Maternal early pregnancy obesity and related pregnancy and pre-pregnancy disorders: Associations with child developmental milestones in the prospective PREDO Study

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Abstract

Background/Objectives

Previous studies have linked maternal pre-pregnancy obesity (BMI ≥30 kg/m^2) with suboptimal neurodevelopment in her offspring; however, the literature is not entirely consistent. Whether these effects are muddled by maternal self-reports of pre-pregnancy weight and height, or are driven or amplified by the well often co-morbid hypertensive and diabetic pregnancy and pre-pregnancy disorders, remains unclear. We examined if maternal early pregnancy obesity is associated with developmental delay in her offspring, and if the associations are driven or amplified by diabetic and hypertensive pregnancy and pre-pregnancy disorders.

Subjects/Methods

2504 mother-child dyads participated in the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study. Data on maternal early pregnancy obesity, pre-pregnancy and gestational hypertension, pre-eclampsia, type 1 and gestational diabetes were derived from the Finnish Medical Birth Register. At the child's mean age of 42.1 (SD=8.2) months the mothers completed the Ages and Stages Questionnaire (ASQ) Third edition for developmental milestones.

Results

Children of obese mothers had 1.81 to 2.74 (p-values<0.02) higher odds of failing to meet the development that is typical for a child's age (developmental domain score ≤ -2SD below the child's age) on the communication, fine and gross motor, problem solving and personal/social skills and children of overweight mothers had 2.14 (p=0.002) higher odds of failing to meet the development that is typical for the child's age on communication skills. Odds of developmental delay were also higher for children of mothers with pre-eclampsia and gestational diabetes. The associations were robust to covariates and confounders, the effects

of overweight/obesity and pre-eclampsia were not driven by the other disorders, and overweight/obesity and hypertensive and diabetic disorders did not show additive effects.

Conclusions

Maternal early pregnancy overweight, obesity, and pre-eclampsia are independently associated with neurodevelopmental delay in her offspring. Further studies unravelling the underlying mechanisms are warranted.

Keywords

Pregnancy, obesity, diabetic and hypertensive pregnancy and pre-pregnancy disorders, neurodevelopment, children

Introduction

Maternal obesity during pregnancy has become one of the major challenges of obstetric care(1). Of the world's adult population of women, including women of the childbearing age, 14% were obese in 2014(1). This number is forecasted to increase to 21% by 2025(1). The risks of obesity for pregnant mothers include gestational diabetes and hypertension spectrum pregnancy disorders, caesarian section delivery and for the offspring preterm birth, intrauterine growth restriction, macrosomia and related illnesses and complications, stillbirth and congenital anomalies(2).

Apart from increasing the long-term health risks for the mother, evidence also suggests that maternal pre-pregnancy/early pregnancy obesity is associated with long-term neurodevelopmental adversities in the offspring(2). These include child's general developmental delay(3), developmental delays in gross motor skills, especially in sitting without support and crawling on hands and knees(4), delays in fine motor skills(5), lower intelligence quotient(6-10), poorer verbal skills(11), increased risk for symptoms of ADHD(11-13), and diagnoses of ASD(3, 11). Yet, some studies have reported null associations between maternal obesity and cognitive and motor function(14), and some even beneficial effects on cognitive and language development in the offspring(15).

With one exception that measured maternal weight and height at the first antenatal clinical visit(13), the previous studies are limited by relying on maternal self-reported, and not objectively verified pre-pregnancy weight and height, in some studies even months after delivery(6, 8, 10, 11), or by using a measure that pools self-reported data with data from medical records(3-5, 7, 9, 12, 14, 15); of note, in the Upstate KIDS study(5) only 1.6% of

maternal weight and height measurements were self-reported. Self-reports of weight and height are well-known to be biased (16, 17). This may result in misclassification of women into groups according to BMI. Hence, it still remains to be verified if neurodevelopmental disadvantages in the offspring can be assigned to maternal pre-pregnancy/early pregnancy obesity, and if some of the discrepancies in the previous literature arise from inaccuracies in anthropometric measurements.

Furthermore, it remains unknown if neurodevelopmental disadvantages in the offspring are specific to maternal pre-pregnancy/early pregnancy obesity, or are driven or amplified by the well often co-morbid pregnancy disorders. Existing data suggests that gestational diabetes(18, 19) and hypertension spectrum pregnancy disorders(20-23) may carry adverse neurodevelopmental consequences on the offspring that are independent of maternal pregnancy BMI or obesity. But whether the same holds true for maternal obesity independent of these other disorders, still remains unknown.

To address these gaps in the literature, we tested the hypothesis that maternal early pregnancy obesity, derived from the Finnish Medical Birth Register (MBR)(24), comprising measurements verified at the first antenatal clinical visit when pregnancy weight gain is still minimal, is associated with delays in developmental milestones in the 23-69-month-old offspring. Because some studies suggest that neurodevelopmental adversities not only characterize offspring from obese, but from overweight pregnancies as well(7, 11), we also tested the hypothesis that maternal overweight is associated with delays in the offspring developmental milestones. We further tested if the associations between overweight/obesity and child neurodevelopment were independent of the common comorbid disorders, namely gestational and pre-pregnancy hypertension, pre-eclampsia, gestational diabetes and type 1

diabetes. We expected that these disorders, that otherwise complicate pregnancy, may partially explain any potential adverse effects of maternal overweight/obesity on offspring developmental milestones as the previous discrepant findings may also arise from different prevalence of these disorders in the previous studies samples. Finally, we tested if exposure to any combination of these disorders amplified adverse neurodevelopmental effects on the offspring.

Subjects and Methods

Study design and participants

The participants came from the Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) Study(25).The PREDO study enrolled 4785 pregnant women, of whom 4777 (8 miscarriages or stillbirths) gave birth to a singleton live-born child between 2006-2010. The women were recruited to the study when they visited antenatal clinics at one of the ten study hospitals in Southern and Eastern Finland for their first ultrasound screening between 12+0 and 13+6 weeks+days of gestation. To enrich the number of women with pre-eclampsia and intrauterine growth restriction in the PREDO sample, 969 women were recruited based on having one or more risk factors of pre-eclampsia, including pre-pregnancy obesity(25).

In 2011-2012, 4586 women and their children were invited for a follow-up (one child had died, 33 did not have data in the MBR, 55 women had declined participation in a follow-up, for 100 women addresses were not traceable). Of them, 2667(58.2%) participated at a child's mean age of 42.1 months (range 23.2-68.8 months) and 2504(54.6%) provided valid age-appropriate data on child developmental milestones (163, 6.1%, filled in the developmental

milestones questionnaire too early or too late for age, we allowed 30% deviation from questionnaire-specific age translating into 3 weeks at the youngest age group and 2.7 months in the oldest age group).

In comparison to those who were invited and did not participate (n=1919), mothers of the children who participated were older (31.8 vs 31.1 years), more often primiparous (41.2% vs 35.4%), and had a higher level of education (37.5% vs 46.4% secondary or less, 26.6% vs 25.0% lower tertiary, 35.9% vs 28.6% upper tertiary) (p-values < 0.001); there were no differences in other obstetric/perinatal characteristics.

Ethics committee approval

Ethics Committees of the Helsinki and Uusimaa Hospital District and participating hospitals approved the study protocol. All participants and parents/guardians provided written informed consent.

Overweight, obesity and related pregnancy and pre-pregnancy disorders

Data were extracted from the MBR. Each diagnosis was further verified by a clinical jury for the subsample recruited based on their increased risk of pre-eclampsia and intrauterine growth restriction.

Early pregnancy BMI was calculated from weight and height verified by a nurse at the first visit to the antenatal clinic (M=8+4 weeks+days, SD= 1+3 weeks+days of gestation), and categorized to normal weight (24.99 kg/m^2 or less), overweight (25-29.99kg/m^2), and obese (30 kg/m^2) groups according to the WHO criteria; 86 women (3.4%) had a BMI below 18.5 kg/m^2 indicating underweight; the underweight and normal weight groups were pooled for the

analyses (from here on referred to as 'normal weight'). At the mean 8th gestational week, pregnancy weight gain is still minimal. Hence, this measurement is a close proxy of pre-pregnancy BMI.

Gestational diabetes was defined as fasting, 1h or 2h plasma glucose during a 75g oral glucose tolerance test ≥5.1, 10.0 or 8.5 mmol/L that emerged or was first identified during pregnancy; Gestational hypertension as blood pressure ≥140/90 mmHg on ≥ 2 occasions at least 4 h apart in a woman who was normotensive before 20th week of gestation; Preeclampsia as blood pressure ≥140/90 mmHg on ≥2 occasions at least 4 h apart in a women who was normotensive before 20th week of gestation with proteinuria ≥300 mg/24 h.

We also identified women with type 1 diabetes (none of the women in our sample had type 2 diabetes) and with pre-pregnancy/chronic hypertension defined as blood pressure≥140/90 mmHg present pre-pregnancy or diagnosed before 20th week of gestation.

Developmental milestones

The Ages and Stages Questionnaires (ASQ) Third edition(26) (translated into Finnish, back-translated and approved by the publisher) is a tool with excellent test-retest reliability, intra-observer reliability, internal consistency and concurrent validity, high sensitivity and specificity to screen children requiring further developmental assessment, monitoring or special education(26-28). It comprises 30 age-appropriate items (in our sample for children aged 22.2-26.2, n=83, 24.5-29.5, n=83, 27.5-32.5, n=108, 30.5-35.5, n=241, 33.0-41.5, n=450, 37.0-47.0, n=564, 42.0-53.0, n=702, 55.0-59.0, n=239, and 54.0-69.0 months, n= 34) measuring communication, gross motor, fine motor, problem solving and personal/social skills.

Each of the five domains comprise six questions with response 'yes' (scored 10) indicating the child can master the skill, 'sometimes' (scored 5) if the skill is emerging or occasional, and 'not yet' (scored 0) if the child is not able perform the skill. On each of these domains, the scores range from 0 to 60 with the highest value indicating that the child can master the skill. According to the ASQ manual and validation studies(26-29), children whose domain score is ≤-2 SDs below the mean of the child's age were considered to fail to meet the development that is typical for the child's age, and hence display developmental delay on that specific domain. Scores between -2SDs> and ≤-1SDs below the mean of the child's age on any of the ASQ domains were considered to indicate milder developmental delay(29). This milder criteria has also been recommended for screening purposes for agencies that have sufficient resources(26). Children with scores >-1SD of the mean of the child's age were considered to display no developmental delay and hence to be developing typically for child's age. We also summed up the number of times the child displayed no developmental delay for child's age (scored 0), mild developmental delay for child's age (scored 1) and failed to meet the development that is typical for child's age (scored 2) on any of the five ASQ domains (range 0-10). This sum-score reflected severity and pervasiveness of the child's developmental delay across the five developmental domains.

Covariates and confounders

The following factors were included as covariates in our analysis: maternal age at childbirth (years), parity (primiparous/multiparous), delivery mode (vaginal/caesarian), maternal smoking during pregnancy (did not smoke/quit during first trimester/smoked throughout pregnancy), child's gestational age at delivery (weeks), birth weight (grams), and sex (boy/girl) with data extracted from patient case reports and/or the MBR, and maternal alcohol

use during pregnancy (yes/no/missing) and education level (basic/secondary vs. tertiary) as self-reported in a questionnaire given to the mothers at 12+0-13+6 weeks+days of gestation; and child's age at follow-up (years) which was reported in conjunction with filling in the ASQ.

Statistical analyses

We used multinomial logistic regression to test if children of overweight and obese women in comparison to children of normal weight women had higher odds for displaying mild developmental delay or failed to meet the development that is typical for the child's age on any of the ASQ domains. We used continuation-ratio ordinal logistic regression when the developmental delay severity/pervasiveness sum-score was the outcome. We repeated these analyses by replacing maternal overweight/obesity by maternal gestational hypertension, pre-eclampsia and pre-pregnancy/chronic hypertension using women without these disorders as the comparison group; and maternal gestational and type 1 diabetes using women without these disorders as the comparison group. Unstandardized regression coefficients represent odds ratios (OR), and 95% Confidence Intervals (95% CI). In addition to the unadjusted effects, we report these associations as adjusted for the covariates and confounders.

To test if any potential effects on child's developmental milestones were specific to maternal overweight, obesity, or related hypertensive and diabetic pregnancy and pre-pregnancy disorders, we conducted two additional analyses. First, we made adjustments for the mutual effects of these conditions. We then tested the effects of these conditions by excluding women with the other conditions from the analyses, e.g. when we tested the effects of overweight/obesity we excluded women with hypertensive and diabetic pregnancy and pre-

pregnancy disorders from the analyses; Because overweight/obesity and the disorders were highly co-morbid in our sample (Supplemental Table 1) and because we used the ASQ -2SD and -1SD cutoffs to identify developmental delay, our sample size permitted us to conduct the latter 'restricted' analyses only when we used the child's developmental delay severity/pervasiveness sum-score as the outcome.

Finally, we tested if exposure to any combination of overweight/obesity, and comorbid disorders (sum-score categorized into no disorder, one, two or more disorders) added to the neurodevelopmental adversity in the offspring. An effect was considered additive if the increment in the odds of displaying more severe and pervasive developmental delay was significantly higher for children of mothers with two or more than just one disorder.

All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Characteristics of the sample according to maternal early pregnancy normal weight, overweight and obesity are presented in Table 1. Supplemental Table 1 shows the prevalence of hypertensive and diabetic pregnancy and pre-pregnancy disorders according to maternal early pregnancy weight categories. Prevalence ratio of any one hypertensive or diabetic pregnancy and pre-pregnancy disorder was 2.05 and 3.86 times higher in the overweight and obese groups as compared to the normal weight group respectively, and of any two hypertensive and diabetic pregnancy and pre-pregnancy disorders 5.75 and 16.86 times higher in the overweight and obese groups as compared to the normal weight group, respectively. Overweight and obesity partook in over 93% cases of co-morbidities (Table 1).

Table 2 shows the numbers of children who displayed mild developmental delay (-2SD > -≤ SD) and failed to meet the development that is typical for the child's age (≤-2SD) according to maternal early pregnancy BMI and hypertensive and diabetic pregnancy and pre-pregnancy disorders groups. The number of children in the delay categories in women with type 1 diabetes was too small for any analyses, therefore we do not present findings on type 1 diabetes.

Associations between maternal early pregnancy overweight and obesity and child's developmental milestones

Table 3 shows that in the unadjusted models children of overweight mothers had higher odds of displaying mild developmental delay on communication and fine motor skills and of failing to meet the development on the communication skills that is typical for the child's age. These associations remained significant when we adjusted for covariates and confounders, and for comorbid disorders (Table 3).

Children of obese mothers had higher odds of displaying mild developmental delay on fine motor skills and of failing to meet the development on communication, fine motor, gross motor, problem solving and personal-social skills that is typical for the child's age (Table 3). All the associations remained significant after adjustments for covariates and confounders and for comorbid disorders, except for two: the association with the mild delay in fine motor skills was rendered non-significant when adjusted for covariates and confounders and the association with failure to meet the development on problem solving skills that is typical for the child's age was rendered non-significant when adjusted for comorbid disorders (Table 3).

Table 4 shows that after all covariate and confounder adjustments and in models adjusted for comorbid disorders, children of overweight and obese mothers had higher odds of displaying more severe and pervasive developmental delay across the five ASQ domains. These effects did not change either when we excluded women with comorbid disorders from the analyses (Table 4 'restricted model').

Associations between maternal hypertensive and diabetic pregnancy and pre-pregnancy disorders and child's developmental milestones

Table 3 shows that children of mothers with pre-eclampsia had higher odds of mild developmental delay on communication skills and of failing to meet the development on communication and gross motor skills that is typical for the child's age (Table 3). The latter association with the communication skills was rendered non-significant when adjusted for maternal overweight/obesity and diabetic pregnancy and pre-pregnancy disorders (Table 3).

In the unadjusted and all adjustment models, children of mothers with gestational diabetes had higher odds of mild developmental delay on personal social skills and of failing to meet the development on communication skills that would be typical for the child's age (Table 3). Maternal gestational diabetes was also associated with higher odds of failing to meet the development on gross motor and problems solving skills that would be typical for child's age, but these associations were rendered non-significant when adjusted for maternal overweight/obesity and hypertensive pregnancy and pre-pregnancy disorders (Table 3).

Table 4 shows that children of mothers with pre-eclampsia and gestational diabetes had higher odds of displaying more severe and pervasive developmental delay across the five ASQ domains (Table 4). The association of pre-eclampsia remained significant across all

adjustment models and in the ‘restricted model’ with women with overweight/obesity and diabetic disorders excluded, but association of gestational diabetes was rendered non-significant in the ‘restricted model’ (Table 4).

Finally, we tested if the effects of maternal early pregnancy overweight/obesity and hypertensive and diabetic pregnancy and pre-pregnancy disorders were additive. While children of mothers with one (OR=1.32, 95% CI 1.1,1.60, p=0.004) and two or more of these conditions (OR=1.52, 95% CI 1.18,1.98 p=0.001) had an increased odds for displaying more severe and pervasive developmental delay, the increment in the odds between one and two or more conditions was not statistically significant (p-value=0.19).

Discussion

In this prospective pregnancy cohort study, maternal early pregnancy obesity was associated with delay in developmental milestones in her offspring aged 23-69 months. Children of obese women had 1.81-2.74 higher odds of failing to meet the development in communication, fine and gross motor, problems solving and personal-social skills that is typical for the child’s age. When tested across all of these five domains, the delay these children displayed was more severe and pervasive. Maternal early pregnancy overweight was also associated with delay in developmental milestones, but this delay was evident on a narrower spectrum of skills, namely on communication and fine motor skills, and the delay in communication skills was mild. Yet, maternal early pregnancy overweight also predicted a more severe and pervasive developmental delay of the child across the five ASQ domains. These associations changed only a little when we adjusted for covariates and confounders and comorbid disorders. Exclusion of women with the comorbid disorders in the restricted

analyses allowed us to entirely eliminate potential confounding/effect modification by the comorbid disorders, and for the first time to demonstrate the independent effects of overweight and obesity on the severity and pervasiveness of the child's developmental delay across the different developmental domains.

Our study also revealed that maternal pre-eclampsia was associated with developmental delays in communication and gross motor skills and gestational diabetes with delays in communication, gross motor, problem solving and personal social skills. Both pre-eclampsia and gestational diabetes were associated with the score indicating more severe and pervasive developmental delay across the five ASQ domains. While these associations were not explained by the covariates and confounders, the restricted analyses revealed that only the associations between pre-eclampsia and the severity/pervasiveness score of developmental delay remained significant when women with overweight/obesity and diabetic pregnancy and pre-pregnancy disorders were excluded from the analyses.

These findings combined with the finding that there were no additive effects of maternal early pregnancy overweight/obesity and comorbid disorders on child neurodevelopmental adversity suggest that maternal overweight, obesity and pre-eclampsia may carry harmful effects on developmental delay of the child that are not, contrary to what we expected, explained by the comorbid disorders. Gestational diabetes carries similar harmful effects, but these are at least partially explained by maternal overweight/obesity and the other disorders. As the prevalence rates of maternal overweight and obesity and comorbid disorders are increasing, our findings carry an important public health message: prevention and effective management of maternal overweight/obesity and comorbid conditions should not only improve the quality of life and

wellbeing of the pregnant mothers themselves, but decrease the burden of neurodevelopmental adversities in the next generation.

A major strength of the study relates to the study design: a fifth of our sample was recruited based on their known risk factor status for pre-eclampsia and IUGR. This resulted in an enrichment of the pregnancy and pre-pregnancy disorders in our sample, amplifying the statistical power to study their independent effects. Of note, when this study was performed, guidelines for gestational diabetes screening in Finland were changed from risk-based to comprehensive screening. Thus, our study is likely to include milder cases of gestational diabetes than previous studies(30). Inclusion of milder cases of GDM may have resulted in finding associations with milder developmental delays in some skills, which is in line with our findings on overweight, suggesting dose-response associations. However, in interpretation the small number of children failing to meet the age-appropriate skills should be taken into account. The other strengths include a prospective study design, data of exposures derived from the MBR and medical records, and unlike in a majority of the previous studies measurements of weight and height conducted in the first antenatal clinic visit in early pregnancy, and a large and homogenous study sample. Even though the developmental milestones data were mother-reported, which may introduce a bias, and ASQ is a screening tool rather than a diagnostic instrument, the ASQ has been shown to be reliable, it is well-validated, and demonstrates high sensitivity and specificity to screen children requiring further developmental assessment, monitoring or special education(26-28).

However, the underlying mechanisms still remain unknown. Experimental work in rodents suggests that the mechanisms that link maternal obesity with cognitive dysfunction in the offspring may include alterations in insulin, glucose and leptin regulation, inflammation, and

decreased expression of brain-derived neurothropic factor, particularly in the hippocampus and cortex(31, 32). A recent study showed that hyperglycemia in the pregnant rat can retard dendritic development in the fetal brain and that these changes are a result from abnormal insulin/IGF-I signaling in the fetal brain(33). It is also possible that insulin resistance, characterizing human neonates from obese pregnancies(34, 35), impedes neuronal growth in the fetal brain. Obesity is also associated with changes in the maternal microbiota(36); and these microbial changes are transferred from mothers to infants during delivery and breastfeeding(37), with caesarian section/vaginal delivery, and breastfeeding/not breastfeeding influencing infant's microbiota differently(38). Of note is that obese mothers have disproportionally high rates of caesarian section deliveries(39). There is also evidence that maternal obesity is associated with delayed lactogenesis and reduced rates of breastfeeding(40). Other mechanisms may relate to lifestyle behaviors, including unhealthier diet, and concomitant alterations in micro- and macronutrients, smoking, alcohol use and physical inactivity during pregnancy, and maternal socio-economic position. In our study the associations were independent of maternal smoking and alcohol use during pregnancy and maternal education, however. Clearly further studies unraveling the underlying mechanisms are warranted.

Another major study limitation is the follow-up sample attrition, which was not independent of maternal characteristics. The mothers of children who participated in this study were older, more often primiparous, and had on average higher educational attainment as compared to those who were eligible, but did not participate. This would be expected to cause bias only if the associations between maternal metabolic conditions and child development differ between participants and non-participants. Further, even though our study design resulted in a large number of overweight/obese women and women with hypertensive and diabetic pregnancy and pre-pregnancy disorders, the number of women with type 1 diabetes was small and

precluded studying its effect entirely. In addition, although we were able to control for a number of potential covariates, we cannot entirely exclude the possibility of residual confounding. However, since the associations were consistently significant in largely all of the studied analytic models, we do not anticipate residual confounding to be a source of false-positive associations.

Conclusion

In all, our study findings show that maternal early pregnancy overweight, obesity, and pre-eclampsia are associated, independently of each other and the other comorbid disorders, with neurodevelopmental harm for the developing offspring. Gestational diabetes also carried neurodevelopmental harm, which was partially explained by maternal overweight/obesity and hypertensive disorders. Our findings suggest that efforts to optimize weight management and to reduce the incidence of modifiable pregnancy and pre-pregnancy disorders are likely to result in neurodevelopmental benefits in the offspring.

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Conflict of Interest

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References:

1. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. Lancet (London, England). 2016;387(10026):1377-96.
2. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG, et al. Influence of maternal obesity on the long-term health of offspring. The lancet Diabetes & endocrinology. 2016.
3. Krakowiak P, Walker CK, Bremer AA, Baker AS, Ozonoff S, Hansen RL, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. Pediatrics. 2012;129(5):e1121-8.
4. Wylie A, Sundaram R, Kus C, Ghassabian A, Yeung EH. Maternal prepregnancy obesity and achievement of infant motor developmental milestones in the upstate KIDS study. Obesity (Silver Spring, Md). 2015;23(4):907-13.
5. Yeung EH, Sundaram R, Ghassabian A, Xie Y, Buck Louis G. Parental Obesity and Early Childhood Development. Pediatrics. 2017;139(2).
6. Bliddal M, Olsen J, Stovring H, Eriksen HL, Kesmodel US, Sorensen TI, et al. Maternal pre-pregnancy BMI and intelligence quotient (IQ) in 5-year-old children: a cohort based study. PLoS One. 2014;9(4):e94498.
7. Casas M, Chatzi L, Carsin AE, Amiano P, Guxens M, Kogevinas M, et al. Maternal pre-pregnancy overweight and obesity, and child neuropsychological development: two Southern European birth cohort studies. International journal of epidemiology. 2013;42(2):506-17.
8. Pugh SJ, Richardson GA, Hutcheon JA, Himes KP, Brooks MM, Day NL, et al. Maternal Obesity and Excessive Gestational Weight Gain Are Associated with Components of Child Cognition. The Journal of nutrition. 2015;145(11):2562-9.
9. Huang L, Yu X, Keim S, Li L, Zhang L, Zhang J. Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project. International journal of epidemiology. 2014;43(3):783-92.
10. Basatemur E, Gardiner J, Williams C, Melhuish E, Barnes J, Sutcliffe A. Maternal prepregnancy BMI and child cognition: a longitudinal cohort study. Pediatrics. 2013;131(1):56-63.
11. Jo H, Schieve LA, Sharma AJ, Hinkle SN, Li R, Lind JN. Maternal prepregnancy body mass index and child psychosocial development at 6 years of age. Pediatrics. 2015;135(5):e1198-209.
12. Van Lieshout RJ, Schmidt LA, Robinson M, Niccols A, Boyle MH. Maternal pre-pregnancy body mass index and offspring temperament and behavior at 1 and 2 years of age. Child psychiatry and human development. 2013;44(3):382-90.
13. Rodriguez A. Maternal pre-pregnancy obesity and risk for inattention and negative emotionality in children. Journal of child psychology and psychiatry, and allied disciplines. 2010;51(2):134-43.
14. Polanska K, Muszynski P, Sobala W, Dziewirska E, Merecz-Kot D, Hanke W. Maternal lifestyle during pregnancy and child psychomotor development - Polish Mother and Child Cohort study. Early human development. 2015;91(5):317-25.
15. Torres-Espinola FJ, Berglund SK, Garcia-Valdes LM, Segura MT, Jerez A, Campos D, et al. Maternal Obesity, Overweight and Gestational Diabetes Affect the Offspring Neurodevelopment at 6 and 18 Months of Age--A Follow Up from the PREOBE Cohort. PLoS One. 2015;10(7):e0133010.

16. Stommel M, Schoenborn CA. Accuracy and usefulness of BMI measures based on self-reported weight and height: findings from the NHANES & NHIS 2001-2006. BMC public health. 2009;9:421.
17. Brunner Huber LR. Validity of self-reported height and weight in women of reproductive age. Maternal and child health journal. 2007;11(2):137-44.
18. Fraser A, Almqvist C, Larsson H, Langstrom N, Lawlor DA. Maternal diabetes in pregnancy and offspring cognitive ability: sibling study with 723,775 men from 579,857 families. Diabetologia. 2014;57(1):102-9.
19. Fraser A, Nelson SM, Macdonald-Wallis C, Lawlor DA. Associations of existing diabetes, gestational diabetes, and glycosuria with offspring IQ and educational attainment: the Avon Longitudinal Study of Parents and Children. Experimental diabetes research. 2012;2012:963735.
20. Tearne JE, Allen KL, Herbison CE, Lawrence D, Whitehouse AJ, Sawyer MG, et al. The association between prenatal environment and children's mental health trajectories from 2 to 14 years. European child & adolescent psychiatry. 2015;24(9):1015-24.
21. Ghassabian A, Sundaram R, Wylie A, Bell E, Bello SC, Yeung E. Maternal medical conditions during pregnancy and gross motor development up to age 24 months in the Upstate KIDS study. Developmental medicine and child neurology. 2015.
22. Tuovinen S, Raikkonen K, Kajantie E, Leskinen JT, Henriksson M, Pesonen AK, et al. Hypertensive disorders in pregnancy and intellectual abilities in the offspring in young adulthood: the Helsinki Birth Cohort Study. Annals of medicine. 2012;44(4):394-403.
23. Tuovinen S, Eriksson JG, Kajantie E, Lahti J, Pesonen AK, Heinonen K, et al. Maternal hypertensive disorders in pregnancy and self-reported cognitive impairment of the offspring 70 years later: the Helsinki Birth Cohort Study. American journal of obstetrics and gynecology. 2013;208(3):200.e1-9.
24. Gissler M. Finnish health and social welfare registers in epidemiological research. Norsk Epidemiologi. 2004;14(1):113-20.
25. Girchenko P, Hamalainen E, Kajantie E, Pesonen AK, Villa P, Laivuori H, et al. Prediction and Prevention of Preeclampsia and Intrauterine Growth Restriction (PREDO) study. International journal of epidemiology. 2016.
26. Squires J, Bricker D, Potter L. Revision of a parent-completed development screening tool: Ages and Stages Questionnaires. Journal of pediatric psychology. 1997;22(3):313-28.
27. Bricker D, Squires J, Kaminski R, Mounts L. The validity, reliability, and cost of a parent-completed questionnaire system to evaluate at-risk infants. Journal of pediatric psychology. 1988;13(1):55-68.
28. Kerstjens JM, Bos AF, ten Vergert EM, de Meer G, Butcher PR, Reijneveld SA. Support for the global feasibility of the Ages and Stages Questionnaire as developmental screener. Early human development. 2009;85(7):443-7.
29. Steenis LJ, Verhoeven M, Hessen DJ, van Baar AL. Parental and professional assessment of early child development: the ASQ-3 and the Bayley-III-NL. Early human development. 2015;91(3):217-25.
30. Ellenberg A, Sarvilinna N, Gissler M, Ulander VM. New guidelines for screening, diagnosing, and treating gestational diabetes- evaluation of maternal and neonatal outcomes in Finland from 2006 to 2012. Acta obstetricia et gynecologica Scandinavica. 2016.
31. Bilbo SD, Tsang V. Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2010;24(6):2104-15.
32. Cordner ZA, Tamashiro KL. Effects of high-fat diet exposure on learning & memory. Physiology & behavior. 2015;152(Pt B):363-71.

33. Jing YH, Song YF, Yao YM, Yin J, Wang DG, Gao LP. Retardation of fetal dendritic development induced by gestational hyperglycemia is associated with brain insulin/IGF-I signals. International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience. 2014;37:15-20.
34. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance in utero. Diabetes care. 2009;32(6):1076-80.
35. Dyer JS, Rosenfeld CR, Rice J, Rice M, Hardin DS. Insulin resistance in Hispanic large-for-gestational-age neonates at birth. The Journal of clinical endocrinology and metabolism. 2007;92(10):3836-43.
36. Nehra V, Allen JM, Mailing LJ, Kashyap PC, Woods JA. Gut Microbiota: Modulation of Host Physiology in Obesity. Physiology (Bethesda, Md). 2016;31(5):327-35.
37. Garcia-Mantrana I, Collado MC. Obesity and overweight: Impact on maternal and milk microbiome and their role for infant health and nutrition. Molecular nutrition & food research. 2016;60(8):1865-75.
38. Azad MB, Konya T, Maughan H, Guttman DS, Field CJ, Chari RS, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2013;185(5):385-94.
39. Papachatzi E, Paparrodopoulos S, Papadopoulos V, Dimitriou G, Vantarakis A. Pre-pregnancy maternal obesity in Greece: A case-control analysis. Early human development. 2016;93:57-61.
40. Lepe M, Bacardi Gascon M, Castaneda-Gonzalez LM, Perez Morales ME, Jimenez Cruz A. Effect of maternal obesity on lactation: systematic review. Nutricion hospitalaria. 2011;26(6):1266-9.

Table 1. Characteristics of the study population according to maternal early pregnancy normal weight, overweight and obesity

	Normal weight n=1741	Overweight n=456	Obese n=307	P-values between groups
	N (%) or M (SD)	N (%) or M (SD)	N (%) or M (SD)	
Maternal characteristics :				
Age at delivery (years)	31.5 (4.5)	32.2 (4.7)	32.6 (5.1)	<0.0001
Data not available, n (%)	0	0	0	
Education				<0.0001
Lower secondary or less	583 (33.5%)	200 (43.9%)	158 (51.5%)	
Upper secondary	449 (25.8%)	131 (28.7%)	82 (26.7%)	
Tertiary	706 (40.6%)	125 (27.4%)	67 (21.8%)	
Data not available, n (%)	3 (0%)	0	0	
Parity				0.73
Primiparous	736 (42.3%)	183 (40.3%)	130 (42.3%)	
Multiparous	1002 (57.7%)	271 (59.7%)	177 (57.7%)	
Data not available, n (%)	3 (0%)	2 (0%)	0	
Smoking during pregnancy				0.09
No	1637 (94.2%)	416 (91.2%)	287 (93.5%)	
Quit during first trimester	50 (2.9%)	24 (5.2%)	8 (2.6%)	
Smoked throughout pregnancy	51 (2.9%)	16 (3.5%)	12 (3.9%)	
Data not available, n (%)	3 (0%)	0	0	
Alcohol use during pregnancy				0.19
No	1301 (74.7%)	341 (74.8%)	249 (81.1%)	
Yes	273 (15.7%)	70 (15.4%)	34 (11.1%)	
Data not available, n (%)	167 (9.6%)	45 (9.9%)	24 (7.8%)	
Delivery mode				<0.0001
Vaginal	1490 (85.7%)	364 (79.8%)	215 (70.0%)	
Caesarean	241 (13.8%)	88 (19.3%)	90 (29.3%)	
Data not available, n (%)	10 (0.5%)	4 (0.9%)	2 (0.7%)	
Hypertensive pregnancy and pre-pregnancy disorders				<0.0001
Normotension	1604 (92.1%)	390 (85.5%)	222 (72.3%)	
Gestational hypertension	53 (3.0%)	19 (4.2%)	23 (7.5%)	
Pre-eclampsia	52 (3.0%)	27 (5.9%)	27 (8.8%)	
Pre-pregnancy / Chronic hypertension	32 (1.8%)	20 (4.4%)	35 (11.4%)	
Data not available, n (%)	0	0	0	
Diabetic pregnancy and pre-pregnancy disorders				<0.0001
No diabetes	1652 (94.9%)	383 (84.0%)	212 (69.1%)	
Gestational diabetes	85 (4.9%)	69 (15.1%)	94 (30.6%)	
Type 1 diabetes	4 (0.2%)	4 (0.9%)	1 (0.3%)	
Data not available, n (%)	0	0	0	
Number of hypertensive or diabetic pregnancy and pre-pregnancy disorders				<0.0001
No disorders	1529 (87.8%)	335 (73.5%)	155 (50.5%)	
Any one disorder	198 (11.4%)	103 (24.2%)	124 (29.2%)	
Any two disorders	14 (0.8%)	18 (4.0%)	28 (9.1%)	
Data not available, n (%)	0	0	0	
Child characteristics:				
Sex				0.34
Girls	866 (49.7%)	231 (50.7%)	140 (45.6%)	
Boys	875 (50.3%)	225 (49.3%)	167 (54.4%)	
Data not available, n (%)	0	0	0	
Gestational age, weeks	39.9 (1.5)	39.9 (1.5)	40.0 (1.6)	0.58

Data not available, n (%)	0	0	0	
Birth weight, grams	3498 (503.7)	3549.8 (506.4)	3659 (517.2)	<0.0001
Data not available, n (%)	0	0	0	
Birth length, centimetres	50.1 (2.2)	50.2 (2.4)	50.7 (2.3)	0.0001
Data not available, n (%)	0	0	0	
Age at follow-up, months	41.8 (8.2)	42.3 (8.2)	43.6 (8.4)	0.002
Data not available, n (%)	0	0	0	

Table 2. Number of cases and prevalence of mild developmental delay and failure to achieve developmental milestones in children according to maternal weight category, hypertensive and diabetic disorders status

Maternal pre-pregnancy and pregnancy conditions	Mild developmental delay N (%)	Failure to achieve developmental milestone N (%)
Normal weight		
Communication skills	82 (4.7%)	51 (2.9%)
Fine motor skills	126 (7.2%)	73 (4.2%)
Gross motor skills	125 (7.2%)	79 (4.5%)
Problem solving skills	115 (6.6%)	71 (4.1%)
Personal social skills	157 (9.0%)	59 (3.4%)
Any domain	332 (19.1%)	235 (13.5%)
Overweight		
Communication skills	34 (7.5%)	27 (5.9%)
Fine motor skills	56 (12.3%)	20 (4.4%)
Gross motor skills	34 (7.5%)	30 (6.6%)
Problem solving skills	30 (6.6%)	28 (6.1%)
Personal social skills	50 (11.0%)	20 (4.4%)
Any domain	100 (21.9%)	78 (17.1%)
Obesity		
Communication skills	17 (5.5%)	23 (7.5%)
Fine motor skills	32 (10.4%)	29 (9.4%)
Gross motor skills	22 (7.2%)	26 (8.5%)
Problem solving skills	21 (6.8%)	22 (7.2%)
Personal social skills	27 (8.8%)	19 (6.2%)
Any domain	56 (18.2%)	67 (21.8%)
Normotension		
Communication skills	113 (5.1%)	83 (3.8%)
Fine motor skills	185 (8.4%)	106 (4.8%)
Gross motor skills	162 (7.3%)	113 (5.1%)
Problem solving skills	152 (6.9%)	99 (8.4%)
Personal social skills	204 (9.2%)	84 (3.8%)
Any domain	429 (19.4%)	328 (14.8%)
Gestational Hypertension		
Communication skills	2 (2.1%)	5 (5.3%)
Fine motor skills	10 (10.5%)	8 (8.4%)
Gross motor skills	5 (5.3%)	4 (4.2%)
Problem solving skills	3 (3.2%)	8 (8.4%)
Personal social skills	8 (8.4%)	4 (4.2%)

Any domain	15 (15.8%)	15 (15.8%)
Preeclampsia		
Communication skills	11 (8.3%)	8 (7.9%)
Fine motor skills	12 (11.3%)	3 (2.8%)
Gross motor skills	11 (10.4%)	12 (11.3%)
Problem solving skills	4 (3.8%)	9 (8.5%)
Personal social skills	15 (14.2%)	4 (3.8%)
Any domain	30 (28.3%)	22 (5.8%)
Pre-pregnancy / Chronic Hypertension		
Communication skills	7 (8.1%)	5 (5.8%)
Fine motor skills	7 (8.1%)	5 (5.8%)
Gross motor skills	3 (3.5%)	6 (6.9%)
Problem solving skills	7 (8.1%)	5 (5.8%)
Personal social skills	7 (8.1%)	6 (6.9%)
Any domain	14 (2.9%)	15 (4.0%)
No diabetes		
Communication skills	116 (5.2%)	77 (3.4%)
Fine motor skills	190 (8.5%)	105 (4.7%)
Gross motor skills	164 (7.3%)	114 (5.1%)
Problem solving skills	145 (6.5%)	102 (4.5%)
Personal social skills	199 (8.9%)	87 (3.9%)
Any domain	430 (19.4%)	331 (14.7%)
Gestational diabetes		
Communication skills	16 (6.5%)	23 (9.3%)
Fine motor skills	21 (8.5%)	17 (6.9%)
Gross motor skills	15 (6.1%)	21 (8.5%)
Problem solving skills	21 (8.5%)	19 (7.7%)
Personal social skills	34 (13.7%)	11 (4.4%)
Any domain	54 (21.8%)	48 (19.4%)
Type 1 diabetes		
Communication skills	1 (11.1%)	1 (11.1%)
Fine motor skills	3 (33.3%)	0
Gross motor skills	2 (22.2%)	0
Problem solving skills	0	0
Personal social skills	1 (11.1%)	0
Any domain	4 (44.4%)	1 (11.1%)

Table 3. Associations between maternal pregnancy and pre-pregnancy disorders and mild developmental delay/developmental delay defined as 1 SD/2 SD from the age specific mean ASQ score

	Unadjusted model		Adjusted model*		Adjusted model**	
Pregnancy and pre-pregnancy disorders	Odds Ratio (95% Confidence Interval)	P-value	Odds Ratio (95% Confidence Interval)	P-value	Odds Ratio (95% Confidence Interval)	P-value
Overweight						
Communication skills, mild developmental delay	1.67 (1.11 to 2.53)	0.001	1.59 (1.03 to 2.41)	0.04	1.59 (1.04 to 2.43)	0.03
Fine motor skills, mild developmental delay	1.77 (1.27 to 2.47)	0.0008	1.81 (1.27 to 2.56)	0.001	1.77 (1.26 to 2.49)	0.0009
Gross motor skills, mild developmental delay	1.06 (0.71 to 1.57)	0.78	1.04 (0.70 to 1.56)	0.85	1.07 (0.72 to 1.60)	0.74
Problem solving skills, mild developmental delay	1.0 (0.66 to 1.52)	1.0	0.94 (0.61 to 1.45)	0.78	0.99 (0.65 to 1.51)	0.95
Personal social skills, mild developmental delay	1.26 (0.90 to 1.77)	0.18	1.27 (0.89 to 1.80)	0.18	1.17 (0.83 to 1.65)	0.37
Communication skills, failure to meet developmental milestone	2.14 (1.32 to 3.45)	0.002	2.10 (1.28 to 3.43)	0.003	1.88 (1.15 to 3.07)	0.01
Fine motor skills, failure to meet developmental milestone	1.09 (0.66 to 1.81)	0.73	1.18 (0.70 to 1.99)	0.53	1.10 (0.66 to 1.84)	0.72
Gross motor skills, failure to meet developmental milestone	1.48 (0.96 to 2.28)	0.08	1.42 (0.91 to 2.23)	0.13	1.39 (0.89 to 2.16)	0.15
Problem solving skills, failure to meet developmental milestone	1.51 (0.96 to 2.37)	0.07	1.53 (0.96 to 2.45)	0.07	1.41 (0.89 to 2.23)	0.14
Personal social skills, failure to meet developmental milestone	1.34 (0.80 to 2.26)	0.27	1.39 (0.81 to 2.38)	0.23	1.35 (0.80 to 2.27)	0.27
Obesity						
Communication skills, mild developmental delay	1.26 (0.74 to 2.16)	0.40	1.07 (0.61 to 1.87)	0.81	1.12 (0.63 to 2.0)	0.69
Fine motor skills, mild developmental delay	1.59 (1.06 to 2.40)	0.03	1.49 (0.96 to 2.31)	0.08	1.66 (1.08 to 2.57)	0.02
Gross motor skills, mild developmental delay	1.04 (0.65 to 1.67)	0.87	0.91 (0.56 to 1.49)	0.71	1.13 (0.69 to 1.86)	0.63
Problem solving skills, mild developmental delay	1.07 (0.66 to 1.73)	0.79	1.03 (0.62 to 1.70)	0.92	1.01 (0.60 to 1.70)	0.97
Personal social skills, mild developmental delay	1.01 (0.66 to 1.55)	0.96	0.95 (0.61 to 1.50)	0.83	0.85 (0.54 to 1.35)	0.50
Communication skills, failure to meet developmental milestone	2.74 (1.65 to 2.56)	0.0001	2.62 (1.53 to 4.50)	0.0005	2.06 (1.18 to 3.60)	0.01
Fine motor skills, failure to meet developmental milestone	2.49 (1.59 to 3.91)	<0.0001	2.59 (1.59 to 4.22)	<0.0001	2.47 (1.52 to 4.02)	0.0003

Gross motor skills, failure to meet developmental milestone	1.94 (1.22 to 3.08)	0.005	1.94 (1.19 to 3.17)	0.007	1.67 (1.02 to 2.79)	0.04
Problem solving skills, failure to meet developmental milestone	1.81 (1.10 to 2.98)	0.02	1.87 (1.11 to 3.17)	0.02	1.51 (0.88 to 2.58)	0.13
Personal social skills, failure to meet developmental milestone	1.89 (1.11 to 3.23)	0.02	1.86 (1.05 to 3.30)	0.03	1.83 (1.03 to 3.26)	0.04
Gestational Hypertension						
Communication skills, mild developmental delay	0.40 (0.10 to 1.66)	0.21	0.40 (0.10 to 1.67)	0.21	0.38 (0.09 to 1.58)	0.18
Fine motor skills, mild developmental delay	1.35 (0.68 to 2.65)	0.39	1.38 (0.68 to 2.79)	0.37	1.22 (0.61 to 2.42)	0.57
Gross motor skills, mild developmental delay	0.71 (0.28 to 1.76)	0.46	0.68 (0.27 to 1.72)	0.42	0.69 (0.27 to 1.72)	0.42
Problem solving skills, mild developmental delay	0.46 (0.15 to 1.49)	0.20	0.47 (0.15 to 1.51)	0.20	0.46 (0.14 to 1.47)	0.19
Personal social skills, mild developmental delay	0.92 (0.44 to 1.92)	0.82	0.88 (0.41 to 1.87)	0.73	0.89 (0.42 to 1.88)	0.76
Communication skills, failure to meet developmental milestone	1.37 (0.54 to 3.46)	0.51	1.45 (0.56 to 3.74)	0.44	1.11 (0.43 to 2.85)	0.82
Fine motor skills, failure to meet developmental milestone	1.88 (0.88 to 4.0)	0.10	1.76 (0.80 to 3.88)	0.16	1.60 (0.75 to 3.45)	0.22
Gross motor skills, failure to meet developmental milestone	0.81 (0.29 to 2.24)	0.68	0.75 (0.27 to 2.11)	0.59	0.75 (0.26 to 2.02)	0.54
Problem solving skills, failure to meet developmental milestone	1.90 (0.89 to 4.03)	0.10	1.82 (0.84 to 3.94)	0.13	1.74 (0.81 to 3.73)	0.15
Personal social skills, failure to meet developmental milestone	1.11 (0.40 to 3.11)	0.84	1.09 (0.38 to 3.13)	0.87	1.02 (0.36 to 2.89)	0.98
Preeclampsia						
Communication skills, mild developmental delay	2.32 (1.20 to 4.47)	0.01	2.48 (1.25 to 4.95)	0.01	2.15 (1.10 to 4.19)	0.02
Fine motor skills, mild developmental delay	1.40 (0.75 to 2.60)	0.29	1.45 (0.75 to 2.81)	0.28	1.18 (0.63 to 2.23)	0.61
Gross motor skills, mild developmental delay	1.59 (0.83 to 3.04)	0.16	1.53 (0.78 to 3.0)	0.22	1.49 (0.77 to 2.89)	0.24
Problem solving skills, mild developmental delay	0.56 (0.20 to 1.54)	0.26	0.59 (0.21 to 1.65)	0.31	0.56 (0.20 to 1.56)	0.27
Personal social skills, mild developmental delay	1.62 (0.92 to 2.86)	0.09	1.58 (0.87 to 2.88)	0.13	1.59 (0.89 to 2.82)	0.12
Communication skills, failure to meet developmental milestone	2.30 (1.08 to 4.90)	0.03	2.47 (1.10 to 5.59)	0.03	1.81 (0.83 to 3.93)	0.13
Fine motor skills, failure to meet developmental milestone	0.61 (0.19 to 1.96)	0.40	0.51 (0.15 to 1.69)	0.27	0.52 (0.16 to 1.68)	0.27
Gross motor skills, failure to meet developmental milestone	2.49 (1.32 to 4.69)	0.005	1.82 (0.91 to 3.62)	0.09	2.23 (1.17 to 4.26)	0.01
Problem solving skills, failure to meet developmental milestone	1.92 (0.94 to 3.93)	0.07	1.74 (0.81 to 3.71)	0.15	1.75 (0.85 to 3.62)	0.13

Personal social skills, failure to meet developmental milestone	1.05 (0.38 to 2.93)	0.94	1.09 (0.38 to 3.18)	0.87	0.95 (0.34 to 2.67)	0.92
Pre-pregnancy/Chronic hypertension						
Communication skills, mild developmental delay	1.65 (0.74 to 3.67)	0.22	1.71 (0.74 to 3.91)	0.21	1.49 (0.66 to 3.39)	0.33
Fine motor skills, mild developmental delay	0.97 (0.44 to 2.13)	0.93	0.97 (0.42 to 2.22)	0.94	0.81 (0.36 to 1.82)	0.61
Gross motor skills, mild developmental delay	0.46 (0.14 to 1.46)	0.19	0.43 (0.13 to 1.41)	0.16	0.44 (0.14 to 1.43)	0.17
Problem solving skills, mild developmental delay	1.23 (0.56 to 2.72)	0.61	1.18 (0.52 to 2.68)	0.69	1.16 (0.51 to 2.61)	0.72
Personal social skills, mild developmental delay	0.93 (0.42 to 2.04)	0.85	0.86 (0.38 to 1.96)	0.73	0.86 (0.38 to 1.91)	0.71
Communication skills, failure to meet developmental milestone	2.61 (0.63 to 4.09)	0.32	1.95 (0.74 to 5.12)	0.18	1.02 (0.39 to 2.67)	0.97
Fine motor skills, failure to meet developmental milestone	1.21 (0.48 to 3.05)	0.69	1.18 (0.45 to 3.10)	0.74	0.85 (0.33 to 2.22)	0.75
Gross motor skills, failure to meet developmental milestone	1.31 (0.56 to 3.06)	0.54	1.22 (0.51 to 2.95)	0.66	1.02 (0.43 to 2.44)	0.97
Problem solving skills, failure to meet developmental milestone	1.35 (0.53 to 3.42)	0.53	1.36 (0.52 to 3.55)	0.53	1.09 (0.42 to 2.82)	0.86
Personal social skills, failure to meet developmental milestone	1.93 (0.81 to 4.57)	0.13	2.24 (0.93 to 5.91)	0.07	1.61 (0.66 to 3.92)	0.29
Gestational diabetes						
Communication skills, mild developmental delay	1.34 (0.78 to 2.30)	0.29	1.22 (0.70 to 2.12)	0.49	1.19 (0.67 to 2.11)	0.55
Fine motor skills, mild developmental delay	1.01 (0.63 to 1.63)	0.96	0.93 (0.57 to 1.51)	0.76	0.83 (0.51 to 1.36)	0.46
Gross motor skills, mild developmental delay	0.85 (0.49 to 1.47)	0.56	0.85 (0.49 to 1.49)	0.57	0.85 (0.48 to 1.51)	0.58
Problem solving skills, mild developmental delay	1.38 (0.85 to 2.23)	0.19	1.31 (0.80 to 2.15)	0.28	1.40 (0.84 to 2.32)	0.20
Personal social skills, mild developmental delay	1.65 (1.11 to 2.43)	0.01	1.53 (1.01 to 2.31)	0.04	1.69 (1.12 to 2.56)	0.01
Communication skills, failure to meet developmental milestone	2.90 (1.78 to 4.72)	<0.0001	2.90 (1.74 to 4.72)	<0.0001	2.17 (1.28 to 3.66)	0.003
Fine motor skills, failure to meet developmental milestone	1.48 (0.87 to 2.53)	0.15	1.46 (0.84 to 2.56)	0.18	1.11 (0.63 to 1.95)	0.73
Gross motor skills, failure to meet developmental milestone	1.71 (1.05 to 2.78)	0.03	1.66 (1.0 to 2.76)	0.05	1.40 (0.83 to 2.35)	0.21
Problem solving skills, failure to meet developmental milestone	1.78 (1.07 to 2.96)	0.03	1.80 (1.06 to 3.05)	0.03	1.47 (0.85 to 2.53)	0.17
Personal social skills, failure to meet developmental milestone	1.22 (0.64 to 2.32)	0.54	1.18 (0.61 to 2.31)	0.62	0.94 (0.47 to 1.85)	0.85

Pre-pregnancy Type 1 diabetes						
Communication skills, mild developmental delay	2.50 (0.31 to 20.50)	0.39	2.43 (0.27 to 21.96)	0.43	1.78 (0.21 to 15.01)	0.60
Fine motor skills, mild developmental delay	5.04 (1.25 to 20.31)	0.02	3.94 (0.87 to 17.88)	0.07	4.14 (1.0 to 17.13)	0.05
Gross motor skills, mild developmental delay	3.39 (0.70 to 16.45)	0.13	3.02 (0.57 to 16.17)	0.20	3.18 (0.63 to 15.97)	0.16
Problem solving skills, mild developmental delay	***		***		***	
Personal social skills, mild developmental delay	1.22 (0.15 to 9.83)	0.85	1.30 (0.15 to 11.14)	0.81	1.04 (0.13 to 8.48)	0.95
Communication skills, failure to meet developmental milestone	3.77 (0.46 to 31.0)	0.22	2.40 (0.25 to 23.13)	0.45	2.69 (0.32 to 22.64)	0.36
Fine motor skills, failure to meet developmental milestone	***		***		***	
Gross motor skills, failure to meet developmental milestone	***		***		***	
Problem solving skills, failure to meet developmental milestone	***		***		***	
Personal social skills, failure to meet developmental milestone	***		***		***	

*Adjusted for maternal age at delivery, mode of delivery, parity, maternal smoking and alcohol use during pregnancy, maternal education, child's gestational age, birthweight, sex and age at follow-up.
** Adjusted for other pregnancy and pre-pregnancy disorders
***Number of cases born to the mothers with type 1 diabetes is too small to calculate OR

Table 4. Associations between maternal pregnancy and pre-pregnancy disorders and any mild delay, any failure to achieve developmental milestone, and severity of developmental delay in their children defined as total number of SD below the mean for the five ASQ subscales

Pregnancy and pre-pregnancy disorders	Unadjusted model (N=2504)		Adjusted model* (N=2482)		Adjusted model** (N=2504)		Restricted models*** ($N_{BMI=}$2019, $N_{HD=}$1652, $N_{DIABETES=}$1604)		
	OR (95% Confidence Interval)	P-value	OR (95% Confidence Interval)	P-value	OR (95% Confidence Interval)	P-value	OR (95% Confidence Interval)	P-value	Number of cases
Overweight									
Any mild delay	1.27 (0.98 to 1.65)	0.07	1.22 (0.94 to 1.60)	0.14	1.22 (0.94 to 1.59)	0.13	1.27 (0.94 to 1.71)	0.12	72
Any failure to achieve developmental milestone	1.40 (1.05 to1.87)	0.02	1.40 (1.04 to1.90)	0.03	1.36 (1.02 to1.82)	0.04	1.33 (0.95 to1.86)	0.10	54
Severity/pervasiveness of developmental delay	1.38 (1.12 to 1.70)	0.002	1.38 (1.11 to 1.72)	0.003	1.34 (1.09 to 1.66)	0.006	1.32 (1.04 to 1.68)	0.02	335
Obesity									
Any mild delay	1.08 (0.78 to 1.49)	0.66	0.98 (0.70 to 1.37)	0.89	1.01 (0.72 to 1.43)	0.94	1.11 (0.71 to 1.73)	0.65	28
Any failure to achieve developmental milestone	1.82 (1.33 to 2.49)	0.0002	1.80 (1.28 to 2.52)	0.0007	1.70 (1.22 to 2.38)	0.002	1.87 (1.23 to 2.86)	0.003	34
Severity/pervasiveness of developmental delay	1.51 (1.18 to 1.94)	0.001	1.48 (1.14 to 1.92)	0.003	1.43 (1.10 to 1.86)	0.008	1.58 (1.13 to 2.20)	0.007	155
Gestational Hypertension									
Any mild delay	0.79 (0.44 to 1.39)	0.41	0.76 (0.42 to 1.36)	0.35	0.76 (0.43 to 1.34)	0.34	0.74 (0.32 to 1.68)	0.47	7
Any failure to achieve developmental milestone	1.03 (0.58 to 1.82)	0.93	0.96 (0.53 to 1.74)	0.88	0.93 (0.52 to 1.65)	0.80	0.88 (0.37 to 2.12)	0.78	6
Severity/pervasiveness of developmental delay	0.88 (0.56 to 1.38)	0.58	0.85 (0.53 to 1.34)	0.48	0.82 (0.53 to 1.29)	0.40	0.67 (0.34 to 1.32)	0.24	48
Preeclampsia									
Any mild delay	1.89 (1.19 to 2.99)	0.007	1.91 (1.18 to 3.07)	0.008	1.78 (1.11 to 2.83)	0.02	2.35 (1.19 to 4.64)	0.01	14
Any failure to achieve developmental milestone	1.81 (1.09 to 3.02)	0.02	1.59 (0.92 to 2.74)	0.09	1.61 (0.96 to 2.69)	0.07	2.80 (1.37 to 5.75)	0.005	12
Severity/pervasiveness of developmental delay	1.65 (1.14 to 2.40)	0.008	1.55 (1.04 to 2.30)	0.03	1.52 (1.04 to 2.23)	0.03	2.19 (1.30 to 3.70)	0.003	48
Pre-pregnancy / Chronic Hypertension									
Any mild delay	0.82 (0.45 to 1.49)	0.51	0.75 (0.41 to 1.39)	0.37	0.76 (0.41 to 1.39)	0.37	0.78 (0.26 to 2.30)	0.64	4

Any failure to achieve developmental milestone	1.15 (0.64 to 2.01)	0.64	1.12 (0.61 to 2.05)	0.73	0.92 (0.51 to 1.67)	0.78	1.08 (0.36 to 3.21)	0.89	4
Severity/pervasiveness of developmental delay	1.06 (0.67 to 1.67)	0.79	1.04 (0.65 to 1.67)	0.86	0.89 (0.93 to 1.62)	0.63	1.0 (0.44 to 2.30)	1.0	27
Gestational diabetes									
Any mild delay	1.29 (0.92 to 1.78)	0.15	1.18 (0.83 to 1.67)	0.34	1.26 (0.89 to 1.79)	0.19	1.52 (0.88 to 2.64)	0.13	19
Any failure to achieve developmental milestone	1.48 (1.04 to 2.09)	0.03	1.41 (0.98 to 2.03)	0.07	1.22 (0.85 to 1.76)	0.29	1.0 (0.48 to 2.08)	0.99	9
Severity/pervasiveness of developmental delay	1.40 (1.08 to 1.81)	0.01	1.31 (1.0 to 1.72)	0.05	1.23 (0.94 to 1.62)	0.13	1.20 (0.74 to 1.91)	0.46	74
Type 1 diabetes									
Any mild delay	3.46 (0.86 to 13.88)	0.08	4.14 (0.89 to 19.27)	0.07	2.90 (0.71 to 11.88)	0.14	****		0
Any failure to achieve developmental milestone	1.12 (0.13 to 10.07)	0.92	1.15 (0.11 to 11.77)	0.91	0.91 (0.10 to 8.27)	0.94	****		0
Severity/pervasiveness of developmental delay	1.85 (0.58 to 5.84)	0.30	1.77 (0.51 to 6.19)	0.37	1.51 (0.47 to 4.83)	0.49	****		1

*Adjusted for maternal age at delivery, mode of delivery, parity, maternal smoking and alcohol use during pregnancy, maternal education, child's gestational age, birthweight, sex and age at follow-up.
** Adjusted for other pregnancy and pre-pregnancy disorders
****Women with other pregnancy disorders are excluded (i.e., analyses of pre-pregnancy body mass index excludes women with gestational hypertension, preeclampsia, pre-pregnancy/chronic hypertension, gestational diabetes and pre-pregnancy type 1 diabetes; analyse of hypertensive disorder excludes women with pre-pregnancy overweight, obesity, and gestational diabetes and pre-pregnancy type 1 diabetes; analyses of diabetes excludes women with pre-pregnancy overweight, obesity and gestational hypertension, preeclampsia, and pre-pregnancy/chronic hypertension,)
****Only one woman with type 1 diabetes was normal weight and normotensive.

Table 5. Additive effects of maternal pregnancy and pre-pregnancy disorders on any mild developmental delay, failure to meet any developmental milestone, and severity of developmental milestones delay in the offspring

	Unadjusted model		Adjusted model*	
Number of pregnancy and pre-pregnancy disorders	OR (95% Confidence Interval)	P-value	OR (95% Confidence Interval)	P-value
Mild developmental delay in any of the developmental milestones				
No disorders	0.81 (0.65 to 1.02)	0.08	0.83 (0.65 to 1.05)	0.12
One disorder	Reference		Reference	
Two and more disorders	1.10 (0.77 to 1.55)	0.61	1.02 (0.71 to 1.46)	0.93
Failure to meet any developmental milestone				
No disorders	0.71 (0.55 to 0.91)	0.007	0.70 (0.54 to 0.92)	0.009
One disorder	Reference		Reference	
Two and more disorders	1.26 (0.88 to 1.81)	0.21	1.17 (0.80 to 1.72)	0.41
Severity of developmental delay				
No disorders	0.74 (0.62 to 0.90)	0.002	0.73 (0.60 to 0.88)	0.001
One disorder	Reference		Reference	
Two and more disorders	1.20 (0.91 to 1.59)	0.19	1.10 (0.83 to 1.47)	0.51

*Adjusted for maternal age at delivery, mode of delivery, parity, maternal smoking and alcohol use during pregnancy, maternal education, child's gestational age, birthweight, sex and age at follow-up.
**Calculated from the unadjusted model