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The role of systemic inflammation linking maternal BMI to neurodevelopment in children

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Children of obese mothers are at increased risk of developmental adversities. Maternal obesity is linked to an inflammatory *in utero* environment, which, in turn, is associated with neurodevelopmental impairments in the offspring. This is an integrated mechanism review of animal and human literature related to the hypothesis that maternal obesity causes maternal and fetal inflammation, and that this inflammation adversely affects the neurodevelopment of children. We propose integrative models in which several aspects of inflammation are considered along the causative pathway linking maternal obesity with neurodevelopmental limitations.

The prevalence of obesity in 2011–2012 was 35% among adult women in the United States, with no significant change compared with 2002–2004 (1). The prevalence of obesity among adult women in Europe was 12% in 2010 (2). Nearly 30% (2.1 billion people) of the world's population today are estimated to be overweight or obese (3). This prevalence is projected to continue to increase, presenting a major public health epidemic in both the developing and developed world (4).

Just before pregnancy, almost two out of three women (64%) in the United States are either overweight or obese (5). Prepregnancy overweight and obesity are associated with gestational diabetes, pre-eclampsia, labor complications, and maternal hypertension during pregnancy (6). Maternal obesity is also associated with chorioamnionitis and pregnancy-related infection, such as group B streptococcal disease (7).

In addition to these potential risks to the mother, maternal obesity also may have life-long repercussions for her offspring. For example, children of obese mothers are prone to obesity (8,9), metabolic syndrome (10), neural tube defects (11), and cognitive impairment (12–16).

The causal pathway by which a mother's obesity contributes to adverse neurodevelopmental outcomes among her offspring remains to be elucidated (12,17). Prepregnancy BMI studies focusing on pediatric outcomes are challenging because it is possible that characteristics and/or exposures associated with both prepregnancy BMI and neurodevelopmental outcomes influence the postnatal environment. In this review, we offer evidence from laboratory and human studies in support of the hypothesis that maternal obesity influences fetal, neonatal, and later developmental outcomes by increasing the risk of systemic and (18,19) and brain (20,21) inflammation.

We first address the reported associations between maternal obesity and long-term neurodevelopment in offspring. In the subsequent sections, we outline an explanatory model (**Figure 1**) in which a series of inflammatory processes are hypothesized to account for neurodevelopmental limitations.

INTEGRATED MECHANISM REVIEW

We used an integrated mechanism review method as outlined by Dammann and Gressens (22) to propose a hypothesis that explains the causal pathway for why children of obese mothers are at increased risk of developmental adversities. As suggested for integrated mechanism review, we first identified basic, clinical, and epidemiologic research on the neurodevelopment of children born to obese mothers. We then developed a graphic to illustrate possible causal models to explain the elevated risk of undesirable outcomes among the children of obese mothers. Finally, we reviewed available studies that could be used to support (or reject) each proposed incremental pathway of our explanatory model. The following sections summarize our findings.

Results of Maternal Obesity and Neuropsychological Outcomes

Children of mothers who were overweight or obese during pregnancy were at elevated risk of four major categories of neurodevelopmental deficits, including cognitive and intelligence deficits, attention deficit hyperactivity disorder (ADHD), autism, and psychoses (**Table 1**). The most studied area was the relationship between the weight status of the mother before or during pregnancy and cognition/intelligence of the offspring.

Cognitive Deficits and Intelligence

By and large, children born to obese mothers have lower mental development scores than their peers born to normal weight

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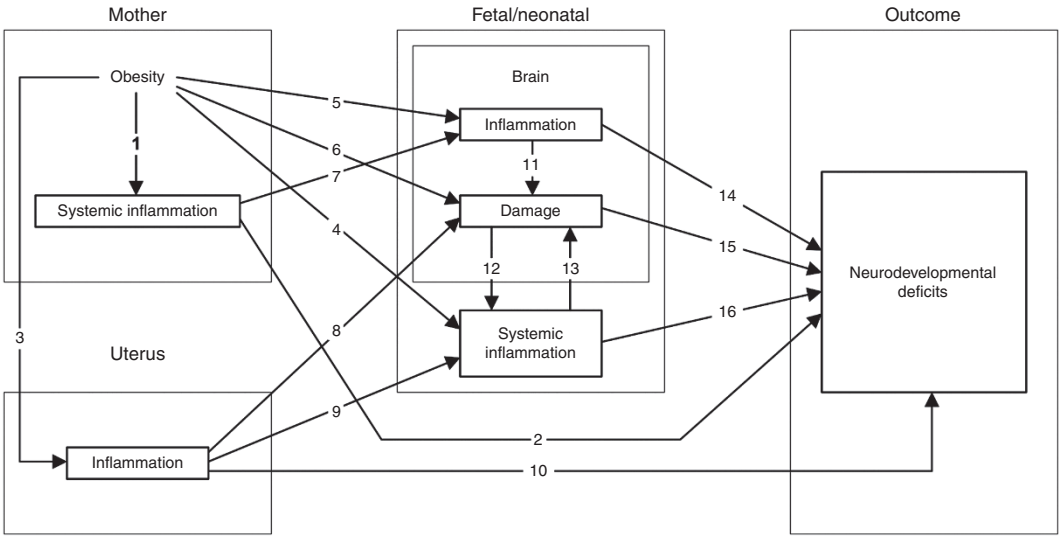

Figure 1. Proposed mechanistic framework outlining inter-relationships between maternal obesity, inflammation, and neurodevelopmental deficits. Numbers along arrows correspond to numbers identifying sections in this article.

women (14,16,23–33). Children whose mother was overweight near the time of the pregnancy tend to have mental development scores that are intermediate between obese and healthy weight mothers (16). No association was found between maternal prepregnancy BMI and motor skills (25,27,30).

ADHD

Maternal prepregnancy overweight and obesity were associated with child inattention and related symptoms at the age of 5 y (34), and with ADHD symptoms in children aged 7–12 y (35), and 9–17 y (36). The authors of a study of 7-y-old children that found a 2.8-fold increase in the prevalence of ADHD among children of obese compared to those of nonobese mothers attributed some of what they found to impaired executive function (37).

Autism

Two studies found that autistic children were more likely than their nonautistic peers to have a mother who was obese before the pregnancy (29), or had a prepregnancy weight ≥ 90 kg (38). Only one study showed a weak association between maternal obesity and ASD risk (39).

Psychoses

Of four studies that evaluated the relationship between maternal BMI and the risk of schizophrenia in the offspring, two found that the adult children born to obese women were two- to threefold more likely to be given a diagnosis of schizophrenia than the adult offspring of normal weight women (40,41). Another reported a progressive increase in the risk of schizophrenia in offspring was associated with each unit increase of maternal BMI (42). Only one of the four studies reported no relationship between maternal obesity and psychoses among their offspring. The BMI of mothers of adults with schizophrenia did not differ from the BMI of mothers of adults without schizophrenia (43). However, a review of the four studies raised the possibility that "the discrepant findings from one study could be attributable to sample characteristics and other factors" (44).

INTEGRATED EXPLANATORY MODEL

In **Figure 1**, we illustrate the possible interrelationships between maternal obesity (on the left) and neurodevelopmental deficits of the offspring (on the right). Arrows indicate proposed pathways between exposures and outcomes. The numbers with each arrow in the figure refer to the following subsections and provide the available evidence to support each link in the model.

Not all intermediate steps in the proposed pathways are addressed in the model. For example, section 7 (Maternal systemic inflammation and fetal brain inflammation) appears to bypass the involvement of the uterus. We include such by-pass sections when the reports deal with an exposure (e.g., lipopolysaccharide administered into the peritoneal cavity) and an outcome (expression of the proinflammatory cytokines in the fetal rat brain), and do not report on, or discuss the likely intermediate steps.

1. Maternal Obesity and Maternal Systemic Inflammation

Obesity can contribute to chronic systemic inflammation (45,46), as can pregnancy (47,48). Beyond their many other functions, cytokines serve as signaling molecules between the immune and nervous systems (49). C-reactive protein is an acute phase protein that promotes further inflammation, while leptin is an adipokine associated not only with satiety and energy homeostasis, but also with inflammation (50–53). The systemic responses to pregnancy, including IL-6, C-reactive protein, and leptin, were exaggerated in women with prepregnancy obesity (54–56). At 4 wk of gestation, obese women had higher levels of C-reactive protein compared to normal weight pregnant women (57,58).

Table 1. Studies reporting data on maternal obesity during pregnancy and offspring developmental outcomes

Author (reference number)	Year	Country	*N*	Age	Test	Weeks of gestation	Outcome
Cognitive deficits and intelligence							
Kerstjens (23)	2013	The Netherlands	834	43–49 mo	ASQ	32–36	Developmental delay: Prepregnancy obesity: OR 2.7 (1.4–5.5)
Casas (16)	2013	Spain, Greece	Spain: 1866, Greece: 397	11–22 mo	BSID	>36	Cognitive development scores: Spain: β (95% CI) Ov vs. Nw −0.9 (−2.6, 0.9), Ob vs. Nw −2.7 (−5.4, −0.1); Greece: Ov vs. Nw 1.4 (−2.3, 5.1), Ob vs. Nw −3.7 (−8.5, 1.0)
Helderman (24)	2012	United States	921	2 y	MDI	<28	MDI < 55 score: Maternal BMI > 30; OR 2.0 (1.1, 3.5), MDI <55–69: Maternal BMI > 30; OR 1.3 (0.9, 2.3)
Hinkle (25)	2012	United States	6,850	2 y	MDI, PDI	≥ 37	MDI score: β (95% CI) Ov vs. Nw −0.2 (−0.9, 0.5) Ob I vs. Nw −0.6 (−1.6, 0.5) Ob II and III vs. Nw −2.1 (−3.3–0.9), PDI score: β (95% CI) Ov vs. Nw 0.1 (−0.5, 0.8) Ob I vs. Nw 0.2 (−0.8, 1.3) Ob II and III vs. Nw −0.3 (−1.7–1.1)
Craig (26)	2013	United States	Dataset A: 3,961, Dataset B: 25,030	2 y, 8 y	BSID-III, WISC-III	≥ 36	BSID-III ≥1 score <85: Ob vs. non-ob OR 3.9 (1.4–11.3), WISC-III ≥1 score <85: Ob vs. non-ob OR 5.2 (1.5–18.2)
Neggers (27)	2003	United States	355	5.3 y	GIA, GMS	All	GIA score: β (SE); *P* value Ov (BMI ≥ 26.1 to ≤29) vs. Nw (BMI ≥ 19.8 to ≤26): −1.1 (2.0) Ob (BMI > 29) vs. Nw: −4.7 (1.4), GMS: Ov (BMI ≥ 26.1 to ≤ 29) vs Nw (BMI ≥ 19.8 to ≤26): −0.47 (2.6) Ob (BMI > 29) vs. Nw: −5.6 (1.8)
Tanda (14)	2013	United States	3412	60–83 mo	PIAT	37 - 42	Reading recognition: *B* (SE) Ov vs. Nw −0.8 (0.6), Ob vs. Nw -3.1 (0.8); Mathematics: *B* (SE) Ov vs. Nw −0.8 (0.6), Ob vs. Nw −2.4 (0.8)
Heikura (28)	2008	Finland	Cohort 1 1966: 12,058, Cohort 2 1986: 9,432	11.5 y	ID	>28	Severe intellectual disability (IQ < 50) Cohort 1: Ov vs. Nw OR 0.9 (0.5–1.6), Ob vs. Nw OR 1.0 (0.4 –2.5) Cohort 2: Ov vs. Nw OR 1.4 (0.6–3.1) Ob vs. Nw OR 2.6 (0.9–7.7); mild intellectual disability (IQ 50–70) Cohort 1: Ov vs. Nw OR 0.2 (0.2–1.6) Ob vs. Nw OR 0.5 (0.1–3.8) Cohort 2: Ov vs. Nw OR 0.7 (0.3–1.7), Ob vs. Nw OR 2.9 (1.3–6.1)
Krakowiak (29)	2012	United States	1,004	2–5 y	SCQ	All	DD vs. TD OR 2.1 (1.2–3.6)
Hinkle (30)	2013	United States	5,200	57–85 mo	BSID	≥ 37	BSID score: RR (95% CI) Ov vs. Nw 1.1 (0.8–1.3), Ob I vs. Nw 1.2 (0.9–1.7), Ob II and III vs. Nw 1.7 (1.3–2.2)
Huang (31)	2014	United States	30,212	7 y	WISC	≥ 37	Ob vs. Nw. $\beta = -2.0$ (−3.5–0.5)
Basatemur (15)	2013	United Kingdom	19,517	5 and 7 y	BAS-II	All	Age 5 ($B = -0.08$, $P \leq 0.01$); Age 7: ($B = -0.17$, $P \leq 0.001$). A 10-point increase in maternal prepregnancy BMI corresponds to a decrease in cognitive performance of 1.5 (~1/10th of an SD)
Gage (32)	2013	United Kingdom	4 y: 5,832 8 y: 5,191 16 y: 7,339	4, 8, and 16 y	4 y: SEA 8 y: WISC 16; SFE	≥ 37	Mean SD difference per 1 kg (95% CI) SEA: −0.004 (−0.005 to −0.002) WISC: −0.004 (−0.006 to −0.002) OR (95% CI) Adequate final examination results: 0.99 (0.98–0.99)
Bliddal (33)	2014	Denmark	1,783	5 y	WPPSI-R	All	*B* IQ point (95%CI) for every unit increase iin BMI −0.40 (−0.64 to −0.17)
ADHD							
Rodriguez (34)	2010	Sweden	1,714	5 y	DSM-IV ADHD	≥ 37	Ov vs. Nw OR 2.0 (1.2–3.4), Ob vs. Nw OR 2.1 (1.2–4.8)

Table 1. Continued

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Author (reference number)	Year	Country	*N*	Age	Test	Weeks of gestation	Outcome
Rodriguez (35)	2008	Sweden, Denmark, Finland	14,519	7–8 y	SDQ: Sweden Denmark: RB2	All	Ov vs. Nw OR 1.4 (1.1–1.8), Ob vs. Nw OR 1.9 (1.1–3.2)
Buss (37)	2012	United States	174	7 y	CBC Go/no-go task (executive function)	≥ 35	Ob (link partially mediated by executive function): $F = 4.80$, $P = 0.03$. Cohen's $d = 0.54$, $\beta = 0.18$. Ob: $F = 8.37$, $P = 0.004$. Cohen's $d = 0.62$. NS for Ov
Chen (36)	2014	Sweden	673,632	9–17 y	ICD-10/DSM-IV	All	HR overweight = 1.12, 95% CI 1.18–1.27 HR obesity = 1.64, 95% CI 1.57–1.73
Autism							
Krakowiak (29)	2012	United States	1,004	2–5 y	ADOS	All	ASD vs. TD OR 1.7 (1.1–2.6)
Dodds (38)	2011	Canada	129,733	1–17 y	ICD-9 or ICD-10	≥ 20	Prepregnancy weight ≥ 90 kg: RR (95% CI); 1.6 (1.3–2.0)
Suren (39)	2014	Norway	92,909	4–13 y	DSM-IV	All	OR (95% CI) for ASD in children of obese mothers 1.34 (0.84–2.12)
Psychosis							
Jones (43)	1998	Finland	10,578	28 y	DSM-III-R	38–42	Maternal prepregnancy BMI of offspring with schizophrenia ($N = 76$): mean (SD); 23.6 (4.3); Maternal prepregnancy BMI of offspring of unaffected population ($N = 10{,}502$): 23.1 (3.2)
Schaefer (40)	2000	United States	6,633	30–38	DIGS	All	RR (95% CI) for schizophrenia Ov (BMI 27–29.9) vs. Nw (BMI 20–26.9): 1.8 (0.8–4.3), Ob (BMI ≥ 30) vs. Nw: 2.9 (1.3–6.6)
Wahlbeck (41)	2001	Finland	6,509	63–72	HDR	All	OR (95% CI) for schizophrenia BMI ≤ 24 3.8 (1.4–9.9), BMI ≤ 26 3.0 (1.2–7.8), BMI ≤ 28 3.1 (1.2–7.9), BMI ≤ 30 3.1 (1.1–8.4)
Kawai (42)	2004	Japan	336	19	DSM-IV	All	OR for schizophrenia 1.2 (1.0–1.41)

ADOS, autism diagnostic observation schedule; ASD, autism spectrum disorder; ASQ, Ages and Stages Questionnaire; BAS-II, British Ability Scales, second edition; BSID, The Bayley Scales of Infant Development; CBC, child behavior checklist; CI, confidence interval; DD, developmental delays; DIGS, The Diagnostic Interview for genetic Studies; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; GIA, General Intellecutal Ability score; GMS, Gross motor score; HDR, Hospital Discharge Register; ICD, International Statistical Classification of Diseases and Related Health Problems; ID, intellectual disability (IQ < 70) based on standardized psychometric tests administered by a psychologist; MDI, Bayley Mental Developmental Index; NS, nonsignificant; Nw, normal weight (BMI 18.5–24.9); Ob, obese (BMI ≥ 30); Ob I, BMI 30–34.9; Ob II and III = BMI ≥ 35; Ov, overweight (BMI 25–29.9); PIAT, Peabody Individual Achievement Test; PDI, Bayley psychomotor development index; RB2, Rutter scale; SCQ, Social Communication Questionniare; SEA, School Entry Assessment Score; SFE, School Final Examination results; SDQ, Strengths and Difficulties Questionnaire; TD, typical development; WISC, Wechsler Intelligence Scale for Children; WPPSI-R, Wechsler Primary and Preschool Scales of Intelligence.

2. Maternal Systemic Inflammation and Long-Term Neurodevelopmental Deficits

Children of women who had high circulating levels of TNF-α (59) and IL-8 (60) during pregnancy were at increased risk of schizophrenia. Other inflammatory phenomena during fetal development might also contribute to the occurrence of autism (61). In a mouse model, systemic maternal inflammation with lipopolysaccharide combined with neonatal hyperoxic exposure appears to decrease oligodendrocyte numbers in the cerebral cortex and hippocampus in adulthood (62).

3. Maternal Obesity and Intrauterine Inflammation

Compared to the placentas of their lean peers, the placentas of obese women tend to have increased $CD68^+$ and $CD14^+$ cells, along with increased expression of the proinflammatory cytokines IL-1, TNF-α, IL-6, and C-reactive protein (54). Histologic inflammation was much more common in the placentas of obese women than in the placentas of normal-weight women (63). The higher a pregnant woman's BMI, the higher her blood concentrations of cytokines and activation of placental p38-MAPK and STAT3 inflammatory pathways activated by MCP-1 and TNF-α (64).

4. Maternal Obesity and Systemic Inflammation in the Offspring

Preterm newborns of overweight and obese women were more likely than their peers born to women with lower BMIs to have systemic inflammation, but only among those delivered for maternal or fetal indications (65). The association was more prominent for protein elevations observed on two or more days than for elevations present on 1 d only, especially among the infants of overweight women. These findings suggest that mother's prepregnancy overweight or obesity can contribute to a prolonged proinflammatory state in very preterm infants delivered for maternal or fetal indications.

At the age of 12 y, children born to obese mothers tended to have higher blood levels of C-reactive protein, but not IL-6, TNF-α, or adiponectin, than children born to nonobese mothers (19). In a study of adults (mean age 57 y), those with two obese parents (vs. none or one parent) had higher levels of C-reactive protein, but not IL-6, TNF, or adiponectin (18). Since the children of obese adults are at increased risk of becoming obese themselves (66), these reports support the hypothesis that maternal obesity increases susceptibility to an inflammatory state in the offspring perhaps even before the onset of obesity, suggesting that inflammation may

be a precursor to the development of obesity rather than a consequence.

5. Maternal Obesity and Neuroinflammation in the Offspring

In a rat model, maternal high-fat-diet consumption (a correlate/contributor to maternal obesity) appears to sensitize offspring to the brain inflammation effects of their own high fat diet (67). These effects include increased reactivity of astrocytes and microglia, as well as increased levels of IL-6 and impaired water maze performance. Proinflammatory cytokines, including IL-1β and IL-1receptor 1, as well as markers of microglia activation, were upregulated in the hypothalamus of fetal macaques whose mothers received a high-fat-diet during pregnancy (68). The 90-d-old offspring of rats fed hydrogenated vegetable trans-fats, had increased IL-6, TNF-α, and IL1-β levels in their hypothalamus, compared to rats born to dams fed standard chow (69). Offspring of dams fed a high-saturated-fat or a high-*trans*-fat diet tended to have more microglial activation markers, TLR4 mRNA expression, and higher IL-1β levels in the hippocampus at birth compared to offspring of control-fed dams (70). The pups also displayed impaired spatial learning.

6. Maternal Obesity and Fetal/Neonatal Brain Damage

Four studies evaluated the relationship between maternal obesity and cerebral palsy. One study found that children of overweight and obese mothers had a 3.5-fold increased risk of cerebral palsy (71). Another study reported that maternal obesity was associated with a 30% increased risk of having a child with cerebral palsy. This risk was even higher among infants born to a morbidly-obese mother (72). Two studies found no association between maternal weight and cerebral palsy (73,74).

In a rat model, maternal obesity during pregnancy is associated with diminished proliferation and neuronal maturation of stem-like cells in the cerebral cortex of the pups' brains, possibly resulting in impaired neurodevelopment at a later age (75). At postnatal day 21, the hypothalamic tissue of pups born to high-fat-diet dams shows upregulation of the toll-like receptor 4 (TLR4) signaling cascade, as well as increased phosphorylation of c-Jun N-terminal kinase 1 (JNK1) and IκB kinase-β (IKKβ) (76). Although murine responses to inflammatory stresses do not correlate well with human responses (77), activation of TLR4, JNK, and IKKβ can promote the synthesis and release of proinflammatory cytokines (78–80).

7. Maternal Systemic Inflammation and Fetal/Neonatal Brain Inflammation

When injected into the peritoneal cavity of pregnant rodents, lipopolysaccharide, an endotoxin synthesized by Gram-negative bacteria, increased the expression of TNF-α and IL-1β mRNA, in the fetal rat brain within hours, and promoted the presence of glial fibrillary acidic protein-positive astrocytes in the brain accompanied by decreased myelin basic protein (81).

8. Intrauterine Inflammation and Fetal/Neonatal Brain Damage

Placenta inflammation (chorioamnionitis) can induce a systemic fetal inflammatory response that contributes to white matter injury in the fetal brain (82,83). Inflammation in the placenta is also associated with neonatal brain damage (84–86). The inflammation signal, likely transmitted across the blood–brain barrier, initiates a neuroinflammatory response that has been offered as an explanation for later neurodevelopmental complications including cerebral palsy, autism, schizophrenia, and cognitive impairments (82,87,88). The authors of a review that found no support for an association between chorioamnionitis and central nervous system impairment in humans born preterm raised the possibility "that inflammation enhances maturation of the preterm infant and therefore has protective effects balancing its potential harmful effects" (89). Preconditioning might also be invoked to explain some of these inconsistent findings (*v.i.,* 5.1 Systemic inflammation, preconditioning and sensitization).

9. Intrauterine Inflammation and Fetal/Neonatal Systemic Inflammation

Preterm newborns whose umbilical cord was inflamed (funisitis) tended to have higher blood concentrations of inflammation-related proteins, including C-reactive protein, MPO, IL1β, IL8, TNF-α, ICAM3, and MMP on postnatal day 7 than their peers without funisitis (90).

10. Intrauterine Inflammation and Neurodevelopmental Deficits

Brain damage in both preterm and term mice following intrauterine inflammation is accompanied by increased TNF-α expression and alterations of other gene pathways in the brain thought to influence neurobehavioral, motor, and psychosocial behavior (91). Placenta inflammation is also associated with a decreased number of dendritic processes in the offspring's brain, resulting in impaired learning and memory (91,92). Additionally, intrauterine inflammation in pregnant sheep resulted in microglial activation and macrophage infiltration in the fetal brain (93). Among humans born before the 28th week of gestation, placenta inflammation and the presence of microorganisms in the placenta were not associated with low Bayley Scales Mental Development Index scores at the age of 2 y (24).

11. Fetal/Neonatal Brain Inflammation and Fetal/Neonatal Brain Damage

Experimental and epidemiological studies document that perinatal inflammation can be a risk factor for abnormalities in brain structure and function (61,85,88,94). Cytokines such as TNF-α released during intrauterine inflammation are a possible cause of brain damage observed in animal studies linking preterm birth and periventricular white matter damage (61,85,94). Five mechanisms of cytokine-induced brain injury have been proposed (95). The first mechanism is the direct effect of cytokines (IL-6) on the cerebral circulation (96). Second, inflammation promotes coagulation which in turn can increase the risk of brain damage via vessel obstruction (90) or enhanced inflammation (97,98). Third, activated microglia can cause direct toxic effects on oligodendrocytes and myelin, in part, via microglial production of cytokines (99), which leads to neuronal loss and

impaired neuronal guidance (99,100), as well as inhibition of oligodendrocyte maturation (101). Fourth, the activation of microglia leads to production of free radicals, which contribute to oligodendrocyte death via oxidative stress (99,102). Fifth, inflammation can promote excitotoxic mechanisms resulting in damage to both neurons and oligodendrocytes (103). All of these mechanisms are enhanced by the increased permeability of the developing blood–brain barrier that has been documented following intraperitoneal injection of lipopolysaccharide (104).

12. Fetal/Neonatal Brain Damage and Fetal/Neonatal Systemic Inflammation

The systemic inflammation that follows brain damage has two explanations (105). One postulates that what is seen in the blood is merely persistence of the inflammation that caused the brain damage. Another postulates that what is seen in the blood is the "spill over" of the inflammation in the brain. What is impressive is how long the local and systemic inflammation can continue (106).

13. Fetal/Neonatal Systemic Inflammation and Fetal/Neonatal Brain Damage

Among infants born before 28 wk gestation, elevated levels of inflammation-related proteins in blood collected on both postnatal days 7 and 14 were associated with ventriculomegaly on an ultrasound scan of the brain when the very preterm newborn was in the intensive care nursery (107). Because the ventriculomegaly is not accompanied by macrocephaly, the ventricular enlargement is usually attributed to processes that lead to hydrocephalus *ex vacuo*.

14. Fetal/Neonatal Brain Inflammation and Clinical Neurodevelopmental Deficits

Rats that have increased reactivity of astrocytes and microglia, as well as increased levels of IL-6 in the brain, are more likely than others to have impaired retention of what they learned in a water maze (67). Compared to control rat pups, those with elevated IL-1β levels in the hippocampus at birth displayed impaired spatial learning (70).

15. Fetal/Neonatal Brain Damage and Neurodevelopmental Deficits

Fetal brain damage is linked with neurodevelopmental deficits in early childhood (108). Reductions and other modifications in total and regional volume of the cerebellum, as well as central and occipital regions of the cerebrum at term-equivalent age predict neurodevelopmental impairment in early childhood (109). Indicators of cerebral white matter damage also convey information about heightened risk of developmental disorders (110–112).

16. Fetal/Neonatal Systemic Inflammation and Neurodevelopmental Deficits

Newborn mice injected with IL-1β twice-daily over 5 d, had later memory deficits (113). Among infants born before 32 wk gestation, those who had elevated levels of proinflammatory and modulatory cytokines in blood obtained during the first 72 postnatal hours were at increased risk of cerebral palsy and less severe motor limitations at the age of 2 y (114). Among infants born before 28 wk gestation, elevated levels of inflammation-related proteins in blood collected on both postnatal days 7 and 14 were associated with impaired mental and motor development (115) as well as microcephaly (116) at the age of 2 y.

OTHER MECHANISMS EXPLAINING LINK WITH NEURODEVELOPMENTAL OUTCOMES

Systemic Inflammation, Preconditioning, and Sensitization

Exposing the brain of a fetus to a subdamaging stimulus can protect against a subsequent insult (117,118). This phenomenon has been given two names, preconditioning, and tolerance. The same type of subdamaging stimulus can also sensitize the perinatal brain to a subsequent subdamaging insult (119,120). Among the characteristics of the subdamaging exposure that influence whether the result is preconditioning (tolerance) or sensitization are duration of the interval between first and second exposures (120) and postnatal age (121). The mechanisms that mediate preconditioning mechanisms in the immature brain likely differ from those observed in the adult (122). **Figure 1** shows that maternal obesity associated with the increased risk of brain damage is linked to systemic inflammation. Due to this systemic inflammation, the preterm newborn is exposed to subdamaging stimuli within a narrow time range, resulting in greater injury explaining the higher risk for adverse neurodevelopmental outcomes in these children.

Confounding Factors

It is possible that characteristics and/or exposures associated with both maternal obesity and systemic inflammation, and not the obesity *per se*, explain the links with neurodevelopmental outcomes. One of these confounding factors might be maternal distress, as obesity has been related to mental health problems, which have been linked to developmental limitations (123).

In a study that adjusted for maternal stress and depression symptoms during and after pregnancy, the association between prenatal maternal obesity and ADHD symptoms and emotional problems did not change (34). This suggests that maternal obesity and maternal distress may possibly act through separate mechanisms influencing fetal brain development.

Studies of the relationship between maternal obesity and the child's development need to address the potential confounding due to variables that are related to both the mother's obesity and her child's development. For example, obese women and their families are more likely than others to have low socioeconomic status (124), micronutrient deficiencies (125), emotional distress (126,127), child behavior problems (36,42), and mental health dysfunctions in general (128). Another confounder of maternal obesity is paternal obesity, which has been associated with autistic disorder and Asperger (39).

It is also possible that maternal obesity increases the risk of neurodevelopmental limitations in the offspring via epigenetic phenomena (129–132).

CONCLUSION

We offer support for the claim that the contribution of maternal obesity to adverse brain development is achieved in part via inflammatory phenomena. The majority of data delineating the role of systemic inflammation in this association included animal and basic research studies. Therefore, studies of humans are needed that follow offspring from infancy into adulthood measuring their neurodevelopment in cognition and mental illnesses, as well as inflammatory phenomena. With these studies, the full impact of being exposed to maternal obesity *in utero* can be better understood. Attempts to better control maternal obesity could lead to important benefits for the cognitive and psychiatric functioning of offspring. The exact mechanisms remain unknown. We, however, offer a model with several pathways with support for each component of these pathways.

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