Exploring the Relationship Between Early Life Exposures and the Comorbidity of Obesity and Hypertension: Findings from the 1970 The British Cohort Study (BCS70)

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Abstract

Background: Epidemiological research commonly investigates single exposure-outcome relationships, while children's experiences across a variety of early lifecourse domains are intersecting. To design realistic interventions, epidemiological research should incorporate information from multiple risk exposure domains to assess effect on health outcomes. In this paper we identify exposures across five pre-hypothesised childhood domains and explored their association to the odds of combined obesity and hypertension in adulthood.

Methods: We used data from 17,196 participants in the 1970 British Cohort Study. The outcome was obesity (BMI of ≥30) and hypertension (blood pressure>140/90mm Hg or self-reported doctor's diagnosis) comorbidity at age 46. Early life domains included: 'prenatal, antenatal, neonatal and birth', 'developmental attributes and behaviour', 'child education and academic ability', 'socioeconomic factors' and 'parental and family environment'. Stepwise backward elimination selected variables for inclusion for each domain. Predicted risk scores of combined obesity and hypertension for each cohort member within each domain were calculated. Logistic regression investigated the association between domain-specific risk scores and odds of obesity-hypertension, controlling for demographic factors and other domains.

Results: Adjusting for demographic confounders, all domains were associated with odds of obesity-hypertension. Including all domains in the same model, higher predicted risk values across the five

domains remained associated with increased odds of obesity-hypertension comorbidity, with the strongest associations to the parental and family environment domain (OR1.11 95%CI 1.05-1.18) and the socioeconomic factors domain (OR1.11 95%CI 1.05-1.17).
Conclusions: Targeted prevention interventions aimed at population groups with shared early-life characteristics could have an impact on obesity-hypertension prevalence which are known risk factors for further morbidity including cardiovascular disease.

Introduction

Obesity and hypertension are major public health issues [1-2]. In England, 26% of adults are obese [3], and 30% of adults have hypertension [4]. Both conditions are associated with morbidities later in the lifecourse, including Type 2 diabetes, heart disease, kidney disease, renal disease, strokes, and some cancers, including breast and bowel cancer [5-8]. There is evidence suggesting that in England and Scotland since 2014, obesity and excess body fat have contributed to more deaths among people in middle- and old-age than smoking [9]. On a global level, in 2019 and across 204 countries, the leading Level 2 risk factor for attributable deaths was high systolic blood pressure, and between 2010 to 2019, one of the largest increases in risk exposure was for high body-mass index [10].
Obesity and hypertension often co-occur [11], and their combination significantly increases the likelihood of adverse health outcomes such as cardiovascular disease [12]. Previous literature has identified obesity and hypertension as common sentinel conditions, defined as the first long-term condition in the development of multiple long-term conditions [13-16].
A substantial body of evidence suggests that experiences in early life are crucial in determining outcomes such as obesity and hypertension. Developmental Origins of Health and Disease has become an established research field linking the aetiology of diseases such as obesity with environmental exposures in utero and early life [17]. Preconception and pregnancy are important periods and the concept of 'fetal programming' has emerged whereby a stimulus or insult in utero can have permanent effects on structure, physiology and metabolic system of offspring [18-21].
Socioeconomic disadvantage in early life is also key in shaping cardiovascular risk linked to obesity and hypertension [22]. Analyses of the Hertfordshire cohort study demonstrated that paternal social class was associated with future multimorbidity, including hypertension [23]. In the Aberdeen Children of the 1950s cohort, lower father's social class at birth was associated with early-onset multimorbidity, including hypertension [24], and in the 1970 British Cohort Study those with fathers from unskilled occupational groups (vs. professional) at birth had 43% higher risk of early-onset (age 46-48) multimorbidity including hypertension [25].
Many wider determinants acting in childhood are likely to increase the risk of disease in adulthood, and in previous research [26,27] we identified exposures across five pre-defined childhood domains covering a range of social, economic, developmental, educational and environmental factors. Yet, most previous research focuses on single exposure-outcome relationships, potentially to reduce

statistical complexity, or to focus policy attention onto a specific aspect. However, children are likely to be exposed to combinations of risk factors across these domains. Ideally, research needs to be able to incorporate information from multiple domains into the same analysis, so that we understand how different experiences across a range of social, economic and environmental domains may influence the risk of developing long-term conditions. This will provide actionable insights into how to support people to live more healthily for longer.

In this paper we aimed to explore the association between five pre-defined [26,27] domains and the odds of experiencing both obesity and hypertension at midlife, we explore these multiple pre-defined domains simultaneously to understand which early life domain may have the strongest association to obesity-hypertension at midlife. This work is conducted as part of the Multidisciplinary Ecosystem to study Lifecourse Determinants and Prevention of Early-onset Burdensome Multimorbidity (MELD-B) project [28], which aims to identify lifecourse time periods and targets for the prevention of early-onset, burdensome multimorbidity.

Methods

Dataset

We used the 1970 British Cohort Study (BCS70) [29] that has followed 17,196 cohort members born in England, Scotland, Wales and Northern Ireland born in one week in 1970, to date, there have been 10 sweeps of data collection – 4 in childhood and 6 in adulthood. The comorbidity outcome of obesity and hypertension was measured at age 46 within a biomedical sweep conducted by a research nurse. All other variables were measured either at birth or age 10.

Outcome

The outcome was a combined obesity-hypertension phenotype at age 46. Blood pressure was measured via three systolic and diastolic blood pressure readings during a single appointment and administered by a research nurse. Hypertension was defined as an average blood pressure reading of over 140/90 mm Hg. We additionally classified hypertension if a participant reported (at age 46) that they had received a doctor's diagnosis of high blood pressure or hypertension, even if the blood pressure measurement was less than 140/90 mm Hg, since diagnosed hypertension may be accompanied by intake of antihypertensive medication, thus lowering blood pressure readings at the time of cohort measurement. Body mass index (BMI) was calculated via height and weight measurements taken during the same nurse appointment using the following formula: BMI = weight (kg) / height $(m)^2$. Obesity was defined as a BMI of 30 or over.

Exposures (Five pre-hypothesised domains)

Previously we developed a conceptualisation of 12 domains of early life risk factors of future multimorbidity risk informed through a scoping literature/policy review and patient and public engagement [26], and a data audit of these domains [27]. In this paper we focus our analysis on 5 out of the 12 domains chosen because they showed unadjusted associations with the outcomes:

1. *Prenatal, antenatal, neonatal and birth domain* focused on the period from conception to the onset of labour, the circumstances and outcomes surrounding a birth, and the period immediately following birth.
2. *Developmental attributes and behaviour domain* focused on the developmental markers of children relating to cognition, coordination, personality types and behavioural traits.
3. *Child education and academic ability domain* related to the process of learning and educational achievement, especially in educational settings, and the knowledge an individual gains from these educational institutions.
4. *Socioeconomic factors domain* included factors relating to differences between individuals or groups of peoples caused mainly by their social and economic situation.
5. *Parental and family environment domain* incorporated the interactions between children and care givers, parenting styles, parental beliefs, attitudes and discipline, and wider family factors such as kin networks.

Supplementary Materials Table 1 includes all the variables that were initially considered for each domain. These variables were selected and categorised based on a previous data audit and PCA analysis [27] that identified early-life variables from multiple sweeps of data that fitted into five domains of early-life domains of future multimorbidity risk. This previous work reduced the dimensionality of the data and structured each of the five domains into mutually exclusive groups of variables based on similar characteristics [26,27].

Demographic confounders

We adjusted for the following demographic confounders chosen based on a priori knowledge and recorded at age 10: sex (man/woman), ethnicity (White British/Other), parental death (yes/no) and parental separation (yes/no).

Sample

The analytical sample included all cohort members who had measured BMI and blood pressure at age 46 (n = 7858), this represented 45.7% of the original birth cohort. To preserve sample size and reduce bias in the estimates due to missing data we used multiple imputation. Multiple imputation was conducted by chained equations for missing observations at birth, age 10, and 46 [30]. 50 imputation cycles were constructed under the missing-at-random assumption [31-33], which has been found to be highly plausible in the British birth cohorts [34]. All variables were included in the imputation

process. The outcome was included in the imputed models, but imputed outcome values were not used. For reference we include regression results based on complete case analysis in Supplementary Materials Tables 2 and 3.

Statistical analysis

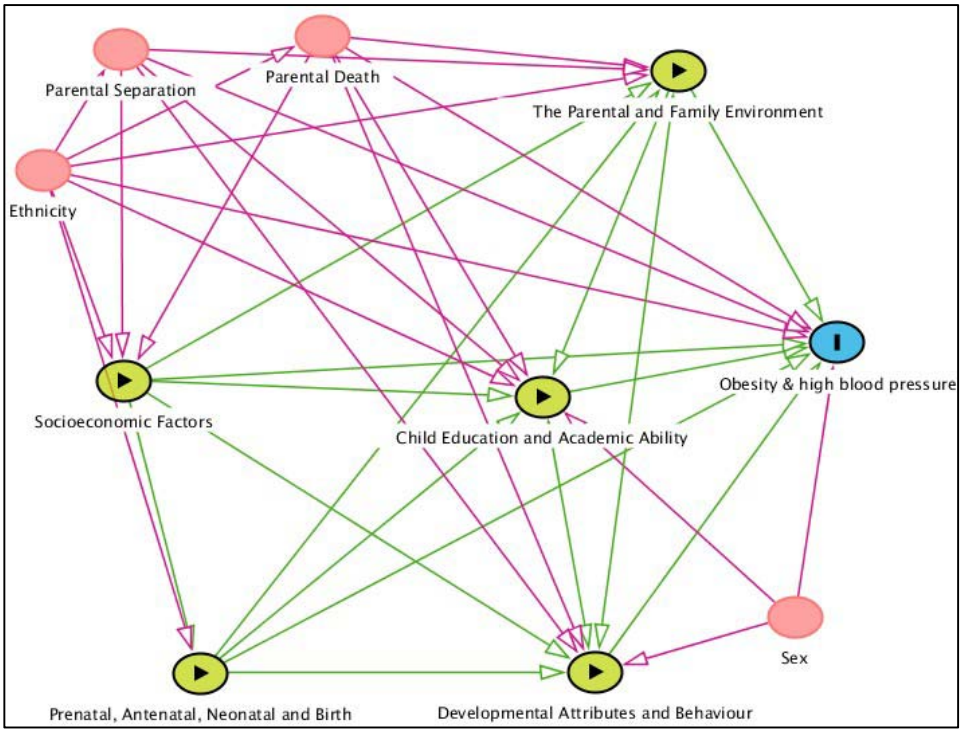
Stepwise backward elimination was used to select variables for inclusion separately for each domain. This method started with all potential variables identified for each domain as outlined in Supplementary Materials 1, then variables were removed sequentially based on a series of hypothesis tests. In backward elimination, variables were removed sequentially if the p-value for a variable exceeded the specified significance level which was set at 0.157. This level was chosen conservatively to reduce the risk of overfitting and is the equivalent to the Akaike information criterion (AIC) [35,36].

Logistic regression models explored the relationship between retained variables following stepwise backwards elimination and odds of obesity-hypertension comorbidity, and predicted risk scores of obesity and hypertension for each cohort member within each domain were calculated. The risk scores for each individual within each domain were centred on the mean risk score, and risk scores were bound between 0 and 1. A Pearson correlation matrix explored the correlation between domain-specific risk scores.

Logistic regression was used to assess the importance of domain-specific risk scores on the outcome of combined obesity and hypertension adjusting for demographic confounders. Finally, we included all five domain-specific risk scores in a multivariate model adjusting for demographic confounders. This allowed us to understand the most important domain for odds of obesity-hypertension holding all other factors constant.

Regression models were informed by a directed acyclic graph (DAG) using DAGitty v3.0 (Figure 1). In this DAG, exposures are domains rather than individual variables; however, this was intentional given that our aim was to explore multiple pre-constructed domains simultaneously to understand which domain may have the strongest association to obesity-hypertension. The DAG differs from a traditional approach that would have considered one variable as the main exposure while treating other variables as confounders or mediators. The DAG confirmed the need to include all domains in the fully adjusted model. All analysis was carried out using STATA version 17 [37].

Figure 1. A DAG of five early life domains and risk of obesity and hypertension in adulthood.



Results

Descriptive Results

Table 1 identifies the retained variables following stepwise backwards elimination for each domain by the reporting of combined obesity and hypertension at age 46. Among the 7858 cohort members at age 46, 597 (7.6%) had obesity-hypertension comorbidity at age 46. As shown in Table 1, where the descriptive statistics were based on the specific sample available at the sweep in which the variable was reported or measured, greater early life adversity was related to the increased reporting of obesity-hypertension at age 46. In the prenatal, antenatal, neonatal domain, 8.8% of cohort members whose mothers smoked during pregnancy had obesity and hypertension at age 46. In the education and academic ability domain 10.1% of cohort members who reported some difficulty with reading at age 10 had obesity-hypertension at age 46. For the parent and family environment domain, cohort members with a father by adoption (10.4%), stepfather (10.3%) or another father figure such as a grandparent (11.2%) at age 10 had obesity-hypertension at age 46. For the developmental attributes and behaviour domain cohort members who had obesity-hypertension comorbidity had a hand control rating of 28.2 at age 10, whilst those who did not have obesity-hypertension had a hand control rating of 30.3. Finally, in the socioeconomic factors domain 9.2% of cohort members whose gross family income (per week) was below £49 had obesity-hypertension at age 46 (9.2%), and 4.2% of cohort members whose gross family income was above £250 had obesity-hypertension at age 46.

Table 1. Variables included in the five domains risk scores following stepwise backwards elimination, and the reporting of combined obesity and hypertension at age 46. The total sample size was based on the specific sample available at the sweep in which the variable was reported or measured.

			Obesity and High Blood Pressure		
			No N (%)	Yes N (%)	*Total Sample*
Prenatal, antenatal, neonatal and birth domain	Mothers parity at birth of cohort member	0	2849 (91.9%)	251 (8.1%)	*3100*
		1	2475 (93.1%)	183 (6.9%)	*2658*
		2	1127 (92.7%)	89 7.3%	*1216*
		3	460 (93.1%)	34 (6.9%)	*494*
		4	201 (89.3%)	24 (10.7%)	*225*
		5+	148 (89.7%)	17 (10.3%)	*165*
	Maternal smoking during pregnancy	Non-smoker	3190 (93.3%)	229 (6.7%)	*3419*
		Stopped pre/during	1272 (92.8%)	993 (7.2%)	*1371*
		Smoker	2758 (91.2%)	266 (8.8%)	*3024*
	Birthweight	No obesity-hypertension - mean (SD)		3318g (523g)	*7254*
		Yes obesity-hypertension - mean (SD)		3246g (483g)	*596*
	Maternal age at birth of cohort member	No obesity-hypertension - mean (SD)		26.0 (5.3)	*7220*
		Yes obesity-hypertension - mean (SD)		25.6 (5.6)	*594*
Education and academic ability domain	Ability spelling – cohort member's assessment	Good ability	3210 (93.2%)	234 (6.9%)	*3444*
		Poor ability	2605 (91.0%)	258 (9.0%)	*2863*
	Difficulty writing – teacher's assessment	No difficulty	5173 (92.9%)	396 (7.1%)	*5569*
		Some difficulty	1050 (90.2%)	114 (9.8%)	*1164*
		Great difficulty	127 (94.8%)	7 (5.2%)	*134*
	Difficulty reading – teacher's assessment	No difficulty	5260 (92.9%)	402 (7.1%)	*5662*
		Some difficulty	950 (89.9%)	107 (10.1%)	*1057*
		Great difficulty	161 (93.6%)	11 (6.4%)	*172*
	Edinburgh Reading Test Scores	No obesity-hypertension - mean (SD)		42.5 (12.1)	*5776*
		Yes obesity-hypertension - mean (SD)		40.1	*493*

				(12.2)	
Parent and family environment domain	Father interest in education – teacher's assessment	Very interested	2200 (93.6%)	150 (6.4%)	*2350*
		Moderate interest	1136 (92.1%)	97 (7.8%)	*1233*
		Very little interest	178 (90.8%)	18 (9.2%)	*196*
		Uninterested	144 (92.3%)	12 (7.7%)	*156*
		Cannot say/no father	1658 (90.6%)	172 (9.5%)	*1830*
	Mother interest in education – teacher's assessment	Very interested	3058 (93.2%)	203 (6.8%)	*3281*
		Moderate interest	1694 (91.8%)	151 (8.2%)	*1845*
		Very little interest	242 (90.3%)	26 (9.7%)	*268*
		Uninterested	99 (90.8%)	10 (9.2%)	*109*
		Cannot say/no mother	636 (89.5%)	75 (10.6%)	*711*
	Family go on outings	Often	3570 (92.7%)	281 (7.3%)	*3851*
		Sometimes	2602 (91.9%)	229 (8.1%)	*2831*
		Rarely or never	216 (92.7%)	17 (7.3%)	*233*
	Father helps manage cohort member	Equal or similar amount	3346 (92.1%)	287 (7.9%)	*3633*
		Smaller part than mother	2118 (93.2%)	154 (6.8%)	*2272*
		Very small part	437 (92.4%)	36 (7.6%)	*473*
		Does not help	442 (91.1%)	43 (8.9%)	*485*
	Father Figure	Biological father	5584 (92.7%)	440 (7.4%)	*6024*
		Father by adoption	86 (89.6%)	10 (10.4%)	*96*
		Step father	235 (89.7%)	27 (10.3%)	*262*
		Other	111 (88.8%)	14 (11.2%)	*125*
		No father figure	415 (91.6%)	38 (8.4%)	*453*
Developmental attributes and behaviour domain	Rutter behaviour	No obesity-hypertension - mean (SD)		424.0 (209.2)	*6047*
		Yes obesity-hypertension - mean (SD)		449.7 (196.8)	*497*
	Number of steps walking backwards	No obesity-hypertension - mean (SD)		15.7 (5.4)	*5975*
		Yes obesity-hypertension - mean (SD)		15.0 (5.6)	*488*
	Hand control rating	No obesity-hypertension - mean (SD)		30.3	*5815*

				(12.2)	
		Yes obesity-hypertension - mean (SD)		28.2 (12.2)	*496*
Socioeconomic factors domain	Parental social class	I professional	439 (94.2%)	27 (5.8%)	*466*
		II managerial	1691 (94.1%)	106 (5.9%)	*1797*
		III non-manual	710 (92.8%)	55 (7.2%)	*765*
		III manual	2432 (91.5%)	226 (8.5%)	*2658*
		IV partly skilled	762 (89.5%)	89 (10.5%)	*851*
		V Unskilled	206 (91.9%)	18 (8.1%)	*224*
	Gross Income per week	£250+	408 (95.8%)	16 (4.2%)	*426*
		£200-£249	421 (92.3%)	35 (7.7%)	*456*
		£150-£199	1061 (94.0%)	68 (6.0%)	*1129*
		£100-£149	2072 (91.7%)	188 (8.3%)	*2260*
		£50-£99	1602 (91.0%)	158 (9.0%)	*1760*
		Under £49	334 (90.8%)	34 (9.2%)	*368*
	Housing tenure	Owned outright	737 (93.1%)	55 (6.9%)	*792*
		Private rent	191 (93.2%)	14 (6.8%)	*205*
		Being purchased (mortgage)	3585 (93.0%)	270 (7.0%)	*3855*
		Council rent	1685 (90.5%)	177 (9.5%)	*1862*
		Other	198 (92.1%)	17 (7.9%)	*215*

Given there was likely to be correlation between domain-specific risk scores, in Supplementary Materials Table 4 we present a Pearson correlation matrix exploring correlation across domains. As demonstrated the strongest correlation was between both the developmental attributes and behaviour domain and the child education and academic ability domain (coefficient 0.29), and between the parental and family environment domain and the socioeconomic factors domain (coefficient 0.32). However, all correlation coefficients were below a coefficient of 0.7 suggesting that the predicted risk values for each domain were not highly correlated with one another [38].

In Supplementary Materials Table 5-9, we include the regression coefficients of obesity-hypertension for the retained variables following stepwise backwards elimination, and for each domain separately. Table 2 presents odds of obesity-hypertension at age 46 in relation to domain-specific risk scores for

two separate models; adjusting for demographic confounders and adjusting for the domains and demographic confounders. Adjusting for demographic confounders demonstrated that for every one unit increase in the predicted risk value in the child education and academic ability domain there was a 15% increase in the odds of obesity-hypertension (OR1.15, 95%CI 1.10-1.20). A one unit increase in the predicted risk value in the developmental attributes and behavior domain was associated with a 16% increase in the odds of obesity-hypertension (OR1.16, 95%CI 1.10-1.22). There was a 13% increase in the odds of obesity-hypertension with every unit increase in the predicted risk value in the prenatal, antenatal neonatal and birth domain (OR 1.13, 95% CI 1.07-1.19), and a 19% increase in the odds of obesity-hypertension with every unit increase in the predicted risk value in the parental and family environment domain (OR 1.19, 95% CI 1.13-1.26). Finally, for every unit increase in the predicted risk value in the socioeconomic factors domain there was an 18% increase in the odds of obesity-hypertension (OR1.18, 95%CI 1.12-1.24).

In the model adjusting for confounders and holding all other domains constant the significant relationships identified in the previous models were maintained, although the odds ratios were reduced for all domains. The strongest associations with the outcome were for the parental and family environment domain and the socioeconomic factors domain. A one unit increase in the domain-specific risk score in each of the parental and family environment and the socioeconomic factors domains were associated with a 11% increase in the odds of obesity-hypertension (OR1.11 95%CI 1.05-1.18 and OR1.11 95%CI 1.05-1.17 respectively). The full breakdown of the final model is presented in Supplementary Materials Table 10.

Table 2. Odds of obesity-hypertension at age 46 in relation to domain-specific risk score of obesity-hypertension for five early life domains. Multiple imputed data (50 Imputations).

	Model adjusting for confounders		Model adjusting for confounders and other domains	
	OR	95%CI	OR	95%CI
Child education and academic ability domain predicted risk value	**1.15**	**1.10-1.20**	**1.06**	**1.01-1.12**
Developmental attributes and behaviour domain predicted risk value	**1.16**	**1.10-1.22**	**1.09**	**1.03-1.15**
Prenatal, antenatal, neonatal and birth domain predicted risk value	**1.13**	**1.07-1.19**	**1.06**	**1.00-1.12**
Parental and family environment domain predicted risk value	**1.19**	**1.13-1.26**	**1.11**	**1.05-1.18**
Socioeconomic factors domain predicted risk value	**1.18**	**1.12-1.24**	**1.11**	**1.05-1.17**
Sample				*7858*

Discussion

Our research demonstrates the importance of considering domains of early life determinants simultaneously as this may provide a better life course perspective to the development of health and disease opposed to considering individual exposures. When all early life domains were included in the same model, greater adversity in all of the domains remained associated with increased odds of obesity-hypertension comorbidity.

Once we include all domain-specific risk scores in the same model, we found the strongest association to odds of obesity-hypertension were for the parental and family environment domain and the socioeconomic factors domain. This therefore provides actionable insights to the domains that any intervention may wish to target in order to support people to live more healthily for longer. Our results also support previous research suggesting that socioeconomic disadvantage is key in shaping multimorbidity [22-25], and we have demonstrated that this relationship remains even after considering the confounding role of other childhood lifecourse domains. Calculating domain-specific risk scores and using these to assess importance having adjusted for all other factors represents a good approach to reduce dimensionality of the individual variables, while preserving the structure of the key domains.

The findings that the parental and family environment remains important even after considering the confounding role of other childhood lifecourse domains is important. Our results indicate that there may be lifelong health impacts stemming from the interaction between children and the primary care giver, parenting styles, parental beliefs, attitudes and discipline, and wider family factors such as kin networks in childhood. Our results support recent policy documents such as the 2022 Public Heath Wales report which highlights that the relationship between the parent and child, between the child's parents, and the family's relationships with their wider family, are key components influencing children's wellbeing and development [39]. Additionally, we add to literature that has found parenting and family support, parenting warmth and parenting styles to be important determinants of psychiatric comorbidity [40]. These results highlight the importance of current UK policy interventions and research endeavours such as 'A Better Start', 'Family Hubs' and 'Start for Life' programmes that aim to give children and families the best start in life [41,42]. Identifying and supporting vulnerable families to develop parenting skills, ensuring children have a healthy and safe home environment are all interventions that may reduce multimorbidity in later life. In addition, continued efforts are needed to address the wider determinants of health such as income and equitable access to good quality housing and healthy food to support people to have healthy lives for longer.

We have discussed how research tends to investigate single exposure-outcome relationships, while children's experiences across a variety of early lifecourse behavioural, social, economic and transgenerational areas are intersecting, and therefore research needs to be able to incorporate information from multiple domains into the same analysis. However, it is also important research

reflects on modifiable risk factors for ill health that focus on both direct and indirect factors as well as wider systemic and structural determinants of disease and health inequalities [43]. Our results represent one approach to achieve these goals. We moved beyond the influence of one specific factor on health outcomes to focus on the multidetermined nature of a combination of determinants on health. Producing evidence quantifying the effect of acting on a combination of risk determinants in early life can make it easier to engage policy makers and practitioners in acting on the wider determinants of health. We have demonstrated that analyses which consider only a single domain, as opposed to considering multiple domains could lead to incorrect policy formation. Adversity in one domain is likely to be confounded with other adversity in other domains, and it may be within these other domains where intervention is best placed. For example, we have demonstrated that considering each domain independently of one another they are all seemly important for the odds of obesity and hypertension. However, reflecting on the confounding influence of the other domains it is the parental and family environment and socioeconomic factors domains where interventions might have the biggest impact.

There are a number of important next steps. Firstly, we have identified the domains, and individual variables within domains that most strongly influence the odds of developing obesity-hypertension at age 46, it is therefore important research considers modelling prevention scenarios within these domains. This could be achieved via modelling hypothetical scenarios where exposure to a variable within a domain is changed and the reduction in odds of obesity-hypertension measured. Secondly, it is important to expand the methods presented here to consider the relationship to other multimorbidity outcomes that additionally explore the burdensome dimension of multimorbidity. Finally, in previous research [27] we audited the early life /variables available in two other cohort datasets. The data available in these datasets provide the opportunity to validate and compare our results.

Strengths and limitations

Data from a large cohort study provided some of the richest and most in-depth data in Britain and allowed us to capture a wide array of biological, social, environmental, behavioural and family variables in childhood to represent five early lifecourse domains. This depth of information would not have been available from most electronic health care records in either primary or secondary care. Additionally, the prospective longitudinal data provided the opportunity to analyse exposures measured earlier in the life course and their association with adult outcomes and hence provide some potential causal relationships. The data also afforded the opportunity to analyse objective measures of both obesity and hypertension.

However, the cohort is representative of births occurring in Britain in 1970 and as such lacks ethnic diversity. It was beyond the scope of this paper to explore mediating role of known adult determinants of obesity-hypertension such as diet and physical exercise. Additionally, no differentiation was made

between the burdensome impact of different diseases or disease severity to the individual. For example, mild controlled hypertension or just making the threshold for obesity is unlikely to have the same impact on an individual's quality of life compared to unmanaged hypertension or clinically severe obesity (BMI over 40). Further, despite using measured rather than self-reported BMI, the BMI measurement continues to have a risk of overestimating body fat in those who have muscular builds. It is also important to consider the possibility that we have over-adjusted within our models, resulting in overadjustment bias through adjusting for mediators or colliders [44]. This was unavoidable given our exposures were combined risk factors rather than individual variables. Given the nature of the domains, it was more likely that there would be causal pathways between them when drawing the DAG, potentially more so than when depicting individual variables. However, this was intentional given children's experiences across a variety of early life course domains are intersecting and we argue that research needs to be able to incorporate information from multiple domains into the same analysis. We therefore felt it was important to explore multiple domains simultaneously to understand which domain may have the strongest association to obesity-hypertension. We considered taking a more traditional, epidemiological approach where we would consider the relationship between a single domain or a single variable within a domain and odds of obesity-hypertension, controlling for select individual variables from the other domains. However, the choice of domain would have been arbitrary, and this method would not have addressed our research question.

Conclusions

Higher predicted risk values across the five domains are associated with increased odds of obesity-hypertension comorbidity, with the strongest associations to the parental and family environment domain and the socioeconomic factors domain. Developing methods for exploring the multidetermined nature of combined childhood risk factors for health such as the work presented here, can help to challenge existing understanding of the aetiology of health, develop new ideas and solutions, and facilitate improvements in developing and recognising health as a complex and multidetermined concept from a lifecourse perspective. We have demonstrated that if large scale longitudinal studies are used it is possible to move beyond considering the influence of one factor on health to consider combined risk factors simultaneously. Targeted prevention interventions aimed at population groups with shared early-life characteristics could have an impact on obesity-hypertension prevalence which are known risk factors for further morbidity including cardiovascular disease.

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Conflict of Interest

R.O. is a member of the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee, member of the NICE Decision Support Unit (DSU), and associate member of the NICE Technical Support Unit (TSU). She has served as a paid consultant to the pharmaceutical industry and international reimbursement agencies, providing unrelated methodological advice. She reports teaching fees from the Association of British Pharmaceutical Industry (ABPI). R.H. is a member of the Scientific Board of the Smith Institute for Industrial Mathematics and System Engineering.

Author Contributions

S.F., N.A., R.H., S.P., R.O., S.S. and A.B. contributed to the conceptualisation of the MELD-B project. S.S., N.A., and S.F. obtained the datasets. All authors contributed to the conceptualisation of the paper. S.S., and N.A. led the design and planning of the paper. R.O. led the design of the statistical analysis. S.S., N.A., A.B., N.Z., R.H., and R.O. supported the design, planning and reviewing of the statistical analysis. S.S. performed the statistical analysis with support from N.Z. S.S. prepared all figures and graphs. S.S., and N.A. produced the initial draft of the manuscript. All authors were involved in editing and reviewing the manuscript, and approved the final manuscript. S.S., N.A., and S.F. take responsibility for the data and research governance.

Data Availability Statement

The BCS70 datasets generated and analysed in the current study are available from the UK Data Archive repository (available here: http://www.cls.ioe.ac.uk/page.aspx?&sitesectionid=795).

Ethical Approval

The study is conducted in accordance with the UK Policy Framework for Health and Social Care Research. Ethics approval for MELD-B has been obtained from the University of Southampton Faculty of Medicine Ethics committee (ERGO II Reference 66810).

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