# Change in modifiable maternal characteristics and behaviours between consecutive pregnancies and offspring adiposity: a systematic review

## Abstract

### Background

Causal evidence links modifiable maternal exposures during the periconceptional period with offspring obesity. The interconception period may be an important time to intervene. We systematically identified studies examining change in modifiable maternal exposures between pregnancies and offspring adiposity.

### Methods

We searched for longitudinal studies published between 1990 and 2019, which included measurements taken on at least two occasions in the period from one year prior to the conception of the first birth to the time of the second birth, and which included a measure of adiposity in second, or higher order, siblings. Age, ethnicity and genetics were not considered modifiable; all other factors including length of the interpregnancy interval were.

### Results

Eleven studies satisfied the inclusion criteria. Higher interpregnancy weight gain or loss, maternal smoking inception, mothers smoking in their first pregnancy and quitting, increasing the number of cigarettes smoked and longer interpregnancy intervals were positively associated with adiposity in second or higher order children. Vaginal birth after caesarean delivery was protective.

### Conclusion

Further research is needed to ascertain whether the risk of adiposity is fixed based on first pregnancy exposures or if interpregnancy change alters the risk for a subsequent child. This can inform the type and effectiveness of interventions for mothers prior to a subsequent pregnancy.

## Introduction

The World Health Organisation estimated that in 2016 there were 41 million children worldwide under the age of 5 and 340 million children and adolescents aged 5 - 19 who were affected by overweight or obesity 1. More than 1.9 billion adults were affected by overweight and, of these, 650 million (11% of men and 15% of women) were affected by obesity 1. Early intervention and prevention is key since childhood weight is strongly associated with adult weight 2 and obesity raises the risk of many non-communicable diseases including cardiovascular disease 3, type 2 diabetes 4, osteoarthritis 5, other musculoskeletal disorders 6 and a number of different types of cancer 1.

The Developmental Origins of Health and Disease (DOHaD) concept links exposures during the periconceptional period and pregnancy to lasting effects on developmental programming of the foetus and to subsequent susceptibility to non-communicable disease 7. A number of modifiable maternal characteristics and behaviours in the preconception, pregnancy and interpregnancy period (defined by the World Health Organisation as the period from the birth of one child until the conception of the subsequent pregnancy 8) have been associate with offspring adiposity 9-12. These include, but are not limited to maternal obesity, with or without maternal gestational diabetes mellitus (GDM) 13, gestational weight gain 14, smoking 15, severe pre-pregnancy stress 16 , birth by caesarean section 17and inequalities in socioeconomic status18,19.

Whilst there is much in the literature examining associations between the exposures in one pregnancy and the outcome for that child, there is little research on whether this risk is then fixed for subsequent children based on those earlier predictors, or whether a change in exposure between pregnancies changes the risk for a subsequent child. The majority of research which has examined interpregnancy change focuses on birth or neonatal outcomes such as large or small-for-gestational-age and premature birth 20-23.

We aimed to systematically review the literature for longitudinal studies which characterised modifiable maternal exposures between successive live pregnancies and determine their associations with adiposity in second, or higher order siblings.

## Methods

### Search Strategy

An electronic search was conducted using the bibliographic databases EMBASE (via Ovid), MEDLINE (via Ovid), CINAHL (via EBSCO), PsycINFO (via EBSCO) and Web of Science. A specialist librarian was consulted in advance and the search was run on 30 March 2019. Studies were restricted to those based on human participants, and published in English since 1990 to ensure that only the most up- to-date literature was reviewed. The protocol for this review was published on the international prospective register of international reviews, PROSPERO, reference CRD42019124344 24 and this review is reported in line with the PRISMA guidelines 25. The following search strategy was piloted on EMBASE and adapted for the other platforms:

[exp family planning/] OR ((interpregnan\* or inter-pregnan\* or consecutive pregnan\* or interconception or inter-conception or between pregnan\* or family planning or inter-natal or multipar\* or multigravid\* or conception).mp.)] AND

[exp obesity/ OR exp body mass/ OR exp overnutrition/ OR ((obes\* or overweight or overnutrition or adiposity or weight or body mass).mp.)] AND

[exp progeny/ OR exp child/ or exp sibling/ OR ((child\* or offspring or infant or sibling\* or progeny).mp.)]

### Inclusion and exclusion criteria

We only included longitudinal studies. Case control studies, cross sectional studies and case reports were excluded.

We did not consider age, ethnicity or genetics to be modifiable, but considered all other maternal behaviours and characteristics to be potentially modifiable exposures. Studies where measurements of the main exposure were taken on at least two occasions in the period from one year prior to the conception of the first pregnancy up to the time of the second birth were considered. At least one measurement should have been recorded in the period from one year prior to the conception of the first pregnancy and the first birth (Period 1) and at least one in the period from the time of the first birth to the time of the second birth (Period 2). Figure 1 below represents the relevant timeline.

The length of the inter-pregnancy interval was specifically included as a modifiable exposure as defined per individual study, even if the World Health Organisation definition of the interpregnancy interval was not used (the period from the birth of one child to the conception of the subsequent pregnancy) 8.

We considered studies where outcomes included a measure of adiposity in second or higher order siblings. Appropriate outcome measurements included categorical and continuous offspring BMI, weight for height z-scores, skinfold measurements and body adiposity. All time points were considered after the age of 1, without an upper age limit. The lower bound was given as 1 year to exclude studies focussing on neonatal outcomes, including foetal macrosomia.

### Screening process

The screening management software Rayyan 26 was used to screen titles for eligibility. A randomly selected sample of 10% of these titles were independently screened by two reviewers (EJT and SW). A 10% sample was chosen as a recent simulation study has shown that if the fraction being sampled for independent review is increased, there is no decrease in selection bias 27. At the title screening stage, the percentage agreement between the two reviewers was 98.9% and discrepant titles were included for abstract screening. One author (EJT) reviewed the remaining titles. The same process was then followed for reviewing the abstracts of papers remaining after title screening. The agreement rate between the two reviewers (EJT and SW) was 100% and, accordingly, one author (EJT) reviewed the remaining abstracts.

Following abstract screening, the full texts of the remaining titles were accessed and reviewed by two reviewers (EJT and SW), with one exception where the discrepant title was only considered by one reviewer (EJT), due to copyright restrictions, and was excluded in any event.

### Data extraction, quality assessment and analysis

A modified version of the Cochrane Collaboration data extraction form was used to conduct data extraction 28 and this was undertaken by two reviewers (EJT and SW or EJT and NZ).

All eligible data were extracted, including for sub-group analysis and exposure multiple time points where these were reported. Where reported, confidence intervals which did not overlap the null were used to identify statistically significant associations. If these where not reported, *p*-values were used.

Quality assessment was also undertaken by two reviewers (EJT and SW). Key strengths and weaknesses of each of the cohort studies 29-38 were formed using the National Heart Lung and Blood Institute assessment tool for observational cohort and cross-sectional studies 39. The remaining study is an individual patient data meta-analysis 40, and in this instance, we used the PRISMA-IPD checklist 41. The overall rating for addressing the risk of bias (good/fair/poor) is included in Table 1.

Since we expected significant variation in study exposures and design, a qualitative synthesis was planned *a priori* rather than a meta-analysis. Studies have been grouped based on the exposures being considered and we summarise the effect sizes and precision for each included study.

## Results

All stages of data screening were documented using a PRISMA flow diagram 25 (Figure 2). Our searches identified 10,131 records of which 2,805 were duplicates. A total of 7,323 titles were screened and of these, 48 abstracts were screened. Full texts of 22 papers were assessed for inclusion and, of these, 11 have been included in the qualitative synthesis.

Three of the included studies were based on populations in Sweden 31,34,37, two each in America 35,38, Australia 29,36 and Brazil 32,33 and one in Scotland 30. The remaining study 40 used data from 5 underlying datasets from Australia, Canada and America; one of which was the Collaborative Perinatal Project which was also used by one of the other studies *35*. Three studies included maternal interpregnancy weight change as the exposure 29,30,37, three examined maternal smoking status 30,34,40, two considered mode of birth 36,38 and four the length of the interpregnancy interval 31-33,35. Further study characteristics are detailed in Table 1. Associations between change in exposures and the risk of offspring adiposity are summarised in Table 2. A summary of the statistical analysis undertaken, adjustments made and significant results reported in each study is given in Table 3.

### Characteristics of the included studies

Table 1 summarises the included studies. With the exception of the individual patient data meta-analysis 40, all included studies use data from cohorts 29,32,33,35,38 and data-linkage studies 30,31,34,36,37 . These studies showed considerable variation in terms of the exposure and outcome measurements.

Studies where the exposure was interpregnancy weight change 29,30,37, smoking status 30,34,40 or mode of birth 36,38 had a measurement taken during Period 1 and a further measurement in Period 2, as defined above (Figure 1). Most studies included only one time-point for outcome measurement and the timings varied by study; the youngest mean age for offspring was 19 months 33 and the highest 30.2 years 32. Both of these studies 32,33 followed children whose mothers formed part of the 1982 Pelotas (Brazil) Birth Cohort Study 42. One study from America followed offspring from ages 9-14 years through ages 20-28 years, considering annual time-points for 5 years and biennial time points thereafter 38. One study from Sweden used measurements taken at comprehensive health checks when the child was 4 years of age and used these to predict BMI on the child’s actual 4th birthday 37. Two studies utilised Swedish conscription data and only include outcome measurements for males 31,34.

Across the eleven studies there was one categorical and a number of continuous outcomes. Three studies considered more than one relevant outcome 30,32,37 (Table 1). For studies other than the meta-analysis 40, these outcome measurements were taken by school nurses 30, military personnel 31,34, research centre staff 32,33, clinic staff 35,37 and nurses 36. In one case measurements were self-reported 38 and in another, mothers were provided with measuring tapes and instructions on how to take measurements 29.

The four maternal exposures which emerged from this review are reviewed in turn below and summarised in Tables 1-3.

### Length of the interpregnancy interval

Of the four studies which considered the length of the interpregnancy interval as the exposure, one was judged to be good 31, two fair32,33 and one poor35 in terms of their risk of bias (Table 1).

Barclay and Kolk 31 considered the long-term consequences of the length of both preceding and subsequent (not considered here) interpregnancy intervals on offspring health. They found that, compared with a birth interval of 25 to 30 months men born after an interval of at least 31 months had a higher probability of being affected by overweight/obesity in young adulthood. Between-family analysis showed an increasing trend as the interpregnancy interval increased and within-family analysis showed a broadly similar pattern 31 (Table 3).

Both Devakumar *et al 32* and Huttly *et al* 33 followed children whose mothers formed the 1982 Pelotas (Brazil) Birth Cohort Study 42 but both studies considered different outcome measurements and timepoints (Table 1). Huttly *et al 33* reported mean weight-for height *z*-scores which generally increased with the length of the interval (Table 3). Devakumar *et al 32* found a positive association for fat-free mass and visceral fat 32 for female offspring where the birth interval was treated as a continuous variable and a positive association with offspring fat-free mass when the birth interval was treated as a binary variable (Table 3).

In contrast, Li *et al* 35 did not find an association between the length of the interpregnancy period and offspring BMI *z-*score at age 7 years.

These four studies had objectively measured outcomes 31-33,35, but in the case of two, the exposure was based on maternal recall 32,33. One study was limited to considering shorter birth intervals since the duration from recruitment to the last birth was 6 years 35. Maternal weight change

Three studies considered maternal interpregnancy weight change as the exposure and these were all judged to be fair 29,37 or good 30 in terms of their risk of bias (Table 1).

Adane *et aI 29* found twice the odds of being affected by obesity where there was high interpregnancy weight gain (≥ 4 kg/m2 ) but reported no increase in odds of offspring obesity for interpregnancy weight loss (> 1 kg/m2), small gain (1 to < 2 kg/m2) or moderate gain (2 to < 4 kg/m2) 29 (Table 3).

Willmer *et al 37* examined interpregnancy weight loss due to bariatric surgery between pregnancies. They found no association between differences in BMI in week 10 of the pregnancy prior to, and the pregnancy after, surgery with differences in sibling’s BMI at age 4 years.

The primary focus of the paper by Aucott *et al* was maternal smoking but they also provide results for children being affected by overweight/obesity based on percentage maternal weight change between pregnancies 30. They found for a loss of ≥ 10% (compared with a change of ± 3%) the odds of children being affected by overweight or obesity were increased by 30% and 90% respectively and that mean BMI *z*-score was also higher for a gain of ≥ 10% (compared with a change of ± 3%) 30 (Table 3).

The studies by Aucott *et al* 30 and Willmer *et al 37* utilised routinely collected population level data in Scotland and Sweden respectively and included objectively measured outcomes but in the former, maternal and child records were linked in only 44% of cases while in the latter, full details were only available for 71 child-woman triads. All the exposure and outcome measurements in the Adane *et al 29* study were self-reported and only 34% of women responded to the survey asking for their children’s details.

### Maternal smoking status

Three studies considered maternal smoking status as the exposure and these were judged to be good 30,34 and fair 40 in terms of their risk of bias (Table 1).

Aucott *et al* 30 found that siblings born after a mother had started smoking between pregnancies (i.e. she did not smoke in her first pregnancy but did in her second) had higher mean BMI *z*-scores at age 5 than older siblings who were unexposed 30 (Table3). BMI *z*-score was also higher in the younger sibling compared to the older sibling where a mother smoked in both pregnancies but they found no significant difference where a mother quit smoking between pregnancies (i.e. where she was a smoker in the first but not the second pregnancy) 30.

Without sibling analysis, and compared to never smokers, mean offspring BMI *z*-score and the odds of overweight/obesity where mothers started smoking between pregnancies, always smoked or quit between pregnancies were higher 30 (Table 3).

Iliadou *et al* 34 found increased odds of being affected by overweight only where the mother smoked in both male pregnancies, compared with mothers who did not smoke during either pregnancy 34 (Table 3). The odds were not increased where a mother smoked only in her first or only in her second pregnancy. They found no effect where the association was evaluated within full and half sibling pairs 34.

Albers *et al* 40 performed an individual patient data meta-analysis on five studies to analyse differences in the number of cigarettes smoked across successive pregnancies and the dose dependent relationship with offspring BMI (Table 1). They found that each additional cigarette smoked a day in sibling pregnancies increased offspring BMI z-score 40 (Table 3).

In both the Aucott *et al* 30 and Iliadou 34 *et al* studies, smoking status was self-reported at a single point during pregnancy. Three of the underlying studies used by Albers *et al 40* had multiple self-reported measures of the numbers of cigarettes smoked during different stages of pregnancy and they used the maximum number at any time point in their analysis.

### Mode of birth

Two studies considered mode of birth as the exposure and these were judged to be good36 and fair38 in terms of their risk of bias (Table 1).

Smithers *et al 36* examined the association between mothers who had previously given birth by caesarean section and who subsequently went on to give birth vaginally or by elective caesarean with the second child’s BMI. They found no association between elective caesarean section for the subsequent birth and BMI *z*-score 36. Those who gave birth to their subsequent child by emergency caesarean, or who had an instrumental birth, were excluded from the analysis 36 but over 85% of the subsequent deliveries were by caesarean section.

The association between caesarean section birth and the risk of offspring being affected by obesity also formed part of the study undertaken by Yuan *et al* 38. They compared siblings who were discordant in their mode of birth and found that amongst women with a previous caesarean birth, the risk of offspring being affected by obesity after a subsequent vaginal birth was reduced by 31% (compared to a repeat caesarean birth) 38 (Table 3). For women who had a previous vaginal birth, the estimated risk of offspring being affected by obesity for a successive caesarean birth was not significant 38. Their study does not make a distinction between emergency and elective caesarean sections and includes no data on intrapartum indicators of caesarean birth, or any detailed labour/birth information 38.

## Discussion

This systematic review included eleven studies that assessed maternal interpregnancy weight change, differences in maternal smoking status, changes in mode of birth and the length of the interpregnancy interval between successive pregnancies in relation to adiposity in second or higher order siblings from age one onwards. Higher interpregnancy weight gain or loss, starting smoking between pregnancies, smoking at the first pregnancy only, or an increase in the number of cigarettes smoked during successive pregnancies and longer interpregnancy intervals showed a positive association. Vaginal birth after caesarean had a protective effect. To our knowledge, this is the first time that evidence on this subject has been systematically reviewed.

The quality assessment and overall rating for addressing the risk of bias has been judged to be either good or fair for all but one of the included studies (Table 1). The study judged as poor reported no results of significance 35 . There was much variability in the confounders controlled for in the different analyses (Table 3). All but one 40 of the included studies control for maternal age and the majority for maternal smoking 29,35-38 and maternal weight in some form 29,30,32,34,35,38,40, where these were not the exposures under consideration. Most studies included at least one socio-economic factor 13,29,30,32-36,38,40. Only a minority of studies were able to take account of exposures in pregnancy such as diabetes and hypertension 35,36,38. Only one study included any adjustment for paternal confounders 34. Most studies did not specifically state which pregnancy the confounders related to.

A number of studies have made adjustments for covariates which are potential mediators between the exposure and offspring adiposity. Examples of such adjustments made in the included studies are breastfeeding 40 , gestational weight gain 34 and birthweight 30,34-36,38 and both of the included studies which consider mode of birth adjust for birthweight in some form 36,38 even though this is a potential mediator (Table 3). Children exposed to diabetes (including gestational diabetes mellitus) in utero are at high risk of childhood adiposity, although breastfeeding has been shown to attenuate this risk 43 44. Gestational weight gain has been shown to mediate the relationship between a mother’s BMI and offspring adiposity 45. Misclassification of confounders and mediators affects the magnitude of the total effect of the exposure on the outcome 46; both the direct effect, which is not through the mediator, and the indirect effect, through the mediator 47. Overadjustment bias can affect the direct effect of the strength of associations and arises when controlling for variables which are on the causal pathway between exposure and outcome 48. Unnecessary adjustments of other variables on the causal pathway can affect the precision 47,48.

All the studies were based on data from high or upper middle income countries, which will have had an effect on the prevalence of adiposity 49 and individual risk factors, including the level of antenatal care 50, rates of birth by caesarean section 51 and smoking 52. This limits our ability to generalise the findings to lower income countries. In addition, potential biases may have arisen because many of the included studies had low response rates to questionnaires or surveys asking for details about children 29 , low rates of data linkage 30,36,53 or only included male outcomes 31,34. Further, the data used in one study were relatively old, with only 6 years from recruitment to the final birth and with final outcome measurements taken in 1972 35.

Most of the exposure and outcome measurements were objectively recorded by professionals, but where these were self-reported, for example in the case of smoking status in pregnancy, potential information bias due to under-reporting 54 may have arisen. Longitudinal cohort studies which use population level data and are linked to objectively measured child outcomes are needed to avoid bias in recruitment and in measurement. A number of the included studies have low response or linkage rates 29,30,36 or only have details available for very small numbers of participants 37.

This review has a number of strengths. The initial search was adapted and run through a variety of different online databases. It is unlikely that this search was too narrow since a very large number of studies were retrieved for consideration (Figure 2). Our search was, however, limited to studies published in English and it is possible that there may be literature published in other languages which could have formed part of this review.

We did not include grey literature in our search and there may therefore be an element of publication bias towards statistically significant associations 55. This does not appear to have been the case, as although most of the studies reported at least one non-null finding, a number only reported non-significant associations 34-37 (Table 2).

Agreement between two authors (EJT and SW) at the screening stage of a random 10% sample of titles and abstracts was very high (98.9% and 100%) and two reviewers considered the full texts of studies remaining after abstract screening (EJT and SW). Data extraction and risk of bias assessments were undertaken by two authors (EJT and SW or EJT and NZ). We then followed a recent approach and listed strengths and weaknesses for each study using two commonly used checklists 18. This allowed identification of important criteria in each study.

There are a number of exposures which are known to have an impact on offspring adiposity which were not found in the literature searched for this review; for example gestational weight gain 14, maternal pre-pregnancy stress 16, supplement intake and lower maternal vitamin D status 56, and measures of social and economic status such as education and area of residence 18. Further research into changes in exposures and into combinations and interactions between exposures and the association with the magnitude of the risk of children being affected by overweight/obesity is recommended. We specifically recommend studies which examine differences in vitamin D, folic acid and other vitamin supplementation, and those which consider different levels of gestational weight gain. We do not know whether a change in exposure between pregnancies modifies the risk of adiposity for a second or subsequent child or whether the risk is based on past exposures. The World Health Organisation recommend a birth to conception interval of at least 24 months in order to avoid a range of poor maternal, perinatal, neonatal and birth outcomes which are particularly associated with intervals under 18 months 8. A number of included studies have found associations between the longest interpregnancy intervals and childhood adiposity and research which combines the effect of the length of the preceding birth interval with other changes in maternal exposures is also recommended.

## Conclusion

Change in a number of exposures across successive pregnancies showed associations with greater adiposity in second or higher order siblings; substantial interpregnancy weight gain or loss, smoking in the first or second pregnancy only, or increasing the number of cigarettes smoked and longer interpregnancy intervals. Vaginal birth after a caesarean birth had a protective effect. There was considerable heterogeneity in the quality and methodology of the included studies.

Further research into changes in modifiable maternal exposures and behaviours between successive pregnancies is recommended to see if the risk of adiposity for second or subsequent children is fixed based on earlier predictors or if this risk changes as exposures and behaviours change.

## Conflicts of interest

KMG has received reimbursement for speaking at conferences sponsored by companies selling nutritional products and is part of an academic consortium that has received research funding from BenevolentAI Bio Ltd, Abbott Nutrition, Nestec and Danone. All other authors declare no conflicts of interest.

## Author contributions

NAA conceived the review idea. All authors contributed to the design of the study and to the protocol and all have edited and approved the final manuscript. EJT was responsible for drafting the protocol, conducting the search, screening, quality assessment and drafting of the manuscript. SW and NZ contributed to screening, data extraction and quality assessment.

## Acknowledgements

This research is supported by an NIHR Southampton Biomedical Research Centre and University of Southampton Primary Care, Population Sciences and Medical Education PhD studentship to EJT and an Academy of Medical Sciences and Wellcome Trust grant to NAA (Grant no: AMS\_HOP001\1060). KMG is supported by the UK Medical Research Council (MC\_UU\_12011/4), the National Institute for Health Research (NIHR Senior Investigator (NF-SI-0515-10042), NIHR Southampton 1000DaysPlus Global Nutrition Research Group) and NIHR Southampton Biomedical Research Centre), the European Union (Erasmus+ Programme Early Nutrition eAcademy Southeast Asia-573651-EPP-1-2016-1-DE-EPPKA2-CBHE-JP), the US National Institute On Aging of the National Institutes of Health (Award No. U24AG047867) and the UK ESRC and BBSRC (Award No. ES/M00919X/1) and the British Heart Foundation (RG/15/17/3174). The research funders had no input on research design or on manuscript drafting. The authors wish to thank Paula Sands (Site and Research Engagement Librarian, University of Southampton) for her contribution to the search design.

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## Figure Legends

Figure 1: Diagram representing the period of time under consideration in this systematic review. At least one exposure measurement should have been recorded in Period 1 and at least one in Period 2. Outcome measurements should be recorded in second, or higher order, siblings after the age of one year, without upper bound.

Figure 2: PRISMA flow diagram

## Table Legends

Table 1: Included study characteristics

Table 2: Associations between interpregnancy change in maternal exposures and childhood adiposity in second or higher order siblings across the eleven included studies

Table 3: Summary of statistical analysis, adjustments made and significant results reported across the eleven included studies