Early Human Development 125 (2018) 8–16

Contents lists available at ScienceDirect

Early Human Development

journal homepage: www.elsevier.com/locate/earlhumdev

Neurodevelopment in 3–4 year old children exposed to maternal hyperglycemia or adiposity in utero

John E. Krzeczkowski[a,*], Khrista Boylan[b], Tye E. Arbuckle[c], Linda Dodds[d], Gina Muckle[e], William Fraser[f], Lindsay A. Favotto[g], Ryan J. Van Lieshout[b], on behalf of The MIREC Study Group

[a] Neuroscience Graduate Program, McMaster University, Hamilton, Ontario, Canada
[b] Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada
[c] Population Studies Division, Environmental Health Science and Research Bureau, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario, Canada
[d] Perinatal Epidemiology Research Unit, IWK Health Center, Dalhousie University, Halifax, Nova Scotia, Canada
[e] Faculty of Social Sciences, Laval University, Montreal, Quebec, Canada
[f] Centre de Recherche du Centre Hospitalier, Universitaire de Sherbrooke, Sherbrooke, Quebec, Canada
[g] Department of Health Research, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada

ARTICLE INFO

Keywords:
Obesity
Hyperglycemia
Prenatal programming
Prenatal nutrition
Child
Wechsler Preschool and Primary Scale of Intelligence III

ABSTRACT

Background: Prenatal exposure to maternal metabolic complications has been linked to offspring neurodevelopmental problems. However, no studies investigating these links have examined the role of maternal prenatal diet.

Aims: To determine if prenatal exposure to maternal adiposity or hyperglycemia is associated with neurodevelopmental problems in 3–4 year old children, and if links persist following adjustment for confounding variables, including prenatal diet.

Method: 808 mother-child pairs from the Maternal-Infant Research on Environmental Chemicals-Child Development Plus cohort were used to examine associations between pre-pregnancy body mass index (BMI), hyperglycemia and offspring verbal, performance and full-scale IQ scores, as well as internalizing and externalizing problems. Associations were examined before and after adjustment for prenatal diet along with home environment, maternal depression, education and prenatal smoking. Semi-partial correlations were examined post-hoc to assess the impact of each confounder in the adjusted models.

Results: In the unadjusted models, BMI and hyperglycemia predicted lower verbal and full-scale IQ. BMI was also linked to externalizing problems. However, associations were not significant after adjustment. In adjusted models, post-hoc analysis revealed that prenatal diet and home environment accounted for significant variance in verbal and full-scale IQ. The home environment and maternal depression accounted for significant variance in externalizing problems.

Conclusion: In the adjusted models, maternal metabolic complications were not associated with offspring neurodevelopment. Even while adjusting for well-known risk factors for adverse offspring cognition (home environment, maternal depression), we show for the first time that maternal prenatal diet is an important confounder of the links between maternal metabolic complications and offspring cognition.

1. Introduction

Nearly 40% of women are overweight or obese during pregnancy, and up to 16% of pregnancies are complicated by maternal hyperglycemia (i.e., impaired glucose tolerance or diabetes mellitus) [1–3]. Given the rapid rate of prenatal neurodevelopment, the fetal brain is particularly vulnerable to the pathological effects of prenatal adiposity and/or hyperglycemia [4,5]. Indeed, both pre-pregnancy adiposity and hyperglycemia have been linked to abnormalities of central nervous system development including defects of the neural tube [6–8]. As a

Abbreviations: BMI, body mass index; BASC-II, behavior assessment scale for children; FFQ, food frequency questionnaire; GDM, gestational diabetes mellitus; HEI-2010, Healthy Eating Index (2010); IGT, impaired glucose tolerance; MIREC, Maternal-Infant Research on Environmental Chemicals; WPPSI-III, Wechsler Preschool and Primary Scale for Intelligence; 95% CI, 95% confidence interval

* Corresponding author at: Neuroscience Graduate Program, McMaster University, 1280 Main St W, Hamilton, ON L8S 4L8, Canada.
E-mail address: krzeczkj@mcmaster.ca (J.E. Krzeczkowski).

https://doi.org/10.1016/j.earlhumdev.2018.08.005
Received 30 May 2018; Received in revised form 20 July 2018; Accepted 9 August 2018

result, prenatal metabolic complications may have the potential to affect more complex neural systems underlying the development of higher mental functions such as cognition and emotion regulation.

In keeping with the developmental origins of health and disease (DOHaD) hypothesis, prenatal exposure to excess maternal adiposity has been linked to poorer cognitive and language skills in children [9–11]. Higher rates of attention deficit hyperactivity disorder and externalizing problems are also seen in the children of overweight/obese women [12,13]. Similar outcomes have been noted in children born to those with hyperglycemia during gestation including a doubling of the risk of both cognitive and behavioral problems [14,15].

Despite this accumulating evidence, the impact of potential unmeasured confounding variables on the associations between prenatal metabolic complications and offspring neurodevelopment remains a significant issue in the field. In an attempt to address these limitations, researchers have utilized twin and sibling studies, as well as paternal obesity as a negative control in order to strengthen the case for causal links between prenatal metabolic complications and offspring neurodevelopmental problems. However, while maternal adiposity had a stronger association with offspring cognitive and behavioral problems relative to paternal obesity in four studies [16–19], in three others it did not [20–22]. Prenatal metabolic complications were also linked to poorer neurodevelopment in one twin [23] and one sibling study [9], but two others using sibling designs reported null results [24,25].

Despite the advantages of sibling and twin studies in adjusting for genetic and other familial factors, current studies lack the ability to adjust for important *environmental* confounding variables, particularly for those that may be modifiable. Indeed, no studies have adjusted for overall prenatal diet quality when examining the associations between maternal metabolic complications and offspring neurodevelopment. Controlling for overall prenatal diet quality in pregnancy would significantly advance our understanding of these links and could help us move closer to identifying more specific targets for intervention.

Given high rates of excess maternal adiposity and dysglycemia, and the importance of early cognition and behavior to health and success in life, understanding potential mechanisms underlying these links is of significant importance. Therefore, we utilized data from the pan-Canadian Maternal-Infant Research on Environmental Chemicals-Child Development Plus (MIREC-CD+) cohort to: a) determine if prenatal exposure to maternal overweight/obesity or hyperglycemia is associated with cognitive and behavioral problems in 3–4 year old offspring, and b) if these links persist following adjustment for confounding variables including prenatal diet quality, a previously unmeasured confounding variable of these links.

2. Methods

2.1. Subjects

MIREC is a longitudinal pregnancy cohort that recruited women from ten Canadian cities during their first trimester (< 14 weeks gestation) between 2008 and 2011 [26]. Eligibility criteria included fluency in English or French, maternal age > 18 years, plans to deliver locally, and an agreement to provide a cord blood sample. Women were excluded if there were abnormalities or malformations of the fetus in the current pregnancy, a history of medical complications such as heart disease, or a history of illicit drug use. Women provided sociodemographic information over three prenatal visits (one per trimester), and clinical information was obtained from medical charts following delivery.

The current study utilized data from the MIREC-CD Plus cohort (a sub-study of the original MIREC cohort) designed to assess cognitive and behavioral outcomes in 808 3–4 year old children (m_{age} = 40.7 months, SD = 3.73). Parents provided written consent prior to participation and study procedures were approved by research ethics boards at Health Canada and all recruitment sites.

2.2. Predictors

We examined the independent impact of pre-pregnancy adiposity and hyperglycemia separately on each of our outcomes since not all overweight women develop hyperglycemia, and not all women with hyperglycemia are overweight.

2.2.1. Pre-pregnancy adiposity-body mass index (BMI)

Maternal pre-pregnancy BMI was calculated at the first trimester visit by dividing self-reported pre-pregnancy weight (kg) by height (m^2), obtained by research staff. BMI was considered both a continuous and a dichotomous variable (normal: 18.5 < BMI < 25 vs. overweight/obese: BMI > 25) [27]. Underweight cases (BMI < 18.5, n = 20) were excluded since complications in pregnancy associated with being underweight are different from complications due to maternal overweight/obesity [28,29].

2.2.2. Hyperglycemia (GDM/IGT)

Of the women who participated in MIREC-CD Plus, 594 were assessed for hyperglycemia based on medical chart review. A dichotomous variable for hyperglycemia (gestational diabetes mellitus (GDM) or impaired glucose tolerance (IGT)) was created where GDM or IGT status = 1 and no GDM or IGT status = 0. GDM/IGT was determined based on the results of a glucose challenge test (GCT), or a 50 g or 100 g oral glucose tolerance test (OGTT). GDM was diagnosed if 1) fasting glucose levels after a 1 h 50 g GCT result exceeded 10.3 mmol/L, or 2) if two or more of the following cut-off values were exceeded following either a 50 g or 100 g OGTT: [50 g OGTT criteria: a) 1 h post > 10.6 mmol/L, b) 2 h > 8.9 mmol/L, or c) fasting plasma glucose level > 5.3 mmol/L; 100 g OGTT criteria: a) 1 h post > 10.6 mmol/L, b) 2 h > 9.2 mmol/L, c) 3 h > 8.0 mmol/L, or d) fasting plasma glucose level > 5.8 mmol/L]. IGT was diagnosed if 1 of these OGTT levels was exceeded. GDM and IGT were combined because adverse health outcomes in offspring have been observed following exposure to maternal glycemic levels below diagnostic criteria for gestational diabetes mellitus [30].

2.3. Outcomes

2.3.1. Cognition: Wechsler Preschool and Primary Scale of Intelligence-III (WPPSI-III)

Qualified research staff assessed child cognitive functioning using the WPPSI-III, a gold standard measure of intellectual function in children aged 2½ to 7½ years. Age-corrected verbal IQ, performance IQ and full-scale IQ scores served as our cognitive outcomes. The verbal IQ scale measures acquired knowledge, verbal comprehension and reasoning. The performance scale measures spatial abilities including visual and motor skills. Full-scale IQ score measures general intelligence. Software provided by the test publishers was used to calculate these three scales. Composite scales have a mean of 100, a standard deviation of 15, and a maximum possible score of 160.

2.3.2. Behavior: the Behavioral Assessment System for Children-Second Edition (BASC-II)

Mothers completed the 134-item BASC-II which measures emotional and behavioral problems in 2 to 5 year old children. Individual items are scored on a 4-point Likert scale (0 = never to 3 = almost always) with higher scores indicating more problems. T-scores on the internalizing and externalizing composite scales were utilized. Each t-score has a mean of 50 and a standard deviation of 10. The externalizing scale is comprised of 22 items from the aggression and hyperactivity subscales (α = 0.93), and the internalizing problems scale consists of 37 items drawn from the anxiety, depression, and somatization subscales (α = 0.90).