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An examination of sex differences in associations between cord blood adipokines and childhood adiposity

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Summary

Background: Though the physiological roles of adipokines in metabolism, insulin resistance and satiety are clear, literature regarding associations between cord blood adipokine levels and childhood adiposity is equivocal.

Objectives: To determine whether cord blood levels of leptin and adiponectin are associated with adiposity in children 2 to 5 years of age, and whether such associations are modified by sex.

Methods: Leptin and adiponectin levels were measured in cord blood and anthropometric measures were completed on 550 children enrolled in the Maternal–Infant Research on Environmental Chemicals Child Development Plus study (MIREC-CD Plus). We used multivariable linear and Poisson regression models to determine associations between cord blood adipokine levels and child body mass index (BMI), triceps and subscapular skinfold thickness and risk of overweight/obesity and to assess effect modification by child sex.

Results: Cord blood adiponectin was significantly associated with modest increases in BMI and the sum of triceps and subscapular skinfold z-scores in boys but not girls. A doubling of adiponectin levels was associated with a 30% increased risk of overweight/obesity in boys (RR = 1.30; 95% CI: 1.02, 1.64). Leptin was not associated with anthropometric measures in either sex.

Conclusions: The observed associations between adiponectin and adiposity in boys were statistically significant, of moderate magnitude, and underscore the value of considering sex-specific patterns.

KEYWORDS

body mass index, childhood obesity, cord blood adipokines, skinfold

1 | INTRODUCTION

In recent decades, childhood obesity has increased dramatically in both developed and developing countries.[1] Childhood obesity tracks into adulthood and is associated with an increased risk of developing chronic conditions such as cardiovascular disease and metabolic syndrome, resulting in significant public health and economic burdens.[2,3] While caloric imbalance remains the primary mechanism behind the obesity epidemic, recent studies have explored whether childhood obesity has etiological roots in fetal development.[4,5] Umbilical cord

blood adipokines, particularly leptin and adiponectin, have been hypothesized as potential biomarkers of early life adiposity.[6,7] Leptin, an adipocyte-derived protein, is an established marker for fetal adiposity.[7,8] Studies have shown that cord blood leptin levels positively correlate with fetal adiposity at birth.[6,7,9] In addition, leptin may play a role in later life obesity by acting on hypothalamic receptors to regulate energy homeostasis and satiety.[10,11] Individuals with obesity may develop leptin resistance and subsequently lose the ability to regulate satiety and gain weight.[12] Adiponectin is exclusively produced by adipocytes and plays an important role in the regulation of insulin sensitivity in adults. In contrast to leptin, adiponectin is found in lower circulating levels among adults with obesity.[13] At birth, adiponectin may promote fat deposition,[14,15] but potential obesity programming mechanisms are not well established.

Recent studies have explored associations between cord blood adipokines and child adiposity, but findings are largely conflicting and have primarily evaluated associations in the overall study population rather than among boys and girls separately. Though cord blood leptin has been inversely associated with adiposity[16-19] and accelerated weight gain during childhood,[19-22] null[18,21] and positive[23,24] associations between leptin and child growth have also been reported. Similarly, there is lack of consensus regarding the role of adiponectin in early childhood growth or adiposity with null,[19,25,26] inverse,[26] and positive[19,25,26] associations being reported depending on the age of child, specific anthropometric measure and choice of confounders.

Our primary objective was to quantify associations between cord blood levels of leptin and adiponectin and child adiposity in a population of Canadian preschool children. Our secondary objective was to examine potential effect modification by child sex, in light of the lack of attention devoted to potential sex-specific effects of cord blood adipokines on child growth in the literature. Girls are known to have higher cord blood leptin levels and lower average birthweight[27,28] than males. It is, therefore, possible that the potential effects of cord blood adipokine levels on childhood growth may differ by child sex.

2 | METHODS

2.1 | Study population

Our study population included children enrolled in the Maternal–Infant Research on Environmental Chemicals Child Development Plus (MIREC-CD Plus) study. The study profile and detailed eligibility criteria of the original MIREC cohort have been previously reported.[29] Women were recruited during their first trimester of pregnancy from 10 Canadian sites between 2008 and 2011. Leptin and adiponectin levels were measured in 1363 umbilical cord blood samples.[30] MIREC-CD Plus, a follow-up study, recruited 784 MIREC families with children 2 to 5 years of age from six participating sites (Vancouver, Toronto, Kingston, Montreal and Halifax). The children had both neurobehavioral and anthropometric follow-up assessments. Participants were eligible for inclusion in this analysis if the mother delivered a live term, singleton infant without a congenital anomaly, had an analyzed cord blood sample and participated in the MIREC-CD Plus Study. We excluded children born prior to 37 weeks gestation as, consistent with previous research,[31] we observed that cord blood leptin and adiponectin levels were lower in this group.

2.2 | Exposure: cord blood adipokines

Cord blood samples were collected following delivery. Leptin and total adiponectin concentrations were measured using assay kits from Meso Scale Discovery (MSD) (Rockville, MD, USA) at Mt. Sinai Laboratory (Toronto, ON, Canada). The inter- and intra-assay coefficient of variations were 12% and 9%, respectively, for leptin and 8% and 9%, respectively, for adiponectin. All samples were above the limits of detection (leptin: 0.04 ng/mL, adiponectin: 0.005 μg/mL).

2.3 | Outcome: child anthropometry variables

Our primary outcome measures were body mass index (BMI), skinfold (SF) sum and ratio z-scores. The sum of subscapular (SSF) and triceps (TSF) skinfold thicknesses is a feasible and reliable measure of estimating total adiposity, whereas the ratio of SSF to TSF provides an estimate of the relative distribution of adiposity.[32,33] Both of the composite measures have been used in previous studies of the association between adipokines and child adiposity.[17,19,22]

At the MIREC-CD Plus biomonitoring home visit, trained research personnel measured the child's weight with a calibrated scale (Seca model 874 [Seca Corporation, Hanover, MD, USA]), standing height using a calibrated stadiometer (Seca model 217 [Seca Corporation, Hanover, MD, USA]) and SSF and TSF using a Lange skinfold caliper (Cambridge Scientific Instruments, Cambridge, MA, USA). All measurements were completed in duplicate and the average of both measured values was used. If the two measures differed by a pre-determined value (weight > 0.1 kg, height > 0.5 cm, SSF > 2 mm, TSF > 2 mm), a third measurement was performed. A third weight, height, TSF and SSF measurement was performed in 24%, 10%, 3% and less than 1% of individuals, respectively. Age- and sex-specific z-scores for BMI were calculated for each child based on WHO Child Growth Standards.[34] Due to the lack of reference standards for skinfold sum and ratio, we developed age- and sex-specific percentile curves within the study sample for these two measures using the LMS method[35]; the raw values from the percentiles were then converted into z-scores.

Individuals with values of z-scores that were greater than five or less than negative five for any of the outcomes measures were removed from the analysis as these values are considered biologically implausible.[36]

2.4 | Covariates

Trained research staff administered questionnaires on sociodemographic characteristics, lifestyle habits and medical and

reproductive history during the first and third trimesters.[29] Maternal height and weight were measured in each trimester; pre-pregnancy weight was self-reported by the mothers and used to calculate pre-pregnancy BMI. Paternal height and weight were measured at the MIREC-CD Plus home visit or reported by the mother if the father was not in attendance. Birthweight and gestational age at delivery data were extracted from medical charts. Each child's birthweight for gestational age z-score was calculated based on a Canadian population-based standard.[37]

2.5 | Statistical analysis

Sample characteristics are presented as counts and percentages, the median (interquartile range [IQR]) of leptin and adiponectin levels were calculated for each stratum, and BMI, SF sum and SF ratio z-scores were summarized using mean and standard deviation (SD). We quantified the association of cord blood leptin and adiponectin with child anthropometric measures (BMI z-score, SF sum z-score and SF ratio z-score) using separate linear regression models. Due to the skewed distributions of both adipokines, we log2-transformed leptin and adiponectin prior to modelling. Using base 2 log transformation allows easy interpretation of regression estimates as a one unit increase in the transformed variable is equivalent to a doubling of the raw variable. We also evaluated the association between cord blood adipokines and risk of having overweight or obesity based on a BMI z-score greater than one using Poisson regression with robust standard errors.[38] Model fit was assessed with regression diagnostics.

Confounders were identified using a directed acyclic graph based on previous literature of determinants of cord blood adipokines and child anthropometric measures and included maternal age,[17] pre-pregnancy BMI,[17,19,30,39,40] gestational weight gain[17,40] and paternal BMI.[17,39] Due to the high correlation between cord blood leptin and birthweight,[7,19] we attempted to remove the effect of birthweight on associations between cord blood adipokines and child growth by additionally adjusting the regression models for birthweight for gestational age z-score. We also tested for interactions and stratified the analyses by child sex. To account for missingness in the covariates, we performed multiple imputation with chained equations (m = 30, 30 iterations).[41]

This study received ethics approval from the Research Ethics Board at the IWK Health Centre (Halifax, NS, Canada), the Research Ethics Board at Health Canada and the Research Ethics committee at Ste. Justine's Hospital (Montreal, QC, Canada). All mothers provided written consent for themselves and their infants. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC) and R version 3.5.2.[42]

3 | RESULTS

Out of the 579 children in MIREC-CD Plus who had cord blood adipokines and anthropometric follow-up assessments, 550 mother–child pairs were included in the present analysis. Of these, 541 children had complete BMI z-score data, 500 had complete SF sum data and 498 had complete SF ratio data. In addition to exclusions due to plurality and prematurity, three children were removed due to either a BMI z-scores greater than 5 or a SF ratio z-scores greater than 5. Mothers of children in this analysis were primarily over 30 years of age at time of delivery, had a normal pre-pregnancy BMI and were of moderate to high socioeconomic status, Caucasians and non-smokers (Table 1). The mean age of children at the time of the MIREC-CD Plus follow-up visit was 42 months (range: 22–75 months). Mean (SD) of BMI, SF sum and SF ratio z-scores were 0.49 (0.88), 0.05 (0.99) and 0.01 (1.07). Twenty-five percent of children were classified as being overweight or having obesity. Median cord blood leptin and adiponectin concentrations were 11 ng/mL (IQR 5.3, 23) and 16 μg/mL (IQR 10, 23), respectively. Median leptin concentrations were 15 (IQR 7.3, 28) among girls and 8.6 among boys (IQR 4.3, 18). Median adiponectin concentrations were similar between boys (16, IQR 9.7, 23) and girls (16, IQR 10, 24). Cord blood adipokines levels by sample characteristics are shown in Table 1.

We observed no statistically significant association between cord blood adipokines and the anthropometric measures in the overall sample (Table 2). In the sex-stratified analyses (Table 3), leptin was weakly inversely associated with BMI z-score among girls in the model adjusted for birthweight for gestational age (model 3). No statistically significant association was observed between leptin and the skinfold measures in either boys or girls. We observed no effect modification between leptin and sex for any of the outcomes (p value for heterogeneity >0.1 for each outcome). Adiponectin was positively associated with both BMI z-score and SF sum z-score in boys but not girls. A doubling of adiponectin was associated with a 0.1 (95% CI 0.01, 0.2) and 0.1 (95% CI 0.01, 0.3) increase in BMI z-scores and SSF + TSF z-scores, respectively. We observed effect modification between adiponectin and sex in the BMI (p = 0.04) and SSF + TSF (p = 0.03) models, but not in the SSF/TSF model (p = 0.68).

We observed no association between either adipokine and overweight/obesity in the overall sample. (Table 4). When stratified by sex and adjusted for the base covariates (model 2), adiponectin was positively associated with overweight/obesity in boys (risk ratio = 1.30, 95% CI 1.02, 1.64) but not in girls. Results were similar in the model adjusted for birthweight for gestational age z-score (model 3). No associations were observed for leptin with overweight/obesity in either boys or girls.

4 | DISCUSSION

In this cohort of Canadian preschool children, we observed sex-specific differences in the associations between cord blood adipokines and child growth. Specifically, cord blood adiponectin levels were positively associated with modest increases in BMI z-scores and the sum of skinfolds in boys but not girls. A doubling of cord blood adiponectin levels was associated with a 30% increased risk of overweight and

TABLE 1 Maternal cord blood leptin and adiponectin concentrations by sociodemographic and pregnancy characteristics (n = 550)

			Leptin [ng/mL]		Adiponectin [μg/mL]	
Characteristic	**Number**	**Percent (%)**	**Median (IQR)**		**Median (IQR)**	
Maternal age at enrollment (years)						
≤ 24	19	(3.5)	13	(5.7, 22)	21	(9.2, 27)
25–29	122	(22)	12	(6.8, 23)	16	(9.7, 23)
30–34	208	(38)	11	(5.5, 23)	16	(10, 23)
≥ 35	201	(37)	10	(4.8, 21)	15	(10, 23)
Pre-pregnancy BMI (kg/m^2)						
< 25	341	(63)	7.3	(1.4, 34)	15	(10, 23)
25–29.9	112	(21)	10	(4.8, 21)	15	(9.5, 23)
≥ 30	86	(16)	12	(6.6, 25)	17	(11, 22)
Parity						
Nulliparous	231	(42)	12	(5.4, 25)	16	(10, 24)
Parous	319	(58)	11	(5.2, 21)	16	(10, 22)
Education						
High school or less	33	(6.0)	10	(4.7, 17)	16	(10, 21)
College, trade school	137	(25)	11	(5.1, 18)	15	(8.3, 23)
Undergraduate degree	238	(43)	12	(5.7, 23)	16	(11, 23)
Graduate degree	140	(26)	10	(4.9, 25)	16	(11, 24)
Household income (CAD)						
≤ $50,000	80	(15)	12	(5.6, 22)	15	(9.2, 23)
$50,001–$100,000	236	(43)	12	(5.7, 24)	16	(10, 24)
≥ $100,001	234	(43)	11	(4.9, 21)	16	(9.8, 23)
Ethnicity						
Caucasian	465	(85)	11	(5.2, 23)	16	(10, 23)
Not Caucasian	85	(15)	11	(6.6, 22)	16	(11, 21)
Maternal smoking						
Never/before pregnancy	503	(91)	11	(5.3, 23)	16	(10, 23)
Quit when pregnant	33	(6.0)	12	(4.6, 20)	13	(8.0, 21)
Current	14	(2.6)	14	(6.7, 23)	19	(12, 33)
Gestational weight gain (IOM)						
Inadequate	86	(16)	11	(4.5, 22)	13	(8.2, 21)
Adequate	165	(32)	9.9	(4.7, 21)	17	(11, 23)
Excessive	272	(52)	12	(5.8, 25)	16	(11, 24)
Paternal BMI (kg/m^2)						
< 25	155	(29)	9.9	(4.8, 20)	16	(11, 23)
25–29.9	254	(47)	11	(5.3, 24)	15	(8.8, 23)
≥ 30	128	(24)	13	(6.5, 23)	17	(11, 24)
Child sex						
Boys	287	(52)	8.6	(4.3, 18)	16	(10, 23)
Girls	263	(48)	15	(7.3, 28)	15	(10, 23)

Note. Missing: Pre-pregnancy BMI 11, Education 2, Income 16, GWG 27, Paternal BMI 13.
Abbreviations: BMI, body mass index; CAD, Canadian Dollar; IOM, Institute of Medicine; IQR, interquartile range.

obesity in boys. No consistent patterns of association were observed in girls. Similarly, analyses of the overall sample revealed no statistically significant association between cord blood adipokine levels and childhood growth.

Though the etiological role of cord blood leptin in child growth has been evaluated in several longitudinal birth cohort studies,[16,19,22,24,25] only two evaluated effect modification by sex.[16,22] The Project Viva Study, a cohort that includes approximately 500

TABLE 2 Linear regression estimates of log2 cord blood leptin and adiponectin and child anthropometric measure z-scores

	BMI	SSF + TSF	SSF/TSF
Model	β (95% CI)	β (95% CI)	β (95% CI)
Leptin [ng/mL]			
M1	0.04 (−0.006, 0.08)	0.02 (−0.03, 0.08)	0.004 (−0.05, 0.06)
M2	0.02 (−0.02, 0.06)	0.01 (−0.04, 0.06)	0.01 (−0.05, 0.07)
M3	−0.04 (−0.09, 0.002)	0.0004 (−0.06, 0.06)	0.007 (−0.06, 0.07)
Adiponectin [μg/mL]			
M1	0.08 (0.007, 0.1)	0.05 (−0.04, 0.1)	0.1 (−0.02, 0.2)
M2	0.07 (−0.03, 0.1)	0.03 (−0.05, 0.1)	0.1 (−0.03, 0.2)
M3	0.03 (−0.03, 0.1)	0.03 (−0.06, 0.1)	0.09 (−0.04, 0.2)

Note. M1: Unadjusted; M2: Adjusted for pre-pregnancy BMI, paternal BMI, maternal age, gestational weight gain; M3: Model 2 plus birthweight for gestational age z-score.
Abbreviations: BMI, body mass index; CI, confidence interval; SSF, subscapular skinfold; TSF, triceps skinfold.

TABLE 3 Linear regression estimates of log2 cord blood leptin and adiponectin and child anthropometric measure z-scores among boys and girls

	BMI	SSF + TSF	SSF/TSF
Model	β (95% CI)	β (95% CI)	β (95% CI)
BOYS			
Leptin (ng/mL)			
M1	0.05 (−0.01, 0.1)	0.02 (−0.06, 0.09)	0.01 (−0.07, 0.09)
M2	0.04 (−0.02, 0.1)	0.007 (−0.07, 0.09)	0.01 (−0.07, 0.09)
M3	−0.02 (−0.08, 0.05)	0.001 (−0.09, 0.09)	−0.002 (−0.09, 0.09)
Adiponectin (μg/mL)			
M1	0.2 (0.07, 0.3)*	0.1 (0.02, 0.3)*	0.05 (−0.08, 0.2)
M2	0.2 (0.05, 0.3)*	0.1 (0.01, 0.3)*	0.05 (−0.08, 0.2)
M3	0.1 (0.01, 0.2)*	0.1 (0.01, 0.3)*	0.05 (−0.09, 0.2)
GIRLS			
Leptin (ng/mL)			
M1	0.04 (−0.02, 0.1)	0.03 (−0.05, 0.1)	−0.004 (−0.09, 0.08)
M2	0.001 (−0.07, 0.07)	0.01 (−0.07, 0.09)	0.004 (−0.09, 0.1)
M3	−0.07 (−0.1, −0.001)*	0.001 (−0.08, 0.09)	0.003 (−0.09, 0.1)
Adiponectin (μg/mL)			
M1	−0.002 (−0.1, 0.09)	−0.002 (−0.1, 0.09)	0.04 (−0.08, 0.2)
M2	−0.02 (−0.1, 0.07)	−0.04 (−0.1, 0.08)	0.04 (−0.09, 0.2)
M3	−0.05 (−0.1, 0.04)	−0.04 (−0.1, 0.07)	0.04 (−0.09, 0.2)

Note. M1: Unadjusted; M2: Adjusted for pre-pregnancy BMI, paternal BMI, maternal age, gestational weight gain M3: Model 2 plus birthweight for gestational age z-score.
Abbreviations: BMI, body mass index; CI, confidence interval; SSF, subscapular skinfold; TSF, triceps skinfold.
*$p < 0.05$.

mother–child pairs recruited from Massachusetts, USA, examined cord blood leptin and child growth at age 3 years. Consistent with our findings, the authors found no association between maternal leptin and BMI z-score at age 3; sex-specific results were not presented.[16] The Rhea study, a cohort of Greek mother–child pairs (n = 578), reported an inverse association between cord blood leptin levels and BMI that was slightly stronger in boys than girls at age 4.[22] These findings contrast our observed lack of statistically significant interactions in the leptin models, but the use of raw BMI rather than BMI z-score as the primary outcome measure in the Rhea study precludes direct comparison with our results.

To our knowledge, no study has evaluated sex-specific results of the association between cord blood adiponectin and child growth. This finding is interesting considering that, unlike cord blood leptin

TABLE 4 Poisson regression of the association between log2 cord blood adiponectin and child overweight or obesity

	Overweight or obesity RR (95% CI)		
Model	**All**	**Boys**	**Girls**
Leptin [ng/mL]			
M1	1.05 (0.965, 1.15)	1.08 (0.958, 1.22)	1.05 (0.908, 1.21)
M2	1.02 (0.938, 1.12)	1.07 (0.945, 1.22)	0.972 (0.847, 1.11)
M3	0.949 (0.864, 1.04)	1.02 (0.887, 1.17)	0.879 (0.762, 1.02)
Adiponectin [μg/mL]			
M1	1.15 (0.977, 1.35)	1.35 (1.09, 1.68) *	0.985 (0.804, 1.21)
M2	1.13 (0.962, 1.33)	1.30 (1.02, 1.64) *	0.963 (0.790, 1.17)
M3	1.09 (0.932, 1.28)	1.26 (1.02, 1.57) *	0.929 (0.767, 1.13)

Note. BMI z-score ≥ 1. M1: Unadjusted; M2: Adjusted for pre-pregnancy BMI, smoking, paternal BMI, maternal age, gestational weight gain; M3: M2 plus birthweight for gestational age z-score.
Abbreviations: BMI, body mass index; CI, confidence interval; RR, risk ratio.

where sex-specific differences are apparent at birth, adiponectin levels are relatively similar in both sexes throughout childhood, yet may diverge in adolescence. A study of Mexican-American children reported no differences in adiponectin levels between boys and girls from birth to age 9.[43] In non-stratified analyses, cord blood adiponectin has been positively associated with the SSF/TSF ratio at age 3 in Project Viva,[19] with body composition at age 3 in twins[23] and with fat mass at 2 weeks but not 3 months in offspring of African American women.[26] In addition, authors of a study in Oklahoma reported that cord blood levels of high molecular weight adiponectin were positively associated with three measures of adiposity (SSF, body weight and percent fat) in male and female infants at 1 month of age.[44] Null findings between adiponectin and multiple anthropometric measures (eg, BMI z-score and fat mass) have also been observed at age 9[24] and age 5.[25] Our finding of stronger associations in males raises the question of whether the population-level effects observed in these studies would have been strengthened in the subset of male study participants.

Several physiological mechanisms may underlie the observed differences by sex in the adiponectin-growth associations. Lower oestrogen concentrations in males may heighten male susceptibility to the adverse effects of maternal adiposity and fetal hormone concentrations. The placenta of male fetuses may be more susceptible to environmental stressors and obesity than the female placenta.[45] It is possible that these oestrogen- and placental-driven mechanisms translate into sex differences in the adiponectin but not leptin models. Males and females may respond to adipokine hormone differently due to underlying differences in fat distribution with males being characterized by a greater distribution of visceral fat than subcutaneous fat. For example, the brains of male rats have been shown to be more sensitive to insulin than female rats.[46] We raise the question of whether adiponectin, as an indicator of insulin resistance, may similarly evoke different responses in males compared to females. Cord blood adiponectin has been shown to be positively associated with reduced beta cell function at age 1 in a pregnancy cohort in Montreal, Canada[47]; sex-specific differences were not reported. On the other hand, because fetal fat distribution is similar between sexes,[48] it is possible that sex-specific hormonal responses may not be apparent until later in life.

Adiponectin levels are highest at birth and decrease with age. The positive correlation between adiponectin and birthweight transitions to a negative correlation between adiponectin and both adult weight and insulin resistance.[14] Children with higher rates of weight gain and BMI during infancy tend to have lower adiponectin levels in early adolescence.[43] There is limited evidence that low adiponectin levels in early adolescence are linked to an increased risk of metabolic syndrome.[49] In light of these temporal changes and the complexity of adiponectin's physiological effects, it is not possible to infer long-term clinical implications from the present study. Further follow-up of children in the MIREC study will also enable analyses of the trajectory of adiponectin to determine if boys with high cord blood levels tend to have lower levels in adolescence.

Our findings of largely null associations with leptin in the full sample are relatively consistent with previous research demonstrating null or small effects. Studies that have found inverse associations between leptin and early childhood growth tended to observe that inverse associations are present in childhood prior to adolescence – during the time of leptin sensitivity – and are attenuated with increasing age as tolerance to the effects of leptin on metabolism and satiety are developed.[17,24]

The strengths of this study are the prospective national-level data and ability to control for key confounders. We were limited by a relatively small sample size and lack of uniform follow-up time; we attempted to correct for the latter issue using age and sex specific z-scores. Moreover, given the unique composition of the MIREC cohort, our findings may not be generalizable to studies of differing socioeconomic composition or ethnicity.

In conclusion, we observed that cord blood adiponectin was positively associated with modest differences in child adiposity in boys but not girls. These findings underscore the importance of evaluating potential effect modification by sex and motivate further investigation regarding the temporal patterns of adiponectin, child growth and

development of adverse body composition and cardiometabolic profiles.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests. All authors have completed the ICMJE COI disclosure form and have no conflicts to disclose.

AUTHOR CONTRIBUTIONS

JAM wrote the initial manuscript draft, conducted the analysis, and contributed to the design of the study. MDK contributed to the data analyses and writing of the manuscript. LD and SK conceptualized and designed the study and contributed to the analysis. GM is a principal investigator of the MIREC-CD Plus study and TEA and WDF of the MIREC study. LD, AE, GM, BL, PM and MF are all co-investigators on the MIREC study. All authors reviewed, revised and approved the final manuscript as submitted.

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