

Role of maternal adiposity prior to and during pregnancy in cognitive and psychiatric problems in offspring

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The purpose of this review is to summarize studies that have examined associations between maternal adiposity prior to and during pregnancy and cognitive and psychiatric problems in offspring. Of the 11 studies published since a 2011 systematic review, four examined cognitive outcomes alone, four assessed psychopathology exclusively, and three reported on both cognitive and psychiatric endpoints. Ten studies provided evidence of a link. These data suggest that the offspring of women who are overweight or obese during pregnancy are at increased risk for cognitive deficits, externalizing problems (particularly attention-deficit/hyperactivity disorder), and internalizing psychopathology in childhood and adolescence; however, the effect sizes were small to medium and a definitive causal association remains to be proven.

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INTRODUCTION

Maternal overweight and obesity are among the most common complications of pregnancy in the developed world, affecting up to 40% of women.¹ Although the adverse effects of obesity on maternal health are widely known, rates of prepregnancy obesity in the United States rose by 69.3% in the 1990s.² While data on the costs of obesity in pregnancy are scarce, the United States spent \$147 billion on obesity-related medical care in 2008 alone,³ a figure that does not include the human suffering associated with obesity and, in the case of pregnant women, its potential impact on future generations.

In addition to being associated with elevated rates of maternal health problems,⁴ the intrauterine environment associated with obesity appears to be suboptimal for fetal development. Infants born to obese women have higher rates of congenital malformations⁵ and appear to be at increased risk for obesity⁶ and asthma⁷ later in life.

The causes of links between prenatal exposures and later health problems are not fully understood but may be due to a pathological dysregulation of normal develop-

ment,⁸ attempts by the fetus to anticipate its postnatal environment (i.e., fetal predictive adaptive responses), or confounding variables (e.g., genetic inheritance, environment factors).⁹ Understanding associations between prenatal exposures and later health problems in offspring can make important contributions to population health by identifying modifiable risk factors that are present during pregnancy and are causally related to health outcomes in offspring. Ideally, this research would lead to the development of primary preventive interventions. The elucidation of noncausal associations is also of value because such associations can help identify those individuals at increased risk early on and can result in the application of secondary preventive interventions. Causality is difficult to establish, however, and the predictive value of these exposures must be high enough to justify their application to humans.

In the past 10 years, associations between maternal adiposity and suboptimal neurodevelopmental outcomes in offspring have emerged.¹⁰ This is not surprising because the intrauterine environment accompanying obesity is characterized by a number of perinatal factors,

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including suboptimal maternal diet and/or nutrient deficiencies,¹¹ diabetes mellitus,¹² psychosocial stress,¹³ proinflammatory cytokines,¹⁴ and obstetric complications,¹⁵ which have also been linked to problems with central nervous system development in offspring. Data from animal models suggest that the offspring of mothers who are obese during pregnancy manifest decreased central serotonergic¹⁶ and dopaminergic signaling¹⁷ in brain regions that have been implicated in the development of cognitive and psychiatric problems in humans (e.g., the hippocampus and prefrontal cortex),^{17,18} and that these changes may be due to epigenetic alterations.¹⁷

More direct evidence of a link between fetal exposure to maternal adiposity and suboptimal central nervous system development in humans comes from studies that report elevated rates of neural tube defects in offspring.⁵ In 2011, Van Lieshout et al.¹⁰ conducted a systematic review that identified 12 epidemiological studies that had examined associations between maternal prepregnancy and pregnancy obesity and neurodevelopmental problems in offspring. Eight of these studies provided support for a link, including three of four studies of schizophrenia, one of two studies of eating disorders, two of three cohorts examining cognitive function, and both studies of attention-deficit/hyperactivity disorder (ADHD). Most of these studies, however, exhibited methodological flaws that limited causal inferences.¹⁰ For example, while parental psychopathology,¹⁹ cognitive problems,²⁰ and socioeconomic disadvantage²¹ are important risk factors for obesity, as well as for cognitive and/or psychiatric problems in offspring, these confounding variables were not always examined. Exposures such as gestational diabetes mellitus and stress during pregnancy are other important omissions. Moreover, only three studies examined more than one neurodevelopmental outcome, making it difficult to determine whether offspring are at risk for cognitive problems, psychiatric problems, or both.

As a result, it is premature to claim that maternal prepregnancy weight loss and/or intrapartum weight management strategies would be beneficial to the cognitive and emotional development of offspring. Moreover, the small-to-medium effect sizes observed in these studies do not support the allocation of resources to postnatal secondary preventive efforts aimed at the offspring of overweight and obese women.

A significant amount of data has accumulated since the publication of the 2011 systematic review. As a result, the findings of studies published since 2011 that examined associations between maternal adiposity prior to and during pregnancy, weight gain during pregnancy, and neurodevelopmental outcomes in offspring are reviewed here.

METHODS

MEDLINE and EMBASE databases were searched from September 22, 2010, to October 5, 2012, for studies in all languages that examined the association between maternal perinatal adiposity and neurodevelopmental problems in offspring. The following search strategy was utilized for MEDLINE: ([pregnan* OR pre-pregnancy body mass index] AND [exp body mass index OR exp obesity OR exp overweight]) AND (exp mental disorders OR behav* OR exp brain diseases OR cognit* OR neuropsych* OR executive function* OR development* OR exp human development OR exp child development OR exp developmental disabilities OR exp personality development OR exp learning disorders OR math* OR arithmetic OR exp reading OR spelling OR exp dyslexia OR exp schools OR academic OR exp communication disorders OR exp psychomotor disorders OR exp perceptual disorders). This search was limited to studies on humans. The EMBASE search utilized the equivalent terms in that database and is available upon request.

Studies that examined any definition of adiposity or weight gain as a predictor of its main outcomes were eligible. These studies could examine any cognitive, psychological, behavioral, emotional, or psychiatric outcome assessed after 1 month of age.

The titles and abstracts yielded by the search were evaluated to determine whether articles met eligibility criteria. The reference section of each relevant article from the initial screening was also manually searched for additional relevant studies. Studies were chosen for full-text review if it was deemed that there was any possibility that the article was eligible. Adjusted estimates of the association between maternal obesity and the study outcome were the main outcomes considered. Data on sample size, study design, and the obesity definition used as well as each study's methodological limitations were also extracted.

Study results were classified in terms of whether they provided evidence in support of an *a priori* hypothesis of an association between maternal adiposity and an elevated risk of neurodevelopmental problems. Given the heterogeneity of eligible study outcomes, a decision was made to not perform a meta-analysis of study results.

RESULTS

The initial search identified 581 studies in MEDLINE and 322 in EMBASE. Twenty-nine full-text articles were examined. Eleven studies were eligible.^{22–32} A summary of the methodological issues and the substantive results of these studies appears in Table 1, and the major findings are highlighted below.

Table 1 Studies of maternal pregnancy adiposity and offspring neurodevelopment.

Reference	Sample size	Study design	Predictor	Outcome	Main findings	Limitations
Hinkle et al. (2012) ²²	USA <i>n</i> = 6,850	Birth cohort	Prepregnancy BMI. BMI 25–29.99 kg/m ² (overweight). BMI 30–34.99 kg/m ² (obese). BMI ≥35 kg/m ² (obese class ≥II). Self-reported	BSID-II Short Form at 2 yrs. Mental Development Index (language/cognition). Psychomotor development index (fine/gross motor skills)	Overweight, obese findings NS. Obese class ≥II: total score: $\beta = -2.13$ (95%CI: -3.32 to -0.93). Severe delay: OR = 1.54 (95% CI, 1.14–2.10). NS for all categories <i>r</i> = -0.16 (language only). <i>r</i> = -0.20 (performance IQ only) NS after adjusting for all confounders	Control of error: no measure of parental cognition
Craig et al. (2012) ²³	USA <i>n</i> = 101 (2 yrs) <i>n</i> = 118 (8 yrs)	Controls from case-control study	2 nd trimester BMI. Objectively measured	BSID-III at 2 yrs.		Control of error: no measure of maternal cognition
Veldwijk et al. (2011) ²⁴	Netherlands <i>n</i> = 236	Birth cohort	Prepregnancy BMI. Objectively measured	WISC-III at 8 yrs K-ABC at 4 yrs and 7 yrs		Study design: link b/w BMI and cognition was not the primary research question
Tanda et al. (2013) ²⁵	USA <i>n</i> = 3,412	Pregnancy cohort	Prepregnancy BMI. BMI 25–29.99 kg/m ² (overweight). BMI ≥30 kg/m ² (obese). Gestational weight gain. Self-reported	PIAT reading recognition and math tests at 5–7 yrs	Obese: reading recognition 0.23 SD units (1.3 pts) Obese: mathematics 0.16 SD units (1.2 pts). No link with weight gain	Control of error: no adjustment for paternal cognition or maternal DM
Van Lieshout et al. (2013) ²⁶	Australia <i>n</i> = 2,785	Pregnancy cohort	Prepregnancy BMI. Self-reported	Temperament at 1 yr. CBCL Internalizing and Externalizing Scales at 2 yrs	No association. $\beta = 0.13$ (95%CI, 0.01–0.25) for externalizing	Control of error: limited control over parental psychiatric risk
Jongeling et al. (2010) ²⁷	Australia <i>n</i> = 2,312	Pregnancy cohort	Prepregnancy BMI ≥30.	ADHD at 5, 10, or 14 yrs (parent report)	OR = 2.58 (95%CI, 1.22–5.45)	Control of error: no measure of maternal ADHD
Robinson et al. (2013) ²⁸	Australia <i>n</i> = 2,785	Pregnancy cohort	Prepregnancy BMI 25–29.99 kg/m ² (overweight). BMI ≥30 kg/m ² (obese). Self-reported	CBCL DSM Affective Problems Scale (clinical cutoff)	Overweight: OR = 1.51 (95%CI, 1.08–2.12). Obese: OR = 1.72 (95%CI, 1.11–2.67)	Control of error: did not control for parental psychiatric risk
Van Lieshout et al. (2013) ²⁹	Australia <i>n</i> = 2,785	Pregnancy cohort	Prepregnancy BMI. Self-reported	CBCL Internalizing Scale (5–17 yrs). CBCL Externalizing Scale (5–17 yrs)	Increasing strength of association over time (interaction: OR = 0.02; 95%CI, 0.01–0.04). Stable association over time (OR = 0.19; 95%CI, 0.07–0.31)	Control of error: limited control over parental psychiatric risk
Krakowiak et al. (2012) ³⁰	USA <i>n</i> = 1,004 (517 ASD, 172 DD, 315 Controls)	Case-control study	Prepregnancy BMI ≥30 kg/m ² (obese). Objectively measured	Autism spectrum disorder. Developmental delay	ASD OR = 1.67 (95%CI, 1.10–2.56). DD OR = 2.08 (95%CI, 1.20–3.61)	Case-control design
Brion et al., (2011) ³¹	UK and Netherlands ALSPAC, N=5,000 & Generation R, <i>n</i> =2,500	Two pregnancy cohorts	Prepregnancy BMI ≥25 kg/m ² (overweight). Self-reported	ALSPAC: MacArthur Toddler Communication Questionnaire (38 mos). DANVA faces subtest at 8 yrs. WISC-II at 8 yrs. SDQ parent at 4 yrs. SDQ teacher at 8 yrs. Generation R: Language development survey at 30 mos. PARCA at 30 mos. CBCL parent at 36 mos.	↓sentence length OR = 0.88 (95%CI, 0.77–1.00). ↓IQ OR = 0.84 (95%CI, 0.73–0.98). Others NS. CBCL total problems: OR = 1.21 (95%CI, 1.00–1.47). CBCL externalizing: OR = 1.21 (95%CI, 1.00–1.47). Others NS	Control of error: no measure of parental cognition or psychiatric risk in either cohort
Buss et al. (2012) ³²	USA <i>n</i> = 174	Pregnancy cohort	Prepregnancy BMI. BMI 25–29.99 kg/m ² (overweight). BMI ≥30 kg/m ² (obese). Gestational weight gain. Objectively measured	CBCL inattention scale at 7 yrs. Go/no-go task (executive function)	Obese: $^aF = 4.80$, $P = 0.03$. Cohen's $d = 0.54$, $\beta = 0.18$. Obese: $F = 8.37$, $P = 0.004$. Cohen's $d = 0.62$. NS for overweight and weight gain	Study design: highly selected sample (multiple exclusion criteria)

^a Link partially mediated by executive function.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ALSPAC, Avon Longitudinal Study of Parents and Children; ASD, autism spectrum disorder; BMI, body mass index; b/w, between; BSID, Bayley Scales of Infant Development; CBCL, Child Behavior Checklist; CI, confidence interval; DANVA, Diagnostic Analysis of Nonverbal Accuracy; DD, developmental delay; DM, diabetes mellitus; DSM, Diagnostic and Statistical Manual of Mental Disorders; K-ABC, Kaufman Assessment Battery for Children; NS, nonsignificant; OR, odds ratio; PARCA, Parent Report of Children's Abilities; PIAT, Peabody Individual Achievement Test; R, correlation; SD, standard deviation; SDQ, Strength and Difficulties Questionnaire; WISC-II, Wechsler Intelligence Scale for Children.

Four studies examined cognitive outcomes alone,^{22–25} four assessed psychopathology exclusively,^{25–28} and three reported on both cognitive and psychiatric endpoints.^{30–32} Sample sizes ranged from 174 to 6,850 mother-offspring pairs. One study used a case-control design,²³ another used controls from a nested case-control study,³⁰ and the remainder used subjects from cohort studies. All studies assessed individuals 17 years of age or younger. Ten utilized prepregnancy body mass index (BMI) as a predictor (four had objective measurements of weight,^{23,24,30,32} and the remainder, maternal self-reports), and one used second trimester BMI.²⁴ Four studies examined maternal BMI as a continuous predictor, three looked at both overweight and obese status categorically, two studied obesity alone, and one examined BMI as both a continuous and a categorical predictor. Three of the studies examined links between gestational weight gain and offspring outcomes.

After adjusting for confounders, 10 of the 11 studies reported statistically significant links between maternal adiposity and at least one type of neurodevelopmental problem in offspring (Table 1).^{22,23,25–32} Three of four studies that exclusively examined cognitive outcomes found some evidence of an association between maternal adiposity and lower scores.^{22–24} Hinkle et al.²² reported that 2-year-olds born to women with a BMI of ≥ 35 kg/m² versus normal-weight women scored two points lower on the Mental Development Index of a short form of the Bayley Scales of Infant Development (BSID)-II (effect size 0.21). They were also more likely to have an elevated risk of delayed mental development (OR 1.38, 95% CI 1.03–1.84). A recent study by Craig et al.²³ reported negative correlations between second trimester maternal BMI and language scores on the BSID-III at 2 years of age and performance IQ on the Wechsler Intelligence Scale for Children-III at 8 years of age. Tanda et al.²⁵ found that 5- to 7-year-olds born to obese versus normal-weight women had scores on the Peabody Individual Achievement Test (PIAT) reading recognition and mathematics tests that were three and two points lower, respectively. These corresponded to effect sizes of 0.23 for math and 0.16 for reading. Finally, Veldwijk et al.²⁴ did not find statistically significant links between maternal prepregnancy BMI and scores at 4 or 7 years of age on the Kaufman Assessment Battery for Children (K-ABC). However, prior to adjustment for confounders, significant negative associations were noted in this study between maternal BMI and the mental, sequential, and simultaneous processing scale scores of offspring.

All four studies that exclusively examined emotional and behavioural outcomes in offspring found evidence of an association with pre-pregnancy adiposity. However, all four of these studies utilized the same Western Australian

Pregnancy Cohort.^{26–29} Van Lieshout et al. noted a link between maternal prepregnancy BMI and externalizing problems that first emerged at age 2²⁶ and persisted through age 17.²⁹ This was due mainly to elevated scores on the aggressive and inattentive subscales of the Child Behavior Checklist (CBCL). Jongeling et al.²⁷ also reported that the offspring of obese women had an elevated risk of clinically significant ADHD symptoms during childhood relative to those of normal-weight women. In terms of internalizing psychopathology, Van Lieshout et al.²⁹ observed an interaction between maternal BMI and child age such that youth born to mothers with higher maternal prepregnancy BMIs had more rapid increases in internalizing scores as they got older. This finding was supported by the study of Robinson et al.,²⁸ who, using the CBCL DSM Affective Problems scale, found an elevated risk of clinically significant affective problems in the offspring of overweight and obese women.

Another three studies examined links between maternal prepregnancy adiposity and both cognitive and psychiatric outcomes in offspring. Krakowiak et al.³⁰ noted associations of maternal obesity with autism spectrum disorders as well as with developmental delay in offspring. Brion et al.³¹ noted small but statistically significant associations between maternal overweight and parent-reported CBCL total and externalizing problems at age 3 years in the Dutch Generation R cohort, but not in the Avon Longitudinal Study of Parents and Children. They also noted an increased risk of lower IQ among the offspring of overweight versus normal-weight women. Finally, Buss et al.³² reported statistically significant links between maternal obesity and the CBCL inattention scale. However, an association was also noted between maternal adiposity and executive functioning in 7-year-olds that partially mediated the link between maternal adiposity and CBCL scores.

DISCUSSION

Synthesis of findings to date

In the past 2 years, 11 studies have examined associations between maternal adiposity and neurodevelopmental problems in offspring. This is just one fewer than the number of studies that had been published in the previous 50 years. Ten of these 11 studies (3 of 4 exclusively assessing cognition, all 4 examining only emotional and behavioral outcomes, and the remaining 3 assessing both types of outcomes) suggest that a link exists between maternal adiposity during gestation and neurodevelopmental problems in offspring. Taken together with the results of the previous systematic

review published in this area in 2011, 18 of 23 studies, containing nearly 90,000 mother-infant pairs, support the existence of an association. The strongest data published to date support links between maternal prepregnancy adiposity and difficulties with cognition and externalizing behavior in offspring, particularly ADHD in children.

Cognition

While negative associations between maternal overweight/obesity and offspring cognition seem to emerge as early as 2 years of age, study heterogeneity in the scales used and in the concepts measured has led to an unclear picture of the neurodevelopmental trajectories of children exposed to maternal adiposity in utero. For example, while Hinkle et al.²² reported that cognitive and language scores were decreased in the offspring of obese women at 2 years of age, Craig et al.²³ found an association only for language scores. While this may be related to deficiencies in measurement or statistical power, Craig et al.²³ subsequently found that, at 8 years of age, associations were present only for performance IQ and not for verbal or full-scale IQ scores. As a result, more work is required to delineate the specific types of cognitive problems seen in those exposed to maternal adiposity during gestation, and how these evolve as children get older.

Emotional and behavioral problems

A lack of specificity is also present in the findings of studies examining emotional and behavioral problems. Recent work suggests that the offspring of overweight and obese women may not only be at elevated risk for ADHD, but may also manifest increased levels of aggressive behavior.²⁹ While the elevated risk for externalizing problems appears early in development, emerging research indicates that an increased risk for internalizing problems may appear later in life. It is unclear if the delayed expression of internalizing symptoms (i.e., those of depression and anxiety) is due to an accumulation of stresses related to earlier externalizing problems, the age-related emergence of a latent predisposition to internalizing problems, or heterotypic continuity.

What neurodevelopmental trajectories do these offspring take?

Most studies that have examined links between maternal adiposity during pregnancy and cognitive and psychiatric outcomes in offspring have been conducted in children and adolescents. While some research suggests that

the offspring of obese women are at increased risk for schizophrenia later in life, this disorder is rare. As a result, it remains unclear if the majority of the problems seen in youth born to overweight and obese mothers persist into adulthood and, if they do, what precise form they take. Studies are needed that follow these individuals into adulthood and use objective measures of both cognition and mental illness (i.e., structured psychiatric interviews) so that the full impact of being exposed to maternal adiposity in utero can be understood.

Strengthening the case for causation

Since brain plasticity is highest during gestation and infancy, early detection and intervention strategies applied at this time offer the most efficient means to reduce the prevalence and severity of neurodevelopmental problems.³³ The evidence-based initiation of primary prevention programs, however, requires evidence of causal associations. In observational studies, the argument for causality can be strengthened via control of genetic and postnatal socioeconomic confounders. While studies published in the past 2 years have more frequently adjusted for both types of confounders in the mothers (7 of 11),^{23–26,29,30,32} the issue of unmeasured confounders is not yet resolved. Studies utilizing more specific measures of genetic risk and examining psychopathology or cognition in both biological parents would represent an advance. Further control of error relating to genetic or familial risk may be provided by within-family studies comparing siblings born to the same woman (particularly before and after significant weight loss), by the use of Mendelian randomization,³⁴ and/or by examining the offspring of women conceiving via certain assisted reproductive technologies.³⁵ Future studies would also benefit by adjusting for confounders such as gestational diabetes mellitus and maternal psychosocial stress.

While existing studies satisfy a number of Sir Bradford Hill's criteria for causation (temporality, biological plausibility, experimental animal data, biological gradient), the use of experimental designs in humans would add greatly to the current understanding of these links. While conducting randomized controlled trials of pre-conception weight-loss interventions in overweight and obese women is challenging from a practical standpoint, such studies are critical to determining whether primary preventive interventions aimed at maternal adiposity could reduce the risk of neurodevelopmental problems in offspring. Furthermore, given that one study has reported a link between gestational weight gain and ADHD in offspring,³⁶ trials of interventions aimed at achieving healthy weight gain during pregnancy may also be helpful.

Putative mechanisms

Since overweight and obesity are associated with so many biochemical abnormalities, it is possible that one or more of these could underlie the observed associations between adiposity during pregnancy and neurodevelopmental problems in offspring. Understanding the role these factors play in the links between maternal adiposity and offspring neurodevelopment could further illuminate the mechanisms underlying these associations and provide targets for potential preventive interventions. The most likely candidates include suboptimal maternal diet and nutritional deficiencies,¹¹ as well as proinflammatory cytokines¹⁴ and hormone levels³⁷ during pregnancy and the epigenetic alterations they may produce. Additional factors that could play a role in links between maternal adiposity in pregnancy and offspring psychopathology include breastfeeding,³⁸ child BMI,³⁹ and offspring cognitive problems. The interesting finding that deficits in executive functioning mediate the association between maternal adiposity and ADHD in offspring³² raises the possibility that the core deficit in these children is actually cognitive in nature, but future work is needed to replicate this. Finally, it must be remembered that certain maladaptive personality traits (e.g., high neuroticism, low conscientiousness), are associated with both obesity⁴⁰ and compromised parenting⁴¹ and may well partially explain the association between obesity and behavioral problems in offspring.

Limitations

While the inclusion and exclusion criteria, the search terms, and the assessment of study limitations were all identical to those of the previous systematic review published in 2010, the present report did not utilize another reviewer to assess manuscript eligibility and to extract data.

CONCLUSION

Despite the benefits to maternal health of attaining a normal weight prior to pregnancy and achieving healthy weight gain during pregnancy, it is premature to promote these measures for their positive effects on the neurodevelopment of offspring because a causal association has not been proven and the effect sizes reported to date are small to medium. Nevertheless, the increasing prevalence of maternal obesity is a strong incentive for attempting to more conclusively determine whether a causal association exists between maternal pregnancy BMI and neurodevelopmental outcomes in offspring. For if an association is proven, attempts to better control

maternal BMI could lead to important benefits for the cognitive and psychiatric functioning of offspring.

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REFERENCES

1. Guelinckx I, Devlieger R, Beckers K, et al. Maternal obesity: pregnancy complications, gestational weight gain and nutrition. *Obes Rev.* 2008;9:140–150.
2. Kim SY, Dietz PM, England L, et al. Trends in pre-pregnancy obesity in nine states, 1993–2003. *Obesity (Silver Spring).* 2007;15:986–993.
3. Finkelstein EA, Trogdon JG, Cohen JW, et al. Annual medical spending attributable to obesity: payer- and service-specific estimates. *Health Aff.* 2009;28:w822–w831.
4. Stothard KJ, Tennant PW, Bell R, et al. Maternal overweight and obesity and the risk of congenital anomalies. *JAMA.* 2009;301:636–650.
5. Rowlands I, Graves N, de Jersey S, et al. Obesity in pregnancy: outcomes and economics. *Semin Fetal Neonatal Med.* 2010;15:94–99.
6. Drake AJ, Reynolds RM. Impact of maternal obesity on offspring obesity and cardiometabolic disease risk. *Reproduction.* 2010;140:387–398.
7. Reichman NE, Nepomnyaschy L. Maternal prepregnancy obesity and diagnosis of asthma in offspring at age 3 years. *Matern Child Health J.* 2008;12:725–733.
8. Barker DJ, Eriksson JG, Forsen T, et al. Fetal origins of adult disease: strength of effects and biological basis. *Int J Epidemiol.* 2002;31:1235–1239.
9. Gluckman P, Hanson M. *The Fetal Matrix: Evolution, Development and Disease.* London: Cambridge University Press; 2005.
10. Van Lieshout RJ, Taylor VH, Boyle MH. Pre-pregnancy and pregnancy obesity and neurodevelopmental outcomes in offspring: a systematic review. *Obes Rev.* 2011;12:e548–e559.
11. Garcia OP, Long KZ, Rosado JL. Impact of micronutrient deficiencies on obesity. *Nutr Rev.* 2009;67:559–572.
12. Van Lieshout RJ, Voruganti LP. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. *J Psychiatry Neurosci.* 2008;33:395–404.
13. Lacoursiere DY, Baksh L, Bloebaum L, et al. Maternal body mass index and self-reported postpartum depressive symptoms. *Matern Child Health J.* 2006;10:385–390.
14. Meyer U, Feldon J, Yee BK. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. *Schizophr Bull.* 2009;35:969–972.
15. Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry.* 2002;159:1080–1092.
16. Bilbo SD, Tsang V. Enduring consequences of maternal obesity for brain inflammation and behaviour of offspring. *FASEB J.* 2010;24:2104–2115.
17. Vucetic Z, Kimmel J, Totoki K, et al. Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. *Endocrinology.* 2010;151:4756–4764.
18. Sullivan EL, Grayson B, Takahashi D, et al. Chronic consumption of a high-fat diet during pregnancy causes perturbations in the serotonergic system and increased anxiety-like behaviour in nonhuman primate offspring. *J Neurosci.* 2010;30:3826–3830.
19. Taylor VH, McIntyre RS, Remington G, et al. Beyond pharmacotherapy: understanding the links between obesity and chronic mental illness. *Can J Psychiatry.* 2012;57:5–12.
20. Yu ZB, Han SP, Cao XG, et al. Intelligence in relation to obesity: a systematic review and meta-analysis. *Obes Rev.* 2010;11:656–670.
21. Wang Y, Beydoun MA. The obesity epidemic in the United States – gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev.* 2007;29:6–28.
22. Hinkle SN, Schieve LA, Stein AD, et al. Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. *Int J Obes (Lond).* 2012;36:1312–1319.
23. Craig WY, Palomaki GE, Neveux LM, et al. Maternal body mass index during pregnancy and offspring cognitive development. *Obstet Med.* 2013;6:20–25.
24. Veldwijk J, Scholtens S, Hornstra G, et al. Body mass index and cognitive ability of young children. *Obes Facts.* 2011;4:264–269.

25. Tanda R, Salsberry PJ, Reagan PB, et al. The impact of prepregnancy obesity on children's cognitive scores. *Matern Child Health J.* 2013;17:222–229.
26. Van Lieshout RJ, Schmidt LA, Robinson M, et al. Maternal pre-pregnancy body mass index and offspring temperament and behavior at 1 and 2 years of age. *Child Psychiatry Hum Dev.* 2013;44:382–390.
27. Jongeling B, Smith G, Russell C, et al. Maternal and early life risk factors for a later diagnosis of attention-deficit/hyperactivity disorder. Abstract presented at: 30th World Congress of Internal Medicine; 20–25 March 2010; Melbourne, Australia.
28. Robinson M, Zubrick SR, Pennell CE, et al. Pre-pregnancy maternal overweight and obesity increase the risk for affective disorders in offspring. *J DOHaD.* 2013;4:42–48.
29. Van Lieshout RJ, Robinson M, Boyle MH. Maternal pre-pregnancy body mass index and internalizing and externalizing problems in offspring. *Can J Psychiatry.* 2013;58:151–159.
30. Krakowiak P, Walker CK, Bremer AA, et al. Maternal metabolic conditions and risk for autism and other neurodevelopmental disorders. *Pediatrics.* 2012;129:e1121–e1128.
31. Brion M-J, Zeegers M, Jaddoe V, et al. Intrauterine effects of maternal prepregnancy overweight on child cognition and behaviour in 2 cohorts. *Pediatrics.* 2011;127:e202–e211.
32. Buss C, Entinger S, Poggi Davis E, et al. Impaired executive function mediates the association between maternal pre-pregnancy body mass index and child ADHD symptoms. *PLoS ONE.* 2012;7:e37758.
33. Kolb B, Gibb R, Robinson TE. Brain plasticity and behavior. *Curr Dir Psychol Sci.* 2003;12:1–5.
34. Youngman L, Keavney B, Palmer A, et al. Plasma fibrinogen and fibrinogen genotypes in 4685 cases of myocardial infarction and in 6002 controls: test of causality by “Mendelian randomisation”. *Circulation.* 2000;102(Suppl II):31–32.
35. Rice F, Harold GT, Boivin J, et al. Disentangling prenatal and inherited influences in humans with an experimental design. *Proc Natl Acad Sci U S A.* 2009;106:2464–2467.
36. Rodriguez A, Miettinen J, Henriksen TB, et al. Maternal adiposity prior to pregnancy is associated with ADHD symptoms in offspring: evidence from three prospective pregnancy cohorts. *Int J Obes (Lond).* 2008;32:350–357.
37. Kyrou I, Tsigos C. Stress hormones: physiological stress and regulation of metabolism. *Curr Opin Pharmacol.* 2009;9:787–793.
38. Mojckicki JM. Maternal prepregnancy body mass index and initiation and duration of breastfeeding: a review of the literature. *J Womens Health.* 2011;20:341–347.
39. Janssen I, Craig WM, Boyce WF, et al. Associations between overweight and obesity with bullying behaviours in school-aged children. *Pediatrics.* 2004;113:1187–1194.
40. Terracciano A, Sutin AR, McCrae RR, et al. Facets of personality linked to underweight and overweight. *Psychosom Med.* 2009;71:682–689.
41. Prinzie P, Stams GJJM, Dekovic M, et al. The relations between parents' big five personality factors and parenting: a meta-analytic review. *J Pers Soc Psychol.* 2009;97:351–362.