4 ± 5.9	28.2 ± 5.9	28.1 ± 6.0	27.3 ± 5.9	28.2 ± 5.9
BMI at booking, kg/m^2	25.5 ± 5.5	25.6 ± 5.5	26.1 ± 5.9	25.5 ± 5.5	25.1 ± 5.1	25.2 ± 5.2	25.3 ± 5.5	25.1 ± 5.1
Maternal ethnicity								
White	90.4 (90.0 to 90.7)	90.5 (90.1 to 90.8)	88.5 (87.5 to 89.4)	90.4 (90.0 to 90.7)	92.1 (91.6 to 92.6)	91.7 (91.2 to 92.2)	86.1 (84.6 to 87.5)	92.1 (91.6 to 92.6)
Mixed	1.1 (1.0 to 1.2)	1.1 (1.0 to 1.2)	1.2 (0.9 to 1.5)	1.1 (1.0 to 1.2)	1.0 (0.8 to 1.1)	1.0 (0.8 to 1.2)	1.8 (1.2 to 2.4)	1.0 (0.8 to 1.1)
Asian	6.1 (5.8 to 6.3)	5.9 (5.7 to 6.2)	7.0 (6.2 to 7.8)	6.1 (5.8 to 6.3)	5.0 (4.6 to 5.4)	5.2 (4.8 to 5.6)	8.7 (7.5 to 10.0)	5.0 (4.6 to 5.3)
Black/African/ Caribbean	1.5 (1.3 to 1.6)	1.5 (1.3 to 1.6)	2.2 (1.8 to 2.7)	1.5 (1.3 to 1.6)	1.0 (0.8 to 1.1)	1.0 (0.8 to 1.2)	1.9 (1.4 to 2.6)	1.0 (0.8 to 1.1)
Other	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.1)	1.2 (0.9 to 1.6)	1.0 (0.9 to 1.1)	1.0 (0.9 to 1.2)	1.1 (0.9 to 1.3)	1.5 (1.0 to 2.1)	1.0 (0.8 to 1.2)
Outcome								
Normal weight	85.2 (84.8 to 85.6)	85.1 (84.7 to 85.5)	84.4 (83.3 to 85.5)	85.2 (84.8 to 85.6)	75.4 (74.7 to 76.2)	75.2 (74.4 to 76.0)	72.8 (70.9 to 74.7)	75.4 (74.7 to 76.2)
Clinically overweight/obese	14.8 (14.4 to 15.2)	14.9 (14.5 to 15.3)	15.6 (14.5 to 16.7)	14.8 (14.4 to 15.2)	24.6 (23.8 to 25.3)	24.8 (24.0 to 25.6)	27.2 (25.3 to 29.1)	24.6 (23.8 to 25.3)

All available data: Uses all available data for that variable
Complete case: Uses observations that are complete for all variables considered for model development
Multiply imputed data: Uses all observations averaged across multiply imputed datasets

7.2.5 Outcome measurement

As part of the NCMP, children in all state-maintained schools in England are measured at Year R (4-5 years) and Year 6 (10-11 years). In the UK, children start school in the September after their fourth birthday and they can be measured at any point during the school year. As the data were obtained from the community trusts (Southern Health NHS Foundation Trust and Solent NHS Trust) who is commissioned by the local authority to collect this data through the school nursing service, there was no identifier in the dataset to indicate if the measurement was part of the NCMP. For the purposes of this study, this was defined as the first measurement of weight and height on the same day between the ages of 4 and 6 years. Similarly, the Year 6 measurement was defined as the first measurement of weight and height on the same day between the ages of 10 and 12 years. Thus, all children with a valid weight and height measurement at Year R constituted the sample for outcome at Year R and similarly for Year 6. There could be several reasons for the outcome not being measured in this dataset which included child age (not old enough to be measured), not eligible for measurement (not attending state-run school), opted out of measurement, no longer resident in the area or changes in database or recording practices (see section 4.1.3 and 4.8 in Chapter 4).

BMI was then calculated as weight/(height)^2. This was then converted to age- and sex- adjusted BMI z-scores according to the UK 1990 growth reference charts using the command "zanthro" in Stata (Vidmar *et al.*, 2004).

The NCMP uses the 85th and 95th percentile cut-offs for population monitoring of overweight and obesity (Public Health England, 2016) and in the published reports. However, the 91st and 98th percentiles for clinical overweight and obesity is used for parental feedback (Public Health England, 2016). Prediction models were developed using both population monitoring cut-offs and the overweight clinical cut-off of 91st centile. It was decided not to run the model using the obesity clinical cut-off of 98th centile as these would only identify the more extreme cases and the evidence on adverse effects of childhood obesity is at lower cut-offs (Reilly and Kelly, 2011).

Z-scores of +1.04, +1.33 and +1.65 equates to the 85th, 91st and 95th percentiles respectively. Three binary outcome variables were created at each age. For the

models predicting the outcome of obesity using the population monitoring cut-off of 95th centile only, those with a z-score of +1.04 to <+1.65 (85th to <95th percentile) were excluded from the model sample, as children with a BMI z-score in this range were identified as overweight and likely to be different to normal weight children. Prediction models using the 91st centile are presented in this chapter as this cut-off is most relevant to healthcare professionals in the UK. The results for the complete case analysis for the 85th percentile are presented in Appendix G and the 95th percentile in Appendix H.

7.2.6 Model development

7.2.6.1 Candidate predictors

The prediction model was developed in stages, incorporating data collected at the booking appointment, birth and early life. Thus, model predictors were identified at each of these stages. For later time-points (birth and early life), the candidate predictors are in addition to all the candidate predictors from the earlier stage.

The candidate predictors identified at the booking appointment are presented in Box 7.1. Maternal date of birth is recorded at the booking appointment and converted to age (in years) on extraction of the dataset to maintain anonymity. Maternal weight in kilograms was measured at the booking appointment by the midwife and height was self-reported. Smoking was self-reported as current smoking or non-smoking. Non-smokers were further asked if they had ever smoked or had previously smoked and quit. This was categorised as non-smoker, ex-smoker or current smoker. Highest maternal educational attainment was recorded as primary, secondary, college, undergraduate, postgraduate, graduate and none. This was condensed to three categories - secondary (GCSE) and under, college (A levels) and university degree or above. Self-reported ethnicity was recorded under 16 categories and condensed to White, Mixed, Asian, Black/African/Caribbean and Other. Categories of not asked and not stated were coded as missing. Employment status was categorised as employed, unemployed, in education, and not specified. Intake of folic acid supplements was categorised as taking before becoming pregnant, started taking once pregnant and not taking supplement. Maternal first language English, history of stillbirth/miscarriage, previous caesarean section, maternal disability status, maternal substance use and partnership status was categorised as yes or no. Infertility treatment was

categorised as no, yes (hormonal only, in-vitro fertilisation, gamete intrafallopian transfer and other surgical) and investigations only.

Box 7.1: The list of candidate predictors identified at the booking appointment

Objectively recorded:

- Maternal age
- Maternal BMI at booking (measured weight)

Self-reported:

- Gestational age at booking (based on last menstrual period)
- Maternal smoking status at booking
- Highest maternal educational attainment
- Maternal employment status at booking
- Maternal ethnicity
- Intake of folic acid supplements
- Maternal first language English (yes/no)
- Infertility treatment
- History of mental health illness
- History of stillbirth/miscarriage
- Previous caesarean section
- Parity
- Maternal diet
- Maternal disability status
- Maternal substance use
- Partnership status
- Family history of diabetes
- Family history of cardiovascular disease
- Family history of mental health conditions
- Obstetric history of diabetes
- Obstetric history of hypertension
- Obstetric history of pre-eclampsia

Maternal history, obstetric history and family history were asked as separate questions such as "do you have an existing medical conditions" and recorded if any existing conditions were reported to each of the three questions. Parity was recorded as the number of previous live births reported and condensed to 0, 1, 2 and ≥3 for this analysis. Maternal diet was recorded as no special diet, pescatarian, vegetarian, vegan and other.

Box 7.2: The list of candidate predictors identified at birth

Objectively recorded:

- Birthweight
- Gestational age at birth
- Sex
- Mode of birth
- Gestational diabetes in current pregnancy
- Gestational hypertension in current pregnancy
- Pre-eclampsia in current pregnancy

The candidate predictors identified at birth are presented in Box 7.2. Birthweight (grams) was measured by healthcare professionals at birth. Gestational age was based on a dating ultrasound scan which takes place between 10 weeks and 13 weeks 6 days gestation (National Institute for Health Care and Excellence, 2008a). Birth method was recorded as spontaneous vertex, spontaneous other cephalic, low forceps not breech, ventouse vacuum extraction, breech, breech extraction, elective caesarean section, emergency caesarean section and other. This was condensed and categorised as vaginal and caesarean. In this population, an oral glucose tolerance test was used for screening for GDM in women with one or more risk factors (BMI > 30kg/m^2; GDM in previous pregnancy; previous baby weighing ≥4.5kg; diabetes in parents or siblings and of Asian, African-Caribbean or Middle Eastern ethnicity) (National Institute for Health Care and Excellence, 2015). GDM diagnosis was then reported in the database. Pre-eclampsia is usually diagnosed during routine pregnancy checks and is reported in the database if diagnosed.

Box 7.3: The list of candidate predictors identified during early life

Self-reported:

Breastfeeding status and duration

Objectively recorded:

Early life weight

Breastfeeding status was reported at hospital discharge and during early life. The recording during early life was done differently by the two community trusts that we received data from. One used NHS read codes and thus was recorded at 10 days, 2 weeks, 6 weeks, 4 months and 9 months. At each point, this was recorded as breastfed, bottle-fed or breast and bottle fed. Breastfeeding could be recorded at any or all of the time-points specified by the read codes. There was also a read code of breastfeeding stopped that had been used with a date of when this was recorded so the age could be calculated. The other community trust recorded breastfeeding at 56 days (8 weeks) as yes or no so there was no information on whether this was exclusive or partial breastfeeding. The 10 days and 2 weeks categories were combined into one as there were very few instances of the 2 weeks category recorded and the two categories are only four days apart. Using all the information available, a breastfeeding variable was derived with categories of no breastfeeding, minimum 10 days, minimum 6 weeks, minimum 8 weeks, minimum 4 months and minimum 9 months. Minimum duration was chosen as there was no information how long breastfeeding was continued for beyond the point of the last record.

Early life weight was calculated at two ages – 1 year and 2 years. To maximise the number of records and accounting for the routine development checks offered within the NHS where children are measured (9 to 12 months and 2 to 2.5 years), weight measured between 9 and 13 months was used as the 1 year weight. Similarly, weight measured between 23 and 30 months was used as the 2 year weight. However, despite this approach, a large proportion of missing data remained for these two variables.

7.2.6.2 Data handling and transformation of continuous predictors

Data handling includes collapsing categorical variables into fewer categories or creating new variables from existing ones (Royston *et al.*, 2009). Continuous variables may not be linear in a multivariable prediction model and thus it is important to model these appropriately. Converting continuous variables into categorical variables leads to loss of information and power and thus is not advised (Sun *et al.*, 1996; Altman and Royston, 2006). It is better to consider transforming a continuous variable if it is not linear. Multivariable fractional polynomials use combinations of transformation to achieve a better model fit (Sauerbrei and Royston, 1999). The increased complexity in variable transformation can lead to added difficulty in interpreting predictor effects and an increased potential for overfitting.

7.2.6.3 Variable selection for inclusion in the multivariable model

Stepwise backward elimination was used to select variables to be included in the model (Royston *et al.*, 2009). This automatic selection procedure starts with the full model (including all candidate predictor variables) and sequentially removes variables based on a series of hypothesis tests. Automatic selection procedures are data driven and make decisions regarding inclusion/exclusion of variables based on hypothesis tests with a pre-specified significance level for inclusion/exclusion. In backward elimination, variables are removed sequentially if the p-value for a variable exceeds the specified significance level which was set at 0.157 for this analysis which was chosen conservatively to reduce the risk of overfitting. This is equivalent to the Akaike information criterion (AIC) (Atkinson, 1980).

7.2.6.4 Events per variable (EPV) and sample size requirements

EPV is used to ensure that the sample size is large enough to avoid issues related to precision and over-fitting especially when using automatic selection procedures. A rule of thumb from simulation studies is that there should be a minimum of 10 events per variables (Harrell Jr *et al.*, 1996; Peduzzi *et al.*, 1996). Continuous variables count as one variable whereas categorical variables with more than two categories count as the number of categories and not just as one

variable. This is because indicator variables are generated for each category (for example, employment status at booking appointment coded as "employed', "unemployed" and 'student/in training' will require three parameters to be estimated). Thus, to include one continuous and one categorical variable with five categories and apply the EPV rule of thumb, we would need at least 60 cases of the outcome of interest. Considering this in model development, there were sufficient cases of the outcomes to develop a prediction model using booking and birth factors at Year R and Year 6. However, there were insufficient cases of outcome during early life at both ages so it was decided to include fewer candidate predictors at the model development stage in these models. Predictors included were guided by the literature and those that remained in the booking and birth models.

7.2.6.5 Modelling

As the outcome was binary, the models were developed using logistic regression. The candidate predictors were included together in full logistic models as independent variables. Selection was based on the statistical significance of their adjusted relationship with the outcome. All continuous variables were retained as continuous to avoid loss of information.

The relationship between continuous predictors and outcome were studied. Fractional polynomials were used to investigate non-linear relationships between continuous candidate predictors and the outcome. The best identified transformation for each continuous predictor was used when fitting the models. As the full models had more than one continuous candidate predictors, the multivariable fractional polynomial (MFP) algorithm available in Stata was used. A backward selection process is used by the algorithm to select predictors and transformations that best predict the outcome. The MFP algorithm simultaneously selects predictors and transformations, thus preserving the nominal probability of Type I error.

7.2.6.6 Internal validation

Internal validation is used to evaluate model performance in the same data as that was used for model development. Several methods exist for internal validation. These include split-sample analysis or resampling methods such as cross-validation and bootstrapping. Split-sample analysis involves splitting the

dataset into development and validation samples in which the model performance is determined on independent but similar data. Disadvantages of this method include inefficient use of the data, reduced power, increased potential for overfitting and model performance can vary depending on the split and the case mix in the two datasets. Cross validation is a method in which a random part of the dataset is reserved for validation and the model is developed in the rest of the dataset. The process is repeated multiple times based on the percentage split, for example if 10% of the sample if reserved for internal validation then the process is carried out 10 times. Bootstrapping is a method of internal validation that validates the modelling process as the variable selection procedure is performed in each bootstrap sample (Moons *et al.*, 2012). A bootstrap sample is obtained by sampling with replacement from the original data to obtain a sample of the same size as the original data. The model is then developed in the bootstrap sample using the same process as that used in the development of the original model following which the apparent performance of the new model is estimated in both the original dataset and the bootstrap sample. The difference between the apparent performance in each bootstrap sample and the original dataset is estimated. This is repeated many times by taking many bootstrap samples to obtain the average optimism estimate. This estimate indicates the optimism in the original developed model and thus the performance estimates for the original model can be adjusted for optimism by subtracting the optimism from the apparent performance (Moons *et al.*, 2012).

Bootstrapping (1000 repetitions) was chosen as the method for internal validation as this method provides stable estimates with low bias (Steyerberg *et al.*, 2001). It also provides an estimate of the expected optimism which can be used to weight down the model parameter estimates. Bootstrapping was chosen instead of the classical approach of split-sample validation. This is because split-sample validation reduces power, is inefficient and can lead to more overfitting due to chance. Large datasets are needed to overcome these issues and the model performance depends on the split used. On the other hand, the advantages of bootstrapping include efficient use of data, stable estimates with low bias and provides an estimate of optimism which can be used to weight down the model parameter estimates.

Internal validation was only carried out in complete cases. This was because the complexities involved in model development (combination of variable selection,

fractional polynomials and multiple imputation) in the multiple imputation models meant that the steps involved could not replayed. Thus these models could not be internally validated using bootstrapping. Instead, I assessed apparent model performance in the multiply imputed models and compared to the complete case models.

7.2.7 Model performance

Model performance was assessed using discrimination and calibration. Discrimination is a measure of how well the model differentiates between individuals who had the outcome and those that did not. The area under receiver operating characteristic curve (AUC) was used to summarise the overall discriminatory ability of the models. The AUC was classified as: 0.6-0.7 poor, 0.7-0.8 fair, 0.8-0.9 good and 0.9-1.0 excellent.

Calibration measures how well the predicted outcome of the model agrees with the observed outcome on average. A calibration plot is one where patients are categorised into risk groups (such as deciles) of predicted probability of having the event. The predicted probability (x-axis) is plotted against the observed outcome proportion (y-axis) for each risk group. The slope of a line fitted through the points on the graph is the calibration slope and has been calculated for the models. Calibration slope would be equal to one in a well-calibrated model. A slope of less than one or greater than one indicates over-prediction and under-prediction respectively (Steyerberg and Vergouwe, 2014).

7.2.8 Shrinkage

Prediction models tend to be optimistic in the development data as a result of overfitting. As a result, use of a newly developed model in independent data tends to lead to worse predictions. Predictor selection based on p-values, modelling non-linear relationships and small EPV are factors that contribute to overfitting. Heuristic shrinkage factors were calculated for each model to estimate the extent of overfitting present in the developed models (Van Houwelingen and Le Cessie, 1990).

The heuristic shrinkage factor is calculated as:

$$(\text{model } \chi^2 - \text{df}) / \text{ model } \chi^2$$

where model χ^2 is the model likelihood ratio and df is the degrees of freedom in the fitted model. A shrinkage factor of 1 implies no shrinkage.

The regression coefficients from the models were multiplied by the shrinkage factor to adjust the models for optimism. A logistic model was then fitted for the outcome to estimate the shrinkage of the intercept by including the linear predictor calculated using the shrunken coefficients as the only independent variable and constraining its coefficient to one.

7.2.9 Sensitivity, specificity and predictive value

Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated at several risk score cut-off points.

Sensitivity is the proportion of true positives that are correctly identified. Specificity is the proportion of true negatives that are correctly identified.

Positive predictive value is the proportion of individuals with positive outcome (high risk) that are correctly identified. Negative predictive value is the proportion of individuals with negative outcome that are correctly identified (Akobeng, 2007). Both PPV and NPV take the prevalence of the condition into account.

No standard criteria for identifying a risk threshold exist for the prediction of childhood obesity, therefore sensitivity, specificity, PPV and NPV were used to guide the selection of the risk threshold to identify children at risk.

7.2.10 Calculating risk score

The log-odds (Y) can be calculated using the regression equation as follows:

$$Y = \text{constant} + [\text{estimate}_1 \times \text{predictor}_1] + [\text{estimate}_2 \times \text{predictor}_2] + \ldots\ldots\ldots\ldots\ldots\ldots + \text{estimate}_n \times \text{predictor}_n]$$

The log-odds (Y) is then converted into probability (P) as follows:

$$P = 1/[1 + \exp(-Y)]$$

where P is the probability of developing the outcome and Y is the log-odds estimated using the model.

7.3 Results

Weight and height were measured in 30,958 children aged 4-5 years. This reduced to 29,060 children after exclusions for unfeasible gestational age, maternal weight and maternal height measurements and multiple births (twins/triplets). Of these, 4,311 children (14.8%) were overweight/obese (≥91st centile).

Weight and height were measured in 14,611 children aged 10-11 years. This reduced to 13,482 children after exclusions for unfeasible gestational age, maternal weight and maternal height measurements and multiple births (twins/triplets). Of these, 3,312 children (24.6%) were overweight/obese (≥91st centile).

7.3.1 Maternal baseline characteristics

The maternal baseline characteristics of the Year R and Year 6 sample are summarised separately in Table 7.3. Baseline characteristics were similar between the Year R and Year 6 sample. Mothers of the Year 6 sample were more likely to be current smokers and of lower educational attainment.

7.3.1.1 Year R

Maternal age at booking was 28.4 years (SD 5.9). Mean maternal BMI at booking was in the overweight range (25.5 kg/m^2, SD 5.5). Over 50% of women reported being ex- (33.6%) or current- (17.4%) smokers. A quarter of the women had a university degree or above and over two-thirds of the sample were employed at the booking appointment. Eight percent of mothers reported being a lone parent at the booking appointment. A small percentage (0.1%) of mothers reported substance use. Nearly half the mothers reported no breastfeeding.

7.3.1.2 Year 6

Maternal age at booking was 28.2 years (SD 5.9). Mean maternal BMI was in the overweight range (25.1 kg/m^2, SD 5.1). Almost a quarter of women reported being current smokers (19.1%) at the booking appointment. A fifth of the women had a university degree or above with similar proportions having college or secondary school education. Two-thirds of the sample were employed at the booking appointment. Eight percent of mothers reported being a lone parent at

the booking appointment. Breastfeeding status and duration could not be reported as was missing for 99% of records and thus could not be reliably imputed.

Table 7.3: Summary of baseline characters (candidate predictors) for the SLOPE sample using the multiply imputed data

Variable	Year R	Year 6
N	29,060	13,482
	Mean ± SD	Mean ± SD
Maternal age at booking, years	28.4 ± 5.9	28.2 ± 5.9
Gestation at booking, days	80 ± 19	86 ± 19
Maternal BMI at booking, kg/m^2	25.5 ± 5.5	25.1 ± 5.1
Birthweight, kg	3.4 ± 0.6	3.4 ± 0.6
Gestation at birth, days	279 ± 13	278 ± 13
Infant weight at 1 year, kg	9.4 ± 1.2	9.2 ± 1.2
Infant weight at 2 years, kg	13.0 ± 1.6	13.0 ± 1.7
	%, 95% CI	%, 95% CI
Maternal smoking status at booking		
Never smoked	49.0 (48.4 to 49.5)	48.5 (47.7 to 49.4)
Ex-smoker	33.6 (33.1 to 34.2)	32.4 (31.6 to 33.2)
Current smoker	17.4 (17.0 to 17.9)	19.1 (18.4 to 19.8)
Maternal highest educational attainment		
Undergraduate or above	25.5 (25.0 to 26.0)	19.8 (19.1 to 20.5)
College	40.9 (40.4 to 41.5)	41.1 (40.3 to 41.9)
Secondary school or below	33.6 (33.1 to 34.1)	39.1 (38.2 to 39.9)
Maternal employment status at booking		
Employed	68.9 (68.4 to 69.5)	68.1 (67.3 to 68.9)
Unemployed	28.8 (28.3 to 29.4)	30.0 (29.2 to 30.7)
Student or in training	2.2 (2.1 to 2.4)	1.9 (1.7 to 2.2)
Maternal ethnicity		
White	90.4 (90.0 to 90.7)	92.1 (91.6 to 92.6)
Mixed	1.1 (1.0 to 1.2)	1.0 (0.8 to 1.1)
Asian	6.1 (5.8 to 6.3)	5.0 (4.6 to 5.3)
Black/African/Caribbean	1.5 (1.3 to 1.6)	1.0 (0.8 to 1.1)
Other	1.0 (0.9 to 1.1)	1.0 (0.8 to 1.2)

Variable	Year R	Year 6
Intake of folic acid supplements		
Taking prior to pregnancy	31.0 (30.4 to 31.5)	31.2 (30.4 to 32.0)
Started taking once pregnant	58.3 (57.7 to 58.8)	55.1 (54.3 to 56.0)
Not taking supplement	10.8 (10.4 to 11.1)	13.6 (13.0 to 14.2)
Maternal first language English		
No	2.9 (2.7 to 3.1)	1.9 (1.7 to 2.1)
Yes	97.1 (96.9 to 97.3)	98.1 (97.9 to 98.3)
Partnership status at booking		
Partnered	91.7 (91.4 to 92.0)	91.1 (90.6 to 91.6)
Single	8.3 (8.0 to 8.6)	8.9 (8.4 to 9.4)
Infertility treatment		
No	92.5 (92.2 to 92.8)	92.9 (92.5 to 93.4)
Yes	4.2 (4.0 to 4.4)	4.2 (3.9 to 4.6)
Investigations but no treatment	3.3 (3.1 to 3.5)	2.8 (2.5 to 3.1)
History of mental health illness		
No	79.5 (79.0 to 79.9)	80.7 (80.1 to 81.4)
Yes	20.5 (20.1 to 21.0)	19.3 (18.6 to 19.9)
Previous stillbirth		
No	99.2 (99.1 to 99.3)	99.3 (99.2 to 99.4)
Yes	0.8 (0.7 to 0.9)	0.7 (0.6 to 0.8)
Parity at booking		
0	45.0 (44.5 to 45.6)	44.6 (43.7 to 45.4)
1	35.2 (34.6 to 35.7)	35.2 (34.4 to 36.0)
2	13.0 (12.6 to 13.4)	13.3 (12.8 to 13.9)
3	6.8 (6.5 to 7.1)	6.9 (6.5 to 7.3)
Previous caesarean section		
0	87.9 (87.5 to 88.2)	88.5 (87.9 to 89.0)
1	10.1 (9.7 to 10.4)	9.8 (9.3 to 10.3)
2	2.0 (1.9 to 2.2)	1.8 (1.6 to 2.0)
Maternal diet		
No special diet	93.3 (93.0 to 93.6)	91.9 (91.4 to 92.4)
Pescatarian	2.3 (2.2 to 2.5)	2.9 (2.6 to 3.2)
Vegetarian	2.2 (2.1 to 2.4)	2.4 (2.1 to 2.7)
Vegan	0.1 (0.1 to 0.1)	0.1 (0.0 to 0.1)
Other	2.1 (1.9 to 2.2)	2.7 (2.4 to 3.0)

Variable	Year R	Year 6
Maternal disability status		
No	99.0 (98.9 to 99.1)	98.9 (98.7 to 99.1)
Yes	1.0 (0.9 to 1.1)	1.1 (0.9 to 1.3)
Maternal substance use		
No	99.9 (99.8 to 99.9)	100.0
Yes	0.1 (0.1 to 0.2)	-
Obstetric history of GDM		
No	99.1 (99.0 to 99.3)	99.3 (99.1 to 99.4)
Yes	0.9 (0.7 to 1.0)	0.7 (0.6 to 0.9)
Obstetric history of pre-eclampsia		
No	99.8 (99.8 to 99.9)	99.9 (99.8 to 100.0)
Yes	0.2 (0.1 to 0.2)	0.1 (0.0 to 0.2)
Family history of diabetes		
No	85.8 (85.4 to 86.2)	86.9 (86.3 to 87.5)
Yes	14.2 (13.8 to 14.6)	13.1 (12.5 to 13.7)
Family history of hypertensive disorder		
No	68.4 (67.9 to 69.0)	69.3 (68.6 to 70.1)
Yes	31.6 (31.0 to 32.1)	30.7 (29.9 to 31.4)
Family history of mental health conditions		
No	83.9 (83.4 to 84.3)	85.7 (85.1 to 86.3)
Yes	16.1 (15.7 to 16.6)	14.3 (13.7 to 14.9)
Delivery method		
Vaginal	77.8 (77.3 to 78.2)	78.3 (77.6 to 79.0)
Caesarean section	22.2 (21.8 to 22.7)	21.7 (21.0 to 22.4)
Gestational diabetes in current pregnancy		
No	98.0 (97.8 to 98.1)	99.1 (98.9 to 99.2)
Yes	2.0 (1.9 to 2.2)	0.9 (0.8 to 1.1)
Pre-eclampsia in current pregnancy		
No	99.5 (99.4 to 99.6)	99.4 (99.3 to 99.6)
Yes	0.5 (0.4 to 0.6)	0.6 (0.4 to 0.7)
Child sex		
Male	51.2 (50.6 to 51.8)	51.0 (50.2 to 51.9)
Female	48.8 (48.2 to 49.4)	49.0 (48.1 to 49.8)

Variable	Year R	Year 6
Duration of breastfeeding		
No breastfeeding	48.2 (47.4 to 49.0)	-
Minimum 10 days	19.6 (19.0 to 20.2)	-
Minimum 6 weeks	21.8 (21.1 to 22.5)	-
Minimum 8 weeks	9.5 (9.1 to 10.0)	-
Minimum 4 months	0.3 (0.2 to 0.4)	-
9 months	0.6 (0.4 to 0.7)	-

7.3.2 Multivariable models

Models developed using the multiply imputed datasets are presented here and the complete case tables are presented in Appendix F. The predictors selected for inclusion were the same in the complete case and multiply imputed models for the booking and birth models. Some differences were observed between the multiply imputed and complete cases models during early life with fewer booking and birth predictors selected for inclusion into the model. However, the complete case sample was much smaller at these stages due to missing data. The coefficients are presented throughout this chapter as this is required for the risk calculation. The odds ratios for the multiply imputed models using the clinical cut-off of ≥91st centile is presented in Appendix E. Complete case models using the population monitoring cut-offs are presented in Appendix G (≥85th centile) and Appendix H (≥95th centile).

A summary of the predictors selected for inclusion in the Year R and Year 6 models is presented in Figure 7.2. Predictors selected for inclusion into the model were similar for the outcome at Year R and Year 6. The key differences between the models for the outcome at Year R and Year 6 were that maternal age and parity were predictors only in the Year R and maternal employment status was a predictor only in the Year 6 models. Educational attainment was a predictor in the models for both outcome points (Year R and Year 6) at all stages except for the booking model for outcome at Year R.

7.3.2.1 Year R

The prediction models for the risk of overweight and obesity at Year R are presented in Table 7.4. Eight predictors were selected for inclusion in the final model at booking: maternal age, BMI, smoking status, ethnicity, intake of folic

acid supplements, first language, partnership status and parity. For the outcome at birth, the same predictors were selected for inclusion in the final model with the addition of maternal educational attainment, birthweight and gestational age at birth. At early life, all maternal predictors with the exception of first language and parity were included. Child predictors included birthweight, sex and weight at ~1 or ~2 years respectively. Gestational age at birth remained a predictor at ~1 year but not at ~2 years. Transformations were identified through the mfp algorithm on Stata for maternal age, maternal BMI and birthweight.

Predictors included in the model in the complete case and multiple imputation were the same for the booking and birth models. However, there were some differences in the predictors included in the early life models. Maternal age at booking and gestational age at birth were included in the early life model at ~1 year in the multiple imputation analysis but not in the complete cases. Maternal ethnicity and intake of folic acid supplements were included in all the models in the multiple imputation analysis but not in the early life model at ~2 years in the complete cases. Birthweight was only included in the birth model in the complete case analysis but was additionally included in both early life models in the multiple imputation analysis.

Predictors included in the complete case models were similar for the different cut-offs but there was less consistency in predictors across the stages. Only maternal BMI and smoking status were included across all stages for all cut-offs. Ethnicity was not included in the early life model at ~2 years for the outcomes defined as ≥85th and ≥91st centiles. Additional predictors not included in the models for outcome at ≥91st centile include obstetric history of GDM and mode of birth at ≥85th centile, obstetric history of pre-eclampsia and gestational age at booking at ≥95th centile and breastfeeding at both population monitoring cut-offs.

7.3.2.1 Year 6

The prediction models for the risk of overweight and obesity at 10-11 years are presented in Table 7.5. Seven predictors were selected for inclusion in the final model at booking: maternal BMI, smoking status, employment status, educational attainment, ethnicity, intake of folic acid supplements and first language. All these predictors were retained in the birth model and partnership status, birthweight, gestational age at birth, infant sex and obstetric history of GDM were added. For the early life models, all booking predictors with the exception of first

language were included as well as birthweight weight and child weight. The model at ~1 year additionally included gestational age at birth. Transformations were identified through the mfp algorithm on Stata for maternal BMI and birthweight.

Predictors included in the model in the complete case and multiple imputation were the same for the booking and birth models. Differences in the early life models between multiple imputation and complete cases were educational attainment (not in ~1 year complete case model); maternal employment, intake of folic acid supplements and birthweight (not in both early life complete case models); partnership status (in the ~1 year complete case model only) and child sex (in the ~2 year complete case model only).

Maternal BMI, ethnicity and smoking status were included across all stages using complete cases for all cut-offs (85th, 91st and 95th). Additional predictors included GDM and pre-eclampsia in current pregnancy (≥85th) and family history of hypertensive disorders (≥95th). Most predictors included across the stages were comparable across the outcome cut-offs.

Figure 7.2: Summary of predictors included the prediction models at Year R and Year 6

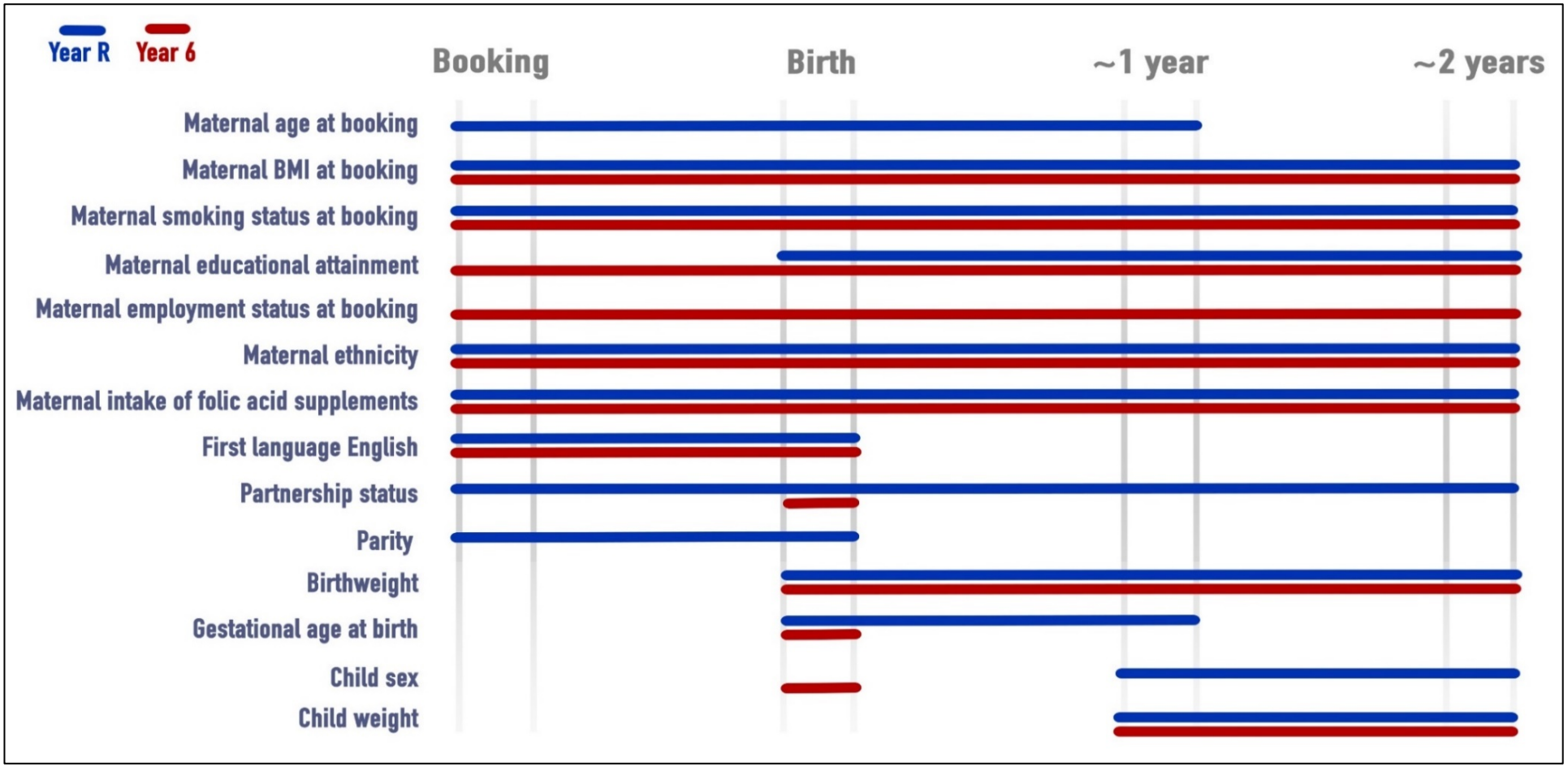


Table 7.4: Estimates of the final models for the prediction of outcome of overweight and obesity (≥91st centile) in children aged 4-5 years including discrimination and calibration

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Intercept	0.877	0.593 to 1.16		2.215	1.348 to 3.082		-5.186	-6.318 to -4.053		-10.510	-11.135 to -9.886	
Maternal age at booking, years	1.394	0.842 to 1.946	<0.001	1.114	0.512 to 1.716	<0.001	-0.006	-0.013 to 0.001	0.095			
Maternal BMI at booking, kg/m^2	-7.061	-7.507 to -6.615	<0.001	-6.371	-6.835 to -5.908	<0.001	-6.733	-7.25 to -6.215	<0.001	-6.687	-7.253 to -6.122	<0.001
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	0.099	0.02 to 0.178	0.014	0.080	-0.003 to 0.163	0.059	0.047	-0.041 to 0.135	0.298	0.044	-0.05 to 0.138	0.361
Current smoker	0.436	0.341 to 0.532	<0.001	0.583	0.481 to 0.685	<0.001	0.532	0.419 to 0.645	<0.001	0.536	0.414 to 0.659	<0.001
Maternal educational attainment												
University or above				Ref			Ref			Ref		
College				0.088	-0.01 to 0.186	0.077	0.130	0.028 to 0.233	0.013	0.116	0.006 to 0.225	0.038
Secondary or lower				0.103	-0.004 to 0.21	0.059	0.190	0.077 to 0.302	0.001	0.174	0.053 to 0.295	0.005

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal ethnicity												
White	Ref			Ref						Ref		
Mixed	0.020	-0.304 to 0.343	0.904	0.105	-0.238 to 0.447	0.550	0.098	-0.25 to 0.446	0.580	0.019	-0.355 to 0.394	0.919
Asian	0.274	0.121 to 0.428	<0.001	0.444	0.283 to 0.605	<0.001	0.589	0.424 to 0.754	<0.001	0.402	0.223 to 0.581	<0.001
Black/African/Caribbean	0.655	0.418 to 0.892	<0.001	0.778	0.519 to 1.037	<0.001	0.771	0.507 to 1.034	<0.001	0.511	0.226 to 0.796	<0.001
Other	0.084	-0.267 to 0.434	0.640	0.124	-0.237 to 0.484	0.501	0.235	-0.153 to 0.624	0.235	-0.073	-0.487 to 0.341	0.729
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref			Ref			Ref		
Started taking once pregnant	0.094	0.013 to 0.175	0.023	0.120	0.037 to 0.203	0.005	0.156	0.067 to 0.245	0.001	0.155	0.058 to 0.252	0.002
Not taking supplement	0.053	-0.072 to 0.178	0.402	0.084	-0.044 to 0.213	0.198	0.160	0.023 to 0.296	0.022	0.159	0.002 to 0.317	0.047
Maternal first language English												
No	Ref			Ref								
Yes	-0.319	-0.515 to -0.122	0.001	-0.285	-0.496 to -0.074	0.008						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Partnership status at booking												
Partnered	Ref			Ref			Ref			Ref		
Single	0.182	0.067 to 0.297	0.002	0.193	0.075 to 0.31	0.001	0.196	0.066 to 0.327	0.003	0.176	0.033 to 0.319	0.016
Parity at booking												
0	Ref			Ref								
1	0.017	-0.062 to 0.095	0.678	-0.108	-0.186 to -0.029	0.007						
2	0.093	-0.014 to 0.2	0.088	-0.057	-0.169 to 0.055	0.318						
3	0.173	0.037 to 0.308	0.012	0.019	-0.125 to 0.162	0.799						
Birthweight, kg				0.107	0.097 to 0.117	<0.001	0.129	0.031 to 0.226	0.010	-0.114	-0.196 to -0.032	0.007
Gestational age at birth, days				-0.011	-0.014 to -0.008	<0.001	-0.008	-0.012 to -0.004	<0.001			
Child sex												
Male							Ref			Ref		
Female							0.426	0.343 to 0.509	<0.001	0.366	0.283 to 0.45	<0.001
Child weight, kg							0.753	0.694 to 0.813	<0.001	0.825	0.78 to 0.869	<0.001

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Transformations:												
Maternal age at booking	(Maternal age/10)^-2			(Maternal age/10)^-2								
Maternal BMI at booking	(Maternal BMI/10)^-1			(Maternal BMI/10)^-1			(Maternal BMI/10)^-1			(Maternal BMI/10)^-1		
Birthweight				Birthweight^2								
Discrimination and calibration:												
AUC	0.66 0.65 to 0.67			0.69 0.68 to 0.70			0.78 0.77 to 0.79			0.83 0.82 to 0.84		
Calibration slope (standard error)	0.98 (0.03)			0.98 (0.03)			0.99 (0.01)			0.99 (0.01)		

Table 7.5: Estimates of the final models for the prediction of outcome of overweight and obesity (≥91st centile) in children aged 10-11 years

Predictors	Birth			Early life (~1 year)			Early life (~2 years)			Booking		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Intercept	1.811	1.405 to 2.216		2.948	1.893 to 4.003		1.612	0.298 to 2.927		-0.287	-1.173 to 0.598	
Maternal BMI at booking, kg/m^2	-8.115	-8.693 to -7.537	<0.001	-7.813	-8.414 to -7.212	<0.001	-9.908	-10.72 to -9.096	<0.001	-10.362	-11.248 to -9.477	<0.001
Maternal smoking status												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	0.198	0.101 to 0.296	<0.001	0.194	0.095 to 0.293	<0.001	0.153	0.048 to 0.258	0.004	0.159	0.051 to 0.267	0.004
Current smoker	0.574	0.458 to 0.689	<0.001	0.641	0.519 to 0.764	<0.001	0.561	0.425 to 0.696	<0.001	0.584	0.444 to 0.723	<0.001
Maternal education												
Undergraduate or above	Ref			Ref			Ref			Ref		
College	0.280	0.155 to 0.404	<0.001	0.294	0.167 to 0.421	<0.001	0.287	0.155 to 0.42	<0.001	0.264	0.126 to 0.402	<0.001
Secondary school or lower	0.316	0.187 to 0.445	<0.001	0.331	0.198 to 0.464	<0.001	0.338	0.195 to 0.481	<0.001	0.291	0.135 to 0.448	<0.001
Maternal employment status												
Employed	Ref			Ref			Ref			Ref		
Unemployed	-0.006	-0.101 to 0.088	0.896	-0.018	-0.116 to 0.079	0.712	-0.005	-0.111 to 0.101	0.925	0.066	-0.046 to 0.179	0.247
Student or in training	0.467	0.186 to 0.747	0.001	0.430	0.154 to 0.706	0.002	0.390	0.098 to 0.682	0.009	0.474	0.162 to 0.787	0.003

Predictors	Birth			Early life (~1 year)			Early life (~2 years)			Booking		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal ethnicity												
White	Ref			Ref			Ref			Ref		
Mixed	0.510	0.101 to 0.92	0.015	0.538	0.098 to 0.978	0.017	0.514	0.057 to 0.97	0.027	0.531	0.066 to 0.996	0.025
Asian	0.706	0.503 to 0.91	<0.001	0.804	0.588 to 1.02	<0.001	0.881	0.669 to 1.093	<0.001	0.921	0.7 to 1.143	<0.001
Black/African/Caribbean	0.783	0.385 to 1.181	<0.001	0.836	0.412 to 1.26	<0.001	0.868	0.437 to 1.298	<0.001	0.868	0.432 to 1.304	<0.001
Other	0.342	-0.08 to 0.763	0.112	0.386	-0.056 to 0.828	0.087	0.503	0.046 to 0.959	0.031	0.523	0.056 to 0.99	0.028
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref			Ref			Ref		
Started taking once pregnant	0.189	0.09 to 0.287	<0.001	0.183	0.084 to 0.281	<0.001	0.190	0.086 to 0.293	<0.001	0.174	0.065 to 0.283	0.002
Not taking supplement	0.205	0.066 to 0.344	0.004	0.187	0.045 to 0.329	0.010	0.207	0.055 to 0.359	0.008	0.181	0.018 to 0.344	0.030
Maternal first language English												
No	Ref			Ref								
Yes	-0.304	-0.601 to -0.008	0.044	-0.299	-0.622 to 0.024	0.070						

Predictors	Birth			Early life (~1 year)			Early life (~2 years)			Booking		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Partnership status												
Partnered				Ref								
Single				0.139	-0.008 to 0.286	0.063						
Birthweight, kg				1.218	0.918 to 1.518	<0.001	-0.022	-0.157 to 0.112	0.744	-0.158	-0.262 to -0.055	0.003
Gestational age at birth, days				-0.010	-0.014 to -0.005	<0.001	-0.004	-0.008 to 0.000	0.041			
Gender												
Male				Ref								
Female				-0.209	-0.293 to -0.125	<0.001						
Infant weight, kg							0.447	0.346 to 0.548	<0.001	0.424	0.357 to 0.491	<0.001
Transformations:												
Maternal BMI	(Maternal BMI/10)^-1			(Maternal BMI/10)^-1			(Maternal BMI/10)^-0.5			(Maternal BMI/10)^-0.5		
Birthweight				Ln(Birthweight)								
Discrimination and calibration:												
AUC	0.69 0.67 to 0.70			0.70 0.69 to 0.71			0.73 0.71 to 0.74			0.75 0.73 to 0.77		
Calibration slope	0.99 (0.03)			0.99 (0.03)			0.99 (0.02)			1.00 (0.02)		

7.3.3 Model performance

Discrimination (AUC) improved across the stages identified for model development (booking appointment, birth and early life). The improvement in AUC was more pronounced for outcome at Year R (0.66 at booking to 0.83 at ~2 years) (Table 7.4) compared to Year 6 (0.69 at booking to 0.75 at ~2 years) (Table 7.5). AUC for the Year R models were the same in the multiply imputed and after internal validation in the complete case models. However, in the Year 6 models, AUC was slightly higher in the multiply imputed (0.69 at booking, 0.70 at birth, 0.73 at ~1 year and 0.75 at ~2 years) compared to the complete case models after internal validation (0.68 at booking, 0.69 at birth, 0.71 at ~1 year and 0.73 at ~2 years).

Calibrations plots overlaying the results of the analysis of the imputed datasets for the Year R model stages are presented in Figure 7.3, Figure 7.4, Figure 7.5 and Figure 7.6 and for Year 6 in Figure 7.7, Figure 7.8, Figure 7.9 and Figure 7.10. The calibration across all models was consistently strong as evidenced by the calibration slope and the gradient. The calibration across the imputed datasets were similar across the booking and birth models for outcomes at both Year R and Year 6. There was more variation across the imputed datasets in the early life models particularly for outcome at Year R, however this is the stage with the highest percentage of missing data and thus more variation across the datasets is to be expected.

Shrinkage factors showed a small amount of optimism in the models suggesting all models to be stable. The estimated shrinkage factors was 0.98 or 0.99 for all models suggesting that only a small percentage of the model fit was noise. The shrunken coefficients and intercepts are presented in Table 7.6 and Table 7.7 for Year R and Year 6 respectively.

Figure 7.3: Calibration plot of the prediction model (overlying the results of the analysis on the 70 imputed datasets) at booking for outcome at Year R

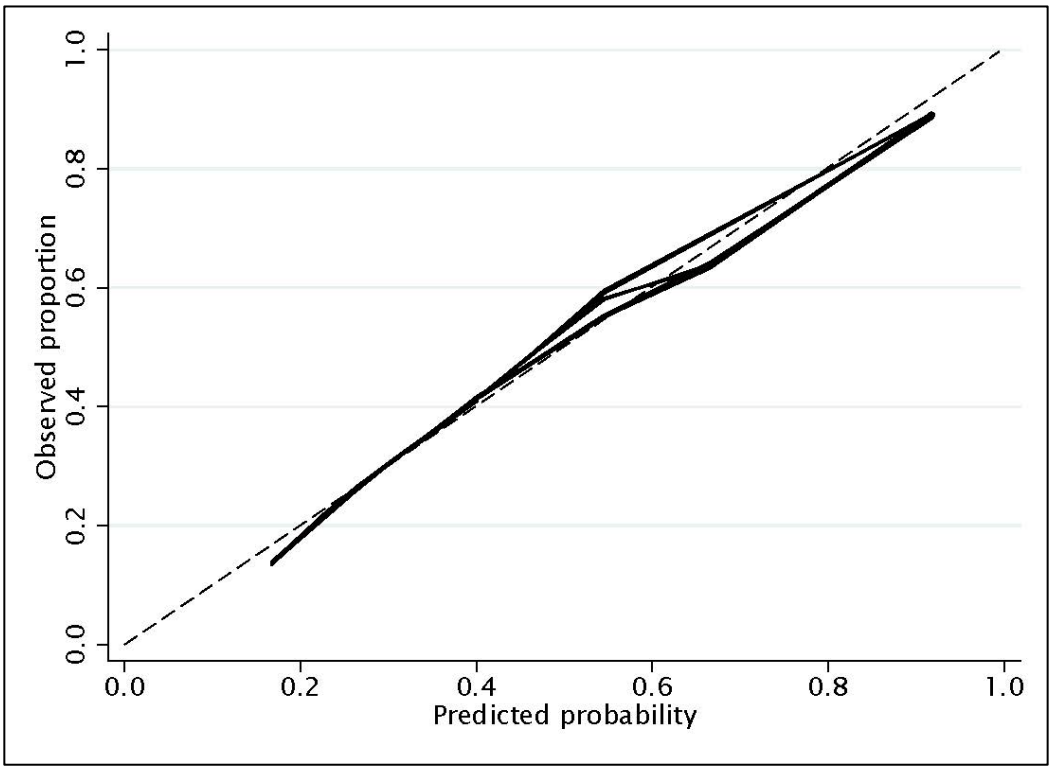


Figure 7.4: Calibration plot of the prediction model (overlying the results of the analysis on the 70 imputed datasets) at birth for outcome at Year R

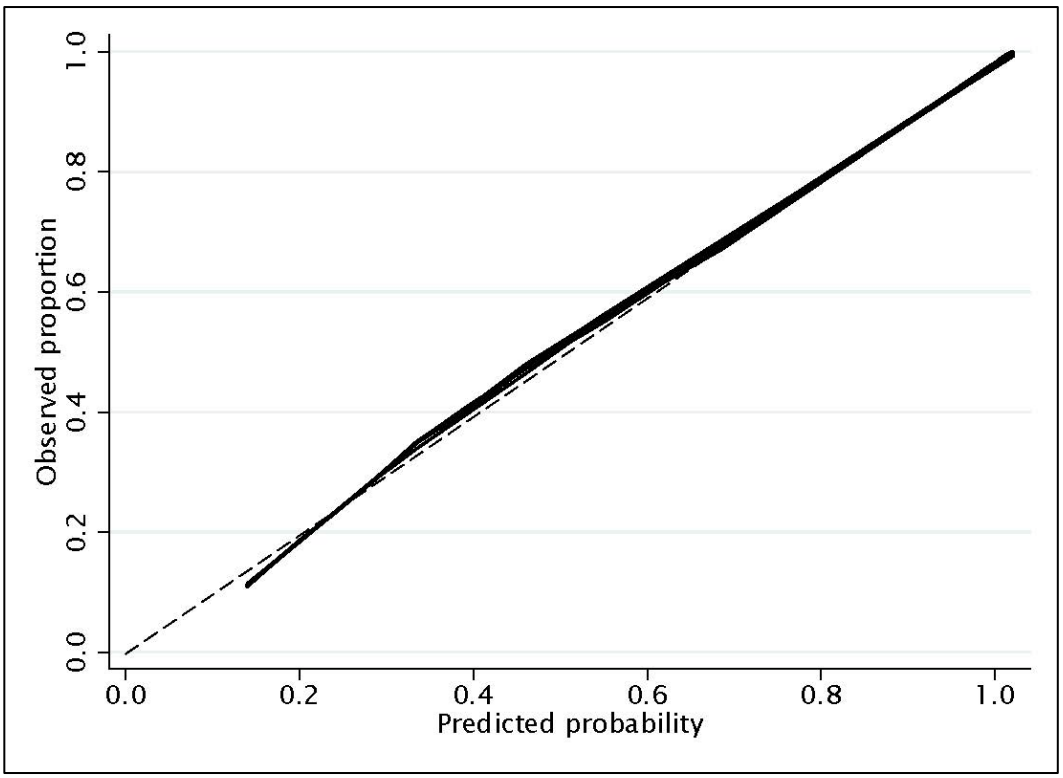


Figure 7.5: Calibration plot of the prediction model (overlying the results of the analysis on the 70 imputed datasets) at early life (~1 year) for outcome at Year R

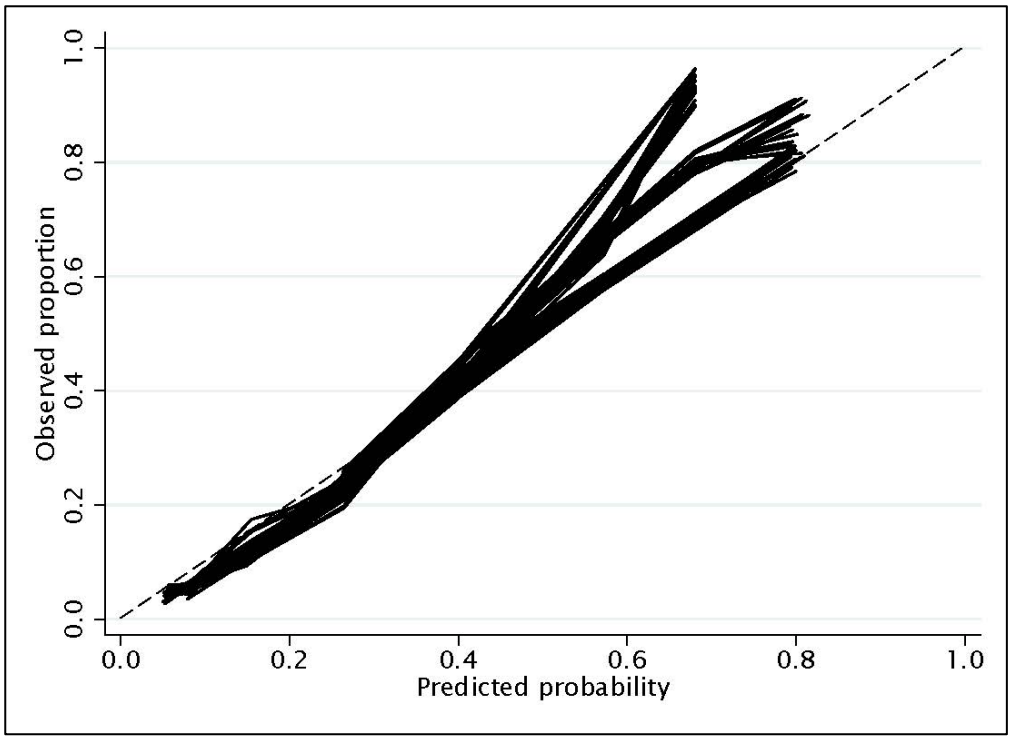


Figure 7.6: Calibration plot of the prediction model (overlying the results of the analysis on the 70 imputed datasets) at early life (~2 years) for outcome at Year R

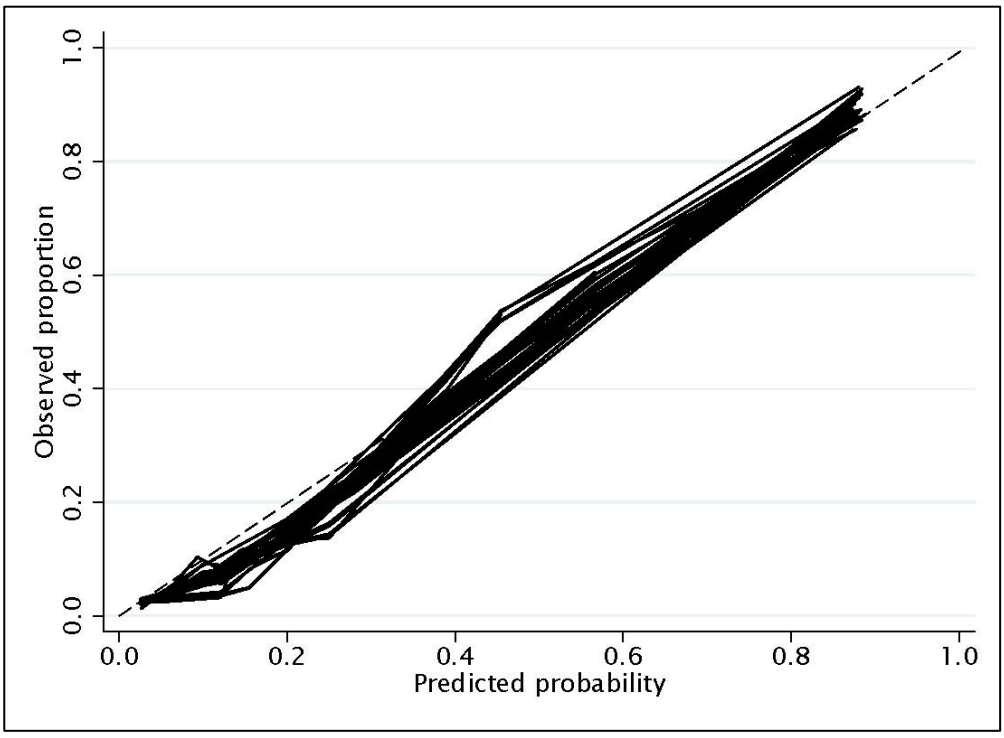


Figure 7.7: Calibration plot of the prediction model (overlying the results of the analysis on the 85 imputed datasets) at booking for outcome at Year 6

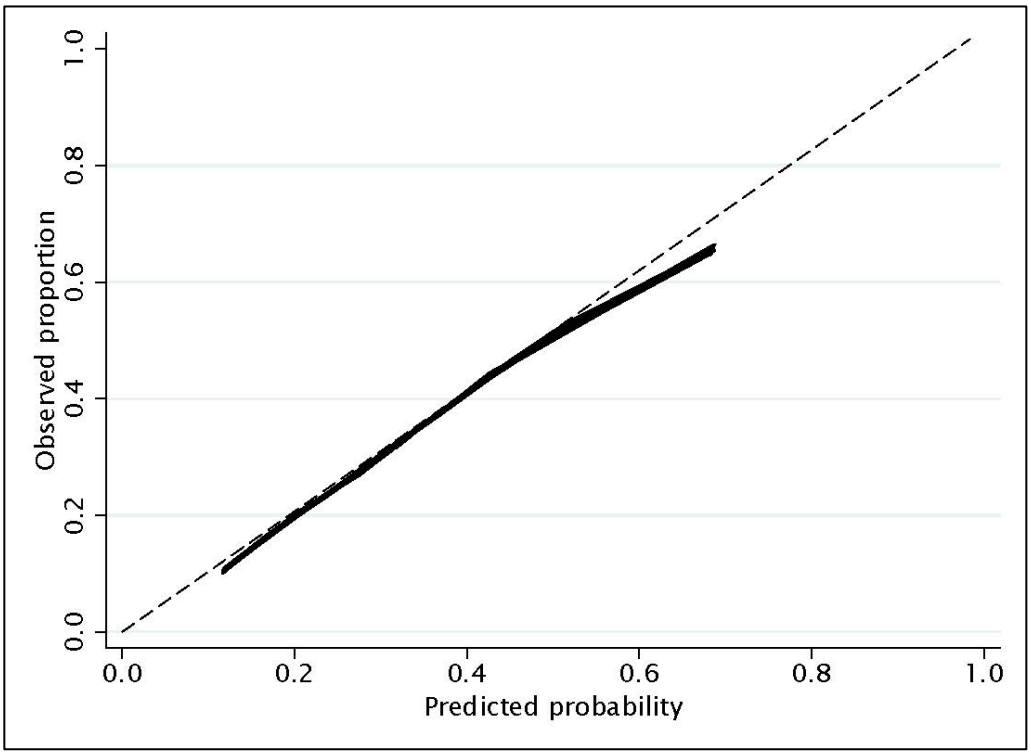


Figure 7.8: Calibration plot of the prediction model (overlying the results of the analysis on the 85 imputed datasets) at birth for outcome at Year 6

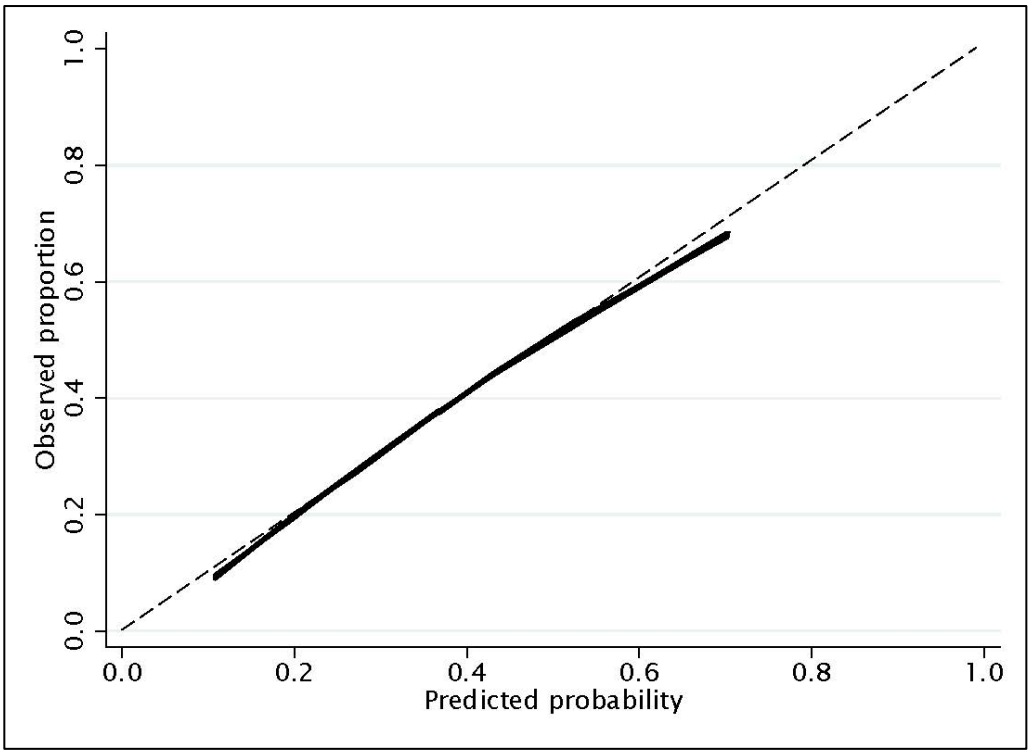


Figure 7.9: Calibration plot of the prediction model (overlying the results of the analysis on the 85 imputed datasets) at early life (~1 year) for outcome at Year 6

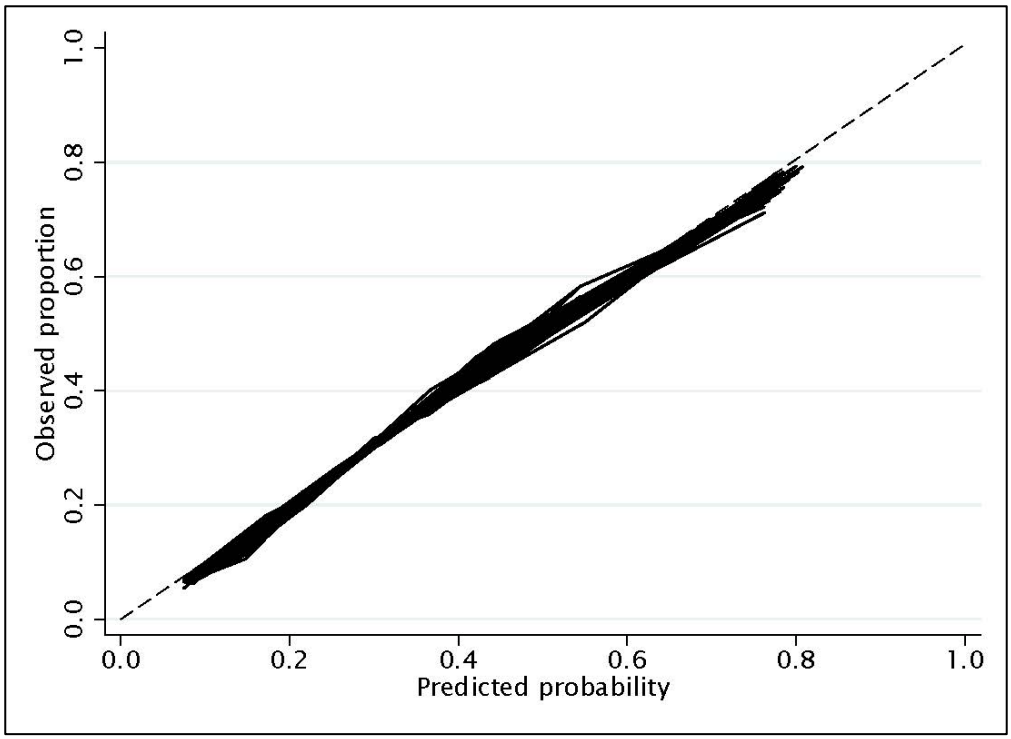


Figure 7.10: Calibration plot of the prediction model (overlying the results of the analysis on the 85 imputed datasets) at early life (~2 years) for outcome at Year 6

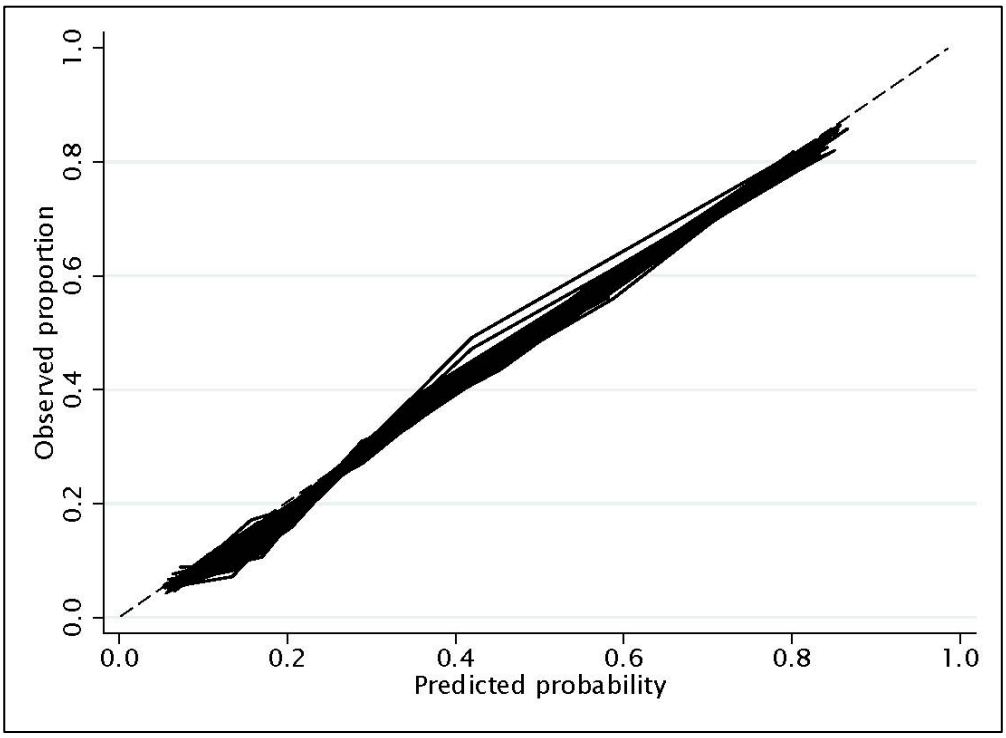


Table 7.6: Intercept and regression coefficients of the prediction models for overweight and obesity (≥91st centile) in children aged 4-5 years before and after shrinkage

Predictors	Booking		Birth		Early life (~1 year)		Early life (~2 years)	
	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient
Intercept	0.877	0.845	2.215	2.169	-5.186	-5.160	-10.510	-10.466
Maternal age at booking, years	1.394	1.377	1.114	1.101	-0.006	-0.006		
Maternal BMI at booking, kg/m^2	-7.061	-6.971	-6.371	-6.295	-6.733	-6.686	-6.687	-6.656
Maternal smoking status at booking								
Never smoked	Ref		Ref		Ref		Ref	
Ex-smoker	0.099	0.098	0.080	0.079	0.047	0.047	0.044	0.044
Current smoker	0.436	0.431	0.583	0.576	0.532	0.528	0.536	0.534
Maternal educational attainment								
University or above			Ref		Ref		Ref	
College			0.088	0.087	0.130	0.129	0.116	0.115
Secondary or lower			0.103	0.102	0.190	0.188	0.174	0.173
Maternal ethnicity								
White	Ref		Ref		Ref		Ref	
Mixed	0.020	0.020	0.105	0.103	0.098	0.098	0.019	0.019
Asian	0.274	0.271	0.444	0.439	0.589	0.585	0.402	0.400
Black/African/Caribbean	0.655	0.647	0.778	0.769	0.771	0.766	0.511	0.509
Other	0.084	0.083	0.124	0.122	0.235	0.234	-0.073	-0.073

Predictors	Booking		Birth		Early life (~1 year)		Early life (~2 years)	
	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient		Coefficient	Shrunken coefficient	Coefficient
Maternal intake of folic acid supplements								
Taking prior to pregnancy	Ref		Ref		Ref		Ref	
Started taking once pregnant	0.094	0.093	0.120	0.118	0.156	0.155	0.155	0.154
Not taking supplement	0.053	0.053	0.084	0.083	0.160	0.158	0.159	0.159
Maternal first language English								
No	Ref		Ref					
Yes	-0.319	-0.315	-0.285	-0.282				
Partnership status at booking								
Partnered	Ref		Ref		Ref		Ref	
Single	0.182	0.179	0.193	0.190	0.196	0.195	0.176	0.175
Parity at booking								
0	Ref		Ref					
1	0.017	0.016	-0.108	-0.106				
2	0.093	0.092	-0.057	-0.056				
3	0.173	0.171	0.019	0.018				
Birthweight, kg			0.107	0.106	0.129	0.128	-0.114	-0.113
Gestational age at birth, days			-0.011	-0.011	-0.008	-0.008		

Predictors	Booking		Birth		Early life (~1 year)		Early life (~2 years)	
	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient
Infant gender								
Male					Ref		Ref	
Female					0.426	0.423	0.366	0.364
Infant weight, kg					0.753	0.748	0.825	0.821
Shrinkage factor	0.99		0.99		0.99		0.99	

Table 7.7: Intercept and regression coefficients of the prediction models for overweight and obesity (≥91st centile) in children aged 10-11 years before and after shrinkage

Predictors	Booking		Birth		Early life (~1 year)		Early life (~2 years)	
	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient		Coefficient	Shrunken coefficient	Coefficient
Intercept	1.811	1.769	2.996	2.921	1.612	1.569	-0.287	-0.296
Maternal BMI at booking, kg/m^2	-8.115	-7.997	-7.842	-7.696	-9.908	-9.742	-10.362	-10.222
Maternal smoking status at booking								
Never smoked	Ref		Ref		Ref		Ref	
Ex-smoker	0.198	0.196	0.193	0.189	0.153	0.150	0.159	0.157
Current smoker	0.574	0.565	0.641	0.629	0.561	0.551	0.584	0.576

Predictors	Booking		Birth		Early life (~1 year)		Early life (~2 years)	
	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient		Coefficient	Shrunken coefficient	Coefficient
Maternal educational attainment								
Undergraduate or above	Ref		Ref		Ref		Ref	
College	0.280	0.276	0.295	0.290	0.287	0.283	0.264	0.260
Secondary school or lower	0.316	0.311	0.331	0.325	0.338	0.332	0.291	0.287
Maternal employment status								
Employed	Ref		Ref		Ref		Ref	
Unemployed	-0.006	-0.006	-0.015	-0.015	-0.005	-0.005	0.066	0.066
Student or in training	0.467	0.460	0.429	0.421	0.390	0.383	0.474	0.468
Maternal ethnicity								
White	Ref		Ref		Ref		Ref	
Mixed	0.510	0.503	0.538	0.528	0.514	0.505	0.531	0.524
Asian	0.706	0.696	0.809	0.794	0.881	0.866	0.921	0.909
Black/African/Caribbean	0.783	0.772	0.839	0.823	0.868	0.853	0.868	0.856
Other	0.342	0.337	0.386	0.379	0.503	0.494	0.523	0.516
Maternal intake of folic acid supplements								
Taking prior to pregnancy	Ref		Ref		Ref		Ref	
Started taking once pregnant	0.189	0.186	0.183	0.180	0.190	0.187	0.174	0.171
Not taking supplement	0.205	0.202	0.188	0.184	0.207	0.204	0.181	0.179

Predictors	Booking		Birth		Early life (~1 year)		Early life (~2 years)	
	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient		Shrunken coefficient	Coefficient
Maternal first language English								
No	Ref		Ref					
Yes	-0.304	-0.300	-0.302	-0.296				
Partnership status at booking								
Partnered			Ref					
Single			0.138	0.135				
Birthweight, kg			1.230	1.208	-0.022	-0.022	-0.158	-0.156
Gestational age at birth, days			-0.010	-0.010	-0.004	-0.004		
Gender								
Male			Ref					
Female			-0.208	-0.204				
Gestational diabetes in previous pregnancy								
No			Ref					
Yes			-0.348	-0.342				
Infant weight, kg					0.447	0.439	0.424	0.418
Shrinkage factor	0.98		0.98		0.98		0.99	

7.3.4 Risk threshold

The percentage identified at risk, sensitivity, specificity, PPV and NPV for different risk score cut-offs are presented in Table 7.8 for the Year R models and in Table 7.9 for the Year 6 models. The pattern was similar for the models at Year R and Year 6 but the sensitivity was higher, PPV was higher in the models at ~2 years and specificity and NPV correspondingly lower at similar risk thresholds in the models for outcome at Year 6. This is likely to be reflective of the increased prevalence of the outcome at Year 6.

To consider an example, a 20% risk cut-off using the Year R early life model at ~2 years identifies 24.1% of children as at risk. Sensitivity indicates that of all the children who will be overweight and obese by Year R, 65.5% would be correctly classified as 'at risk'. Specificity indicates that of all the children who will not be overweight and obese by Year R, 83.1% would be correctly classified as 'not at risk'. PPV indicates that 40.3% of children classified as at risk will be overweight and obese by Year R whereas NPV indicates that 93.3% of children classified as not at risk will not be overweight and obese by Year R. This same risk cut-off in the Year 6 early life model at ~2 years identifies 50.3% of children at risk. Of these, sensitivity indicates 77.1% of those identified at risk would be correctly classified, specificity indicated that 58.7% of those identified as not at risk would be correctly classified. PPV indicates that 37.7% of children classified at risk will be overweight and obese by Year 6 whereas NPV indicates that 88.7% of children classified as not at risk will not be overweight and obese by Year 6.

The sensitivity, specificity, PPV and NPV at each risk threshold cut-off improved across the Year R model stages but remained comparable across the stages for Year 6. For example, sensitivity at 20% risk cut-off for Year R was 37.1% at booking, 41.4% at birth, 56.9% at ~1 year and 65.5% at ~2 years. Similarly for Year 6, sensitivity at 20% risk cut-off was 75.9% at booking, 76.6% at birth, 76.5% at ~1 year and 77.1% at ~2 years.

PPV increased and NPV decreased as the risk threshold increased. For example, for the booking model at Year R, PPV of 18.2% and NPV of 92.7% at risk threshold of 10%, PPV of 25.9% and NPV of 88.2% at risk threshold of 20% and PPV of 35.3% and NPV of 86.3% at risk threshold of 30%. The same pattern was observed in the PPV and NPV values for the Year 6 models.

It is necessary to identify a risk threshold above which children would be considered high risk for the implementation of the risk score in practice. As a definitive method for doing this could not be identified from the literature, we decided to be guided by the sensitivity, specificity, PPV and NPV as well as the number of individuals identified as high risk based on this threshold. For example, for outcome at Year R, the specificity and sensitivity is comparable at a risk threshold of 15% but this identifies around 40% of the sample at risk whereas the prevalence of the outcome is 14.8%. A risk threshold of 20% would identify around 20% of the sample at risk with higher specificity but lower sensitivity and slight increase in PPV. Sensitivity and specificity are improved in the later stages (birth and early life) compared to booking. The high NPV at this risk threshold provides confidence that the majority of children identified as not at risk will not become overweight or obese.

As the models have been designed in a sequential manner and risk can be calculated at each of these stages, it is important to understand the accumulation of risk for individuals over time if the model is applied at each of these stages. This could help in the development of an intervention that is applied in stages or tailored to modify risk across the stages. Figure 7.11 shows the categorisation of children as high risk or low risk if the model is applied at each stage using a risk threshold of 20% in children aged 4-5 years. Based on this, 57.9% of the sample is consistently identified as low risk and 7.5% is consistently identified as high risk. The remaining 34.6% are identified at risk at one or two stages but not consistently. Figure 7.12 shows the same categorisation in children aged 10-11 years using a risk threshold of 30%. Using this threshold at Year 6, identifies a similar proportion (56.8%) consistently as low risk but 16.8% of the sample is now consistently at high risk.

We recommend a threshold of 20% for outcome at Year R and 30% for outcome at Year 6. This is a pragmatic recommendation based on the sensitivity and specificity and percentage of individuals identified at risk. However, a stakeholder meeting is planned for discussion on the identification of a suitable threshold being pragmatic about the implementation of the prediction tool in practice and the implications of the percentages of children identified at risk. A final decision on the risk threshold recommendation will be made after this meeting.

Table 7.8: The predictive ability of the risk score for the outcome of overweight and obesity (≥91st centile) in children aged 4-5 years

Cut-point	% at or above cut-point	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
Booking					
≥10.0	69.0	84.7 83.6 to 85.9	33.7 33.1 to 34.3	18.2 17.7 to 18.7	92.7 92.1 to 93.2
≥15.0	39.3	59.5 58.0 to 61.0	64.2 63.6 to 64.8	22.5 21.7 to 23.2	90.1 89.7 to 90.5
≥20.0	21.2	37.1 35.6 to 38.5	81.6 81.1 to 82.1	25.9 24.8 to 27.0	88.2 87.7 to 88.6
≥25.0	11.1	22.2 20.9 to 23.4	90.8 90.5 to 91.1	29.6 28.1 to 31.3	87.0 86.6 to 87.4
≥30.0	5.1	12.3 11.3 to 13.3	96.1 95.8 to 96.3	35.3 32.9 to 42.7	86.3 85.9 to 86.7
Birth					
≥10.0	64.2	83.9 82.7 to 84.9	39.3 38.6 to 39.9	19.4 18.8 to 20.0	93.3 92.8 to 93.8
≥15.0	38.1	60.8 59.4 to 62.3	65.9 65.3 to 66.4	23.7 22.9 to 24.5	90.6 90.2 to 91.0
≥20.0	21.8	41.4 39.9 to 42.9	81.6 81.1 to 82.1	28.1 29.9 to 29.2	88.9 88.5 to 89.3
≥25.0	12.6	27.7 26.3 to 29.0	90.0 89.6 to 90.4	32.5 31.9 to 34.1	87.7 87.3 to 88.1
≥30.0	7.0	16.9 15.8 to 18.1	94.7 94.4 to 95.0	35.6 33.6 to 37.8	86.7 86.3 to 87.1

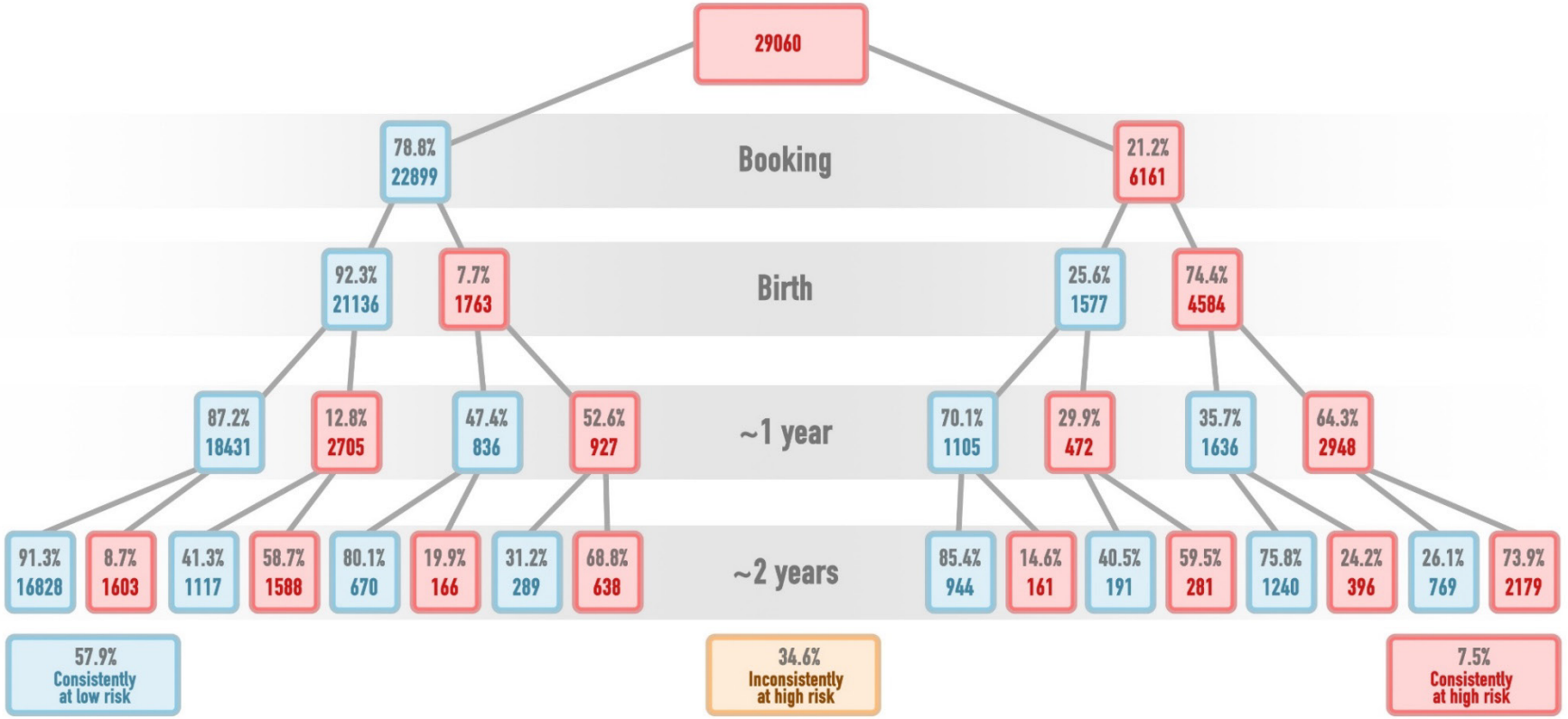
Cut-point	% at or above cut-point	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
Early life (~1 year)					
≥10.0	50.9	83.6 82.5 to 84.7	54.8 54.1 to 55.4	24.3 23.7 to 25.0	95.0 94.7 to 95.4
≥15.0	34.7	69.6 68.2 to 70.9	71.3 70.8 to 71.9	29.7 28.8 to 30.6	93.1 92.7 to 93.4
≥20.0	24.3	56.9 55.4 to 58.4	81.4 80.9 to 81.9	34.2 33.6 to 35.9	91.6 91.2 to 91.9
≥25.0	17.3	46.0 44.5 to 47.5	87.7 87.3 to 88.1	39.4 38.9 to 40.8	90.3 89.9 to 90.7
≥30.0	12.5	36.8 35.4 to 38.3	91.7 91.4 to 92.1	43.7 42.1 to 45.3	89.3 88.9 to 89.7
Early life (~2 years)					
≥10.0	43.5	84.6 83.5 to 85.6	63.7 63.1 to 64.3	28.9 28.1 to 29.7	96.0 95.6 to 96.2
≥15.0	31.8	74.8 73.5 to 76.1	75.7 75.2 to 76.2	34.9 33.9 to 35.9	94.5 94.2 to 94.8
≥20.0	24.1	65.5 64.0 to 66.9	83.1 82.6 to 83.6	40.3 39.1 to 41.4	93.3 92.9 to 93.6
≥25.0	18.8	57.2 55.7 to 58.6	87.9 87.5 to 88.3	45.2 43.9 to 46.5	92.2 91.8 to 92.5
≥30.0	14.8	59.7 58.2 to 51.2	91.3 90.9 to 91.6	49.9 48.4 to 50.7	91.2 90.9 to 91.6

Table 7.9: The predictive ability of the risk score for the outcome of overweight and obesity (≥91st centile) in children aged 10-11 years

Cut-point	% at or above cut-point	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
Booking					
≥10.0	92.6	97.8 97.2 to 98.3	9.1 8.6 to 9.7	26.0 25.2 to 26.7	92.8 91.0 to 94.3
≥15.0	75.5	89.0 87.9 to 90.1	28.9 28.0 to 29.7	29.0 28.1 to 29.9	89.0 87.9 to 90.1
≥20.0	56.9	75.9 74.4 to 77.3	49.3 48.3 to 50.2	32.7 31.7 to 33.8	86.2 85.3 to 87.1
≥25.0	40.5	61.3 59.6 to 62.9	66.3 65.4 to 67.2	37.2 35.8 to 38.5	84.0 83.2 to 84.8
≥30.0	28.3	47.0 45.3 to 48.7	77.8 77.0 to 78.6	40.8 39.2 to 42.4	81.8 81.0 to 82.6
Birth					
≥10.0	90.7	97.4 96.8 to 97.9	11.5 10.9 to 12.2	26.4 25.6 to 27.2	93.1 91.6 to 94.5
≥15.0	73.7	89.1 88.0 to 90.2	31.3 30.4 to 32.2	29.7 28.8 to 30.6	89.9 88.8 to 90.8
≥20.0	55.9	76.6 75.2 to 78.1	50.8 49.9 to 51.8	33.7 32.6 to 34.8	87.0 86.1 to 87.8
≥25.0	40.8	61.5 60.5 to 63.8	66.5 65.3 to 67.1	37.5 36.2 to 38.8	84.3 83.5 to 85.1
≥30.0	28.9	48.8 47.1 to 50.5	77.6 76.7 to 78.4	41.5 39.9 to 43.0	82.3 81.5 to 83.1

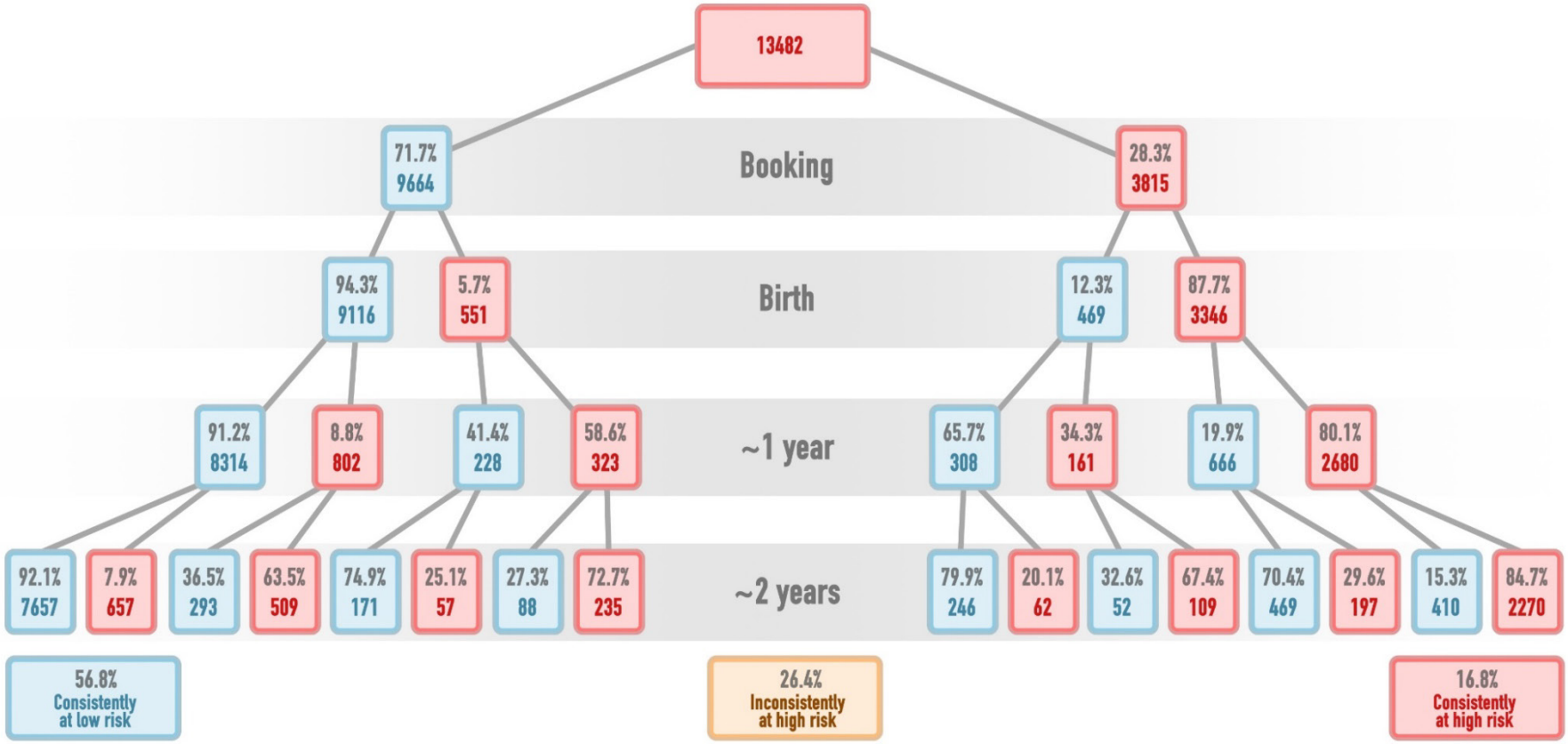
Cut-point	% at or above cut-point	Sensitivity	Specificity	Positive predictive value (PPV)	Negative predictive value (NPV)
Early life (~1 year)					
≥10.0	85.1	96.1 95.4 to 96.8	18.4 17.7 to 19.4	27.7 26.9 to 28.6	93.6 92.4 to 94.6
≥15.0	68.4	87.8 86.6 to 88.9	37.9 36.9 to 38.8	31.5 30.6 to 32.5	90.5 89.6 to 91.4
≥20.0	52.7	76.5 75.1 to 78.0	55.1 54.1 to 56.1	35.7 34.6 to 36.8	87.8 87.0 to 88.6
≥25.0	39.7	64.5 62.8 to 66.1	68.4 67.5 to 68.6	39.9 38.6 to 41.2	85.5 84.8 to 86.3
≥30.0	29.5	52.8 51.1 to 54.5	78.1 77.3 to 78.9	44.0 42.4 to 45.6	83.6 82.8 to 84.3
Early life (~2 years)					
≥10.0	79.8	95.0 94.2 to 95.7	25.1 24.3 to 26.0	29.2 28.4 to 30.1	93.9 92.9 to 94.8
≥15.0	64.1	86.7 85.5 to 87.8	43.3 42.3 to 44.2	33.2 32.2 to 34.2	90.9 90.0 to 91.7
≥20.0	50.3	77.1 75.6 to 78.5	58.7 57.5 to 59.4	37.7 36.5 to 38.9	88.7 87.9 to 89.4
≥25.0	39.2	66.8 65.1 to 68.4	69.8 68.9 to 70.7	41.8 40.1 to 43.2	86.6 85.8 to 87.3
≥30.0	30.4	56.8 55.1 to 58.5	78.2 77.4 to 79.0	45.9 44.4 to 47.5	84.8 84.0 to 85.5

Figure 7.11: The categorisation of children as high risk (red) or low risk (blue) if the prediction model is applied at each stage using the risk threshold of 20% in children aged 4-5 years



Consistently at low risk: At low risk at all four stages
Inconsistently at high risk: At high risk at one or more of the four stages but not at all four stages
Consistently at high risk: At high risk at all four stages

Figure 7.12: The categorisation of children as high risk (red) or low risk (blue) if the prediction model is applied at each stage using the risk threshold of 30% in children aged 10-11 years



Consistently at low risk: At low risk at all four stages
Inconsistently at high risk: At high risk at one or more of the four stages but not at all four stages
Consistently at high risk: At high risk at all four stages

7.3.5 Application of the model

This section describes how the model can be used in practice. The following example equation is required to make prediction of the risk of overweight and obesity at 4-5 years of age at booking using the SLOPE model:

Y = 0.877 + [1.377 x (maternal age at booking/10)^-2] + [-6.971 x (maternal BMI/10) ^-1] + 0.098 [ex-smoker] + 0.431 [current smoker] + 0.020 [Mixed ethnicity] + 0.271 [Asian ethnicity] + 0.647 [Black/African/Caribbean] + 0.083 [Other ethnicity] + 0.093 [started taking folic acid once pregnant] + 0.053 [not taking folic acid] – 0.315 [first language English] + 0.179 [lone parent at booking] + 0.016 [parity 1 at booking] + 0.092 [parity 2 at booking] + 0.171 [parity 3 at booking]

The log-odds (Y) is then converted into probability (P) as follows:

$$P = 1/[1 + \exp(-Y)]$$

where P is the probability of developing the outcome and Y is the log-odds estimated using the model.

Consider the following example:

Asian women aged 30 years, BMI of 27.9kg/m^2, booked at 86 days gestation, ex-smoker, not taking folic acid supplements with parity of 1 at booking, first language English and has history of GDM, university educated, caesarean section delivery at 274 days gestation, female baby with birthweight of 3.34 kg, weight at one year 10.8kg, weight at 2 years 15.2kg

We can apply the above equation to calculate the risk of overweight and obesity at 4-5 years as follows:

Y = 0.845 + [1.377 x (maternal age at booking/10)^-2] - [6.971 x (maternal BMI/10) ^-1] + 0.098 [ex-smoker] + 0.271 [Asian ethnicity] + 0.053 [not taking folic acid] – 0.315 [first language English] + 0.016 [parity 1 at booking]

= 0.845 + 0.153 – 2.499 + 0.098 + 0.271+ 0.053 – 0.315 + 0.016

= -1.378

The log-odds (Y) is then converted into probability (P):

$$P = 1/[1 + \exp(-Y)] = 1/[1 + \exp(1.378)] = 1/4.965$$

$$= 0.201 \ (20.1\%)$$

The estimated probability of overweight and obesity in the offspring for this mother at booking would be 20.1%.

If we assessed this baby at birth, this could be updated as follows:

$$Y = 2.169 + [1.101 \times (\text{maternal age at booking}/10)^{-2}] - [6.295 \times (\text{maternal BMI}/10)^{-1}] + 0.079 \ [\text{ex-smoker}] + 0.439 \ [\text{Asian ethnicity}] + 0.083 \ [\text{not taking folic acid}] - 0.282 \ [\text{first language English}] - 0.106 \ [\text{parity 1 at booking}] + [0.106 \times \text{birthweight}] - [0.011 \times \text{gestational age at birth}]$$

$$= 2.169 + 0.122 - 2.256 + 0.079 + 0.438 + 0.083 - 0.282 - 0.106 + 1.182 - 3.014$$

$$= -1.583$$

The log-odds (Y) is then converted into probability (P):

$$P = 1/[1 + \exp(-Y)] = 1/[1 + \exp(1.583)] = 1/5.871$$

$$= 0.170 \ (17\%)$$

If we assessed this baby at 1 year, this could be updated as follows:

$$Y = -5.160 - [0.006 \times (\text{maternal age at booking}] - [6.686 \times (\text{maternal BMI}/10)^{-1}] + 0.047 \ [\text{ex-smoker}] + 0.585 \ [\text{Asian}] + 0.158 \ [\text{not taking folic acid}] + [0.128 \times \text{birthweight}] - [0.008 \times \text{gestational age at birth}] + 0.423 \ [\text{female}] + [0.748 \times \text{infant weight}]$$

$$Y = -5.160 - 0.18 - 2.396 + 0.047 + 0.585 + 0.158 + 0.428 - 2.192 + 0.423 + 8.078$$

$$Y = -0.209$$

The log-odds (Y) is then converted into probability (P):

$$P = 1/[1 + \exp(0.209)] = 1/2.233 = 0.448 \ (44.8\%)$$

The estimated probability of overweight and obesity in the offspring for this mother would now be revised to 44.8% when the child is aged around 1 year. In

this example, the child would inconsistently be high risk based on the suggested risk threshold of 20%.

7.4 Discussion

Childhood obesity is a major public health challenge with rates in England continuing to rise. This chapter details risk prediction equations developed using routine data collected during pregnancy and early life. These equations can be used to identify high risk groups at each of these stages to provide additional support and intervene as early as possible. Although the model at 2 years had better discrimination for both outcomes (0.83 and 0.75 for Year R and Year 6 respectively) than the models at booking (0.66 and 0.69 at Year R and Year 6 respectively), the maternal predictors remain fairly consistent across models and thus high-risk groups could be identified at this early stage with more precise estimation as the child grows.

The risk factors for overweight and obesity during the early years (pregnancy and first two years of life) have been extensively researched as presented in Chapter 2. However, the accumulation of risk through the combination of risk factors has received less attention. Consistent predictors from the literature that have been included in the prediction equations include maternal BMI, ethnicity, smoking status, parity, birthweight and infant weight during early life.

English as maternal first language, partnership status and intake of folic acid supplements were consistent predictors in the models. Offspring of women who reported English as their first language were at lower risk compared to offspring of women who reported English as not their first language. This could be indicative of likelihood or ability to seek care or support. It could also be indicative of communication skills and social networks that women may be less able to access. Lone mothers are at higher risk of poverty (Bastos *et al.*, 2009) and ill health (Whitehead *et al.*, 2000) which could lead to increased levels of stress or anxiety. Eleven percent of single mothers in this cohort reported feeling unsupported by family or friends during pregnancy. Single mothers reported lower educational attainment, were more likely to be smokers and more likely to be unemployed than mothers with a partner. This pattern was further exacerbated in single unsupported mothers.

Folic acid supplementation is recommended to women when trying to get pregnant and during the first twelve weeks of pregnancy to reduce the risk of neural tube defects (National Institute for Health Care and Excellence, 2008b). The uptake of folic acid supplementation pre-pregnancy and during pregnancy remains low in the UK. In this dataset, less than a third of women reported intake of folic acid supplements before pregnancy, over half the sample reported intake once pregnancy was confirmed and around a tenth reported no folic supplement intake. Some countries have introduced mandatory fortification with folic acid to increase intake particularly in those with the lowest intakes and the UK government is currently consulting on the introduction of mandatory fortification. Although there is little evidence of the effect of folic acid supplementation on the risk of childhood overweight and obesity, it could be a proxy for a variety of factors such as planned pregnancy, health literacy, maternal nutrient intake status and income. As folic acid supplementation is recommended in women trying to conceive, it is more likely that the group taking supplements represent women who seek medical advice before conception or women who are aware or look into recommendations before conception. Folic acid supplements are purchased over the counter and thus could also be related to income and affordability. Predictors for folic acid supplementation in a Norwegian birth cohort included higher education (maternal and paternal), planned pregnancies and infertility treatments/chronic diseases (Nilsen *et al.*, 2006). A systematic review found that intake of folic acid supplements from preconception reduced the risk of SGA births (Hodgetts *et al.*, 2015) which is a risk factor for overweight and obesity if the child then exhibits catch-up growth in early life.

The use of routine data in the development of these prediction equations means that these can be readily implemented unlike prediction models developed using birth cohort data which would need to incorporate data not routinely collected such as paternal BMI (Weng *et al.*, 2013) which would be challenging to collect in a systematic way as all fathers may not attend booking appointments and missing data would be non-random. Additionally, the application of the risk prediction tool could lead to better data recording, for instance of breastfeeding status and duration which in the current dataset was poorly recorded (69% missing for outcome at Year R and 99% missing for outcome at Year 6). The higher percentage of missing data in Year 6 could potentially be attributed to changes in recording systems and practices. The lower percentage of missing data in

comparison at Year R indicates an improvement in recording although large potential for improvement remains. Health visitor records in early life tend to be documented on the system as free text and thus it is possible that breastfeeding status may be better recorded than it appears to be in the linked dataset. However, as free text needs to be screened for potential identifiable and/or sensitive information, accessing this for research is usually problematic as it requires more resources from the data holder to carry out this screening. Additionally, this screening may need to be done by individuals involved in care as opposed to data analysts and thus might prove unfeasible within existing workloads.

Other risk prediction equations have included conditional weight gain as a predictor which requires the conversion of weights into z-scores and thus needs to be incorporated into an electronic tool for use. We have incorporated weights as measured instead of converting to z-scores so the models can be used as an electronic or a paper version can be developed if deemed necessary. Although electronic tools are more accessible to both families and health professionals, the availability of a paper tool can be useful.

I applied the two models that could be applied to this dataset to test the validity of the models (Druet *et al.*, 2012; Santorelli *et al.*, 2013). One of the models had six versions, one with and without maternal BMI, and three versions of each incorporating weight gain from birth to 6 months, birth to 9 months and birth to 12 months (Santorelli *et al.*, 2013). Weight at 1 year was going to be used in my analysis so I applied the model incorporating weight gain from birth to 12 months with and without maternal BMI. Inclusion of maternal BMI slightly improved the model however the AUC was much lower in the SLOPE dataset (0.70 without maternal BMI and 0.71 including maternal BMI) compared to the development/validation dataset (both 0.91) for the outcome of obesity at 4-5 years (Appendix I). This was even lower for outcomes at 10-11 years (0.59 without maternal BMI and 0.60 including maternal BMI). This model had been developed to predict the outcome at 2 years of age and application in this dataset implies that longer term prediction may not be as valid. On applying the other model, AUC was the same as that achieved in the development cohort at 4-5 years (0.77) but was lower at 10-11 years (0.69). This model was developed using outcome data at 7-11 years and used the International Obesity Task Force to define the outcome of obesity which are based on and linked to the

corresponding adult BMI cut-offs and thus cannot be expressed as BMI centiles or SD scores. Additionally, this was developed by performing a meta-analysis of individual level data from three studies which had a lower prevalence of the outcome (3% compared to 9.5% at 4-5 years and 17.8% at 10-11 years in my linked dataset). This was because the three included studies recruited children born 1959-66, 1981-84 and 1991-92. Thus, neither model was that predictive of the outcome in the SLOPE data particularly at 10-11 years.

Of the predictors included in the prediction models, maternal BMI, maternal smoking status, intake of folic acid supplements, birthweight and child weight are considered modifiable. Maternal first language English was included as a predictor and although this is not directly modifiable, it is possible to provide additional support for these women. Parity is non-modifiable but intervening early (after first pregnancy) to modify risks identified in this thesis such as interpregnancy interval and maternal weight change as well as other changes could modify the risk in higher order pregnancies. As these are predictors, the relationship with the outcome is not necessarily causal and thus interventions do not have to act on factors identified by the model.

For the booking and birth models where the percentage of missing data was low, the models were similar. However, there were differences between the multiple imputation and complete case early life models which is likely to be due to the high percentage of missing data at this stage. Key modifiable maternal predictors (maternal BMI, smoking status and intake of folic acid supplements) remained consistent across the stages. Identifying these high risk groups and intervening early could modify long-term risk for both mother and child as well as subsequent children particularly if identified at first pregnancy.

The development of prediction models in a large population-based sample is a key strength of this analysis which enhances the generalisability. We used robust statistical methods to develop the models (retained continuous variables as continuous, investigated variable transformations using multivariable fractional polynomials and corrected for optimism by calculating model shrinkage) and to assess the performance of the models where possible. Limitations include the high percentage of missing data for some variables (weight during early life and breastfeeding). Both early life time-points (1 and 2 years) considered in this analysis align with two of the five NHS child health and development reviews (9-

12 months and 2-2.5 years) at which weight is measured. However, a high percentage of missing weight data was observed during early life for outcome at both Year R (70%) and Year 6 (85%). Multiple imputation of missing data was carried out which generally enables more robust analyses but requires some caution in interpretation due to the high percentage of missing data and thus the number of imputations required. The issue of definition of childhood overweight and obesity using BMI also needs to be considered and is discussed in detail below.

A model usually performs better in the data that is used for development and hence external validation is needed to check the performance of the model and to assess generalizability of the model in similar but new patients. This is evaluated by assessing model performance in data that is external to the development data. Thus, the next steps for this analysis will be to carry out external validation of the models followed by model update as necessary. The ideal scenario would be a routine dataset from another part of the UK but as maternal and child records are held separately the same process of data linkage would need to be carried out which was deemed unfeasible with regards to the timeline of this PhD. Routine data in Scotland are available with maternal pregnancy data linked to the child record however the cost associated with access was not available to the research team during the course of this project. So, the possibility of external validation in birth cohort data was explored and we have received approval to use data from the Born in Bradford (BiB) cohort. BiB is a longitudinal multi-ethnic birth cohort of children (and their parents) born between 2007 and 2010 in Bradford Royal Infirmary and follow-up data has been supplemented with routine data. Predictive performance of a model should be checked across clinical settings, populations and subgroups as performance can vary across settings/populations (Riley *et al.*, 2016). External validation using BiB data gives the opportunity to examine performance in a more ethnically diverse population in a different geographical location within the country. This will be followed by a pilot study to test the feasibility and usability of the tool as well as to plan an intervention strategy. Steps to improve the AUC of the prediction models will also be considered such as the inclusion of Year R weight in the Year 6 model to try and identify children at high risk of overweight and obesity between these stages given the increased prevalence at Year 6.

BMI provides a useful population-level measure of overweight and obesity status, as it is the same regardless of gender or age once adulthood is attained. Additionally, it is easy and cheap to measure. However, it is only a rough guide, as it does not account for differences in body composition (muscle and fat mass) thus overestimating fatness in people who are muscular (Prentice and Jebb, 2001). BMI is the most commonly used marker of overweight and obesity (Dinsdale *et al.*, 2011) and is the marker used in the NCMP in England after adjusting for age and sex. However, the validity of BMI as a marker of body fat remains limited particularly in ethnic minority populations with a systematic underestimate of body fat in South-Asian children and a systematic overestimate in Black African children (Nightingale *et al.*, 2011). Ethnicity specific adjustments for children aged 4 to 12 years have been derived using pooled data from four studies which used the deuterium dilution method to measure total body water in the UK. These adjustment factors were the same in South Asian children aged 4 to 12 years irrespective of age and fat mass but varied with age and fat mass in Black African children (Hudda *et al.*, 2017a). Applying these adjustment factors to NCMP data showed marked increases in the percentages of overweight and obesity in South Asian children and decreases in Black children. Thus, in comparison to White children, the prevalence of overweight and obesity were higher in South Asian children and lower in Black children except girls aged 10 to 11 years on BMI adjustment (Hudda *et al.*, 2017b). The lack of adjustment factors for children of mixed race or other ethnic backgrounds is a limitation in the usability of these adjustment factors and is the reason that these adjustment factors have not been used in this analysis.

A systematic review on diagnostic accuracy of childhood measures of obesity found little evidence to suggest that any obesity measure had better diagnostic performance than BMI (Simmonds *et al.*, 2015). The National Institute of Health and Care Excellence (NICE) in the UK recommend the use of age- and sex-adjusted BMI as a practical estimate of adiposity in children and young people to identify overweight and obesity (National Institute for Health Care and Excellence, 2014). However, the UK has centile cut-offs for population monitoring (85th for overweight/obese and 95th for obese) and clinical diagnosis (91st for overweight and 98th for clinical obesity). Clinical cut-offs for children are used for parental feedback in the NCMP. This may be because NICE guidelines have information on follow-up for children over these cut-offs, however parents of children with BMI

between the 85th to 90th percentile are being informed that their child is of normal weight. The 85th and 95th percentiles are used as the BMI-for-age cut-offs in the USA based on the rationale that the 85th and 95th percentile in the USA population corresponds to a BMI of 25kg/m^2 and 30kg/m^2 respectively in young adults (National Center for Chronic Disease Prevention and Health Promotion, 2014). However, the scientific rationale for the UK cut-offs is not obvious and appears to be a historical precedent selected pragmatically at the time to serve a specific purpose. The 85th and 95th centiles in the UK were selected as the exact values to estimate population prevalence whereas the 91st and 98th correspond to major centile lines on the UK growth charts. Although the cut-offs continue to be used and serve the specific purpose that they were selected for, they can give rise to confusion and inconsistency in reporting. For example, the parents of a child at the 87th percentile are being informed that their child is normal weight whereas the same child is being considered as overweight in the national reporting figures. Parental recognition of childhood overweight and obesity was increased on receiving feedback about weight status however recognition still remained low at 38% in this study (Falconer *et al.*, 2014). A study examining behavioural change after receiving the NCMP parental feedback letter found that parental recognition of overweight was a key predictor of behavioural intentions but these did not translate into behaviours with 72% reporting intention to change and 55% reporting behavioural change (Park *et al.*, 2014). Thus, informing parents that their child is at risk of overweight if they are ≥85th percentile might need to be considered. Risk prediction equations have been developed using the population monitoring cut-offs (≥85th for overweight, ≥95th for obesity) and the clinical cut-off of 91st centile as the aim is to implement this in clinical practice and thus clinical cut-offs will be preferred as guidance exists on follow-up of children ≥ 91st which could be implemented in children who are at high risk of being above this cut-off.

7.5 Conclusion

Most maternal predictors remained consistent across models indicating that risk could be identified at pregnancy, with more precise estimation at birth/in early-years. These models could form the basis of a risk identification system to strengthen the long-term preventive element of antenatal and early years care by quantifying clustering of future obesity risk to provide more support to these families.

Chapter 8 Development of prediction model of childhood overweight and obesity at 4-5 years incorporating interpregnancy change

This chapter outlines the development of a prediction model for childhood overweight and obesity in the second born child incorporating the findings of the interpregnancy analysis presented in Chapter 5 and Chapter 6. The methods section in this chapter only presents the differences to the methodology reported in Chapter 7.

8.1 Methods

8.1.1 Data considerations

Only women who had their first and second live birth pregnancies were included in model development to predict risk of childhood overweight and obesity in the second born child.

8.1.2 Candidate predictors

Box 8.1 below shows the candidate predictors that are included in this analysis.

Box 8.1: The list of candidate predictors identified during booking appointment for the second pregnancy

Objectively recorded:

- Maternal age
- Maternal BMI at booking (measured weight) - additionally used to calculate interpregnancy weight change
- Interpregnancy interval

Self-reported:

- Gestational age at booking (based on last menstrual period)
- Maternal smoking status at booking
- Highest maternal educational attainment
- Maternal ethnicity
- Intake of folic acid supplements
- Obstetric history of GDM
- Obstetric history of pre-eclampsia

Maternal BMI recorded at the start of each pregnancy was used to calculate interpregnancy weight change between first and second pregnancy. Interpregnancy interval was defined as the interval between the first live birth and

conception of the second pregnancy. The other predictors included are the same as those included in developing the prediction model in Chapter 7. The number of predictors is fewer as certain variables (family history) are likely to remain the same in women between pregnancies and partner information in the dataset was insufficient to identify if the partner at both pregnancies were the same or not. We were also guided by the variables in the developed prediction model at Year R in the full sample.

8.2 Results

8.2.1.1 Baseline characteristics

Of the 29,060 children with measured outcome at Year R, 6,358 children were the second child of women who had given birth to their first child at UHS.

Mean maternal age at booking was 28.9 years (SD 5.5) (Table 8.1). Mean maternal BMI was in the normal weight range (24.7 kg/m^2, SD 4.8). Nearly half the women gained weight from the previous pregnancy and mean change in maternal BMI was 1.1 kg/m^2 (SD 2.7). Over a quarter of the women had a university degree or above. Nearly half the mothers reported no breastfeeding.

Table 8.1: Summary of baseline characters (candidate predictors) for second born children in the SLOPE sample using the multiply imputed data

Variable	Mean ± SD
n	6,358
Maternal age at booking, years	28.9 ± 5.5
Gestation at booking, days	79 ± 24
Maternal BMI at booking, kg/m^2	24.7 ± 4.8
Change in maternal BMI from previous pregnancy, kg/m^2	1.1 ± 2.7
Inter-pregnancy interval, months	26 ± 16
Birthweight, kg	3.5 ± 0.5
Gestation at birth, days	279 ± 11
Infant weight at 1 year, kg	9.5 ± 1.2
Infant weight at 2 years, kg	13 ± 1.6

Variable	%, 95% CI
Maternal smoking status at second pregnancy booking	
Never smoked	57.0 (55.8 to 58.2)
Ex-smoker	29.5 (28.4 to 30.6)
Current smoker	13.5 (12.7 to 14.4)
Maternal highest educational attainment	
Undergraduate or above	28.9 (27.8 to 30.0)
College	42.0 (40.9 to 43.2)
Secondary school or below	29.1 (28.0 to 30.2)
Maternal ethnicity	
White	91.9 (91.2 to 92.5)
Mixed	1.1 (0.8 to 1.3)
Asian	4.9 (4.3 to 5.4)
Black/African/Caribbean	1.5 (1.2 to 1.7)
Other	0.8 (0.5 to 1.0)
Maternal intake of folic acid supplements	
Taking prior to pregnancy	34.3 (33.2 to 35.4)
Started taking once pregnant	57.1 (55.9 to 58.2)
Not taking supplement	8.6 (8.0 to 9.3)
Maternal BMI change from previous pregnancy	
Weight loss >1 BMI unit	17.2 (16.3 to 18.1)
Weight stable (-1 to 1 BMI unit)	35.3 (34.2 to 36.4)
Weight gain 1-3 BMI units	28.8 (27.7 to 29.9)
Weight gain ≥3 BMI units	18.7 (17.8 to 19.7)
Obstetric history of GDM	
No	98.8 (98.5 to 99.1)
Yes	1.2 (0.9 to 1.5)
Delivery method	
Vaginal	81.4 (80.5 to 82.4)
Caesarean section	18.6 (17.6 to 19.5)
Gestational diabetes in current pregnancy	
No	98.1 (97.8 to 98.4)
Yes	1.9 (1.6 to 2.2)
Child gender	
Male	51.7 (50.5 to 52.9)
Female	48.3 (47.1 to 49.5)

Duration of breastfeeding	
No breastfeeding	46.7 (45.0 to 48.4)
Minimum 10 days	19.1 (17.9 to 20.4)
Minimum 6 weeks	21.9 (20.6 to 23.2)
Minimum 8 weeks	11.5 (10.4 to 12.6)
Minimum 4 months	0.2 (0.1 to 0.4)
9 months	0.5 (0.3 to 0.8)

8.2.1.2 Multivariable models

The estimates for the prediction of risk in the second-born offspring are presented in Table 8.2. Five predictors were selected for inclusion in the booking model: maternal age at second pregnancy, baseline BMI at first pregnancy, maternal BMI change from previous pregnancy, ethnicity and smoking status at second pregnancy. The birth model included all the booking predictors with the exception of maternal BMI change from previous pregnancy but instead included interpregnancy interval. Additional predictors from birth included birthweight, gestational age at birth and child sex. The early life models included the same early life predictors (child sex and child weight) but only the model at ~1 year included a birth predictor (birthweight). Consistent maternal booking predictors were maternal age, baseline maternal BMI, maternal ethnicity and smoking status at booking. Maternal BMI change from previous pregnancy was included in the early life model at ~1 year whereas interpregnancy interval was included in the model at ~2 years. A transformation was identified for baseline maternal BMI in all models.

Similar to the full sample model, the predictors included in the booking and birth multiply imputed model were the same as the complete case model with the exception of child sex which was not included in the complete case birth model but was included in the multiple imputed birth model. However, the predictors included in the multiply imputed early life models were very different from the complete case models. The only consistent maternal predictor in the complete case model was baseline maternal BMI. Additionally the complete case models identified more transformations of continuous variables than the multiply imputed models including maternal BMI change from previous pregnancy, interpregnancy interval, birthweight, child weight and gestational age at birth.

Table 8.2: Estimates of the final models for the prediction of outcome of overweight and obesity (≥91st centile) in second-born children aged 4-5 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Intercept	0.278	-0.241 to 0.796		1.004	-1.199 to 3.206		-5.997	-7.351 to -4.644		-10.354	-11.89 to -8.818	
Maternal age at booking, years	-0.024	-0.039 to -0.009	0.001	-0.031	-0.046 to -0.016	<0.001	-0.026	-0.042 to -0.009	0.002	-0.032	-0.05 to -0.014	<0.001
Baseline maternal BMI at booking (first pregnancy), kg/m^2	0.022	-0.003 to 0.046	0.080	-8.429	-9.776 to -7.081	<0.001	-6.880	-8.036 to -5.725	<0.001	-6.239	-7.508 to -4.97	<0.001
Interpregnancy interval, months				0.006	0.001 to 0.01	0.014				0.006	0.000 to 0.011	0.045
Maternal BMI change from previous pregnancy, kg/m^2	0.022	-0.003 to 0.046	0.080				0.023	-0.004 to 0.05	0.095			
Maternal ethnicity												
White	Ref			Ref			Ref			Ref		
Mixed	-0.187	-0.993 to 0.62	0.650	-0.030	-0.836 to 0.777	0.943	-0.058	-0.901 to 0.786	0.893	-0.046	-0.975 to 0.883	0.923
Asian	0.554	0.214 to 0.893	0.001	0.762	0.416 to 1.108	<0.001	0.746	0.372 to 1.12	<0.001	0.563	0.141 to 0.986	0.009
Black/African/Caribbean	0.504	-0.077 to 1.086	0.089	0.631	0.044 to 1.218	0.035	0.713	0.101 to 1.324	0.022	0.436	-0.248 to 1.119	0.211
Other	-0.206	-1.245 to 0.832	0.697	-0.198	-1.25 to 0.853	0.711	-0.140	-1.231 to 0.952	0.802	-0.424	-1.638 to 0.79	0.493

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	0.175	0.006 to 0.344	0.043	0.155	-0.017 to 0.327	0.077	0.129	-0.052 to 0.311	0.163	0.137	-0.068 to 0.341	0.191
Current smoker	0.417	0.195 to 0.639	<0.001	0.592	0.363 to 0.822	<0.001	0.558	0.31 to 0.807	<0.001	0.582	0.309 to 0.854	<0.001
Birthweight, kg				0.860	0.695 to 1.025	<0.001	0.252	0.072 to 0.432	0.006			
Gestational age at birth, days				-0.014	-0.022 to -0.006	0.001						
Gender												
Male				Ref			Ref			Ref		
Female				0.111	-0.038 to 0.26	0.145	0.475	0.302 to 0.647	<0.001	0.502	0.31 to 0.693	<0.001
Infant weight, kg							0.651	0.527 to 0.776	<0.001	0.841	0.747 to 0.935	<0.001
Transformations:												
Maternal BMI at booking	(Maternal BMI at booking/10) ^-2			(Maternal BMI at booking/10) ^-2			(Maternal BMI at booking/10) ^-1			(Maternal BMI at booking/10) ^-1		

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Discrimination and calibration:												
AUC	0.66 0.64 to 0.68			0.69 0.67 to 0.71			0.76 0.73 to 0.78			0.84 0.82 to 0.86		
Calibration slope (standard error)	0.97 (0.06)			0.98 (0.05)			0.99 (0.03)			0.99 (0.02)		

Table 8.3: Intercept and regression coefficients of the prediction models for outcome of overweight and obesity (≥91st centile) in second-born children aged 4-5 years before and after shrinkage

Predictors	Booking		Birth		Early life (~1 year)		Early life (~2 years)	
	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient
Intercept	0.278	0.199	1.004	0.905	-5.997	-5.881	-10.354	-10.205
Maternal age at booking, years	-0.024	-0.023	-0.031	-0.030	-0.026	-0.025	-0.032	-0.031
Baseline maternal BMI at booking (first pregnancy), kg/m^2	-9.324	-8.958	-8.429	-8.119	-6.880	-6.698	-6.239	-6.135
Interpregnancy interval, months			0.006	0.005			0.006	0.005
Maternal BMI change from previous pregnancy, kg/m^2	0.022	0.021			0.023	0.022		

Predictors	Booking		Birth		Early life (~1 year)		Early life (~2 years)	
	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient	Coefficient	Shrunken coefficient
Maternal ethnicity								
White	Ref		Ref		Ref		Ref	
Mixed	-0.187	-0.179	-0.030	-0.028	-0.058	-0.056	-0.046	-0.045
Asian	0.554	0.532	0.762	0.734	0.746	0.726	0.563	0.554
Black/African/Caribbean	0.504	0.485	0.631	0.607	0.713	0.694	0.436	0.428
Other	-0.206	-0.198	-0.198	-0.191	-0.140	-0.136	-0.424	-0.417
Maternal smoking status at booking								
Never smoked	Ref		Ref		Ref		Ref	
Ex-smoker	0.175	0.168	0.155	0.149	0.129	0.126	0.137	0.134
Current smoker	0.417	0.401	0.592	0.570	0.558	0.544	0.582	0.572
Birthweight, kg			0.860	0.828	0.252	0.245		
Gestational age at birth, days			-0.014	-0.014				
Gender								
Male			Ref		Ref		Ref	
Female			0.111	0.107	0.475	0.462	0.502	0.494
Infant weight, kg					0.651	0.634	0.841	0.827
Shrinkage factor	0.96		0.96		0.97		0.98	

8.2.2 Model performance

Similar to the models developed in the full sample, discrimination (AUC) improved across the stages identified for model development (booking appointment, birth and early life). The AUC improved from the booking to the early life model at ~2 years (0.66 at booking to 0.84 at ~2 years) (Table 8.2). AUC for the Year R models were higher in the multiply imputed models compared to after internal validation in the complete case models.

Calibrations plots overlaying the results of the analysis of the imputed datasets for the Year R model stages are presented in Figure 8.1, Figure 8.2, Figure 8.3 and Figure 8.4. The calibration across the booking and birth models was strong as evidenced by the calibration slope and the gradient. Although the calibration was strong in the early life models, there was more variation between the imputed however this is the stage with the highest percentage of missing data and thus more variation across the datasets is to be expected.

Figure 8.1: Calibration plot of the prediction model (overlying the results of the analysis on the 70 imputed datasets) at booking for outcome in the second born child at Year R

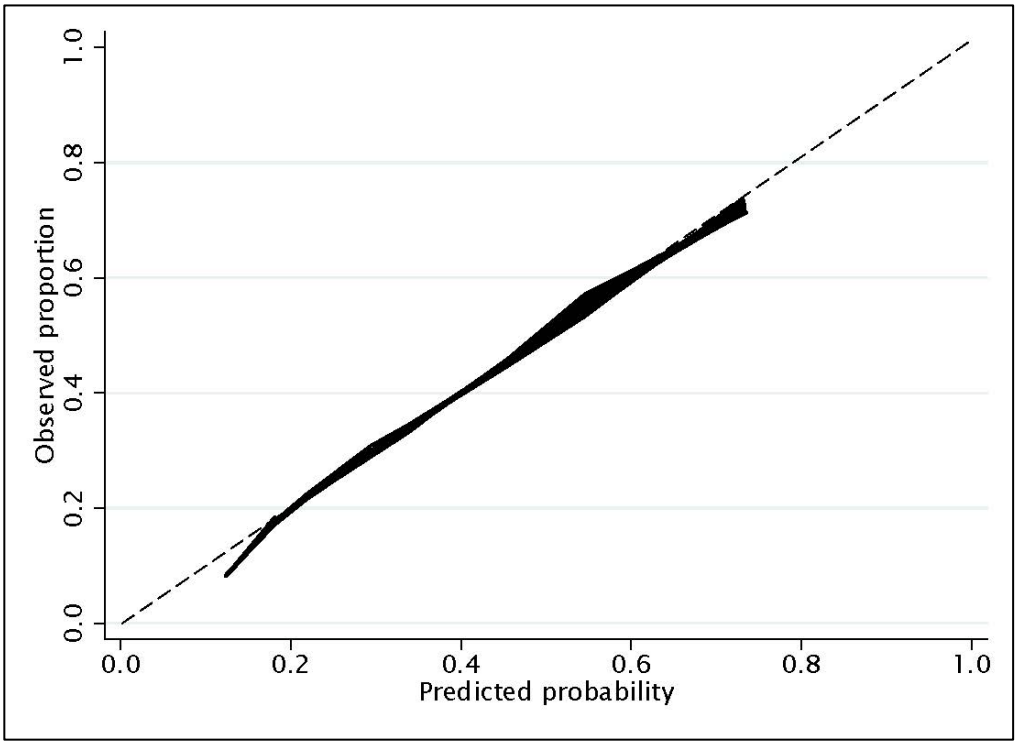


Figure 8.2: Calibration plot of the prediction model (overlying the results of the analysis on the 70 imputed datasets) at birth for outcome in the second born child at Year R

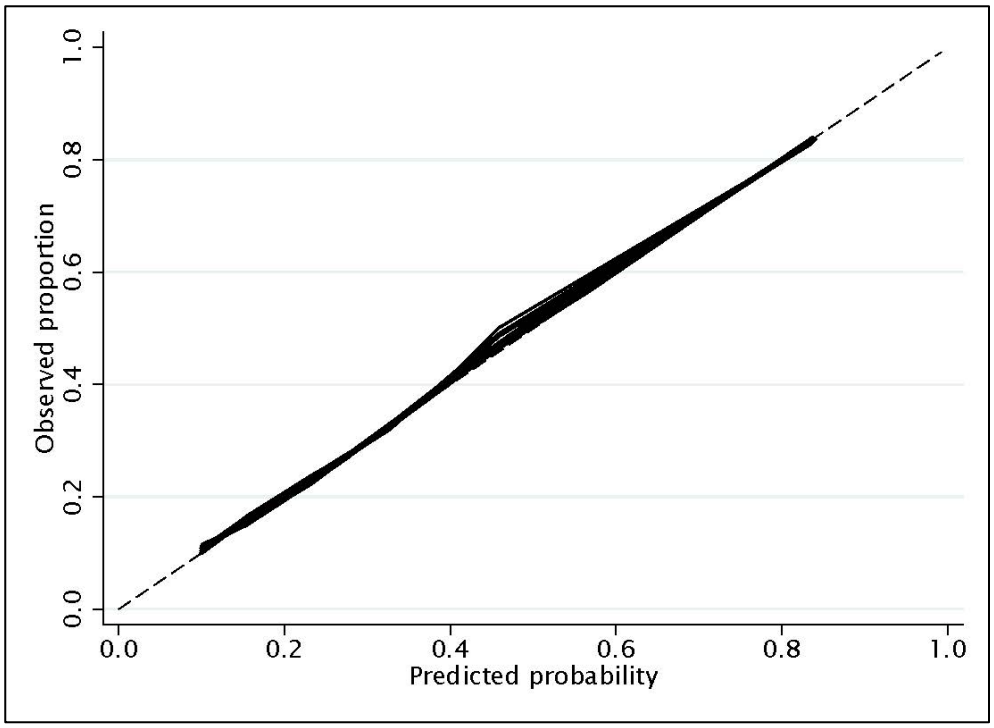


Figure 8.3: Calibration plot of the prediction model (overlying the results of the analysis on the 70 imputed datasets) at early life (~1 year) for outcome in the second born child at Year R

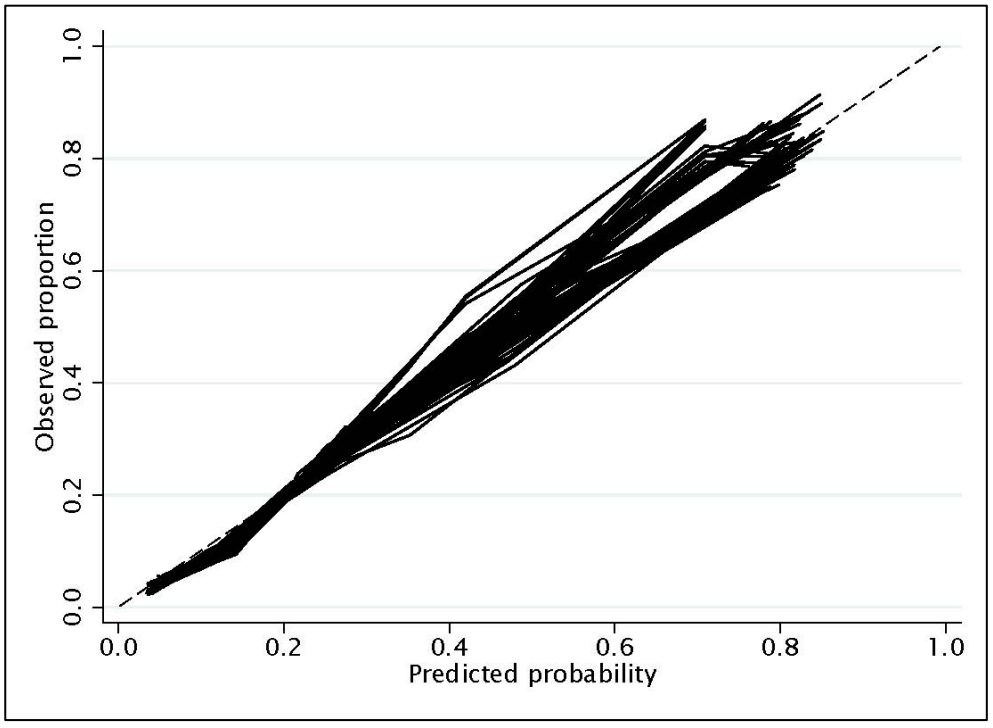
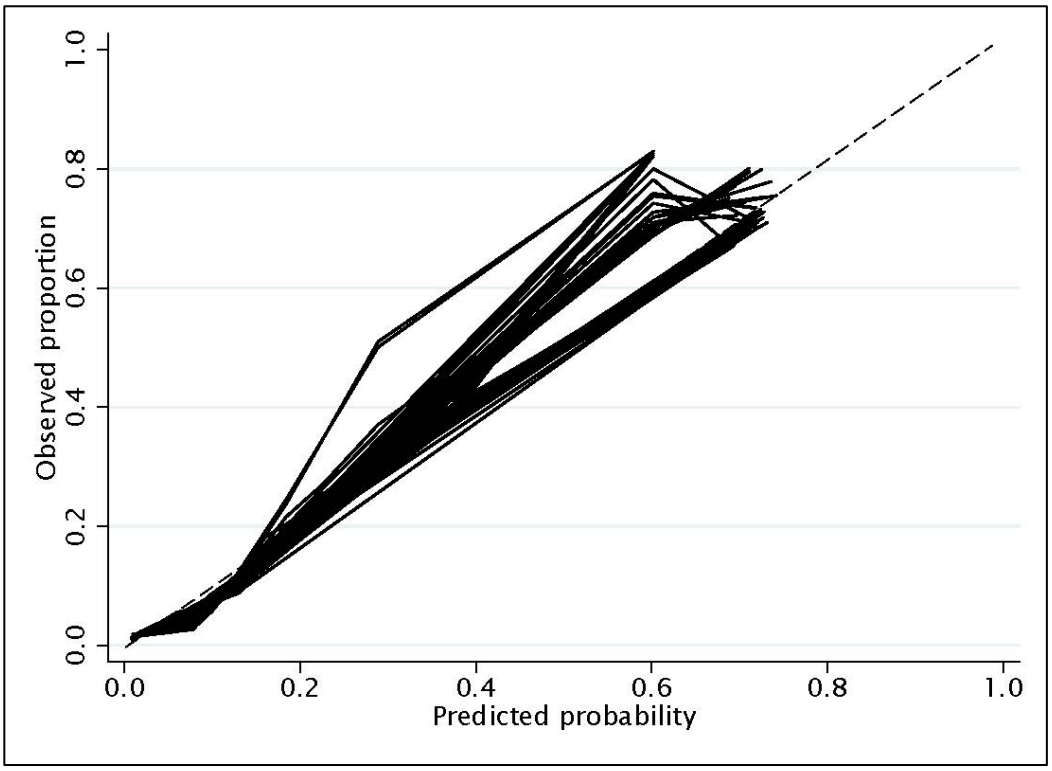


Figure 8.4: Calibration plot of the prediction model (overlying the results of the analysis on the 70 imputed datasets) at early life (~2 years) for outcome in the second born child at Year R



Shrinkage factors showed a small amount of optimism in the models suggesting all models to be stable. The estimated shrinkage factors ranged from 0.96 to 0.98 for all models suggesting that only a small percentage of the model fit was noise. The shrunken coefficients and intercepts are presented in Table 8.3.

8.2.3 Risk threshold

The percentage identified at risk, sensitivity, specificity, PPV and NPV for different risk score cut-offs is presented in Table 8.4. Although specificity remained comparable at the 20% risk threshold across the stages, sensitivity was lower in the earlier stages (34.7% at booking, 40.8% at birth and 52.8 at ~1 year).

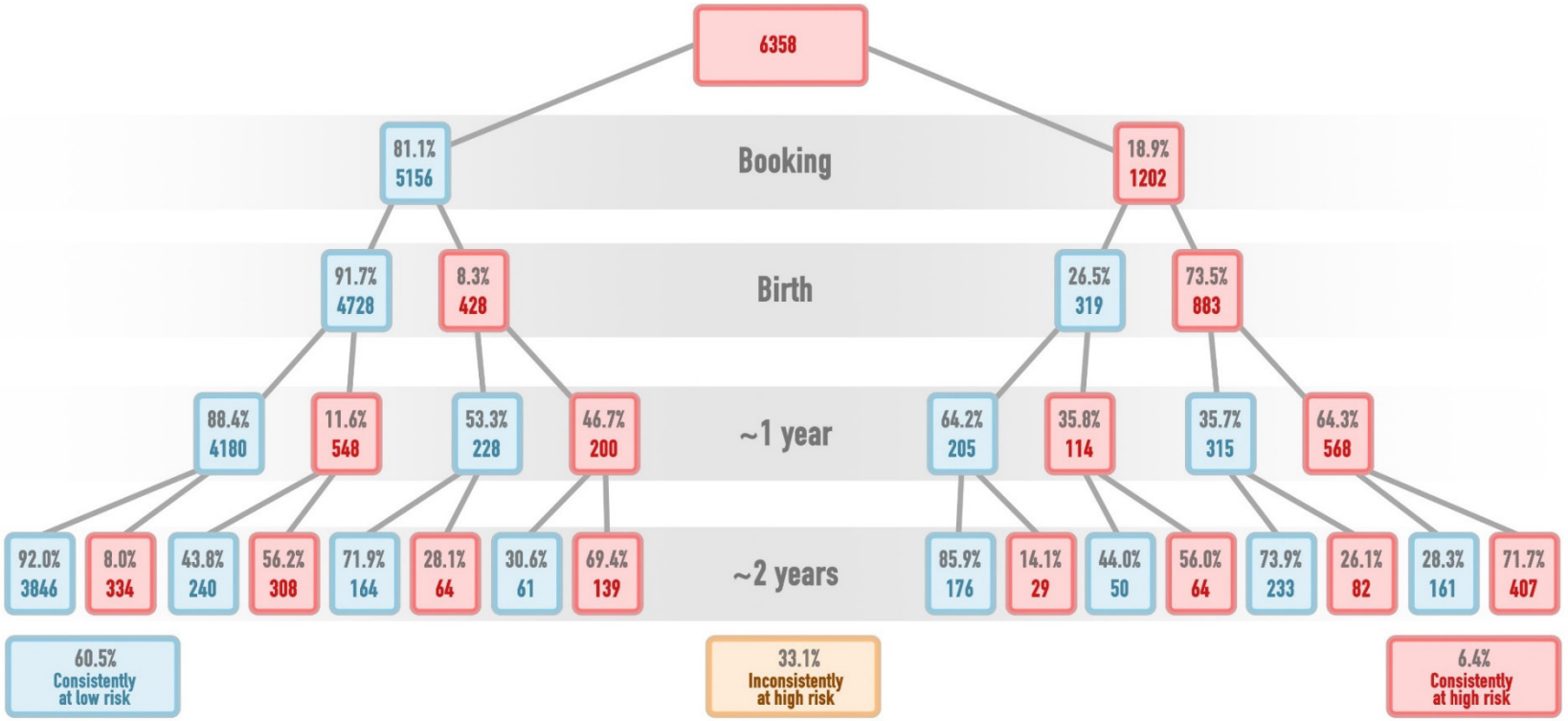
PPV increased and NPV decreased as the risk threshold increased. For example, for the booking model at Year R, PPV of 18.1% and NPV of 93.0% at risk threshold of 10%, PPV of 26.0% and NPV of 88.6% at risk threshold of 20% and PPV of 32.7% and NPV of 86.7% at risk threshold of 30%.

Table 8.4: The predictive ability of the risk score for the outcome of overweight and obesity (≥91st centile) in second-born children

Cut-point	% at/above cut-point	Sensitivity	Specificity	PPV	NPV
Booking					
≥10.0	64.5	82.5 79.9 to 84.9	38.5 37.2 to 39.8	18.1 17.0 to 19.3	93.0 91.9 to 94.0
≥15.0	36.1	56.3 53.1 to 59.5	67.3 66.0 to 68.5	22.1 20.5 to 23.8	90.3 89.4 to 91.2
≥20.0	18.9	34.7 31.7 to 37.8	83.7 82.7 to 84.7	26.0 23.6 to 28.6	88.6 87.7 to 89.4
≥25.0	9.6	20.1 17.6 to 22.8	92.2 91.5 to 92.9	29.9 26.4 to 33.6	87.5 86.6 to 88.3
≥30.0	4.6	10.5 8.6 to 12.6	96.4 95.8 to 96.9	32.7 27.4 to 38.3	86.7 85.8 to 87.5
Birth					
≥10.0	61.1	81.4 78.8 to 83.9	42.3 41.0 to 43.6	18.9 17.7 to 20.2	93.2 92.2 to 94.2
≥15.0	36.5	60.9 57.7 to 64.0	67.5 66.3 to 68.7	23.6 22.0 to 25.4	91.3 90.4 to 92.1
≥20.0	20.7	40.8 37.7 to 44.0	82.7 81.7 to 83.6	28.0 25.6 to 30.4	89.4 88.6 to 90.2
≥25.0	11.2	25.2 22.6 to 28.1	91.1 90.4 to 91.9	32.0 28.6 to 35.4	88.1 87.2 to 88.9
≥30.0	5.9	14.3	95.5	34.2	87.2

		12.1 to 16.5	94.9 to 96.0	29.5 to 39.1	86.2 to 87.9
Early life (~1 year)					
≥10.0	50.7	82.5 80.0 to 84.9	54.6 53.3 to 55.9	23.1 21.7 to 24.7	94.8 94.2 to 95.7
≥15.0	33.4	66.5 63.4 to 69.5	72.1 70.9 to 73.3	28.3 26.4 to 34.5	92.9 92.1 to 93.6
≥20.0	22.5	52.8 49.6 to 56.0	82.5 81.5 to 83.5	33.3 30.9 to 35.8	91.4 90.6 to 92.1
≥25.0	15.6	41.8 38.6 to 45.0	88.7 87.9 to 89.5	38.0 35.0 to 41.0	89.1 89.4 to 91.0
≥30.0	10.9	32.7 29.7 to 35.8	92.7 92.0 to 93.4	42.5 38.8 to 46.1	89.3 88.5 to 90.1
Early life (~2 years)					
≥10.0	41.0	84.2 81.7 to 86.4	66.1 64.9 to 67.4	29.1 27.4 to 30.9	96.2 95.6 to 96.6
≥15.0	29.8	74.2 71.3 to 76.9	77.5 76.4 to 78.6	35.3 33.2 to 37.4	94.8 94.1 to 95.4
≥20.0	22.4	64.8 61.7 to 67.8	84.7 83.7 to 85.6	40.4 38.4 to 43.5	93.6 92.9 to 94.2
≥25.0	17.6	56.8 53.6 to 60.0	88.9 88.0 to 89.7	45.8 42.9 to 48.7	92.6 91.8 to 93.3
≥30.0	14.0	49.4 46.2 to 52.6	91.8 91.1 to 92.5	49.9 46.6 to 53.1	91.6 90.9 to 92.4

Figure 8.5: The categorisation of children as high risk (red) or low risk (blue) if the prediction model is applied at each stage using the risk threshold of 20% in children aged 4-5 years



Consistently at low risk: At low risk at all four stages
Inconsistently at high risk: At high risk at one or more of the four stages but not at all four stages
Consistently at high risk: At high risk at all four stages

Figure 8.5 shows the categorisation of children as high risk or low risk if the model is applied at each stage using a risk threshold of 20% in children aged 4-5 years. Based on this, 60.5% of the sample is consistently identified as low risk and 6.4% is consistently identified as high risk. The remaining 33.1% are identified at risk at one or two stages but not consistently.

The same pragmatic recommendation of risk threshold for the prediction model in the full sample at Year R (20%) would apply here.

8.2.4 Application of the model

Using the same example from the previous chapter but with the additional interpregnancy predictors:

Asian women aged 30 years, BMI of 27.9kg/m^2, booked at 86 days gestation, ex-smoker, not taking folic acid supplements with parity of 1 at booking, first language English and has history of GDM, university educated, caesarean section delivery at 274 days gestation, female baby with birthweight of 3.34 kg, weight at one year 10.8kg, weight at 2 years 15.2kg

BMI change from previous pregnancy of +1.5kg/m^2 and interpregnancy interval of 20 months

We can apply the above equation to calculate the risk of overweight and obesity at 4-5 years as follows:

$$Y = 0.199 - [0.023 \times 30] - [8.958 \times (26.4/10)^{-2}] + [0.021 \times 1.5] + 0.532\ [\text{Asian ethnicity}] + 0.168\ [\text{ex-smoker}]$$

$$= 0.199 - 0.69 - 1.29 + 0.03 + 0.532 + 0.168$$

$$= -1.051$$

The log-odds (Y) is then converted into probability (P):

$$P = 1/[1 + \exp(-Y)]$$

$$= 1/[1 + \exp(1.051)]$$

$$= 1/3.861$$

$$= 0.259\ (25.9\%)$$

The estimated probability of overweight and obesity in the offspring for this mother at booking would be 25.9% compared to 20.1% using the full sample model.

If we assessed this baby at birth, this could be updated as follows:

$$Y = 0.905 - [0.030 \times \text{maternal age at booking}] - [8.119 \times (\text{maternal BMI}/10)^{-2}] + [0.005 \times \text{interpregnancy interval}] + 0.149\ [\text{ex-smoker}] + 0.734\ [\text{Asian ethnicity}] + [0.828 \times \text{birthweight}] - [0.014 \times \text{gestational age at birth}] + 0.107\ [\text{female}]$$

$$= 0.905 - 0.9 - 1.165 + 0.1 + 0.149 + 0.734 + 2.766 - 3.836 + 0.107$$

$$= -1.24$$

The log-odds (Y) is then converted into probability (P):

$$P = 1/[1 + \exp(-Y)] = 1/[1 + \exp(1.24)] = 1/4.455$$

$$= 0.224\ (22.4\%)$$

The estimated probability would now be 22.4% compared to 17.0% using the full sample model.

8.3 Discussion

Consistent maternal predictors that were included in all the models were maternal BMI, age, ethnicity and smoking; all of which are factors that were included in the prediction model in the full sample. Interpregnancy predictors (maternal BMI change from previous pregnancy and interpregnancy interval) were included as predictors of the risk of childhood overweight and obesity in the second born child. However, both predictors were not consistently included in the models – maternal BMI change from previous pregnancy was included in the booking and early life model at ~1 years whereas interpregnancy interval was included in the two other stages (birth and early life at ~2 years). The inclusion of both these predictors shows the importance of these factors in the risk of overweight and obesity in the second child.

On application of the interpregnancy models, the predicted risk was similar to that in the full sample models. However, the slight differences observed between the probabilities and the lower proportion of overall sample consistently

identified as high risk (6.4% compared to 7.5% in the full sample) implies that children close to the risk threshold could potentially be classified differently based on the model used (high risk using full sample model and low risk using interpregnancy models or vice versa).

This model only considers two aspects of the interpregnancy period – interval and maternal BMI change – but other changes can occur during this period. These could include changes in smoking behaviour, diet, physical activity, employment or other lifestyle changes. The models across all stages included smoking as a predictor but some women may quit smoking before or at the start of their first pregnancy and not take up smoking again after birth of the first child whereas others may quit during pregnancy but start smoking again after birth. Other women may smoke during their first pregnancy but may quit ahead of their second pregnancy. Although smoking status at second pregnancy is included in the models, it is possible that changes to smoking behaviour during pregnancy and in the interpregnancy period could modify risk to the offspring. Further research to gain an understanding of these changes and potential interactions is needed as a consideration of these factors in combination could modify risk further and is undergoing as part of the SLOPE project.

8.4 Conclusion

Consistent maternal predictors of childhood obesity from the full sample included as candidate predictors were consistent predictors in the interpregnancy models. Both interpregnancy BMI change and interpregnancy interval were included as predictors but were not consistent across the models. These models lend further support to the need to strengthen the long-term preventive element of antenatal and early years care in families with a consideration of interpregnancy changes.

Chapter 9 Discussion

There is increasing evidence of developmental factors shaping the risk of childhood overweight and obesity (Whitaker and Dietz, 1998), however the change in risk factors between pregnancies and the effect of a combination of risk factors has received less attention. The findings from this thesis provide new insights in this area. Firstly, an understanding of the change in maternal weight between pregnancies and its association with the interpregnancy interval and size at birth. Parity is usually adjusted for in analysis of maternal factors and health outcomes and this analysis helps understand some of the individual factors that could be contributing to the effect observed under parity. Secondly, this project demonstrates the feasibility of linking routine maternal antenatal care and birth data with child data held by different organisations in England. Finally, the prediction models developed using routine data as part of this thesis consider risk from a very early stage thus aiding in early identification and providing the ability of early intervention to aid in prevention.

This chapter aims to summarise and discuss the main findings of this thesis following the more detailed discussions presented in each chapter.

9.1 Summary of results

9.1.1 Data access and linkage

The feasibility of data linkage including the ethics and governance around data access and linkage was explored as well as data access from a variety of sources. The linkage method utilised in this thesis was deemed most feasible. The success of this linkage means that this can be repeated to include more recent data or can be applied in other places within the UK to access similar data. The timeline was approximately two years from starting discussions on the data access to the complete linked dataset. However, once the requirements were navigated, I had the complete linked dataset within six months of receiving ethical approval.

9.1.2 Interpregnancy changes

Analysis presented in this thesis shows that a high proportion of women are at a higher weight at the start of their second pregnancy. Weight gain of 1-3 kg/m^2 was observed in 27.9% and large gains (≥3 kg/m^2) in 19.8% of women. The lowest risk of weight gain was found with an interpregnancy interval of 12 to 23 months between the first and second pregnancy. This interval was also associated with a lower risk of SGA birth at second pregnancy. No association was observed between risk of SGA with other intervals or LGA and interpregnancy interval. However, a higher proportion of second pregnancy births were LGA (7% at first pregnancy and 13% at second pregnancy). Analysis of maternal interpregnancy weight change and risk of LGA showed an increased risk of LGA birth in the second pregnancy in women that gained weight in the full sample. Overweight women who lost ≥1 kg/m^2 had a reduced risk of recurrent LGA. Normal weight women who gained 1–3 kg/m^2 and both normal weight and overweight women who gained ≥3 kg/m^2 between pregnancies had an increased risk of LGA birth in their second pregnancy after a non-LGA birth in the first.
Thus, an interval of 12-23 months was associated with the lowest risk of weight gain and SGA birth in the second pregnancy. Between pregnancy weight gain in normal and overweight women was associated with increased risk of new LGA birth in the second pregnancy. Maternal overweight and obesity has been identified as one of the key predictors of offspring outcomes including childhood overweight and obesity (Poston *et al.*, 2016). Normal weight women who gain 1-3 kg/m^2 between pregnancies may still be normal weight at the second pregnancy and thus this analysis emphasises the importance of maternal weight even in women who are not overweight or obese. Preventing weight gain in all women except those who are underweight and supporting weight loss in overweight and obese women is important to achieve better maternal and child outcomes.

9.1.3 Risk prediction

The systematic review reported in Chapter 3 identified eight existing prediction models for the risk of childhood overweight and/or obesity. Half the models were externally validated but none of the models have been compared to each other to assess predictive performance. The review also identified some methodological limitations in model development and validation. This combined with non-standard reporting limit the usability of these prediction models. Additionally,

none of the papers identified a risk threshold for the application of the model. The results of the prediction model were reported either using an arbitrary risk threshold or without pre-determined thresholds and without recommendation of an appropriate threshold.

Prediction models were developed in stages (booking appointment, birth and early life) for outcome at Year R (4-5 years of age) and at Year 6 (10-11 years of age). Maternal predictors included in the models remained comparable across both outcome points. Key maternal predictors that appeared consistently across the model stages included maternal BMI, smoking status at booking appointment, highest educational attainment, maternal ethnicity and intake of folic acid supplements. Other maternal predictors included maternal age (Year R) and employment status at booking (Year 6). First language English, partnership status, parity and obstetric history of GDM were also predictors but only at some stages (booking appointment and/or birth). Child predictors included birthweight, gestational age at birth, child sex and child weight at 1 or 2 years.

To take into account the findings of the interpregnancy analysis, a prediction model of risk of childhood overweight and obesity in the second-born child at Year R was also developed. Maternal age, baseline maternal BMI, interpregnancy interval, maternal BMI change from previous pregnancy, maternal ethnicity and smoking status at booking were included predictors. Child predictors remained the same as for the other prediction models.

I paid particular attention to the methodology used to develop these prediction models and set a conservative p value for variable inclusion into the model to minimise overfitting. I carried out both complete case and multiple imputation analysis due to the high percentage of missing data in early life. Although some caution is necessary for the early life models due to the high percentage of missing data and thus imputation cycles, predictors included in these models for the booking and birth stages were comparable to the models at these stages. Predictors from early life included in the models were child sex and weight, both of which have been associated with risk of childhood overweight and obesity in the literature. Breastfeeding status and duration was only a predictor in the complete case model at 2 years for both the population monitoring outcomes (≥85th percentile and ≥95th percentile) and additionally at 1 year just for the outcome ≥95th percentile. The evidence on breastfeeding and childhood

overweight and obesity is conflicting and was only included as a predictor in two of the eight models identified in the systematic review.

9.2 Strengths, limitations and implications for data recording

The strengths and limitations of each analysis has been discussed as part of each chapter but this section aims to summarize the general strengths and limitations.

A key strength of this analysis is the use of routine healthcare data to access a relatively large population-based cohort which is representative of the local population. This study demonstrates the value of data linkage for research purposes and this can be used to access further data as well to examine relationships with other key outcomes during the life-course. However, there are implications for clinical recording as well (Table 9.1). For example, alcohol consumption at the booking appointment was only reported in 5% of women. The prevalence of drinking in early pregnancy in the UK as reported by previous studies has been variable but substantially higher than in this population cohort. Over two-thirds of women reported drinking in early pregnancy in a prospective cohort in Leeds (78.6%) (Nykjaer *et al.*, 2014), in Southampton (69%) (Crozier *et al.*, 2009) and in the UK centres of a multi-centre prospective cohort (69%) (Keeffe *et al.*, 2015). Although both the clinical and research cohort alcohol intake data have been collected through self-report, the cohort data are collected through questionnaires with detailed questions whereas the clinical data are collected through two questions in a face-to-face interview with a midwife. This could be a key factor contributing to the difference in prevalence given the advice of not drinking during pregnancy. As it is not possible to check or confirm responses to questions in anonymised data, the alcohol consumption during pregnancy variable was not included in any of the analysis. Feedback regarding concerns with the recording of the alcohol consumption variable has been provided to the clinical team to help improve future recording. Data in the maternity system at booking appointment were generally well recorded with a low percentage of missing data (<10%). However, there was a high percentage of missing data in variables recorded at discharge (breastfeeding status (53.5%) and smoking status (51.2%)). This could be because care moves to other healthcare professionals at

discharge and recording of information that is not directly related to or needed for care is less consistent.

Lack of consistency in recording practices can arise from the use of different systems for capturing similar data within different NHS trusts. For example, breastfeeding status was recorded using read codes at a maximum of five different time points (10 days, 2 weeks, 6 weeks, 4 months and 9 months) in Solent NHS Trust whereas it was recorded at one time-point (8 weeks) in Southern Health NHS Foundation Trust. This is assumed to be a time-point identified by the Trust as a read code does not exist for recording at this time point. Additionally, this was recorded as a yes/no variable and thus there was no indication of breastfeeding exclusivity in the Southern Health NHS Foundation Trust data. It could be easier in practice to record this categorically at a common time point (no/partial/exclusive) as well as recording breastfeeding initiation (yes/no) and the age in months when breastfeeding was stopped.

Better recording of key variables may result from the national Maternity and Children's Data Sets (MCDS) which have been developed to help achieve better care outcomes for mothers and children. It incorporates the Maternity Services Data Set (MSDS), Children and Young People's Health Services Data Set (CYPHS) and the Child and Adolescent Mental Health Services Data Set (CAMHS) (NHS Digital, 2015). Data items for inclusion in each of these individual datasets has been defined by NHS Digital. All NHS-funded maternity and community services have been required to provide data for these datasets since 2015. All three trusts that provided data used in this project provide data to the MSDS (University Hospital Southampton NHS Foundation Trust) and CYPHS (Solent NHS Trust and Southern Health NHS Foundation Trust). This data reporting requirement should improve recording of the key variables identified for inclusion in these datasets such as breastfeeding (6-8 weeks) and nutrition.

Information about the child's health and development, weight, height and vaccinations are recorded in the personal child health record, commonly known as the red book. This is a national standard health and development record that is given to parents at the birth of a child in the UK. Weight measurements in the red book include the measurement at birth, in the first two weeks (to ensure that birthweight is being regained) and that measured at the statutory health and development reviews (6-8 weeks, 9-12 months and 2-2.5 years). Additionally,

parents can take their child to be measured at baby weighing clinics that are held weekly at general practice surgeries or community centres. The data received from Southern Health NHS Foundation Trust had the weight or height measurements assigned a category based on the health reviews as well as the date of measurement. Measurements outside of these reviews were the exception in the dataset (0.3% of children had 6 or more weight measurements). However, data received from Solent NHS Trust had a weight or height measurement with the date of measurement with no health review category assigned and there was a lot of variation in the data available per child (18.2% of children had 6 or more weight measurements). This suggests that routine recording of measurements onto the child's electronic record may be inconsistent with variation in recording practice across community trusts. An electronic red book for parents is being trialled and rolled out across the UK but it is not clear how much of this data will be accessible for research.

Table 9.1: Summary of recommendations to improve clinical recording

Data source	Time point	Variable	Recommendation
Maternal antenatal care and birth data	Booking appointment	Alcohol consumption	Consider ways to improve accuracy
	Discharge	Breastfeeding status	Improve completion rate
		Smoking status	Improve completion rate
Child data	Early life	Breastfeeding status	Record breastfeeding initiation Identify consistent time-points across different systems Record age at which breastfeeding stopped
		Weaning	Record age at introduction of solid foods
		Anthropometric measurements	Consistent electronic recording

Clinical data remains a key resource for research purposes. The use of data for research has benefits to clinical recording if a process of feedback can be developed, maintained and implemented. An understanding of the clinical recording systems could lead to simple modifications to the data recording system to improve the recording which could be beneficial to both clinical and research teams. For example, if the instances of pregnancy progressing to beyond 42 weeks is rare, then the database should provide a warning message when closing the record for these instances so that this is confirmed. An upper limit of gestational age at birth can be applied to the database as there is a definite point beyond which pregnancies do not progress and so records progressing beyond this point should trigger a notification. On speaking to a midwife at UHS about the records with an unfeasible gestational age, I learnt that these unfeasible records are reviewed on an excel sheet at the end of each month and then updated. Similarly, unfeasible weights and heights were recorded at all stages and imposing lower and upper limits here may be a consideration. Although the range of height and weight can vary with age, this would filter out unfeasible values and trigger a double check of extreme values. There are costs involved in developing and maintaining databases but these are considerations that could be implemented when other changes are being implemented or data recording moves on to a new database which could limit the costs.

This project illustrates the value of routine clinical data and implications of linking this data to enrich it further or examine outcomes. However, it also raises the question around the data that is collected and if enough data is being collected or if there is more data that should be collected. One of the key limitations mentioned as part of the analysis reported in this thesis is the lack of data on weight gain during pregnancy. This is due to clinical practice in the UK where women are not routinely weighed during pregnancy. Regular weighing during pregnancy was stopped as it was believed to cause pregnant women anxiety for little or no clinical gain (Ellison and Holliday, 1997). There are no UK guidelines on optimal weight gain during pregnancy. US guidelines exist and this has often been used in research (IOM (Institute of Medicine) and NRC (National Research Council), 2009). NICE guidance on weight before, during and after pregnancy is currently being reviewed and updated. Given the prevalence of maternal obesity and the evidence on risk to offspring from maternal obesity and excessive weight gain during pregnancy both as individual factors and in

combination, regular weighing during pregnancy might be needed. Midwives might need guidance and training to offer women the best possible support and care incorporating advice on weight gain during pregnancy.

Similarly, breastfeeding is a key component of care during early life. There are several sources of support that women can access to help initiate and continue breastfeeding. Despite being recorded by all three data providers that we accessed data from, there was still a high proportion of missing data. In relation to the outcome considered, 69% missing for the outcome at Year R and 99% missing for the outcome at Year 6 thus limiting the usability of this variable. Children with an outcome at Year 6 in this dataset would be born in the early 2000s and thus it could be a positive sign that there is a lower percentage in the younger children as this could be an indication of improvement in recording practice over time. However, some of these missing data could be attributable to change in databases within the community trusts which meant that older data were not available. Given the value of clinical data in research, it is important that access to data is not lost when implementing changes to recording databases or practices.

Age at introduction of complementary foods or information on first foods is not routinely recorded. There is no clear association between timing of introduction of complementary foods and childhood overweight and obesity but early introduction of complementary foods (at or before four months of age) may increase the risk of childhood overweight and obesity (Pearce *et al.*, 2013). High protein intake at 2-12 months of age could be associated with an increase in BMI (Pearce and Langley-Evans, 2013) but given the age group, this could be from both formula milk and complementary foods. Despite the lack of clear evidence, introduction of complementary foods is a key stage in development and could be additional relevant data to record. However, this is likely to be recorded retrospectively as the UK recommendation is to start weaning around six months of age and the closest statutory development review after this age is the 9-12 month review. The duration between the introduction of complementary foods and the developmental review is relatively short but could be subject to recall bias.

9.3 Further research

The next step is to operationalize the risk prediction tool through external validation, and model update if necessary, followed by a feasibility study to test the acceptability and usability of the tool. The feasibility study is planned in collaboration with the health visiting service in Southampton and Portsmouth. On public involvement, mothers have expressed interest in early identification of risk with support and advice to help modify risk. Thus, as part of the feasibility study, we are testing the use of this tool as an aid to health visitors to guide delivery of an intervention on the healthy weight pathway in the health visiting service, rather than a screening test. Our practitioner consultation work suggests that health professionals would like an 'objective' way to stratify risk rather than individualised clinical judgement, as this feels subjective and can make the conversation with the family more sensitive. The risk estimation tool is envisaged to enable the provision of obesity prevention intervention at an early stage before the child is overweight or obese by providing a prompt for the health professional to introduce this topic and to help target extra support in resource-limited settings. However, the application of the tool may increase anxiety among parents and this will be explored as part of the feasibility study. Some individuals identified at risk may not develop the disease and the potential harms of intervening in these individuals need to be considered. Interventions for childhood overweight and obesity are generally focussed on behavioural and lifestyle changes related to physical activity and diet (Waters *et al.*, 2011). The potential harms to the individual of a behavioural intervention are likely to be lower than that of a clinical or medicinal intervention.

Due to the lack of consensus on the optimal risk threshold for risk prediction tools, these are set through consideration of the performance of the tool at selected thresholds and the potential benefits and harms of identifying individuals at risk. The feasibility study will additionally examine the acceptability of the suggested thresholds. The PPV for the ~2 year model at the suggested 20% risk threshold is 40% and the NPV is 93%. This means that a significant proportion of children identified at risk will not become overweight or obese. However, the high NPV provides confidence that very few children identified as low risk will become overweight or obese and therefore miss out on a targeted intervention. Provided we examine the population impact and cost effectiveness of using a risk

estimation tool based on routinely collected data as a decision strategy, targeting obesity prevention interventions, which would in an ideal world be universally available if resources were not limited, is unlikely to produce harms. The potential harms of a behavioural, environmental or social support complex intervention to tackle obesity are likely to be low compared to a clinical intervention.

9.4 Public health implications

The risk prediction tool can be used to intervene early in high risk individuals. However, obesity is a complex disorder and one single thing is not going to make a difference. In addition to individual factors, area-level factors may play a role in obesity. Evidence on longitudinal associations of area-level exposures during preconception, pregnancy and early life is limited but a recent systematic review I co-authored identified several area-level factors (storm induced maternal stress, nitrogen oxides exposure, traffic noise and proximity) that were associated with increased risk of childhood adiposity on exposure in early life (Wilding *et al.*, 2019b). Cross-sectional factors associated with childhood overweight and obesity include neighbourhood and individual socioeconomic deprivation (El-Sayed *et al.*), parental perception of neighbourhood safety (An *et al.*), fast food availability (Cobb *et al.*), access to green spaces and equipment and facilities for physical activity (Dunton *et al.*).

Achieving individual or family-based behavioural change can be difficult and this can be even more difficult to achieve in an environment that is not conducive to change. This raises the public health question of whether moderation of social and environmental factors needs to be considered alongside the individual factors and the feasibility of modification. High risk groups tend to be the more disadvantaged groups (Woo Baidal *et al.*, 2016; Twaits and Alwan, 2019; Wilding *et al.*, 2019a) and thus behavioural and lifestyle modification may not be feasible within the available resources. Environmental factors such as access to food stores, places for recreational activity, walkability and neighbourhood safety are all factors that influence healthy diet and sufficient physical activity.

The availability of healthy foods and variety is lowest at corner and convenience stores compared with large chain supermarkets with variation in foods available within corner shops in different neighbourhoods such that shops in disadvantaged neighbourhoods had lower availability of healthy foods than those

in more advantaged neighbourhoods (Cannuscio *et al.*, 2013). Access to a large supermarket for food shopping is dependent on the proximity of the supermarket and access to transport. Analysis of national survey data from 2015/16 (household expenditure from Living Costs and Food Survey and disposable income from Family Resources Survey) showed that households with children in lowest income decile would need to spend 30% of their disposable income (after housing) to meet the UK government's Eatwell Guide recommendation for a healthy diet compared to 12% in the top half income deciles (Scott *et al.*, 2018). These figures indicate the challenge faced by low income households in affording a healthy diet. This implies that more families in the UK are struggling to afford to consume a healthy diet and thus are more likely dependent on inexpensive and higher caloric food (Pechey and Monsivais, 2016).

In younger children, exposures to the food environment are likely to be controlled by the parents but with increasing independence in adolescence, school and commuting food environments are likely to become more important. Income and neighbourhood fast food exposure were associated individually and jointly with obesity in a large sample of UK adults such that lowest income and highest proportion of fast food outlet exposure was associated with highest risk (Burgoine *et al.*). A cross-sectional study of UK adults found that individuals living furthest away from their nearest supermarket were at increased risk of obesity with risk increasing further in individuals with lower education (Burgoine *et al.*, 2017). In adults, the home food environment only contributes to approximately 30% of the exposure with work and commuting food environments contributing equally to the exposure with highest exposure to takeaway food outlets being near work (Burgoine and Monsivais, 2013).

The creation of 'health-promoting environments' has been included as one of the WHO's objectives for preventing non-communicable diseases (2013-2020). This is in recognition of the fact that exposure to risk factors begins in childhood and there is a need to engage with State and non-State actors to prevent risk factors such as physical inactivity, unhealthy diet and adverse impacts of marketing in children (World Health Organization, 2013). The European Union 2014-2020 Action Plan has identified pre-schools, schools and deprived neighbourhoods as conducive to obesity but not the early life environment (European Commission, 2014). The UK Government's action plan has identified the importance of schools and early-year settings in defining habits (HM Government, 2016; Department of

Health and Social Care, 2018). However, none of these have included consideration of the preconception and pregnancy environments on subsequent offspring health.

Antenatal and postnatal (including early life) care in the UK is provided primarily by midwives and health visitors. Antenatal care rests primarily with midwives with consultant appointments if necessary with one health visiting appointment after 28 weeks of pregnancy. The healthcare focus during pregnancy is for a good pregnancy with the best possible outcome (healthy mother and baby). Care after birth is then passed on to the health visitor at around 10 days after birth. Health visiting is focused on improving health and reducing inequalities and remains a public health preventative role. The focus is on normal development and safeguarding of the child including identifying need for additional support. There are tiers of support and families identified as needing further support are supported through provision of additional visits or referral to other services as deemed necessary. Longer-term weight and health of mother and baby is a consideration of postpartum/early life care but this is low priority in the presence of issues related to maternal mental health or child safety. Thus, support for weight and overall health during this period is likely to only be offered in the absence of or after high priority issues have been resolved or are under control. Additional support and visits is a key part of care but the caseload of the health professionals needs to be considered alongside the requirements for care particularly in vulnerable families. Given the increasing evidence of the importance of the pre-conception and pregnancy periods on long-term health, care needs to evolve to incorporate longer term health impacts to both mother and child as a priority during the pre-conception, pregnancy and postpartum periods.

9.5 Intervention considerations

The risk prediction tool can be applied at different stages of the lifecourse, starting with pregnancy, and thus early intervention is possible in high risk families. Intervening early could be seen as a high risk approach however the benefits in this instance could extend to subsequent pregnancies and children. Maternal BMI and change in maternal BMI from previous pregnancy are key predictors and thus preventing weight gain or supporting weight loss before the

second pregnancy modifies the risk for the subsequent child with benefits to the mother's health.

Although a high proportion remain at low or high risk consistently across the stages, individuals move between low and high risk between the stages. To intervene early, an intervention will need to take this movement of individuals into consideration. Withdrawing intervention or support from individuals who have previously been deemed high risk but are now low risk can have negative consequences on their risk at the next stage. However, it may not be feasible to maintain an intensive intervention during all stages given the total proportion of the sample being identified. Thus, intervention would need to be in stages or layers which would enable movement of individuals between low or high levels of support.

Interventions need to balance the cost of intervening with the cost of not intervening. An example of intervention based on a risk prediction tool in the UK is the NICE recommendation of the use of the QRISK prediction tool for the assessment of risk of cardiovascular disease. The risk threshold for QRISK suggested by the authors who developed the tool was 20% (Hippisley-Cox *et al.*, 2008) but this was halved to 10% in the NICE recommendation (National Institute for Health Care and Excellence, 2019), thus identifying a larger proportion of the population at risk. Individuals identified as high risk are recommended to change their lifestyle with support through referral to services if needed and then offered statin treatment if lifestyle modification is inappropriate or unsuccessful. The modified risk threshold identifies more individuals as at risk but will reduce cardiac events and the benefits of this approach were deemed sufficiently significant to implement. Cardiovascular disease affects individuals and if high risk individuals are successful in changing their lifestyle as recommended (with or without statin treatment), then the benefits of this lifestyle change may extend to family who may implement this change to support the individual. Obesity, on the other hand, can affect more than one member of the family. Data from the Health Survey for England (HSE) showed that 28% of children of obese mothers were obese compared to 8% of children whose mothers were not overweight or obese. Similarly, 24% of children of obese fathers were obese compared to 9% of those whose fathers were not overweight or obese (NHS Digital, 2018a). Thus, the benefits of a successful family based intervention may be beneficial to the entire family and could outweigh the potential harms.

Modelling of obesity prevention in early childhood in Australia has identified significant health benefits over the lifetime (36496 health adjusted life years) and cost savings (301 million Australian dollars in 2010) if the intervention effect is maintained over the lifetime (Brown *et al.*, 2019). The modelling was carried out using intervention effect estimates from two systematic review of interventions and the benefits and savings quoted above are based on the conservative intervention estimate (Askie *et al.*) with benefits approximately doubling if using estimates from the other systematic review (Waters *et al.*, 2011). Both benefits and savings reduced if intervention effects showed a decay and were not maintained over the lifetime. Short-, mid- and long-term benefits of an intervention should be considered alongside the costs incurred. This modelling has been carried out based on an intervention in individual children but the benefits could be higher in family-based interventions if an effect is observed among the whole family. The benefits have been modelled assuming several scenarios of duration of intervention effect being maintained however the duration of intervention or follow-up to ensure this effect maintainence needs to be determined as well as the cost-effectiveness of the intervention.

Intervening early to prevent obesity means that the child is not necessarily going to be visibly overweight or obese at this stage which presents a challenge as parental recognition of existing childhood overweight and obesity is not always accurate. Data from HSE shows that approximately half the parents of obese children and the majority of parents of overweight children (90% of mothers and 87% of fathers) thought their child was about the right weight (NHS Digital, 2018a). A meta-analysis found that 50.7% of parents of overweight and obese children and 14% of parents of normal weight children underestimated their weight status. Parents were more likely to underestimate weight status in children closer to the overweight threshold so these children were at greater risk of being misclassified (Lundahl *et al.*, 2014). Thus, the first step to successful intervention might be to increase awareness among parents about the health risks associated with childhood overweight and obesity, the importance of early intervention and to correctly recognise their child's weight status. It is key that these messages are communicated effectively in a way that is engaging and accessible to ensure it resonates with parents. A qualitative study using focus groups in 18 mothers of preschool children from low-income families, all of whom were overweight or obese with the exception of one, found that mothers were more likely to consider

being teased about weight or limitations in physical activity as indicators of overweight rather than growth charts. Additionally, there was a belief among mothers that they were unlikely to affect a predisposition to being overweight (Jain *et al.*, 2001). A study of 482 mother-child pairs in Germany found that 20% of mothers were not convinced of the need for prevention or intervention until the child's BMI exceeds the 97th percentile at which point the child is already obese (Warschburger and Kröller, 2012).

Misperception of child overweight remains a barrier to enrolment in lifestyle modification or healthy weight programmes (Kelleher *et al.*, 2017). The proportion of parents taking recommended action after feedback about their child's weight status remains low which may be linked to parental recognition of weight status (Falconer *et al.*, 2014). Parental response to the NCMP feedback letter identifying children as overweight ranged from shock, denial and self-blame to acceptance, worry and intention to seek help whereas parents whose children were identified as normal weight expressed relief and happiness (Nnyanzi *et al.*, 2016). A trial investigating whether modifications to the NCMP feedback letter would lead to behavioural change found an increase in uptake of weight management services in the intervention group. Although overall uptake of services remained low, uptake in the intervention group was double that in the control group. The modification to the letter included a visual tool to aid in recognition of overweight, a social norms statement and in obese children a prepopulated booking form for weight management services (Sallis *et al.*, 2019). Interventions need to be engaging to families (both parents and children) to ensure uptake and continued involvement.

9.6 Existing interventions and future work

Obesity prevention interventions in early life (first 1000 days) have been targeted during pregnancy, pregnancy and infancy or infancy alone (some extended into childhood) but none target pre-conception or extend across all stages from pre-conception to infancy/childhood (Reilly *et al.*, 2017). A systematic review of obesity prevention interventions in children from birth to 18 years found that 71% targeted children aged 6 to 12 years and 78% were implemented in school settings (Waters *et al.*, 2011). Interventions did not always target established risk factors and maternal smoking was a key risk factor that was not included in any

of the existing interventions (Reilly *et al.*, 2017). Family based interventions have primarily targeted children aged 2-10 years with a small percentage of studies targeting the prenatal period or adolescents. Some interventions targeted media use or sleep but the majority focused on diet and physical activity with 13 interventions targeting all four factors. Interventions targeting ethnic minorities and non-traditional families are limited (Ash *et al.*, 2017).

Although interventions have improved diet or feeding and/or behavioural practices, the impact on child weight was limited (Redsell *et al.*, 2016a). Few interventions have been shown to be effective in preventing childhood overweight and obesity (Bluford *et al.;* Ciampa *et al.*). So far, interventions that combine diet and physical activity interventions in school settings have been demonstrated to have the greatest effectiveness, however evidence on preschool-, community- and home-based interventions and effectiveness is limited due to design heterogeneity and paucity of studies (Bleich *et al.*, 2018). Efficacious interventions have shown a modest effect on BMI in the short term but have attenuated on longer-term follow up. More substantial and longer-term effects may be achieved through interventions that extend across several life-course stages (Reilly *et al.*, 2017).

A more holistic approach to tackling childhood overweight and obesity may be achieved through involving stakeholders from across the system to implement a whole systems approach. Systems thinking encourages looking at the big picture to consider how different components and interventions may operate together to influence health (Egan *et al.*, 2019). Systems can adapt to an intervention and change over time or new developments may change the system thus impacting the approach making feedback loops an integral part. In 2019, Public Health England published a guide to support local authorities to promote healthy weight through a whole systems approach (Public Health England, 2019). Evidence-based guidance on feasible combined strategies that are successful in the long-term to prevent or treat overweight and obesity remains limited. Limited evidence on interventions in minority populations and focus on specific risk factors inhibit the development of comprehensive interventions. Once successful long-term intervention components are identified, prevention needs to move towards identifying the best way to embed effective intervention components into health and education systems to achieve long-term sustainable impact.

9.7 Conclusion

This chapter has discussed the overall findings of the thesis as a whole. The implications of the results and suggestions for future research have also been presented. The success of data linkage in this project provides insight into the feasibility and requirements of routine data linkage projects for research.

Most multiparous women start their pregnancy (second or higher) with a higher weight than their previous one. Utilising contact and intervening in the inter-conception period to prevent maternal weight gain is key to achieving better maternal and offspring health outcomes.

As obesity can be difficult to treat once established, it is preferable to predict obesity in younger children so targeted preventative measures can be implemented supporting population-level interventions. The prediction models can form the basis of a risk identification system that can be used to identify and quantify clustering of risk as early as the first trimester of pregnancy. This will strengthen the long-term preventative element of antenatal and early years care by stratifying of future risk to guide the nature and amount of support provided to families to foster health and wellbeing.

Appendix A Published papers and abstracts

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Pediatric Obesity

Predicting childhood overweight and obesity using maternal and early life risk factors: a systematic review

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Summary

Background: Childhood obesity is a serious public health challenge, and identification of high-risk populations with early intervention to prevent its development is a priority. We aimed to systematically review prediction models for childhood overweight/obesity and critically assess the methodology of their development, validation and reporting.

Methods: Medline and Embase were searched systematically for studies describing the development and/or validation of a prediction model/score for overweight and obesity between 1 to 13 years of age. Data were extracted using the Cochrane CHARMS checklist for Prognosis Methods.

Results: Ten studies were identified that developed (one), developed and validated (seven) or externally validated an existing (two) prediction model. Six out of eight models were developed using automated variable selection methods. Two studies used multiple imputation to handle missing data. From all studies, 30,475 participants were included. Of 25 predictors, only seven were included in more than one model with maternal body mass index, birthweight and gender the most common.

Conclusion: Several prediction models exist, but most have not been externally validated or compared with existing models to improve predictive performance. Methodological limitations in model development and validation combined with non-standard reporting restrict the implementation of existing models for the prevention of childhood obesity.

Keywords: Childhood obesity, maternal factors, overweight, prediction models.

Abbreviations: AUROC, area under receiver operating curve; DOHaD, developmental origins of health and disease; IQR, interquartile range; WHO, World Health Organization.

Introduction

The World Health Organization (WHO) has identified childhood overweight and obesity as one of the most serious public health challenges of the 21st century with 42 million children aged under 5 years estimated as overweight globally in 2014 (1). Data from the National Child Measurement Programme in England showed that in 2014/2015, 22% of children in Reception (aged 4 to 5 years) and 33% in Year 6 (aged 10 to 11 years) were classified as overweight or obese with children in most deprived areas twice as likely than children in least deprived areas to be obese (2). In 2012, the WHO published a report on population-based approaches to childhood obesity prevention, which identified improved government structures to support policy and intervention as well as population-based and community-based interventions as actions to prevent childhood obesity (3). In 2014, the European Union published a 6-year action plan on childhood obesity with the goal of contributing to halting the rise in childhood overweight and obesity by 2020. In 2016, the UK Government published a plan for action for tackling childhood obesity with

the aim to significantly reduce rates of childhood obesity within the next 10 years by supporting healthier choices in children and engaging communities, schools and industry to make food and drink healthier (4).

There is evidence that the in utero environment induces a response in the foetus, which can lead to enhanced susceptibility for diseases in later life (5). This concept is described as the 'developmental origins of health and disease (DOHaD)'. Developing foetuses adapt to an adverse in utero environment by undergoing structural, physiological and hormonal changes, which are beneficial for short-term survival, but at a cost for future health (6), which could be transmitted through generations (7). The 'maternal resources hypothesis' suggests that non-genetic evolution has led to a competitive dominance of adipocytes over other cell types in the acquisition and sequestering of energy in the body, which is maintained by the co-existence of excess maternal resources and sedentary behaviour during pregnancy leading to continued dysfunction in foetal metabolism (8). Behavioural patterns are transmitted between generations through socially mediated learning (9), and the postnatal environment could affect the behaviour of infants and young children based on that of the primary caregiver (8). Thus, it has been suggested that DOHaD should include all aspects of environment and all sensitive windows (preconception, pregnancy, early childhood and any others yet to be identified) (7).

Hence, the WHO Commission on Ending Childhood Obesity considered it essential to address critical time periods in development including pre-conception and pregnancy as well as treating children identified as obese (10). The increasing prevalence of obesity in women of reproductive age affects the health of the mother and puts the offspring at risk of developing childhood obesity and its consequences (11). Given the lack of evidence on effective long-term treatments, the focus of reducing childhood obesity rates should be on prevention (12). Key to an effective prevention strategy is the ability to identify individuals at particular risk. There is increased risk of persistence of childhood weight status into adulthood (13–16) particularly in children with two obese parents (17–19) with a meta-analysis concluding a low probability of weight change without weight loss treatment (20). Although this tracking of childhood body mass index (BMI) to adulthood was weaker in late adulthood (21), the identification of high-risk populations and intervening as early as possible to prevent the development of overweight and obesity should be a priority (22) because of the increased risk of adult morbidity and mortality associated with overweight and obesity in childhood and adolescence (23). Once high-risk populations are identified, mathematical models on childhood obesity trajectories that predict energy imbalance including excess energy intake underlying obesity (24,25) and calculate the magnitude of intervention necessary to achieve change in weight (25) can be used to guide the intervention.

The aim of this study was to systematically review studies of prediction models for childhood overweight and obesity using maternal and/or early life risk factors and critically assess the development and reporting of the methodology used to develop these models.

Methods

Medline and Embase were searched from their start dates to December 2016 using recommended filters, and the bibliographies and citations of all included studies were hand searched (using Web of Science Core Collection). The outcome considered was overweight and obesity between 1 and 13 years of age. No criteria were defined for overweight and obesity as different criteria can be considered given the age under consideration. The following search strategy was used:

{Pediatric Obesity/ OR Fetal Macrosomia/ OR

[(child or childhood or children or p#ediatric* or infant* or toddler or embry* or prenatal* or neonat*).mp. AND (obes*.mp. OR overnutrition/ or obesity/ or overweight/ OR overweight.mp. OR over weight.mp.)]} AND

[exp causality/ OR ((Reinforc* or Enabl* or predispos*) and factor*).mp. OR (risk* or predict* or causal* or prognos* or causation).mp.] AND

[exp Maternal Behavior/ OR maternal.mp. OR mother*.mp. OR early life.mp.]

Eligibility criteria

All studies that reported on one or more multivariable prediction models or scores that have been developed for individual estimation of future risk of childhood overweight and obesity were included. Studies that developed, developed and validated or just validated a risk score were not differentiated. The review was limited to studies conducted in humans and published in English. No limits were imposed on study timing or setting.

Data extraction and critical appraisal

The list of data extraction was based on the CHARMS checklist published by the Cochrane Prognosis Methods Group (26). The Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement was used to assess transparency in reporting (27). N. Z. assessed all articles and extracted the data. Items extracted from studies describing model development included study design, study population and location, number of study participants, outcome and age of outcome if available, method of modelling, method of internal validation (random split

of data, bootstrapping or cross-validation), number of predictors considered and included in the final model, model presentation and predictive performance including measures of discrimination and calibration where available.

For studies describing external model validation alone, items extracted included study design, study population and location, number of study participants and model performance. Predictors were checked to confirm that these were the same as the original model.

We have critically assessed the conduct and reporting of the methods used to develop these risk prediction models. However, a quantitative synthesis of the prediction models' results was not performed as formal methods for meta-analysis of models are not yet fully developed and was beyond the scope of this review.

Results

From the 11,867 articles identified by the search strategy, 143 full articles were reviewed of which nine articles were identified for inclusion in this review (Fig. 1). An additional study was identified through hand searching the citations of the included studies. Eight of the studies developed a risk score, seven of which were internally (six) and/or externally (two) validated in the same publication, and two were external validation studies of two of the eight existing prediction models (Table 1).

Study reporting

Using the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (27) reporting recommendation, a median of 23 (interquartile range [IQR], 22 to 24) items out of 37 (31 for derivation or validation alone) were reported suggesting some shortcomings (Table 2). As this review assessed the extent of reporting, authors were not contacted to seek further information.

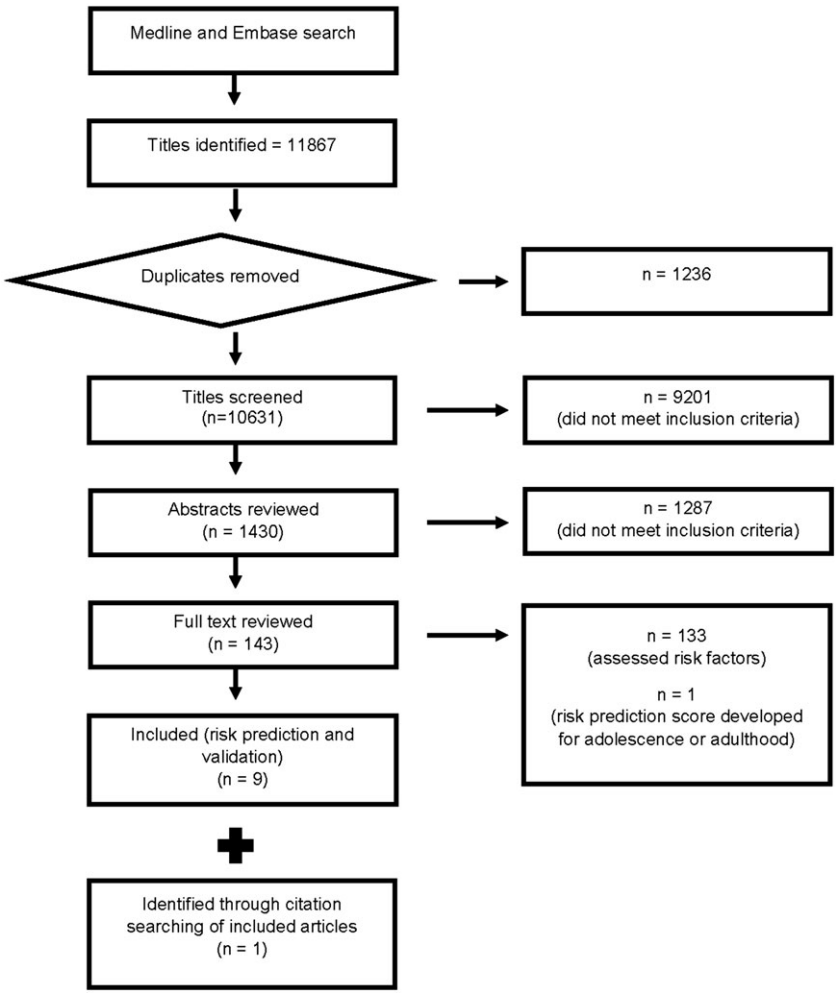

Figure 1 Literature search flow chart.

Table 1 Summary of prediction models in the included studies

Author, year	Druet 2012 (34)	Manios 2013 (31)	Manios 2016 (37)	Morandi 2012 (35)	Pei 2013 (28)	Redsell 2016 (36)	Robson 2016 (32)	Santorelli 2013 (33)	Steur 2011 (29)	Weng 2013 (30)
N, derivation	8,236	2,294	–	4,032	1,515	–	166	1,868	1,687	10,810
N, validation	8,236	–	5,946	1,503	757	980		867–880	–	2,703
Country	United Kingdom, Europe, America and Seychelles	Greece	Greece	Finland Validation – Italy, USA	Germany	United Kingdom	USA (Latino cohort)	United Kingdom	The Netherlands	United Kingdom
Design	Meta-analysis of three birth cohorts	Cross-sectional with retrospective data collection	Cross-sectional with retrospective data collection	Prospective birth cohort (Finland, USA); Retrospective cohort (Italy)	Prospective birth cohorts	Prospective birth cohort	Birth cohort	Prospective birth cohorts	Prospective birth cohort	Prospective birth cohort
Outcome	Childhood obesity	Childhood obesity (9–13 years)	Childhood obesity (6–15 years)	Obesity and overweight at 7 years	Overweight at age 10 years	Obesity at age 5 years	Obesity at 5 years	Obesity at age 1 year	Overweight at age 8 years	Overweight at age 3 years
Variables included	4	5	5	6	5	7	10 (full model), 5 (reduced model)	4	6	7
Derivation AUROC	–	0.64	–	0.67 (overweight–obesity), 0.78 (obesity)	–	–	0.84 (full model), 0.82 (reduced model)	0.91	–	0.72
Validation AUROC	0.77	–	0.64	0.70, 0.73	–	0.67 (original model), 0.93 (recalibrated)	–	0.89	–	0.76
TRIPOD	21	19	20	28	23	23	24	29	24	23

AUROC, area under receiver operating curve; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis.

Table 2 TRIPOD items reported in the 10 studies

Title and abstract		TRIPOD item description	Reported
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population and the outcome to be predicted	8
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results and conclusions	10
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models	9
	3b	Specify the objectives, including whether the study describes the development or validation of the model, or both	10
Source of data	4a	Describe the study design or source of data (e.g. randomized trial, cohort or registry data), separately for the development and validation datasets, if applicable	10
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up	10
Participants	5a	Specify key elements of the study setting (e.g. primary care, secondary care and general population) including number and location of centres	10
	5b	Describe eligibility criteria for participants	10
	5c	Give details of treatments received, if relevant	-
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed	10
	6b	Report any actions to blind assessment of the outcome to be predicted	0
Predictors	7a	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured	8
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors	0
Sample size	8	Explain how the study size was arrived at	10
Missing data	9	Describe how missing data were handled (e.g. complete-case analysis, single imputation and multiple imputation) with details of any imputation method	4
Statistical analysis methods	10a	Describe how predictors were handled in the analyses	9
	10b	Specify type of model, all model-building procedures (including any predictor selection) and method for internal validation	8
	10c	For validation, describe how the predictions were calculated	8
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models	8
	10e	Describe any model updating (e.g. recalibration) arising from the validation, if carried out	3
Risk groups	11	Provide details on how risk groups were created, if carried out	0
Development vs validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome and predictors	2
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful	6
	13b	Describe the characteristics of the participants (basic demographics, clinical features and available predictors), including the number of participants with missing data for predictors and outcome	7
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome)	1
Model development	14a	Specify the number of participants and outcome events in each analysis	4
	14b	If carried out, report the unadjusted association between each candidate predictor and outcome	1
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e. all regression coefficients, and model intercept or baseline survival at a given time point)	6
	15b	Explain how to use the prediction model	6
Model performance	16	Report performance measures (with CIs) for the prediction model	7
Model updating	17	If carried out, report the results from any model updating (i.e. model specification, model performance)	1
Discussion			
Limitations	18	Discuss any limitations of the study (such as non-representative sample, few events per predictor and missing data)	10
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data	3
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies and other relevant evidence	10
Implications	20	Discuss the potential clinical use of the model and implications for future research	10
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator and datasets	6
Funding	22	Give the source of funding and the role of the funders for the present study	9

CI, confidence interval; TRIPOD, Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis.

Study designs, population and sample size

Most of the studies used data from prospective birth cohorts, and two studies used cross-sectional studies in childhood with retrospective data collection of maternal and early life factors. All the studies were in high-income countries with the exception of data from Seychelles in the study that pooled cohort data from three studies.

Outcomes, number of patients and events

The outcome was overweight (three) (28–30), obesity (three) (31–33) or both (two) (34,35) in the eight included studies that developed a score, and the age at which this was predicted varied from 1 to 13 years of age in children. Sex-specific and age-specific BMI was calculated using the International Obesity Task Force (29–31,34,35), Centres for Disease Control (32), WHO (28) and UK90 growth chart (33) criteria and appropriate thresholds for overweight or obesity applied.

The number of participants used to develop the prediction models was clearly reported in all studies. The number of participants was 30,475 from all studies, and the median number was 2,015 (IQR 1,644 to 5,083) across the studies. Six (29,30,32–35) out of eight studies reported the prevalence of the outcome in the study population of which two reported the prevalence of both overweight and obesity (12–23% overweight and 3–32% obesity). Where recorded, the median number of events that was used in model development was 821 (IQR 549 to 1,374) for overweight and 133 (IQR 104 to 170) for obesity.

Risk predictors

Across the studies analysed, 57 putative predictors (Table 3) with a median of 11 risk predictors (IQR 8 to 19) were considered in the development models. These were defined a priori in six studies (29,30,32–35), identified through previous multivariable regression (31) or defined a priori for maternal predictors and through univariable regression for child predictors (28). Only four of the six studies that defined predictors a priori provided the rationale or references for including these predictors.

Twenty-five predictors were included in the final risk prediction models. However, 18 of these predictors were only included in one risk score model. The final reported prediction models included a median of six (IQR 5 to 6) predictors with maternal pre-pregnancy BMI, birthweight and infant gender included in seven out of eight scores (Table 3). Two studies assessed risk at birth (using preconception, antenatal and birth factors) (29,35) whereas other scores incorporated weight gain in the first year of life (30–34) predicting risk from the age of 12 months and over or childhood age-adjusted and sex-adjusted BMI at 5 years of age (28) to predict risk at 10 years of age.

Treatment of continuous risk predictors

Four (50%) risk prediction models retained continuous predictors as continuous (28,29,32,35), two (25%) categorized or dichotomized all continuous predictors and one (12.5%) retained some continuous predictors as continuous and categorized some predictors (33). It was unclear how continuous risk predictors were treated in one study but a categorical score chart developed, so it is likely that all continuous variables were categorized or dichotomized (30).

Missing data

Four studies only included cases with complete data in model development (28,29,33,34), two studies carried out multiple imputation (32,35) and one study did not report the presence or handling of missing data (31). The remaining study included participants with full anthropometric data at follow-up when outcome was assessed, but it is unclear if there were missing data at previous data collection points and how this was handled (30).

One of the studies that carried out multiple imputation had on average 1.7% (range 0 to 11.4%) (35) missing data for each predictor whereas 17% of the other study (32) participants had missing data for at least one predictor. Two of the studies that carried out complete case analysis; 23.8% (29) and 27.2% (28) of the sample were excluded because of the missing data, but it is unclear what percentage of sample was excluded for missing data alone in the other studies (33,34).

Model building

Six (75%) studies used automated variable selection (stepwise, backward deletion) to derive the final predictive model (29,30,32–35).

All studies were clear on the method used to develop the prediction model – logistic regression was used in seven studies (29–35) whereas linear regression was used in one study (28). One study had selected predictor variables based on previous multivariable logistic regression analysis and only carried out univariable logistic regression to assign integer values to the categories of risk predictor variables without any further modelling (31). Two models (29,33) included interaction terms whilst modelling whereas there was no mention of interaction terms whilst modelling in the other studies.

Table 3 Predictor variables assessed (−) and included (+) in the models

Author, year	Druet 2012 (34)	Manios 2013 (31)	Morandi 2012 (35)	Pei 2013 (28)	Robson 2016 (32)[a]	Santorelli 2013 (33)	Steur 2011 (29)	Weng 2013 (30)
Gender	+	+	−	+	+	+	+	+
Gestational age	−					−		
Weight change 0–6 months					**+**			
Weight gain 0–1 year (categorized)	−	+						+
Weight gain 0–1 year (continuous)	+					+		
Weight gain 0–5 years (categorized)				−				
Standardized BMI at 60–64 months				+				
Birthweight	+		+	+	**+**	+	+	+
Maternal age					**+**			−
Maternal BMI	+	+	+		**+**	+	+	+
Maternal education		+					−	−
Pre-pregnancy maternal smoking			−					
Maternal smoking during pregnancy		+	+	+		−	−	+
Maternal occupation			+					
Maternal employment							−	−
Employment in pregnancy								−
Single parenthood/marital status			−					+
Gestational weight gain			−					
Maternal alcohol consumption								−
Maternal feelings of depression								−
Maternal health								−
Maternal diabetes								−
Gestational diabetes						−		
Hospital delivery							+	
Delivery type							−	−
Number of household members			+					
Obesity predisposing single-nucleotide polymorphisms			−					
Paternal BMI			+				+	+
Paternal education							−	
Paternal employment							−	
Family income (categorized)				+				−
Parental education (categorized)				+				
Solids introduced at < or >6 months					+			−
Exclusive breastfeeding at 4–6 weeks					**+**			
Any breastfeeding at 6 months					+		−	
Ever breastfed in first year								+
Breastfeeding duration								−
Ever formula fed								−
First child/older siblings/number of own children					+		−	−
English language proficiency					+			
Ethnicity						−	−	+
Smoking in the parental house							+	
Living in a highly urbanized environment (≥2,500 address km^{-2})							−	
Maternal vegetable consumption during pregnancy							−	
Premature birth of child							−	
Region of birth							−	
Financial status								−
Child care arrangements								−
Unhappy when feeding interrupted								−
Makes a fuss going to sleep								−
Makes a fuss after waking								−
Upset when not getting things								−
Does the infant sit up?								−
Does the infant stand?								−

(*Continues*)

Table 3 (Continued)

Author, year	Druet 2012 (34)	Manios 2013 (31)	Morandi 2012 (35)	Pei 2013 (28)	Robson 2016 (32)[a]	Santorelli 2013 (33)	Steur 2011 (29)	Weng 2013 (30)
Does the infant grab objects?								–
Does the infant hold objects?								–
Can the infant walk?								–

[a] is **+** included in both full and reduced model and + included in full model only.
BMI, body mass index.

Predictive performance

Model performance was assessed in all studies, seven of which used area under the receiving operator curve (AUROC) in either the derivation, validation or both cohorts. The other study tested for specificity and predictive value alone (28). Although model performance was assessed and validated in all studies, only one study reported change in regression co-efficient post validation and updating the model (29). Two studies from the UK used data from the same birth cohort (Avon Longitudinal Study of Parents and Children) for validation of the same outcome but at different ages (two (33) and five (36) years). Model development AUROC ranged from 0.64 to 0.91 (median 0.78, IQR 0.70 to 0.81). The AUROC of 0.91 was replicated in internal validation using bootstrapping and only decreased to 0.89 on external validation (33).

Three studies (29,32,35) carried out Hosmer–Lemeshow tests to test calibration, two of which did so during model development both achieving $p > 0.5$. All studies assessed model classification (sensitivity and specificity) although one study (31) did not present positive and negative predictive values.

Internal validation

With the exception of two, all studies internally validated the models by random split of data (30,34), random split followed by cross-validation (28) or bootstrapping (29,32,33). Of the studies that did not internally validate the model, one validated the model externally in two separate cohorts (35) whereas the other was externally validated in a subsequent publication with overlapping authors in the development and validation papers (31,37). Additionally, one of the studies that internally validated the model using random split was also externally validated in a subsequent publication by the same authors (30,36). Model validation AUROC ranging from 0.75 to 0.91 (median 0.78, IQR 0.77 to 0.81) was achieved, and the original model was updated in one study only (29). Of the studies that carried out Hosmer–Lemeshow test for calibration, one did not report the exact p value, but that $p > 0.5$ was achieved (32) whereas the other achieved $p = 0.30$ on recalibration post validation (29).

External validation

Only four of eight models have been externally validated – once for three models all of which used data from the same country for validation (33,36,37) and twice for one model that was developed in Finland and validated in Italy and USA (35). Of the models validated using data from the same country, two studies calculated AUROC, which were 0.89 (36) and 0.67 (36). The only study that externally validated the model in two countries other than that in which it was developed (35) found that AUROC (0.70, confidence intervals 0.63 to 0.77) and calibration (Hosmer–Lemeshow $p = 0.12$) were satisfactory in one population, but although AUROC (0.73, confidence intervals 0.67 to 0.80) was satisfactory in the other, calibration (Hosmer–Lemeshow $p = 0.02$) was not. The predictors and model were then tailored to these populations by carrying out a replication analysis using stepwise logistic regression such that calibration achieved satisfactory levels. The initial model developed in Finland included six risk factors and reduced to three and five for the Italian and US cohort, respectively, with only two factors remaining consistent across all three models (maternal and paternal BMI). Ethnicity was introduced in the risk prediction score for the USA, and this was primarily because the birth cohort in Finland had high ethnic homogeneity. One of the external validation studies (36) also developed a recalibrated model using multivariable logistic regression to apply a recalibrated algorithm reflecting the characteristics of the validation cohort, imputed model for missing risk factor prediction and a recalibrated imputed model, which incorporated the two. This led to an increase in discrimination compared with the original model from 2% in the recalibrated to 25% in the recalibrated imputed model.

Model presentation

The complete regression formula (including all regression coefficients) was presented in six studies (29,30,32–35), and two of these studies provided a decision rule/score chart or risk score algorithm (29,30). Of the remaining two

studies, one provided the regression coefficients (28) whereas the other only provided a score chart (31).

Discussion

To our knowledge, this is the first systematic review to examine prediction models for childhood overweight and obesity. Eight studies that developed prediction models were identified; however, four of these prediction scores have been externally validated once or twice, and there is no evidence of further validation or validation in populations outside of those in which this was developed. Additionally, new models have been developed with no evidence of comparison with already existing models, and none of the models have been compared with each other to assess predictive performance. There were inadequacies identified in reporting of the methodology of development of risk prediction models, and there is no evidence of implementation of the risk scores. Whilst there is clear overlap between risk factors included in the prediction models, no single risk factor has been included in all prediction models with maternal pre-pregnancy BMI, infant gender and birthweight being the most commonly included. Thus, it is difficult to recommend the use of any one score, as there are no consistent predictors, no comparison between models and the outcome has been variable and predicted at different ages through childhood up to 13 years of age.

The question of predictors considered for inclusion in the model also needs to be considered. Although not included in the final prediction model, several predictors around infant temperament were considered. These are self-reported by parents and highly likely to be subjective. Additionally, these factors were identified a priori based on a previous systematic review, but the conclusion of the review was that the evidence was inconclusive because of limited number of studies (38).

Thirteen of the 25 risk factors identified were preconception, and thus, some of these could prove impactful in planned pregnancies such as maternal and paternal BMI whereas others are non-modifiable such as ethnicity. Although factors such as maternal education, occupation and income are modifiable, it is difficult to do so. Maternal smoking during pregnancy and hospital delivery were the only two antenatal risk factors identified and included in risk prediction. Eight of the 10 early life risk factors identified can be broadly classified into weight gain particularly in the first year of life and breastfeeding including weaning both of which are modifiable. The other two risk factors were gender and birthweight, of which gender is non-modifiable but birthweight can be monitored and is considered modifiable by factors known to affect foetal growth (39).

Some key aspects of multivariable model development and validation need to be considered. These include handling missing data, method of treatment of continuous variables, selecting variables for inclusion in the model and methods of validation including assessing discrimination and calibration (40). Missing data were identified in most studies, which can introduce bias if inappropriately handled, thus impeding the construction of a valid prediction model (41). Multiple imputation minimizes the effect of missing data provided that data are missing at random (42) and enables the use of all available data but was only performed in 25% of studies included in this review. All other studies excluded participants with missing data, which is an acceptable approach only if the amount of missing data are small (43); however, these studies did not provide any indication of how much data were missing per individual and per variable to enable readers to reach their own judgement of the validity of the prediction.

At least three prediction models categorized some or all continuous variables for inclusion in the model. However, discarding information through categorization of continuous variables to estimate a continuous relationship between a predictor variable and risk has been shown to lead to a substantial loss of power and precision (44), thus reducing the efficiency of the analysis with increased probability of biased estimates (45) and Type 1 (46). In addition, a model that categorizes continuous variables is unrealistic as individuals close to but on opposite side of the category cut-point will be characterized as having very different outcome when a very similar outcome is more likely (47). It is recommended that continuous predictors are retained as continuous and suitable functions such as fractional polynomial are used (47,48). Although this is true from a methodological point of view, the clinical practice in terms of implementation of any score needs to be considered. For example, the National Institute for Health and Care Excellence in the UK recommends action before, during and after pregnancy in women with BMI greater than 30 (49). Thus, including this categorization could make the prediction rule easier to incorporate into clinical practice.

Although predictors shown to have little effect on the outcome should not be included in the prediction, the method of selection of predictor variables for inclusion is crucial. The majority of studies (75%) used an automated variable selection method, which increases the likelihood that variables that do not truly predict the outcome will be identified as a predictor (50). This is because it is a data-driven approach that cannot account for clinical relevance leading to biased regression estimates and poor predictions as true predictors could be excluded because of lack of power (51,52). It also leads to loss of information due to inclusion of variables based on a binary decision. It has been suggested that a more reasonable reduction of variables using automated selection procedures could be achieved by using a liberal selection

criteria such as $p = 0.50$ (52) instead of 0.05, which is more commonly used and has been used in all the prediction models included in this review that used this procedure. It could also be important to retain predictors known to be important from literature but does not achieve statistical significance in the model development dataset (51).

Once developed, the performance of a model needs to be evaluated to demonstrate usability. Although a biased model could provide useful clinical separation into groups if the predictor information entered into the model is strong (53), evidence is needed that the model performs well in populations other than that in which it was developed (54). Validation can be internal or external using a completely different sample, thus also examining the generalizability of the model (54). Six studies (75%) internally validated the model through random split of the dataset (two), random split and cross-validation (one) or bootstrapping (three). Four studies (50%) externally validated the model, only one of which externally validated the model in cohorts from different countries. This was followed by replication analysis to rebuild the model in these two cohorts resulting in only two predictors being retained across all three models in this study (maternal and paternal BMI). As the use of random split sample decreases the precision of estimates and increases the frequency of missing important independent variable (55), there is limited value in doing so unless the sample size is particularly large (51). A non-random or chronological split has been suggested as a more precise approach, but internal methods such as bootstrapping and cross-validation remain more informative (53).

This review has been carried out with a systematic approach, thus identifying all studies that have developed and/or validated a risk prediction model for childhood overweight and obesity. However, heterogeneity exists at many levels particularly the outcome (overweight, obesity or both) under consideration and age at which outcome is predicted. This heterogeneity combined with the deficiency of external validation limits the applicability of these scores. Additionally, poor reporting in aspects of development of the prediction models was observed with insufficient detail on steps involved in model building. Risk prediction models have nearly all been developed or validated in developed countries, but almost half and one-quarter of the estimated 42 million overweight children under the age of 5 years live in Asia and Africa, respectively (1). Models tailored to these countries are important, as associations are known to vary between ethnic groups.

Conclusion

Despite the existence of several models for the prediction of childhood overweight and obesity, most have not been externally validated or compared with existing models to assess predictive performance. Moreover as the outcome has been predicted at different ages, it may not be possible to combine or compare all models against each other. This review also highlights methodological limitations in model development and validation combined with non-standard reporting, thus limiting the usability of these prediction models.

There remains a need to develop new methods for combining findings from existing prediction models and develop prediction models using robust methods of development followed by external validation and recalibrating to populations, which would then enable assessment of impact of the implementation of the score.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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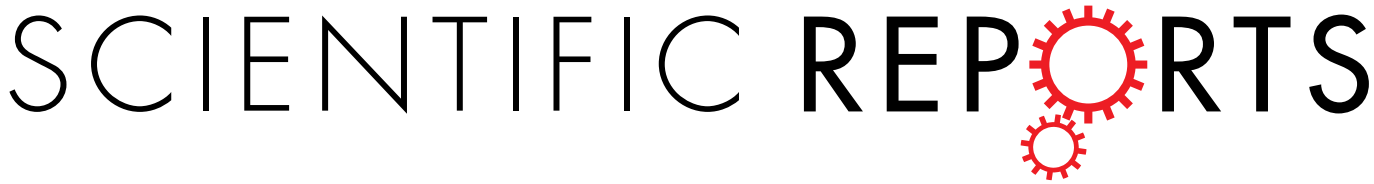

OPEN

The duration of the interpregnancy interval in multiparous women and maternal weight gain between pregnancies: findings from a UK population-based cohort

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Maternal obesity in pregnancy increases the risk of adverse long-term health outcomes in both mother and offspring. A population-based cohort of prospectively collected routine antenatal healthcare data collected between January 2003 and September 2017 at University Hospital Southampton, UK was utilised to investigate the association between duration of interpregnancy interval between successive pregnancies and gain in maternal body mass index by the start of the next pregnancy. Records of 19362 women with two or more consecutive singleton live births were analysed. Two-thirds had gained weight when presenting to antenatal care for their subsequent pregnancy with 20% becoming overweight/obese. Compared to an interval of 24–35 months, an interval of 12–23 months was associated with lowest risk of weight gain (adjusted RR 0.91, 99% CI 0.87 to 0.95, $p < 0.001$) and ≥36 months with greatest risk (adjusted RR 1.11, 99% CI 1.07 to 1.15, $p < 0.001$) for the first to second pregnancy. This study shows that most multiparous women start their pregnancy with a higher weight than their previous one. An interval of 12–23 months is associated with the lowest risk of starting the second pregnancy with a higher body weight accounting for age. In countries with high prevalence of maternal obesity, birth spacing may merit exploration as a factor impacting on perinatal morbidity.

Pregnancy is a period of metabolic and behavioural changes, the effects of which last beyond the immediate pregnancy for both mother and child[1] thus affecting subsequent children. Biological and behavioural changes on childbearing can lead to weight gain and can alter a woman's weight trajectory[2]. Maternal obesity is a key predictor of maternal and fetal pregnancy outcomes as well as long-term health outcomes in the mother and child such as diabetes and cardiovascular disease[3]. Overweight and obesity prevalence has been increasing over the last few decades with data from the Health Survey for England 2015 indicating that an average of 52.1% of women aged 16 to 54 years are overweight or obese[4]. This rise in obesity in women of childbearing age and its associated effects on maternal and offspring health[3] make maternal weight change between pregnancies an important consideration as this could modify risk of subsequent offspring.

Women who have given birth are at higher risk of developing obesity than women who have not[5]. Additionally, women with excess gestational weight gain who failed to lose pregnancy weight by six months postpartum were at increased risk of subsequent obesity[6]. Although overweight and obesity in nulliparous women is associated with increased risk of adverse outcomes[7], evidence on association with increased risk of postpartum weight retention is conflicting[8–10] with a review concluding that gestational weight gain rather than pre-pregnancy body mass index (BMI) determines postpartum weight retention[11]. A systematic review reported that postpartum weight follows a steep decrease in the first three months followed by a continuous decrease until 12 months following

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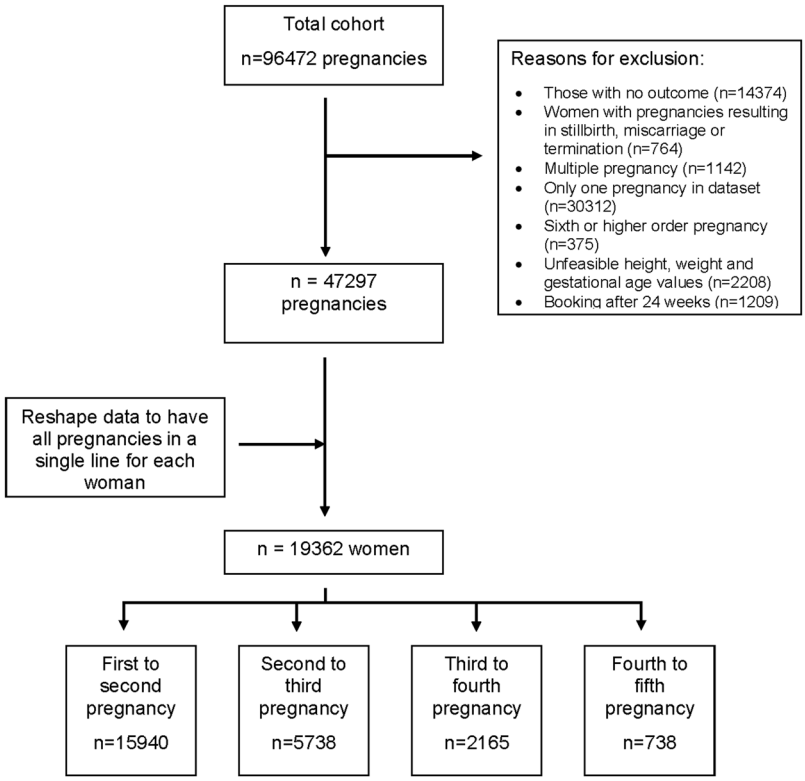

Figure 1. Flow diagram showing the data preparation process.

which an increase in weight was reported. However, this was only assessed in two cohorts[2]. Post-partum weight retention is variable with women on average retaining 0.5 to 3 kg, however a substantial number (12–20%) retain a considerable amount of weight[12]. Approximately two-thirds of women presenting for antenatal care for a second pregnancy in Ireland an average of 18 months after delivery had gained weight with 20% in a higher compared to 5.8% in a lower BMI category than the first pregnancy[13].

The World Health Organization technical consultation on birth spacing in 2005 recommended an interval of 2 years or more however evidence on maternal obesity as an outcome was not considered[14]. One of the major concerns with a short interval is maternal nutritional depletion because of inadequate time to recover from one pregnancy before entering the next[15]. In the US, nearly a third of second order or higher births were conceived within 18 months of the previous with 5% conceived within six months[16]. There is evidence that interpregnancy interval gets shorter as maternal age at first pregnancy increases, with women who delay the start of childbearing to $\geq$35 years having increased odds of intervals less than six months[17]. Data from 1969–2006 in Switzerland showed that maternal age at first pregnancy had increased from 25.0 to 30.1 years with shorter intervals between pregnancies[18]. Short (<18 months) and long (>59 months) intervals between pregnancies has been associated with increased risk of adverse perinatal outcomes[19] such as preterm birth, low birth weight and small-for-gestational age[19,20].

Weight retention is highest after the first pregnancy[21], and gestational weight gain and postpartum weight retention in subsequent pregnancies follow a similar pattern to the first[8]. Analysis of a retrospective cohort of 37178 women with three pregnancies in Canada found that women with short interpregnancy intervals (<12 months compared to 18–23 months) were more likely to enter the subsequent pregnancy obese[22]. However, BMI at the start of the previous pregnancy and socioeconomic status were not taken into account.

To our knowledge, no previous epidemiological studies have examined gain in maternal BMI in multiparous women in relation to birth spacing. The aim of this study was therefore to examine, in a population-based cohort of antenatal healthcare data in the South of England, patterns of gain in first-trimester maternal BMI, and examine its association with the length of the interpregnancy interval between consecutive live births.

Results

The main sample consisted of 19362 women with at least two consecutive live birth pregnancies (Fig. 1). Of the 15940 women who had their first two pregnancies in the dataset, 12636 women only had first two, 2654 had three, 530 had four and 120 had five consecutive pregnancies. A further 1884 women had their second to third, 430 second to fourth, 136 second to fifth, 758 third to fourth, 207 third to fifth and 7 fourth to fifth pregnancies. A description of the sample characteristics by pregnancy order is shown in Table 1. Mean maternal BMI at first pregnancy was 24.6 kg/m^2 (standard deviation 5.0) and increased with pregnancy order. Overweight and obesity in the sample increased with higher order pregnancies with 13.0% obese at first pregnancy to 31.6% obese at fifth pregnancy. The proportion of women who stopped smoking when pregnancy was confirmed was highest in the

	First pregnancy	Second pregnancy	Third pregnancy	Fourth pregnancy	Fifth pregnancy
N	15940	18954	6844	2533	738
Maternal age (mean ± SD)	25.9 ± 5.5	28.6 ± 5.4	29.3 ± 5.0	30.3 ± 4.9	31.6 ± 4.8
Timing of first booking appointment, weeks (mean ± SD)	11.3 ± 2.7	11.2 ± 2.5	11.5 ± 2.8	11.8 ± 3.1	12.0 ± 3.3
Maternal BMI (mean ± SD)	24.6 ± 5.0	25.8 ± 5.6	26.5 ± 6.0	27.3 ± 6.2	28.2 ± 6.6
Maternal BMI (%, 99% CI)					
Underweight (<18.5)	3.9 (3.5 to 4.3)	2.9 (2.6 to 3.2)	2.5 (2.0 to 3.0)	2.1 (1.5 to 3.0)	1.5 (0.6 to 3.1)
Normal weight (18.5 to 24.9)	59.2 (58.2 to 60.2)	51.6 (50.6 to 52.5)	46.1 (44.5 to 47.7)	41.1 (38.6 to 43.7)	36.2 (31.7 to 40.9)
Overweight (25.0 to 29.9)	23.9 (23.0 to 24.7)	26.6 (25.8 to 27.5)	28.7 (27.3 to 30.2)	28.4 (26.1 to 30.8)	30.8 (26.5 to 35.3)
Obese (≥30.0)	13.0 (12.4 to 13.7)	18.9 (18.2 to 19.7)	22.7 (21.4 to 24.0)	28.3 (26.0 to 30.7)	31.6 (27.2 to 36.2)
Maternal smoking status (%, 99% CI)					
Never smoked/quit	53.3 (52.3 to 54.4)	57.5 (56.5 to 58.4)	50.8 (49.3 to 52.4)	47.6 (45.0 to 50.2)	45.3 (40.5 to 50.1)
Stopped >1 year before conceiving	12.0 (11.4 to 12.7)	16.2 (15.5 to 16.9)	14.7 (13.6 to 15.8)	12.7 (11.1 to 14.5)	11.1 (8.3 to 14.4)
Stopped <1 year prior to conceiving	7.3 (6.8 to 7.8)	4.1 (3.8 to 4.5)	4.2 (3.6 to 4.8)	3.2 (2.4 to 4.2)	5.4 (3.5 to 7.9)
Stopped when pregnancy confirmed	12.1 (11.4 to 12.7)	7.4 (6.9 to 7.9)	7.5 (6.7 to 8.3)	7.6 (6.3 to 9.1)	6.4 (4.3 to 9.0)
Continued smoking	15.3 (14.6 to 16.0)	14.8 (14.2 to 15.5)	22.8 (21.5 to 24.2)	28.9 (26.6 to 31.3)	31.8 (27.5 to 36.4)
Maternal education (%, 99% CI)					
Secondary (GCSE) or under	23.7 (22.9 to 24.6)	24.9 (24.1 to 25.7)	36.3 (34.8 to 37.8)	45.9 (43.3 to 48.5)	51.8 (47.0 to 56.5)
College (A levels)	43.0 (42.0 to 44.0)	43.2 (42.3 to 44.1)	44.0 (42.5 to 45.6)	41.8 (39.3 to 44.4)	41.7 (37.1 to 46.5)
University degree or above	33.3 (32.3 to 34.3)	31.9 (31.0 to 32.8)	19.7 (18.5 to 21.0)	12.3 (10.7 to 14.1)	6.5 (4.4 to 9.2)
Maternal employment (%, 99% CI)					
Employed	80.0 (79.1 to 80.8)	64.0 (63.1 to 64.9)	45.4 (43.8 to 46.9)	28.8 (26.5 to 31.2)	20.5 (16.8 to 24.5)
Unemployed	15.7 (14.9 to 16.4)	34.3 (33.4 to 35.1)	52.3 (50.7 to 53.9)	68.7 (66.3 to 71.1)	77.5 (73.3 to 81.3)
In education	4.0 (3.6 to 4.4)	1.1 (0.9 to 1.3)	1.3 (1.0 to 1.7)	1.3 (0.8 to 2.0)	1.1 (0.3 to 2.5)
Not specified	0.4 (0.3 to 0.6)	0.7 (0.5 to 0.9)	1.0 (0.7 to 1.4)	1.2 (0.7 to 1.9)	0.9 (0.3 to 2.3)
Ethnicity (%, 99% CI)					
White	86.9 (86.1 to 87.5)	85.7 (85.0 to 86.3)	82.6 (81.4 to 83.7)	81.2 (79.1 to 83.1)	81.7 (77.8 to 85.2)
Mixed	1.2 (1.0 to 1.4)	1.2 (1.0 to 1.5)	1.2 (1.0 to 1.6)	1.4 (0.9 to 2.1)	1.9 (0.8 to 3.6)
Asian	5.8 (5.3 to 6.3)	6.3 (5.8 to 6.8)	9.4 (8.5 to 10.4)	10.0 (8.5 to 11.6)	9.6 (7.0 to 12.8)
Black/African/Caribbean	1.4 (1.2 to 1.7)	1.7 (1.5 to 1.9)	2.5 (2.1 to 3.1)	3.4 (2.5 to 4.4)	3.4 (1.9 to 5.5)
Chinese	0.6 (0.4 to 0.7)	0.5 (0.4 to 0.7)	0.3 (0.1 to 0.5)	0.3 (0.1 to 0.7)	0.1 (0.0 to 1.0)
Other	1.0 (0.8 to 1.2)	1.2 (1.0 to 1.4)	1.4 (1.1 to 1.8)	1.5 (0.9 to 2.2)	1.8 (0.8 to 3.4)
Not specified	3.2 (2.9 to 3.6)	3.4 (3.1 to 3.8)	2.6 (2.1 to 3.1)	2.3 (1.6 to 3.2)	1.5 (0.6 to 3.1)

Table 1. Pregnancy characteristics by gestational order for period of January 2003 - September 2017, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, England.

first pregnancy and decreased in subsequent pregnancies. The proportion of women who continued smoking through pregnancy was highest in later pregnancies. Women with college education or lower tended to have higher number of pregnancies and higher BMI. There was a slight shift in ethnic distribution from first to higher order pregnancies with a decrease in the proportion of White women and an increase in the proportion of Asian and Black/African/Caribbean women.

Table 2 summarizes the interpregnancy interval and change in maternal BMI between consecutive pregnancies. Median interpregnancy interval followed a u-shaped pattern and was shortest from first to second pregnancy, increased from second to third pregnancy but decreased for subsequent pregnancies and was similar to the interval between first to second pregnancy. However, the proportion of women with an interval of 0–11 months between pregnancies increased from 17.5% in the first to second pregnancy to 28.5% in the fourth to fifth pregnancy. Between 47–52% of women had intervals of 2 years or more between pregnancies. The median overall change in maternal BMI from first to second pregnancy was 0.9 kg/m^2 (interquartile range IQR −0.4 to 2.4) however the change in women who lost weight was 1.0 kg/m^2 (IQR −1.9 to −0.5) and in women who gained weight, it was 1.8 kg/m^2 (IQR 0.9 to 3.4). The change remained similar across pregnancies with approximately two-thirds of women having gained weight when presenting for antenatal care for the subsequent pregnancy. Over a fifth were in a higher BMI category by start of the next pregnancy with 1–2% having moved two BMI categories (for example, normal weight to obese).

Figure 2 shows the percentage of women gaining weight by BMI category and interpregnancy interval from first to second pregnancy. A substantial proportion of women within each BMI category gained weight across all intervals however, the lowest proportion of women gaining weight and changing BMI category across all BMI categories was in the 12–23 months interval. A similar pattern was observed across all pregnancies (data not presented).

	First to second pregnancy	Second to third pregnancy	Third to fourth pregnancy	Fourth to fifth pregnancy
N	15940	5738	2165	738
Interpregnancy interval, months (median, IQR)	22.9 (14.6 to 35.5)	25.0 (14.0 to 43.1)	22.6 (12.3 to 40.7)	22.9 (10.8 to 41.1)
Interpregnancy interval, categorised (%, 99% CI)				
0–11 months	17.5 (16.8 to 18.3)	19.7 (18.4 to 21.1)	24.7 (22.3 to 27.1)	28.5 (24.3 to 32.9)
12–23 months	35.3 (34.3 to 36.3)	28.2 (26.7 to 29.8)	28.5 (26.0 to 31.0)	23.8 (19.9 to 28.1)
24–35 months	23.1 (22.2 to 23.9)	18.7 (17.4 to 20.0)	16.7 (14.7 to 18.9)	18.0 (14.5 to 21.9)
36 months or more	24.1 (23.3 to 25.0)	33.4 (31.8 to 35.0)	30.2 (27.6 to 32.8)	29.7 (25.4 to 34.2)
24 months or more	47.2 (46.2 to 48.2)	52.1 (50.4 to 53.8)	46.9 (44.1 to 49.7)	47.7 (42.9 to 52.5)
Direction of change of maternal BMI (%, 99% CI)				
No change	2.9 (2.6 to 3.3)	2.9 (2.3 to 3.5)	3.2 (2.3 to 4.3)	3.5 (2.0 to 5.7)
Lost BMI units	31.3 (30.3 to 32.2)	31.8 (30.2 to 33.4)	31.7 (29.1 to 34.3)	27.4 (23.2 to 31.8)
Gained BMI units	65.8 (64.9 to 66.8)	65.3 (63.7 to 66.9)	65.1 (62.4 to 67.8)	69.1 (64.5 to 73.4)
Change in maternal BMI (median, IQR)	0.9 (−0.4 to 2.4)	0.9 (−0.4 to 2.5)	0.9 (−0.4 to 2.8)	1.3 (−0.2 to 2.8)
Change in maternal BMI in women who lost weight	−1.0 (−1.9 to −0.5)	−1.2 (−2.2 to −0.5)	−1.3 (−2.4 to −0.6)	−1.1 (−2.3 to −0.6)
Change in maternal BMI in women who gained weight	1.8 (0.9 to 3.4)	1.9 (0.9 to 3.4)	2.1 (1.0 to 3.8)	2.2 (1.1 to 3.6)
Weight gained by interpregnancy interval (%, 99% CI)				
0–11 months	65.3 (62.9 to 67.6)	61.7 (57.9 to 65.4)	62.4 (56.8 to 67.7)	61.0 (51.9 to 69.5)
12–23 months	60.3 (58.6 to 61.9)	60.3 (57.1 to 63.4)	62.8 (57.6 to 67.8)	63.1 (53.2 to 72.3)
24–35 months	66.2 (64.2 to 68.2)	64.5 (60.7 to 68.3)	60.8 (53.9 to 67.3)	73.7 (62.7 to 82.9)
36 months or more	74.0 (72.1 to 75.8)	72.2 (69.5 to 74.8)	72.0 (67.2 to 76.4)	79.0 (71.1 to 85.6)
Change in maternal BMI category (%, 99% CI)				
No change in BMI category	71.6 (70.7 to 72.5)	71.2 (69.6 to 72.7)	69.6 (66.9 to 72.1)	69.4 (64.8 to 73.7)
Underweight (<18.5)	1.5 (1.3 to 1.8)	1.4 (1.0 to 1.8)	1.0 (0.5 to 1.7)	1.4 (0.5 to 2.9)
Normal weight (18.5 to 24.9)	45.1 (44.1 to 46.1)	39.1 (37.5 to 40.8)	34.0 (31.4 to 36.7)	30.4 (26.1 to 34.9)
Overweight (25.0 to 29.9)	13.6 (12.9 to 14.3)	15.2 (14.0 to 16.5)	15.7 (13.7 to 17.8)	15.7 (12.4 to 19.5)
Obese (≥30.0)	11.4 (10.9 to 11.9)	15.5 (14.3 to 16.7)	18.8 (16.7 to 21.1)	22.0 (18.2 to 26.1)
% decreased to normal weight	3.7 (3.3 to 4.1)	3.7 (3.1 to 4.4)	4.2 (3.2 to 5.5)	3.9 (2.3 to 6.2)
% decreased to overweight	1.5 (1.2 to 1.7)	2.5 (2.0 to 3.1)	2.2 (1.5 to 3.2)	2.6 (1.3 to 4.5)
% increased to overweight	11.7 (11.0 to 12.3)	11.5 (10.5 to 12.7)	11.2 (9.5 to 13.1)	12.5 (9.5 to 15.9)
% increased to obese	7.9 (7.4 to 8.5)	7.7 (6.8 to 8.6)	9.9 (8.3 to 11.6)	9.6 (7.0 to 12.8)

Table 2. Change in maternal body mass index (BMI) measured at the first antenatal visit between consecutive pregnancies by gestational order.

Figure 3 summarizes the longer-term change in maternal BMI between pregnancies defined as the change in maternal BMI during the course of all her pregnancies in the dataset. The proportion of women who gained weight increased from 65.7% by second pregnancy in women who had their first two to 88.5% by fifth pregnancy in women who had their first five pregnancies.

In both unadjusted and adjusted linear regression analyses, there was a significant positive association between change in maternal BMI with each year of interpregnancy interval (adjusted increase in maternal BMI per year of interpregnancy interval 0.25 kg/m^2, 99% CI 0.21 to 0.28) for first to second pregnancy. The coefficient remained similar across pregnancies and increased for the fourth to fifth pregnancy (adjusted increase in maternal BMI per year of interpregnancy interval 0.36 kg/m^2, 99% CI 0.22 to 0.50) (Table 3).

The logistic regression models show that there is a significantly increased risk of starting the next pregnancy with a higher weight compared to the previous one with an interval of 36 months or more (adjusted RR 1.11, 99% CI 1.07 to 1.15 for first to second; adjusted RR 1.13, 99% CI 1.05 to 1.21 for second to third; adjusted RR 1.18, 99% CI 1.04 to 1.33 for third to fourth pregnancy) (Table 4, Fig. 4). In contrast, there was a significantly decreased risk of weight gain between pregnancies in those with an interval of 12 to 23 months (adjusted RR 0.91, 99% CI 0.87 to 0.95 for first to second; adjusted RR 0.93, 99% CI 0.86 to 1.01 for second to third; adjusted RR 1.02, 99% CI 0.89 to 1.16 for third to fourth pregnancy). The only exception was in women with five pregnancies where birth spacing was not significantly associated with interpregnancy weight gain in the period between their fourth and fifth pregnancies.

Discussion

This study examined the association of change in maternal BMI between pregnancies with interpregnancy interval in 19362 women in Hampshire, England. The rate of obesity increased from 13.0% at first pregnancy to 31.6% at fifth pregnancy, with approximately two thirds of the study sample gaining weight by the start of their subsequent pregnancy compared to the start of their previous one. An interval of 12 to 23 months between the first and

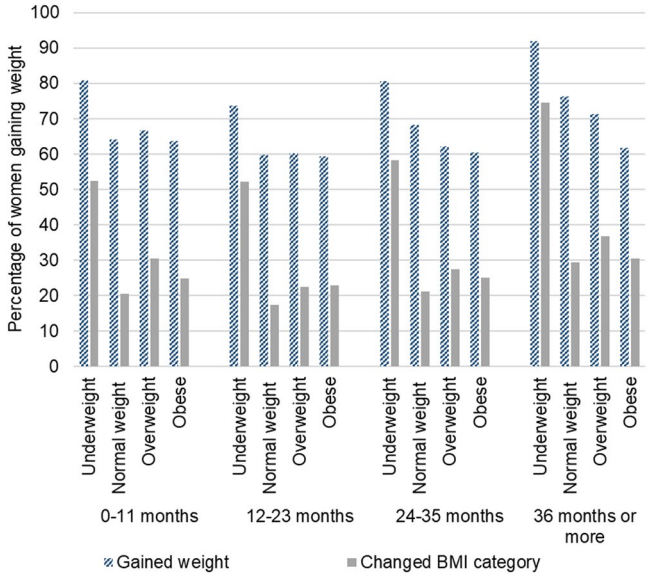

Figure 2. The percentage of weight gain by interpregnancy interval and maternal body mass index (BMI category) between first to second pregnancy.

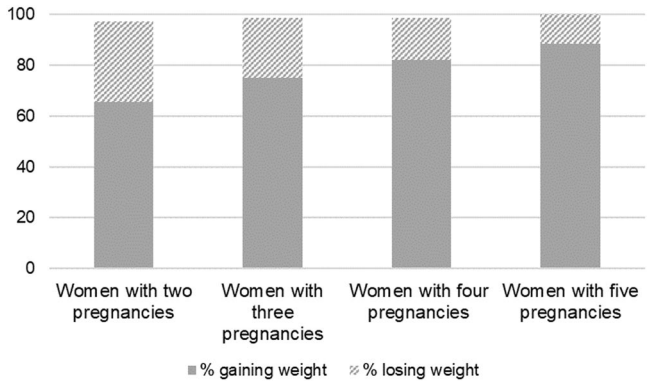

Figure 3. The percentage of weight gain and loss in women with two and more pregnancies across all their pregnancies.

second pregnancy was found to confer the lowest risk of weight gain, and hence of starting the next pregnancy with a higher weight. This association remained statistically significant after adjusting for maternal age and starting maternal BMI.

About 22% of women presented to antenatal care for their subsequent pregnancy in a higher BMI category, compared to 4–6% in a lower BMI category than the previous pregnancy. These findings are comparable to those from a previous study of a longitudinal cohort in Dublin[13]. Only two percent of women in a higher BMI category at the start of a subsequent pregnancy were underweight at the previous pregnancy and so had moved up into the healthier category of normal weight. An additional eight percent of women were obese at the start of a subsequent pregnancy with this rising to 10% in higher order (fourth and fifth) pregnancies. This pattern of weight gain was seen across pregnancies and thus we additionally show that this persists through subsequent pregnancies and not just from the first to second.

Relatively small BMI gains (1–2 units) increases the risk of perinatal complications in the subsequent pregnancy even if the woman remains normal weight[23]. In this sample, women changed one BMI unit between pregnancies on average whereas in the two-thirds that gained weight the average gain was two BMI units with some women gaining substantially more. The proportions of overweight and obesity in this sample were higher in subsequent pregnancies compared to the first. It is not possible to attribute weight change between pregnancies purely to pregnancy related factors but with two-thirds of the women in this cohort gaining weight and under a third losing weight, the likelihood is that pregnancy plays an influential role in this weight change, particularly given the small percentage (2.5%) whose weight did not change.

To our knowledge, this is the first cohort study investigating the association between birth spacing and maternal weight change between pregnancies. The study sample is based on a relatively large population-based cohort

	First to second pregnancy			Second to third pregnancy			Third to fourth pregnancy			Fourth to fifth pregnancy		
	n	Maternal BMI per year (99% CI)	p	n	Maternal BMI per year (99% CI)	p	n	Maternal BMI per year (99% CI)	p	n	Maternal BMI per year (99% CI)	p
Unadjusted	15940	0.27 0.23 to 0.30	<0.001	5738	0.22 0.17 to 0.27	<0.001	2165	0.24 0.16 to 0.32	<0.001	738	0.34 0.21 to 0.48	<0.001
Model 1	15940	0.27 0.24 to 0.31	<0.001	5738	0.22 0.18 to 0.27	<0.001	2165	0.25 0.17 to 0.33	<0.001	738	0.33 0.20 to 0.47	<0.001
Model 2	15259	0.25 0.21 to 0.28	<0.001	5498	0.24 0.19 to 0.29	<0.001	2081	0.25 0.16 to 0.33	<0.001	711	0.36 0.22 to 0.50	<0.001
Model 3	15259	0.25 0.21 to 0.28	<0.001	5498	0.24 0.19 to 0.29	<0.001	2081	0.25 0.16 to 0.33	<0.001	711	0.36 0.22 to 0.50	<0.001
Model 4	4667	0.17 0.07 to 0.26	<0.001	1608	0.19 0.04 to 0.33	0.001	617	0.07 −0.19 to 0.32	0.51	213	0.32 −0.06 to 0.71	0.03

Table 3. Linear regression estimates for association between change in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy and the length of the interpregnancy interval (in years). Model 1 is adjusted for: timing of first (booking) antenatal appointments (as this is when maternal BMI is measured). Model 2 is adjusted for: timing of first (booking) antenatal appointments, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking and employment status. Model 3 is adjusted for: first (booking) antenatal appointment, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking, employment status and baseline maternal BMI (for the first pregnancy in the dataset). Model 4 is adjusted for: first (booking) antenatal appointments, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking, employment status, baseline maternal BMI and breastfeeding or not at hospital discharge.

including women from all socioeconomic backgrounds, thus representative of the regional population. One city may not be representative of the general population of the country and according to the UK Department of Communities and Local Government English indices of deprivation report, Southampton is more deprived than average with the situation having worsened between 2010 and 2015[24]. However, about half of the women included in this analysis reside in surrounding areas to Southampton in Hampshire, many of which are much less deprived. The sample was 87% White comparable to the 2011 England and Wales population census of 86% White[25]. The analysis was adjusted for several key confounders that were reasonably complete (96% complete for ethnicity and employment status).

An important limitation was the lack of information on weight gain during pregnancy, which is a key factor influencing post-partum weight. Women who had their first booking appointment later into the pregnancy (more than 24 weeks) were excluded from the analysis in order to ensure comparability of weight measurements between pregnancies. BMI was measured in early pregnancy at the booking appointment at a median of 11 weeks, however 13–21% of women across the pregnancies were measured between 14 to 24 weeks of pregnancy and thus weight could be slightly overestimated which is why timing of booking appointment was adjusted for in all analyses. Breastfeeding initiation and duration can also influence post-partum weight. No information was available on breastfeeding duration and although breastfeeding initiation (at discharge) was available, this was only recorded in a little over a third of the pregnancies included. Another limitation is that these findings are based on observational data so inferences about causation cannot be drawn and the risk of residual confounding influencing the results needs to be considered. However, it is not feasible or ethical to conduct a randomised trial to address the aim of this study.

To our knowledge, the only international guideline on birth spacing is the 2005 WHO technical consultation published in 2007 which recommends waiting at least 24 months after a previous live birth[14]. This was based on evidence on maternal, perinatal, infant and child health outcomes from a wide range of countries. However, in light of the rising rates of maternal obesity and its consequences on pregnancy outcomes and maternal and offspring health, updated recommendations on the optimal interpregnancy interval would benefit from incorporating evidence around this such as that generated by this study. A shorter optimal interval is further supported by the findings of a meta-analysis of 62 studies that an interpregnancy interval of 18 to 23 months was associated with the lowest risk of adverse perinatal outcomes in the offspring with both shorter (<18 months) and longer (>59 months) intervals being associated with increased risk[20].

A qualitative study in Sweden in women who had retained ≥10 kg postpartum found that the first year postpartum is a neglected year in women with the focus of care being on the baby with little or no weight loss support. The main areas identified related to weight retention were a lack of knowledge, misconceptions, eating for relief, lack of support and barriers to physical activity including tiredness and competing responsibilities[26]. Another study reported that women considered their personal health was not top priority during the early postpartum period and identified childcare, time management and lack of support as barriers to adopting healthier lifestyles[27]. Lifestyle changes were motivated by child's health in women diagnosed with gestational diabetes during pregnancy with vague understanding and low levels of concern of increased future risk of Type 2 diabetes[28]. Another study in Sweden also found that a healthier lifestyle adopted during pregnancy and in early parenthood was motivated by supporting a health-promoting environment for the child[29] and thus weight retention in the context of the health of future children could be a motivator to promoting weight loss.

		Gain in maternal BMI: First to second pregnancy			Gain in maternal BMI: Second to third pregnancy			Gain in maternal BMI: Third to fourth pregnancy			Gain in maternal BMI: Fourth to fifth pregnancy		
		n	Relative risk (RR)* (99% CI)	p	n	RR (99% CI)	p	n	RR (99% CI)	p	n	RR (99% CI)	p
Unadjusted	0–11 m	15940	0.99 0.94 to 1.03	0.45	5738	0.96 0.88 to 1.04	0.16	2165	1.03 0.89 to 1.18	0.63	738	0.83 0.68 to 1.01	0.01
	12–23 m		0.91 0.87 to 0.95	<0.001		0.93 0.86 to 1.01	0.02		1.03 0.90 to 1.18	0.53		0.86 0.70 to 1.05	0.05
	24–35 m		(reference)			(reference)			(reference)			(reference)	
	>=36 m		1.12 1.07 to 1.16	<0.001		1.12 1.04 to 1.20	<0.001		1.18 1.04 to 1.34	<0.001		1.07 0.91 to 1.26	0.26
Model 1	0–11 m	15940	0.98 0.93 to 1.02	0.22	5738	0.95 0.87 to 1.03	0.13	2165	1.01 0.88 to 1.17	0.79	738	0.84 0.69 to 1.02	0.02
	12–23 m		0.91 0.87 to 0.95	<0.001		0.93 0.86 to 1.01	0.02		1.02 0.89 to 1.17	0.69		0.85 0.70 to 1.04	0.04
	24–35 m		(reference)			(reference)			(reference)			(reference)	
	>=36 m		1.12 1.08 to 1.16	<0.001		1.12 1.05 to 1.21	<0.001		1.19 1.05 to 1.34	<0.001		1.08 0.92 to 1.27	0.22
Model 2	0–11 m	15259	0.97 0.93 to 1.02	0.15	5498	0.95 0.87 to 1.04	0.13	2081	1.02 0.89 to 1.18	0.79	711	0.85 0.69 to 1.04	0.03
	12–23 m		0.91 0.88 to 0.95	<0.001		0.93 0.86 to 1.01	0.03		1.02 0.89 to 1.17	0.80		0.88 0.72 to 1.08	0.12
	24–35 m		(reference)			(reference)			(reference)			(reference)	
	>=36 m		1.11 1.06 to 1.15	<0.001		1.14 1.06 to 1.21	<0.001		1.18 1.04 to 1.34	0.001		1.11 0.94 to 1.31	0.11
Model 3	0–11 m	15259	0.97 0.93 to 1.02	0.14	5498	0.95 0.87 to 1.04	0.14	2081	1.02 0.89 to 1.17	0.70	711	0.84 0.69 to 1.03	0.03
	12–23 m		0.91 0.87 to 0.95	<0.001		0.93 0.86 to 1.01	0.02		1.02 0.89 to 1.16	0.76		0.88 0.72 to 1.07	0.09
	24–35 m		(reference)			(reference)			(reference)			(reference)	
	>=36 m		1.11 1.07 to 1.15	<0.001		1.13 1.05 to 1.21	<0.001		1.18 1.04 to 1.33	0.001		1.11 0.94 to 1.31	0.12
Model 4	0–11 m	4667	0.99 0.92 to 1.08	0.83	1608	0.93 0.81 to 1.07	0.17	617	0.96 0.76 to 1.22	0.68	213	0.78 0.60 to 1.03	0.02
	12–23 m		0.91 0.85 to 0.98	0.001		0.92 0.81 to 1.04	0.09		0.96 0.75 to 1.21	0.62		0.80 0.60 to 1.08	0.06
	24–35 m		(reference)			(reference)			(reference)			(reference)	
	>=36 m		1.12 1.03 to 1.21	0.001		1.08 0.95 to 1.24	0.13		0.99 0.76 to 1.31	0.96		1.00 0.77 to 1.31	0.97

Table 4. Association between interpregnancy gain in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy and the length of the interpregnancy interval (categorised). *Generalised linear model with log link and robust variance estimator used to derive RR. Model 1 is adjusted for: timing of first (booking) antenatal appointments (as this is when maternal BMI is measured). Model 2 is adjusted for: timing of first (booking) antenatal appointments, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking and employment status. Model 3 is adjusted for: first (booking) antenatal appointment, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking, employment status and baseline maternal BMI (for the first pregnancy in the dataset). Model 4 is adjusted for: first (booking) antenatal appointments, maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking, employment status, baseline maternal BMI and breastfeeding or not at hospital discharge.

Stabilizing interpregnancy weight and promoting weight loss in overweight and obese women before the next pregnancy could be important steps in reducing adverse outcomes in subsequent pregnancies. The use of the six to eight week postnatal check to discuss women's weight is part of the National Institute for Health and Care Excellence guidelines[30]. However, only women with a pre-pregnancy BMI of 30 kg/m^2 or more are recommended to have a discussion with their health professional about the increased risk of being obese and encouraged to lose weight, particularly that gained during pregnancy. Additionally, the interpregnancy interval is not discussed as there are no UK guidelines on interval. The health and wellbeing of the mother needs to be considered with an equal focus as to the health of the baby for any preventive measures during the period between pregnancies. More research is needed, considering other short and long-term maternal and offspring outcomes, to investigate the optimal interpregnancy interval in high-income countries.

In conclusion, most women do not maintain their weight across pregnancies, with substantially more gaining than losing weight. An interpregnancy interval of 12–23 months was associated with the lowest risk of starting the second pregnancy with a higher body weight compared to the start of the previous pregnancy. Preventing weight gain and continuing to support weight loss in overweight and obese women between pregnancies are important

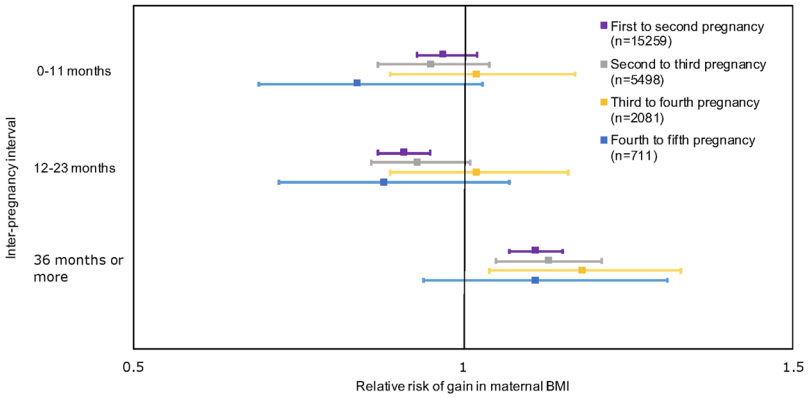

Figure 4. Adjusted association between interpregnancy gain in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy and the length of the interpregnancy interval (categorised).

preventive measures of subsequent adverse maternal and offspring health outcomes. Further research investigating optimal birth spacing in relation to important public health risk factors such as maternal and childhood obesity is needed.

Methods

This is a population-based cohort of prospectively collected routine healthcare data for antenatal care between January 2003 and September 2017 at University Hospital Southampton, Hampshire, UK. This included all women delivering at this hospital, which is a regional centre for maternity care in and around Southampton. Records of women with two or more consecutive singleton live birth pregnancies were included. Analysis was carried out by pregnancy order by using information on parity to categorise the pregnancies as first to second, second to third, third to fourth and fourth to fifth, even if the previous births were not recorded in the analysed dataset (e.g. if the woman had received antenatal care elsewhere). Women with more than five previous births (due to small numbers) and records with unfeasible weight, height and gestational age values were excluded. Only singleton pregnancies were included.

Exposure assessment. The difference in days between two consecutive live births was calculated and gestational age of the latter birth subtracted from this to derive the interpregnancy interval. For multiparous women, no information was available on the interval from a previous pregnancy if delivery was before the start of the study period (2003) or at another hospital. Only women whose pregnancies resulted in live births were included as other pregnancy outcomes (stillbirth, miscarriage) could affect the interpregnancy interval[31]. A categorical variable with categories of 0–11, 12–23, 24–35 and 36 months or more was created. The 24–35 month category was used as the reference category as this was in line with the World Health Organization guideline of at least 2 years[14].

Outcome assessment. Maternal weight in kilograms was measured at the first antenatal (booking) appointment of each pregnancy, which is recommended ideally by 10 weeks gestation in the UK[32]. The booking appointment is booked by midwives once pregnancy is confirmed by general practice. Women are prioritised by gestational age with the aim of booking the appointment during the recommended period. Any woman who had a booking appointment at or after 24 weeks of pregnancy was excluded. BMI was calculated as weight (in kg) divided by height (in metres) squared. BMI was analysed as both a continuous (kg/m^2) and categorical variable. The categorical variable was defined as underweight (BMI $< 18.5\,kg/m^2$), normal weight (18.5 to $24.9\,kg/m^2$), overweight (25.0 to $29.9\,kg/m^2$) and obese ($\geq 30\,kg/m^2$). Change in BMI was calculated as the difference in BMI measured at booking appointment between two consecutive live birth pregnancies. Weight gain was calculated as any gain in weight that led to a change in BMI between the two measurement points. Baseline BMI was defined as the BMI at the first pregnancy that information was available for.

Gestational age (date of last menstrual period) is discussed and recorded at the booking appointment. Gestational age at birth is determined based on an ultrasound-dating scan which usually takes place after the booking appointment.

Covariates. Maternal date of birth is recorded at the booking appointment and converted to age on extraction of the dataset to maintain anonymity. Highest maternal educational qualification was self-reported and categorised as primary, secondary, college, undergraduate, postgraduate, graduate and none. For the purposes of this analysis, this was condensed to three categories - secondary (GCSE) and under, college (A levels) and university degree or above. Self-reported ethnicity was recorded under 16 categories and condensed to White, Mixed, Asian, Black/African/Caribbean, Chinese and Other. Categories of not asked and not stated were coded as missing. Smoking was self-reported as current smoking or non-smoking. Non-smokers were further asked if they had ever smoked or had previously smoked and quit. This was categorised as stopped more than 12 months before conception, stopped less than 12 months before conception or stopped when pregnancy confirmed. Employment was self-reported at booking appointment and categorised as employed, unemployed, in education, and not specified.

Infertility treatment was categorised as no/investigations only and yes (hormonal only, *in-vitro* fertilisation, gamete intrafallopian transfer and other surgical) in either one or both pregnancies. Breastfeeding was recorded at discharge from the hospital as exclusive, partial or no breastfeeding.

Ethical approval. All data were anonymised to the research team. Ethics approval was granted by the University of Southampton Faculty of Medicine ethics committee: study id 25508 on 14/06/2017. All research was performed in accordance with relevant guidelines and regulations.

Statistical analysis. All analysis was performed using Stata 15[33]. Linear regression was used to examine the association of maternal change in BMI between pregnancies (assessed as a continuous variable in kg/m^2) with interpregnancy interval (assessed as a continuous variable in years). Generalised linear regression with log link and robust variance estimator[34] was then used to examine the same association (maternal change in BMI with interpregnancy interval) but by categorising maternal change in BMI into gained weight compared with no change or lost weight using the detailed categorisation of interpregnancy interval described above.

Initial univariable analysis was followed by multivariable models adjusting for potential confounding factors – timing of booking appointment (as this is when BMI is measured), maternal age, ethnicity, highest educational qualification, whether or not undergone infertility treatment, employment status, smoking behaviour and baseline maternal BMI. Finally, the role of a potential mediating factor (breastfeeding behaviour at hospital discharge) was examined in the subgroup in which this data was available.

A statistical significance level of 0.01 with 99% confidence intervals was used in the regression models to reduce the risk of Type I error due to multiple testing.

Data Availability

The authors' ethical approval from the Faculty of Medicine Ethics Committee, University of Southampton (Reference number 25508) restricts public sharing of the data used in this study. Please contact the authors to request data access beyond that included in the manuscript. Further ethical and research governance approval may be required.

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Author Contributions

Study design (N.Z., P.J.R., N.S.M., N.A.A.), data analysis (N.Z.), acquisition and interpretation of the data (N.Z., N.A.A.), drafting of the manuscript (N.Z.), revising for content (N.Z., P.J.R., N.S.M., N.A.A.) and approval of final version before submission (N.Z., P.J.R., N.S.M., N.A.A.).

Additional Information

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Is maternal weight gain between pregnancies associated with risk of large-for-gestational age birth? Analysis of a UK population-based cohort

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ABSTRACT

Objective Maternal overweight and obesity during pregnancy increases the risk of large-for-gestational age (LGA) birth and childhood obesity. We aimed to investigate the association between maternal weight change between subsequent pregnancies and risk of having a LGA birth.

Design Population-based cohort.

Setting Routinely collected antenatal healthcare data between January 2003 and September 2017 at University Hospital Southampton, England.

Participants Health records of women with their first two consecutive singleton live-birth pregnancies were analysed (n=15 940).

Primary outcome measure Risk of LGA, recurrent LGA and new LGA births in the second pregnancy.

Results Of the 15 940 women, 16.0% lost and 47.7% gained weight (≥1 kg/m^2) between pregnancies. A lower proportion of babies born to women who lost ≥1 kg/m^2 (12.4%) and remained weight stable between −1 and 1 kg/m^2 (11.9%) between pregnancies were LGA compared with 13.5% and 15.9% in women who gained 1–3 and ≥3 kg/m^2, respectively. The highest proportion was in obese women who gained ≥3 kg/m^2 (21.2%). Overweight women had a reduced risk of recurrent LGA in the second pregnancy if they lost ≥1 kg/m^2 (adjusted relative risk (aRR) 0.69, 95% CI 0.48 to 0.97) whereas overweight women who gained ≥3 kg/m^2 were at increased risk of new LGA after having a non-LGA birth in their first pregnancy (aRR 1.35, 95% CI 1.05 to 1.75). Normal-weight women who gained weight were also at increased risk of new LGA in the second pregnancy (aRR 1.26, 95% CI 1.06 to 1.50 with gain of 1–3 kg/m^2 and aRR 1.34, 95% CI 1.09 to 1.65 with gain of ≥3 kg/m^2).

Conclusions Losing weight after an LGA birth was associated with a reduced LGA risk in the next pregnancy in overweight women, while interpregnancy weight gain was associated with an increased new LGA risk. Preventing weight gain between pregnancies is an important measure to achieve better maternal and offspring outcomes.

Strengths and limitations of this study

- ► Utilises antenatal care and birth data from a large population-based cohort including women from all socioeconomic backgrounds.
- ► Objective measurement of both exposure (maternal weight) and outcome in two pregnancies per woman.
- ► Self-reported data for covariates.
- ► Lack of information on breastfeeding duration and maternal weight gain during pregnancy.

INTRODUCTION

The prevalence of maternal obesity has been rising over time. It has more than doubled in England between 1989 and 2007 (7.6%–15.6%), with the proportion of normal weight pregnancies showing a 12% decrease from 65.6% to 53.6%.[1] Maternal overweight and obesity is a key risk factor for adverse maternal and birth outcomes. It also increases the risk of long-term health problems in the child including obesity, cardiovascular disease, diabetes and cognitive and behavioural disorders.[2] Birth weight is a key early life predictor of long-term health outcomes such as obesity and cardiovascular disease[3] and potentially acts as a mediator on the causal pathway between maternal obesity and long-term offspring outcomes. The incidence of large-for-gestational age (LGA) birth, defined as >90th percentile weight for gestational age, has increased over time in high-income countries.[4 5] LGA is associated with both childhood[6 7] and adult obesity.[8–10] A key risk factor for LGA birth is gestational diabetes (GDM),[11] the incidence of which has also increased over time.[12 13] Offspring of mothers with GDM have increased risk of childhood overweight and obesity.[14 15] Maternal obesity is an established risk factor for both GDM and LGA birth.[16] Change in maternal body mass index (BMI) between pregnancies could modify the risk of LGA birth in the subsequent pregnancy.

Birth weight, on average, increases with parity. First-born infants tend to have the lowest birth weight among their younger siblings[17–19] up to the fourth pregnancy.[20] However, birth weight was found to decrease with parity for women who had short intervals between their pregnancies (<12 months) while the increase in birth weight with parity was more pronounced in women with long intervals (>24 months).[20] Also, maternal weight change between pregnancies was found to modify the relationship between parity and birth weight. Women who returned to their prepregnancy weight before the next conception had infants who weighed less than infants of women who retained or gained weight between pregnancies.[20] In a UK- based study, women who lost at least 6 kg between their first and second pregnancy had a smaller average increase in birth weight of the second baby compared with women who gained 10 kg or more (in a 1.60 m tall woman, 6 kg equates to ~2.3 kg/m^2 and 10 kg to ~3.8 kg/m^2).[18]

A large US study showed that women were at an increased risk of having an LGA baby in the second pregnancy if their prepregnancy BMI category increased towards overweight or obese between their first and second pregnancies. This applied to all first pregnancy BMI categories, except underweight women who became normal weight by the start of their second pregnancy. Overweight and obese women who dropped BMI category by their second pregnancy remained at an increased risk of LGA birth, but had a lower risk compared with women whose BMI category increased between pregnancies.[21]

Another US-based study showed that interpregnancy weight gain of ≥2 kg/m^2 in obese women was associated with increased risk of LGA. Weight loss of ≥2 kg/m^2 was associated with a lower adjusted LGA risk compared with the women who maintained their weight within 2 kg/m^2 change between pregnancies.[22]

Two studies found a reduced risk of 'new' LGA in the second pregnancy following a non-LGA birth in the first pregnancy with interpregnancy weight loss of >1 kg/m^2, and an increased risk with modest (1–3 kg/m^2) and large (≥3 kg/m^2) weight gain. In stratified analysis, the association was stronger in women with a first pregnancy BMI of <25 kg/m^2.[23 24] A third study only found an increased risk of new LGA in normal weight women who gained ≥4 kg/m^2 between pregnancies and no association in overweight women.[25]

To our knowledge, only one study has examined the risk of recurrent LGA (occurring in both first and second pregnancies) in relation to maternal weight change between pregnancies.[26] The study, conducted in Aberdeen, Scotland, included 24 520 women of which 813 women had LGA births in both pregnancies. Interpregnancy weight gain (≥2 kg/m^2) was associated with increased risk of recurrent LGA, while weight loss (≥2 kg/m^2) was protective. Women with BMI <25 kg/m^2 were at increased risk of recurrent LGA on gaining weight whereas women with BMI ≥25 kg/m^2 were at reduced risk of recurrent LGA on losing weight.[26]

In this study, we aimed to investigate the association between the incidence of LGA, recurrent LGA and new LGA births in the second pregnancy and maternal change in BMI between the first and second pregnancies, stratifying by maternal BMI category in the first pregnancy, in a population-based cohort in the South of England.

METHODS

This is a population-based cohort of prospectively collected routine healthcare data for antenatal care between January 2003 and September 2017 at University Hospital Southampton, Hampshire, UK. This included all women registered for maternity care at this hospital (n=82 098 pregnancies), which is a regional centre for maternity care in and around Southampton. Records of women with their first two consecutive singleton live birth pregnancies were included. Records with unfeasible weight (<30 kg), height (>2 m) and gestational age (>301 days) values were excluded.

Exposure assessment

Maternal weight in kilograms was routinely measured by a midwife at the first antenatal (booking) appointment of each pregnancy, which is recommended to take place ideally by 10 weeks gestation in the UK, according to the National Institute for Health and Care Excellence Guidelines.[27] Any woman who had a booking appointment at or after 24 weeks of pregnancy was excluded. Height was self-reported. BMI was calculated as weight (in kg) divided by height (in metres) squared.

BMI at the start of the first pregnancy was categorised as underweight (BMI <18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (≥30 kg/m^2). Change in BMI was calculated as the difference in BMI measured at the booking appointments of the first two consecutive live birth pregnancies for each woman. This change in BMI was then categorised as weight loss (≥1 kg/m^2), weight stable (−1 to 1 kg/m^2) and two categories of weight gain (1–3 and ≥3 kg/m^2).

Outcome assessment

Birth weight (grams) was measured by healthcare professionals at birth as part of routine care. Gestational age was based on a dating ultrasound scan which routinely takes place between 10 and 13 weeks of gestation.[27] Age- and sex-specific birth weight centiles were calculated using reference values for England and Wales provided in the most recently released national data.[28] LGA was defined as >90th percentile weight for gestational age. This was only defined for babies born between 24 and 42 weeks of gestation as reference values only exist for these gestational ages and with determinate sex.

Covariates

Maternal date of birth is recorded at the booking appointment and converted to age (in years) on extraction of the dataset to maintain anonymity. Highest maternal

educational qualification was self-reported and categorised as primary, secondary, college, undergraduate, postgraduate, graduate and none. For the purposes of this analysis, this was condensed to three categories—secondary (General Certificate of Secondary Education, GCSE) and under, college (A levels) and university degree or above. Self-reported ethnicity was recorded under 16 categories and condensed to White, Mixed, Asian, Black/African/Caribbean and Other. Categories of not asked and not stated were coded as missing. Smoking was self-reported as current smoking or non-smoking. Non-smokers were further asked if they had ever smoked or had previously smoked and quit. This was categorised as stopped >12 months before conception, stopped <12 months before conception or stopped when pregnancy confirmed. Employment status was self-reported at booking appointment and categorised as employed, unemployed, in education and not specified. Infertility treatment was categorised as no/investigations only and yes (hormonal only, in vitro fertilisation, gamete intrafallopian transfer and other surgical) in either one or both pregnancies. In this population, an oral glucose tolerance test was used for screening for GDM in women with one or more risk factors (BMI >30 kg/m^2; GDM in previous pregnancy; previous baby weighing ≥4.5 kg; diabetes in parents or siblings and of Asian, African-Caribbean or Middle Eastern ethnicity).[29] GDM diagnosis was then reported in the database. Interpregnancy interval was defined as the interval between the first live birth and conception of the second pregnancy. The difference in days between two consecutive live births was calculated and gestational age of the latter birth subtracted from this to derive the interpregnancy interval.

Statistical analysis

All analysis was performed using Stata V.15.[30] Univariable comparisons were carried out using Analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. Generalised linear regression with log link[31] was used to examine the association between the categorised variable of maternal change in BMI between pregnancies with risk of LGA in the second pregnancy. This was analysed first in the whole sample and then stratified by 'baseline' maternal BMI category as calculated in the first antenatal appointment of the first pregnancy.

Risk of LGA in the second pregnancy was explored in the whole sample adjusting for previous pregnancy outcome of LGA. The risk of new LGA in second pregnancy after having a non-LGA baby in the first pregnancy was explored in the subsample of women who had non-LGA births in the first pregnancy. The risk of recurrent LGA (LGA in both pregnancies) was explored in a subsample of women who had LGA births in the first pregnancy.

Initial univariable analysis was followed by multivariable models adjusting for potential confounding factors—maternal age, ethnicity, highest educational qualification, whether or not undergone infertility treatment, employment status, smoking behaviour in second pregnancy, baseline BMI, GDM in second pregnancy and interpregnancy interval. Sensitivity analysis was conducted adding gestational age at booking in the second pregnancy to the models.

A statistical significance level of 0.05 with 95% CI was used in the regression models.

Ethical considerations

All data were fully anonymised by the data holder before being accessed by the research team.

Patient and public involvement

Patients and public were not involved in setting the research question or the outcome measures, nor were they involved in developing plans for the design or implementation of the study. However, pregnant woman and mothers of young children have been involved in the planning stages of a research project building on this analysis.

RESULTS

The first and second pregnancies of 15 940 women were included. Of these, 16.0% of women lost ≥1 kg/m^2, 36.3% remained weight stable (−1 to 1 kg/m^2), 27.9% gained 1–3 kg/m^2 and 19.8% gained ≥3 kg/m^2 between their first and second live birth pregnancies. Weight loss of >2 kg/m^2 was observed in 7.3% of women whereas 30.5% gained >2 kg/m^2. Mean BMI at second pregnancy booking was 30.8 kg/m^2 (SD 5.9) in women who gained ≥3 kg/m^2, 25.9 kg/m^2 (SD 4.7) in women who gained 1–3 kg/m^2, 24.1 kg/m^2 (SD 5.1) in women who lost weight and 23.8 kg/m^2 (SD 4.4) women whose weight remained stable between pregnancies (p<0.001) (table 1).

Women who gained ≥3 kg/m^2 by the start of their second pregnancy were more likely to be smokers, unemployed, with lower educational attainment and to have a longer interpregnancy interval, compared with those who maintained a stable weight between pregnancies. Mean maternal age was lowest in the women who gained ≥3 kg/m^2 (27.3 years, SD 5.5) and highest in the women who remained weight stable (29.8 years, SD 5.3). Mean maternal age in women who lost weight was 28.7 years (SD 5.4).

Mothers who gained ≥3 kg/m^2 were more likely to be obese (48.3%) at the start of the second pregnancy compared with 16.1% in women who gained 1–3 kg/m^2, 9.2% in women who remained weight stable and 11.9% in women who lost ≤1 kg/m^2.

Figure 1 shows the percentage of women in each BMI category in the first and second pregnancy and the weight gain over time. There has been a decline in normal weight women at first pregnancy and a slight increase in overweight and obese women over time. There also was a slight decline in the percentage of women gaining ≥3 kg/m^2 and a slight increase in those gaining 1–3 kg/m^2.

Table 1 Maternal and birth characteristics in the second live birth pregnancy categorised by maternal weight change gain from the first live birth pregnancy for the period of January 2003 to September 2017, University Hospital Southampton NHS Foundation Trust, Hampshire, England

	Lost ≤ −1 kg/m^2 from previous pregnancy	Weight stable (> −1 to <1 kg/m^2)	Gained 1–3 kg/m^2 from previous pregnancy	Gained ≥3 kg/m^2 from previous pregnancy	P value*
N	2548	5785	4446	3161	
Maternal age, years (mean±SD)	28.7±5.4	29.8±5.3	29.2±5.4	27.3±5.5	<0.001
Timing of first booking appointment, weeks (mean±SD)	10.8±2.3	11.0±2.3	11.1±2.4	11.0±2.6	<0.001
Maternal BMI at booking, kg/m^2 (mean±SD)	24.1±5.1	23.8±4.4	25.9±4.7	30.8±5.9	<0.001
Maternal BMI at booking in first pregnancy (%, 95% CI)					
Underweight (<18.5)	0.8 (0.5 to 1.2)	4.3 (3.8 to 4.8)	5.3 (4.7 to 6.0)	3.7 (3.1 to 4.4)	<0.001
Normal weight (18.5 to 24.9)	47.6 (45.6 to 49.5)	67.4 (66.2 to 68.6)	62.5 (61.0 to 63.9)	49.0 (47.2 to 50.7)	
Overweight (25.0 to 29.9)	30.1 (28.3 to 31.9)	19.4 (18.4 to 20.5)	22.0 (20.8 to 23.3)	29.5 (28.0 to 31.2)	
Obese (≥30.0)	21.5 (19.9 to 23.2)	8.9 (8.2 to 9.7)	10.2 (9.3 to 11.1)	17.8 (16.5 to 19.2)	
Maternal BMI at booking in second pregnancy (%, 95% CI)					
Underweight (<18.5)	6.9 (5.9 to 7.9)	4.3 (3.8 to 4.8)	0.6 (0.4 to 0.9)	0.0 (0.0 to 0.2)	<0.001
Normal weight (18.5 to 24.9)	61.1 (59.2 to 63.0)	66.8 (65.6 to 68.1)	50.7 (49.2 to 52.1)	14.9 (13.7 to 16.2)	
Overweight (25.0 to 29.9)	20.1 (18.6 to 21.7)	19.7 (18.7 to 20.7)	32.6 (31.2 to 34.0)	36.7 (35.0 to 38.4)	
Obese (≥30.0)	11.9 (10.7 to 13.3)	9.2 (8.5 to 10.0)	16.1 (15.0 to 17.2)	48.3 (46.6 to 50.1)	
Maternal smoking status at booking (%, 95% CI)					
Never smoked/quit	57.2 (55.3 to 59.2)	63.0 (61.8 to 64.3)	60.5 (59.0 to 62.0)	50.7 (48.9 to 52.4)	<0.001
Stopped >1 year before conceiving	16.1 (14.6 to 17.5)	17.2 (16.3 to 18.2)	17.7 (16.5 to 18.8)	14.9 (13.7 to 16.2)	
Stopped <1 year prior to conceiving	4.0 (3.3 to 4.8)	2.8 (2.4 to 3.2)	3.5 (3.0 to 4.1)	4.9 (4.2 to 5.7)	
Stopped when pregnancy confirmed	6.8 (5.8 to 7.8)	5.9 (5.3 to 6.6)	6.9 (6.2 to 7.7)	10.3 (9.3 to 11.4)	
Continued smoking	15.9 (14.5 to 17.4)	11.0 (10.2 to 11.8)	11.4 (10.5 to 12.4)	19.1 (17.8 to 20.6)	
Maternal education (%, 95% CI)					
Secondary (GCSE) or under	30.7 (28.9 to 32.5)	24.0 (22.9 to 25.2)	29.4 (28.1 to 30.8)	36.3 (34.6 to 38.0)	<0.001
College (A levels)	40.4 (38.5 to 42.3)	38.8 (37.6 to 40.1)	39.5 (38.1 to 41.0)	45.8 (44.0 to 47.5)	
University degree or above	28.9 (27.2 to 30.7)	37.1 (35.9 to 38.4)	31.1 (29.7 to 32.5)	17.9 (16.6 to 19.3)	
Maternal employment (%, 95% CI)					
Employed	66.2 (64.3 to 68.0)	71.7 (70.5 to 72.9)	67.2 (65.8 to 68.5)	56.5 (54.8 to 58.2)	<0.001
Unemployed	31.8 (30.0 to 33.7)	26.9 (25.8 to 28.1)	31.1 (29.7 to 32.5)	41.6 (39.8 to 43.3)	
In education	0.9 (0.6 to 1.4)	0.8 (0.6 to 1.1)	1.1 (0.8 to 1.4)	1.3 (0.9 to 1.8)	
Not specified	1.0 (0.7 to 1.5)	0.6 (0.4 to 0.8)	0.7 (0.5 to 1.0)	0.6 (0.4 to 1.0)	
Ethnicity (%, 95% CI)					
White	89.9 (88.7 to 91.1)	88.0 (87.1 to 88.8)	85.1 (84.0 to 86.1)	84.8 (83.5 to 86.1)	<0.001
Mixed	0.8 (0.5 to 1.3)	0.9 (0.7 to 1.2)	1.4 (1.1 to 1.8)	1.6 (1.1 to 2.0)	
Asian	4.8 (4.0 to 5.7)	5.6 (5.0 to 6.0)	7.2 (6.5 to 8.0)	7.7 (6.8 to 8.7)	
Black/African/Caribbean	0.6 (0.4 to 1.0)	1.0 (0.8 to 1.3)	1.6 (1.3 to 2.1)	2.4 (1.9 to 3.0)	

Continued

Table 1 Continued

	Lost ≤ −1 kg/m² from previous pregnancy	Weight stable (> −1 to <1 kg/m²)	Gained 1–3 kg/m² from previous pregnancy	Gained ≥3 kg/m² from previous pregnancy	P value*
Other	0.7 (0.4 to 1.1)	1.0 (0.8 to 1.3)	1.0 (0.8 to 1.4)	1.3 (0.9 to 1.7)	
Not specified	3.1 (2.5 to 3.9)	3.5 (3.0 to 4.0)	3.6 (3.1 to 4.2)	2.2 (1.8 to 2.8)	
Interpregnancy interval (median, IQR)	21.7 (14.4 to 32.7)	21.6 (14.1 to 32.0)	23.7 (14.4 to 35.6)	27.7 (16.0 to 45.6)	<0.001
Interpregnancy interval (%, 95% CI)					
0–11 months	17.4 (15.9 to 18.9)	17.6 (16.6 to 18.6)	18.1 (17.0 to 19.3)	16.6 (15.4 to 17.9)	<0.001
12–23 months	39.8 (37.8 to 41.7)	39.9 (38.6 to 41.1)	33.1 (31.7 to 34.5)	26.3 (24.8 to 27.9)	
24–35 months	22.6 (21.0 to 24.2)	23.6 (22.5 to 24.7)	24.4 (23.2 to 25.7)	20.5 (19.1 to 21.9)	
36 months or more	20.3 (18.7 to 21.9)	18.9 (17.9 to 20.0)	24.3 (23.1 to 25.6)	36.5 (34.9 to 38.2)	
Birth weight, g (mean±SD)	3463±563	3467±523	3507±536	3531±558	
Previous size at birth (first pregnancy)					
Small-for-gestational age	13.1 (11.8 to 14.4)	12.6 (11.8 to 13.5)	11.7 (10.8 to 12.7)	12.4 (11.3 to 13.6)	0.11
Appropriate-for-gestational age	79.6 (77.9 to 81.1)	81.1 (80.0 to 82.1)	81.2 (80.1 to 82.4)	79.9 (78.4 to 81.3)	
Large-for-gestational age	7.4 (6.4 to 8.5)	6.3 (5.7 to 7.0)	7.1 (6.3 to 7.8)	7.7 (6.8 to 8.7)	
Size at birth (second pregnancy)					
Small-for-gestational age	8.7 (7.6 to 9.8)	7.0 (6.4 to 7.7)	6.2 (5.5 to 6.9)	6.7 (5.9 to 7.6)	<0.001
Appropriate-for-gestational age	79.0 (77.3 to 80.5)	81.1 (80.0 to 82.1)	80.3 (79.1 to 81.5)	77.4 (75.9 to 78.9)	
Large-for-gestational age	12.4 (11.1 to 13.7)	11.9 (11.1 to 12.8)	13.5 (12.5 to 14.5)	15.9 (14.6 to 17.2)	

*P values calculated using ANOVA for continuous and χ^2 test for categorical variables.

The proportion of LGA births were higher in all BMI categories in the second pregnancy (figure 2). A lower proportion of babies born to women who lost weight (12.4%) or remained weight stable (11.9%) between pregnancies were LGA compared with 13.5% in women who gained 1–3 kg/m² and 15.9% in women who gained ≥3 kg/m² (p<0.001) (table 1, figure 3). Compared with normal weight women, overweight and obese women were at increased risk of LGA births in both pregnancies with risk highest in obese women (unadjusted relative risk (RR) 2.06, 95% CI 1.78 to 2.38 and 1.86, 95% CI 1.69 to 2.05 in first and second pregnancy, respectively). The lowest proportion of LGA births in the second pregnancy was in underweight women in the first pregnancy who remained weight stable (2.8%), while the highest was in obese women who gained ≥3 kg/m² (21.2%). Within BMI categories, recurrent LGA was lowest in normal weight and overweight women who lost weight and highest in obese women who gained 1–3 kg/m².

Women who gained ≥3 kg/m² were at increased risk of LGA in the second pregnancy in the full sample compared with remaining weight stable (adjusted relative risk (aRR) 1.28, 95% CI 1.14 to 1.44) (figure 3). There was a significantly reduced risk of recurrent LGA birth in the second pregnancy in overweight women who had a LGA infant in the first pregnancy and lost ≥1 kg/m² in weight (aRR 0.69, 95% CI 0.48 to 0.97) (table 2, online supplementary figure 1). No association was observed between risk of recurrent LGA and maternal BMI change between pregnancies in underweight, normal weight and obese women.

There was an increased risk of new LGA birth in the second pregnancy after having a non-LGA infant in the first pregnancy in normal weight women who gained 1–3 kg/m² (aRR 1.26, 95% CI 1.06 to 1.50) and in normal weight and overweight women who had gained ≥3 kg/m² weight (aRR 1.34, 95% CI 1.09 to 1.65, aRR 1.35, 95% CI 1.05 to 1.75, respectively) (table 3, online supplementary figure 2). No association was observed between the risk of new LGA in the second pregnancy and maternal BMI interpregnancy change in obese women.

DISCUSSION

This study examined the association between change in women's BMI between their first and second live birth pregnancies and risk of LGA birth in the second pregnancy in a population-based cohort of 15 940 women in the South of England. Almost half of the sample (48%) of women gained ≥1 kg/m² in the time between the first antenatal care visits during their first and second pregnancies. The proportion of LGA births was significantly higher in women with an interpregnancy weight gain of ≥3 kg/m² (16%) compared with women who lost weight (12%)

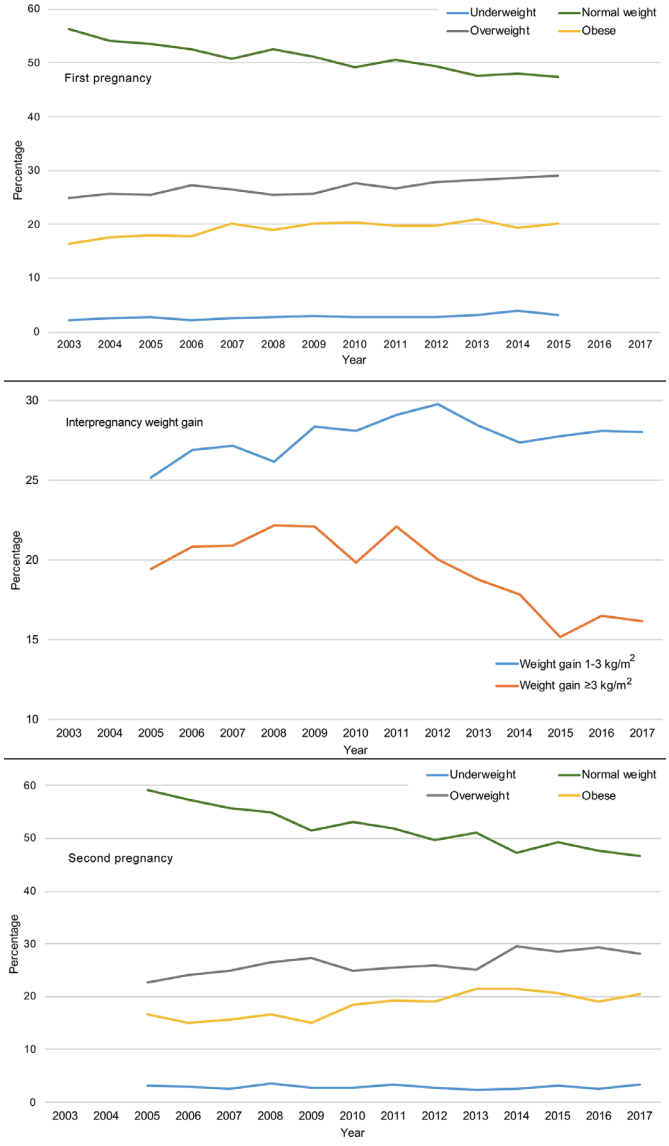

Figure 1 The percentage of women in each body mass index (BMI) category in the first and second pregnancy and weight gain over time in the cohort (2003–2017).

and those who remained weight stable (12%) between pregnancies. Overweight women who lost ≥1 kg/m^2 had a reduced risk of recurrent LGA. Normal weight women who gained 1–3 kg/m^2 and both normal weight and overweight women who gained ≥3 kg/m^2 between pregnancies had an increased risk of LGA birth in their second pregnancy after a non-LGA birth in the first.

Compared with the population-based Swedish cohort which carried out a similar analysis for LGA and other outcomes in 151 025 women using data from 1992 to 2001, a lower proportion of women remained weight stable in our cohort (46% compared with 36%) and a higher proportion lost (11% compared with 16%) or gained (43% compared with 48%) weight. Among women who gained weight, a higher proportion gained ≥3 kg/m^2 in this cohort (20%) compared with the Swedish cohort (11%).[23] Similarly, in comparison to a population-based cohort of 24 520 women in Aberdeen, Scotland; for the

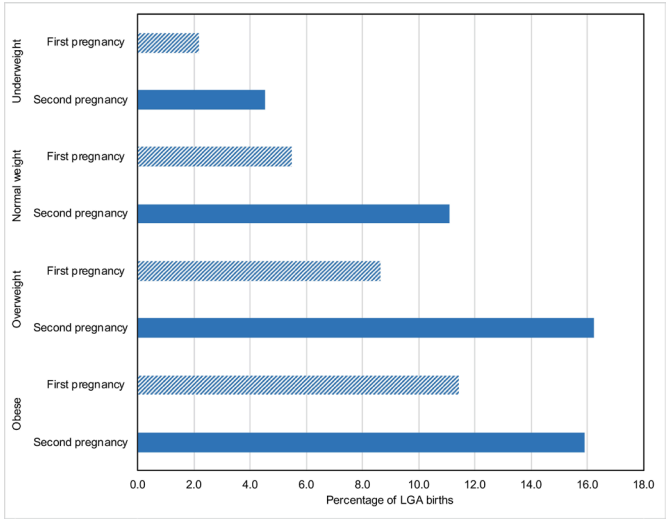

Figure 2 The percentage of large-for-gestational age (LGA) births in first and second pregnancy by maternal body mass index category.

period 1986–2013, a larger proportion of women in our study both lost and gained weight.[26] The differences could reflect the increase in the prevalence of maternal overweight and obesity over time since our data are more recent.

In the adjusted model utilising the full sample, we showed an increased risk of LGA in the second pregnancy for interpregnancy weight gain compared with remaining weight stable. In a population-based cohort in the USA, women were found to be at increased risk of LGA in the second pregnancy if their pre-pregnancy BMI category changed towards overweight or obese from first to second pregnancy regardless of their BMI category in first pregnancy except in underweight women who increased to normal weight.[21] This study is different to ours in that it only examined risk in second pregnancy

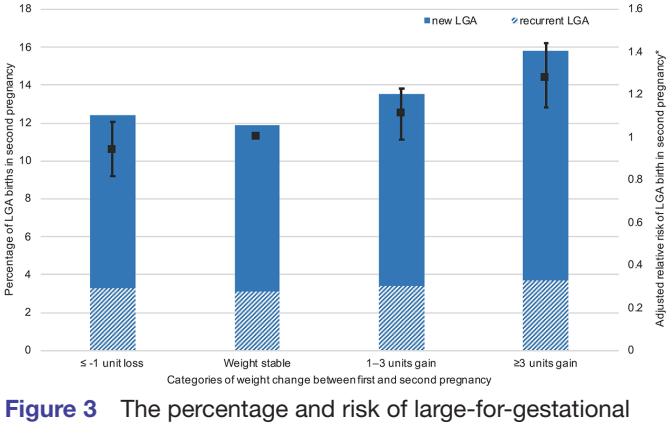

Figure 3 The percentage and risk of large-for-gestational age (LGA) births in second pregnancy stratified by maternal interpregnancy weight change categories. *Relative risk adjusted for maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and interpregnancy interval. BMI, body mass index.

Table 2 Associations between risk of recurrent large-for-gestational age (LGA) birth in the second pregnancy and change in maternal body mass index (BMI) between pregnancies as measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

		Full sample			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
Maternal BMI change (categorised)		**Total n, No of cases**	**Relative risk, (RR)***	**95% CI**	**Total n, No of cases**	**RR***	**95% CI**	**Total n, No of cases**	**RR***	**95% CI**	**Total n, No of cases**	**RR***	**95% CI**
Total unadjusted n, No of cases		1109, 530			521, 234			338, 170			236, 122		
Lost ≤ −1 kg/m^2 from previous pregnancy	Unadjusted	188, 83	0.89	0.74 to 1.08	45, 17	0.80	0.54 to 1.20	74, 30	**0.68**	**0.50 to 0.94**	69, 36	1.16	0.79 to 1.69
	Adjusted†	178, 78	0.88	0.72 to 1.07	44, 16	0.79	0.54 to 1.17	68, 27	**0.69**	**0.48 to 0.97**	66, 35	1.21	0.79 to 1.83
Weight stable (> −1 to <1 kg/m^2)	Unadjusted	365, 181	Ref		212, 100	Ref		98, 58	Ref		51, 23	Ref	
	Adjusted†	353, 176	Ref		204, 96	Ref		97, 57	Ref		49, 23	Ref	
Gained 1–3 kg/m^2 from previous pregnancy	Unadjusted	313, 150	0.97	0.83 to 1.13	162, 74	0.97	0.78 to 1.21	90, 43	0.81	0.62 to 1.06	55, 31	1.25	0.85 to 1.83
	Adjusted†	301, 142	0.98	0.84 to 1.15	156, 70	1.02	0.83 to 1.27	86, 40	0.81	0.61 to 1.08	53, 30	1.28	0.86 to 1.91
Gained ≥3 kg/m^2 from previous pregnancy	Unadjusted	243, 116	0.96	0.81 to 1.14	102, 43	0.89	0.68 to 1.17	76, 39	0.87	0.66 to 1.14	61, 32	1.16	0.79 to 1.71
	Adjusted†	234, 111	1.00	0.83 to 1.20	96, 39	0.91	0.68 to 1.21	73, 38	0.91	0.67 to 1.25	61, 32	1.28	0.84 to 1.94

*Generalised linear model with log link and robust variance estimator used to derive RR.
†Adjusted for maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and interpregnancy interval.
Bold fonts indicate statistical significance at 0.05 level.

Table 3 Associations between the risk of new large-for-gestational age (LGA) birth in the second pregnancy following a non-LGA birth in the first pregnancy and change in maternal body mass index (BMI) between pregnancies measured at the first antenatal visit of each pregnancy stratified by BMI category in the first pregnancy

Maternal BMI change (categorised)		Full sample			Underweight at first pregnancy			Normal weight at first pregnancy			Overweight at first pregnancy			Obese at first pregnancy		
		Total n, No of cases	Relative risk, (RR)*	95% CI	Total n, No of cases	RR*	95% CI	Total n, No of cases	RR*	95% CI	Total n, No of cases	RR*	95% CI	Total n, No of cases	RR*	95% CI
Total unadjusted n, No of cases		14788, 1573			606, 24			8888, 812			3458, 454			1836, 283		
Lost ≤ −1 kg/m^2 from previous pregnancy	Unadjusted	2351, 232	1.05	0.91 to 1.22		–	–	1163, 85	0.88	0.68 to 1.14	690, 79	0.95	0.73 to 1.24	477, 68	0.90	0.67 to 1.23
	Adjusted†	2258, 222	0.94	0.80 to 1.10	–	–	–	1108, 81	0.87	0.68 to 1.12	663, 76	0.96	0.72 to 1.29	466, 65	0.95	0.67 to 1.34
Weight stable (> −1 to <1 kg/m^2)	Unadjusted	5411, 508	Ref		244, 7	Ref		3680, 305	Ref		1024, 123	Ref		463, 73	Ref	
	Adjusted†	5191, 489	Ref		234, 7	Ref		3519, 292	Ref		985, 118	Ref		453, 72	Ref	
Gained 1–3 kg/m^2 from previous pregnancy	Unadjusted	4122, 450	**1.16**	**1.03 to 1.31**	230, 8	1.21	0.45 to 3.29	2606, 259	**1.20**	**1.02 to 1.40**	888, 127	1.19	0.94 to 1.50	398, 56	0.89	0.65 to 1.23
	Adjusted†	3944, 427	1.13	0.99 to 1.28	222, 7	1.04	0.36 to 3.04	2497, 251	**1.26**	**1.06 to 1.50**	839, 115	1.16	0.89 to 1.50	386, 54	0.86	0.61 to 1.22
Gained ≥3 kg/m^2 from previous pregnancy	Unadjusted	2904, 383	**1.40**	**1.24 to 1.59**	111, 9	**2.83**	**1.08 to 7.40**	1439, 163	**1.37**	**1.14 to 1.64**	856, 125	1.22	0.96 to 1.53	498, 86	1.10	0.82 to 1.46
	Adjusted†	2822, 364	**1.34**	**1.17 to 1.54**	104, 6	2.08	0.67 to 6.51	1389, 151	**1.34**	**1.09 to 1.65**	839, 123	**1.35**	**1.05 to 1.75**	490, 84	1.21	0.89 to 1.65

*Generalised linear model with log link and robust variance estimator used to derive RR.
†Adjusted for maternal age, ethnicity, highest educational qualification, whether undergone infertility treatment, smoking status, employment status, baseline BMI, gestational diabetes in current pregnancy and interpregnancy interval.
Bold fonts indicate statistical significance at 0.05 level.

without adjustment for LGA outcome in first pregnancy. It also considered weight change as change in BMI category only, while we studied change in maternal BMI regardless of whether BMI category has changed or not in the second pregnancy.

In obese women in the USA, interpregnancy weight gain of ≥2 kg/m^2 was associated with increased risk of LGA and a weight loss of ≥2 kg/m^2 was associated with decreased risk compared with the reference group of weight maintained (between > −2 and <2 kg/m^2).[22] We found no association between weight change and risk of second pregnancy LGA in women who were obese at the start of their first pregnancy. This may be because obese women are already at increased risk of LGA births, and the average interpregnancy BMI change in this subgroup was not large enough to detect a further increase in risk. Greater efforts are needed for primary prevention of obesity in women of childbearing age and obese women need more effective weight loss strategies in interpartum period to assess impact on LGA and other outcomes.

Risk of recurrent LGA was analysed in one previous study in Scotland which found that interpregnancy weight gain (≥2 kg/m^2) was associated with increased risk of recurrent LGA. In that study, weight loss (≥2 kg/m^2) was associated with reduced LGA risk. Stratification by first pregnancy BMI showed that women with BMI <25 kg/m^2 were at increased risk of recurrent LGA on gaining ≥2 kg/m^2, whereas women with BMI ≥25 kg/m^2 were at reduced risk of recurrent LGA on losing ≥2 kg/m^2 weight.[26] We showed a similar reduction in risk in overweight women who lost ≥1 BMI unit between pregnancies, but found no association in normal weight women. This difference in findings may be because the <25 kg/m^2 group in the previous Scottish study included underweight women whereas our stratified analysis examined normal weight women separately to underweight women.

We showed an increased risk of new LGA in the second pregnancy (after a non-LGA birth in the first pregnancy) with interpregnancy weight gain compared with remaining weight stable. After stratification by BMI, we found that this association between interpregnancy weight gain and new LGA remained only in normal weight and overweight women. The findings from this study are in line with findings with other studies in Scotland[24] and Sweden[23] which found increased risk of new LGA with modest (1–3 kg/m^2) and large (≥3 kg/m^2) weight gain. Both studies also found a decreased risk with interpregnancy weight loss of >1 kg/m^2 which was not found in our study. Both studies stratified BMI as < and ≥25 kg/m^2, while we further stratified the ≥25 kg/m^2 category as overweight (BMI 25–29.9 kg/m^2) and obese (≥30 kg/m^2) and found an increased risk of new LGA in overweight, but not in obese women. We carried out sensitivity analysis merging overweight and obese categories and found increased risk in this category (data not shown) suggesting that the results are comparable to previous studies.

Women included in this analysis had a range of interpregnancy interval of <1 to up to 12 years and thus weight change could be due to postpartum weight retention or late postpartum weight gain. There is evidence that women who do not lose pregnancy weight at 1 year postpartum are more likely to retain weight longer term.[32] We examined the risk of maternal interpregnancy weight gain with length of the interpregnancy interval and found that women with an interval of 12–23 months were least likely to start the next pregnancy at a higher weight.[33] We also examined the length of the inter-pregnancy interval as a predictor for LGA risk adjusting for interpregnancy weight change and found no association.[34]

The development origins of health and disease concept suggests that adverse exposures during development could lead to enhanced susceptibility in the fetus thus increasing the risk of non-communicable diseases in later life. Although the focus has previously been on exposures during pregnancy, the importance of the preconception period is now recognised.[35–37] Efforts to systematically identify women in the preconception period to improve health and lifestyle during conception are underway.[37] Promoting health of all women of childbearing age with targeting of women and partners planning a pregnancy has been identified as an effective approach to improving preconception health.[36] It is difficult to identify all women who are planning a pregnancy but as the interconception period is also the preconception period for the next pregnancy, it is important to engage with women during this period to optimise their and their children's health.

Future research that characterises the predictors of postpartum weight change would help design interventions to support postpartum weight loss and prevent weight gain. Key to this is an understanding of the pattern of weight change during this period as well as identifying the optimal setting and delivery of the intervention. Support with healthy eating and physical activity is more commonly received during pregnancy than after birth. Even when lifestyle advice is received postpartum, it was found not to be associated with healthy diet or physical activity behaviours.[38] Most interventions that have been successful in limiting and promoting postpartum weight loss were combined diet and physical activity interventions with self-monitoring.[39] However, the timing of engaging women and length of intervention or engagement are important with one study showing that an intervention from 16 weeks' pregnancy to 6 months' postpartum was more effective than the same intervention from birth to 6 months' postpartum intervention.[40]

As pregnancy and early postpartum is a period of major change for women and their families, interventions need to be carefully designed to be attractive, flexible, affordable and feasible for women at this stage with competing priorities and time demands. Focus during the postpartum period in the UK healthcare system is mostly on child health and development. The feasibility and effectiveness of better utilising contact time with health professionals during the 2 years after birth to engage and support maternal health needs to be explored. There may also be a role for peer support groups for mothers. There

is additionally a need to recognise that weight management issues are greater in more disadvantaged mothers so there is also the issue of identifying the most effective weight management strategies for such mothers to reduce social inequity in subsequent birth and maternal outcomes. Weight gain does not occur in isolation and usually combined with other risk factors particularly in socioeconomically disadvantaged groups and hence a holistic approach taking into account priority setting for these families should be considered.

Strengths and limitations

This is a relatively large population-based cohort including women from all socioeconomic and ethnic backgrounds delivering at a large maternity centre in Southampton, UK, thus representative of the regional population. According to the UK Department of Communities and Local Government English indices of deprivation report, Southampton is more deprived than average with the situation having worsened between 2010 and 2015[41]. However, about half of the women included in this analysis reside in the rest of Hampshire (the region where Southampton is situated), which is less deprived. Our sample was 87% of White ethnicity, which is comparable to the 2011 England and Wales population census of 86% White.[42] The analysis was adjusted for several key confounders that were reasonably complete (96% complete for ethnicity and employment status). Both the maternal weight (used to calculate exposure) and birth weight in this study were objectively measured by healthcare professionals as part of routine antenatal and delivery care.

An important limitation was the lack of information on gestational weight gain during pregnancy, breastfeeding duration/exclusivity and paternal characteristics/behaviour, which are potential confounders in the association between maternal interpregnancy weight gain and LGA birth.[43] We adjusted for if first feed was breast milk as a proxy for breastfeeding initiation in sensitivity analysis and the results remained unchanged (data not shown). Women who had their first booking appointment later into the pregnancy (>24 weeks) were excluded from the analysis in order to ensure comparability of weight measurements between pregnancies. We also adjusted for gestational age at booking, as this was the point when maternal BMI was measured, in sensitivity analysis and the estimates remained similar. Some of the confounding factors which were accounted for in the analysis were self-reported; however, the information was collected prospectively, therefore any measurement error in likely to be non-differential. Another limitation is that these findings are based on observational data so inferences about causation cannot be drawn and the risk of residual confounding influencing the results needs to be considered.

In conclusion, maternal weight gain of 1 or more kg/m^2 between first and second pregnancy had a prevalence of 48%, and it was associated with risk of LGA in the second pregnancy in this English cohort. Risk of new LGA was higher in normal weight and overweight women who gained weight after a non-LGA birth in their first pregnancy compared with those who remained weight stable. Overweight women were at a lower risk of a recurrent LGA birth in their second pregnancy if they lost weight between pregnancies. Greater efforts are needed for primary prevention of overweight and obesity in women of childbearing age. Supporting efforts to lose weight in overweight and obese women between pregnancies, and stop weight gain in all women planning to have further children (except those who are underweight) are important preventive measures of subsequent adverse maternal and offspring health outcomes.

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Contributors Study design (NZ, PJR, NSM, NAA), data analysis (NZ, SW), acquisition and interpretation of the data (NZ, NAA), drafting of the manuscript (NZ), revising for content (NZ, SW, PJR, NSM, NAA) and approval of final version before submission (NZ, SW, PJR, NSM, NAA).

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval Approval was granted by the University of Southampton Faculty of Medicine Ethics Committee (ID 25508) and the Health Research Authority (HRA) approval (IRAS 242031).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Anonymised data are only available upon request from the authors conditional on approval of the appropriate institutional ethics and research governance processes.

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Use of maternal and early life risk factors to predict childhood overweight and obesity: a systematic review

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Abstract

Background Childhood obesity is a serious public health challenge, and identification of high-risk populations for early intervention to prevent its development is a priority. We aimed to systematically review prediction models for childhood overweight–obesity and critically assess the methodology of their development, validation, and reporting.

Methods Medline and EMBASE were searched from dates of inception to Dec 31, 2016, for studies published in English describing the development, validation, or both, of a model that could predict the development of overweight–obesity between 1 and 13 years using maternal and early life factors. We used the following search terms: {Pediatric Obesity/ OR Fetal Macrosomia/ OR [(child or childhood or children or p#ediatric* or infant* or toddler or embry* or prenatal* or neonat*).mp. AND (obes*.mp. OR overnutrition/ or obesity/ or overweight/ OR overweight.mp. OR over weight.mp.)]} AND [exp causality/ OR ((Reinforc* or Enabl* or predispos*) and factor*).mp. OR (risk* or predict* or causal* or prognos* or causation).mp.] AND [exp Maternal Behavior/ OR maternal.mp. OR mother*.mp. OR early life.mp.]. Data were extracted with the Cochrane CHARMS checklist. The TRIPOD statement was used to assess transparency in reporting.

Findings Ten studies were identified that developed (one), developed and validated (seven), or externally validated an existing (two) prediction model. A median of 23 TRIPOD items (IQR 22–24) out of 37 (31 for derivation or validation alone) were reported. Models, apart from one, were developed with automated variable selection methods. Only four studies included complete cases, and two studies used multiple imputation to handle missing data. Maternal body-mass index, birthweight, and sex were the most commonly included predictors. Median area under the receiver operating characteristic curve was 0·78 in development and internal validation and 0·71 in external validation.

Interpretation Owing to considerable model heterogeneity, it was not possible to combine the results. Some included models have not been externally validated or compared with existing models to assess performance. New methods are needed to combine findings from existing prediction models. Future prediction models need to be developed, validated, and recalibrated to target populations using standard robust methods to refine the applicability of the resulting scores.

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Contributors
NZ carried out the literature search and drafted the first version of the abstract. All authors contributed to the study concept and design, reviewed the abstract, and approved the final version.

Declaration of interests
We declare no competing interests.

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Length of inter-pregnancy interval and subsequent preconception adiposity: Findings from a population-based cohort in the South of England

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Introduction

Maternal obesity is a key predictor of adverse short- and long-term health outcomes for both mother and child. The aim was to investigate the association between duration of the inter-pregnancy interval between successive pregnancies and change in maternal body mass index (BMI) during that period to assess the optimal interval associated with the least likelihood of starting the following pregnancy with a higher body weight.

Methods

A regional population-based cohort of prospectively collected routine healthcare data for antenatal care between January 2003 and September 2017 at University Hospital Southampton was utilised. Records of women with two or more consecutive singleton pregnancies (up to five) were analysed. Information on previous births was used to categorise pregnancies as first to second, second to third, third to fourth and fourth to fifth. Inter-pregnancy interval was defined as timing between a live birth and the next conception calculated by subtracting gestational age according to dating ultrasound scan of the latter birth from the interval between births. BMI was treated as a continuous and categorical variable, which was defined as underweight (BMI < 18.5 kg/m^2), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2) and obese (≥ 30 kg/m^2). Regression analyses was used to examine the association between change in maternal BMI measured at the first antenatal (booking) appointment and inter-pregnancy interval (adjusted for timing of booking appointments, age, ethnicity, highest educational qualification, employment status at booking appointment, baseline BMI, smoking status and whether undergone infertility treatment). Clustering of pregnancies within each woman was also adjusted for.

Findings

In total, 20,571 women of which 12,636 had first two, 2654 had first three, 530 had first four and 120 had first five pregnancies were included. Two-thirds of women had gained weight when first presenting to antenatal care for their subsequent pregnancy with 21–24% moving into a higher compared to 4–6% moving into a lower BMI category. A significant positive linear association was found between change in maternal BMI with each year of inter-pregnancy interval with the coefficient remaining similar across pregnancies (adjusted increase in maternal BMI per year of inter-pregnancy interval 0.25 kg/m^2, 95% CI: 0.22 to 0.28) and increasing for the fourth to fifth pregnancy (adjusted increase in maternal BMI per year of inter-pregnancy interval 0.36 kg/m^2, 95% CI: 0.25 to 0.47). Compared to an interval of 24–35 months, there is a significantly increased risk of starting the next pregnancy with a higher weight than the previous one with an interval of 36 months or more for the second, third and fourth pregnancies (adjusted OR: 1.43, 95% CI: 1.29 to 1.59, $P < 0.001$ for first to second, adjusted OR: 1.51, 95% CI: 1.28 to 1.78, $P < 0.001$ for second to third, adjusted OR: 1.59, 95% CI: 1.20 to 2.11, $P = 0.001$ for third to fourth pregnancy). In contrast, there was a significantly decreased risk of starting the next pregnancy with a higher BMI in those with an interval of 12–23 months for the second and third pregnancies (adjusted OR: 0.77, 95% CI: 0.71 to 0.85, $P < 0.001$; adjusted OR: 0.82, 95% CI: 0.70 to 0.97, $P = 0.02$, respectively) but not higher order pregnancies.

Conclusions

Birth spacing of 12–23 months appears most protective against starting the next pregnancy with a higher body weight, even when adjusting for maternal age. In high-income country settings, getting pregnant within 1–2 years of the previous birth and advising those anticipating longer intervals to limit weight gain could be simple preconception preventive measures in tackling maternal obesity and hence achieving better subsequent maternal and offspring health outcomes.

interest throughout the research process. Effective guidance will need the support of researchers, funders and journals.
Discussion This research has built consensus on the need for guidance, and identified an optimal approach for assessing risk, prevention and management of conflicts of interest in interactions between population health researchers and the food industry. Further work is needed to finalise, pilot test and seek endorsement for evidence informed guidance.

LB4 INDUSTRY REACTIONS TO THE UK SOFT DRINKS INDUSTRY LEVY: UNPACKING THE EVOLVING DISCOURSE FROM ANNOUNCEMENT TO IMPLEMENTATION

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Background Within the context of a global movement toward taxes on sugary drinks, the Soft Drinks Industry Levy (SDIL) is unique in its construction – a two-tiered levy that aims to encourage industry to reformulate soft drinks. Industry decisions regarding reformulation will directly influence the health impacts of the levy, however how these reactions are covered in the media will also shape a wider public discourse on sugar and health. This work will examine the evolution of industry reactions to the levy from announcement to implementation, via articles published in news media and trade press.
Methods We searched the Factiva database of UK news media and trade press. A search strategy was used to identify articles related to sugar or soft drinks and related to the levy covering March 16th 2016 to March 31st 2018. Articles were screened using predefined criteria. Analyses included: (a) description of included articles by industry actor and (b) a longitudinal, case-based, thematic analysis of each industry actor.
Results 526 articles were included covering the ongoing reactions by nine soft drinks industry actors (e.g. AG Barr, Britvic, Coca-Cola European Partners) during six policy development milestones and two national events. Early results demonstrate a discourse of disagreement with the aims of the SDIL immediately after its announcement with emergent themes including 'no evidence that sugar taxes reduce obesity', 'the poor will suffer' and 'this will destroy industry and kill jobs'. Reactions also included contradictory themes such as 'most products are not impacted' and 'we support government actions on obesity'. Throughout the consultation phase and during the Brexit vote and snap election further themes emerged including 'threats of legal action' that were not always consistent across industry actors but dominated until Royal Assent for the legislation. Throughout the parliamentary process the discourse shifted toward acceptance of the levy and undertaking efforts to adapt including 'diversification and innovative marketing efforts' and various 'cost management actions to offset the levy'. As the implementation of the levy approached, acceptance was reinforced by additional themes that sought to ensure perceived profitability with 'claims of strong sales and profits' and 'calls for investment in a sector with clear growth'.
Conclusion The shifting discourse suggests that industry actors are continually navigating issues of public, government and commercial interests, which results in conflicting narratives. Further work is needed to explore the discourses surrounding other related actors such as government, civil society and academics.

LB5 IS THE DURATION OF THE PRECEDING INTER-PREGNANCY INTERVAL ASSOCIATED WITH OFFSPRING'S SIZE AT BIRTH? – ANALYSIS OF A UK POPULATION-BASED COHORT

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Background Short and long intervals between pregnancies have been associated with increased risk of adverse birth outcomes including low birth weight and stillbirth. Birthweight is an indicator of the in-utero environment and a key early life risk factor for long-term health outcomes such as obesity and cardiovascular disease. The World Health Organization recommended in 2005 waiting at least 24 months after a live birth before getting pregnant again. There are no UK guidelines on birth spacing. We aimed to investigate the association between duration of the inter-pregnancy interval between successive live birth pregnancies and risk of having a small-for-gestational age (SGA) or large-for-gestational age (LGA) baby.
Methods A population-based cohort of prospectively collected routine healthcare data for antenatal care between January 2003 and September 2017 (total n=82 098 pregnancies) at University Hospital Southampton, Hampshire, UK was used. Records of women with their first two singleton live-birth pregnancies were analysed (n=15 922 women). Inter-pregnancy interval was defined as timing between a live birth and the next conception. SGA was defined as <10th percentile weight and LGA as >90th percentile weight for gestational age. Logistic regression was used to examine the association between risk of SGA or LGA and inter-pregnancy interval. The models were adjusted for maternal age, ethnicity, highest educational qualification, employment status, baseline maternal BMI, between pregnancy change in maternal BMI, smoking status at second pregnancy booking appointment and conception following infertility treatment. Sensitivity analyses was conducted adjusting for SGA or LGA in previous pregnancies.
Results Twelve percent of first pregnancy and 7% of second pregnancy births were SGA. Seven percent of first pregnancy and 13% of second pregnancy births were LGA. Three percent of women each had SGA and LGA babies in both pregnancies. Compared to an interval of 24–35 months, there was a lower risk of SGA birth in second pregnancy with an interval of 12–23 months (adjusted OR 0.82, 95% CI 0.69 to 0.98, p=0.03). The association remained after adjusting for previous outcome of SGA in sensitivity analysis. No association was observed between risk of SGA with intervals of <12 or ≥36 months or LGA and inter-pregnancy interval.
Conclusion An inter-pregnancy interval of 12–23 months was associated with lower risk of SGA, however the duration of the interval was not associated with LGA risk. In high-income countries with relatively healthy pregnant population, further research considering the potential advantages of shorter optimal interval between pregnancies than that recommended by WHO is needed.

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Rapid fire programme

RF1 THE IMPACT OF FISCAL POLICIES ON POPULATION HEALTH AND HEALTH INEQUALITIES IN SCOTLAND: A MODELLING STUDY

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10.1136/jech-2018-SSMabstracts.90

Background Improving health and reducing health inequalities are important joint policy objectives. Income is a key social determinant of health, but robust evidence about the relative impacts of redistributive policies is rare. Our study aimed to estimate the potential impacts on health (premature mortality) and health inequalities of 15 fiscal policies in Scotland, including changes to income tax, council tax, and benefits, and two Universal Basic Income (UBI) schemes.

Methods EUROMOD, a detailed tax-benefit microsimulation model, was used to estimate changes in household income for each quintile of the Scottish Index of Multiple Deprivation (SIMD). Parametric survival models were used to model baseline mortality rates, and log-log models were used to estimate policy effect sizes. We estimated the impacts of each policy on premature mortality across the Scottish population after 3 years of follow up, compared to the baseline no-policy scenario, and assessed inequalities between SIMD quintiles. Data processing and modelling was conducted in R, Stata and Excel.

Results Policies predicted to both improve health and reduce health inequalities included one UBI scheme (while the other UBI scheme worsened health), replacing council tax with a local income tax, increasing Job Seeker's Allowance and Income Support, increasing tax credits, and increasing the Carer's Allowance. The health-beneficial UBI scheme would result in a 0.2% reduction in premature mortality for the whole Scottish population, a 6.1% reduction for the most deprived quintile, and a 24.7% reduction in relative inequality (as measured by the relative index of inequality). Policies that were less targeted to deprived communities either worsened health but reduced inequalities, or improved health while worsening inequalities.

Conclusion Fiscal policies have the potential for substantial effects on health and health inequalities in Scotland. The most effective policies for reducing health inequalities were those that disproportionately increased incomes in the most deprived areas. The modelling is subject to various assumptions and sources of uncertainty, but nonetheless highlights the importance of applying an inequalities lens to economic policy options.

RF2 DO PEOPLE IN MORE DEPRIVED AREAS HAVE A HIGHER RISK OF ALCOHOL-RELATED HOSPITAL ADMISSION, AFTER ACCOUNTING FOR INDIVIDUALLY RECORD-LINKED DATA ON ALCOHOL CONSUMPTION AND SMOKING?

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Background Greater area deprivation is associated with a higher risk of alcohol-related harm. Few studies have investigated longitudinal patterns of harm using record-linked alcohol consumption, and none considered drink type which is associated with deprivation. This study aims to investigate whether the type of drink is associated with the observed higher risk of alcohol-related hospital admission (ARHA) in people living in deprived areas.

Methods A total of 11 229 people aged 16 and over responded to the Welsh Health Survey in 2013 and 2014, consenting to data linkage. Responses were record-linked within the Secure Anonymised Information Linkage Databank (SAIL) to wholly attributable ARHA (defined by Public Health England) 8 years before the survey month until the end of 2016. They were censored for death or leaving Wales using the Welsh Demographic Service. To each lower super output area (LSOA) at survey month we linked the Welsh Index of Multiple Deprivation 2011, grouping the two more deprived quintiles and three less deprived quintiles. Alcohol consumption and smoking status throughout the study period were estimated from survey responses.

We estimated hazard ratios (HR) with 95% confidence intervals (95% CI) for the risk of (multiple) ARHA for deprivation groups using age-based recurrent-event models. The study period started 3 years before the survey. The first model adjusted for sex, time since the last and number of historic ARHA during 5 years before study start. The second model also adjusted for the number of units reported by drink type (beer and cider; wine and champagne; spirits including alcopops) on the heaviest drinking day in the past week and smoking status.

Results 131 respondents had at least one ARHA. People living in more deprived areas had a higher risk of ARHA (HR 1.52; 95% CI 1.08 to 2.14) compared to less deprived. In model 2, adjustment for units of alcohol drunk and smoking reduced the risk of ARHA for more deprived areas (HR 1.29; 95% CI 0.90 to 1.84) with smoking and historic admission having particularly strong effects. Unit increases of spirits drunk were positively associated with increasing risk of ARHA (HR 1.05; 95% CI 1.01 to 1.10), higher than for other drink types.

Conclusion Respondents living in more deprived areas had only a slightly higher risk of alcohol-related hospital admission, considering similar unit consumption, smoking and historic admission. Although significant, adjusting for units by type of drink did not markedly change the socioeconomic pattern of alcohol-related harm.

Is maternal weight gain between pregnancies associated with risk of large-for-gestational age birth? Analysis of a UK population-based cohort

Nida Ziauddeen, Paul J Roderick, Nicholas S Macklon, Nisreen A Alwan

Abstract

Background **Maternal obesity during pregnancy increases the risk of large-for-gestational age (LGA) infant and childhood obesity. We aimed to investigate the association between maternal weight change between consecutive pregnancies and risk of having a LGA baby.**

Methods **A population-based cohort of routinely collected antenatal health-care data between Jan 1, 2003, and Dec 31, 2017, at University Hospital Southampton, UK, was used. No age restriction was applied, and records of all women with their first two singleton livebirth pregnancies were analysed. Regression analysis was used to examine the association between interpregnancy change in maternal body-mass index (BMI) measured at first antenatal appointment of each pregnancy and LGA (adjusted for age, ethnicity, educational qualification, infertility treatment, smoking, employment status, infant sex, gestational diabetes in current pregnancy, and interpregnancy interval). We also stratified by maternal BMI category and LGA outcome in first pregnancy.**

Findings **15 940 records were analysed. 2548 women (16%) lost weight and 7607 (48%) gained weight (≥1 BMI unit) between pregnancies. LGA incidence was 7% (n=1109) in first and 13% (2106) in second pregnancies; and was 12% (315) in women who lost weight and 12% (690) in women whose weight remained stable between pregnancies compared with 14% (1101) in women who gained weight. Normal-weight and overweight women who gained weight had an increased risk of LGA after having a non-LGA baby in the first pregnancy (adjusted odds ratio 1·37 [95% CI 1·16–1·61], p<0·0001 in normal weight and 1·30 [1·02–1·65], p=0·03 in overweight). Overweight women who had a previous LGA birth were at lower risk of LGA in the second pregnancy if they lost 1 or more BMI unit (0·44 [0·23–0·85], p=0·02).**

Interpretation **Losing weight after LGA birth in overweight women reduces the risk of subsequent LGA, whereas gaining weight increases its risk in women with no previous history of LGA. Avoiding weight gain between pregnancies is an important preventive measure to achieve better maternal and offspring outcomes.**

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Contributors
NZ analysed the data. NZ and NAA acquired and interpreted the data. NZ drafted the abstract. All authors contributed to the study design, revised the abstract for content and approved the final version before submission.

Declaration of interests
We declare no competing interests.

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treated with phlebotomy. We aimed to test *HFE* p.C282Y homozygote associations with prevalent and incident morbidity in the large UK Biobank sample of European descent. We also examined how iron supplement use may affect associations between p.C282Y homozygosity and morbidity.

Methods We studied 451,243 participants of European descent (aged 40 to 70 years) from the UK Biobank. Data were available on prevalent and incident adverse health outcomes from baseline questionnaires and from up to 9.4 years hospital inpatient follow-up (mean 7 years). Participants also reported baseline dietary supplement use. We tested associations between p.C282Y homozygosity, prevalent and incident outcomes, and iron supplement use, using logistic regression and Cox proportional hazard regression, adjusted for age, sex, genotyping array type and genetic principal components.

Results 2,890 participants were p.C282Y homozygotes (0.6%, or 1/156), of whom 7.3% (210/2890) had haemochromatosis diagnosed at baseline, increasing to 15.1% (437/2890) by the end of follow-up. P.C282Y homozygotes had substantial excess prevalent and incident morbidity including haemochromatosis, liver disease, arthritis and diabetes compared to those with no mutations (combined measure of excess incident morbidity; men, HR: 3.37, 95% CI: 2.87–3.97; women, HR: 2.99,95% CI: 2.51–3.55). A sub-analysis of 200,975 older participants (aged 60–70 years) showed that both male and female p.C282Y homozygotes also had an increased likelihood of Fried frailty and chronic pain.

In p.C282Y homozygotes undiagnosed with haemochromatosis, the intake of iron supplements or multivitamins increased the likelihood of frailty (OR: 2.15, 95% CI: 1.22–3.77) and incident osteoarthritis (HR: 1.86, 95% CI: 1.02–3.41)

Conclusion In a large community volunteer sample, *HFE* p.C282Y homozygosity was associated with substantial excess morbidity, frailty and chronic pain in both men and women. In p.C282Y homozygotes undiagnosed with haemochromatosis, taking iron supplements or multivitamins was an additional risk factor for developing morbidity, including frailty and osteoarthritis. Since the p.C282Y associated iron overload can be prevented and treated, these findings suggest there is a need for expanded case finding and screening for hereditary haemochromatosis. It also suggests that warnings and controls on iron containing supplements may be needed.

OP38 PREDICTING THE RISK OF CHILDHOOD OVERWEIGHT AND OBESITY AT 4–5 YEARS USING PREGNANCY AND EARLY LIFE HEALTHCARE DATA

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10.1136/jech-2019-SSMabstracts.38

Background In England, 9.5% of children aged 4–5 years and 20.1% aged 10–11 years are obese, with the prevalence in the most deprived areas being more than twice as that in the least deprived. There is evidence illustrating the developmental origins of obesity, but it focuses on individual risk factors and comes mostly from research birth cohorts which are not necessarily representative of the wider population. There is no system-based early identification of childhood obesity risk at pregnancy stage and onwards.The aim was to develop and validate a risk identification system for childhood obesity using existing routinely collected maternal and early-life population-level healthcare data in Hampshire.

Methods Studying Lifecourse Obesity PrEdictors (SLOPE) study is an anonymised population-based linked cohort of maternal antenatal and delivery records for all births taking place at University Hospital Southampton 2003–2018, and child health records including information on postnatal growth, type of feeding and childhood body mass index (BMI) up to 14 years. Childhood age- and sex- adjusted BMI at 4–5 years was used to define the outcome of overweight and obesity in the models. Logistic regression models together with multivariable fractional polynomials were used to select model predictors and to identify transformations of continuous predictors that best predict the outcome. Predictive accuracy was evaluated by assessing model discrimination and calibration.

Results Childhood BMI was available for approximately 30000 children aged 4–5 years (9% obese). Models were developed in stages, incorporating data collected at first antenatal booking appointment, birth and early life predictors. The area under the curve (AUC) was lowest (0.64) for the model only incorporating maternal predictors from the booking appointment and highest for the model incorporating all factors up to weight at 2 years for predicting outcome at 4–5 years (0.82 for overweight and obesity and 0.89 for obesity excluding overweight). Maternal predictors included BMI, smoking status at first antenatal appointment, age and ethnicity. Early life predictors included birthweight, gender, breastfeeding and weight at 1 or 2 years of age. Although AUC was lower for the booking models, maternal predictors remained consistent across the models, thus high-risk groups could be identified at an early stage with more precise estimation as the child grows.

Conclusion This prediction modelling can be used to identify and quantify clustering of risk for childhood obesity as early as the first trimester of pregnancy, and can strengthen the long-term preventive element of antenatal and early years care.

OP39 DEVELOPMENT OF A SHORT FOOD FREQUENCY QUESTIONNAIRE TO ASSESS DIET QUALITY IN POPULATION STUDIES

[1]SR Crozier*, [2,3]SM Robinson, [1,4]S Shaw, [1,4]HM Inskip, [1,4]J Baird, [1,4]C Cooper, [1,4]C Vogel. [1]*MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK*; [2]*AGE Research Group, Newcastle University, Newcastle upon Tyne, UK*; [3]*NIHR Newcastle Biomedical Research Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University, Newcastle upon Tyne, UK*; [4]*NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Trust, Southampton, UK*

10.1136/jech-2019-SSMabstracts.39

Background Food frequency questionnaires (FFQs) are a popular tool in nutritional epidemiology, enabling estimates of habitual diet in large populations, but are time-consuming to complete. There is an increasing need for a short, accurate dietary tool that characterises healthy dietary patterns for use in observational and interventional research.

Methods The National Diet and Nutrition Survey (NDNS) is a general population national survey. Randomly-selected

Appendix B Ethical approval

Dr Nisreen A Alwan
AC23, South Academic Block,
Southampton General Hospital
Tremona Road
Southampton
SO16 6YD

Email: hra.approval@nhs.net

12 March 2018

Dear Dr Alwan

Letter of HRA Approval

Study title:	**Examining maternal and early life risk associations with childhood overweight and obesity in a population-based cohort**
IRAS project ID:	**242031**
Sponsor:	**University of Southampton**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further from the HRA.

How should I continue to work with participating NHS organisations in England?
You should now provide a copy of this letter to all participating NHS organisations in England, as well as any documentation that has been updated as a result of the assessment.

Following the arranging of capacity and capability, participating NHS organisations should **formally confirm** their capacity and capability to undertake the study. How this will be confirmed is detailed in the "*summary of HRA assessment*" section towards the end of this letter.

You should provide, if you have not already done so, detailed instructions to each organisation as to how you will notify them that research activities may commence at site following their confirmation of capacity and capability (e.g. provision by you of a 'green light' email, formal notification following a site initiation visit, activities may commence immediately following confirmation by participating organisation, etc.).

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland, Scotland and Wales?
HRA Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland, Scotland and Wales.

If you indicated in your IRAS form that you do have participating organisations in one or more devolved administration, the HRA has sent the final document set and the study wide governance report (including this letter) to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with Northern Ireland, Scotland and Wales.

How should I work with participating non-NHS organisations?
HRA Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The attached document *"After HRA Approval – guidance for sponsors and investigators"* gives detailed guidance on reporting expectations for studies with HRA Approval, including:

- Registration of Research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Dr Nisreen Alwan
Tel: 023 8120 4776
Email: N.A.Alwan@soton.ac.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **242031**. Please quote this on all correspondence.

Yours sincerely

Michael Higgs
Assessor

Email: hra.approval@nhs.net

Copy to: Dr Ferdousi Chowdhury, University of Southampton

List of Documents

The final document set assessed and approved by HRA Approval is listed below.

Document	Version	Date
Evidence of Sponsor insurance or indemnity (non-NHS Sponsors only)		24 July 2017
HRA Schedule of Events	2	12 March 2018
HRA Statement of Activities	2	12 March 2018
IRAS Application Form [IRAS_Form_16022018]		16 February 2018
Letter from sponsor		14 February 2018
Referee's report or other scientific critique report [Darren Greenwood]		31 January 2017
Referee's report or other scientific critique report [Sian Robinson]		21 March 2017
Referee's report or other scientific critique report [Robin Poole]		21 March 2017
Research protocol or project proposal	2.0	29 January 2018
Summary CV for Chief Investigator (CI) [Nisreen Alwan]	1.0	16 February 2018
Summary CV for student [Nida Ziauddeen]		16 February 2018

Summary of HRA assessment

The following information provides assurance to you, the sponsor and the NHS in England that the study, as assessed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing, arranging and confirming capacity and capability.

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/ consent documents and consent process	Yes	As research involving retrospective use of data only, there is no participant information in this study.
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	A Statement of Activities and Schedule of Events have been provided for use with participating NHS organisations in England. Exchange of the SoA will confirm capacity and capability of an NHS organisation to host the research.
4.2	Insurance/ indemnity arrangements assessed	Yes	Insurance for the study will be provided by the sponsor.
4.3	Financial arrangements assessed	Yes	External study funding has been secured from the Academy of Medical Sciences/ Wellcome Trust.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	The research team will assemble data from multiple sources. The lead NHS site, University Hospital Southampton NHS Foundation Trust, shall be responsible for coordinating with other data controllers what information should be supplied to the sponsor research team. At no time shall the sponsor receive personally-identifiable information, and at no time shall any other data controllers receive any personally-identifiable information additional to that which they already hold. This includes NHS numbers.
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments

Section	HRA Assessment Criteria	Compliant with Standards	Comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Not Applicable	This study does not require review by an NHS REC because it is limited to the use of previously collected, non-identifiable information.
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	No comments
6.3	Devices – MHRA notice of no objection received	Not Applicable	No comments
6.4	Other regulatory approvals and authorisations received	Not Applicable	No comments

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
There is a single type of participating NHS organisation at which research activity, which shall be data anonymization and extraction, shall take place. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website. If chief investigators, sponsors or principal investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the chief investigator, sponsor or principal investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).
There is no expectation for a principal investigator or local collaborator at participating NHS organisations in England. GCP training is not a generic training expectation, in line with the HRA/MHRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken
As all local research activity will need to be conducted by persons with appropriate access to personally-identifiable information, and so be members of the care team, there is no expectation that access arrangements or pre-engagement checks for external researchers will be relevant.

Other Information to Aid Study Set-up

This details any other information that may be helpful to sponsors and participating NHS organisations in England to aid study set-up.
The applicant has indicated that they intend to apply for inclusion on the NIHR CRN Portfolio. Although no sites have been listed in Part C of the IRAS form, relevant information can be found in the protocol.

Appendix C Interpregnancy interval and maternal BMI

Figure C.1: The percentage of weight gain by interpregnancy interval and maternal body mass index (BMI category) between second to third pregnancy

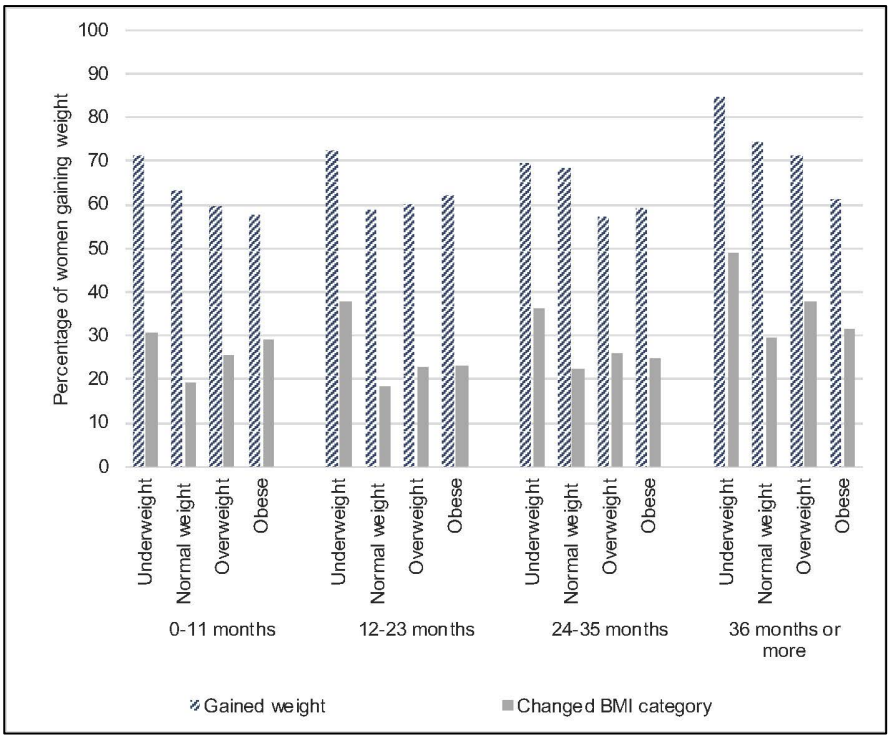


Figure C.2: The percentage of weight gain by interpregnancy interval and maternal body mass index (BMI category) between third to fourth pregnancy

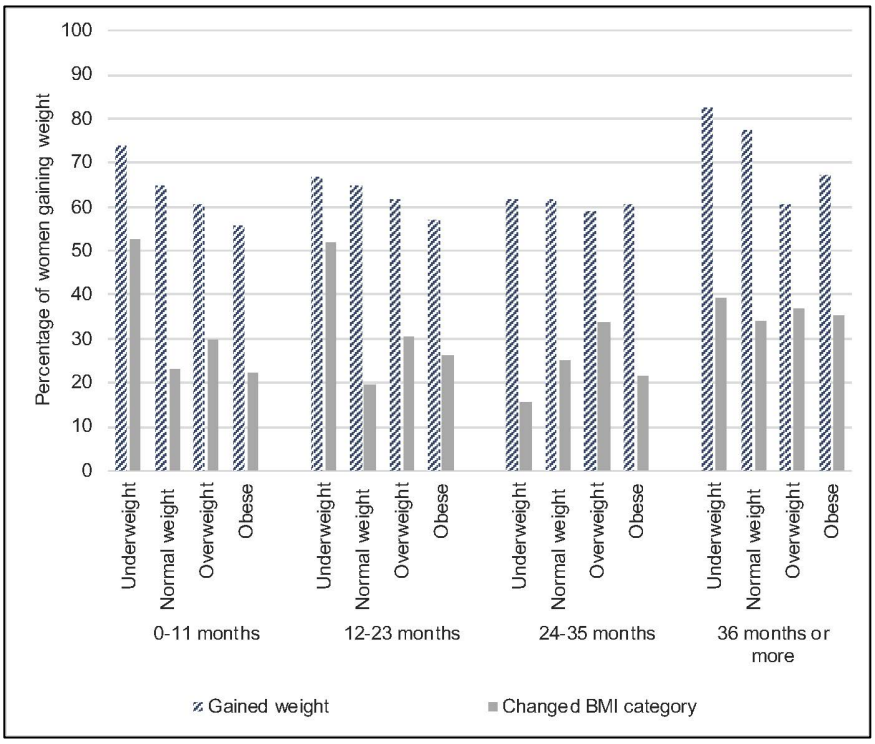


Figure C.3: The percentage of weight gain by interpregnancy interval and maternal body mass index (BMI category) between fourth to fifth pregnancy

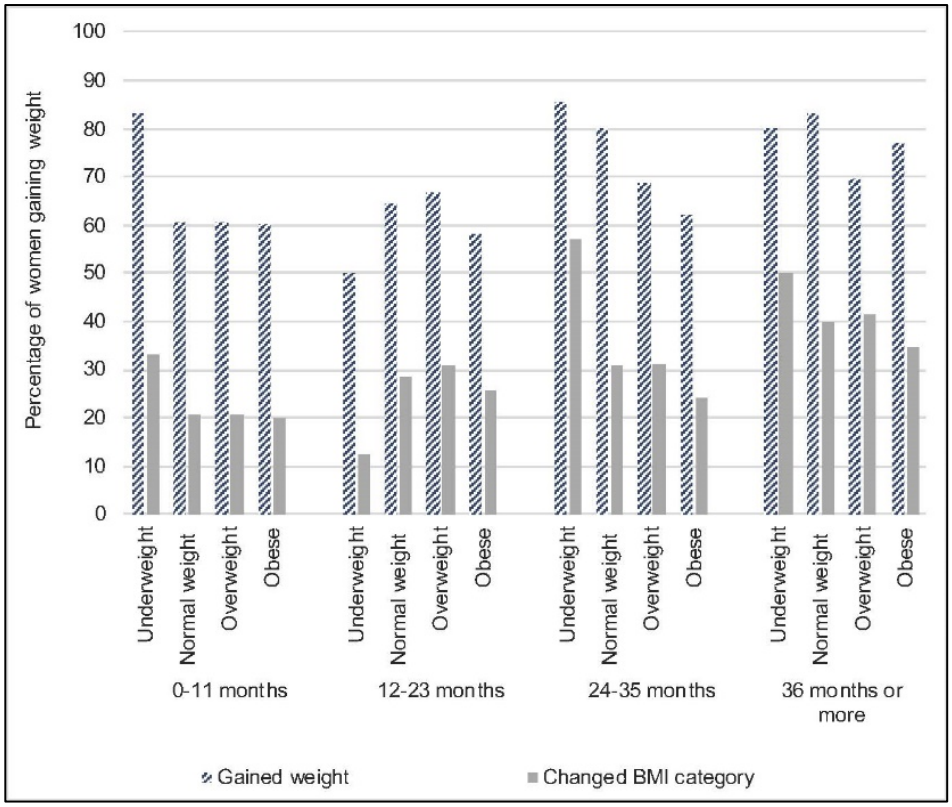


Table C.1: Change in maternal body mass index (BMI) measured at the first antenatal visit between non-consecutive pregnancies in women with three or more pregnancies

	First to third pregnancy	First to fourth pregnancy	First to fifth pregnancy
N	2,654	530	120
Interpregnancy interval, months (median, IQR)	60.1 (44.8 to 80.4)	86.6 (68.4 to 108.1)	92.4 (76.8 to 113.0)
Direction of change of maternal BMI (%, 95% CI)			
No change	1.4 (1.0 to 2.0)	1.3 (0.5 to 2.7)	-
Lost weight/BMI units	23.4 (21.8 to 25.0)	16.6 (13.5 to 20.1)	11.5 (6.1 to 19.3)
Gained weight/BMI units	75.2 (73.5 to 76.8)	82.1 (78.5 to 85.2)	88.5 (80.7 to 93.9)
Change in maternal BMI (median, IQR)	1.7 (0.0 to 4.1)	3.1 (0.8 to 6.1)	3.5 (1.7 to 6.6)
Change in maternal BMI in women who lost weight	-1.2 (-2.4 to -0.5)	-1.6 (-2.5 to -0.7)	-0.9 (-2.6 to -0.5)
Change in maternal BMI in women who gained weight	2.8 (1.3 to 4.9)	4.1 (1.8 to 6.8)	4.0 (2.7 to 7.0)
Change in maternal BMI category (%)			
No change in BMI category	62.8 (60.9 to 64.6)	47.7 (43.4 to 52.1)	44.2 (34.5 to 54.3)
Underweight (< 18.5)	1.3 (0.9 to 1.8)	0.8 (0.2 to 1.9)	1.9 (0.2 to 6.8)
Normal weight (18.5 to 24.9)	39.3 (37.4 to 41.2)	30.9 (27.0 to 35.1)	26.9 (18.7 to 36.5)
Overweight (25.0 to 29.9)	11.3 (10.1 to 12.5)	6.8 (4.8 to 9.3)	3.8 (1.1 to 9.6)
Obese (≥30.0)	10.9 (9.7 to 12.1)	9.2 (6.9 to 12.0)	11.5 (6.1 to 19.3)
% decreased to normal weight	2.2 (1.7 to 2.9)	3.0 (1.7 to 4.9)	3.8 (1.1 to 9.6)
% decreased to overweight	1.8 (1.3 to 2.4)	1.1 (0.4 to 2.4)	-
% increased to overweight	16.2 (14.8 to 17.6)	20.6 (17.2 to 24.3)	24.0 (16.2 to 33.4)
% increased to obese	17.7 (16.3 to 19.2)	26.0 (22.3 to 30.0)	29.8 (21.2 to 39.6)

Table C.2: Maternal demographics and change in body mass index (BMI) measured at the first antenatal visit between pregnancies by interpregnancy interval categorised according to World Health Organisation (WHO) guidelines[1]

	<2years	≥2 years	p	<2years	≥2 years	p	<2years	≥2 years	p	<2years	≥2 years	p
n	8,417	7,523		2,750	2,988		1,150	1,015		386	352	
Maternal age at first pregnancy, years (mean ± SD)	26.4 ± 5.5	25.2 ± 5.4	<0.001	26.7 ± 5.2	25.5 ± 4.6	<0.001	27.5 ± 4.9	26.8 ± 4.2	<0.001	28.6 ± 4.8	28.2 ± 4.2	0.15
Timing of first booking appointment, weeks (mean ± SD)	11.3 ± 2.6	11.4 ± 2.7	<0.001	11.5 ± 2.8	11.7 ± 2.9	0.02	11.5 ± 3.0	11.7 ± 3.1	0.04	11.7 ± 3.0	12.3 ± 3.2	0.009
Change in maternal BMI (median, IQR)	0.6 (-0.5 to 2.1)	1.1 (-0.2 to 2.9)	<0.001	0.6 (-0.6 to 2.1)	1.2 (-0.3 to 3.0)	<0.001	0.7 (-0.5 to 2.4)	1.2 (-0.4 to 3.2)	<0.001	0.8 (-0.6 to 2.3)	1.8 (0.2 to 3.6)	<0.001
Direction of change of maternal BMI (%, 95% CI)												
No change	3.6 (3.2 to 4.0)	2.2 (1.8 to 2.5)	<0.001	3.9 (3.2 to 4.6)	1.9 (1.5 to 2.5)	<0.001	4.6 (3.5 to 6.0)	1.6 (1.0 to 2.5)	<0.001	4.1 (2.4 to 6.6)	2.8 (1.4 to 5.2)	<0.001
Lost BMI units	34.5 (33.5 to 35.5)	27.7 (26.7 to 28.7)		35.3 (33.5 to 37.1)	28.6 (27.0 to 30.3)		32.8 (30.1 to 35.6)	30.4 (27.6 to 33.4)		33.9 (29.2 to 38.9)	20.2 (16.1 to 24.7)	
Gained BMI units	61.9 (60.9 to 63.0)	70.2 (69.1 to 71.2)		60.8 (59.0 to 62.7)	69.4 (67.8 to 71.1)		62.6 (59.7 to 65.4)	68.0 (65.0 to 70.8)		61.9 (56.9 to 66.8)	77.0 (72.2 to 81.3)	
Maternal education (%, 95% CI)												
Secondary (GCSE) or under	27.1 (26.1 to 28.0)	31.2 (30.2 to 32.3)	<0.001	38.4 (36.5 to 40.2)	40.5 (38.7 to 42.3)	0.001	48.8 (45.9 to 51.7)	53.5 (50.4 to 56.6)	0.01	61.4 (56.3 to 66.3)	59.7 (54.3 to 64.8)	0.71
College (A levels)	38.8 (37.7 to 39.8)	42.8 (41.6 to 43.9)		41.5 (39.6 to 43.3)	43.2 (41.5 to 45.0)		40.0 (37.2 to 42.9)	38.6 (35.6 to 41.7)		33.7 (29.0 to 38.6)	34.1 (29.1 to 39.3)	

	<2years	≥2 years	p	<2years	≥2 years	p	<2years	≥2 years	p	<2years	≥2 years	p
University degree or above	34.2 (33.2 to 35.2)	26.0 (25.0 to 27.0)		20.2 (18.7 to 21.7)	16.3 (15.0 to 17.6)		11.2 (9.5 to 13.2)	7.9 (6.3 to 9.7)		4.9 (3.0 to 7.6)	6.3 (4.0 to 9.3)	
Employment status (%,95% CI)												
Employed	80.6 (79.7 to 81.4)	79.3 (78.3 to 80.2)	<0.001	49.6 (47.7 to 51.5)	46.6 (44.8 to 48.4)	0.05	34.8 (32.0 to 37.6)	32.7 (29.8 to 35.7)	0.52	19.7 (15.8 to 24.0)	19.9 (15.8 to 24.4)	0.87
Unemployed	15.9 (15.1 to 16.7)	15.4 (14.6 to 16.2)		48.3 (46.4 to 50.2)	50.9 (49.1 to 52.7)		62.5 (59.7 to 65.3)	64.4 (61.4 to 67.4)		78.2 (73.8 to 82.3)	77.3 (72.5 to 81.5)	
In education	3.2 (2.8 to 3.6)	4.9 (3.2 to 6.5)		1.3 (0.9 to 1.8)	1.7 (1.3 to 2.2)		1.7 (1.1 to 2.7)	2.1 (1.3 to 3.1)		0.8 (0.2 to 2.3)	1.1 (0.3 to 2.9)	
Not specified	0.4 (0.2 to 0.5)	0.5 (0.3 to 0.6)		0.7 (0.4 to 1.1)	0.7 (0.5 to 1.1)		1.0 (0.5 to 1.7)	0.8 (0.3 to 1.5)		1.3 (0.4 to 3.0)	1.7 (0.6 to 3.7)	

[1] Characteristics of women with an interpregnancy interval less than 2 years were compared to those with an interval of 2 years or more using two-sample t-test for continuous variables and chi-squared test for categorical variables

Table C.3: Linear regression estimates for association between change in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy and the length of the inter-pregnancy interval (in years) stratified by maternal age

	First to second pregnancy					
	Maternal age < 30 years			Maternal age ≥ 30 years		
	n	Maternal BMI per year (95% CI)	p	n	Maternal BMI per year (95% CI)	p
Unadjusted	11,455	0.26 0.23 to 0.29	<0.001	4,485	0.21 0.16 to 0.26	<0.001
Model 1	11,455	0.26 0.23 to 0.29	<0.001	4,485	0.22 0.16 to 0.27	<0.001
Model 2	11,005	0.27 0.24 to 0.30	<0.001	4,254	0.22 0.17 to 0.27	<0.001
Model 3	11,005	0.27 0.24 to 0.30	<0.001	4,254	0.22 0.17 to 0.27	<0.001
Model 4	3,187	0.17 0.08 to 0.26	<0.001	1,480	0.19 0.08 to 0.31	0.001

Model 1 is adjusted for: timing of first (booking) antenatal appointments (as this is when maternal BMI is measured)
Model 2 is adjusted for: timing of first (booking) antenatal appointments, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking and employment status
Model 3 is adjusted for: first (booking) antenatal appointment, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking, employment status and baseline maternal BMI (for the first pregnancy in the dataset)
Model 4 is adjusted for: first (booking) antenatal appointments, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking, employment status, baseline maternal BMI and breastfeeding or not at hospital discharge

Table C.4: Logistic regression models testing the association between inter-pregnancy gain in maternal body mass index (BMI) measured at the first antenatal visit of each pregnancy and the length of the inter-pregnancy interval (categorised)

		Gain in maternal BMI: First to second pregnancy					
		Maternal age < 30 years			Maternal age ≥ 30 years		
		n	Relative risk (95% CI)	p	n	Relative risk (95% CI)	p
Unadjusted	0-11m	11,455	1.00 0.96 to 1.04	0.90	4,485	0.96 0.90 to 1.03	0.21
	12-23m		0.92 0.90 to 0.96	<0.001		0.89 0.84 to 0.94	<0.001
	24-35m		(reference)			(reference)	
	>=36m		1.11 1.07 to 1.15	<0.001		1.14 1.07 to 1.21	<0.001
Model 1	0-11m	11,455	0.99 0.95 to 1.03	0.63	4,485	0.95 0.88 to 1.02	0.12
	12-23m		0.92 0.89 to 0.96	<0.001		0.89 0.84 to 0.94	<0.001
	24-35m		(reference)			(reference)	
	>=36m		1.11 1.07 to 1.15	<0.001		1.14 1.07 to 1.21	<0.001
Model 2	0-11m	11,005	0.98 0.94 to 1.02	0.38	4,254	0.95 0.89 to 1.02	0.19
	12-23m		0.93 0.89 to 0.96	<0.001		0.89 0.83 to 0.94	<0.001
	24-35m		(reference)			(reference)	
	>=36m		1.10 1.06 to 1.14	<0.001		1.14 1.07 to 1.21	<0.001
Model 3	0-11m	11,005	0.98 0.94 to 1.02	0.34	4,254	0.96 0.89 to 1.03	0.21
	12-23m		0.92 0.89 to 0.96	<0.001		0.88 0.83 to 0.94	<0.001
	24-35m		(reference)			(reference)	
	>=36m		1.10 1.06 to 1.14	<0.001		1.15 1.08 to 1.22	<0.001

Appendix C

		Gain in maternal BMI: First to second pregnancy					
		Maternal age < 30 years			Maternal age ≥ 30 years		
		n	Relative risk (95% CI)	p	n	Relative risk (95% CI)	p
Model 4	0-11m	3,187	1.02 0.95 to 1.09	0.59	1,480	0.92 0.82 to 1.04	0.21
	12-23m		0.92 0.87 to 0.99	0.02		0.88 0.80 to 0.97	0.01
	24-35m		(reference)			(reference)	
	>=36m		1.10 1.02 to 1.18	0.01		1.19 1.06 to 1.33	0.002

Model 1 is adjusted for: timing of first (booking) antenatal appointments (as this is when maternal BMI is measured)
Model 2 is adjusted for: timing of first (booking) antenatal appointments, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking and employment status
Model 3 is adjusted for: first (booking) antenatal appointment, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking, employment status and baseline maternal BMI (for the first pregnancy in the dataset)
Model 4 is adjusted for: first (booking) antenatal appointments, ethnicity, highest educational attainment, whether undergone infertility treatment, smoking, employment status, baseline maternal BMI and breastfeeding or not at hospital discharge

Appendix D Maternal interpregnancy weight change and size at birth

Figure D.1: Associations between risk of recurrent large-for-gestational age (LGA) birth in the second pregnancy and change in maternal body mass index (BMI) between pregnancies as measured at the first antenatal visit of each pregnancy stratified by BMI category

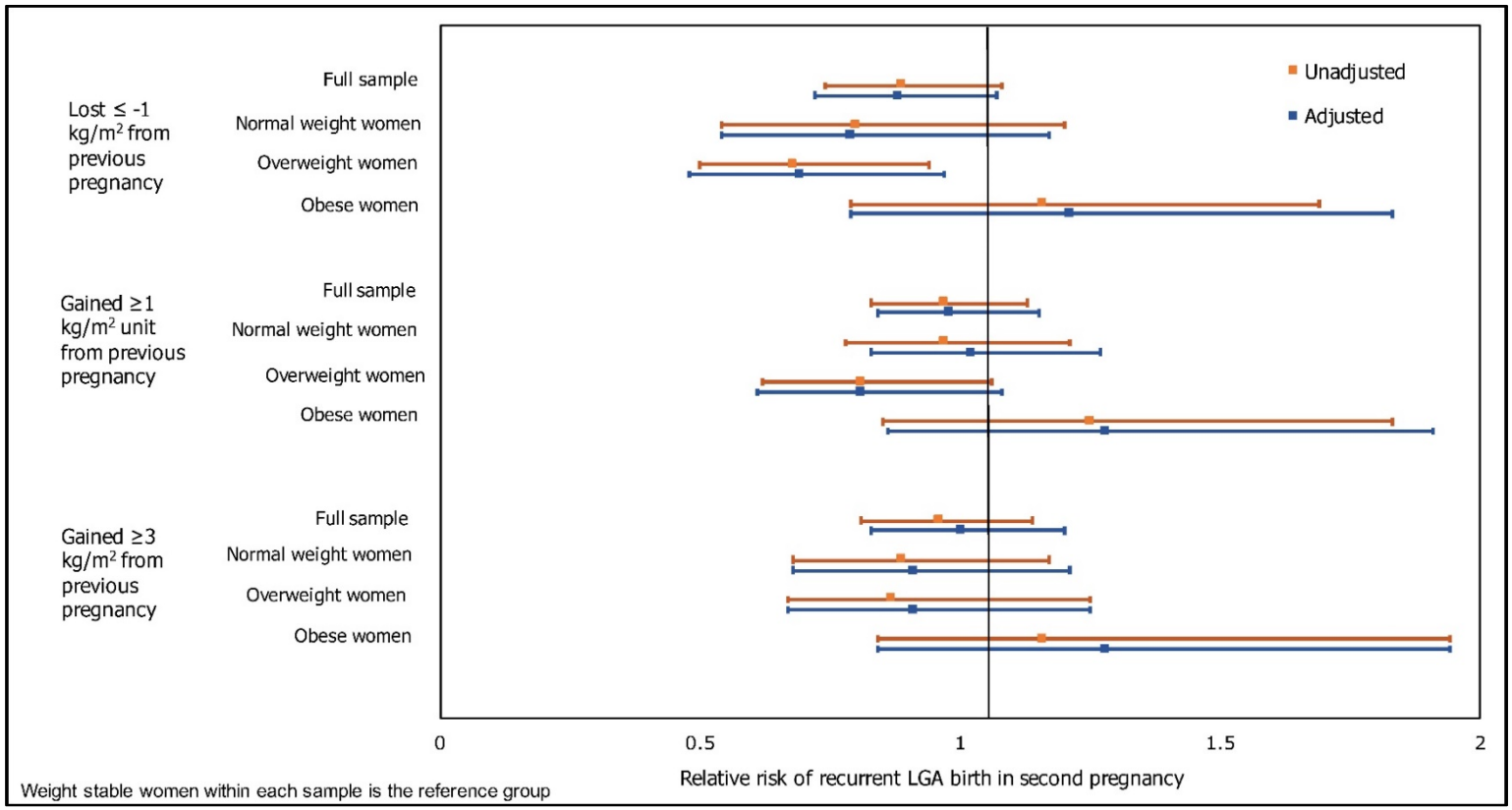
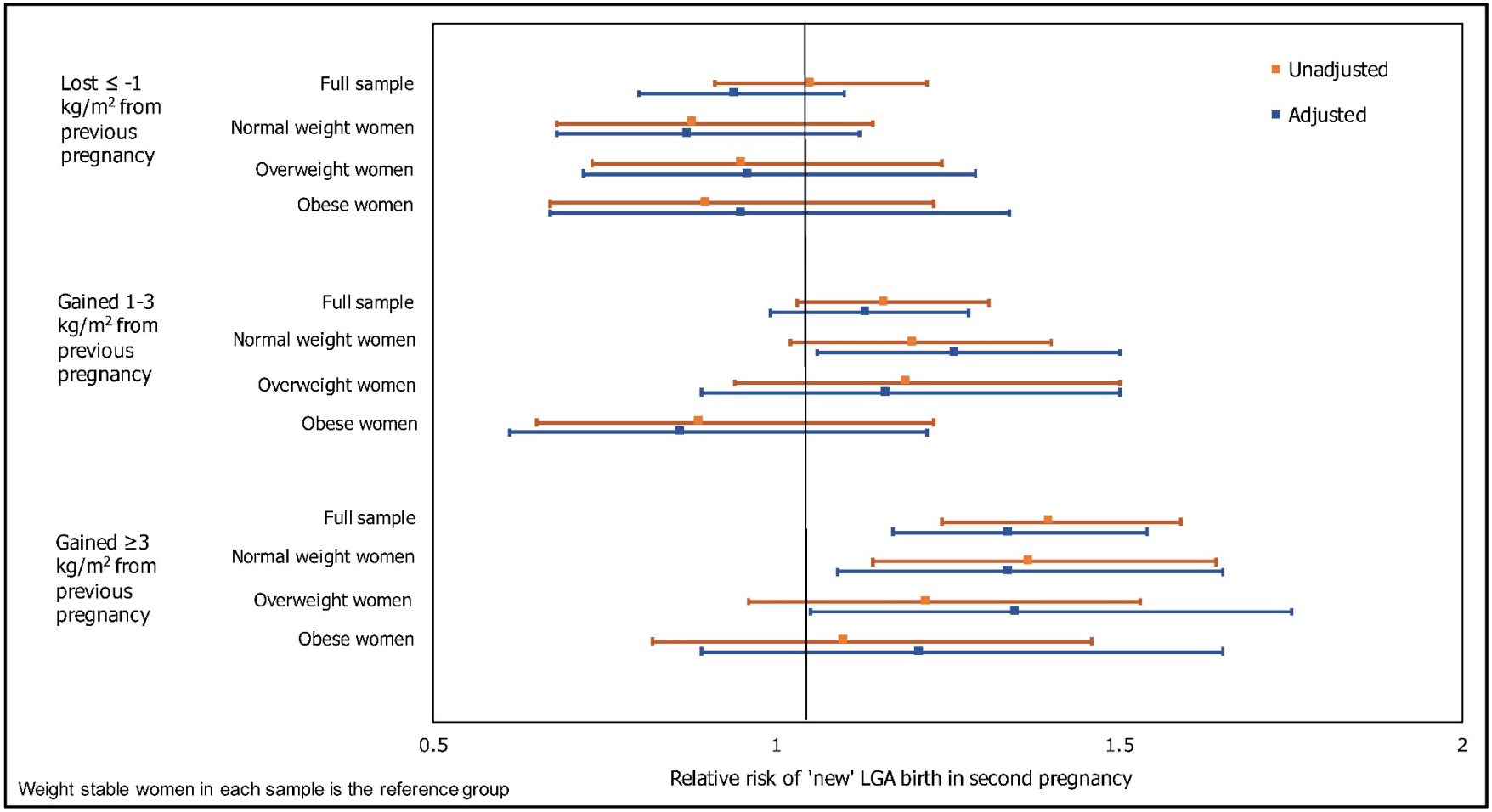


Figure D.2: Associations between the risk of 'new' large-for-gestational age (LGA) birth in the second pregnancy following a non-LGA birth in the first pregnancy and change in maternal body mass index (BMI) between pregnancies measured at the first antenatal visit



Appendix E Odds ratios for prediction models for the clinical outcome of ≥91st centile using multiply imputed data

Table E.1: Estimates (presented as odds ratios) of the final models for the prediction of outcome of overweight and obesity (≥91st centile) in children aged 4-5 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Odds ratio (OR)	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p
Maternal age at booking, years	0.989	0.983 to 0.995	0.001	0.992	0.985 to 0.999	0.030	0.996	0.989 to 1.003	0.246			
Maternal BMI at booking, kg/m^2	1.088	1.082 to 1.094	<0.001	1.079	1.073 to 1.085	<0.001	1.086	1.079 to 1.093	<0.001	1.086	1.078 to 1.093	<0.001
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	1.120	1.034 to 1.212	0.005	1.097	1.01 to 1.192	0.028	1.059	0.969 to 1.156	0.205	1.055	0.96 to 1.159	0.266
Current smoker	1.571	1.428 to 1.728	<0.001	1.838	1.658 to 2.037	<0.001	1.713	1.53 to 1.919	<0.001	1.715	1.517 to 1.939	<0.001

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Odds ratio (OR)	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p
Maternal educational attainment												
University or above				Ref			Ref			Ref		
College				1.104	1 to 1.218	0.050	1.141	1.03 to 1.264	0.012	1.119	1.003 to 1.249	0.044
Secondary or lower				1.130	1.016 to 1.257	0.024	1.209	1.081 to 1.353	0.001	1.183	1.048 to 1.335	0.006
Maternal ethnicity												
White	Ref			Ref			Ref			Ref		
Mixed	1.015	0.735 to 1.402	0.929	1.113	0.79 to 1.57	0.540	1.095	0.773 to 1.551	0.610	1.007	0.693 to 1.464	0.971
Asian	1.303	1.119 to 1.517	0.001	1.562	1.332 to 1.832	<0.001	1.795	1.524 to 2.116	<0.001	1.490	1.247 to 1.781	<0.001
Black/African/Caribbean	1.936	1.527 to 2.453	<0.001	2.197	1.693 to 2.85	<0.001	2.184	1.678 to 2.843	<0.001	1.688	1.27 to 2.246	<0.001
Other	1.090	0.769 to 1.545	0.629	1.135	0.795 to 1.62	0.485	1.266	0.859 to 1.866	0.233	0.930	0.615 to 1.406	0.731

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Odds ratio (OR)	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref			Ref			Ref		
Started taking once pregnant	1.101	1.015 to 1.194	0.020	1.128	1.038 to 1.225	0.004	1.160	1.061 to 1.267	0.001	1.153	1.047 to 1.271	0.004
Not taking supplement	1.067	0.942 to 1.208	0.309	1.096	0.964 to 1.246	0.162	1.166	1.018 to 1.337	0.027	1.160	0.992 to 1.357	0.064
Maternal first language English												
No	Ref			Ref								
Yes	0.740	0.608 to 0.899	0.002	0.764	0.621 to 0.941	0.011						
Partnership status at booking												
Partnered	Ref			Ref			Ref			Ref		
Single	1.214	1.083 to 1.36	0.001	1.223	1.089 to 1.375	0.001	1.208	1.06 to 1.377	0.005	1.179	1.022 to 1.36	0.024

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Odds ratio (OR)	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p
Parity at booking												
0	Ref			Ref								
1	1.008	0.933 to 1.089	0.844	0.882	0.816 to 0.954	0.002						
2	1.085	0.976 to 1.207	0.131	0.924	0.827 to 1.033	0.165						
3	1.177	1.028 to 1.348	0.019	0.998	0.864 to 1.152	0.975						
Birthweight, kg				2.242	2.075 to 2.423	<0.001	1.154	1.047 to 1.272	0.004	0.905	0.834 to 0.983	0.017
Gestational age at birth, days				0.986	0.982 to 0.989	<0.001	0.992	0.989 to 0.996	<0.001			
Child sex												
Male							Ref			Ref		
Female							1.540	1.417 to 1.673	<0.001	1.449	1.333 to 1.575	<0.001
Child weight, kg							2.128	2.005 to 2.258	<0.001	2.285	2.185 to 2.389	<0.001

Table E.2: Estimates of the final models for the prediction of outcome of overweight and obesity (≥91st centile) in children aged 10-11 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Odds ratio (OR)	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	Coef	(95% CI)	p
Maternal BMI at booking, kg/m^2	1.112	1.104 to 1.121	<0.001	1.107	1.098 to 1.117	<0.001	1.111	1.101 to 1.121	<0.001	1.117	1.106 to 1.128	<0.001
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	1.220	1.106 to 1.345	<0.001	1.212	1.097 to 1.339	<0.001	1.165	1.049 to 1.295	0.004	1.172	1.052 to 1.307	0.004
Current smoker	1.767	1.574 to 1.983	<0.001	1.894	1.676 to 2.141	<0.001	1.752	1.53 to 2.005	<0.001	1.794	1.56 to 2.063	<0.001
Maternal educational attainment												
Undergraduate or above	Ref			Ref			Ref			Ref		
College	1.325	1.17 to 1.5	<0.001	1.346	1.186 to 1.528	<0.001	1.338	1.172 to 1.527	<0.001	1.307	1.138 to 1.501	<0.001
Secondary school or lower	1.371	1.204 to 1.56	<0.001	1.393	1.219 to 1.592	<0.001	1.405	1.217 to 1.621	<0.001	1.340	1.146 to 1.567	<0.001

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Odds ratio (OR)	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	Coef	(95% CI)	p
Maternal employment status												
Employed	Ref			Ref			Ref			Ref		
Unemployed	0.981	0.892 to 1.079	0.695	0.974	0.883 to 1.074	0.597	0.985	0.886 to 1.095	0.783	1.058	0.945 to 1.184	0.325
Student or in training	1.537	1.164 to 2.029	0.002	1.483	1.129 to 1.948	0.005	1.434	1.074 to 1.915	0.014	1.560	1.145 to 2.125	0.005
Maternal ethnicity												
White	Ref			Ref			Ref			Ref		
Mixed	1.633	1.089 to 2.45	0.018	1.700	1.105 to 2.617	0.016	1.654	1.055 to 2.592	0.028	1.681	1.062 to 2.662	0.027
Asian	1.975	1.615 to 2.415	<0.001	2.207	1.786 to 2.727	<0.001	2.371	1.925 to 2.92	<0.001	2.466	1.982 to 3.069	<0.001
Black/African/Caribbean	2.210	1.487 to 3.284	<0.001	2.359	1.55 to 3.589	<0.001	2.398	1.564 to 3.676	<0.001	2.397	1.554 to 3.695	<0.001
Other	1.390	0.915 to 2.11	0.123	1.461	0.945 to 2.258	0.088	1.637	1.043 to 2.57	0.032	1.670	1.052 to 2.65	0.030

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Odds ratio (OR)	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	Coef	(95% CI)	p
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref			Ref			Ref		
Started taking once pregnant	1.200	1.088 to 1.324	<0.001	1.192	1.08 to 1.316	<0.001	1.202	1.084 to 1.333	0.001	1.182	1.06 to 1.318	0.003
Not taking supplement	1.209	1.052 to 1.39	0.007	1.190	1.032 to 1.372	0.016	1.215	1.044 to 1.415	0.012	1.183	1.005 to 1.393	0.044
Maternal first language English												
No	Ref			Ref								
Yes	0.745	0.556 to 0.999	0.049	0.746	0.545 to 1.021	0.067						
Partnership status												
Partnered				Ref								
Single				1.138	0.983 to 1.318	0.084	1.138					
Birthweight, kg				1.463	1.333 to 1.605	<0.001	1.463	0.87 to 1.138	0.946	0.868	0.783 to 0.963	0.008
Gestational age at birth, days				0.992	0.989 to 0.996	<0.001	0.992	0.992 to 1.000	0.039			

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Odds ratio (OR)	(95% CI)	p	OR	(95% CI)	p	OR	(95% CI)	p	Coef	(95% CI)	p
Gender												
Male				Ref								
Female				0.815	0.75 to 0.887	<0.001						
Gestational diabetes in previous pregnancy												
No				Ref								
Yes				0.673	0.418 to 1.085	0.104						
Infant weight, kg							1.562	1.412 to 1.728	<0.001	1.528	1.429 to 1.633	<0.001

Appendix F Complete case analysis for the prediction models for the clinical outcome of ≥91st centile

Table F.1: Estimates of the final models for the prediction of outcome of overweight and obesity (≥91st centile) in children aged 4-5 years using complete cases

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Intercept	-1.715	-1.939 to -1.491		-1.857	-2.096 to -1.618		-2.716	-2.98 to -2.453		-2.636	-2.803 to -2.470	
Maternal age at booking, years	1.417	0.83 to 2.004	<0.001	1.155	0.538 to 1.772	<0.001						
Maternal BMI at booking, kg/m^2	-7.033	-7.492 to -6.574	<0.001	-6.390	-6.863 to -5.918	<0.001	-6.862	-8.013 to -5.711	<0.001	-6.087	-6.964 to -5.209	<0.001
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	0.084	0.000 to 0.168	0.049	0.066	-0.018 to 0.151	0.125	0.094	-0.115 to 0.302	0.380	0.057	-0.091 to 0.205	0.451
Current smoker	0.434	0.333 to 0.535	<0.001	0.590	0.485 to 0.694	<0.001	0.699	0.443 to 0.955	<0.001	0.550	0.363 to 0.738	<0.001

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal educational attainment												
University or above				Ref			Ref			Ref		
College				0.092	-0.008 to 0.193	0.072	0.231	-0.002 to 0.464	0.052	0.123	-0.048 to 0.294	0.159
Secondary or lower				0.108	-0.002 to 0.217	0.054	0.185	-0.076 to 0.445	0.165	0.241	0.056 to 0.425	0.010
Maternal ethnicity												
White	Ref			Ref			Ref					
Mixed	0.027	-0.313 to 0.367	0.875	0.107	-0.237 to 0.45	0.543	0.541	-0.169 to 1.251	0.135			
Asian	0.280	0.121 to 0.44	0.001	0.456	0.295 to 0.618	<0.001	0.622	0.297 to 0.946	<0.001			
Black/African/Caribbean	0.686	0.429 to 0.942	<0.001	0.801	0.54 to 1.062	<0.001	0.573	0.061 to 1.086	0.028			
Other	0.091	-0.266 to 0.448	0.616	0.119	-0.241 to 0.48	0.517	0.400	-0.407 to 1.207	0.331			
Maternal first language English												
No	Ref			Ref								
Yes	-0.304	-0.515 to -0.094	0.005	-0.270	-0.485 to -0.055	0.014						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref			Ref					
Started taking once pregnant	0.091	0.007 to 0.175	0.034	0.120	0.035 to 0.204	0.006	0.191	-0.022 to 0.404	0.079			
Not taking supplement	0.035	-0.096 to 0.166	0.600	0.064	-0.068 to 0.196	0.344	0.293	-0.05 to 0.637	0.094			
Partnership status at booking												
Partnered	Ref			Ref						Ref		
Single	0.178	0.06 to 0.296	0.003	0.185	0.064 to 0.305	0.003				0.281	0.056 to 0.506	0.014
Parity at booking												
0	Ref			Ref								
1	0.023	-0.056 to 0.101	0.569	-0.103	-0.183 to -0.023	0.012						
2	0.074	-0.038 to 0.186	0.196	-0.084	-0.199 to 0.031	0.154						
3	0.193	0.052 to 0.334	0.007	0.036	-0.109 to 0.182	0.625						
Birthweight, kg				0.789	0.71 to 0.867	<0.001						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Gestational age at birth, days				-0.014	-0.018 to -0.011	<0.001						
Child sex												
Male							Ref			Ref		
Female							0.466	0.28 to 0.651	<0.001	0.415	0.282 to 0.548	<0.001
Child weight, kg							0.768	0.686 to 0.849	<0.001	0.793	0.744 to 0.841	<0.001
Transformations:												
Maternal age at booking	(Maternal age/10)^-2-.1247146708			(Maternal age/10)^-2-.1244274555								
Maternal BMI at booking	(Maternal BMI/10)^-1-.3908221337			(Maternal BMI/10)^-1-.3906330395			(Maternal BMI/10)^-1-.3843612036			(Maternal BMI/10)^-1-.3865978848		
Birthweight				Birthweight^2								
Gestational age at birth (days)				Gestational age at birth - 278.4223863								
Child weight							Child weight - 9.40670827			Child weight - 12.97302804		
AUC	0.66	0.65 to 0.67		0.69	0.68 to 0.70		0.78	0.77 to 0.80		0.83	0.82 to 0.84	
Calibration slope	1.00			1.00			1.00			1.00		

Table F.2: Estimates of the final models for the prediction of outcome of overweight and obesity (≥91st centile) in children aged 10-11 years using complete cases

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Intercept	0.245	0.17 to 0.354		-1.380	-1.759 to -1.002		-1.373	-1.57 to -1.177		-1.943	-2.278 to -1.609	
Maternal BMI at booking, kg/m^2	0.003	0.000 to 0.001	<0.001	-7.680	-8.327 to -7.033	<0.001	0.098	0.079 to 0.117	<0.001	0.098	0.079 to 0.117	<0.001
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	1.221	1.1 to 1.355	<0.001	0.198	0.09 to 0.306	<0.001	0.247	-0.016 to 0.511	0.066	0.134	-0.118 to 0.387	0.298
Current smoker	1.765	1.559 to 1.998	<0.001	0.616	0.485 to 0.747	<0.001	0.525	0.238 to 0.813	<0.001	0.755	0.474 to 1.036	<0.001
Maternal educational attainment												
University or above	Ref			Ref						Ref		
College	1.295	1.133 to 1.479	<0.001	0.259	0.121 to 0.396	<0.001				0.358	0.02 to 0.696	0.038
Secondary or lower	1.357	1.18 to 1.56	<0.001	0.321	0.178 to 0.465	<0.001				0.396	0.059 to 0.732	0.021

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal employment status												
Employed	Ref			Ref								
Unemployed	0.987	0.892 to 1.092	0.801	-0.014	-0.119 to 0.091	0.789						
Student or in training	1.640	1.239 to 2.172	0.001	0.523	0.236 to 0.809	<0.001						
Maternal ethnicity												
White	Ref			Ref			Ref			Ref		
Mixed	1.725	1.115 to 2.667	0.014	0.613	0.168 to 1.058	0.007	0.783	-0.034 to 1.599	0.060	1.052	0.34 to 1.764	0.004
Asian	2.051	1.651 to 2.547	<0.001	0.817	0.597 to 1.037	<0.001	0.887	0.517 to 1.258	<0.001	0.724	0.345 to 1.103	<0.001
Black/African/Caribbean	2.278	1.489 to 3.485	<0.001	0.932	0.503 to 1.36	<0.001	0.561	-0.13 to 1.251	0.112	0.895	0.203 to 1.586	0.011
Other	1.419	0.912 to 2.208	0.121	0.433	-0.007 to 0.872	0.054	0.867	0.037 to 1.698	0.041	0.795	0.001 to 1.589	0.050
Maternal first language English												
No	Ref			Ref								
Yes	0.747	0.532 to 1.05	0.093	-0.248	-0.594 to 0.097	0.159						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref								
Started taking once pregnant	1.183	1.067 to 1.311	0.001	0.161	0.053 to 0.268	0.003						
Not taking supplement	1.201	1.035 to 1.393	0.016	0.150	-0.005 to 0.305	0.057						
Partnership status at booking												
Partnered				Ref			Ref					
Single				0.154	-0.001 to 0.309	0.052	0.261	-0.042 to 0.565	0.092			
Birthweight, kg				0.338	0.238 to 0.438	<0.001						
Gestational age at birth, days				-0.006	-0.011 to -0.002	0.003						
Child sex												
Male				Ref						Ref		
Female				-0.213	-0.304 to -0.122	<0.001				0.191	-0.018 to 0.4	0.074
Child weight, kg							0.386	0.293 to 0.479	<0.001	0.670	0.557 to 0.783	<0.001

Predictors	Booking	Birth	Early life (~1 year)	Early life (~2 years)
	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) p
Transformations:				
Maternal BMI at booking	(Maternal BMI/10)^-1-.3973109743	(Maternal BMI/10)^-1-.3971708095	Maternal BMI - 25.36115221	Maternal BMI - 25.31718245
Birthweight		Birthweight - 3.399680197		
Gestational age at birth		Gestational age at birth - 278.1002025		
Child weight			Child weight - 9.146992607	Child weight ^3-2.179592732
Discrimination and calibration:				
AUC	0.68 0.67 to 0.70	0.69 0.68 to 0.70	0.71 0.68 to 0.73	0.73 0.71 to 0.75
Calibration slope	1.00	1.00	1.00	1.00

Table F.3: Estimates of the final models for the prediction of outcome of overweight and obesity (≥91st centile) in second-born children aged 4-5 years using complete cases

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Intercept	-1.926	-2.038 to -1.814		-2.020	-2.137 to -1.904		-2.477	-2.772 to -2.183		-2.567	-2.882 to -2.253	
Maternal age at booking, years	-0.024	-0.039 to -0.009	0.002	-0.031	-0.047 to -0.016	<0.001						
Baseline maternal BMI at booking, kg/m^2	-9.083	-10.427 to -7.739	<0.001	-8.200	-9.567 to -6.833	<0.001	0.069	0.038 to 0.101	<0.001	0.049	0.016 to 0.082	0.003
Maternal BMI change from previous pregnancy, kg/m^2	0.022	-0.003 to 0.047	0.079				0.103	0.049 to 0.157	<0.001			
Maternal ethnicity												
White	Ref			Ref			Ref					
Mixed	-0.212	-1.02 to 0.595	0.607	-0.051	-0.859 to 0.758	0.902	-	-	-			
Asian	0.552	0.212 to 0.892	0.001	0.753	0.408 to 1.098	<0.001	1.000	0.481 to 1.519	<0.001			
Black/African/Caribbean	0.512	-0.069 to 1.093	0.084	0.629	0.043 to 1.215	0.035	0.027	-1.06 to 1.114	0.961			
Other	-0.230	-1.274 to 0.813	0.665	-0.217	-1.274 to 0.84	0.687	0.701	-1.039 to 2.44	0.430			

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Maternal smoking status at booking												
Never smoked	Ref			Ref								
Ex-smoker	0.168	-0.005 to 0.34	0.056	0.148	-0.026 to 0.323	0.096						
Current smoker	0.423	0.198 to 0.648	<0.001	0.587	0.355 to 0.819	<0.001						
Interpregnancy interval, months				0.006	0.001 to 0.01	0.016						
Birthweight, kg				0.840	0.674 to 1.005	<0.001						
Gestational age at birth, days				-0.014	-0.022 to -0.005	0.002						
Maternal BMI change from previous pregnancy							0.103	0.049 to 0.157	<0.001			
Child sex												
Male							Ref			Ref		
Female							0.671	0.318 to 1.024	<0.001	0.405	0.026 to 0.784	0.036
Infant weight							0.700	0.548 to 0.851	<0.001	0.861	0.725 to 0.997	<0.001

Predictors	Booking	Birth	Early life (~1 year)	Early life (~2 years)
	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) P
Transformations				
Maternal age at booking	Maternal age at booking-28.94719634	Maternal age at booking-28.94719634		
Baseline maternal BMI	(Baseline maternal BMI/10)^-2-.1646985078	(Baseline maternal BMI/10)^-2-.1646985078	Baseline maternal BMI - 24.81409338	Baseline maternal BMI - 24.97827557
Maternal BMI change from previous pregnancy	Maternal BMI change from previous pregnancy - 1.121808098		Maternal BMI change from previous pregnancy - 1.392795008	
Interpregnancy interval		Interpregnancy interval - 26.00073463		
Birthweight, kg		Birthweight - 3.515982835		
Gestational age at birth, days		Gestational age at birth - 279.4490763		
Infant weight			Infant weight - 9.434509098	Infant weight - 13.06729502
Area under the curve	0.66 0.64 to 0.68	0.69 0.67 to 0.71	0.76 0.73 to 0.80	0.83 0.79 to 0.86

Appendix G Complete case analysis for the population monitoring outcome of ≥85th centile

Table G.1: Estimates of the final models for the prediction of outcome of overweight and obese using the population monitoring cut-off of ≥85th centile in children aged 4-5 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Intercept	-1.069	-1.266 to -0.872		-1.198	-1.399 to -0.997		-1.985	-2.203 to -1.768		-1.946	-2.193 to -1.699	
Mother age at booking, years	1.495	0.990 to 1.999	<0.001	1.451	0.931 to 1.971	<0.001						
Maternal BMI at booking, kg/m^2	-7.980	-8.511 to -7.448	<0.001	-5.598	-6.013 to -5.184	<0.001	-6.166	-7.173 to -5.159	<0.001	-5.499	-6.616 to -4.383	<0.001
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	0.066	-0.004 to 0.137	0.066	0.059	-0.013 to 0.13	0.061	0.058	-0.119 to 0.235	0.519	-0.052	-0.238 to 0.135	0.586
Current smoker	0.334	0.246 to 0.422	<0.001	0.497	0.407 to 0.588	0.599	0.586	0.361 to 0.811	<0.001	0.415	0.167 to 0.662	0.001

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal ethnicity												
White	Ref			Ref								
Mixed	0.039	-0.246 to 0.324	0.790	0.098	-0.196 to 0.392	0.514	0.375	-0.247 to 0.997	0.238			
Asian	0.072	-0.070 to 0.213	0.320	0.238	0.094 to 0.382	0.001	0.427	0.140 to 0.713	0.003			
Black/African/Caribbean	0.398	0.163 to 0.633	0.001	0.510	0.269 to 0.751	<0.001	0.268	-0.188 to 0.724	0.250			
Other	0.023	-0.297 to 0.343	0.888	0.020	-0.300 to 0.340	0.902	-0.124	-0.895 to 0.646	0.752			
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref			Ref			Ref		
Started taking once pregnant	0.099	0.028 to 0.170	0.006	0.129	0.057 to 0.202	<0.001	0.236	0.055 to 0.416	0.011	0.257	0.058 to 0.456	0.011
Not taking supplement	0.050	-0.062 to 0.163	0.382	0.067	-0.049 to 0.184	0.258	0.275	-0.019 to 0.569	0.066	0.203	-0.159 to 0.565	0.272
Maternal first language English												
No	Ref			Ref								
Yes	-0.330	-0.516 to -0.145	<0.001	-0.310	-0.497 to -0.123	0.001						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Partnership status												
No	Ref			Ref						Ref		
Yes	0.176	0.072 to 0.280	0.001	0.181	0.074 to 0.288	0.001				0.350	0.046 to 0.654	0.024
Parity at booking												
0	Ref			Ref								
1	0.043	-0.024 to 0.110	0.173	-0.063	-0.133 to 0.006	0.075						
2	0.112	0.016 to 0.208	0.020	-0.007	-0.106 to 0.092	0.893						
3	0.172	0.044 to 0.300	0.008	0.062	-0.069 to 0.193	0.353						
Gestational diabetes in previous pregnancy												
No	Ref			Ref						Ref		
Yes	-0.276	-0.589 to 0.037	0.084	-0.416	-0.751 to -0.08	0.015				-0.883	-2.18 to 0.415	0.182
Birthweight in kg				0.790	0.721 to 0.858	<0.001						
Gestation (days) at birth				-0.014	-0.017 to -0.011	<0.001						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Mode of birth												
Vaginal				Ref						Ref		
Caesarean section				0.072	-0.001 to 0.145	0.054				0.158	-0.039 to 0.355	0.115
Child gender												
Male							Ref					
Female							0.420	0.260 to 0.580	<0.001	0.414	0.242 to 0.586	<0.001
Infant weight							0.760	0.687 to 0.832	<0.001	0.822	0.756 to 0.887	<0.001
Duration of breastfeeding												
No breastfeeding										Ref		
Minimum 10 days										-0.360	-0.588 to -0.132	0.002
Minimum 6 weeks										-0.105	-0.324 to 0.113	0.346
Minimum 8 weeks										0.403	0.094 to 0.711	0.011
Minimum 4 months										0.103	-1.305 to 1.51	0.886

Predictors	Booking	Birth	Early life (~1 year)	Early life (~2 years)
	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) p
9 months				0.141 -0.897 to 0.790 1.18
Transformations:				
Maternal age	(Maternal age/10)^ -2- 0.1244248493	(Maternal age/10) ^- 2-.1241453016		Maternal age- 28.56244985
Maternal BMI	(Maternal BMI/10)^ -2- 0.152642556	(Maternal BMI/10) ^- 1-.3904225831	(Maternal BMI/10) ^- 1-.3843612036	(Maternal BMI/10 ^- 1-.3827202009
Birthweight		Birthweight -3.404969028		
Gestation (days) at birth transformation		Gestation (days) at birth - 278.50377		
Infant weight at 1 year transformation			Infant weight at 1 year-- 9.40670827	Infant weight at 2 years - 13.08137301
Discrimination:				
Area under the curve	0.64 0.63 to 0.65	0.67 0.66 to 0.68	0.77 0.75 to 0.78	0.82 0.81 to 0.84

Table G.2: Estimates of the final models for the prediction of outcome of overweight and obese in children aged 10-11 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Intercept	-0.837	-1.187 to -0.486		-0.815	-1.174 to -0.457		-1.009	-1.265 to -0.753		-1.268	-1.461 to -1.074	
Maternal BMI at booking, kg/m^2	-8.006	-8.601 to -7.412	<0.001	-7.607	-8.214 to -7.000	<0.001	-8.837	-10.563 to -7.111	<0.001	0.091	0.072 to 0.109	<0.001
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	0.189	0.091 to 0.288	<0.001	0.188	0.089 to 0.287	<0.001	0.258	0.012 to 0.503	0.039	0.221	-0.012 to 0.455	0.063
Current smoker	0.497	0.376 to 0.619	<0.001	0.577	0.453 to 0.700	<0.001	0.540	0.268 to 0.812	<0.001	0.763	0.503 to 1.023	<0.001
Maternal educational attainment												
Undergraduate or above	Ref			Ref								
College	0.186	0.064 to 0.309	0.003	0.198	0.074 to 0.322	0.002						
Secondary school or lower	0.198	0.069 to 0.327	0.003	0.213	0.083 to 0.343	0.001						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal employment status												
Employed	Ref			Ref								
Unemployed	-0.016	-0.113 to 0.081	0.742	-0.010	-0.108 to 0.087	0.836						
Student or in training	0.518	0.241 to 0.795	<0.001	0.510	0.232 to 0.788	<0.001						
Maternal ethnicity												
White	Ref			Ref			Ref			Ref		
Mixed	0.582	0.145 to 1.019	0.009	0.613	0.167 to 1.058	0.007	0.812	-0.006 to 1.631	0.052	1.327	0.535 to 2.119	0.001
Asian	0.622	0.418 to 0.826	<0.001	0.721	0.514 to 0.928	<0.001	0.705	0.333 to 1.077	<0.001	0.732	0.377 to 1.088	<0.001
Black/African/Caribbean	0.756	0.34 to 1.172	<0.001	0.838	0.42 to 1.257	<0.001	0.344	-0.336 to 1.023	0.321	0.965	0.291 to 1.638	0.005
Other	0.474	0.059 to 0.889	0.025	0.511	0.092 to 0.93	0.017	0.861	0.025 to 1.697	0.044	1.161	0.365 to 1.957	0.004
Maternal first language English												
No	Ref			Ref								
Yes	-0.391	-0.716 to -0.065	0.019	-0.362	-0.692 to -0.031	0.032						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref			Ref					
Started taking once pregnant	0.177	0.079 to 0.276	<0.001	0.175	0.076 to 0.274	0.001	0.253	-0.009 to 0.515	0.058			
Not taking supplement	0.148	0.005 to 0.291	0.042	0.147	0.003 to 0.291	0.046	0.251	-0.078 to 0.581	0.135			
Obstetric history of GDM												
No	Ref			Ref								
Yes	-0.370	-0.828 to 0.089	0.114	-0.406	-0.874 to 0.063	0.090						
Partnership status at booking												
Partnered	Ref			Ref								
Single	0.127	-0.017 to 0.272	0.084	0.132	-0.014 to 0.278	0.076						
Birthweight, kg				0.354	0.259 to 0.448	<0.001						
Gestational age at birth, days				-0.006	-0.01 to -0.002	0.004						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Gender												
Male				Ref						Ref		
Female				-0.198	-0.282 to -0.113	<0.001				0.224	0.027 to 0.421	0.026
Infant weight, kg							0.361	0.272 to 0.449	<0.001	0.369	0.309 to 0.43	<0.001
GDM in current pregnancy												
No							Ref					
Yes							0.766	-0.136 to 1.668	0.096			
Pre-eclampsia in current pregnancy												
No				Ref								
Yes				0.475	-0.053 to 1.003	0.078						
Transformations:												
Maternal BMI	(Maternal BMI/10)^-1			(Maternal BMI/10)^-1			(Maternal BMI/10)^-1			(Maternal BMI/10)^-1		
Birthweight				Birthweight -3.399680197								
Gestation at birth				Gestation at birth -278.1002025								

Predictors	Booking	Birth	Early life (~1 year)	Early life (~2 years)
	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) p
Infant weight			Infant weight at 1 year - 9.146992607	Infant weight at 2 years - 12.96545245
Discrimination:				
AUC	0.68 0.67 to 0.69	0.69 0.68 to 0.70	0.70 0.68 to 0.73	0.72 0.70 to 0.74

Table G.3: Estimates of the final models for the prediction of outcome of overweight and obesity (using population monitoring cut-off of 85th centile or above) in second-born children aged 4-5 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Constant	-1.315	-1.407 to -1.223		-1.447	-1.563 to -1.331		-1.859	-2.138 to -1.58		-1.814	-1.99 to -1.637	
Maternal age at booking	-0.032	-0.045 to -0.019	<0.001	-0.035	-0.048 to -0.022	<0.001				-0.041	-0.063 to -0.02	<0.001
Maternal BMI at booking	-8.160	-9.278 to -7.042	<0.001	-7.352	-8.495 to -6.209	<0.001	0.081	0.053 to 0.108	<0.001	0.069	0.048 to 0.09	<0.001
Interval from previous pregnancy (in months)	0.004	0.001 to 0.008	0.025	0.005	0.001 to 0.009	0.014				0.009	0.002 to 0.015	0.009
Maternal BMI change from previous pregnancy	0.031	0.009 to 0.052	0.006	0.023	0.001 to 0.045	0.042	0.082	0.034 to 0.129	0.001			

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Maternal ethnicity												
White	Ref			Ref			Ref					
Mixed	-0.507	-1.233 to 0.219	0.171	-0.378	-1.106 to 0.35	0.309	-1.171	-3.298 to 0.955	0.280			
Asian	0.360	0.063 to 0.656	0.017	0.580	0.277 to 0.883	<0.001	0.885	0.394 to 1.377	<0.001			
Black/African/Caribbean	0.271	-0.251 to 0.793	0.309	0.385	-0.144 to 0.914	0.154	0.210	-0.677 to 1.097	0.643			
Other	0.003	-0.78 to 0.785	0.995	0.019	-0.778 to 0.815	0.964	0.171	-1.547 to 1.89	0.845			
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref					
Ex-smoker	0.140	-0.005 to 0.284	0.058	0.138	-0.008 to 0.284	0.065	0.091	-0.25 to 0.431	0.603			
Current smoker	0.260	0.064 to 0.456	0.009	0.452	0.251 to 0.654	<0.001	0.544	0.141 to 0.946	0.008			
Birthweight				0.834	0.689 to 0.979	<0.001						
Gestational age at birth				-0.011	-0.019 to -0.004	0.002				0.008	-0.009 to 0.024	0.356

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Gender												
Male				Ref			Ref					
Female				0.099	-0.029 to 0.227	0.128	0.479	0.179 to 0.778	0.002	0.313	0.083 to 0.542	0.008
Infant weight, kg							0.729	0.593 to 0.866	<0.001	0.796	0.709 to 0.883	<0.001
Transformations:												
Maternal age at booking, years				Maternal age at booking - 28.94719634						Maternal age at booking - 29.2457265		
Baseline maternal BMI, kg/m^2				(Baseline maternal BMI/10)^-2-.1646985078			Baseline maternal BMI - 24.78718142			Baseline maternal BMI - 24.82568376		
Maternal BMI change from previous pregnancy, kg/m^2				Maternal BMI change - 1.121808098			Maternal BMI change - 1.384864942					
Interpregnancy interval, months				Interpregnancy interval - 26.00073463						Interpregnancy interval - 27.1294173		
Birthweight, kg				Birthweight -3.515982835								
Gestational age at birth, days				Gestational age at birth - 279.4490763								
Child weight, kg							Child weight at 1 year - 9.434845552			Child weight at 2 years - 12.93801496		
AUC	0.65 0.63 to 0.66			0.68 0.66 to 0.69			0.76 0.73 to 0.79			0.80 0.79 to 0.83		

Appendix H Complete case analysis for the population monitoring outcome of ≥95th centile

Table H.1: Estimates of the final models for the prediction of outcome of obese (excluding overweight) using the population monitoring cut-off of ≥95th centile in children aged 4-5 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Intercept	-2.081	-2.348 to -1.814		-2.215	-2.506 to -1.925		-2.775	-3.043 to -2.508		-3.501	-3.833 to -3.169	
Maternal age at booking	1.952	1.213 to 2.691	<0.001	1.648	0.864 to 2.432	<0.001				-0.026	-0.050 to -0.001	0.039
Gestational age at booking	0.001	-0.001 to 0.004	0.194									
Maternal BMI at booking	-8.609	-9.191 to -8.027	<0.001	-7.930	-8.53 to -7.33	<0.001	-7.931	-9.361 to -6.501	<0.001	0.085	0.067 to 0.103	<0.001
Smoking status at booking												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	0.157	0.05 to 0.264	0.004	0.130	0.021 to 0.238	0.019	0.120	-0.134 to 0.375	0.355	0.230	-0.060 to 0.520	0.121
Current smoker	0.600	0.476 to 0.725	<0.001	0.744	0.613 to 0.874	<0.001	0.863	0.561 to 1.165	<0.001	0.407	0.028 to 0.786	0.035

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Maternal ethnicity												
White	Ref						Ref			Ref		
Mixed	0.184	-0.233 to 0.601	0.388	0.296	-0.124 to 0.716	0.168	0.787	-0.134 to 1.708	0.094	0.132	-0.736 to 1.000	0.765
Asian	0.449	0.254 to 0.644	<0.001	0.637	0.438 to 0.836	<0.001	0.960	0.574 to 1.347	<0.001	0.862	0.333 to 1.391	0.001
Black/African/Caribbean	0.842	0.536 to 1.148	<0.001	1.005	0.695 to 1.315	<0.001	0.801	0.211 to 1.391	0.008	0.861	0.113 to 1.609	0.024
Other	0.216	-0.219 to 0.651	0.331	0.256	-0.188 to 0.7	0.259	0.579	-0.399 to 1.558	0.246	0.118	-1.201 to 1.437	0.860
Maternal intake of folic acid supplements												
Taking prior to pregnancy	Ref			Ref								
Started taking once pregnant	0.098	-0.009 to 0.205	0.072	0.124	0.015 to 0.232	0.025						
Not taking supplement	0.009	-0.158 to 0.175	0.917	0.053	-0.114 to 0.22	0.533						
Maternal first language English												
No	Ref			Ref								
Yes	-0.467	-0.715 to -0.22	<0.001	-0.453	-0.71 to -0.196	0.001						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Partnership status at booking												
No	Ref			Ref						Ref		
Yes	0.211	0.063 to 0.358	0.005	0.225	0.074 to 0.376	0.003				0.462	0.03 to 0.893	0.036
Parity at booking												
0	Ref			Ref								
1	0.008	-0.092 to 0.107	0.876	-0.140	-0.242 to -0.037	0.008						
2	0.118	-0.021 to 0.257	0.097	-0.042	-0.186 to 0.102	0.570						
3	0.222	0.047 to 0.396	0.013	0.072	-0.109 to 0.252	0.437						
Obstetric history of pre-eclampsia												
No	Ref											
Yes	-0.939	-2.38 to 0.501	0.201									
Birthweight				0.841	0.74 to 0.942	<0.001						
Gestational age at birth				-0.014	-0.018 to -0.009	<0.001						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Maternal educational attainment												
University or higher				Ref								
College				0.115	-0.014 to 0.245	0.081						
Secondary or lower				0.136	-0.005 to 0.277	0.059						
Gender												
Male							Ref			Ref		
Female							0.513	0.287 to 0.74	<0.001	0.593	0.332 to 0.855	<0.001
Infant weight at 1 year							0.870	0.770 to 0.970	<0.001	-23.116	-25.489 to -20.743	<0.001
										-48.867	-56.098 to -41.635	<0.001
Breastfeeding duration												
No breastfeeding							Ref			Ref		
Minimum 10 days							-0.181	-0.461 to 0.099	0.205	-0.593	-0.947 to -0.239	0.001
Minimum 6 weeks							-0.428	-0.729 to -0.126	0.005	-0.320	-0.663 to 0.023	0.067

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Minimum 8 weeks							-0.949	-1.487 to -0.411	0.001	0.309	-0.18 to 0.797	0.216
Minimum 4 months							0.485	-1.113 to 2.083	0.552	1.120	-0.276 to 2.517	0.116
9 months							-1.177	-2.204 to -0.149	0.025	-1.590	-2.939 to -0.24	0.021
Transformations:												
Maternal age	(Maternal age/10)^ -2-0.1241214058			(Maternal age/10)^ -2-0.1241223403						Maternal age – 28.33567378		
Gestation at booking	Gestation at booking - 79.24167345											
Maternal BMI	(Maternal BMI/10)^ -1-0.3934073369			(Maternal BMI/10)^ -1-0.3933236031			(Maternal BMI/10)^ -1-0.3875345174			Maternal BMI - 25.92338645		
Birthweight				Birthweight - 3.397572443								
Gestation at birth				Gestation at birth - 278.7484214								
Infant weight							Infant weight at 1 year - 9.316279639			(Infant weight at 2 years/10) ^-2-0.5957693836 (Infant weight at 2 years/10) ^-2*ln(Infant weight at 2 years/10)-0.1542749666		
Area under the curve	0.70 0.69 to 0.71			0.73 0.72 to 0.74			0.82 0.80 to 0.84			0.89 0.87 to 0.90		

Table H.2: Estimates of the final models for the prediction of outcome of obesity (excluding overweight) in children aged 10-11 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Constant	-1.657	-2.081 to -1.232		-1.636	-2.071 to -1.202		-1.663	-1.888 to -1.437		-2.456	-2.886 to -2.027	
Maternal BMI at booking, kg/m^2	-11.475	-12.368 to -10.582	<0.001	-11.062	-11.975 to -10.149	<0.001	0.108	0.087 to 0.129	<0.001	0.108	0.087 to 0.13	<0.001
Maternal smoking status												
Never smoked	Ref			Ref			Ref			Ref		
Ex-smoker	0.221	0.097 to 0.345	<0.001	0.215	0.090 to 0.340	0.001	0.347	0.048 to 0.646	0.023	0.106	-0.191 to 0.402	0.485
Current smoker	0.615	0.468 to 0.761	<0.001	0.679	0.530 to 0.828	<0.001	0.590	0.260 to 0.919	<0.001	0.828	0.505 to 1.152	<0.001
Maternal educational attainment												
University or higher	Ref			Ref						Ref		
College	0.310	0.148 to 0.471	<0.001	0.331	0.169 to 0.494	<0.001				0.439	0.022 to 0.855	0.039
Secondary or lower	0.331	0.162 to 0.500	<0.001	0.346	0.176 to 0.517	<0.001				0.325	-0.100 to 0.750	0.134

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Maternal employment												
Employed	Ref			Ref						Ref		
Unemployed	0.009	-0.111 to 0.129	0.883	0.030	-0.091 to 0.150	0.628				0.213	-0.055 to 0.48	0.119
Student or in training	0.404	0.062 to 0.745	0.020	0.418	0.074 to 0.761	0.017				-1.113	-2.503 to 0.277	0.116
Maternal intake of folic acid												
Prior to pregnancy	Ref			Ref								
Started taking once pregnant	0.246	0.121 to 0.372	<0.001	0.245	0.118 to 0.371	<0.001						
Not taking supplement	0.224	0.046 to 0.402	0.014	0.232	0.054 to 0.411	0.011						
Maternal ethnicity												
White	Ref			Ref			Ref			Ref		
Mixed	0.559	0.051 to 1.067	0.031	0.602	0.088 to 1.116	0.022	0.836	-0.136 to 1.808	0.092	1.247	0.397 to 2.097	0.004
Asian	0.732	0.482 to 0.982	<0.001	0.826	0.574 to 1.079	<0.001	0.948	0.529 to 1.366	<0.001	0.762	0.318 to 1.207	0.001
Black/African/ Caribbean	1.129	0.666 to 1.593	<0.001	1.224	0.763 to 1.685	<0.001	0.741	-0.01 to 1.492	0.053	1.291	0.517 to 2.065	0.001

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Other	0.458	-0.047 to 0.964	0.076	0.470	-0.039 to 0.980	0.070	0.466	-0.632 to 1.564	0.405	0.976	-0.090 to 2.041	0.073
Maternal first language English												
No	Ref			Ref								
Yes	-0.490	-0.876 to -0.104	0.013	-0.442	-0.835 to -0.049	0.028						
Partnership status												
No	Ref			Ref			Ref					
Yes	0.189	0.012 to 0.365	0.036	0.190	0.012 to 0.368	0.037	0.286	-0.063 to 0.634	0.108			
Family history of hypertensive disorders												
No	Ref			Ref						Ref		
Yes	0.122	0.01 to 0.233	0.033	0.131	0.019 to 0.243	0.022				0.279	0.022 to 0.536	0.034
Birthweight, kg				0.301	0.203 to 0.399	<0.001						

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p
Gender												
Male				Ref						Ref		
Female				-0.264	-0.368 to -0.159	<0.001				0.212	-0.035 to 0.458	0.092
Pre-eclampsia in current pregnancy												
No				Ref								
Yes				0.750	0.101 to 1.400	0.024						
Infant weight							0.429	0.323 to 0.535	<0.001	0.769	0.637 to 0.901	<0.001
Transformations:												
Maternal BMI	(Maternal BMI/10) ^-.5-0.6322211018			(Maternal BMI/10) ^-.5-0.6321191191			Maternal BMI - 25.26864197			Maternal BMI -25.25374332		
Birthweight				Birthweight - 3.389632931								
Infant weight							Infant weight at 1 year - 9.124277783			(Infant weight at 2 years/10)^3-2.152920712		
Area under the curve	0.72 0.70 to 0.73			0.72 0.71 to 0.74			0.74 0.71 to 0.76			0.77 0.74 to 0.79		

Table H.3: Estimates of the final models for the prediction of outcome of obesity (excluding overweight) in second-born children aged 4-5 years

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Intercept	-2.484	-2.63 to -2.337		-2.596	-2.75 to -2.442					-3.425	-3.887 to -2.963	
Maternal age at booking, years	-0.027	-0.045 to -0.008	0.006	-0.028	-0.048 to -0.009	0.004						
Baseline maternal BMI at booking (first pregnancy), kg/m^2	-8.265	-9.556 to -6.973	<0.001	-7.706	-9.035 to -6.378	<0.001	0.092	0.06 to 0.124	<0.001	0.056	0.012 to 0.099	0.012
Maternal BMI change from previous pregnancy, kg/m^2	0.044	0.013 to 0.075	0.005	0.036	0.004 to 0.067	0.025	0.084	0.023 to 0.145	0.007	0.081	0.001 to 0.161	0.048
Maternal ethnicity												
White	Ref			Ref			Ref					
Mixed	0.252	-0.567 to 1.07	0.546	0.395	-0.426 to 1.216	0.346	-0.132	-2.244 to 1.98	0.902			
Asian	0.619	0.195 to 1.044	0.004	0.807	0.369 to 1.246	<0.001	1.097	0.489 to 1.705	<0.001			
Black/African/Caribbean	0.828	0.179 to 1.478	0.012	0.990	0.331 to 1.648	0.003	1.001	-0.009 to 2.011	0.052			
Other	0.383	-0.674 to 1.44	0.478	0.425	-0.655 to 1.506	0.440	1.379	-0.075 to 2.832	0.063			

Predictors	Booking			Birth			Early life (~1 year)			Early life (~2 years)		
	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	p	Coef	(95% CI)	P
Maternal smoking status at booking												
Never smoked	Ref			Ref			Ref					
Ex-smoker	0.249	0.031 to 0.466	0.025	0.234	0.013 to 0.455	0.038	0.355	-0.055 to 0.764	0.089			
Current smoker	0.537	0.259 to 0.814	<0.001	0.684	0.394 to 0.974	<0.001	0.757	0.247 to 1.268	0.004			
Birthweight, kg				0.844	0.654 to 1.033	<0.001						
Gender												
Male							Ref			Ref		
Female							0.339	-0.029 to 0.707	0.071	0.382	-0.12 to 0.885	0.136
Infant weight, kg							0.785	0.631 to 0.938	<0.001	1.097	0.906 to 1.287	<0.001
Transformations:												
Maternal age at booking	Maternal age - 29.05188679			Maternal age - 29.06971844								
Maternal BMI at booking	(Maternal BMI at booking/10) ^-1-.4088414668			(Maternal BMI at booking/10) ^-1-.4086069642			Maternal BMI at booking - 24.73754865			Maternal BMI at booking - 24.73754865		

Predictors	Booking	Birth	Early life (~1 year)	Early life (~2 years)
	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) p	Coef (95% CI) P
Maternal BMI change from previous pregnancy	Maternal BMI change - 1.090396251	Maternal BMI change - 1.092894106	Maternal BMI change - 24.52550759	Maternal BMI change - 1.30564203
Birthweight, kg		Birthweight - 3.498831643		
Infant weight, kg			Infant weight at 1 year - 9.427715734	Infant weight at 2 years - 12.94859923
AUC	0.69 0.67 to 0.72	0.73 0.71 to 0.75	0.79 0.75 to 0.83	0.89 0.87 to 0.91

Appendix I Validation of existing models

Table I.1: Summary of discrimination values for the two existing prediction models that could be applied to the SLOPE dataset

	Discrimination (AUC, 95% CI)		
	Published development or validation	Year R	Year 6
(Druet *et al.*, 2012)	0.77 0.74 to 0.81	0.77 0.75 to 0.79	0.69 0.66 to 0.72
(Santorelli *et al.*, 2013)			
Model at 1 year excluding maternal BMI	0.91 87.8 to 94.4	0.70 0.69 to 0.71	0.59 0.57 to 0.62
Model at 1 year including maternal BMI		0.71 0.70 to 0.72	0.60 0.58 to 0.63

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