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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Bernadeta Patro Golab[1,2,3], Susana Santos[1,2], Ellis Voerman[1,2], Henrique Barros[4,5], Anna Bergström[6,7], Marie-Aline Charles[8,9], Leda Chatzi[10,11,12], Cécile Chevrier[13], George P. Chrousos[14], Eva Corpeleijn[15], Nathalie Costet[13], Sarah Crozier[16], Graham Devereux[17], Merete Eggesbø[18], Sandra Ekström[6], Maria Pia Fantini[19], Sara Farchi[20], Francesco Forastiere[20], Vagelis Georgiu[11], Keith M. Godfrey[16,21], Davide Gori[19], Wojciech Hanke[22], Irva Hertz-Picciotto[23], Barbara Heude[8,9], Daniel Hryhorczuk[24], Hazel Inskip[16,21], Jesus Ibarluzea[25,26,27,28], Louise C. Kenny[29,30], Leanne K. Küpers[15,31,32], Hanna Lagström[33], Irina Lehmann[34], Virissa Lenters[18], Sabrina Llop[28,35], Per Magnus[36], Renata Majewska[37], Johanna Mäkelä[38], Yannis Manios[39], Fionnuala M. McAuliffe[40], Sheila W. McDonald41, John Mehegan42, Monique Mommers43, Camilla S. Morgen44,45, George Moschonis46, Deirdre Murray29,47, Carol Ní Chaoimh29,48, Ellen A. Nøhr49, Anne□Marie Nybo Andersen45, Emily Oken50, Adriëtte J.J.M., Oostvogels[51], Agnieszka Pac[37], Eleni Papadopoulou[52], Costanza Pizzi[53], Kinga Polanska[22], Daniela Porta[20], Lorenzo Richiardi[53], Sheryl L. Rifas-Shiman[50], Franca Rusconi[54], Ana C. Santos[4,5], Henriette A. Smit[55], Thorkild I.A. Sørensen[45,56], Marie Standl[57], Camilla Stoltenberg[58,59], Jordi Sunyer[28,60,61], Michelle Taylor[31, 32], Elisabeth Thiering[57,62], Carel Thijs[43], Maties Torrent[63], Suzanne C. Tough[41,64], Tomas Trnovec[65], Steve Turner[66], Lenie van Rossem[55], Andrea von Berg[67], Martine Vrijheid[28,60,61],Tanja Vrijkotte[51], Jane West[68], John Wright[68], Oleksandr Zvinchuk[69], Debbie A. Lawlor[31,32], Vincent W.V. Jaddoe*[1,2,70], Romy Gaillard*[1,2]

** Authors contributed equally*

1 The Generation R Study Group, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.

2 Department of Pediatrics, Erasmus MC, University Medical Center, Rotterdam, the Netherlands. 3 Department of Pediatrics, Medical University of Warsaw, Warsaw, Poland.

4 EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Rua das Taipas, nº 135, 4050-600 Porto, Portugal. 7 Department of Public Health and Forensic Sciences and Medical Education, Unit of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, Portugal.

5 Department of Public Health and Forensic Sciences and Medical Education, Unit of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto Medical School, Porto, Portugal.

6 Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

7 Centre for Occupational and Environmental Medicine, Stockholm County Council, Stockholm, Sweden.

8 INSERM, UMR1153 Epidemiology and Biostatistics Sorbonne Paris Cité Center (CRESS), ORCHAD Team, Paris, France.

9 Paris Descartes University, Paris, France.

10 Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California, USA.

11 Department of Social Medicine, Faculty of Medicine, University of Crete, Heraklion, Greece.

12 Department of Genetics and Cell Biology, Maastricht University, the Netherlands.

13 Inserm UMR 1085, Irset - Research Institute for Environmental and Occupational Health, F-35000 RENNES, France.

14 First Department of Pediatrics, Athens University Medical School, Aghia Sophia "Children's Hospital, National and Kapodistrian University of Athens, Athens, Greece.

15 Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.
16 MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK.
17 Liverpool School of Tropical Medicine, Liverpool, UK.
18 Department of Exposure and Environmental Epidemiology, Norwegian Institute of Public Health, Oslo, Norway.
19 The Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy.
20 Department of Epidemiology, Lazio Regional Health Service, Rome, Italy.
21 NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK.
22 Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland.
23 Department of Public Health Sciences, School of Medicine, University of California Davis, Davis, California 95616, USA.
24 Center for Global Health, University of Illinois College of Medicine, Chicago, IL, USA.
25 Subdirección de Salud Pública Gipuzkoa, San Sebastián, Spain.
26 Instituto de Investigación Sanitaria BIODONOSTIA, San Sebastián, Spain.
27 School of Psychology-University of the Basque Country, San Sebastián, Spain.
28 CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain.
29 Irish Centre for Fetal and Neonatal Translational Research, Cork University Maternity Hospital, University College Cork, Cork, Ireland.
30 Department of Obstetrics and Gynaecology, Cork University Maternity Hospital, Cork, Ireland.
31 MRC Integrative Epidemiology Unit at the University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, UK.
32 Population Health Science, Bristol Medical School, University of Bristol, Bristol BS8 2BN, UK.
33 Department of Public Health, University of Turku, Turku, Finland.
34 Department of Environmental Immunology/Core Facility Studies, Helmholtz Centre for Environmental Research – UFZ, Leipzig, Germany.
35 Epidemiology and Environmental Health Joint Research Unit, FISABIO (Foundation for the Promotion of Health and Biomedical Research in the Valencian Region), Valencia, Spain. 36 Division of Health Data and Digitalization, Norwegian Institute of Public Health, Oslo, Norway.
37 Department of Epidemiology, Chair of Epidemiology and Preventive Medicine, Jagiellonian University Medical College, Krakow, Poland. 38 Turku Centre for Biotechnology, University of Turku and Abo Akademi University, Turku, Finland. 39 Department of Nutrition and Dietetics, School of Health Science and Education, Harokopio University, Athens, Greece.
40 UCD Perinatal Research Centre, Obstetrics & Gynaecology, School of Medicine, University College Dublin, National Maternity Hospital, Dublin, Ireland.
41 Department of Pediatrics, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada.
42 UCD Perinatal Research Centre, School of Public Health and Physiotherapy and Sports Science, University College Dublin, Dublin, Ireland. 43 Department of Epidemiology, Care and Public Health Research Institute, Maastricht University, Maastricht, The Netherlands.
44 National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark.
45 Department of Public Health, Section of Epidemiology, University of Copenhagen, Øster Farimagsgade 5, 1014, Copenhagen, Denmark.
46 Department of Rehabilitation, Nutrition and Sport; La Trobe University, Australia
47 Paediatrics & Child Health, University College Cork, Cork, Ireland.

48 Cork Centre for Vitamin D and Nutrition Research, School of Food and Nutritional Sciences, University College Cork, Cork, Ireland.
49 Research Unit for Gynaecology and Obstetrics, Institute for Clinical Research, University of Southern Denmark, Denmark.
50 Department of Population Medicine, Harvard Medical School, Harvard Pilgrim Health Care Institute, Boston, MA, USA.
51 Department of Public Health, Amsterdam Public Health Research Institute, Academic Medical Center, Amsterdam, The Netherlands.
52 Department of Environmental Exposures and Epidemiology, Domain of Infection Control and Environmental Health, Norwegian Institute of Public Health, Lovisenberggata 8, 0477 Oslo, Norway
53 Department of Medical Sciences, University of Turin, Turin, Italy.
54 Unit of Epidemiology "Anna Meyer", Children's University Hospital, Florence, Italy.
55 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. 56 Novo Nordisk Foundation Center for Basic Metabolic Research, Section of Metabolic Genetics, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark.
57 Institute of Epidemiology I, Helmholtz Zentrum München-German Research Center for Environmental Health, Neuherberg, Germany.
58 Norwegian Institute of Public Health, Oslo, Norway. 59 Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway.
60 ISGlobal, Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain.
61 Universitat Pompeu Fabra (UPF), Barcelona, Spain.
62 Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University Munich, Munich, Germany.
63 Ib-salut, Area de Salut de Menorca, Palma, Spain. 64 Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada.
65 Department of Environmental Medicine, Slovak Medical University, Bratislava 833 03, Slovak Republic.
66 Child Health, Royal Aberdeen Children's Hospital, Aberdeen, UK.
67 Research Institute, Department of Pediatrics, Marien-Hospital Wesel, Wesel, Germany. 68 Bradford Institute for Health Research, Bradford Royal Infirmary, Bradford, UK. 69 Department of Medical and Social Problems of Family Health, Institute of Pediatrics, Obstetrics and Gynecology, Kyiv, Ukraine.
70 Department of Epidemiology, Erasmus MC, University Medical Center, Rotterdam, the Netherlands.
Address correspondence to: Romy Gaillard, MD, PhD. The Generation R Study Group (Na29-15). Erasmus MC, University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands (r.gaillard@erasmusmc.nl). Phone: +31 (0) 10 7043405, Fax: +31 (0) 10 7044645

RESEARCH IN CONTEXT

Evidence before this study

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 the offspring. Maternal obesity is a major risk factor for common pregnancy complications, and is also associated with an increased risk of obesity in the offspring. It is not clear whether gestational diabetes and gestational hypertensive disorders affect the risk of offspring obesity independently of the risk conferred by maternal obesity.

Added value of this study

We performed an individual participant data meta-analysis of 160757 mother-offspring pairs from 34 prospective European or North-American contemporary pregnancy/birth cohorts. We observed that children born to mothers with gestational diabetes and gestational hypertension had a higher BMI and

higher risk of being overweight throughout childhood. Pre-eclampsia was associated with a lower BMI in early-childhood. All associations were largely explained by maternal pre/early-pregnancy BMI.
Implications of all the available evidence
Lowering maternal risk of gestational diabetes, gestational hypertension and pre-eclampsia, though important in relation to maternal and fetal pregnancy outcomes, is unlikely to have a direct impact on offspring obesity. Preventive strategies for reducing childhood obesity should not focus on these pregnancy complications.

SUMMARY
Background: Gestational diabetes and gestational hypertensive disorders are associated with offspring obesity. The role of maternal adiposity in these associations remains unclear.
Methods: In this individual participant data meta-analysis of 160757 mother-offspring pairs from 34 prospective European or North-American pregnancy/birth cohorts, we assessed the associations of gestational diabetes, gestational hypertension and pre-eclampsia with childhood BMI and the risk of overweight and obesity throughout childhood. We explored to which extent any association was explained by maternal pre/early-pregnancy BMI.
Findings: Gestational diabetes was associated with a higher risk of overweight throughout childhood (Odds Ratio (OR) 1·59 (95% Confidence Intervals (CI) 1·36, 1·86); OR 1·41 (95% CI 1·26, 1·57); OR 1·32 (95% CI 0·99, 1·78) for early-, mid- and late-childhood, respectively) when compared to uncomplicated pregnancies. These associations attenuated towards the null following adjustment for maternal BMI. Likewise, gestational hypertension was associated with a higher risk of overweight throughout childhood, with the strongest association in late-childhood (OR 1·49 (95% CI 1·30, 1·70)), when compared to uncomplicated pregnancies. Additional adjustment for maternal BMI partly explained these associations. Pre-eclampsia was associated with a lower BMI in early-childhood only (difference in BMI-SDS - 0.05 SDS (95% CI - 0·09, - 0·01)), when compared to uncomplicated pregnancies. This association strengthened upon additional adjustment for maternal BMI.
Interpretation: Our results suggest that lowering maternal risk of gestational diabetes and hypertensive disorders is unlikely to have a direct impact on offspring obesity.
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INTRODUCTION

Gestational diabetes and gestational hypertensive disorders are common pregnancy complications with high global prevalences.[1,2] These complications are major risk factors for maternal and fetal morbidity and mortality, and seem to be associated with obesity in offspring.[1-6] Both fetal exposure to hyperglycemia 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 may influence fetal development, and trigger developmental adaptations in adipose tissue, 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] Thus far, it is not clear whether gestational diabetes and gestational hypertensive disorders affect the risk of offspring obesity independently of the risk conferred by maternal obesity. Previous studies have shown that diabetes during pregnancy is associated with an increased risk of offspring obesity and higher fat mass levels, independent of maternal socio-demographic and lifestyle characteristics.[11-17] Inconsistent findings were reported for the specific role of maternal obesity in these associations. Prospective cohort studies have assessed the relations of gestational hypertensive disorders with offspring blood pressure, but only few have also assessed the relation with offspring adiposity.[18,19] A UK study reported that children of women who had either gestational hypertension or pre-eclampsia had higher risk of obesity at 9 years,

whereas an Australian study found similar associations only in term born young adults of mothers with gestational hypertension, but not with pre-eclampsia.18,19
Using individual participant data (IPD) from 160757 mother-offspring pairs, we assessed the strength and consistency of the associations of maternal gestational diabetes, gestational hypertension and pre-eclampsia with the risks of offspring overweight and obesity throughout childhood. We also explored whether any observed association was independent of maternal pre-/early-pregnancy BMI.

METHODS

Inclusion criteria and participating cohorts

We used data 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 they were able to provide IPD on mothers with singleton live-born children born from 1989 onwards, and had information available on maternal pre/early-pregnancy BMI and birth weight and/or one measure of childhood BMI. We identified 50 potentially eligible cohorts from Europe, North America and Oceania from the existing collaborations or databases concerned with childhood health (EarlyNutrition Project, CHICOS Project, www.birthcohorts.net; last accessed July 2014). We invited all cohorts to participate, and 38 agreed and provided data on 274174 singleton births. For this study, we only included cohorts that were able to provide IPD on maternal gestational diabetes, gestational hypertension or pre-eclampsia, and childhood BMI measured at least once between age 2 and 17·9 years. This resulted in 160757 mothers-offspring pairs available for analyses. Details on study selection process are provided in Supplemental Figure S1. Anonymized datasets were stored on a single central secured data server with access for the main analysts (BPG, SS). All studies were approved by their local institutional review boards/ ethics committees.

Gestational diabetes, hypertensive disorders and pre/early-pregnancy BMI

Information on gestational diabetes, gestational hypertension, pre-eclampsia and maternal BMI was obtained from medical records, through research assessments or was self-reported (cohort-specific information is shown in Supplemental Table S1). Where possible we used maternal pre-pregnancy BMI (<18·5, 18·5 - <25, 25 - <30, ≥30 kg/m2). Five cohorts (including 6,513 participants) did not have information about pre-pregnancy BMI but obtained BMI in early pregnancy (all assessed before or at 20 weeks of gestation).

Childhood BMI

Data on 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, report by parents/caregivers or self-reported (cohort-specific information is provided in Supplemental Table S1). We grouped BMI based on the age of children at assessment into 3 periods: early-childhood (2·0 – 4·9 years), mid-childhood (5·0 – 9·9 years), and late-childhood (10·0-17·9 years of age). If studies had multiple repeated measurements within the same age period, we used data collected at the oldest age. We calculated sex- and age-adjusted standard deviation scores (SDS) of childhood BMI using WHO reference growth charts (Growth Analyzer 4·0, Dutch Growth Research Foundation).20-23
Childhood underweight, normal weight, overweight and obesity were defined based on the age- and sex- specific WHO criteria.20,21

Covariates

Information on covariates was mostly obtained by questionnaires (cohort-specific information is shown in Supplemental Table S1 and S2). As potential confounders other than maternal pre-pregnancy BMI, we considered maternal age (<25·0 years, 25-29·9 years, 30-34·9 years, ≥35·0 years), educational level (low, medium, high), ethnicity (European/White, non-European/non-White), parity (nulliparous,

multiparous), smoking during pregnancy (yes, no), and offspring's sex. We did not adjusted the primary analyses for offspring birth weight and gestational age at delivery, as these birth characteristics are likely to be mediators on the causal pathway and adjustment might introduce bias.24

Statistical analysis

We applied multilevel mixed effects models, taking into account clustering of participants within cohorts, to analyze simultaneously IPD from all cohorts.25 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 SDS 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 risk of childhood underweight, overweight and obesity in the same age windows. Participants exposed to either gestational hypertension or pre-eclampsia were compared to those with none of these conditions, irrespective of their gestational diabetes status. Similarly, those exposed to 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/early-pregnancy BMI (Maternal BMI model). For the associations of pregnancy complications with the risk of childhood underweight, only the basic model was applied due to insufficient sample size. We tested potential interactions between each pregnancy complication and (i) offspring´s sex and (ii) maternal BMI, in their associations with childhood BMI. Since no consistent significant interactions were observed, no further stratified analyses were performed. The amount of missing data on covariates varied between cohorts (percentage missings per cohort given in Supplemental Table S2). To prevent exclusion of non-complete cases, we used missing values in these covariates as an additional group. 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. As sensitivity analysis, we performed a 2-stage random effects meta-analysis and examined whether there was evidence of heterogeneity between cohorts using the I2.25 Analyses were undertaken using the Statistical Package of Social Sciences version 21.0 for Windows (SPSS Inc, Chicago, IL, USA) and Review Manager ((RevMan) Version [5.3.5]. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software.

RESULTS

Subject characteristics

The characteristics of the participants per cohort are presented in Table 1. Out of a total of 160757 mothers, 2618 (1·7%) had gestational diabetes, 9755 (6·5%) had gestational hypertension, and 4836 (3·3%) had pre-eclampsia. 30927 (19·7%) of the mothers were overweight and 12467 (7·9%) obese. Among offspring 5606 (6·6%), 24254 (20·1%) and 3699 (21·3 %) were overweight or obese in early-, mid-, and late-childhood, respectively. Cohort-specific information on childhood age at assessment and BMI is shown in Supplemental Table S4.

Gestational diabetes and childhood body mass index

Figure 1A shows that in the basic and lifestyle characteristics models, gestational diabetes was associated with a higher offspring BMI throughout childhood (difference in BMI-SDS from the lifestyle characteristics models: 0·11 SDS (95% Confidence Intervals (CI) 0·06, 0·16); 0·21 SDS (95% CI 0·16, 0·26); 0·08 SDS (95% CI -0·04, 0·21) in early-, mid- and late-childhood, respectively), as compared to uncomplicated pregnancies. After additional adjustment for maternal BMI, these associations fully attenuated towards the null. Similarly, gestational diabetes was associated with increased risks of overweight and obesity throughout childhood in the basic and lifestyle characteristics

models, with the strongest association in early-childhood (OR 1·59 (95% Confidence Intervals (CI) 1·36, 1·86) (Figure 1B). Adjustment for maternal BMI largely attenuated the effect estimates towards the null. Only the association of gestational diabetes with the risk of early childhood overweight and obesity remained significant (OR 1·35 (95% CI 1·15; 1·58)). Gestational diabetes tended to be associated with a lower risk of underweight throughout childhood in basic model. We were not able to examine adjustment for maternal BMI due to small numbers (Supplemental Table S4). Additional adjustment for gestational hypertension and pre-eclampsia did not affect the observed associations of gestational diabetes with childhood outcomes (data not shown).

Gestational hypertensive disorders and childhood body mass index

Figure 2A shows that, as compared to uncomplicated pregnancies, gestational hypertension was associated with a higher BMI throughout childhood in the basic and lifestyle characteristics models (differences in BMI-SDS in lifestyle characteristics model: 0·07 SDS (95% CI 0·03, 0·11); 0·13 SDS (95% CI 0·10, 0·17); 0·20 SDS (95% CI 0·14, 0·27) in early-, mid- and late-childhood, respectively). These associations were partly explained by maternal BMI (difference in BMI-SDS: 0·01 SDS (95% CI - 0·03, 0·06); 0·04 SDS (95% CI 0·01, 0·07); 0·07 SDS (95% CI 0·01, 0·13) in early-, mid- and late-childhood, respectively). Gestational hypertension was also associated with higher risks of overweight and obesity throughout childhood. The strongest association was observed for late-childhood (OR 1·49 (95% CI 1·30, 1·70)). Additional adjustment for maternal BMI largely attenuated these associations (Figure 2B). In the basic model, gestational hypertension was associated with a lower risk of childhood underweight at all ages (Supplemental Table S4).

Pre-eclampsia was associated with a lower BMI in early-childhood in both the basic and lifestyle characteristics models (difference in BMI-SDS in lifestyle characteristics model: - 0.05 SDS (95% CI - 0·09, - 0·01)) (Figure 3A). This inverse association strengthened upon additional adjustment for maternal BMI. In contrast, we observed a positive association of pre-eclampsia with BMI in mid- and late-childhood in the basic and lifestyle characteristics models (differences in BMI-SDS in lifestyle characteristics model: 0·10 SDS (95% CI 0·06, 0·13); 0·16 SDS (95% CI 0·03, 0·30) in mid- and late-childhood, respectively). These associations fully attenuated after additional adjustment for maternal BMI. The associations of pre-eclampsia with overweight and obesity in mid- and late-childhood also fully attenuated after adjustment for maternal BMI (Figure 3B). In the basic model pre-eclampsia was associated with a higher risk of underweight in early-childhood only (Supplemental Table S4). We were unable to further explore adjustment for maternal BM because of small numbers. Similar associations between both gestational hypertension and pre-eclampsia with childhood outcomes were observed for all models when additionally adjusted for gestational diabetes (data not shown).

2-stage meta-analyses as sensitivity analyses

Analyses performed with 2-stage meta-analyses were consistent with those obtained from our main (1-stage) meta-analyses (Supplemental Figures S2-10). We did not observe substantial heterogeneity between the cohorts (I2 range 0 to 40%, with 6 out of the 9 meta-analyses having I2 <25%; Supplemental Figures S2-10).

DISCUSSION

Results from our IPD analysis of 160757 mothers and children from 18 different countries from Europe and North America, demonstrated that children born to mothers with gestational diabetes and gestational hypertension had a higher BMI and higher risk of being overweight or obese throughout childhood, whereas pre-eclampsia was associated with a lower BMI in early-childhood. These associations were largely explained by maternal pre/early-pregnancy BMI.

Interpretation of main findings

Gestational diabetes, gestational hypertension and pre-eclampsia affect substantial numbers of pregnancies and are associated with a wide range of adverse maternal and fetal pregnancy outcomes.1-3 Gestational diabetes may lead to fetal overnutrition as a result of maternal hyperglycemia during pregnancy.7 Gestational hypertension and pre-eclampsia are related to placental dysfunction, which may lead to impaired fetal nutrient supply.8,26 Both conditions may 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 Our aim was to explore if gestational diabetes and gestational hypertensive disorders affect the risk of offspring obesity independently of the risk conferred by maternal obesity. Disentangling the independent role 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 9 published cohort studies suggested that maternal diabetes during pregnancy was associated with a higher offspring BMI . These associations were no longer present in single studies that adjusted for maternal pre-pregnancy BMI.6,27 Recently, several prospective observational studies reported inconsistent findings for the association of gestational diabetes with offspring BMI after adjustment for maternal BMI.11-17,28-30 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 a higher BMI at the age of 18 years. This association was independent of maternal BMI.17 In contrast, we observed that children of mothers with gestational diabetes had a higher BMI throughout childhood, but this association was largely explained by maternal pre/early-pregnancy BMI. This different finding might be explained by differences in study populations as our IPD included contemporary cohorts only with newer screening and treatment strategies, and mainly included offspring measurements at younger ages. We observed the strongest association of gestational diabetes with offspring obesity in early-childhood. This may be explained by tracking of birth size.31.32 Consistent with our findings, treatment of mild gestational diabetes was found to be beneficial for neonatal outcomes, but did not influence offspring obesity risk at age 5-10 years in a multicenter randomized controlled trial.33 Using the diagnosis of gestational diabetes may insufficiently reflect glycemic status during pregnancy. Maternal glucose levels below current diagnostic criteria of diabetes, are linearly and positively associated with adverse perinatal outcomes.31,34 However, several studies showed that maternal glucose levels during pregnancy were not associated with offspring BMI in early childhood, after adjustment for maternal BMI.35,36 Thus, our findings strongly suggest that the association of gestational diabetes with higher BMI in the 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, which 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 after adjustment for parental BMI.18 In contrast, an Australian cohort study of 1151 mother-offspring pairs born at term showed that offspring of mothers with gestational hypertension had higher BMI and risk of overweight and obesity at 20 years, independently of maternal

BMI.19 No association of pre-eclampsia with offspring BMI was present.19 In the current study, we observed that gestational hypertension was associated with a higher BMI and risk of overweight throughout childhood, but this association was also largely explained by maternal BMI. Pre-eclampsia was associated with a lower BMI in early-childhood, and this inverse association was stronger after adjustment for maternal BMI. In later childhood, no associations independent of maternal BMI were present. This might be explained by tracking of lower birth size into early-childhood among children of mothers with pre-eclampsia due to placental dysfunction and fetal growth restriction.37 Further studies

aiming at detailed assessment of maternal blood pressure and placental vascular function, which provides details on the severity of the disease, may provide more insight into the effects of pre-eclampsia on childhood adiposity development.
Our observations that the associations of gestational diabetes and gestational hypertensive disorders with offspring obesity largely dependent on maternal BMI are important from an etiological and preventive perspective. Interventions to reduce the risk of pregnancy complications or improve the effectiveness of their treatment may be important in relation to a range of problems for the mother and child, but they are unlikely to influence directly the development of obesity in offspring.
Strengths and limitations
Major strengths of our study are the large sample of contemporary populations reflecting current diagnosis and treatment policies and the use individual participant data from a wide selection of existing studies to reduce the risk of publication bias. We were able to adjust for a range of relevant confounding factors, with a particular focus on maternal pre-pregnancy BMI. 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. .Especially, the prevalence of gestational diabetes in our sample was relatively low and varied substantially between cohorts, which might suggest underascertainment of this condition. However, our 2-stage meta-analysis suggested low heterogeneity between studies. We have no information on how any of the pregnancy complications were treated. Effective treatment that reduced circulating glucose and blood pressure during pregnancy may lead to weaker associations of these conditions with offspring obesity. However, this reflects contemporary clinical practice. Finally, due to the observational design, residual confounding cannot be excluded.

CONCLUSIONS

The associations of gestational diabetes, gestational hypertension and pre-eclampsia with childhood obesity are largely explained by maternal pre/early-pregnancy BMI. Interventions focused on prevention or treatment of these pregnancy complications, though important for other maternal and fetal pregnancy outcomes, are unlikely to have a direct impact on offspring BMI.

AUTHOR CONTRIBUTIONS

Bernadeta Patro Golab and Susana Santos had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bernadeta Patro Golab, Susana Santos, Vincent W.V. Jaddoe, Romy Gaillard
Analysis and interpretation of data: Bernadeta Patro Golab, Susana Santos, Vincent W.V. Jaddoe, Romy Gaillard
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Table 1. Characteristics of the participating pregnancy and birth cohorts (n=160757)a,b

Cohort name, number of participants, birth years (country)	Gestational diabetes		Gestational hypertension	Pre-eclampsia		Early childhood (2·0-4·9y)		Mid childhood (5·0-9·9y)	Late childhood (10·0-17·9y)
	Body mass index (SDS)	Overweight and obesity		Body mass index (SDS)	Overweight and obesity	Body mass index (SDS)		Overweight and obesity	
ABCD, n=5512, 2003-2004 (The Netherlands)	120 (2·2)	1045 (19·0)	233 (4·2)	0·3 (-1·5, 2·4)	213 (4·5)	0·1 (-1·7, 2·4)	768 (17·1)	NA	NA
ALSPAC, n=9041, 1991-1992 (United Kingdom)	77 (0·9)	1282 (14·5)	170 (1·9)	0·6 (-1·0, 2·5)	77 (6·5)	0·2 (-1·6, 2·7)	2113 (26·4)	0·2 (-1·9, 2·5)	2063 (26·4)
AOB/F, n=1672, 2008-2010 (Canada)	71 (4·2)	118 (7·1)	104 (6·2)	0·2 (-2·3, 2·7)	96 (5·7)	NA	NA	NA	NA
BAMSE, n=3329, 1994-1996 (Sweden)	56 (1·7)	NA	55 (1·7)	0·6 (-0·9, 2·5)	187 (6·5)	0·5 (-1·2, 2·6)	799 (31·2)	0·1 (-1·7, 2·0)	425 (16·9)
BIB, n=983, 2007-2010 (United Kingdom)	100 (10·2)	51 (5·3)	13 (1·4)	0·5 (-1·4, 2·6)	74 (7·5)	NA	NA	NA	NA
Co.N.ER, n=528, 2004-2005 (Italy)	14 (2·7)	20 (3·8)	12 (2·3)	0·3 (-2·3, 2·9)	47 (9·7)	0·7 (-1·3, 2·9)	102 (35·5)	NA	NA
DNBC, n=40349, 1996-2002 (Denmark)	273 (0·7)	1878 (4·7)	1380 (3·4)	NA	NA	0 (-1·9, 2·1)	6304 (15·6)	NA	NA
EDEN, n=1361, 2003-2005 (France)	92 (6·8)	67 (4·9)	30 (2·2)	0·3 (-1·4, 2·0)	27 (2·2)	0 (-1·5, 2·0)	147 (12·9)	NA	NA
FCOU, n=2332, 1993-1996 (Ukraine)	5 (0·2)	367 (15·7)	148 (6·3)	0·5 (-1·9, 3·1)	140 (10·6)	0 (-2·0, 2·0)	124 (12·6)	-0·1 (-2·0, 1·8)	75 (8·9)
GASPII, n=570, 2003-2004 (Italy)	25 (4·4)	28 (4·9)	5 (0·9)	0·7 (-1·1, 2·9)	52 (9·7)	0·7 (-1·4, 2·7)	172 (37·1)	NA	NA
GECKO Drenthe, n=2119, 2006-2007 (The Netherlands)	72 (3·4)	209 (11·0)	46 (2·4)	NA	NA	0·4 (-1·2, 2·4)	465 (21·9)	NA	NA
GENESIS, n=2143, 2003-2004 (Greece)	30 (1·4)	NA	NA	0·8 (-1·2, 3·6)	297 (14·6)	1·0 (-1·5, 3·9)	45 (42·1)	NA	NA
GENERATION R, n=7550, 2002-2006 (The Netherlands)	80 (1·1)	274 (4·0)	149 (2·3)	0·3 (-1·5, 2·5)	220 (5·1)	0·3 (-1·5, 2·7)	1849 (27·4)	0·4 (-1·5, 2·6)	160 (30·0)
GENERATION XXI, n=5921, 2005-2006 (Portugal)	390 (6·6)	135 (2·3)	90 (1·5)	0·5 (-1·3, 3·1)	485 (10·4)	0·6 (-1·4, 3·2)	2015 (38·0)	NA	NA
GINIplus, n=2313, 1995-1998 (Germany)	61 (2·6)	NA	NA	0·1 (-1·7, 2·0)	53 (2·4)	0 (-1·8, 1·9)	227 (10·6)	0 (-1·9, 2·1)	365 (16·0)

Table 1. Characteristics of the participating pregnancy and birth cohorts (n=160757)a (continued)

Cohort name, number of participants, birth years (country)	Gestational diabetes		Gestational hypertension	Pre-eclampsia	Early childhood (2·0-4·9 y)		Mid childhood (5·0-9·9y)	Late childhood (10·0-17·9y)
Body mass index (SDS)		Overweight and obesity		Body mass index (SDS)	Overweight and obesity	Body mass index (SDS)		Overweight and obesity
HUMIS, n=970, 2003-2008 (Norway)	5 (0·5)	37 (3·8)	70 (7·2)	0·3 (-1·8, 2·4)	53 (6·0)	0·0 (-2·0, 2·3)	63 (17·6)	NA	NA
INMA, n=1933, 1997-2008 (Spain)	191 (11·3)	58 (3·0)	4 (0·9)	0·5 (-1·2, 2·8)	143 (8·2)	0·6 (-1·4, 3·3)	503 (37·6)	0·3 (-1·6, 2·5)	79 (25·3)
KOALA, n=2061, 2000-2002 (The Netherlands)	21 (1·0)	72 (3·5)	26 (1·3)	-0·1 (-2·0, 1·9)	17 (1·7)	-0·2 (-2·2, 1·8)	199 (11·3)	-0·2 (-2·1, 2·2)	19 (18·1)
Krakow Cohort, n=424, 2000-2003 (Poland)	18 (4·2)	19 (4·5)	0 (0·0)	0 (-2·2, 2·3)	11 (4·1)	0·2 (-1·8, 2·6)	90 (26·5)	NA	NA
LISAplus, n=1584, 1997-1999 (Germany)	58 (3·7)	NA	NA	0 (-1·7, 1·9)	33 (2·3)	-0·1 (-1·8, 1·8)	140 (9·9)	0 (1·8, 2·1)	236 (15·2)
MoBa, n=55008, 1999-2009 (Norway)	418 (0·8)	3131 (5·7)	2023 (3·7)	0·4 (-1·8, 2·5)	2456 (6·1)	0·1 (-2·0, 2·3)	6793 (19·5)	NA	NA
NINFEAb, n=1726, 2005-2010 (Italy)	132 (7·7)	136 (7·9)	44 (2·6)	0·1 (-2·3, 2·5)	86 (5·1)	0 (-2·2, 2·4)	90 (21·2)	NA	NA
PÉLAGIE, n=738, 2002-2005 (France)	21 (2·8)	24 (3·3)	8 (1·1)	0·1 (-1·8, 1·9)	15 (2·0)	NA	NA	NA	NA
PIAMA, n=1815, 1996-1997 (The Netherlands)	19 (1·0)	179 (9·9)	46 (2·5)	0·7 (-1·2, 2·5)	78 (8·9)	0·1 (-1·6, 2·4)	325 (20·0)	-0·2 (-1·7, 1·8)	77 (10·0)
Piccolipiù, n=687, 2011-2015 (Italy)	69 (10·1)	24 (3·5)	6 (0·9)	0·3 (-2·1, 2·5)	40 (5·8)	NA	NA	NA	NA
Project Viva, n=1389, 1999-2002 (United States)	64 (4·7)	85 (6·3)	46 (3·4)	0·7 (-1·0, 2·7)	87 (7·1)	0·4 (-1·4, 3·0)	328 (30·8)	0·4 (-1·5, 3·7)	8 (25·8)
REPRO_PL, n=291, 2007-2011 (Poland)	13 (4·5)	17 (5·8)	0 (0·0)	0·3 (-2·2, 2·5)	19 (6·9)	0·6 (-1·5, 3·6)	19 (38·8)	NA	NA
RHEA, n=740, 2007-2008 (Greece)	60 (8·8)	35 (5·2)	5 (0·7)	0·6 (-1·1, 3·6)	91 (12·3)	NA	NA	NA	NA
ROLO, n=283, 2007-2011 (Ireland)	10 (3·5)	NA	NA	0·2 (-1·7, 2·6)	19 (6·7)	NA	NA	NA	NA
SCOPE BASELINE, n=1046, 2008-2011 (Ireland)	NA	129 (12·3)	35 (3·3)	0·6 (-1·0, 2·3)	62 (5·9)	NA	NA	NA	NA

Table 1. Characteristics of the participating pregnancy and birth cohorts (n=160757)a (continued)

Cohort name, number of participants, birth years (country)	Gestational diabetes		Gestational hypertension		Pre-eclampsia	Early childhood (2·0-4·9 y)		Mid childhood (5·0-9·9y)	Late childhood (10·0-17·9y)
	Body mass index (SDS)	Overweight and obesity		Body mass index (SDS)	Overweight and obesity	Body mass index (SDS)	Overweight and obesity		
SEATON, n=872, 1998-1999 (United Kingdom)	NA	119 (13·9)	16 (2·1)	0·7 (-0·9, 2·7)	36 (8·1)	0·6 (-1·1, 2·8)	55 (19·8)	0·4 (-1·6, 2·6)	192 (32·9)
Slovak PCB study, n=524, 2002-2004 (Slovakia)	3 (0·6)	54 (12·4)	NA	1·9 (-2·4, 5·3)	222 (48·2)	0·3 (-1·7, 3·3)	123 (31·0)	NA	NA
STEPS, n=297, 2008-2010 (Finland)	20 (6·7)	NA	NA	0·5 (-1·2, 2·2)	13 (4·4)	NA	NA	NA	NA
SWS, n=2646, 1998-2007 (United Kingdom)	30 (1·1)	162 (6·1)	72 (2·7)	0·5 (-1·3, 2·6)	157 (6·2)	0·2 (-1·5, 2·5)	396 (22·0)	NA	NA

aValues are expressed as medians (95% range) or numbers of subjects (valid %). NA, not available.
b Subset of participants with follow-up completed at 4 years of child's age by the time of data transfer (March 2015).

Figure 1. Associations of gestational diabetes with offspring BMI outcomes in early, mid, and late childhood.a aValues are regression coefficients (95% confidence intervals) from multilevel linear mixed effects models and odds ratios (95% confidence intervals) from multilevel binary logistic models that reflect differences in early childhood (2·0 to 4·9 years), mid childhood (5·0 to 9·9 years) and late childhood (10·0 to 17·9 years) BMI SDS and risk of overweight and obesity, respectively, for children born to mothers with gestational diabetes, as compared with the reference group (children born to mothers with an uncomplicated pregnancy). Lifestyle characteristics models are adjusted for offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy. Maternal BMI models are additionally adjusted for maternal pre/early-pregnancy BMI.

Figure 2. Associations of gestational hypertension with offspring BMI outcomes in early, mid, and late childhood.a aValues are regression coefficients (95% confidence intervals) from multilevel linear mixed effects models and odds ratios (95% confidence intervals) from multilevel binary logistic models that reflect differences in early childhood (2·0 to 4·9 years), mid childhood (5·0 to 9·9 years) and late childhood (10·0 to 17·9 years) BMI SDS and risk of overweight and obesity, respectively, for children born to mothers with gestational hypertension, as compared with the reference group (children born to mothers with an uncomplicated pregnancy). Lifestyle characteristics models are adjusted for offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy. Maternal BMI models are additionally adjusted for maternal pre/early-pregnancy BMI.

Figure 3. Associations of pre-eclampsia with offspring BMI outcomes in early, mid, and late childhood.a aValues are regression coefficients (95% confidence intervals) from multilevel linear mixed effects models and odds ratios (95% confidence intervals) from multilevel binary logistic models that reflect differences in early childhood (2·0 to 4·9 years), mid childhood (5·0 to 9·9 years) and late childhood (10·0 to 17·9 years) BMI SDS and risk of overweight and obesity, respectively, for children born to mothers with pre-eclampsia, as compared with the reference group (children born to mothers with an uncomplicated pregnancy). Lifestyle characteristics models are adjusted for offspring's sex, maternal age, educational level, ethnicity, parity, and smoking during pregnancy. Maternal BMI models are additionally adjusted for maternal pre/early-pregnancy BMI.