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Influence of maternal obesity on the association between common pregnancy complications and risk of childhood obesity: an individual participant data meta-analysis

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Summary

Background Gestational diabetes and gestational hypertensive disorders are associated with offspring obesity, but the role of maternal adiposity in these associations remains unclear. We aimed to investigate whether these pregnancy complications affect the odds of offspring obesity independently of maternal obesity.

Methods We did an individual participant data (IPD) meta-analysis of mother–offspring pairs from prospective birth cohort studies that had IPD on mothers with singleton liveborn children born from 1989 onwards and had information available about maternal gestational diabetes, gestational hypertension or pre-eclampsia, and childhood body-mass index (BMI). We applied multilevel mixed-effects models to assess associations of gestational diabetes, gestational hypertension, and pre-eclampsia with BMI SD scores and the odds of overweight and obesity throughout childhood, adjusting for lifestyle characteristics (offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy). We then explored the extent to which any association was explained by maternal pre-pregnancy or early-pregnancy BMI.

Findings 160 757 mother–offspring pairs from 34 European or North American cohorts were analysed. Compared with uncomplicated pregnancies, gestational diabetes was associated with increased odds of overweight or obesity throughout childhood (odds ratio [OR] 1.59 [95% CI 1.36 to 1.86] for early childhood [age 2.0–4.9 years], 1.41 [1.26 to 1.57] for mid childhood [5.0–9.9 years], and 1.32 [0.97 to 1.78] for late childhood [10.0–17.9 years]); however, these associations attenuated towards the null following adjustment for maternal BMI (OR 1.35 [95% CI 1.15 to 1.58] for early childhood, 1.12 [1.00 to 1.25] for mid childhood, and 0.96 [0.71 to 1.31] for late childhood). Likewise, gestational hypertension was associated with increased odds of overweight throughout childhood (OR 1.19 [95% CI 1.01 to 1.39] for early childhood, 1.23 [1.15 to 1.32] for mid childhood, and 1.49 [1.30 to 1.70] for late childhood), but additional adjustment for maternal BMI largely explained these associations (1.01 [95% CI 0.86 to 1.19] for early childhood, 1.02 [0.95 to 1.10] for mid childhood, and 1.18 [1.03 to 1.36] for late childhood). Pre-eclampsia was associated with decreased BMI in early childhood only (difference in BMI SD score -0.05 SD score [95% CI -0.09 to -0.01]), and this association strengthened following additional adjustment for maternal BMI.

Interpretation Although lowering maternal risk of gestational diabetes, gestational hypertension, and pre-eclampsia is important in relation to maternal and fetal pregnancy outcomes, such interventions are unlikely to have a direct impact on childhood obesity. Preventive strategies for reducing childhood obesity should focus on maternal BMI rather than on pregnancy complications.

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Introduction

Gestational diabetes and gestational hypertensive disorders are among the most common pregnancy complications, with gestational diabetes affecting 10–25% and gestational hypertensive disorders affecting 2–4% of all pregnancies.^{1,2} These complications are major risk factors for maternal and fetal morbidity and mortality.^{1–3} Overall, 12% of maternal deaths globally are attributable to gestational hypertensive disorders, whereas up to 10% of adverse fetal outcomes, such as large for gestational age, are attributable to gestational diabetes.^{4–6} Fetal exposure to hyperglycaemia due to

gestational diabetes or altered utero-placental perfusion due to gestational hypertension and pre-eclampsia affect fetal nutrient supply.^{7,8} Alterations in the fetal supply line might influence fetal development and trigger developmental adaptations in adipose tissue, as well as neuroendocrine and metabolic function, which could predispose offspring to adiposity in later life.⁹

Maternal obesity is a risk factor for gestational diabetes and gestational hypertensive disorders, and is also associated with an increased risk of obesity in offspring.¹⁰ Whether gestational diabetes and gestational hypertensive disorders affect the risk of obesity in offspring

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Research in context

Evidence before this study

We searched Medline (through PubMed) up to Jan 31, 2018, to identify relevant cohort studies and systematic reviews that focused on the associations of gestational diabetes and hypertensive disorders of pregnancy with offspring obesity and the role of maternal obesity in these associations. Our search was a combination of the key words (free text and MeSH terms) related to our exposures of interest (gestational diabetes OR gestational hypertension OR pre-eclampsia) and outcomes (overweight OR obesity OR body mass index OR adiposity). We identified several systematic reviews and some prospective cohort studies that varied in terms of methodological quality. Gestational diabetes and gestational hypertensive disorders are common pregnancy complications associated with increased risks of perinatal mortality and morbidity, and seem to influence the risk of obesity in offspring. Maternal obesity is a major risk factor for common pregnancy complications and is also associated with an increased risk of obesity in offspring. However, whether gestational diabetes and gestational hypertensive disorders affect the risk of obesity in offspring independently of the risk conferred by maternal obesity is not clear.

Added value of this study

We did an individual participant data meta-analysis of 160 757 mother-offspring pairs from 34 prospective European

or North-American contemporary pregnancy and birth cohorts. We observed that children born to mothers with gestational diabetes and gestational hypertension had a higher body-mass index (BMI) and higher odds of being overweight throughout childhood than those born to mothers with uncomplicated pregnancies. Pre-eclampsia was associated with a decreased BMI in early childhood. All associations were largely explained by maternal pre-pregnancy and early-pregnancy BMI.

Implications of all the available evidence

Our findings suggest that the previously observed associations of common pregnancy complications with increased BMI in offspring are largely explained by maternal BMI. Therefore, although lowering maternal risk of gestational diabetes, gestational hypertension, and pre-eclampsia is important in relation to maternal and fetal pregnancy outcomes, such intervention is unlikely to have a direct impact on obesity in offspring among women receiving contemporary medical care in developed countries. Preventive strategies for reducing childhood obesity should focus on maternal BMI rather than on pregnancy complications.

independently of the risk conferred by maternal obesity is not clear. Previous studies have shown that diabetes during pregnancy is associated with an increased risk of obesity and higher fat mass in the offspring, independently of maternal sociodemographic and lifestyle characteristics.^{11–17} Inconsistent findings were reported for the specific role of maternal obesity in these associations. Prospective cohort studies have assessed associations of gestational hypertensive disorders with offspring blood pressure, but only a few have also assessed the association with offspring adiposity.^{18–20} A UK study reported that children of women who had either gestational hypertension or pre-eclampsia had an increased risk of obesity at age 9 years, whereas an Australian study found similar associations only in young adults who were born full term to mothers with gestational hypertension, but not in those born to mothers with pre-eclampsia.^{18,19} For the development of new preventive strategies focused on reducing childhood obesity, insight is needed into the effects of gestational diabetes and gestational hypertensive disorders on obesity in offspring, independently of the effects of maternal obesity.

We aimed to assess the associations of maternal gestational diabetes, gestational hypertension, and pre-eclampsia with the odds of overweight and obesity in offspring throughout childhood. We also aimed to explore whether any observed associations were independent of maternal pre-pregnancy or early-pregnancy body-mass index (BMI).

Methods

Search strategy and selection criteria

For this meta-analysis we used individual participant data (IPD) from an existing international collaboration on maternal obesity and childhood outcomes. Pregnancy and birth cohort studies were eligible for inclusion in this international collaboration if the investigators were able to provide IPD on mothers with singleton liveborn children born from 1989 onwards and had information available about maternal pre-pregnancy or early-pregnancy BMI and birthweight or childhood BMI. We invited 50 cohorts from Europe, North America, and Oceania identified from existing collaborations on childhood health (EarlyNutrition Project, CHICOS Project, Birthcohorts.net; last accessed July, 2014), of which 38 agreed to participate. For this study, we only included cohorts that were able to provide IPD for maternal gestational diabetes, gestational hypertension, or pre-eclampsia, and childhood BMI obtained at least once between age 2.0 years and 17.9 years. Anonymised datasets were stored on a single central secured data server accessible to the main analysts (BPG and SS). All studies were approved by their local institutional review boards. Additional ethics approval was not required for this IPD meta-analysis.

Data collection

Information about gestational diabetes, gestational hypertension, pre-eclampsia, and maternal BMI was

See Online for appendix

obtained from medical records, through research assessments, or was self-reported (cohort-specific information is shown in the appendix). Where possible, we used maternal pre-pregnancy BMI (<18.5 kg/m², 18.5 kg/m² to <25 kg/m², 25 kg/m² to <30 kg/m², and ≥30 kg/m²). Five cohorts (comprising 6513 participants) did not have information about pre-pregnancy BMI but measured BMI in early pregnancy (all assessed before or at 20 weeks of gestation).

Data about childhood weight and height were mostly obtained through direct research assessments, with a small number of studies abstracting information about weight and height, or BMI, from medical records, reports by parents or caregivers, or from self-reported data (cohort-specific information is provided in the appendix). We grouped BMI based on the child's age at assessment into early childhood (2.0–4.9 years), mid childhood (5.0–9.9 years), and late childhood (10.0–17.9 years). These age intervals, which correspond roughly to pre-school children, school-age children, and adolescents, were predefined on the basis of data availability and data for each period were provided by the cohorts. If studies had multiple repeated measurements within the same age period, we used data collected at the oldest age. We calculated sex-adjusted and age-adjusted SD scores of childhood BMI using WHO reference growth charts (Growth Analyzer 4.0, Dutch Growth Research Foundation).^{21–24} Childhood underweight, normal weight, and overweight and obesity (hereafter referred to as overweight) were defined on the basis of age-specific and sex-specific WHO criteria.^{21,22}

Covariates were mostly obtained from questionnaires and provided by cohorts as categorical variables (cohort-specific information is shown in the appendix). To allow handling of missing data, continuous covariates were categorised. As potential confounders other than maternal pre-pregnancy BMI, we considered maternal age (defined on the basis of data availability: <25.0 years, 25.0–29.9 years, 30.0–34.9 years, and ≥35.0 years), educational level (provided by the cohorts as low, medium, or high), ethnicity (European or White vs non-European or non-White), parity (nulliparous or multiparous), smoking during pregnancy (yes or no), and offspring's sex. We did not adjust the primary analyses for offspring birthweight and gestational age at delivery, as these birth characteristics are likely to be mediators on the causal pathway and adjustment could introduce bias.²⁵

Statistical analysis

We assessed the percentage of childhood overweight in early, mid, and late childhood for each combined maternal BMI and pregnancy complication group. We applied multilevel mixed-effects models, taking into account clustering of participants within cohorts, to analyse IPD from all cohorts simultaneously.²⁶ Our models were defined assuming a random intercept at cohort level, which allowed for differences in the

intercepts between cohorts. First, we used multilevel linear mixed-effects models to examine the associations of gestational diabetes, gestational hypertension, or pre-eclampsia with BMI SD scores in early, mid, and late childhood. Second, we used multilevel binary logistic mixed-effects models to examine the associations of these pregnancy complications with the odds of childhood underweight and overweight in the same age categories. Participants with either gestational hypertension or pre-eclampsia were compared to those with neither of these conditions, irrespective of their gestational diabetes status. Similarly, those with gestational diabetes were compared to those with no gestational diabetes, irrespective of whether or not they had gestational hypertension or pre-eclampsia.

For all analyses, we constructed an unadjusted model (basic model), a model adjusted for offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy (lifestyle characteristics model), and a model additionally adjusted for maternal pre-pregnancy and early-pregnancy BMI (maternal BMI model). For the associations of pregnancy complications with the odds of childhood underweight, only the basic model was applied because the sample size was insufficient. Based on findings from previous studies and clinical relevance, we tested potential interactions of each pregnancy complication with offspring's sex and maternal BMI, in their associations with childhood BMI.^{27–29} Since no consistent significant interactions were observed, no further stratified analyses were done.

To avoid exclusion of non-complete cases, we used missing values in the covariates as an additional group (percentages missing per cohort shown in the appendix). We did not include information for a cohort for a specific categorical covariate if information for this variable was available for less than 50% of the cohort sample. Because of the strategy used to handle missing data, confounding factors were included in the models as categorical covariates. For sensitivity analyses, we did two-stage random-effects meta-analyses and tested for heterogeneity between cohorts with the *I*² test.²⁶ Analyses were done with SPSS, version 21.0 for Windows, and Review Manager software (RevMan), version 5.3.5.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. BPG and SS had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of 50 cohorts identified and invited, 38 agreed to participate and 34 were included in these analyses. Four cohorts (113 417 participants) were excluded because of missing data for exposures or outcomes, or both,

	Number of participants; birth years	Gestational diabetes (n=2618)	Gestational hypertension (n=9755)	Pre-eclampsia (n=4836)	Early childhood, 2-0-4-9 years (n=85 411)		Mid childhood, 5-0-9-9 years (n=120 409)		Late childhood, 10-0-17-9 years (n=17 332)	
					BMI SD score	Overweight and obesity (n=5606)	BMI SD score	Overweight and obesity (n=24 254)	BMI SD score	Overweight and obesity (n=3699)
ABCD (Netherlands)	5512; 2003-04	120 (2.2%)	1045 (19.0%)	233 (4.2%)	0.3 (-1.5 to 2.4)	213 (4.5%)	0.1 (-1.7 to 2.4)	768 (17.1%)	NA	NA
ALSPAC (UK)	9041; 1991-92	77 (0.9%)	1282 (14.5%)	170 (1.9%)	0.6 (-1.0 to 2.5)	77 (6.5%)	0.2 (-1.6 to 2.7)	2113 (26.4%)	0.2 (-1.9 to 2.5)	2063 (26.4%)
AOB/F (Canada)	1672; 2008-10	71 (4.2%)	118 (7.1%)	104 (6.2%)	0.2 (-2.3 to 2.7)	96 (5.7%)	NA	NA	NA	NA
BAMSE (Sweden)	3329; 1994-96	56 (1.7%)	NA	55 (1.7%)	0.6 (-0.9 to 2.5)	187 (6.5%)	0.5 (-1.2 to 2.6)	799 (31.2%)	0.1 (-1.7 to 2.0)	425 (16.9%)
BIB (UK)	983; 2007-10	100 (10.2%)	51 (5.3%)	13 (1.4%)	0.5 (-1.4 to 2.6)	74 (7.5%)	NA	NA	NA	NA
Co.N.ER (Italy)	528; 2004-05	14 (2.7%)	20 (3.8%)	12 (2.3%)	0.3 (-2.3 to 2.9)	47 (9.7%)	0.7 (-1.3 to 2.9)	102 (35.5%)	NA	NA
DNBC (Denmark)	40 349; 1996-2002	273 (0.7%)	1878 (4.7%)	1380 (3.4%)	NA	NA	0 (-1.9 to 2.1)	6304 (15.6%)	NA	NA
EDEN (France)	1361; 2003-05	92 (6.8%)	67 (4.9%)	30 (2.2%)	0.3 (-1.4 to 2.0)	27 (2.2%)	0 (-1.5 to 2.0)	147 (12.9%)	NA	NA
FCOU (Ukraine)	2332; 1993-96	5 (0.2%)	367 (15.7%)	148 (6.3%)	0.5 (-1.9 to 3.1)	140 (10.6%)	0 (-2.0 to 2.0)	124 (12.6%)	-0.1 (-2.0 to 1.8)	75 (8.9%)
GASPII (Italy)	570; 2003-04	25 (4.4%)	28 (4.9%)	5 (0.9%)	0.7 (-1.1 to 2.9)	52 (9.7%)	0.7 (-1.4 to 2.7)	172 (37.1%)	NA	NA
GECKO Drenthe (Netherlands)	2119; 2006-07	72 (3.4%)	209 (11.0%)	46 (2.4%)	NA	NA	0.4 (-1.2 to 2.4)	465 (21.9%)	NA	NA
GENERATION R (Netherlands)	7550; 2002-06	80 (1.1%)	274 (4.0%)	149 (2.3%)	0.3 (-1.5 to 2.5)	220 (5.1%)	0.3 (-1.5 to 2.7)	1849 (27.4%)	0.4 (-1.5 to 2.6)	160 (30.0%)
GENERATION XXI (Portugal)	5921; 2005-06	390 (6.6%)	135 (2.3%)	90 (1.5%)	0.5 (-1.3 to 3.1)	485 (10.4%)	0.6 (-1.4 to 3.2)	2015 (38.0%)	NA	NA
GENESIS (Greece)	2143; 2003-04	30 (1.4%)	NA	NA	0.8 (-1.2 to 3.6)	297 (14.6%)	1.0 (-1.5 to 3.9)	45 (42.1%)	NA	NA
GINplus (Germany)	2313; 1995-98	61 (2.6%)	NA	NA	0.1 (-1.7 to 2.0)	53 (2.4%)	0 (-1.8 to 1.9)	227 (10.6%)	0 (-1.9 to 2.1)	365 (16.0%)
HUMIS (Norway)	970; 2003-08	5 (0.5%)	37 (3.8%)	70 (7.2%)	0.3 (-1.8 to 2.4)	53 (6.0%)	0.0 (-2.0 to 2.3)	63 (17.6%)	NA	NA
INMA, (Spain)	1933; 1997-2008	191 (11.3%)	58 (3.0%)	4 (0.9%)	0.5 (-1.2 to 2.8)	143 (8.2%)	0.6 (-1.4 to 3.3)	503 (37.6%)	0.3 (-1.6 to 2.5)	79 (25.3%)
KOALA (Netherlands)	2061; 2000-02	21 (1.0%)	72 (3.5%)	26 (1.3%)	-0.1 (-2.0 to 1.9)	17 (1.7%)	-0.2 (-2.2 to 1.8)	199 (11.3%)	-0.2 (-2.1 to 2.2)	19 (18.1%)
Krakow Cohort (Poland)	424; 2000-03	18 (4.2%)	19 (4.5%)	0 (0.0%)	0 (-2.2 to 2.3)	11 (4.1%)	0.2 (-1.8 to 2.6)	90 (26.5%)	NA	NA
LISAplus (Germany)	1584; 1997-99	58 (3.7%)	NA	NA	0 (-1.7 to 1.9)	33 (2.3%)	-0.1 (-1.8 to 1.8)	140 (9.9%)	0 (1.8 to 2.1)	236 (15.2%)
MoBa (Norway)	55 008; 1999-09	418 (0.8%)	3131 (5.7%)	2023 (3.7%)	0.4 (-1.8 to 2.5)	2456 (6.1%)	0.1 (-2.0 to 2.3)	6793 (19.5%)	NA	NA
NINFEA* (Italy)	1726; 2005-10	132 (7.7%)	136 (7.9%)	44 (2.6%)	0.1 (-2.3 to 2.5)	86 (5.1%)	0 (-2.2 to 2.4)	90 (21.2%)	NA	NA
PÉLAGIE (France)	738; 2002-05	21 (2.8%)	24 (3.3%)	8 (1.1%)	0.1 (-1.8 to 1.9)	15 (2.0%)	NA	NA	NA	NA
PIAMA (Netherlands)	1815; 1996-97	19 (1.0%)	179 (9.9%)	46 (2.5%)	0.7 (-1.2 to 2.5)	78 (8.9%)	0.1 (-1.6 to 2.4)	325 (20.0%)	-0.2 (-1.7 to 1.8)	77 (10.0%)
Piccolipiù (Italy)	687; 2011-15	69 (10.1%)	24 (3.5%)	6 (0.9%)	0.3 (-2.1 to 2.5)	40 (5.8%)	NA	NA	NA	NA
Project Viva (USA)	1389; 1999-2002	64 (4.7%)	85 (6.3%)	46 (3.4%)	0.7 (-1.0 to 2.7)	87 (7.1%)	0.4 (-1.4 to 3.0)	328 (30.8%)	0.4 (-1.5 to 3.7)	8 (25.8%)
REPRO_PL (Poland)	291; 2007-11	13 (4.5%)	17 (5.8%)	0 (0.0%)	0.3 (-2.2 to 2.5)	19 (6.9%)	0.6 (-1.5 to 3.6)	19 (38.8%)	NA	NA
RHEA (Greece)	740; 2007-08	60 (8.8%)	35 (5.2%)	5 (0.7%)	0.6 (-1.1 to 3.6)	91 (12.3%)	NA	NA	NA	NA
ROLO (Ireland)	283; 2007-11	10 (3.5%)	NA	NA	0.2 (-1.7 to 2.6)	19 (6.7%)	NA	NA	NA	NA
SCOPE BASELINE (Ireland)	1046; 2008-11	NA	129 (12.3%)	35 (3.3%)	0.6 (-1.0 to 2.3)	62 (5.9%)	NA	NA	NA	NA
SEATON (UK)	872; 1998-99	NA	119 (13.9%)	16 (2.1%)	0.7 (-0.9 to 2.7)	36 (8.1%)	0.6 (-1.1 to 2.8)	55 (19.8%)	0.4 (-1.6 to 2.6)	192 (32.9%)
Slovak PCB study (Slovakia)	524; 2002-04	3 (0.6%)	54 (12.4%)	NA	1.9 (-2.4 to 5.3)	222 (48.2%)	0.3 (-1.7 to 3.3)	123 (31.0%)	NA	NA
STEPS (Finland)	297; 2008-10	20 (6.7%)	NA	NA	0.5 (-1.2 to 2.2)	13 (4.4%)	NA	NA	NA	NA
SWS (UK)	2646; 1998-2007	30 (1.1%)	162 (6.1%)	72 (2.7%)	0.5 (-1.3 to 2.6)	157 (6.2%)	0.2 (-1.5 to 2.5)	396 (22.0%)	NA	NA

Data are n (valid %) or median (95% range), unless otherwise stated. NA=not available. *Subset of participants with follow-up completed at 4 years of child's age by the time of data transfer (March, 2015).

Table: Characteristics of the participating pregnancy and birth cohorts (n=160 757)

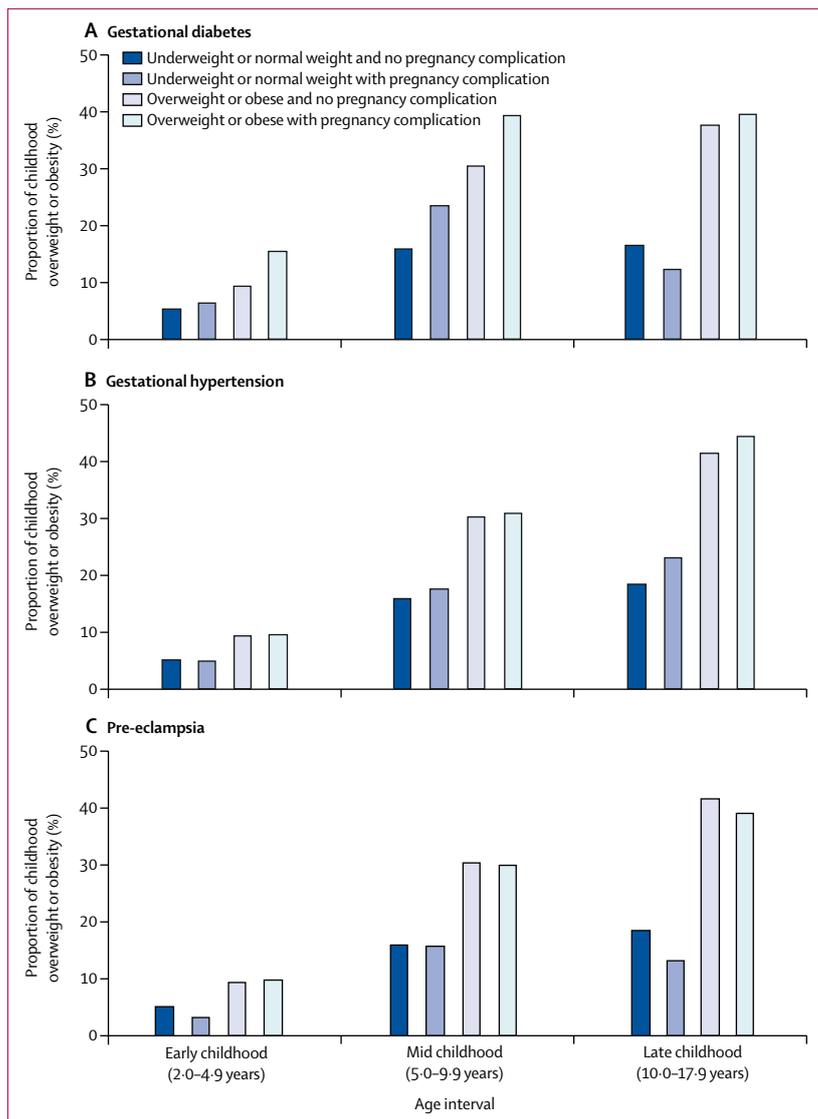


Figure 1: Proportions of childhood overweight according to maternal pre-pregnancy BMI category and presence or absence of gestational diabetes (A), gestational hypertension (B), and pre-eclampsia (C) BMI=body-mass index.

resulting in 160757 mother–offspring pairs available for analysis (appendix).

Of 160757 mothers, 2618 (1.7%) had gestational diabetes, 9755 (6.5%) had gestational hypertension, and 4836 (3.3%) had pre-eclampsia (table). 30927 (19.7%) mothers were overweight and 12467 (7.9%) were obese. Among offspring, 5606 (6.6%) were overweight in early childhood, 24254 (20.1%) were overweight in mid childhood, and 3699 (21.3%) were overweight in late childhood. Cohort-specific information about childhood age at assessment and BMI is shown in the appendix. The highest proportions of childhood overweight were observed in children whose mothers were overweight or obese at the start of pregnancy, independently of whether their mothers had gestational diabetes or gestational

hypertensive disorders (figure 1). In both normal weight and overweight or obese women, the proportion of overweight in their offspring was slightly higher in those with gestational diabetes than in those without, whereas no differences were observed between women with and without gestational hypertensive disorders.

In basic and lifestyle characteristics models, gestational diabetes was associated with increased offspring BMI throughout childhood (differences in BMI SD scores in lifestyle characteristics models: 0.11 SD score [95% CI 0.06 to 0.16] in early childhood, 0.21 [0.16 to 0.26] in mid childhood, and 0.08 [−0.04 to 0.21] in late childhood), compared with uncomplicated pregnancies (figure 2A). After additional adjustment for maternal BMI, these associations largely attenuated towards the null. Similarly, gestational diabetes was associated with increased odds of overweight throughout childhood in basic and lifestyle characteristics models, with the strongest association in early childhood (odds ratio [OR] 1.59 [95% CI 1.36 to 1.86] for early childhood, 1.41 [1.26 to 1.57] for mid childhood, and 1.32 [0.97 to 1.78] for late childhood in lifestyle characteristics models; figure 2B). Adjustment for maternal BMI largely attenuated the effect estimates towards the null (OR 1.35 [95% CI 1.15 to 1.58] for early childhood, 1.12 [1.00 to 1.25] for mid childhood, and 0.96 [0.71 to 1.31] for late childhood). Only the association of gestational diabetes with the odds of early childhood overweight remained significant (OR 1.35 [95% CI 1.15 to 1.58]). Gestational diabetes tended to be associated with decreased odds of underweight throughout childhood in the basic model (appendix). Additional adjustment for gestational hypertension and pre-eclampsia did not affect the observed associations of gestational diabetes with childhood outcomes (appendix). Although no statistical interaction was present, we did sensitivity analyses to explore the associations of gestational diabetes with childhood BMI, stratified by maternal BMI groups, and found similar associations across groups (appendix). Similar associations of gestational diabetes with childhood BMI were observed when the analysis was restricted to pre-pregnancy BMI only (appendix).

Compared with uncomplicated pregnancies, gestational hypertension was associated with increased BMI throughout childhood in basic and lifestyle characteristics models (differences in BMI SD score in lifestyle characteristics models: 0.07 SD score [95% CI 0.03 to 0.11] in early childhood, 0.13 [0.10 to 0.17] in mid childhood, and 0.20 [0.14 to 0.27] in late childhood; figure 3A). These associations were partly explained by maternal BMI (difference in BMI SD score in maternal BMI models: 0.01 SD score [95% CI −0.03 to 0.06] in early childhood, 0.04 [0.01 to 0.07] in mid childhood, and 0.07 [0.01 to 0.13] in late childhood). Gestational hypertension was also associated with increased odds of overweight throughout childhood (OR 1.19 [95% CI 1.01 to 1.39] for early childhood, 1.23 [1.15 to 1.32] for mid

childhood, and 1.49 [1.30 to 1.70] for late childhood). Additional adjustment for maternal BMI largely attenuated these associations (1.01 [95% CI 0.86 to 1.19] for early childhood, 1.02 [0.95 to 1.10] for mid childhood, and 1.18 [1.03 to 1.36] for late childhood; figure 3B). In the basic model, gestational hypertension was associated with decreased odds of childhood underweight at all ages (appendix).

Pre-eclampsia was associated with decreased BMI in early childhood in both basic and lifestyle characteristics models (difference in BMI SD score in lifestyle characteristics model -0.05 SD score [95% CI -0.09 to -0.01]; figure 4A). This inverse association strengthened upon additional adjustment for maternal BMI. By contrast, we observed a positive association of pre-eclampsia with BMI in mid childhood and late childhood in basic and lifestyle characteristics models (differences in BMI SD score in lifestyle characteristics models: 0.10 SD score [95% CI 0.06 to 0.13] in mid childhood and 0.16 [95% CI 0.03 to 0.30] in late childhood). These associations were fully attenuated after additional adjustment for maternal BMI. The associations of pre-eclampsia with overweight in mid and late childhood were also fully attenuated after adjustment for maternal BMI (figure 4B). In the basic model, pre-eclampsia was associated with increased odds of underweight in early childhood only (appendix). Similar associations of both gestational hypertension and pre-eclampsia with childhood outcomes were observed when the analysis was restricted to pre-pregnancy BMI only and when additionally adjusting for gestational diabetes (appendix).

In an analysis of complete cases of maternal pre-pregnancy BMI and age, similar associations between gestational diabetes and hypertensive disorders of pregnancy with childhood BMI were observed when adjusting for these confounding factors as continuous or categorical covariates (appendix). Analyses done with two-stage meta-analyses were consistent with those obtained from our main one-stage meta-analyses (appendix). We did not observe substantial heterogeneity between the cohorts in any association that we assessed (I^2 range 0% to 40%, with six of the nine meta-analyses having $I^2 < 25\%$; appendix).

Discussion

Results from our IPD meta-analysis of 160757 mothers and children from Europe and North America show that children born to mothers with gestational diabetes and gestational hypertension had a higher BMI and higher odds of being overweight throughout childhood than children born to mothers with uncomplicated pregnancy, whereas pre-eclampsia was associated with a lower BMI in early childhood. These associations were of small magnitude and largely explained by maternal pre-pregnancy and early-pregnancy BMI.

Gestational diabetes and gestational hypertensive disorders affect substantial numbers of pregnancies and

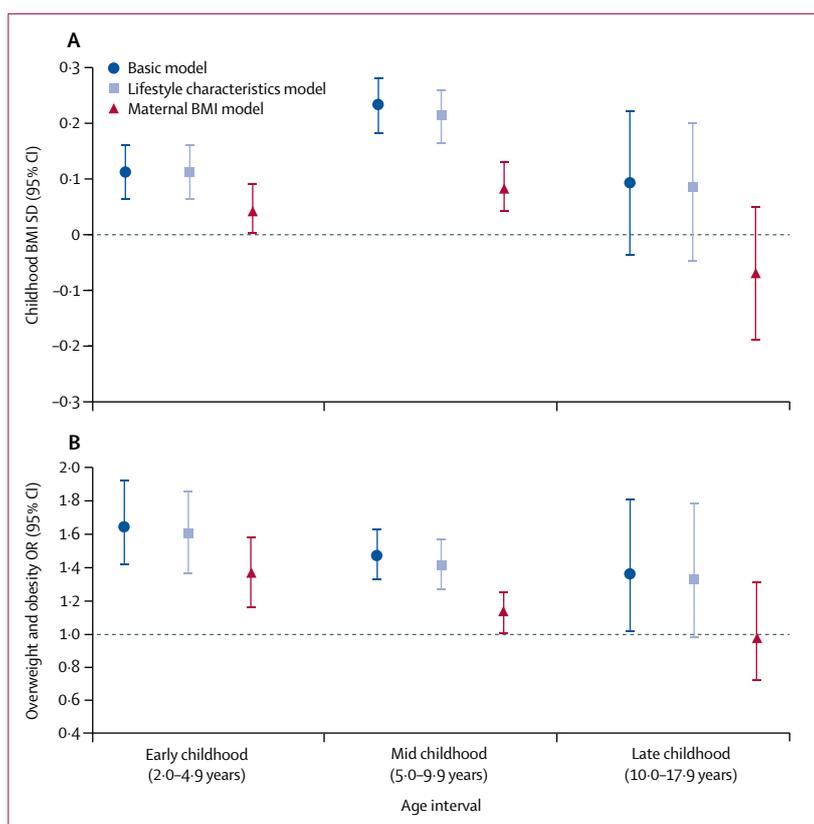


Figure 2: Associations of gestational diabetes with offspring BMI outcomes in early, mid, and late childhood Values are regression coefficients (95% CI) from multilevel linear mixed-effects models that reflect differences in early childhood, mid childhood, and late childhood BMI SD scores and OR (95% CI) from multilevel binary logistic models that reflect differences in risk of overweight and obesity for children born to mothers with gestational diabetes, compared with the reference group (children born to mothers with an uncomplicated pregnancy). Lifestyle characteristics models adjusted for offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy. Maternal BMI models additionally adjusted for maternal pre-pregnancy and early-pregnancy BMI. BMI=body-mass index. OR=odds ratio.

are associated with adverse maternal and fetal pregnancy outcomes.¹⁻³ Gestational diabetes might lead to fetal overnutrition as a result of maternal hyperglycaemia during pregnancy.⁷ Gestational hypertension and pre-eclampsia are related to placental dysfunction, which might lead to impaired fetal nutrient supply.^{8,30} Both conditions might subsequently induce permanent changes in offspring body composition, neuroendocrine systems, and metabolic functions, which predispose offspring to an increased risk of obesity in later life.⁹ We aimed to explore whether gestational diabetes and gestational hypertensive disorders affect the risk of offspring obesity independently of the risk conferred by maternal obesity. Disentangling the independent roles of these maternal pregnancy complications on childhood obesity risk is important for development of future childhood obesity prevention strategies.

Results from two systematic reviews of 12 and nine published cohort studies suggested that maternal diabetes during pregnancy was associated with increased offspring BMI.^{14,31} These associations were no longer present in

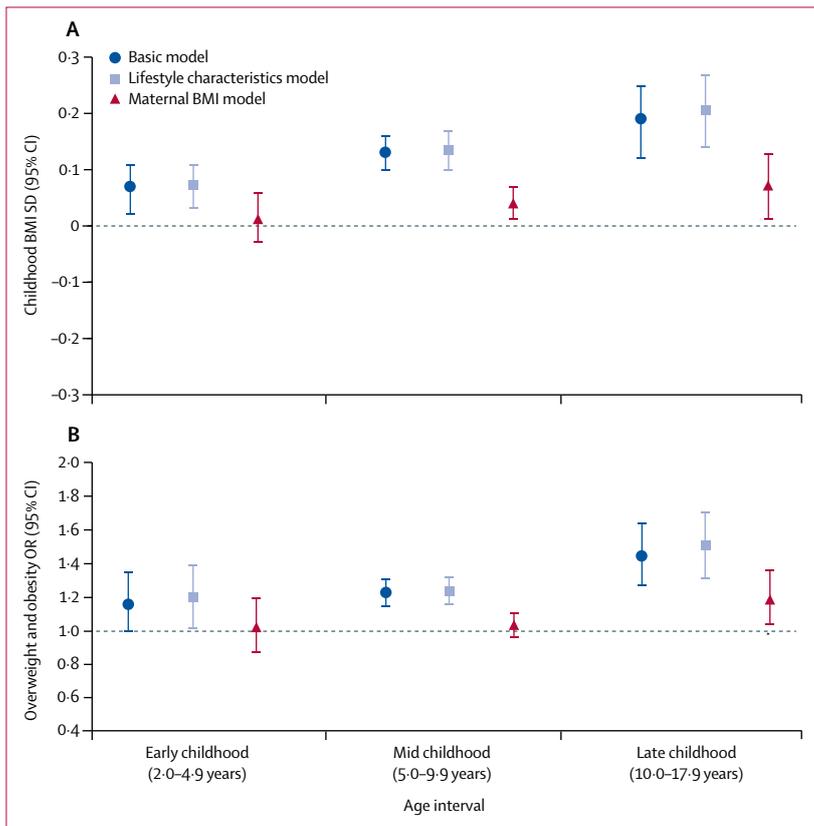


Figure 3: Associations of gestational hypertension with offspring BMI outcomes in early, mid, and late childhood

Values are regression coefficients (95% CI) from multilevel linear mixed-effects models that reflect differences in early childhood, mid childhood, and late childhood BMI SD scores, and OR (95% CI) from multilevel binary logistic models that reflect differences in risk of overweight and obesity for children born to mothers with gestational hypertension, compared with the reference group (children born to mothers with an uncomplicated pregnancy). Lifestyle characteristics models adjusted for offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy. Maternal BMI models additionally adjusted for maternal pre-pregnancy and early-pregnancy BMI. BMI=body-mass index. OR=odds ratio.

single studies that adjusted for maternal pre-pregnancy BMI.^{14,31} Several prospective observational studies have reported inconsistent findings for the association of gestational diabetes with offspring BMI after adjustment for maternal BMI.^{11–13,15–17,32–34} An older prospective cohort study of 280866 Swedish men recruited from 1973 to 1988 suggested that diabetes during pregnancy, including gestational diabetes and pre-existing diabetes, was associated with increased BMI at the age of 18 years. This association was independent of maternal BMI.¹⁷ By contrast, we observed that children of mothers with gestational diabetes had increased BMI throughout childhood, but this association was largely explained by maternal pre-pregnancy and early-pregnancy BMI. This different finding might be explained by methodological differences between our IPD meta-analysis and the Swedish Study, as the Swedish study was focused on men only, measured offspring BMI in adulthood, and does not reflect contemporary clinical practice, which involves newer screening and treatment strategies. We observed

the strongest association of gestational diabetes with offspring obesity in early childhood. This association might be explained by tracking of birth size.^{35,36} Consistent with our findings, treatment of gestational diabetes, defined as fasting glucose less than 95 mg/dL and two of three timed measurements that exceeded established thresholds, was found to be beneficial for neonatal outcomes, but did not influence offspring obesity risk at age 5–10 years in a multicentre randomised controlled trial.³⁷ Diagnosis of gestational diabetes might insufficiently reflect glycaemic status during pregnancy. Maternal glucose concentrations below current diagnostic criteria of diabetes are linearly and positively associated with adverse perinatal outcomes.^{35,38} However, several studies have shown that maternal gestational glucose is not associated with offspring BMI in early childhood, after adjustment for maternal BMI.^{39,40} Thus, our findings suggest that the association of gestational diabetes with increased BMI in offspring is largely explained by maternal BMI.

Few studies have examined the association of gestational hypertensive disorders with childhood adiposity. Data from a UK prospective cohort study of 6343 mother-offspring pairs found a positive association of gestational hypertension with childhood adiposity at age 9 years, which was attenuated after adjustment for parental BMI.¹⁸ This study also found inverse associations of pre-eclampsia with offspring lean mass and adiposity at age 9 years after adjustment for parental BMI.¹⁸ By contrast, an Australian cohort study of 1151 mother-offspring pairs born full term showed that offspring of mothers with gestational hypertension had increased risk of overweight at 20 years, independently of maternal BMI.¹⁹ No association of pre-eclampsia with offspring BMI was present.¹⁹ We observed that gestational hypertension was associated with increased BMI and odds of overweight throughout childhood, but this association was also largely explained by maternal BMI. Pre-eclampsia was associated with a decreased BMI in early childhood, and this inverse association was stronger after adjustment for maternal BMI. In later childhood, pre-eclampsia was associated with increased childhood BMI, but this association was no longer present after adjustment for maternal BMI. This observation might be explained by a smaller size at birth among children of mothers with pre-eclampsia due to placental dysfunction and fetal growth restriction.⁴¹ These children might have accelerated growth in infancy and early childhood, leading to increased BMI in mid and late childhood.⁴² Further studies involving detailed assessments of maternal blood pressure and placental function, which provide details of disease severity, might provide more insight into the effects of pre-eclampsia on development of childhood adiposity.

Our observations are important from an aetiological and preventive perspective. The associations of gestational diabetes and gestational hypertensive disorders with offspring obesity were of limited clinical importance and largely dependent on maternal BMI. Interventions to reduce the risk of pregnancy complications or improve

the effectiveness of their treatment are important in relation to a range of problems for the mother and child, but they are unlikely to directly influence the development of obesity in offspring born to obese as well as normal weight mothers.

Major strengths of our study are the large sample of contemporary populations reflecting current diagnosis and treatment policies and the use of IPD from a wide selection of existing studies to reduce the risk of publication bias. We were able to adjust for multiple confounders, with a particular focus on maternal pre-pregnancy BMI. Of 50 cohorts identified and invited, 38 agreed to participate and 34 were included in these analyses. Only four cohorts (113 417 participants) were excluded because of missing data about exposures or outcomes, or both. Bias in our findings is unlikely since the reasons for not participating are not related to the research question of the study but instead related to study design or follow-up. Although we included cohorts from early 1990s onwards, the study period does not seem to influence our findings since we observed low heterogeneity between all cohorts in the associations assessed. We included data from cohort studies done in Europe and North America, so our findings are mainly applicable to populations in developed countries. Inclusion of data from other regions could have led to large differences in prevalence of maternal and childhood obesity, treatment of pregnancy complications, and ethnic and socio-demographic characteristics, complicating or limiting the possibility to do a meta-analysis. Further studies are needed to assess these associations among populations from low-income and middle-income countries, and to explore potential differences among women from different ethnic backgrounds known to be at higher risk of developing pregnancy complications. Within some cohorts, women with multiple singleton pregnancies might have participated. We were unable to account for within-mother clustering, as these data were not available within our IPD meta-analysis. However, as this clustering would only reflect a small number of women, we consider it unlikely to have affected our results. Our observed associations are applicable for singleton pregnancies. As important differences in placental development and function, fetal nutrient supply, and growth are present among twin pregnancies, further studies are needed to explore whether these findings are also present among twin pregnancies. We are aware that our study cannot overcome potential limitations of individual studies in terms of their design and conduct, differences in measurements, and definitions of exposure and outcome data, variation in missing data, and loss to follow-up. Some cohorts relied on self-reporting to obtain information about pregnancy complications. We were not able to do sensitivity analyses based on the methods of data collection since some cohorts used more than one method to collect data about pregnancy complications. Misclassification of women, if present, might have led to

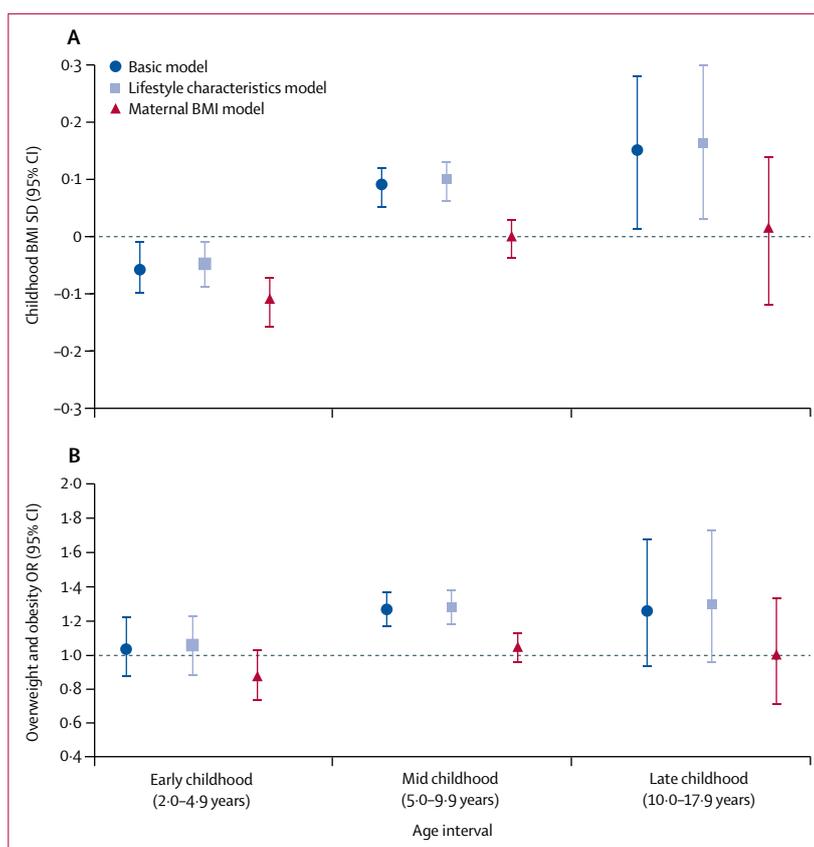


Figure 4: Associations of pre-eclampsia with offspring BMI outcomes in early, mid, and late childhood
Values are regression coefficients (95% CI) from multilevel linear mixed-effects models that reflect differences in early childhood, mid childhood, and late childhood. BMI SD scores and OR (95% CI) from multilevel binary logistic models that reflect risk of overweight and obesity for children born to mothers with pre-eclampsia, compared with the reference group (children born to mothers with an uncomplicated pregnancy). Lifestyle characteristics models adjusted for offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy. Maternal BMI models additionally adjusted for maternal pre-pregnancy and early-pregnancy BMI. BMI=body-mass index. OR=odds ratio.

attenuation of the associations. The prevalence of gestational diabetes in our sample was relatively low and varied substantially between cohorts, which might suggest under-ascertainment of this condition, differences in screening protocols between cohorts, and a selection towards a relatively healthy study population. These factors might affect the generalisability of our findings. We have no information about how any of the pregnancy complications were treated, which might also have differed across cohorts. Effective treatment that reduced circulating glucose and blood pressure during pregnancy might lead to weaker associations of these conditions with offspring obesity. Given that our IPD meta-analysis includes contemporary cohorts reflecting contemporary screening and treatment protocols, it seems likely that a large number of women received treatment for their pregnancy complication. Self-reported maternal pre-pregnancy BMI might also be a source of bias. However, a systematic review showed that reporting error did not bias associations between pregnancy-related weight and birth

outcomes,⁴³ suggesting that bias due to self-reported maternal BMI is unlikely in our results. If pre-pregnancy BMI was not available, we used early-pregnancy BMI, which might have overestimated BMI as a result of gestational weight gain. However, similar results were observed when restricting the analyses to participants with information about pre-pregnancy BMI. Most cohorts relied on clinician-measured childhood weight and height, and so bias based on self-reported weight and height is unlikely. We did not do mediation analyses, which we consider beyond the scope of this study. However, based on our findings, a mediating role of pregnancy complications in the associations of maternal BMI with childhood BMI seems unlikely. Further studies are needed to explore which pregnancy, birth, genetic, or lifestyle characteristics mediate the associations of maternal BMI with childhood BMI. Missing values of covariates were used as an additional group, which might not be optimal, but is a method commonly used in large IPD meta-analyses.⁴⁴ Finally, because of the observational design, residual confounding cannot be excluded.

In conclusion, the associations of gestational diabetes, gestational hypertension, and pre-eclampsia with childhood obesity are largely explained by maternal pre-pregnancy and early-pregnancy BMI. These findings from a large international IPD meta-analysis of contemporary cohorts are important for future public health strategies for childhood obesity. Interventions focused on prevention or treatment of these pregnancy complications, although important for other maternal and fetal pregnancy outcomes, are unlikely to have a direct impact on offspring BMI.

Contributors

BPG and SS had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. BPG, SS, VVWJ, and RG contributed to study concept and design. BPG, SS, EV, VVWJ, and RG contributed to analysis and interpretation of data. BPG, SS, DAL, VVWJ, and RG contributed to drafting of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content.

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Declaration of interests

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