Title: Associations of Cord Blood Leptin and Adiponectin with Children's Cognitive Abilities

Authors: Nan Li*, PhD[1], Tye E Arbuckle, PhD[2], Gina Muckle, PhD[3], Bruce P Lanphear, MD[4,5], Michel Boivin, PhD[3], Aimin Chen, PhD[6], Linda Dodds, PhD[7], William D Fraser, MD[8,9], Emmanuel Ouellet, PhD[10], Jean R Séguin, PhD[8,11], Maria P Velez, PhD[12], Kimberly Yolton, PhD[13], Joseph M Braun, PhD[1]

Affiliations:
[1] Department of Epidemiology, Brown University, Providence, Rhode Island, United States
[2] Population Studies Division, Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario, Canada
[3] School of Psychology, Laval University, Ville de Québec, Québec, Canada
[4] Faculty of Health Sciences, Simon Fraser University, British Columbia, Canada
[5] Child and Family Research Institute, BC Children's Hospital, Vancouver, British Columbia, Canada
[6] Division of Epidemiology, Department of Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States
[7] Perinatal Epidemiology Research Unit, IWK Health Center, Halifax, Canada
[8] Centre hospitalier universitaire (CHU) Sainte-Justine Research Center, Mother and Child University Hospital Center, Montreal, Québec, Canada
[9] Centre de recherche du CHUS (CHU de Sherbrooke), University of Sherbrooke, Sherbrooke, Québec, Canada
[10] CHU de Québec-Université Laval Research Center, Ville de Québec, Québec, Canada
[11] Department of Psychiatry, University of Montréal, Montréal, Québec, Canada
[12] Department of Obstetrics and Gynecology, Queen's University, Kingston, Ontario
[13] Department of Pediatrics, Division of General and Community Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Cincinnati, Ohio, United States

Corresponding Author:
Nan Li
Brown University
Box G-S121-2
Providence, RI 02912
Telephone: +01(401)863-1806
e-mail: nan_li1@brown.edu

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Abstract

Background: Adipocytokines may play a role in fetal programming of neurodevelopment. We aimed to investigate the associations between cord blood adipocytokine concentrations and children's intelligence test scores.

Methods: We used data from two ongoing pregnancy cohorts in North America: the Maternal-Infant Research on Environmental Chemicals (MIREC, n=429) and Health Outcomes and Measures of the Environment (HOME, n=183) Studies. Umbilical cord blood adipocytokine concentrations were measured using enzyme-linked immunosorbent assays. We assessed children's Intelligence Quotient (IQ) and its components using the Wechsler Preschool and Primary Scales of Intelligence-III or Wechsler Intelligence Scale for Children-IV. We used linear regression and linear mixed models to estimate associations between log_2-transformed adipocytokine concentrations and children's IQ after adjusting for sociodemographic, perinatal, and child factors.

Results: After adjusting for covariates, cord blood adiponectin was positively associated with children's full-scale IQ scores at age 3 years in the MIREC Study (β=1.4, 95% confidence interval [CI]: 0.2, 2.5) and at ages 5 and 8 years in the HOME Study (β=1.7, CI: -0.1, 3.5). Adiponectin was positively associated with performance IQ in both studies (MIREC: β=2.0, CI: 0.7, 3.3; HOME: β=2.2, CI: 0.5, 3.9). Adiponectin was positively associated with working memory composite scores at age 8 in the HOME Study (β=3.1, CI: 1.0, 5.2). Leptin was not associated with children's IQ in either study.

Conclusions: Cord blood adiponectin was associated with higher full-scale and performance IQ and working memory composite scores in children. Future studies are needed to explore the mechanisms underlying these associations.

Keywords: adipocytokines, children, cognitive abilities, intelligence quotient

1. Introduction

Leptin and adiponectin are peptide hormones secreted by adipose tissue and the placenta that play a role in metabolism and possibly neurodevelopment (Masuzaki et al., 1997; Chen et al., 2006; Arnoldussen et al., 2014). Leptin receptors are distributed throughout the brain, and leptin acts in multiple brain regions that are important for cognition (Funahashi et al., 2003; Farr et al., 2006; Oomura et al., 2006; Morrison, 2009). In mice, short-term leptin infusions improved memory and learning (Farr et al., 2006; Oomura et al., 2006). In contrast, high leptin levels can lead to leptin resistance in the brain, which may impair cognition (Morrison, 2009; Fadel et al., 2013). Adiponectin, an anti-inflammatory cytokine, interacts with the brain by modulating inflammatory responses (Arnoldussen et al., 2014). Decreases in adiponectin may increase pro-inflammatory cytokine concentrations, which could lead to neuroinflammation and subsequent cognitive impairments (Kasper et al., 2017). In rodents, adiponectin is shown to have neuroprotective effects (Nishimura et al., 2008; Jeon et al., 2009; Ng and Chan, 2017).

Animal studies have shown that adipocytokines may play an important role in fetal neurodevelopment (Udagawa et al., 2007). Few epidemiologic studies have examined the impact of fetal adipocytokines on neurodevelopment, and the findings are inconclusive. Two studies found that fetal leptin was inversely associated with the risk of neurobehavioral problems in children, with one study reporting sex-specific associations (Lesseur et al., 2014; Minatoya et al., 2018). In contrast, a cross-sectional study found that plasma leptin concentrations were associated with lower cognitive scores among infants at age 6-24 months (Camargos et al., 2017). However, most of these studies had limitations, including small or modest sample sizes, cross-sectional design, or neurobehavioral assessment only in infancy. Thus, it is not clear if adipocytokines impact neurobehavioral outcomes later in life, specifically cognition, which tends to stabilize later in childhood and is an important determinant of school performance and later life success (Kuncel et al., 2004).

To address these gaps in the literature and further explore the role of adipocytokines in the fetal programming of neurodevelopment, we investigated the associations between cord blood adipocytokine concentrations and children's cognitive abilities in two similarly-designed prospective studies.

2. Methods

We used data from two prospective pregnancy-birth cohorts in North America: the Maternal-Infant Research on Environmental Chemicals (MIREC) Study and the Health Outcomes and Measures of the Environment (HOME) Study (Arbuckle et al., 2013; Braun et al., 2017). The two studies are similar in design and data collection strategies. All study protocols were approved by the institutional review boards of their participating institutions and participating mothers provided written informed consent for themselves and their children.

2.1. Study Participants

The MIREC Study enrolled 2001 pregnant women in the first trimester of pregnancy from 10 cities (11 study sites) across Canada from 2008-2011 (Arbuckle et al., 2013). Inclusion criteria, recruitment, and follow-up have been described previously (Arbuckle et al., 2013). A total of 1,861 mothers had singleton live births. We conducted in-home visits with participating children around age 3 years to measure children's neurodevelopment. Owing to limited resources, the in-person assessment was conducted on 808 children from seven study sites.

The HOME Study recruited pregnant women in the second trimester of pregnancy from the greater Cincinnati, Ohio area (United States) from 2003-2006. Inclusion criteria, recruitment, and follow-up have been described previously (Braun et al., 2017). Of 468 women enrolled, 389 women remained in the study and had singleton live births. We conducted follow-up visits with participating children at ages 4 weeks and 1, 2, 3, 4, 5, and 8 years.

The current analysis was restricted to 429 children from the MIREC Study and 183 children from the HOME Study who had data available for cord blood leptin and adiponectin

concentrations, covariates, and at least one measurement of full-scale intelligence quotient (FSIQ) at age 3 years (MIREC Study) or ages 5 or 8 years (HOME Study).

2.2. Cord Blood Adipocytokine Measurement

In the MIREC Study, we measured leptin and adiponectin concentrations in umbilical cord plasma samples using an enzyme-linked immunosorbent assay (ELISA) (Meso Scale Discovery, USA) at Mt Sinai Laboratory (Ontario, Canada). We performed repeated analyses of samples when coefficients of variation (CVs) were greater than 15%. The inter- and intra-assay CVs were <12% for leptin and <10% for adiponectin. The limit of detections (LODs) were 0.04 ng/mL for leptin, and <0.005 µg/mL for adiponectin. All participant samples had concentrations above the LODs.

In the HOME Study, we measured leptin and adiponectin concentrations in umbilical cord serum samples using an ELISA assay and BioTeck microtiter ELx 808 plate reader. Each analytic batch included reagent blanks and low- and high-concentration quality control (QC) samples. The CVs of repeated QC measurements for leptin and adiponectin were approximately 11% and 17%, respectively. The LODs were 0.8 ng/mL and <2 µg/mL, for leptin and adiponectin, respectively. All samples were above the LOD for adiponectin. Seven samples were below the LOD for leptin, and the machine values were used.

2.3. Cognitive Outcomes

In both studies, trained examiners assessed children's cognitive abilities using either the Wechsler Preschool and Primary Scales of Intelligence-III (WPPSI-III) or Wechsler Intelligence Scale for Children-IV (WISC-IV) test, based on children's age (Wechsler, 2002; 2003). The two tests assess children's overall intellectual abilities (FSIQ); verbal abilities (Verbal IQ [VIQ], WPPSI-III and Verbal Comprehension Index [VCI], WISC-IV); interpretation, reasoning, and organization of visually presented nonverbal information (Performance IQ [PIQ], WPPSI-III and Perceptual Reasoning Index [PRI], WISC-IV); and speed of mental and graphomotor processing (Processing Speed Quotient [PSQ], WPPSI-III and Processing Speed Index [PSI], WISC-IV).

We measured attention, concentration, and working memory for verbal material (Working Memory Index [WMI]) using the WISC-IV. The scores of FSIQ, VIQ, PIQ, and PSQ from the WPPSI-III are comparable to the scores of FSIQ, VCI, PRI, and PSI from the WISC-IV, respectively (Wechsler, 2002; 2003). FSIQ and component scores were calculated based on Canadian (MIREC) or U.S. (HOME) population-based normative reference data. Standardized scores on these tests have a mean of 100 and standard deviation (SD) of 15 (Wechsler, 2002; 2003). Higher scores indicate better cognitive abilities.

In the MIREC Study, we administered the WPPSI-III during an in-home visit when children were at approximately age 3 years. Study staff made their best attempts to control and standardize the environment, by ensuring the test area in the home was quiet, free from distractions, and well-lit. In the HOME Study, we administered the WPPSI-III and WISC-IV at our study clinic when children were approximately 5 and 8 years old, respectively.

2.4. Covariate Assessment

We identified potential confounders of our exposure-outcome association based on a directed acyclic graph (**Figure S1**). In both studies, maternal age, marital status, education, household income, parity number, gestational alcohol consumption, length of breastfeeding, and children's race were assessed using standardized interviews. Children's sex, birth weight, gestational age, and delivery mode were abstracted from hospital medical charts. Maternal gestational impaired glucose tolerance or diabetes were assessed based on diagnosis or glucose tolerance test results abstracted from hospital medical charts. We calculated pre-pregnancy body mass index (BMI) using the self-reported weight/height, and imputation for some mothers in the HOME Study with missing data (van der Laan et al, 2007). We calculated gestational weight gain by taking the difference between weight at last visit prior to delivery and self-reported pre-pregnancy weight, and converting it to weight gain for gestational age z-scores according to pre-pregnancy BMI categories (Hutcheon et al., 2013). We measured children's weight and height during follow-up visits when cognition was assessed and calculated children's

BMI z-scores based on World Health Organization age- and sex-specific standard data (World Health Organization, 2006). Study staff completed the Home Observation for Measurement of the Environment to assess the caregiving environment at ages 3 years (MIREC) and 12 months (HOME) (Caldwell and Bradley, 2003). Using maternal plasma (MIREC) or serum (HOME) cotinine concentrations, we assessed, gestational tobacco smoke exposure. We assessed mothers' FSIQ in the HOME Study, using the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999).

2.5. Statistical Analyses

For both studies, we calculated children's mean FSIQ scores by categories of each covariate, and compared the FSIQ scores across these categories using the one-way analysis of variance test. We also calculated median concentrations of leptin and adiponectin by categories of each covariate, and compared adipocytokine concentrations across covariate categories using the Kruskal-Wallis test.

In the MIREC Study, we analyzed the associations between continuous adipocytokine concentrations and cognitive test score using multivariable linear regression models, with each exposure (leptin, adiponectin) and outcome (FSIQ, VIQ, PIQ) modeled separately. In the HOME Study, we analyzed these associations using a similar approach, but used linear mixed models given that the outcomes were measured repeatedly at ages 5 and 8. We also examined the associations of adipocytokines with PSQ and WMI composite scores in the HOME Study using linear regression.

Adipocytokine concentrations were $\log_2$-transformed in all analyses. We adjusted for maternal age, education, marital status, pre-pregnancy BMI, parity, and children's sex, race, length of breastfeeding in all multivariable models. Maternal FSIQ was only assessed and adjusted for in the HOME Study. We also adjusted for children's age at cognitive assessment in the linear mixed models. Finally, we examined the shape of the associations between

adipocytokines and cognition using 3-knot restricted cubic polynomial splines (Desquilbet and Mariotti, 2010).

2.6. Secondary and Sensitivity Analyses

We included adipocytokine x sex interaction terms in our models to determine whether associations between adipocytokines and cognition were modified by child sex and considered p-values for interaction terms <0.2 to indicate the association varied by sex. We additionally adjusted for gestational age, delivery mode, birth weight percentile (calculated based on Canadian or U.S. population) (Kramer et al., 2001; Oken et al., 2003), gestational smoking and alcohol consumption, gestational weight gain (Gage et al., 2013; Hutcheon et al., 2013), children's BMI z-score at cognitive assessment, household income, and caregiving environment, given that the presence or directionality of the associations of some of these covariates with exposure and outcome is unclear. Finally, we conducted a sensitivity analysis excluding mother-child pairs with gestational impaired glucose tolerance or diabetes, since children that were born to mothers with gestational diabetes may have metabolic abnormalities and adverse neurodevelopment outcomes (Ornoy, 2005; Fetita et al., 2006). We conducted all statistical analyses using SAS version 9.4 (SAS Institute Inc, USA). All hypothesis tests were 2-sided.

3. Results

3.1. Descriptive Statistics

In the MIREC Study, 50% of children were males, and 90% were White. In the HOME Study, 46% of the children were males, and 63% were White. Among the 429 children in the MIREC Study, median (25^{th},75^{th}) cord plasma leptin and adiponectin concentrations were 11 (5, 23) ng/mL and 15 (9, 22) µg/mL, respectively (**Figure S2)**. In the HOME Study, 183 children were included in the analysis, with a total of 307 repeated measurements of cognitive abilities at ages 5 and 8 years. Median (25^{th},75^{th}) cord serum leptin and adiponectin concentrations were 10 (6, 16) ng/mL and 43 (32, 53) µg/mL, respectively (**Figure S2**). In both cohorts, median leptin

concentrations were higher among children who were female or had mothers who were overweight or obese (BMI≥25 kg/m^2). Median adiponectin concentrations were higher in both cohorts among children who had a mother that was better educated (≥college graduate), or in the HOME Study among children who had a mother that had higher FSIQ. In both cohorts, children's mean FSIQ scores were higher if they were white, breastfed for over 6 months, or born to a mother who was non-obese (BMI≤30 kg/m^2), better educated, had higher FSIQ, or had ≤1 previous pregnancy (**Tables 1-2**).

3.2. Cord Blood Adipocytokines and IQ

After adjusting for covariates, cord blood adiponectin was associated with higher FSIQ in both cohorts (MIREC: β=1.4, 95% confidence interval (CI): 0.2, 2.5, *P*=0.02; HOME: β=1.7, CI: -0.1, 3.5, *P*=0.06) (**Table 3**). Adiponectin was positively associated with children's PIQ in the MIREC Study (β=2.0, CI: 0.7, 3.3, *P*<0.01) and the HOME Study (β=2.2, CI: 0.5, 3.9, *P*=0.01). Adiponectin was positively associated with WMI at age 8 years in the HOME Study (β=3.1, CI: 1.0, 5.2, *P*<0.01). Adiponectin was not associated with VIQ or PSQ scores. Cord blood leptin was not associated with children's FSIQ or individual IQ components in either study.

Using restricted cubic splines, we observed linear associations of adiponectin with FSIQ, PIQ, and WMI in both studies (all non-linearity P-values≥0.40) (**Figures 1-2**). There were suggestive inverted U-shaped associations of leptin with FSIQ and most IQ components; however, the non-linearity p-values were not statistically significant (P≥0.11) (**Figure S3**).

3.3. Results of Secondary and Sensitivity Analyses

Generally, the associations between adipocytokines and cognition did not differ by child sex (**Table S1)**. However, leptin was inversely associated with VIQ among boys, but not among girls in the HOME Study (adipocytokine x sex interaction term P-value=0.04). Results from sensitivity analyses were not substantially different from main findings, except for attenuation in the associations of adiponectin with FSIQ and PIQ when adjusting for caregiving environment in MIREC Study (**Table S2**).

4. Discussion

We investigated the associations between cord blood adipocytokine concentrations and children's cognitive abilities in two prospective cohorts. Adiponectin concentrations were positively associated with PIQ and FSIQ in both cohorts. Adiponectin concentrations were positively associated with WMI in the HOME Study. Cord blood leptin concentrations were not associated with children's cognitive abilities in either cohort.

4.1. Adiponectin and Neurodevelopment

Little is known about the role of adiponectin in neurodevelopment. Adiponectin has multiple functions in peripheral tissues including anti-inflammatory and insulin sensitizing effects; some studies suggest adiponectin can cross the blood-brain barrier (Ebinuma et al., 2007; Kos et al., 2007). Adiponectin receptors are highly expressed in multiple brain regions, including the hypothalamus, cortex, and hippocampus (Fry et al., 2006). Adiponectin affects hippocampal neurogenesis and stimulates proliferation of hippocampal neural stem cells, and was shown to have neuroprotective effects in animal studies (Nishimura et al., 2008; Jeon et al., 2009; Zhang et al., 2011; Yau et al., 2014; Ng and Chan, 2017). In addition, lower adiponectin levels may impair cognition by promoting pro-inflammatory cytokines and neuroinflammation (Kasper et al., 2017).

Two previous studies that investigated the associations between early-life adiponectin and neurobehavioral outcomes found null associations (Camargos et al., 2017; Minatoya et al., 2018). One study examined behaviors rather than cognition, and found that cord blood adiponectin was not associated with behavior problems among Japanese preschool children (Minatoya et al., 2018). The other study found that adiponectin concentrations were not associated with cognitive or motor development in 50 Brazilian infants at ages 6-24 months (Camargos et al., 2017). There are two possible reasons for the discrepancies. First, the Japanese study examined children's behavior, whereas our study assessed cognitive abilities, which may not be correlated with behavioral outcomes. Moreover, we assessed several

domains of cognitive abilities in children at age 3-8 years, but the Brazilian study used a global measure of cognitive abilities in infancy, and not any specific domains (Bayley, 2006). Thus, the Brazilian study may not have been able to observe associations between adiponectin and more specific cognitive domains that can be assessed later in childhood. Second, the Brazilian study was cross-sectional, examining infant plasma adiponectin concentrations and cognition at the same time. Given that adiponectin level changes with age and other factors (Erhardt et al., 2014; Gruszfeld et al., 2016), the adiponectin concentrations measured in infancy may not represent fetal adiponectin concentrations. In contrast, we prospectively investigated the long-term impact of cord blood adiponectin on childhood cognition.

4.2. Leptin and Neurodevelopment

Leptin is important for the formation of normal brain structure and development of brain functions in the fetus (Udagawa et al., 2007). Leptin has receptors expressed in multiple brain regions involved in cognition, and it plays an important role in hippocampal-based learning and memory processing (Farr et al., 2006; Oomura et al., 2006; Morrison, 2009). However, high plasma leptin levels promote pro-inflammatory responses, which may lead to neuroinflammation and cognitive deficits (Calabrese et al., 2014). In our study, leptin was not associated with cognitive abilities. However, we observed suggestive inverted U-shaped associations of leptin with FSIQ and most IQ components, where scores increased, peaked, and then decreased with increasing leptin concentrations (**Figure S3**). Therefore, we speculate that the inverted U-shaped relation between leptin and cognitive scores in these data may represent an optimal level of fetal leptin necessary for proper neurodevelopment.

Previous studies examining the association between fetal leptin and neurobehavior are inconclusive. One study found that higher placental leptin methylation (i.e., reduced leptin gene expression) was associated with increased risk of lethargy and hypotonicity among boys (Lesseur et al., 2014). Among Japanese preschool children, cord blood leptin was inversely associated with hyperactivity/inattention (Minatoya et al., 2018). In validating the WPPSI-III, the

developers reported that children with attention deficit hyperactivity disorder had slightly lower FSIQ and PIQ scores compared to their matched controls, but the differences were not statistically significant (Wechsler, 2003). Therefore, it is not surprising that we did not observe an association between cord blood leptin and children's FSIQ. Given that cognitive abilities may be correlated with certain behaviors, future studies could examine the consistency of the associations of cord blood adipocytokines with cognitive abilities and behaviors.

The Brazilian study reported that plasma leptin concentrations were inversely associated with cognitive scores among 6-24 month old infants (Camargos et al., 2017). It is noteworthy that 50% of the infants in this study were overweight or obese, and they had higher leptin concentrations (Camargos et al., 2017). Therefore, the observed inverse association may have been driven by children with higher BMI, who have a different dose-response relationship for the leptin-cognition association compared to children with lower BMI (Otero et al., 2006; Calabrese et al., 2014).

4.3. Limitations

One limitation of our study is that we only measured adipocytokine concentrations at birth. Given that there are changes in adipocytokine concentrations and neurodevelopment during the pre- and postnatal periods, future studies should consider examining trajectories of adipocytokine concentrations from birth to childhood in relation to children's cognitive abilities (Erhardt et al., 2014; Gruszfeld et al., 2016). Moreover, we cannot exclude the possibility of residual confounding, even though both studies had rich sets of covariate data. Specifically, maternal IQ was not measured in the MIREC Study. However, we adjusted for maternal education, a surrogate for maternal IQ. There is also the possibility of residual confounding from other biomarkers that are correlated with adiponectin (e.g., other adipocytokines) (Mantzoros et al., 2010). The median adiponectin concentrations were 15 µg/mL in the MIREC Study and 43 µg/mL in the HOME Study, which are comparable with median adiponectin concentrations reported in previous studies (15-76 µg/mL) (Sivan et al., 2003; Mantzoros et al., 2009; Meyer et

al., 2017; Simpson et al., 2017). The differences in the concentrations across the present cohorts may be partly explained by differences in specificity characteristics of immunoassays for various adiponectin oligomers (Pajvani et al., 2003; Tabara et al., 2008; Melmed, et al., 2011) and different matrices used for adiponectin measurement (cord serum vs. cord plasma) (Yu et al., 2011). Finally, it is possible that fetal or childhood adiposity could mediate the association between adiponectin and cognition. While adiponectin plays a role in regulating metabolism and childhood adiposity is related to cognitive abilities (Li et al., 2018), studies investigating the associations of cord blood adiponectin with birth weight and childhood growth are inconsistent (Lindsay et al., 2003; Mantzoros et al., 2009; Zhang et al., 2016). However, when we adjusted for birth weight or children's BMI at the time of cognition assessment, our results were essentially unchanged, suggesting that neither birth weight nor children's BMI is a mediator of the association between adiponectin and cognition.

4.4. Strengths

Our study had several strengths. We used data from two prospective cohorts. Compared to the cross-sectional design in the previous studies, the prospective design enabled us to examine the long-term association of cord blood adipocytokines, representing the prenatal period, with children's cognitive abilities from ages 3-8 years. Moreover, despite the demographic differences in the source populations, results from the two studies were consistent and the effect sizes were comparable, which strongly supports the robustness of our findings. Furthermore, children's overall intellectual abilities and individual IQ components were assessed using valid and reliable tests. Additionally, we collected detailed covariate information in both cohorts, which enabled us to adjust for many potential confounding factors. Finally, by demonstrating associations of adiponectin with children's PIQ and FSIQ scores at different ages, our results suggest a possible long-term impact of cord blood adipocytokines on childhood cognition.

4.5. Conclusions

In conclusion, these results provide new insights into factors that affect the fetal programming of neurodevelopment. Specifically, cord blood adiponectin concentrations were positively associated with several aspects of children's cognitive abilities in two prospective cohorts from North America. Future studies should confirm these findings, and laboratory or molecular epidemiology studies are needed to explore the underlying biological mechanisms. If our findings are confirmed, there is the potential to improve children's IQ by intervening on modifiable factors that influence cord blood adiponectin levels, such as first trimester gestational weight gain and maternal protein intake (Mantzoros et al., 2010; Rifas-Shiman et al., 2017).

References

World Health Organization Multicentre Growth Reference Study Group, 2006. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development.

Arbuckle, T.E., Fraser, W.D., Fisher, M., Davis, K., Liang, C.L., Lupien, N., Bastien, S., Velez, M.P., von Dadelszen, P., Hemmings, D.G., Wang, J., Helewa, M., Taback, S., Sermer, M., Foster, W., Ross, G., Fredette, P., Smith, G., Walker, M., Shear, R., Dodds, L., Ettinger, A.S., Weber, J.P., D'Amour, M., Legrand, M., Kumarathasan, P., Vincent, R., Luo, Z.C., Platt, R.W., Mitchell, G., Hidiroglou, N., Cockell, K., Villeneuve, M., Rawn, D.F., Dabeka, R., Cao, X.L., Becalski, A., Ratnayake, N., Bondy, G., Jin, X., Wang, Z., Tittlemier, S., Julien, P., Avard, D., Weiler, H., Leblanc, A., Muckle, G., Boivin, M., Dionne, G., Ayotte, P., Lanphear, B., Seguin, J.R., Saint-Amour, D., Dewailly, E., Monnier, P., Koren, G., Ouellet, E., 2013. Cohort profile: the maternal-infant research on environmental chemicals research platform. Paediatr. Perinat. Epidemiol. 27, 415-425.

Arnoldussen, I.A., Kiliaan, A.J., Gustafson, D.R., 2014. Obesity and dementia: adipokines interact with the brain. Eur. Neuropsychopharmacol. 24, 1982-1999.

Bayley, N., 2006. Bayley Scales of Infant and Toddler Development, 3rd ed. Harcourt Assessment, San Antonio.

Braun, J.M., Kalloo, G., Chen, A., Dietrich, K.N., Liddy-Hicks, S., Morgan, S., Xu, Y., Yolton, K., Lanphear, B.P., 2017. Cohort Profile: The Health Outcomes and Measures of the Environment (HOME) study. Int. J. Epidemiol. 46, 24.

Calabrese, F., Rossetti, A.C., Racagni, G., Gass, P., Riva, M.A., Molteni, R., 2014. Brain-derived neurotrophic factor: a bridge between inflammation and neuroplasticity. Front. Cell Neurosci. 8, 430.

Caldwell, B., Bradley, R., 2003. Home Inventory Administration Manual. University of Arkansas at Little Rock, Little Rock.

Camargos, A.C., Mendonca, V.A., Oliveira, K.S., de Andrade, C.A., Leite, H.R., da Fonseca, S.F., Vieira, E.L., Teixeira Junior, A.L., Lacerda, A.C., 2017. Association between obesity-related biomarkers and cognitive and motor development in infants. Behav. Brain. Res. 325, 12-16.

Chen, J., Tan, B., Karteris, E., Zervou, S., Digby, J., Hillhouse, E.W., Vatish, M., Randeva, H.S., 2006. Secretion of adiponectin by human placenta: differential modulation of adiponectin and its receptors by cytokines. Diabetologia. 49, 1292-1302.

Desquilbet, L., Mariotti, F., 2010. Dose-response analyses using restricted cubic spline functions in public health research. Stat. Med. 29, 1037-1057.

Ebinuma, H., Miida, T., Yamauchi, T., Hada, Y., Hara, K., Kubota, N., Kadowaki, T., 2007. Improved ELISA for selective measurement of adiponectin multimers and identification of adiponectin in human cerebrospinal fluid. Clin. Chem. 53, 1541-1544.

Erhardt, E., Foraita, R., Pigeot, I., Barba, G., Veidebaum, T., Tornaritis, M., Michels, N., Eiben, G., Ahrens, W., Moreno, L.A., Kovács, E., Molnár, D., consortium, I., 2014. Reference values for leptin and adiponectin in children below the age of 10 based on the IDEFICS cohort. Int. J. Obes. (Lond) 38 Suppl 2, S32-38.

Fadel, J.R., Jolivalt, C.G., Reagan, L.P., 2013. Food for thought: the role of appetitive peptides in age-related cognitive decline. Ageing. Res. Rev. 12, 764-776.

Farr, S.A., Banks, W.A., Morley, J.E., 2006. Effects of leptin on memory processing. Peptides. 27, 1420-1425.

Fetita, L.S., Sobngwi, E., Serradas, P., Calvo, F., Gautier, J.F., 2006. Consequences of fetal exposure to maternal diabetes in offspring. J. Clin. Endocrinol. Metab. 91, 3718-3724.

Fry, M., Smith, P.M., Hoyda, T.D., Duncan, M., Ahima, R.S., Sharkey, K.A., Ferguson, A.V., 2006. Area postrema neurons are modulated by the adipocyte hormone adiponectin. J. Neurosci. 26, 9695-9702.

Funahashi, H., Yada, T., Suzuki, R., Shioda, S., 2003. Distribution, function, and properties of leptin receptors in the brain. Int. Rev. Cytol. 224, 1-27.

Gage, S.H., Lawlor, D.A., Tilling, K., Fraser, A., 2013. Associations of maternal weight gain in pregnancy with offspring cognition in childhood and adolescence: findings from the Avon Longitudinal Study of Parents and Children. Am. J. Epidemiol. 177, 402-410.

Gruszfeld, D., Kułaga, Z., Wierzbicka, A., Rzehak, P., Grote, V., Martin, F., Poncelet, P., Closa-Monasterolo, R., Escribano, J., Verduci, E., Riva, E., Koletzko, B., 2016. Leptin and Adiponectin Serum Levels from Infancy to School Age: Factors Influencing Tracking. Child. Obes. 12, 179-187.

Hutcheon, J.A., Platt, R.W., Abrams, B., Himes, K.P., Simhan, H.N., Bodnar, L.M., 2013. A weight-gain-for-gestational-age z score chart for the assessment of maternal weight gain in pregnancy. Am. J. Clin. Nutr. 97, 1062-1067.

Jeon, B.T., Shin, H.J., Kim, J.B., Kim, Y.K., Lee, D.H., Kim, K.H., Kim, H.J., Kang, S.S., Cho, G.J., Choi, W.S., Roh, G.S., 2009. Adiponectin protects hippocampal neurons against kainic acid-induced excitotoxicity. Brain Res. Rev. 61, 81-88.

Kasper, J.M., Milton, A.J., Smith, A.E., Laezza, F., Taglialatela, G., Hommel, J.D., Abate, N., 2017. Cognitive deficits associated with a high-fat diet and insulin resistance are potentiated by overexpression of ecto-nucleotide pyrophosphatase phosphodiesterase-1. Int. J. Dev. Neurosci.

Kos, K., Harte, A.L., da Silva, N.F., Tonchev, A., Chaldakov, G., James, S., Snead, D.R., Hoggart, B., O'Hare, J.P., McTernan, P.G., Kumar, S., 2007. Adiponectin and resistin in human cerebrospinal fluid and expression of adiponectin receptors in the human hypothalamus. J. Clin. Endocrinol. Metab. 92, 1129-1136.

Kramer, M.S., Platt, R.W., Wen, S.W., Joseph, K.S., Allen, A., Abrahamowicz, M., Blondel, B., Bréart, G., System, F.I.H.S.G.o.t.C.P.S., 2001. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics 108, E35.

Kuncel, N.R., Hezlett, S.A., Ones, D.S., 2004. Academic performance, career potential, creativity, and job performance: can one construct predict them all? J. Pers. Soc. Psychol. 86, 148-161.

Lesseur, C., Armstrong, D.A., Murphy, M.A., Appleton, A.A., Koestler, D.C., Paquette, A.G., Lester, B.M., Marsit, C.J., 2014. Sex-specific associations between placental leptin promoter DNA methylation and infant neurobehavior. Psychoneuroendocrinology 40, 1-9.

Li, N., Yolton, K., Lanphear, B.P., Chen, A., Kalkwarf, H.J., Braun, J.M., 2018. Impact of Early-Life Weight Status on Cognitive Abilities in Children. Obesity (Silver Spring) 26, 1088-1095.

Lindsay, R.S., Walker, J.D., Havel, P.J., Hamilton, B.A., Calder, A.A., Johnstone, F.D., Pregnancy, S.M.S.o.D., 2003. Adiponectin is present in cord blood but is unrelated to birth weight. Diabetes Care 26, 2244-2249.

Mantzoros, C.S., Rifas-Shiman, S.L., Williams, C.J., Fargnoli, J.L., Kelesidis, T., Gillman, M.W., 2009. Cord blood leptin and adiponectin as predictors of adiposity in children at 3 years of age: a prospective cohort study. Pediatrics 123, 682-689.

Mantzoros, C.S., Sweeney, L., Williams, C.J., Oken, E., Kelesidis, T., Rifas-Shiman, S.L., Gillman, M.W., 2010. Maternal diet and cord blood leptin and adiponectin concentrations at birth. Clin. Nutr. 29, 622-626.

Masuzaki, H., Ogawa, Y., Sagawa, N., Hosoda, K., Matsumoto, T., Mise, H., Nishimura, H., Yoshimasa, Y., Tanaka, I., Mori, T., Nakao, K., 1997. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. Nat. Med. 3, 1029-1033.

Meyer, D.M., Brei, C., Stecher, L., Much, D., Brunner, S., Hauner, H., 2017. Cord blood and child plasma adiponectin levels in relation to childhood obesity risk and fat distribution up to 5 y. Pediatr. Res. 81, 745-751.

Melmed, S., Polonsky K.S., Larsen, P.R., Kronenberg, H.M., 2011. Williams Textbook of Endocrinology, 12th ed. Saunders Elsevier, Philadelphia.

Minatoya, M., Itoh, S., Araki, A., Tamura, N., Yamazaki, K., Miyashita, C., Kishi, R., 2018. Association between Fetal Adipokines and Child Behavioral Problems at Preschool Age: The Hokkaido Study on Environment and Children's Health. Int. J. Environ. Res. Public Health 15.

Morrison, C.D., 2009. Leptin signaling in brain: A link between nutrition and cognition? Biochim. Biophys. Acta. 1792, 401-408.

Ng, R.C., Chan, K.H., 2017. Potential Neuroprotective Effects of Adiponectin in Alzheimer's Disease. Int. J. Mol. Sci. 18.

Nishimura, M., Izumiya, Y., Higuchi, A., Shibata, R., Qiu, J., Kudo, C., Shin, H.K., Moskowitz, M.A., Ouchi, N., 2008. Adiponectin prevents cerebral ischemic injury through endothelial nitric oxide synthase dependent mechanisms. Circulation 117, 216-223.

Oken, E., Kleinman, K.P., Rich-Edwards, J., Gillman, M.W., 2003. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC Pediatr. 3, 6.

Oomura, Y., Hori, N., Shiraishi, T., Fukunaga, K., Takeda, H., Tsuji, M., Matsumiya, T., Ishibashi, M., Aou, S., Li, X.L., Kohno, D., Uramura, K., Sougawa, H., Yada, T., Wayner, M.J., Sasaki, K., 2006. Leptin facilitates learning and memory performance and enhances hippocampal CA1 long-term potentiation and CaMK II phosphorylation in rats. Peptides 27, 2738-2749.

Ornoy, A., 2005. Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. Pediatr. Endocrinol. Rev. 3, 104-113.

Otero, M., Lago, R., Gomez, R., Dieguez, C., Lago, F., Gómez-Reino, J., Gualillo, O., 2006. Towards a pro-inflammatory and immunomodulatory emerging role of leptin. Rheumatology (Oxford) 45, 944-950.

Pajvani, U.B., Du, X., Combs, T.P., Berg, A.H., Rajala, M.W., Schulthess, T., Engel, J., Brownlee, M., Scherer, P.E., 2003. Structure-function studies of the adipocyte-secreted hormone Acrp30/adiponectin. Implications fpr metabolic regulation and bioactivity. J. Biol. Chem. 278, 9073-9085.

Rifas-Shiman, S.L., Fleisch, A., Hivert, M.F., Mantzoros, C., Gillman, M.W., Oken, E., 2017. First and second trimester gestational weight gains are most strongly associated with cord blood levels of hormones at delivery important for glycemic control and somatic growth. Metabolism 69, 112-119.

Simpson, J., Smith, A.D., Fraser, A., Sattar, N., Lindsay, R.S., Ring, S.M., Tilling, K., Davey Smith, G., Lawlor, D.A., Nelson, S.M., 2017. Programming of Adiposity in Childhood and Adolescence: Associations With Birth Weight and Cord Blood Adipokines. J. Clin. Endocrinol. Metab. 102, 499-506.

Sivan, E., Mazaki-Tovi, S., Pariente, C., Efraty, Y., Schiff, E., Hemi, R., Kanety, H., 2003. Adiponectin in human cord blood: relation to fetal birth weight and gender. J. Clin. Endocrinol. Metab. 88, 5656-5660.

Tabara, Y., Osawa, H., Kawamoto, R., Tachibana-Iimori, R., Yamamoto, M., Nakura, J., Miki, T., Makino, H., Kohara, K., 2008. Reduced high-molecular-weight adiponectin and elevated high-sensitivity C-reactive protein are synergistic risk factors for metabolic syndrome in a large-scale middle-aged to elderly population: the Shimanami Health Promoting Program Study. J. Clin. Endocrinol. Metab. 93, 715-722.

Udagawa, J., Hatta, T., Hashimoto, R., Otani, H., 2007. Roles of leptin in prenatal and perinatal brain development. Congenit. Anom. (Kyoto) 47, 77-83.

van der Laan, M.J., Polley, E.C., Hubbard, A.E., 2007. Super learner. Stat. Appl. Genet. Mol. Biol. 6, 25.

Wechsler, D., 1999. Wechsler Abbreviated Scale of Intelligence. The Psychological Corporation, New York.

Wechsler, D., 2002. Wechsler Preschool and Primary Scale of Intelligence, 3rd ed. The Psychological Corporation, San Antonio.

Wechsler, D., 2003. Wechsler Intelligence Scale for Children-IV, 3rd ed. The Psychological Corporation, San Antonio.

Yau, S.Y., Li, A., Hoo, R.L., Ching, Y.P., Christie, B.R., Lee, T.M., Xu, A., So, K.F., 2014. Physical exercise-induced hippocampal neurogenesis and antidepressant effects are mediated by the adipocyte hormone adiponectin. Proc. Natl. Acad. Sci. U S A 111, 15810-15815.

Yu, Z., Kastenmüller, G., He, Y., Belcredi, P., Möller, G., Prehn, C., Mendes, J., Wahl, S., Roemisch-Margl, W., Ceglarek, U., Polonikov, A., Dahmen, N., Prokisch, H., Xie, L., Li, Y., Wichmann, H.E., Peters, A., Kronenberg, F., Suhre, K., Adamski, J., Illig, T., Wang-Sattler, R., 2011. Differences between human plasma and serum metabolite profiles. PLoS One 6, e21230.

Zhang, D., Guo, M., Zhang, W., Lu, X.Y., 2011. Adiponectin stimulates proliferation of adult hippocampal neural stem/progenitor cells through activation of p38 mitogen-activated protein kinase (p38MAPK)/glycogen synthase kinase 3β (GSK-3β)/β-catenin signaling cascade. J. Biol. Chem. 286, 44913-44920.

Zhang, Z.Q., Lu, Q.G., Huang, J., Jiao, C.Y., Huang, S.M., Mao, L.M., 2016. Maternal and cord blood adiponectin levels in relation to post-natal body size in infants in the first year of life: a prospective study. BMC Pregnancy Childbirth 16, 189.

Table 1. Descriptive Statistics of Leptin and Adiponectin Concentrations in Cord Plasma and Full-Scale Intelligence Quotient (FSIQ) Score at Age 3 Years among the Maternal-Infant Research on Environmental Chemicals Research (MIREC) Study Women and Children (N=429)

	Leptin (ng/mL)			Adiponectin (μg/mL)			3y Full-Scale IQ		
	N	Median (25^{th}, 75^{th})	P values	N	Median (25^{th}, 75^{th})	P values	N	Mean (SD)	P values
Overall	427	11 (5, 23)		429	15 (9, 22)		429	107 (13)	
Child Sex			<0.01			0.73			<0.01
Male	213	9 (4, 17)		214	15 (9, 22)		214	105 (15)	
Female	214	15 (7, 29)		215	15 (10, 22)		215	109 (12)	
Child Race			0.33			0.81			<0.01
White	386	11 (5, 24)		388	15 (10, 22)		388	108 (13)	
Other	41	10 (5, 20)		41	15 (9, 21)		41	100 (13)	
Breastfeeding Duration			0.92			0.94			0.05
0 month	54	11 (4, 25)		54	17 (7, 23)		54	107 (15)	
>0-6 months	97	11 (7, 22)		99	15 (9, 21)		99	104 (14)	
>6 months	276	11 (5, 22)		276	15 (10, 22)		276	108 (13)	
Maternal Age at Delivery			0.09			0.42			0.35
18-25 years	26	12 (4, 22)		26	15 (8, 21)		26	103 (14)	
>25-35 years	282	12 (5, 25)		283	16 (10, 22)		283	107 (13)	
>35 years	119	10 (4, 21)		120	14 (8, 21)		120	107 (14)	
Maternal Education			0.12			0.03			<0.01
≥College graduate	282	12 (5, 25)		282	16 (11, 23)		282	109 (13)	
Tech school/Some College	121	11 (4, 19)		123	14 (8, 21)		123	103 (15)	
≤High school graduate	24	8 (4, 17)		24	13 (8, 19)		24	100 (10)	
Marital Status			0.52			0.59			0.30
Married	304	11 (5, 22)		305	15 (10, 21)		305	107 (13)	
Unmarried	123	11 (5, 26)		124	15 (9, 24)		124	106 (14)	
Parity			0.05			0.97			0.10
0	183	13 (5, 26)		183	15 (9, 23)		183	108 (14)	

1	178	11 (5, 21)		179	15 (10, 21)		179	107 (13)	
≥2	66	9 (4, 21)		67	16 (8, 21)		67	104 (12)	
Pre-pregnancy BMI (kg/m^2)			0.01			0.98			0.08
<25 (lean)	257	10 (5, 21)		259	15 (10, 23)		259	108 (14)	
25-30 (overweight)	93	13 (7, 26)		93	15 (9, 20)		93	107 (13)	
>30 (obese)	77	16 (7, 26)		77	16 (9, 21)		77	104 (13)	

SD: Standard deviation

P values for leptin and adiponectin were calculated using the Kruskal-Wallis test, and p values for FSIQ scores were calculated using the one-way analysis of variance test.

Table 2. Descriptive Statistics of Leptin and Adiponectin Concentrations in Cord Serum, and Full-Scale Intelligence Quotient (FSIQ) Scores at Ages 5 or 8 Years among the Health Outcomes and Measures of the Environment (HOME) Study Women and Children (N=183)

	Leptin (ng/mL)			Adiponectin (μg/mL)			5y Full-Scale IQ			8y Full-Scale IQ		
	N	Median (25^{th}, 75^{th})	P values	N	Median (25^{th}, 75^{th})	P values	N	Mean (SD)	P values	N	Mean (SD)	P values
Overall	174	10 (6, 16)		183	43 (32, 53)		143	104 (14)		164	103 (15)	
Child Sex			<0.01			0.73			0.39			0.37
Male	83	8 (3, 14)		84	44 (32, 53)		61	103 (15)		73	102 (15)	
Female	91	12 (8, 20)		99	42 (31, 55)		82	105 (13)		91	104 (15)	
Child Race			0.04			0.01			<0.01			<0.01
Non-Hispanic White	110	11 (6, 17)		116	45 (35, 58)		92	109 (13)		104	108 (12)	
Non-Hispanic Black	52	10 (7, 15)		54	35 (26, 48)		41	94 (12)		49	92 (13)	
Other	12	6 (1, 9)		13	40 (20, 49)		10	105 (13)		11	110 (16)	
Breastfeeding Duration			0.68			0.17			0.02			0.01
0 month	31	9 (6, 15)		33	34 (26, 50)		24	98 (14)		30	98 (15)	
>0-6 months	68	10 (7, 17)		69	45 (35, 56)		49	103 (14)		62	101 (16)	
>6 months	75	10 (5, 16)		81	41 (32, 50)		70	107 (14)		72	107 (14)	
Maternal Age at Delivery			0.06			0.06			<0.01			<0.01
18-25 years	39	8 (4, 13)		40	39 (26, 46)		26	95 (13)		37	95 (14)	
>25-35 years	114	12 (6, 17)		119	44 (33, 55)		96	105 (14)		103	105 (14)	
>35 years	21	8 (7, 12)		24	46 (27, 57)		21	113 (11)		24	111 (14)	
Maternal Education			0.99			0.07			<0.01			<0.01
≥College graduate	93	11 (6, 15)		97	45 (35, 55)		77	110 (12)		85	110 (12)	
Tech school/Some College	45	10 (6, 17)		49	39 (30, 48)		40	98 (14)		43	99 (14)	
≤High school graduate	36	9 (6, 17)		37	40 (25, 55)		26	96 (12)		36	93 (14)	
Marital Status			0.23			0.01			<0.01			<0.01
Married	120	11 (6, 17)		127	45 (35, 55)		105	108 (13)		111	108 (13)	
Unmarried	54	9 (5, 15)		56	35 (25, 49)		38	94 (12)		53	93 (14)	
Parity			0.60			0.01			<0.10			<0.12

0	78	10 (6, 16)		83	45 (36, 55)		66	106 (15)		74	105 (16)	
1	55	9 (6, 15)		59	41 (30, 53)		44	106 (14)		52	104 (14)	
≥2	41	11 (6, 20)		41	34 (20, 50)		33	100 (12)		38	99 (15)	
Pre-pregnancy BMI (kg/m^2)			0.01			0.32			<0.01			<0.01
<25 (lean)	93	8 (4, 14)		97	43 (33, 51)		75	108 (14)		88	106 (14)	
25-30 (overweight)	42	10 (7, 17)		43	45 (35, 55)		34	105 (14)		39	104 (14)	
>30 (obese)	39	14 (8, 21)		43	40 (21, 55)		34	97 (13)		37	96 (16)	
Maternal Full-scale IQ			0.33			0.02			<0.01			<0.01
1st Tercile 58-99	55	10 (6, 16)		58	40 (26, 50)		44	96 (13)		55	94 (13)	
2nd Tercile >99-114	59	9 (5, 16)		61	42 (33, 50)		47	106 (14)		52	107 (12)	
3rd Tercile >114	60	12 (6, 17)		64	46 (36, 57)		52	110 (12)		57	109 (14)	

SD: Standard deviation

P values for leptin and adiponectin were calculated using the Kruskal-Wallis test, and p values for FSIQ scores were calculated using the one-way analysis of variance test.

Table 3. Adjusted Difference in Children's IQ at Ages 3, 5, or 8 Years, per Unit Increase in log_2-transformed Leptin or log_2-transformed Adiponectin Concentrations.

	Cognitive Abilities at Age 3 Years, MIREC Study		Cognitive Abilities at Ages 5 or 8 Years, HOME Study	
	N	Adjusted Difference [a] (95% CI)	N	Adjusted Difference [b] (95% CI)
WPPSI-III/WISC-IV FSIQ				
Leptin	427	0.4 (-0.3, 1.2)	174	0.0 (-1.4, 1.4)
Adiponectin	429	1.4 (0.2, 2.5)	183	1.7 (-0.1, 3.5)
WPPSI-III/WISC-IV VIQ/VCI				
Leptin	424	0.4 (-0.4, 1.1)	174	-0.5 (-1.8, 0.9)
Adiponectin	426	0.4 (-0.7, 1.5)	183	0.1 (-1.7, 1.8)
WPPSI-III/WISC-IV PIQ/PRI				
Leptin	422	0.4 (-0.5, 1.3)	174	0.5 (-0.8, 1.8)
Adiponectin	424	2.0 (0.7, 3.3)	183	2.2 (0.5, 3.9)
WPPSI-III/WISC-IV PSQ/PSI				
Leptin			174	0.1 (-1.7, 1.8)
Adiponectin			183	0.8 (-1.2, 2.8)
WISC-IV WMI				
Leptin			156	0.3 (-1.4, 2.1)
Adiponectin			164	3.1 (1.0, 5.2)

FSIQ: full-scale intelligence quotient; VIQ: verbal intelligence quotient; VCI: verbal comprehension index; PIQ: performance intelligence quotient; PRI: perceptual reasoning index; PSQ: processing speed quotient; PSI: processing speed index; WMI: working memory index.

[a] Adjusted for continuous variables maternal age, and length of breastfeeding; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), marital status (married, unmarried), child's sex (Male, Female), and race (White, other).

[b] Adjusted for continuous variables maternal age and IQ, children's age at outcome assessment; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), duration of breastfeeding (never, 0-6 month, >6 month), child's sex (Male, Female), and race (non-Hispanic White, non-Hispanic Black, other).

WPPSI-III: Wechsler Preschool and Primary Scales of Intelligence-III. WISC-IV: Wechsler Intelligence Scales for Children-fourth version.

Figure Titles and Footnotes

Figure 1. Adjusted Restricted Cubic Polynomial Spline of Cord Blood Adiponectin Concentrations (on log_2-scale), and Children's Full-Scale IQ, Performance IQ at ages 3, 5 or 8 Years [a]

[a] IQ was assessed at approximately age 3 years in the MIREC Study, and at ages 5 and 8 years in the HOME Study. In the MIREC Study, we adjusted for continuous variables maternal age, and length of breastfeeding; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), marital status (married, unmarried), child's sex (Male, Female), and race (White, other).
In the HOME Study, we adjusted for continuous variables maternal age and IQ, children's age at outcome assessment; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), duration of breastfeeding (never, 0-6 month, >6 month), child's sex (Male, Female), and race (non-Hispanic White, non-Hispanic Black, other).

Figure 2. Adjusted Restricted Cubic Polynomial Spline of Cord Blood Adiponectin Concentrations (on log_2-scale) and Children's Working Memory score at age 8 Years [a]

[a] In the HOME Study, we adjusted for continuous variables maternal age and IQ, children's age at outcome assessment; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), duration of breastfeeding (never, 0-6 month, >6 month), child's sex (Male, Female), and race (non-Hispanic White, non-Hispanic Black, other).

Figure 1

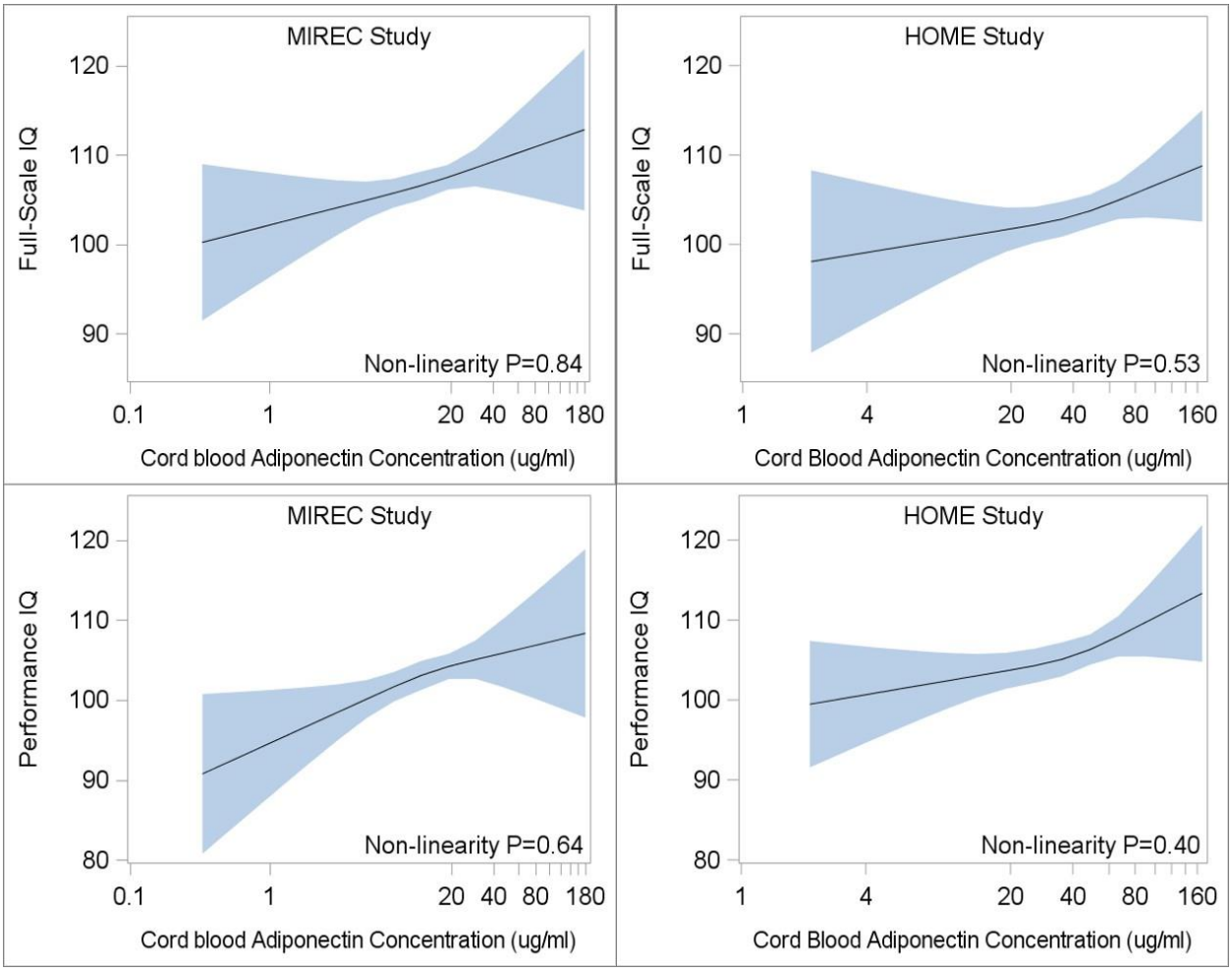
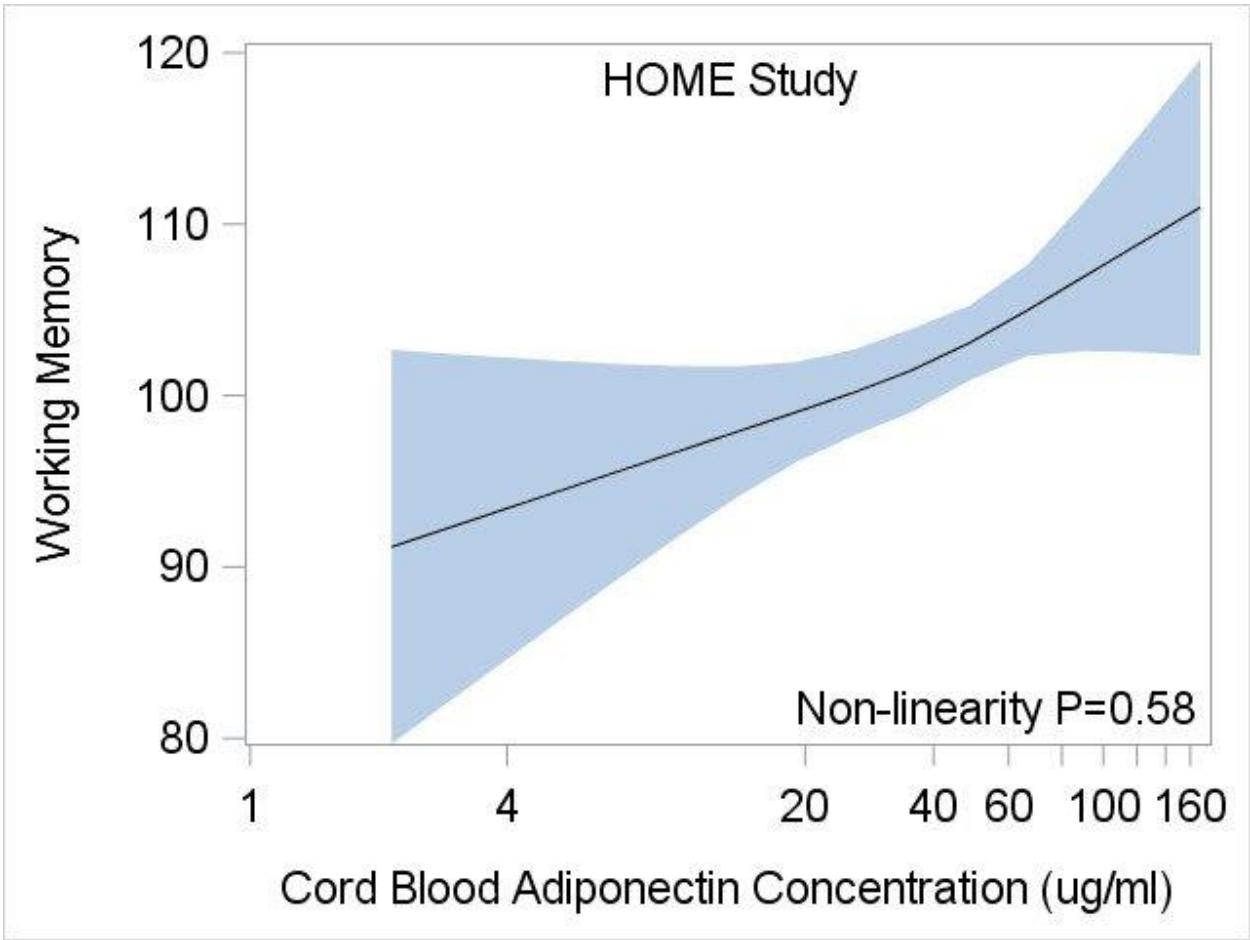

MIREC Study
Full-Scale IQ
120
110
100
90
Non-linearity P=0.84
0.1
1
20 40 80 180
Cord blood Adiponectin Concentration (ug/ml)
HOME Study
Full-Scale IQ
120
110
100
90
Non-linearity P=0.53
1
4
20 40 80 160
Cord Blood Adiponectin Concentration (ug/ml)
MIREC Study
Performance IQ
120
110
100
90
80
Non-linearity P=0.64
0.1
1
20 40 80 180
Cord blood Adiponectin Concentration (ug/ml)
HOME Study
Performance IQ
120
110
100
90
80
Non-linearity P=0.40
1
4
20 40 80 160
Cord Blood Adiponectin Concentration (ug/ml)

Figure 2


HOME Study
Working Memory
120
110
100
90
80
Non-linearity P=0.58
1
4
20
40
60
100
160
Cord Blood Adiponectin Concentration (ug/ml)

Supplemental Materials

Title: Associations of Cord Blood Leptin and Adiponectin with Children's Cognitive Abilities

Authors: Nan Li, PhD, Tye E. Arbuckle, PhD, Gina Muckle, PhD, Bruce P. Lanphear, MD, Michel Boivin, PhD, Aimin Chen, PhD, Linda Dodds, PhD, William D. Fraser, MD, Emmanuel Ouellet, PhD, Jean R. Séguin, PhD, Maria P. Velez, PhD, Kimberly Yolton, PhD, Joseph M. Braun, PhD

Corresponding Author:
Nan Li
Brown University
Box G-S121-2
Providence, RI 02912
E-mail: nan_li1@brown.edu

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Table S1. Adjusted Difference in Children's IQ at Ages 3, 5, or 8 Years, per Unit Increase in log_2-transformed Leptin or log_2-transformed Adiponectin Concentrations, Stratified by Child Sex.

Table S2. Sensitivity Analyses: Additionally Adjusted for Gestational Age, Birth Weight Percentile, Mode of Delivery, Maternal Tobacco Exposure, Maternal Alcohol Consumption, Children's BMI Z-Score at Cognitive Assessment, Annual Household Income, Caregiving Environment, Maternal Weight Gain for Gestational Age Z-Score, or Excluded Mother-Child Pairs with Gestational Impaired Glucose Tolerance or Diabetes. [a]

Figure S1. Directed Acyclic Graph of Potential Confounders of the Association between Cord Blood Adipocytokine Concentrations and Children's IQ.

Figure S2. Violin Plots of the Distribution of Leptin and Adiponectin Concentrations in the MIREC and HOME Study Cohorts. [a]

Figure S3. Adjusted Restricted Cubic Polynomial Spline of Cord Blood Leptin or Adiponectin Concentrations (on log_2-scale), and Children's cognitive abilities, at Ages 3, 5 or 8 Years. [a]

Table S1. Adjusted Difference in Children's IQ at Ages 3, 5, or 8 Years, per Unit Increase in log_2-transformed Leptin or log_2-transformed Adiponectin Concentrations, Stratified by Child Sex.

	Adjusted Difference (95% CI)		P for
	Boys	Girls	Interaction
Cognitive Abilities at Age 3 Years, MIREC Study [a]			
Total N	214	215	
WPPSI-III FSIQ			
Leptin	0.6 (-0.6, 1.8)	0.5 (-0.5, 1.4)	0.65
Adiponectin	1.1 (-0.7, 2.9)	1.9 (0.4, 3.3)	0.69
WPPSI-III VIQ			
Leptin	0.6 (-0.6, 1.7)	0.3 (-0.7, 1.3)	0.66
Adiponectin	0.3 (-1.5, 2.0)	0.8 (-0.6, 2.2)	0.66
WPPSI-III PIQ			
Leptin	0.7 (-0.6, 2.1)	0.4 (-0.8, 1.6)	0.49
Adiponectin	1.7 (-0.2, 3.7)	2.4 (0.7, 4.2)	0.91
Cognitive Abilities at Ages 5 or 8 Years, HOME Study [b]			
Total N	84	99	
WPPSI-III/WISC-IV FSIQ			
Leptin	-1.1 (-3.5, 1.3)	0.8 (-0.6, 2.3)	0.34
Adiponectin	1.1 (-1.8, 3.9)	1.8 (-0.3, 3.9)	0.73
WPPSI-III/WISC-IV VCI			
Leptin	-2.0 (-4.2, 0.2)	0.6 (-0.9, 2.1)	0.04
Adiponectin	-1.2 (-4.3, 1.9)	0.6 (-1.4, 2.5)	0.26
WPPSI-III/WISC-IV PRI			
Leptin	0.6 (-1.7, 2.9)	0.1 (-1.3, 1.5)	0.35
Adiponectin	1.7 (-2.0, 5.5)	2.4 (0.6, 4.2)	0.98
WPPSI-III/WISC-IV PSI			
Leptin	-0.8 (-3.3, 1.8)	1.0 (-1.2, 3.2)	0.57
Adiponectin	1.4 (-2.5, 5.4)	0.2 (-2.1, 2.5)	0.75
WPPSI-III/WISC-IV WMI			
Leptin	-0.9 (-3.7, 1.8)	1.5 (-0.9, 4.0)	0.21
Adiponectin	4.4 (0.2, 8.7)	2.8 (0.3, 5.2)	0.82

FSIQ: full-scale intelligence quotient; VIQ: verbal intelligence quotient; VCI: verbal comprehension index; PIQ: performance intelligence quotient; PRI: perceptual reasoning index; PSQ: processing speed quotient; PSI: processing speed index; WMI: working memory index. WPPSI-III: Wechsler Preschool and Primary Scales of Intelligence-III. WISC-IV: Wechsler Intelligence Scales for Children-fourth version.

[a] Adjusted for continuous variables maternal age, and length of breastfeeding; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), marital status (married, unmarried), and race (White, other).

[b] Adjusted for continuous variables maternal age and IQ, children's age at outcome assessment; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), duration of breastfeeding (never, 0-6 month, >6 month), and race (non-Hispanic White, non-Hispanic Black, other).

Table S2. Sensitivity Analyses: Additionally Adjusted for Gestational Age, Birth Weight Percentile, Mode of Delivery, Maternal Tobacco Exposure, Maternal Alcohol Consumption, Children's BMI Z-Score at Cognitive Assessment, Annual Household Income, Caregiving Environment, Maternal Weight Gain for Gestational Age Z-Score, or Excluded Mother-Child Pairs with Gestational Impaired Glucose Tolerance or Diabetes. [a]

	The MIREC Study		The HOME Study	
	N	β and 95% CI	N	β and 95% CI
Adiponectin and Full-Scale IQ				
Unadjusted	429	1.6 (0.4, 2.8)	183	2.7 (0.6, 4.7)
Model 1[b]	429	1.4 (0.2, 2.5)	183	1.7 (-0.1, 3.5)
model 1 + gestational age	429	1.3 (0.2, 2.4)	183	1.4 (-0.4, 3.3)
Model 1 + birth weight percentile	429	1.3 (0.1, 2.4)	183	1.7 (-0.1, 3.5)
Model 1 + maternal smoking	421	1.4 (0.2, 2.5)	183	1.7 (0.0, 3.4)
Model 1 + children's BMI z-score	403	1.5 (0.4, 2.7)	183	1.7 (-0.1, 3.4)
Model 1 + alcohol consumption	418	1.3 (0.2, 2.5)	183	1.6 (-0.1, 3.4)
Model 1 + mode of delivery	429	1.4 (0.2, 2.5)	183	1.6 (-0.1, 3.4)
Model 1 + annual household income	414	1.4 (0.2, 2.6)	183	1.5 (-0.3, 3.3)
Model 1 + gestational weight gain	393	1.7 (0.5, 2.8)	182	1.7 (-0.1, 3.4)
Model 1 + caregiving environment	416	1.0 (-0.1, 2.2)	173	1.6 (-0.2, 3.5)
Model 1, exclude gestational diabetes	300	1.8 (0.4, 3.1)	176	1.6 (-0.2, 3.4)
Adiponectin and Performance IQ				
Unadjusted	424	2.2 (0.9, 3.5)	183	2.9 (0.9, 4.9)
Model 1[b]	424	2.0 (0.7, 3.3)	183	2.2 (0.5, 3.9)
model 1 + gestational age	424	2.0 (0.6, 3.3)	183	1.8 (0.1, 3.6)
Model 1 + birth weight percentile	424	2.0 (0.6, 3.3)	183	2.1 (0.4, 3.8)
Model 1 + maternal smoking	416	1.9 (0.5, 3.2)	183	2.2 (0.6, 3.8)
Model 1 + children's BMI z-score	399	2.1 (0.8, 3.5)	183	2.2 (0.5, 3.9)
Model 1 + alcohol consumption	413	2.1 (0.8, 3.4)	183	2.2 (0.5, 3.9)
Model 1 + mode of delivery	424	2.0 (0.7, 3.3)	183	2.2 (0.5, 3.9)
Model 1 + annual household income	409	2.1 (0.8, 3.5)	183	2.1 (0.3, 3.8)
Model 1 + gestational weight gain	389	2.2 (0.9, 3.6)	182	2.1 (0.4, 3.9)
Model 1 + caregiving environment	411	1.6 (0.3 2.9)	173	1.9 (0.3, 3.6)
Model 1, exclude gestational diabetes	296	2.2 (0.7, 3.8)	176	2.1 (0.3, 3.8)
Adiponectin and Working Memory				
Unadjusted			164	3.4 (1.2, 5.7)
Model 1[b]			164	3.1 (1.0, 5.2)
model 1 + gestational age			164	3.0 (0.9, 5.2)
Model 1 + birth weight percentile			164	3.1 (1.0, 5.2)
Model 1 + maternal smoking			164	3.2 (1.1, 5.2)
Model 1 + children's BMI z-score			164	3.1 (1.0, 5.2)
Model 1 + alcohol consumption			164	3.1 (1.0, 5.2)
Model 1 + mode of delivery			164	3.1 (1.0, 5.2)
Model 1 + annual household income			164	3.1 (0.9, 5.2)
Model 1 + gestational weight gain			163	3.1 (1.0, 5.3)
Model 1 + caregiving environment			154	3.4 (1.2, 5.6)
Model 1, exclude gestational diabetes			157	3.0 (0.9, 5.1)

[a] In the MIREC Study, gestational age, birth weight percentile, children's BMI z-score at outcome assessment, and weight gain for gestational age z-score, were modeled as continuous variables; maternal smoking (active smoking vs. none active smoking, using first trimester plasma cotinine concentration of 5.21ng/ml as cut-off point), maternal alcohol drinking (yes, no), mode of delivery (vaginal, cesarean), caregiving environment (<45, ≥45), and household income (<C$50K, C$50-100K, >C$100K) were modeled as categorical variables. In the HOME Study, gestational age, birth weight percentile, maternal smoking (mean of $\log_{10}$-transformed serum cotinine concentrations during 16 and 26 weeks of pregnancy), children's BMI z-score, and weight gain for gestational age z-score, were modeled as continuous variables; maternal alcohol drinking (yes, no), mode of delivery (vaginal, cesarean), household income (<$40K, $40-80K, >$80K) and caregiving environment (≤40, >40) were measured as categorical variable.
[b] Model 1 for the MIREC Study adjusted for continuous variables maternal age, and length of breastfeeding; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), marital status (married, unmarried), child's sex (Male, Female), and race (White, other); and model 1 for the HOME Study adjusted for continuous variables maternal age and IQ, children's age at outcome assessment; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), duration of breastfeeding (never, 0-6 month, >6 month), child's sex (Male, Female), and race (non-Hispanic White, non-Hispanic Black, other).

Figure S1. Directed Acyclic Graph of Potential Confounders of the Association between Cord Blood Adipocytokine Concentrations and Children's IQ.

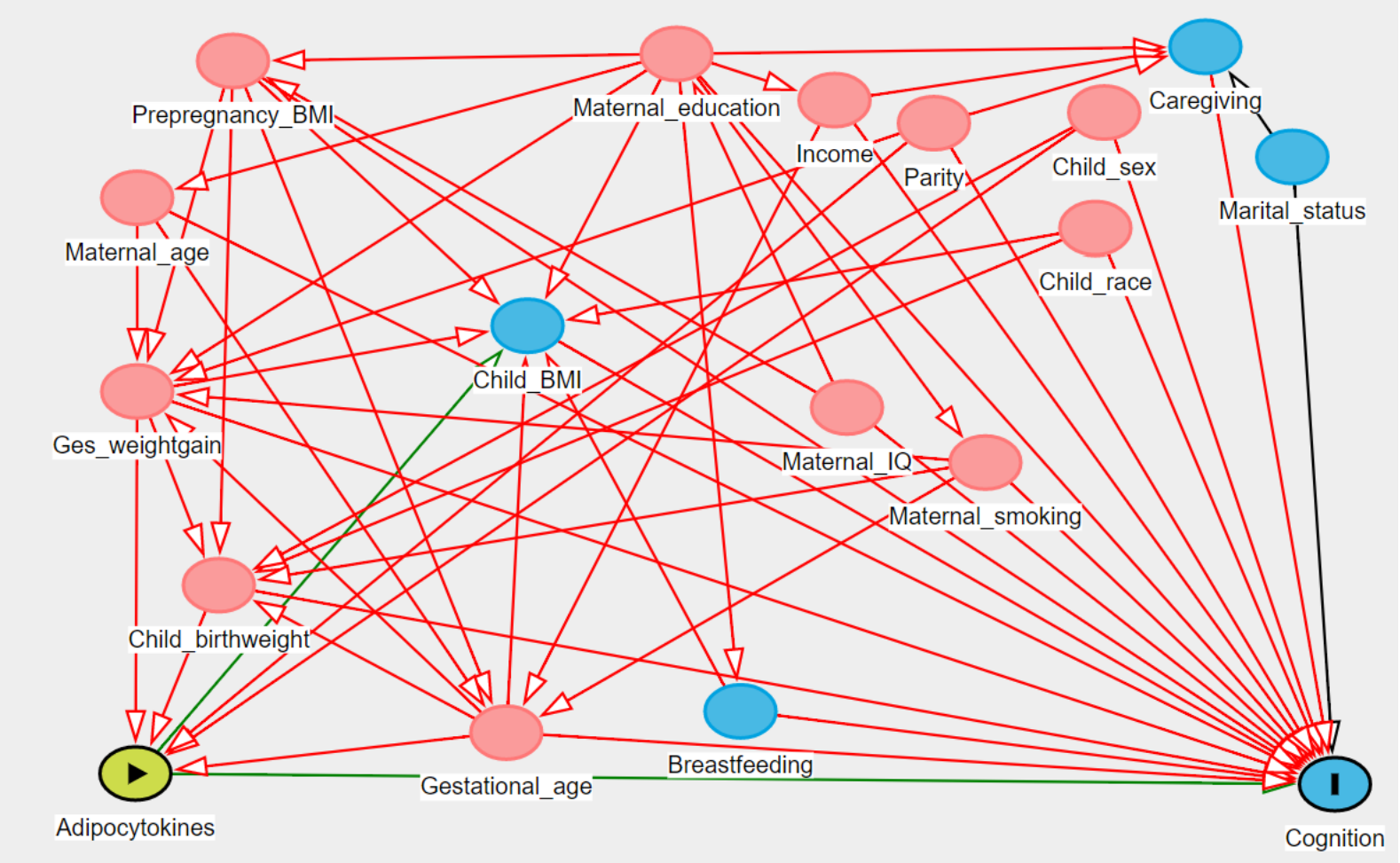
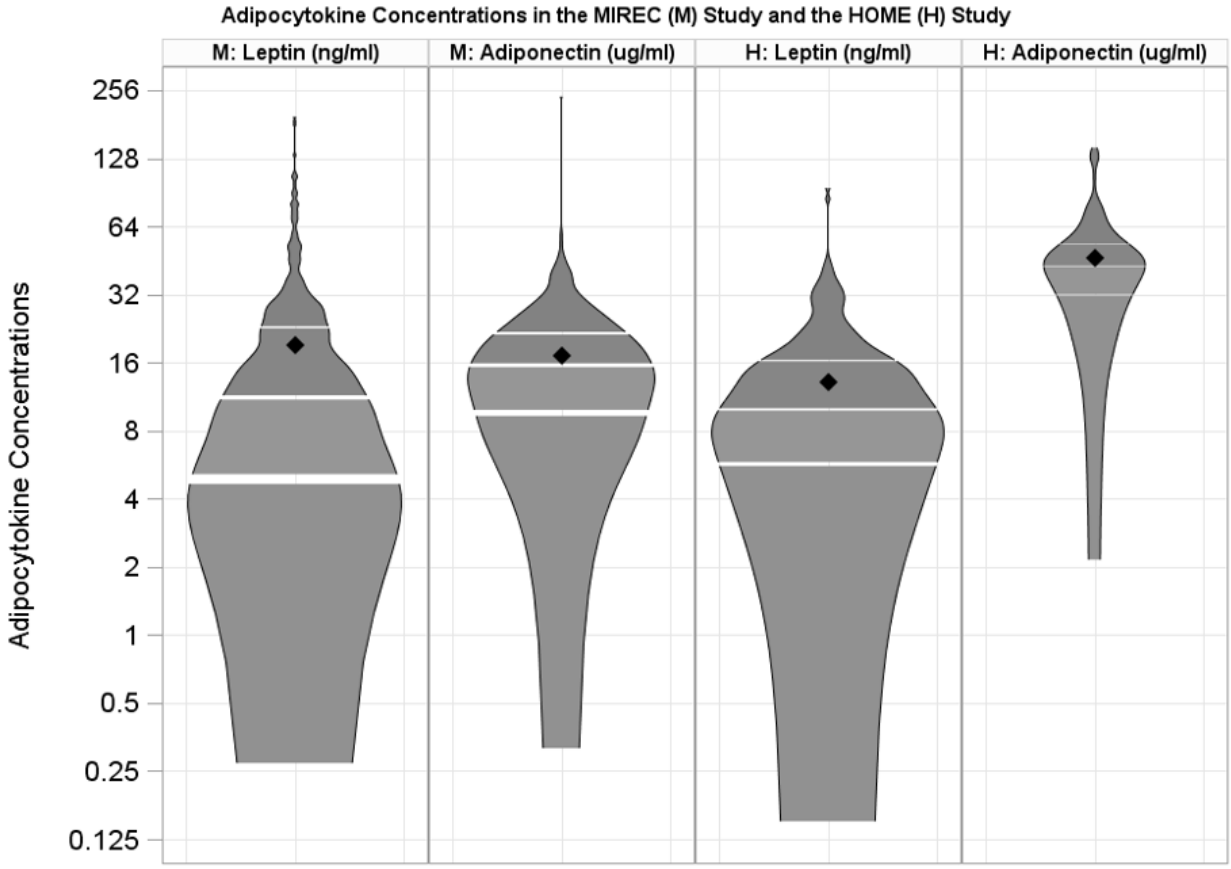
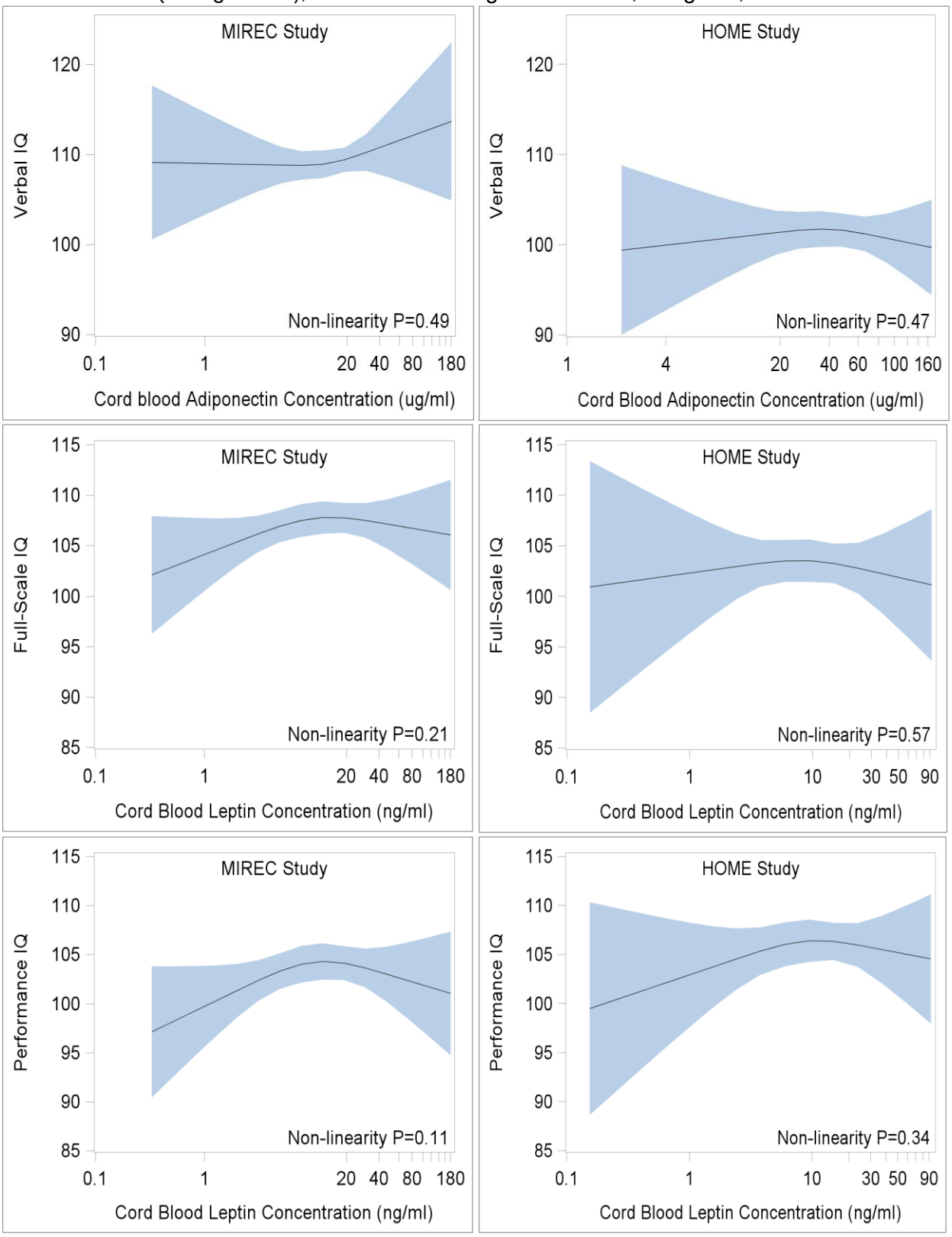


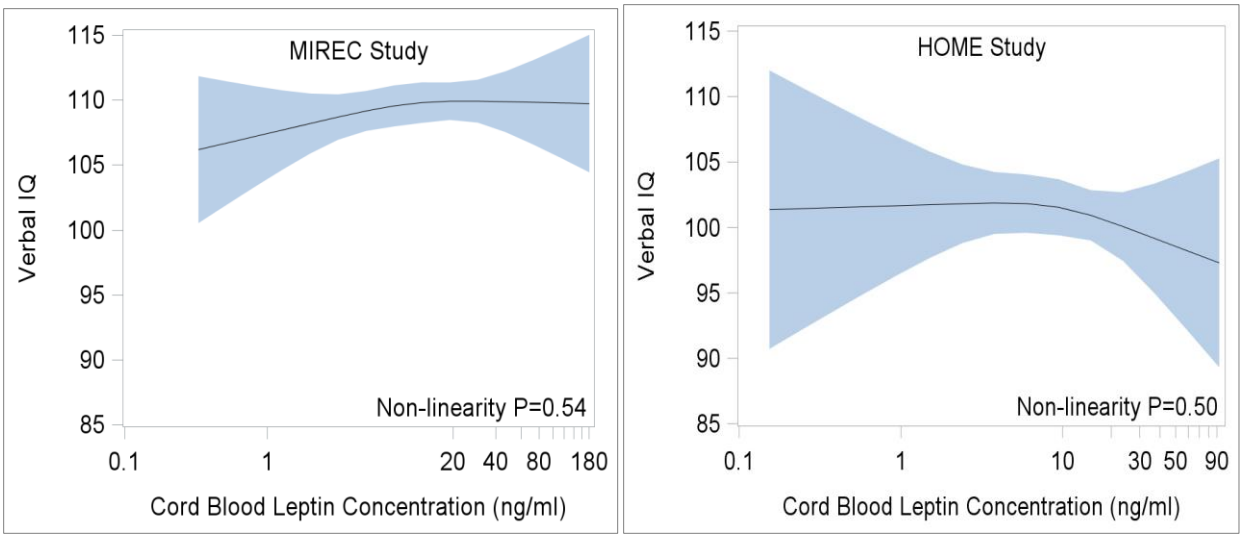
Figure S2. Violin Plots of the Distribution of Leptin and Adiponectin Concentrations in the MIREC and HOME Study Cohorts. [a]



[a]The diamond represents the mean, the shaded area is the density function of leptin/adiponectin concentrations, and the four shaded areas represent the four quartiles.

Figure S3. Adjusted Restricted Cubic Polynomial Spline of Cord Blood Leptin or Adiponectin Concentrations (on log_2-scale), and Children's cognitive abilities, at Ages 3, 5 or 8 Years. [a]





[a] IQ was assessed at approximately age 3 years in the MIREC Study, and at ages 5 and 8 years in the HOME Study.
In the MIREC Study, we adjusted for continuous variables maternal age, and length of breastfeeding; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), marital status (married, unmarried), child's sex (Male, Female), and race (White, other).
In the HOME Study, we adjusted for continuous variables maternal age and IQ, children's age at outcome assessment; and categorical variables maternal education (high school graduate or less, tech school or some college, college graduate or above), marital status (married, unmarried), pre-pregnancy BMI (<25, ≥25 kg/m^2), parity number (0, 1, ≥2), duration of breastfeeding (never, 0-6 month, >6 month), child's sex (Male, Female), and race (non-Hispanic White, non-Hispanic Black, other).