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Maternal obesity and development of the preterm newborn at 2 years

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Abstract

Aim—To evaluate to what extent extremely preterm children (<28 weeks' gestational age) of overweight (BMI 25-29) or obese (BMI ≥ 30) women are at increased risk of adverse development at 2 years measured with the Bayley Scales of Infant Development II in a multi-center prospective cohort study.

Methods—Heights and pre-pregnancy weights of the mothers of 852 preterm born children were collected and included in multinomial logistic regression models.

Results—Compared to newborns born to mothers with normal BMIs, newborns of obese mothers, but not those of overweight mothers, were more likely to have Bayley Scales indices more than 3 standard deviations below the reference mean (mental: OR = 2.1; 95% CI: 1.3, 3.5) (motor: OR = 1.7; 95% CI: 1.1, 2.7). These associations were even more prominent in children who did not have the intermittent or sustained systemic inflammation profile previously shown to be associated with severely impaired development (mental: OR = 4.6; 95% CI: 1.6, 14) (motor: OR = 3.7; 95% CI: 1.5, 8.9).

Conclusion—Maternal obesity is associated with an increased risk of impaired offspring development. Some of this impaired development cannot be attributed to confounding due to immaturity, socio-economic correlates, or neonatal systemic inflammation.

Keywords

Bayley; maternal obesity; prematurity

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Surviving children of obese mothers seem to be at increased risk of adversities, including developmental (1, 2), as well as reading and mathematics problems (3). The relationship between maternal obesity and offspring development is limited and inconsistent (4, 5). While most studies of children born near term report that pre-pregnancy obesity is a risk factor for impaired development (6, 7) some do not, (8) or do so inconsistently (9, 10). In our large prospective cohort of extremely low gestation age newborns (ELGANs), infants of overweight and obese mothers were more likely to have impaired early cognitive function, than infants of women with lower BMIs (11). In this report, we evaluated to what extent potential confounders and possible intermediates accounted for this association. We also investigated to what extent the relationship between maternal obesity and low developmental scores is attributable to early systemic inflammation, because systemic inflammation in the newborn is more likely among children of obese mothers than among children of normal weight mothers (12), and systemic inflammation in the newborn is also associated with severely impaired early cognitive function (13).

Patients and Methods

Details about the ELGAN Study are provided elsewhere (14, 15). The 852 children who had a developmental assessment at age 2 years and whose mother's pre-pregnancy BMI was known constitute the sample for this report. The developmental assessment included the Bayley Scales of Infant Development-Second Edition (BSID-II) (16).

Additional details about the methods are in the supplement.

Data analysis

We evaluated the null hypothesis that children whose mother was overweight or obese were no more likely than their peers to have Bayley Scales indices more than 3 SD below the reference mean. Univariable analyses document that children whose mother was overweight or obese were considerably more likely than children whose mother had a lower BMI to have very low Bayley Scales indices (Table S1). This observation prompted us to create Tables S2 - S4 to identify potential confounders of the relationship between maternal pre-pregnancy BMI and low mental and motor indices in the offspring. In essence, we were looking for characteristics that varied with BMI and also with the two Bayley Scales. The potential confounders identified this way and from a review of the literature included government-provided insurance, gestational age categories, severe fetal growth restriction (birth weight Z-score < -2), mother's identification as Black, mother's identification as single, mother's age < 21 years, mother did not graduate from high school, and no fertility therapy. These were then included in multinomial logistic regression models of low Bayley Scales that compared the children of overweight and obese women to children of normal weight women (Table 1). These models allowed us to calculate odds ratios and their 95% confidence intervals.

Systemic inflammation in the newborn is more likely among children of obese mothers than among children of normal weight mothers (12). In addition, systemic inflammation in the newborn is associated with severely impaired early cognitive function (13). To determine if the relationship we found between maternal obesity and low developmental scores was

attributable to early systemic inflammation, we repeated the analyses reported in the top of Table 1 in a sub-sample that excluded children who had a concentration in the top quartile of any of the following inflammation-related proteins on 2 days a week apart during the first two postnatal weeks: IL-6, TNF- α , TNF-R2, IL-8, MIP-1 β , ICAM-1, VCAM-1, E-SEL, CRP, SAA, VEGF-R2, IGFBP-1.

Results

The sample for Tables S1 - S4 and the top of Table 1 is comprised of the 852 children who satisfied three criteria: their mother provided information for her own pre-pregnancy BMI, the concentrations of their inflammation-related proteins on 2 or more days were measured in blood spots obtained during the first two postnatal weeks, and they had Bayley Scales assessments at approximately age two years. Of these children, 296 did not have concentrations on multiple days during the first two postnatal weeks in the top quartile of any of the 12 inflammation-related proteins associated with a Mental Development Index (MDI) < 55. These children are the subjects of the bottom half of Tables S1 and 1. Text describing the contents of Table S1 as well as the search for potential confounders (Tables S2--S4) is included in the supplement.

Multivariable analyses (Table 1)

In models that adjusted for potential confounders, children of obese mothers were at increased risk of a very low MDI (odds ratio = 2.1; 95% confidence interval (CI): 1.3, 3.5) and a very low PDI (odds ratio = 1.7; 95% CI: 1.1, 2.7) in the total sample. In the sample that excluded children who had any component of the systemic inflammation profile associated with a very low MDI the children of obese mothers were at even higher risk of a very low MDI (odds ratio = 4.6; 95% confidence interval (CI): 1.6, 14.4) and a very low PDI (odds ratio = 3.7; 95% CI 1.5, 8.9). Children of overweight women were not at increased risk of a very low MDI or a very low PDI. Maternal overweight and obesity were not associated with increased risks of an MDI or PDI between 55 and 69.

Discussion

Our main finding is that compared to the children born very preterm to women of normal weight, preterm newborns of obese mothers had lower scores on the Bayley mental and motor scales. This association was even more prominent in the subsample of children who did not have any components of the intermittent or sustained systemic inflammation profile associated, in our sample, with a very low MDI. This suggests inflammation might not account for all of the relationship between a woman's obesity and her child's impaired development.

Potential intermediate: inflammation

In this sample, children who had elevated concentrations of inflammation-related proteins in blood obtained within the first two postnatal weeks were at increased risk of impaired cognitive function at age 2 years (13). Because the children of obese mothers also show evidence of early systemic inflammation (12), we considered the possibility that early

systemic inflammation might be in the causal chain between maternal obesity and limited development in the offspring. Our finding that the relationship between maternal obesity and limited development was more pronounced among children who did not have sustained or recurrent early systemic inflammation than in the total sample leads to the inference that measurable inflammation does not account for the link between maternal obesity and a child's very low scores on the MDI and PDI.

Non-inflammatory mechanisms of brain damage associated with maternal obesity

Our subsample analysis allowed us to demonstrate an association between mother's obesity and her child's impaired development, even among children who did not have any of the components of the systemic inflammation profile associated with severely impaired development. This finding suggests that non-inflammatory mechanisms are involved in the pathways linking maternal obesity to impaired development in the child. Alternatively, inflammatory processes might have been involved, but we did not identify them.

Adipose dysfunction has been linked to the secretion of a variety of metabolically adverse adipose-derived hormones, such as adipokines and lipokines, as well as other manifestations of inflammation and oxidative stress (17). In addition, an obese mother can pass on epigenetic changes, not provoked by inflammatory mechanisms, to her child that might influence brain function (18–21). Thus, it is possible that a mother's obesity and components of her diet contribute to her child's brain dysfunction by non-inflammatory disturbances that damage the vulnerable brain.

Because some view gestational age as a possible collider between an exposure and an outcome (22–24), we have assessed the relationship between maternal BMI categories and Bayley Scales categories in models that included gestational age categories and also in models that excluded gestational age categories (Table 1). We document that gestational age does not appreciably distort the relationship between maternal pre-pregnancy overweight or obesity and low scores on the mental or motor components of the Bayley Scales at age 2 years.

Additional discussion comments are in the supplement.

Strengths and limitations

The strengths of this study include the large number of preterm infants and the recruitment of infants based on gestational age rather than birth weight (25). A weakness of our study is that we are unable to distinguish between causation and association as explanations for what we have found, due to the observational nature of our study.

Conclusion

In this sample of children who were born before the 28th week of gestation, those whose mother was obese were at greater risk of impaired development than their peers whose mother had a normal weight just before the pregnancy. Only some of this increased risk is explained by neonatal systemic inflammation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CRP	C-Reactive Protein
CD62E	E-selectin
IGFBP-1	Insulin-like Growth Factor Binding Protein-1
ICAM-1	Intercellular Adhesion Molecule -1 (CD54)
IL-6	Interleukin-6
IL-8	Interleukin-8 (CXCL8)
MIP-1β	Macrophage Inflammatory Protein-1 β (CCL4)
MDI	Mental Development Index
PDI	Psychomotor Development Index
SAA	Serum Amyloid A
TNF-R2	Tumor Necrosis Factor Receptor-2
TNF-α	Tumor Necrosis Factor- α
VCAM-1	Vascular Cell Adhesion Molecule-1 (CD106)
VEGF-R2	Vascular Endothelial Growth Factor Receptor-2 (KDR)

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Key notes

- The relationship between maternal obesity and offspring development is limited and inconsistent.
- We found that infants born before 28 weeks whose mother was obese are at increased risk of low Bayley Scales of Infant Development at age 2 years.
- Some of this increased risk is not explained by the newborn's systemic inflammation shortly after birth.

Table 1

Risk ratios (point estimates and 95% confidence intervals) for the characteristic at the top of the column associated with the BMI category listed on the left in models that adjust for potential confounders[§]. The **MDI** subsample is limited to children who did not have the intermittent or sustained systemic inflammation protein profile associated with increased risk of MDI <55. **Bold** numbers indicate statistical significance at $p < 0.05$.

Variables	Bayley Scales			
	Mental Scale		Motor Scale	
	<55	55–69	<55	55–69
Total sample - adjusted for gestational age and other potential confounders (full adjustment)				
BMI 25, < 30	1.2 (0.7, 2.0)	1.0 (0.6, 1.7)	0.8 (0.5, 1.3)	1.3 (0.8, 2.1)
BMI 30	2.1 (1.3, 3.5)	1.5 (0.9, 2.5)	1.7 (1.1, 2.7)	1.2 (0.7, 2.0)
Total sample – limited adjustment (full adjustment excluding gestational age)				
BMI 25, < 30	1.2 (0.7, 1.9)	1.0 (0.6, 1.7)	0.8 (0.5, 1.3)	1.3 (0.8, 2.1)
BMI 30	2.2 (1.4, 3.5)	1.5 (0.9, 2.5)	1.9 (1.1, 2.8)	1.2 (0.7, 2.0)
Sample without any component of the MDI < 55 protein profile ^{MDI} - full adjustment				
BMI 25, < 30	1.9 (0.6, 6.2)	2.0 (0.6, 5.9)	0.9 (0.3, 2.4)	0.6 (0.2, 1.4)
BMI 30	4.6 (1.6, 14)	2.8 (0.9, 8.7)	3.7 (1.5, 8.9)	1.1 (0.4, 2.8)
Sample without any component of the MDI < 55 protein profile ^{MDI} - limited adjustment				
BMI 25, < 30	2.0 (0.6, 6.5)	2.1 (0.7, 6.2)	1.0 (0.4, 2.6)	0.6 (0.2, 1.4)
BMI 30	4.3 (1.5, 13)	2.5 (0.8, 7.8)	3.4 (1.4, 8.1)	1.0 (0.4, 2.6)

[§] The full adjustment models include adjustment for government-provided insurance, gestational age categories, severe fetal growth restriction (birth weight Z-score < -2), mother identified herself as Black, mother identified herself as single, mother's age < 21 years, mother did not graduate from high school, no fertility therapy. The limited adjustment models adjust for all of these variables except gestational age.

MDI Consists of all children who did **not** have a concentration of **any** of the following proteins on 2 days a week apart: IL-6, TNF- α , TNF-R2, IL-8, MIP-1 β , ICAM-1, VCAM-1, E-SEL, CRP, SAA, VEGF-R2, IGFBP-1. Total sample: 852 children; subsample: 296 children.