Prenatal exposure to very severe maternal obesity is associated with adverse neuropsychiatric outcomes in children

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Background. Prenatal maternal obesity has been linked to adverse childhood neuropsychiatric outcomes, including increased symptoms of attention deficit hyperactivity disorder (ADHD), internalizing and externalizing problems, affective disorders and neurodevelopmental problems but few studies have studied neuropsychiatric outcomes among offspring born to very severely obese women or assessed potential familial confounding by maternal psychological distress.

Method. We evaluated neuropsychiatric symptoms in 112 children aged 3–5 years whose mothers had participated in a longitudinal study of obesity in pregnancy (50 very severe obesity, BMI ≥ 40 kg/m², obese class III and 62 lean, BMI 18.5–25 kg/m²). The mothers completed the Conners’ Hyperactivity Scale, Early Symptomatic Syndrome Eliciting Neuropsychological Clinical Examination Questionnaire (ESSENCE-Q), Child’s Sleep Habits Questionnaire (CSHQ), Strengths and Difficulties Questionnaire (SDQ), and Child Behavior Checklist (CBCL) to assess child neuropsychiatric symptoms. Covariates included child’s sex, age, birthweight, gestational age, socioeconomic deprivation levels, maternal age, parity, smoking status during pregnancy, gestational diabetes and maternal concurrent symptoms of anxiety and depression assessed using State Anxiety of Spielberger State-Trait Anxiety Index (STAI) and General Health Questionnaire (GHQ), respectively.

Results. Children exposed to prenatal maternal very severe obesity had significantly higher scores in the Conners’ Hyperactivity Scale; ESSENCE-Q; total sleep problems in CSHQ; hyperactivity, conduct problems and total difficulties scales of the SDQ; and Child Behavior Checklist (CBCL) to assess child neuropsychiatric symptoms. Covariates included child’s sex, age, birthweight, gestational age, socioeconomic deprivation levels, maternal age, parity, smoking status during pregnancy, gestational diabetes and maternal concurrent symptoms of anxiety and depression assessed using State Anxiety of Spielberger State-Trait Anxiety Index (STAI) and General Health Questionnaire (GHQ), respectively.

Conclusions. Prenatal maternal very severe obesity is a strong predictor of increased neuropsychiatric problems in early childhood.

Introduction

Neuropsychiatric disorders in children are a major public health problem; 3.4% of children worldwide are diagnosed with attention deficit hyperactivity disorder (ADHD) and 5.7% with disruptive disorders (Polanczyk et al. 2015). Children with neuropsychiatric problems face social and educational challenges, and interventions including special assistance during education years, therapies and/or appropriate medication incur significant financial burden (Buescher et al. 2014; Le et al. 2014). As childhood neuropsychiatric problems persist into adulthood (Caspi et al. 1996; Pihlakoski et al. 2006), understanding predisposing factors is essential for the development of appropriate preventive measures to enable these children to reach their full potential.

Studies have demonstrated increased symptoms of ADHD (Rodriguez et al. 2008; Rodriguez 2010; Buss et al. 2012; Chen et al. 2014; Jo et al. 2015; Pugh et al. 2016), externalizing, internalizing and aggressive
behaviour problems (van Lieshout et al. 2013; Antoniou et al. 2014; Pugh et al. 2016), affective disorders (Robinson et al. 2013) and autism spectrum disorders (ASD) (Gardner et al. 2015; Jo et al. 2015; Li et al. 2015) in children exposed to prenatal maternal obesity. The upward trends in the prevalence of neuropsychiatric disorders including ADHD and autism (Boyle et al. 2011; Atladottir et al. 2015) appears to parallel the rise in pre-pregnancy obesity over the same period (Fisher et al. 2013). If prenatal maternal obesity is truly a new risk factor for the development of increased neuropsychiatric symptoms in the offspring, this adds significantly to the current public health challenges arising from obesity in pregnancy. One in five women are obese during pregnancy [body mass index (BMI) > 30 kg/m², obese class I; WHO] (Chu et al. 2009; Heslehurst et al. 2010) and maternal obesity is linked to obstetric complications and mortality risk (Norman & Reynolds, 2011) and is also a major risk factor for future cardio-metabolic problems in the offspring (Reynolds et al. 2013).

However the association between maternal obesity and childhood neuropsychiatric outcomes have been inconsistent particularly among offspring of overweight and obese class I mothers (Brion et al. 2011) and in younger children (van Lieshout et al. 2013). The effect of maternal obesity has been argued to be due to genetic predisposition (Chen et al. 2014), although a twin study later concluded that maternal obesity remains an important non-genetic (in utero or common) factor in explaining the variance of children’s neuropsychiatric problems (Antoniou et al. 2014). Only recent studies have considered obesity-linked obstetric complications (e.g. gestational diabetes) and postnatal factors such as breastfeeding (Buss et al. 2012; Robinson et al. 2013; Gardner et al. 2015; Jo et al. 2015) as potential confounders of the obesity effect on childhood neuropsychiatric outcomes. Moreover, no study has assessed maternal concurrent psychological wellbeing, which may introduce respondent’s bias, on the prenatal obesity effect on childhood neuropsychiatric outcomes. This is important since women with obesity have increased odds of anxiety and depression symptoms (Molyneaux et al. 2014; Mina et al. 2015), and since increased maternal psychological distress is associated with higher risk of childhood psychopathology (Van den Bergh et al. 2005; Goodman et al. 2011; van Batenburg-Eddes et al. 2013).

The current work aimed to assess childhood neuropsychiatric problems in children exposed to prenatal maternal very severe obesity (BMI \( \geq 40 \) kg/m², obese class III). We hypothesized that exposure to prenatal very severe obesity would be associated with increased childhood symptoms across multiple neuropsychiatric domains including increased symptoms of ADHD, internalizing and externalizing behaviour, and neurodevelopmental problems. We envisaged that these associations would be independent of the prenatal and socio-demographic confounders identified in previous studies (Rodriguez et al. 2008; Rodriguez 2010; Buss et al. 2012; Robinson et al. 2013; van Lieshout et al. 2013; Antoniou et al. 2014; Chen et al. 2014; Gardner et al. 2015; Jo et al. 2015; Li et al. 2015; Pugh et al. 2016), and examined whether they also occur independently of maternal concurrent anxiety and depressive symptoms.

Method

Participant recruitment and consent

The current work was a follow-up of a longitudinal pregnancy cohort of women with very severe obesity (BMI \( \geq 40 \) kg/m² or obesity class III at their first antenatal booking; WHO) and lean controls (BMI 18.5–25 kg/m²) in Midlothian, Scotland, UK (Mina et al. 2015). Maternal BMI was measured by midwives (Mina et al. 2015) and none of the women had pre-existing type 2 diabetes. Ethical approval was obtained from the local research ethics committee (REC: 14/|WS/1046, R&D: 2014/0278) and the study was conducted in the Wellcome Trust Clinical Research Facility (WTCRF), the Royal Hospital for Sick Children, Edinburgh. We screened 357 prospective participants (135 lean, 222 very severe obesity) from the pregnancy study for study eligibility and excluded mothers who had moved out of Midlothian, or whose child was under a child protection register alert.

Supplementary Fig. S1 summarizes the recruitment for the study, including the breakdown of participation through the clinic visits and reasons for attrition. Children with known diagnoses of neuropsychiatric problems were excluded as the follow-up study included neuropsychological assessments that are challenging to complete among children with neurodevelopmental disabilities and could introduce unnecessary distress. Overall we obtained consent from 116 (62 lean, 54 very severe obesity) mother-and-child dyads, but for the current analysis data are only available from 112 (62 lean, 50 very severe obesity) participants as four very severe obesity mothers did not return a complete study package. In those not recruited to the follow-up study, there was a significantly higher proportion of very severe obesity and higher levels of socioeconomic deprivation (Supplementary Table S1).

Questionnaires on child psychiatric and neuropsychiatric symptoms

Mothers completed the Conners’ Hyperactivity Scale (Erhart et al. 2008), Early Symptomatic Syndrome Eliciting Neurodevelopmental Clinical Examination
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Questionnaire (ESSENCE-Q: Gillberg 2010), the abbreviated Child’s Sleep Habits Questionnaire (CSHQ) – adopted for preschool children (Goodlin-Jones et al. 2008), Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997), and Child Behavior Checklist for 1½–5-year-olds (CBCL/1½–5) (ASEBA® by Thomas Achenbach, Burlington, USA).

The Conner’s Hyperactivity Scale includes 10 items assessing the severity of ADHD symptoms. ESSENCE-Q is a 10-item questionnaire examining the presence of neurodevelopmental syndromes. The CSHQ contains 45 items evaluating eight domains of sleep problems, child’s waking, sleeping time on weekdays/weekend and the duration of nap. The CBCL/1½–5 comprises 99 items and SDQ 25 items on child psychiatric problems. The SDQ yields five psychiatric symptom scales (hyperactivity, emotional problems, conduct problems, peer problems, total difficulties) and one scale on the child’s strengths. The CBCL/1½–5 yields scores for three main scales (internalizing, externalizing, total problems), eight syndrome scales (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behaviour, other problems) and five Diagnostic and Statistical Manual for Mental Disorders (DSM)-oriented scales (affective, anxiety, pervasive developmental, attention deficit hyperactivity, oppositional defiant problems). In the analyses, we used the t scores of the CBCL main scales and the raw scores of the syndrome and DSM-oriented scales.

The CBCL (Achenbach & Rescorla, 2000), SDQ (Croft et al. 2015), Conners’ (Erhart et al. 2008) and CSHQ (Goodlin-Jones et al. 2008) are well-validated questionnaires with good psychometric properties. The upper age limit for the CCBL is 5 years so nine children aged >5 years did not complete this scale. The ESSENCE-Q scale is a novel, less validated scale and children exposed to maternal prenatal very severe obesity status as the independent variable and children’s neuropsychiatric outcomes as dependent variables. The first regression model (model 1) included infant’s sex and age-at-visit as covariates. Model 2 included model 1 covariates + maternal socioeconomic deprivation, maternal smoking during pregnancy, year of visit, maternal smoking during pregnancy, and infant follow-up (Mina et al. 2015). Infant birthweight was sex- and gestational age-standardized to British population (SDS) using UK-WHO growth chart (http://healthforallchildren.com, version 2.77, Oxford, UK). The most recent maternal postcode was used to assess socioeconomic deprivation levels of the family, which were grouped into low (score <3) and high (score ≥4) (McLoone, 2004). Child’s age was recorded at the visit. Maternal anxiety and depressive symptoms concurrently when rating the child’s neuropsychiatric symptoms were assessed with the Spielberger State-Trait Anxiety Index (STAI, clinical cut-off ≥39) and General Health Questionnaire (GHQ, clinical cut-off ≥3), respectively.

Statistical analysis

All statistical analyses were performed using SPSS v. 20.0 (IBM Corp., USA). Data distribution was verified by examining the skewness, kurtosis scores, and histogram, and abnormally distributed data were transformed using various statistical methods where appropriate. Square-root transformation (√) was applied to maternal scores of GHQ and child’s scores of ESSENCE-Q, CBCL syndrome scales, CBCL main scales and CBCL DSM-IV-oriented scales. Log transformation was applied to the ‘total difficulty’ component of SDQ. Rank transformation using Blom’s formula was applied to gestational age and the ‘Strength’ component of SDQ. Due to the small numbers of mothers who were current smokers during pregnancy, the ‘current smoking’ was merged with ‘ex-smoker’ to make a combined category of ‘smoker’ for the statistical analysis. Unless otherwise indicated, all continuous measures of demographic and neuropsychiatric outcomes were subsequently standardized into z scores to facilitate the comparison of effect sizes.

Descriptive statistics comparing the outcomes of children exposed to maternal prenatal very severe obesity to children of lean mothers were performed using parametric means including Spearman’s ρ correlation, Student’s t test, and χ² test, where appropriate. Multiple linear regressions were performed using maternal very severe obesity status as the independent variable and children’s neuropsychiatric outcomes as dependent variables. The first regression model (model 1) included infant’s sex and age-at-visit as covariates. Model 2 included model 1 covariates + maternal socioeconomic deprivation, maternal smoking during pregnancy, age, parity as covariates. This was followed by model 3, which comprised model 2 + maternal gestational diabetes, SDS birthweight and rank-normalized gestational age (using Blom’s formula). Finally model 4 encompassed model 3 + maternal concurrent psychological wellbeing, assessed using STAI as a measure of state anxiety and z-GHQ as a measure of depressive symptoms. Univariate general linear model was used to explore interactions between
maternal very severe obesity status and infant’s sex on child neuropsychiatric problems.

**Ethical standards**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

**Results**

**Mother and child demographics**

At follow-up very severely obese mothers had significantly higher levels of socioeconomic deprivation (Table 1), consistent with previous findings (Mina et al., 2015). Children of very severely obese mothers were more likely to be exposed to maternal GDM, have higher birthweight and were ±0.42 years older at follow-up than children of lean mothers (Table 1). Very severely obese mothers also had higher levels of anxiety and depressive symptoms (Table 1).

Supplementary Table S2 details the data availability for each item of neuropsychiatric assessment and Supplementary Table S3 the correlations of the covariates with neuropsychiatric measures. Boys had higher scores of Conners’ SDQ total difficulty and externalizing problems. Children with higher socioeconomic deprivation level had higher scores of CBCL externalizing and total problems as well as CSHQ sleep problems. Children who had shorter gestational age had higher scores of SDQ total difficulty and CSHQ sleep problems, whereas children with lower SDS birthweight had higher scores of ESSENCE-Q. Furthermore, children who were exposed to maternal GDM had higher CSHQ sleep problems. Higher maternal state anxiety was correlated with higher measures of all representative neuropsychiatric measures except for CSHQ sleep problems. Higher maternal current

| Mother and child demographics | Lean (n = 62) | SO (n = 50) | p   |
|------------------------------|--------------|------------|-----|
| Socioeconomic deprivation level, n (%)<sup>a</sup> | Low, levels 1–3 52 (85.25) 18 (36.00) | 0.001<sup>b</sup> |
| Smoking status at pregnancy, n (%) | High, levels 4–7 9 (14.75) 32 (64.00) | 0.341<sup>b</sup> |
| Parity, n (%) | Never 36 (58.06) 25 (50.00) | 0.341<sup>b</sup> |
| Maternal age at first antenatal booking, years, mean (s.d.) | 31.3 (4.49) | 0.030<sup>c</sup> |
| Maternal GDM, n (%) | 3 (4.84) | 0.006<sup>b</sup> |
| Maternal blood pressure at week 17 pregnancy, mmHg, mean (s.d.) | Systolic 105 (8.7) 117 (10.8) | 0.001<sup>c</sup> |
| | Diastolic 62 (6.6) 79 (7.9) | 0.001<sup>c</sup> |
| Child’s SDS birthweight, mean (s.d.) | 0.13 (0.99) | 0.047<sup>c</sup> |
| Child’s gestational age, days, mean (s.d.) | 281.03 (9.79) | 0.693<sup>c</sup> |
| Infant’s sex, n (%) | Male 29 (46.77) 23 (46.00) | 0.935<sup>b</sup> |
| | Female 33 (53.23) 27 (54.00) | 0.935<sup>b</sup> |
| Child’s age at admission in year, mean (s.d.) | 4.07 (0.58) | 0.001<sup>c</sup> |
| Anxiety symptoms | Raw ‘State’ score of STAI, mean (s.d.) 29.28 (8.40) 32.52 (10.04) | 0.068<sup>c</sup> |
| | State STAI ≥ 39, n (%) 9 (15.00) 16 (32.00) | 0.034<sup>b</sup> |
| Depression symptoms | Raw GHQ, mean (s.d.) 1.18 (1.26) 3.3 (3.32) | <0.001<sup>d</sup> |
| | GHQ ≥ 3, n (%) 8 (13.11) 26 (52.00) | <0.001<sup>b</sup> |

SO, Mothers with very severe obesity; GDM, gestational diabetes mellitus; SDS, British standard deviation score; STAI, State Trait Anxiety Index (min-max = 0–80); GHQ, General Health Questionnaire (minimum-maximum = 0–15).

Bold text: p < 0.05, underlined text: p < 0.1.

<sup>a</sup>Socioeconomic deprivation category is based on postcode in the Midlothian, Scotland (McLoone, 2004).

<sup>b</sup>χ².

<sup>c</sup>Student’s t test.
depressive symptoms were correlated with higher scores in ESSENCE-Q, SDQ total difficulty and CSHQ sleep problem scores. Socioeconomic deprivation was associated with significantly higher child CBCL externalizing and total problems and increased CSHQ sleep problems. The main neuropsychiatric outcomes were not significantly different according to child’s age at visit, parity and smoking status in pregnancy (Supplementary Table S3).

**Prenatal maternal very severe obesity is strongly associated with increased childhood neuropsychiatric problems independent of all major confounders**

In unadjusted analyses (Table 2), children exposed to pre-pregnant maternal very severe obesity scored significantly higher across the different neuropsychiatric symptom scales. On the general psychiatric problem scales, children born to very severely obese mothers had higher scores for hyperactivity, conduct problems and total difficulties scales of the SDQ. On the CBCL, they had higher externalizing and total problems main scale scores, higher anxious/depressed, aggressive behaviour and other problem syndrome scale scores, and higher DSM-oriented affective, anxiety and ADHD problem scores. Children born to very severely obese mothers also showed higher levels of Conners’ ADHD symptoms and neurodevelopmental problems in the ESSENCE-Q. Children of very severely obese mothers also had more sleep problems, and were more likely to wake up and sleep later at the weekend than the children of lean mothers. The total sleep duration at the weekend among children of very severely obese mothers (mean, s.d. = 11.72 h, 0.75) was similar to that of the lean group (mean, s.d. = 11.73 h, 0.75, p = 0.946).

In model 1 (B1, Table 2), the overall results remained unchanged although the higher SDQ peer-problem score among children of very severely obese mothers was no longer significant. In model 2 which adjusted for demographic factors (B2, Table 2), prenatal maternal very severe obesity remained strongly associated with increased children’s neuropsychiatric problems, with the exception on the CBCL syndrome score on sleep problems. In model 3 with prenatal factors as potential causal pathway of very severe obesity, maternal prenatal very severe obesity remains associated with multiple different problem scales (B3, Table 2) and also emerged as a predictor of children’s CBCL higher internalizing problems. In model 4, prenatal maternal very severe obesity remained a strong predictor of increased children’s neuropsychiatric problems across multiple scales independent of maternal current psychological wellbeing (B4, Table 2).

In exploratory analyses the interaction between maternal SO status and child’s sex in SDQ peer-problem scores was significant (F 1,106 = 4.933, p = 0.029), where maternal SO status predicts increased SDQ peer-problem scores in male (B1: 0.73, 95% CI 0.12–1.34) but not in female offspring (B1: 0.09, 95% CI −0.43 to 0.62). This sex difference remained in model 2 [B2male: 0.73, 95% CI 0.04–1.43] but not in model 3, and no other maternal obesity-sex interactions for the other neuropsychiatric symptom scales were found (all p values > 0.05, Supplementary Table S4).

**Discussion**

The evidence supporting maternal obesity as a predictor of adverse childhood neuropsychiatric outcomes is inconsistent. Here, using multiple validated scales we demonstrated that maternal very severe obesity is a significant predictor of increased general neuropsychiatric problems, externalizing behaviour problems including symptoms of ADHD and aggressive behaviour, sleep problems and neurodevelopmental problems in their children. Pre-pregnancy very severe obesity also predicted higher anxiety problems but had no consistent effects on the main scale internalizing problems. The effects of maternal very severe obesity on child neuropsychiatric problems were independent of socio-demographic confounders, prenatal factors and most importantly, of maternal concurrent symptoms of anxiety and depression. Our findings are in accord with findings from large prospective cohort studies in women with less severe levels of obesity and more limited assessments of neuropsychiatric outcomes (Rodriguez et al. 2008; Rodriguez, 2010; Jo et al. 2015) and with the findings of increased developmental problems in children exposed to obesity-linked metabolic complications in utero (Krakowiak et al. 2012).

To our knowledge only one study has specifically analysed outcomes according to combined class II and class III obesity separately from class I obesity and that study also reported significantly increased risks of multiple types of neuropsychiatric problems (SDQ problem total difficulties, emotional symptoms, and peer problems, diagnoses of ADHD, ASD, developmental delay and affective disorders) among the children born to classes II and III obese mothers. A clear segregation of obesity group and the assessment at appropriate age group are critical as previous studies reported absence of associations in the less severe obesity levels [overweight and obese classes I and II (Brion et al. 2011), and in younger children (2–3 years old)] where certain neuropsychiatric problems are yet to be manifest (van Lieshout et al. 2013). Our findings are consistent with previous observations (Jo et al. 2015) and support the concept of ‘dose-dependent/saturation’ obesity effect on childhood neuropsychiatric problems.
Table 2. Prenatal maternal very severe obesity is strongly associated with increased child’s neuropsychiatric problems independent of demographic and prenatal confounders and maternal current well-being

| Neuropsychiatric outcomes in z scores, t (s.d.) | Lean (n = 62) | Obese (n = 50) | p | B1 (n = 110) | B2 (n = 107) | B3 (n = 105) | B4 (n = 104) |
|-----------------------------------------------|--------------|---------------|---|-------------|-------------|-------------|-------------|
| **Conner’s Hyperactivity scale** | | | | | | | | |
| Emotional problem scale | | | | | | | | |
| Conduct problem scale | | | | | | | | |
| Peer-problem scale | | | | | | | | |
| Total difficulty scores | | | | | | | | |
| Strength scores | | | | | | | | |
| CBCL syndrome scales | | | | | | | | |
| Emotionally reactive | | | | | | | | |
| Anxious/depressed | | | | | | | | |
| Somatic complaints | | | | | | | | |
| Withdrewn | | | | | | | | |
| Sleep | | | | | | | | |
| Attention | | | | | | | | |
| Agressive behaviour | | | | | | | | |
| Other problems | | | | | | | | |
| CBCL DSM-IV oriented scales | | | | | | | | |
| Anxiety | | | | | | | | |
| Pervasive developmental | | | | | | | | |
| Attention deficit hyperactivity | | | | | | | | |
| Oppositional defiant | | | | | | | | |
| Internalizing problems | | | | | | | | |
| Externalizing problems | | | | | | | | |
| Total problems | | | | | | | | |
| CSHQ Sleep problem scores | | | | | | | | |
| CSHQ Sleeping time in weekdays | | | | | | | | |
| CSHQ Sleeping time in weekend | | | | | | | | |

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Waking time in weekdays

|              |       |       |       |       |
|--------------|-------|-------|-------|-------|
|              | 6:59  | 0.050 | 0.39  | 0.48  |
|              | (0:28 |       | (−0.02 to 0.80) | (0.01 to 0.96) |
|              |       |       | 0.38  | (−0.12 to 0.88) |
|              |       |       | 0.34  | (−0.18 to 0.87) |
| Waking time in weekend

|              |       |       |       |       |
|--------------|-------|-------|-------|-------|
|              | 7:14  | 0.001 | 0.56  | 0.47  |
|              | (0:33 |       | (0.16 to 0.96) | (0.01 to 0.93) |
|              |       |       | 0.35  | (−0.13 to 0.84) |
|              |       |       | 0.39  | (−0.12 to 0.90) |

ESSENCE-Q, Early Symptomatic Syndrome Eliciting Neurodevelopmental Clinical Examination Questionnaire; CBCL, Child Behavior Checklist; CSHQ, Child’s Sleep Habits Questionnaire; SDS, British standard deviation score; GHQ, General Health Questionnaire; SDQ, Strengths and Difficulties Questionnaire.

P, Unadjusted p values from Student’s t test. Bold text: p values ≤ 0.05. The regression output was standardized coefficients for maternal very severe obesity status B1-B4 and their 95% confidence intervals (CI).

B1, Effect of maternal obesity following linear regression adjusted for sex and age at visit; B2, B1 + adjusted for parity at pregnancy, maternal age, maternal smoking status and socio-economic deprivation level; B3, B2 + adjusted for maternal gestational diabetes, SDS birthweight and rank-standardized gestational age; B4, B3 + adjusted for maternal z scores of State Anxiety and z scores of √ (maternal general depression score).

Square-root transformation (√) was applied to maternal scores of GHQ and child’s scores of ESSENCE-Q, CBCL syndrome scales, CBCL main scales and CBCL DSM-IV-oriented scales. Log to base 10 transformation was applied to CSHQ scales. Natural logarithm transformation was applied to the ‘total difficulty’ component of SDQ. Rank transformation using Blom’s formula was applied to gestational age and the ‘Strength’ component of SDQ.

All preliminary output prior to regressions was displayed in z scores except output from sleep questionnaire, which is displayed in raw scores. Sleeping and waking time are expressed in hour: minute format.
not be necessarily constrained within gestation. Our findings and those of (Jo et al. 2015) were independent of maternal GDM, and gestational hypertensive disorders could not independently explain increased affective disorders in children born to obese mothers (Robinson et al. 2013). Other potential oetiological factors of neuropsychiatric problems include maternal chronic inflammation (Bilbo & Schwarz, 2012; Brown et al. 2014) and altered prenatal glucocorticoid exposure, either directly through altered placental glucocorticoid barrier (Räikkönen et al. 2015) and/or epigenetic modification of glucocorticoid receptors (Heinrich et al. 2015; Parade et al. 2016). In addition, there may be non-biological explanations of the findings. For example, women with very severe obesity in this cohort were known to have increased depressive symptoms during pregnancy and postpartum and to have high socioeconomic deprivation levels (Mina et al. 2015). Furthermore, maternal depression and higher socioeconomic deprivation levels are associated with poorer child-rearing practices (Lovejoy et al. 2000; Reising et al. 2013) that, in turn, have been consistently associated with increased neuropsychiatric problems in children (Reising et al. 2013; Yap & Jorm, 2015; Madigan et al. 2016). Hence, the combination of socioeconomic deprivation and maternal distress among obese mothers resulting in inadequate and/or compromised child-rearing could be potential non-biological mechanisms that explain the effect of maternal very severe obesity on increased neuropsychiatric problems in children.

The strengths of our study are the prospective cohort design with a very clear definition of very severe obesity, detailed participant characterization including concurrent assessment of maternal anxiety and depressive symptoms, and multiple validated questionnaires measuring neuropsychiatric problems in children. The limitations are that we were unable to fully control for rating biases (parental compared to teacher’s rating) and a more reliable estimate of the associations would have been gained with multiple informants. Although we considered maternal current psychological wellbeing we did not specifically determine whether this was due to child’s neuropsychiatric problems. However, the reliability of our findings is increased as we administered multiple validated scales and found consistent results. Furthermore, since children under the Scottish child protection register (including due to, but not exclusively, diagnosed neuropsychiatric and/or neurodevelopmental disorders) were excluded from the study and since more very severely obese mothers declined the follow-up. Since the prevalence of preterm birth (Mina et al. 2015) and the proportion of exclusive breastfeeding were very low in our sample, we could not assess their potential confounding role on the associations found. We could not distinguish the effect of paternal factors and/or parental genetic factor. However neither paternal factors (Rodriguez, 2010; Brion et al. 2011; Buss et al. 2012; Robinson et al. 2013) nor genetic factors alone (Antoniou et al. 2014) appear to fully account for the associations between the prenatal obesity and adverse childhood neuropsychiatric outcomes.

Conclusion
Maternal very severe obesity is a robust predictor of increased childhood neuropsychiatric problems in children. Future studies should focus on whether prenatal intervention and/or management of maternal very severe obesity and/or early postnatal intervention of the child could alleviate childhood neuropsychiatric problems.

Supplementary material
The supplementary material for this article can be found at http://dx.doi.org/10.1017/S0033291716002452.

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Declaration of Interest
None

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