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Profiles and predictors of child neurodevelopment and anthropometry: The maternal-infant research on environmental chemicals study

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Abstract

Background: Evaluating individual health outcomes does not capture co-morbidities children experience.

Purpose: We aimed to describe profiles of child neurodevelopment and anthropometry and identify their predictors.

Methods: Using data from 501 mother-child pairs (age 3-years) in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a prospective cohort study, we developed phenotypic profiles by applying latent profile analysis to twelve neurodevelopmental and anthropometric traits. Using multinomial regression, we evaluated odds of phenotypic profiles based on maternal, sociodemographic, and child level characteristics.

Results: For neurodevelopmental outcomes, we identified three profiles characterized by Non-optimal (9%), Typical (49%), and Optimal neurodevelopment (42%). For anthropometric outcomes, we observed three profiles of Low (12%), Average (61%), and Excess Adiposity (27%). When examining joint profiles, few children had both Non-optimal neurodevelopment and Excess Adiposity (2%). Lower household income, lower birthweight, younger gestational age, decreased caregiving environment, greater maternal depressive symptoms, and male sex were associated with increased odds of being in the Non-optimal neurodevelopment profile. Higher pre-pregnancy body mass index was associated with increased odds of being in the Excess Adiposity profile.

Conclusions: Phenotypic profiles of child neurodevelopment and adiposity were associated with maternal, sociodemographic, and child level characteristics. Few children had both non-optimal neurodevelopment and excess adiposity.

Keywords

Anthropometry, child health, co-occurring conditions, multimorbidity, neurodevelopment, phenome

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Introduction

One in eleven children in Canada, (age 4-11) have a neurodevelopmental disability.[1]

Children with developmental disabilities are more likely to have other diagnosed psychopathology and poorer physical health than typically developing peers.[2,3] The presence of co-occurring conditions creates additional barriers above and beyond challenges of individual health conditions.[4] Thus, studying multiple dimensions of children's health may more accurately identify vulnerable subgroups experiencing multimorbidity.

Prior research has highlighted the importance of evaluating all aspects of health by characterizing its parts as a 'phenome' – patterns and profiles of disease states across the life course.[2,3,5] Considering multimorbidity has been increasingly adopted in psychology as research moves away from distinct psychiatric disorders classified within the Diagnostic and Statistical Manual of Mental Disorders (DSM) towards Research Domain Criteria because bio-behavioral features often overlap with heterogeneously defined disorder categories.[6] The notion that children experience shared symptomatology across discretely defined disorder diagnostic categories has also be applied in clinical settings (e.g., Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations [ESSENCE]) to recognize the need for multiple practitioners to support children experiencing multimorbidity.[7] In fact, clinical practice focused on individual childhood conditions may disadvantage children with multimorbidity.[8] For example, individuals with autism spectrum disorder often also have attention deficit hyperactivity disorder,[9] and are more likely to have overweight or obesity compared to their typically developing peers.[10,11,12] Several early life risk factors are associated with both adverse physical and neurodevelopment outcomes. For instance, children who are born preterm are at heightened risk of atypical neurodevelopment and adverse physical health outcomes.[13,14] Moreover, some environmental pollutants (i.e., lead[15]) are risk factors for altered growth and atypical neurodevelopment, suggesting shared mechanisms that these factors disrupt. Thus, there is a need to consider both salutogenesis, as in the study of the origins of health,[16] as well as pathogenesis, as in the factors that cause disease,[17] when investigating the predictors of child health. Additionally, other fields of children's health, including children's environmental health, have emphasized the need to evaluate the complex existence of multiple exposures at once, applying sophisticated methods to capture the effects of exposure mixtures. However, health outcomes are commonly evaluated individually, despite evidence for multimorbidity, emphasizing the need to employ statistical approaches to characterize the co-occurrence of child health outcomes. While pediatricians have recognized that some children experience multimorbidity, relatively little research has characterized aspects of the child health phenome as a primary outcome.

The purpose of this study was to describe patterns and predictors of neurodevelopment and adiposity using exploratory data analysis, clustering, and multivariable techniques in a prospective birth cohort.

Methods

Study participants

We used data from the Maternal-Infant Research on Environmental Chemicals (MIREC) Study, a pan-Canadian, prospective cohort designed to assess the impact of environmental chemical and nutritional exposures on maternal, infant, and child health.[18] Pregnant women in their 1st trimester were recruited from 10 cities (11 sites) across Canada from 2008-2011. Eligibility including: ≥ 18 years of age, <14 weeks' gestation, willing to provide cord blood samples, planning on delivering at a local hospital, and no known fetal abnormalities or serious medical complications. Of 8,716 women invited to participate, 5,108 were eligible, 2,001 consented, and 1,861 delivered singleton live births. In-person follow-up around age 3-years was completed at 7 study sites (6 cities) on 610 children. Note, distributions of participant characteristics for those who completed in-person follow-up were similar between those from eligible sites for the child follow-up visits as well as the original MIREC pregnancy cohort.[19] After excluding those with missing outcome data (n=109), our final analytic sample was 501 children (eFigure S1).

The MIREC Study was approved by the Research Ethics Board of Health Canada, and all participating study sites' ethics review committees. All mothers provided informed consent for themselves and their participating children.

Child Neurodevelopment and anthropometry

Neurodevelopmental assessments and anthropometric measures of children were done at age 3-years (range: 3-3.9; SD: 0.32) in the participants' homes or study clinics. Research staff assessed child cognitive abilities using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III).[10] The WPPSI is a validated assessment of child full scale intelligence for children aged 2.5 years to 7 years, administered by trained examiners.[20,21] The WPPSI derives a full-scale composite score (mean: 100 and SD: 15) and also provides subsets and composite scores including verbal compression and working memory. Scores were found to be stable overtime within children based on test-retest analyses.[22]

Behavior problems were assessed by maternal-report using the Behavioral Assessment System for Children (BASC-2).[23] The BASC-2 is a reliable and valid assessment

of child problem behaviors for children.[24] This 185-item behavior checklist can be administered by parents, teachers, or even via self-report. There are four primary composite scores including externalizing problems, internalizing problems, behavior symptoms index, and adaptive skills, with an additional 12 clinical subscales. Raw scores were converted to sex-normalized T-scores (mean: 50, SD: 10) based on US reference data.

Finally, social cognition was assessed with the Social Responsiveness Scale (SRS-2).[25] The SRS is a 65-item, Likert style questionnaire used to assess social reciprocity and autism-related traits that yields dimensional scores.[24,25] Based on caregiver report, individual items are scored and summed to yield a total raw score. Raw scores were converted to sex-normalized T-scores (mean: 50, SD: 10) based on US reference data. Higher scores are indicative of more autism-related behaviors. The SRS has well-established psychometric properties within both autism specific and general population samples,[26,27] and demonstrated validity against the gold standard Autism Diagnostic Interview-Revised (r=0.7).[25,28] See section "Child Health Components" for methods related to select phenome components.[29,30]

Trained research assistants assessed weight, height, head/waist/hip circumferences, and subscapular and triceps skinfold thickness at the time of, or within 6 months of the neurobehavioral visit. Length was measured with a portable stadiometer to the nearest 0.1 cm and weight using a digital scale to the nearest 2 grams. Head, waist, and hip circumferences were measured using a measuring tape and established protocols.[31] Using standardized procedures, a caliper was used to estimate subscapular and triceps skinfold thickness. Two measures were taken for all anthropometric characteristics, except in cases of discrepancies, which required a third measure.

Covariates

We identified maternal, reproductive, and child level characteristics as potential predictors *a priori* based on subject matter knowledge for their associations with child health outcomes based on prior literature. Mothers reported covariate information during the 1st trimester (baseline), as well as during the age 3-year follow-up visit using standardized questionnaires. Mothers self-reported parity and pre-pregnancy body mass index (BMI) using standardized questionnaires during the baseline visit and information on breastfeeding practices at the 3-year visit. Increased parity may negatively correlate with child neurodevelopment, in part due to the impact of multiple children on familial resources.[32] Increased pre-pregnancy BMI has been associated with both atypical neurodevelopment[33] and increased adiposity in children.[34]

Breastfeeding has been found to have a dose-response relation with elevated cognition scores in and may even be protective against conduct disorder development in children.[11] Additionally, at least three months of exclusive breastfeeding was found to decrease the risk to child obesity, even across maternal pre-pregnancy BMI categories.[12] Study staff measured plasma cotinine in the 1st trimester to assess active and environmental tobacco smoke exposure.[35] Both first and secondhand tobacco smoke exposure during pregnancy have been associated with increases in child autism-related traits,[36] decreases in IQ scores,[37] and increased likelihood of overweight or obesity.[38] Infant birthweight and gestational age at birth were ascertained via medical chart review. Low birth weight and preterm birth are established risk factors for neurodevelopmental outcomes like autism[39] and intellectual disability.[40] Study staff measured quality and quantity of the caregiving environment using the Home Observation for Measurement of the Environment (HOME Inventory),[41] and assessed maternal depressive symptoms using the Center for Epidemiologic Studies Depression scale (CES-D) at the 3-year visit.[42] Prior work has observed associations between higher quality caregiving environments with child cognitive development.[43] Additionally, elevated maternal depressive symptoms may be inversely related to child cognition[44] and executive functioning.[45]

Statistical analyses

Child health components. We conducted exploratory analysis to examine associations between neurodevelopmental and anthropometric outcomes. First, we examined univariate distributions of characteristics for neurodevelopment and anthropometry (e.g., range, central tendency). Then, we calculated correlations among individual measures, examining both composite and subscale scores for neurodevelopmental outcomes.

Next, we conducted principal component analyses (PCA) to determine which individual outcomes to include in phenotypic profiles, which were identified using LPA, given that some individual health measures may be highly correlated with each other and each might not be distinctly informative of multimorbidity patterns (e.g., subscales of cognitive tests). We conducted PCAs that were restrictive (only summary scales) and comprehensive (inclusion of subscales and composite scores). We examined Scree plots and evaluated principal components with Eigenvalues ≥ 1. Through these analyses, we included the WPPSI-III full scale intelligence quotient (FSIQ), SRS total T-score, and four BASC composite scores: Externalizing Problems, Internalizing Problems, Behavioral Symptoms Index (BSI), and Adaptive Skills. For anthropometric health outcomes, we considered all available measures including head, waist, and hip circumferences, subscapular and triceps skinfold thickness, and derived BMI from weight and height measures.

Phenotypic profiles. Our goal was to develop distinct neurodevelopmental and anthropometric profiles using latent profile

analysis (LPA, R package tidyLPA) and then examine their joint distribution and predictors. To account for varying scales of individual outcomes, we converted all measures to z-scores. For anthropometric outcomes, we derived age- and sex-standardized z-scores using World Health Organization (WHO) standards[46] and used the R package "anthro". For anthropometric outcomes without WHO standards, we regressed their values on child sex, age, and a sex/age interaction term to estimate age and sex-specific values from the residuals of these models. Next, we calculated Pearson correlation coefficients to assess bivariate associations between individual neurodevelopmental and anthropometric outcomes.

Given that neurodevelopmental and anthropometric outcomes were not correlated, we conducted independent LPAs within each domain of neurodevelopment and anthropometry. LPA is a dimension reduction technique used to identify clusters (latent classes) based on observed variables, allowing for the identification of distinct subpopulations based on similarities of selected observed variables.[47] LPA is a type of 'soft clustering' technique, in that it assigns individuals a probability of cluster assignment, offering a more flexible approach to identifying latent class membership than k-means or other techniques.[47] We refer to the latent classes of neurodevelopment and anthropometry as phenotypic profiles. We assumed equal variance and zero covariance between individual health measures when conducting LPAs. We ran separate analyses assuming 2, 3, and 4 clusters. To identify the best fitting model, we considered both Bayesian Information Criterion values and the sample size of resulting clusters.

We created joint phenotype profiles by cross classifying profile assignments based on results from domain-specific LPA analyses to identify participants with optimal neurodevelopment and anthropometry, those with non-optimal neurodevelopment or adiposity only, and those with both non-optimal neurodevelopment and excess adiposity.

Patterns and predictors of phenotypic profiles. Using multinomial logistic regression, we calculated the odds of phenotypic profile membership based on identified predictors, examining each variable in a separate model. Given the relation between birthweight and gestational age, we also included a model with both birthweight and gestational age. From these analyses, we identified a set of covariates predictive of profile membership based on results from individual models (p-value ≤ 0.05). We standardized associations for continuous variables (i.e., maternal age) to the standard deviation difference in exposure. We then conducted multivariable multinomial logistic regression analyses where we included all previously identified significant covariates associated with phenotypic profile membership. The Typical neurodevelopmental profile and the Average Adiposity anthropometric profile served as domain specific reference groups.

To account for uncertainty in latent class assignment, we conducted sensitivity analyses incorporating classification error into our parameter estimates.[48] We conducted multinomial regression with complex survey design, using the R package svyVGAM, where each individual participant was a cluster, using an independent correlation matrix.

We used R version (4.1.0) for all statistical analyses.

Results

Participant characteristics

Mothers were mostly 30 years old at delivery, university-educated (68%), with annual household incomes ≥ $80,000 (58%) (Table 1). Most were Canadian born (83%), did not smoke during pregnancy (65%), used prenatal vitamins (87%), had normal or underweight pre-pregnancy BMI (58%), almost half were nulliparous (44%) and exclusively breastfed for at least 6 months (43%). Distributions of mother and child characteristics were similar among the analytic sample and those who were eligible for participation at age 3-years, but were excluded (Table 1).

Most children had optimal neurodevelopment and anthropometry (eTable 1). For example, measures of child cognitive abilities were higher than the expected average of 100 (FSIQ mean: 107, SD: 14), and mean BMI was slightly higher than the WHO reference sample (mean: 16.1; SD: 1.3).[49] Individual neurodevelopmental measures and anthropometric outcomes were correlated within domains, but not across (Figure 1, eTable 2).

Profile description. We identified 3 profiles of neurodevelopment characterized as Non-optimal, Typical, and Optimal (eFigure 2). Non-optimal profiles of neurodevelopment (n=45, 9%) were characterized by lower FSIQ and BASC Adaptive Skills scores, and higher SRS, BASC Externalizing, BASC Internalizing, and BASC BSI scores, indicating lower cognitive abilities, less adaptive behaviors, reduced reciprocal social behaviors, and more problem behaviors (eTable 1). Typical (n=247, 49%) and Optimal (n=219, 42%) neurodevelopmental profiles were characterized by average and above average FSIQ scores, respectively, and lower SRS, BASC Adaptive Skills, Externalizing, Internalizing, and BSI scores compared to the non-optimal profile. BASC BSI scores displayed the largest differences between Non-optimal (mean: 64, SD: 4.2), Typical (mean: 53, SD: 3.2), and Optimal (mean: 45, SD: 3.6) neurodevelopmental profiles. Average values of anthropometry did not vary between neurodevelopmental profiles (Figure 2, eTable 1).

We identified three profiles of anthropometry. Children in Low (n=60, 12%), Average (n=306, 61%), and Excess (n=135, 27%) Adiposity profiles were characterized by lower, average,

Table 1. Mother and child sociodemographic and perinatal characteristics among MIREC Study Participants.

	Analytic sample	Eligible for age 3-years
Variable	N (%)	N (%)
Overall	501 (100)	1,568 (100)
Maternal age		
<25 years	13 (3)	94 (6)
25 - <30 years	107 (21)	358 (23)
30 - <35 years	209 (42)	585 (37)
35 + years	172 (34)	531 (34)
Missing	0	0
Maternal education		
High school or less	20 (4)	132 (8)
Some college	19 (4)	78 (5)
College/Trade school	119 (24)	361 (23)
University degree	341 (68)	995 (63)
Missing	2	2
Maternal country of origin		
Canadian born	414 (83)	1256 (80)
Foreign born	87 (17)	312 (20)
Missing	0	0
Annual income (terciles)		
<$70k	129 (26)	465 (30)
$70-$100k	160 (32)	439 (28)
>$100k	195 (39)	601 (38)
Missing	17	63
Maternal smoking status[a]		
Unexposed	328 (65)	840 (54)
Second-hand smoking	153 (31)	612 (39)
Active smoking	14 (3)	95 (6)
Missing	6	21
Parity		
0	222 (44)	695 (44)
1	215 (43)	640 (41)
2 +	64 (13)	233 (15)
Missing	0	0
Pre-pregnancy BMI (kg/m2)		
Normal/Underweight <25	293 (58)	924 (59)
Overweight ≥25 - <30	93 (19)	325 (21)
Obese ≥30	78 (16)	209 (13)
Missing	37	110
Prenatal vitamin use		
Yes	434 (87)	1367 (87)
No	67 (13)	200 (13)
Missing	0	1
Child sex		
Male	248 (50)	735 (47)
Female	253 (50)	834 (53)
Missing	0	0
Exclusive breastfeeding		
≥ 6 months	214 (43)	255 (16)
< 6 months	168 (34)	193 (12)
Missing	119	1120

(continued)

Table 1. (continued)

Variable	Analytic sample N (%)	Eligible for age 3-years N (%)
Gestational age		
< 34 weeks	<6 (1)	37 (2)
34 - < 37 weeks	>21 (4)	42 (3)
≥ 37 weeks	>473 (95)	1419 (90)
Missing	0	24
Birthweight (grams)		
Mean (SD)	3455 (518)	3435 (518)
Missing	2	2

MIREC: Maternal-infant research on environmental chemicals study; BMI: Body Mass Index; SD: Standard deviation.
[a]maternal smoking during pregnancy estimated based on maternal plasma cotinine concentrations during pregnancy. Values ≤ 0.15ng/ml were considered unexposed, >0.15 - 3.0 ng/ml as second-hand smoking, and >3.0 ng/ml as active smoking.Note, in an effort to protect participant confidentiality, we did no present exact values for cells less than 6.

and higher BMI, waist and hip circumference, as well as triceps and subscapular skinfold thickness measures, respectively (eTable 1, Figure 2). Head circumference values were similar between the Low and Average Adiposity profiles and were only slightly higher for the Excess Adiposity profile. Waist circumference provided the clearest differentiation of class assignment for Low (mean: 43.6cm, SD: 2.37), Average (mean: 49.5cm, SD: 2.19), and Excess Adiposity profiles (mean: 54.9cm, SD: 2.82).

When cross-classifying neurodevelopmental and anthropometric profiles, we identified four profiles characterized by Optimal/Typical neurodevelopment and Low/Average Adiposity (n=331, 66%: Phenotypic Profile 1), Optimal/Typical neurodevelopmental and Excess Adiposity (n=125, 24%: Phenotypic Profile 2), Non-optimal neurodevelopment and Low/Average Adiposity (n=35, 6%: Phenotypic Profile 3), Non-optimal neurodevelopment and Excess Adiposity (n=10, 2%: Phenotypic Profile 4) (eTable 3, Figure 2). Given small sample sizes, we did not conduct statistical analyses on joint profiles.

Predictors of profiles. Lower maternal age, annual household income, male child sex, younger child age at testing, lower HOME scores, lower birthweight, lower gestational age at birth, and higher CES-D scores were associated with increased odds of Non-optimal neurodevelopmental profile assignment (Figure 3, eTable 4). For example, each standard deviation increase in maternal CES-D scores was associated with 42% increased odds of the child being assigned to the Non-optimal versus the Typical neurodevelopmental profile (95% CI: 1.08, 1.87). Children assigned to the Optimal neurodevelopmental profile were more likely to be female, and had mothers who were older, with higher household incomes, and lower plasma cotinine concentrations (eTable 5). In multivariable models, child sex, child age, HOME scores, and CES-D scores remained predictive of profile membership (eTable 6). When we further examined HOME and CES-D scores as quartiles, we found that both were monotonically associated with odds of Optimal or Non-Optimal neurodevelopmental profile assignment (Figure 5, eTable 7).

Higher birthweight (including adjusted for gestational age) or having a mother with overweight or obese pre-pregnancy BMI, was associated with higher odds of Excess Adiposity profile assignment (Figure 4, eTable 4). For example, compared with those who were classified as having normal or underweight pre-pregnancy BMIs, children with mothers who had pre-pregnancy obesity had 67% increased odds of being in the Excess Adiposity profile (95% CI: 0.96, 2.90). We also found that maternal nativity (birth outside Canada), higher annual household income, and shorter gestational ages at birth were associated with greater odds of membership in the Low Adiposity profile (eTable 8). In multivariable models, overweight pre-pregnancy BMI, birthweight, and gestational age at the time of birth remained predictive of anthropometric profile membership (eTable 6).

Characteristics of mothers and children in the joint profiles were similar to analyses examining distinct profiles of neurodevelopment and anthropometry (eTable 9). For example, children who had mothers with higher pre-pregnancy BMIs were more likely to be classified in Phenotypic Profile 2 compared to 1 and 3. Boys were more likely to be classified in Phenotypic Profile 3 compared to girls. However, result should be interpreted with caution given the small sample size of this joint profile. Note, we did not present results pertaining to Phenotypic Profile 4 given the small sample size to protect participant confidentiality.

Sensitivity analyses

Accounting for classification error in the probability of an individual being assigned to a given phenotypic profile did not substantially alter the pattern of results. Point estimates remained largely the same, and in some cases, precision slightly increased, indicating attenuation bias (eTables 10-12).

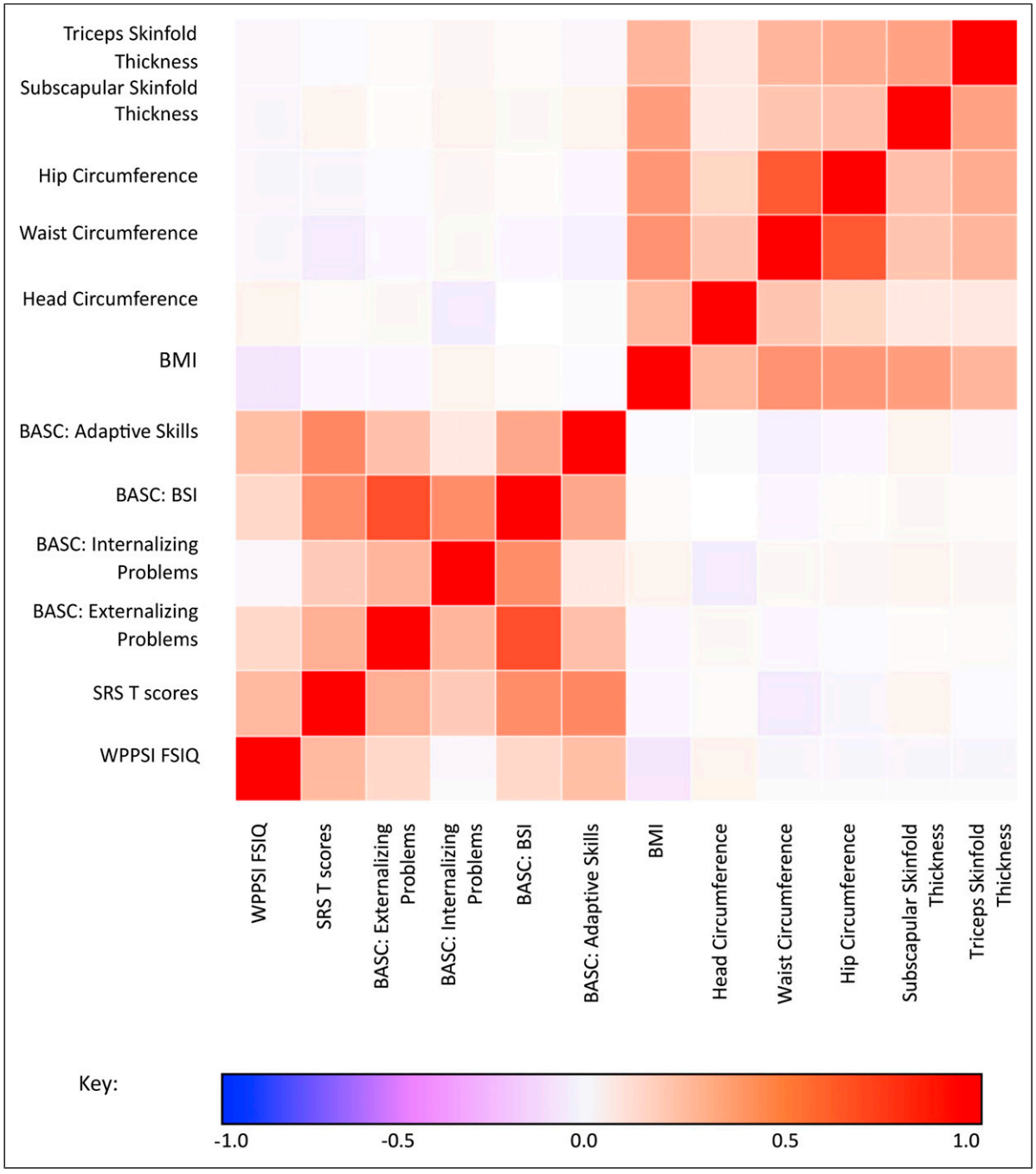

Figure 1. Heat map of Pearson correlations among all individual phenome z-score components among MIREC Study Participants. Z-scores of selected outcomes (SRS T-scores, BASC: Externalizing Problems, BASC: Internalizing Problems, BASC: Behavioral Symptoms Index) were reverse scored so the direct of the scores would be the same across all neurodevelopmental outcomes. For example, lower WPPSI FSIQ scores indicate lower cognitive abilities, and reverse scored SRS T-scores indicate more autism related traits.

Discussion

Using dimension reduction techniques to classify parts of the child health phenome, we identified 3 neurodevelopmental profiles, characterized by Non-optimal, Typical, and Optimal neurodevelopment, and 3 profiles of anthropometry, defined by Low, Average, and Excess Adiposity using LPA. When neurodevelopmental and anthropometric profiles were examined jointly, few children had Non-optimal neurodevelopment and Excess Adiposity. Some sociodemographic, maternal, and child characteristics predicted profile membership in both domains, while others

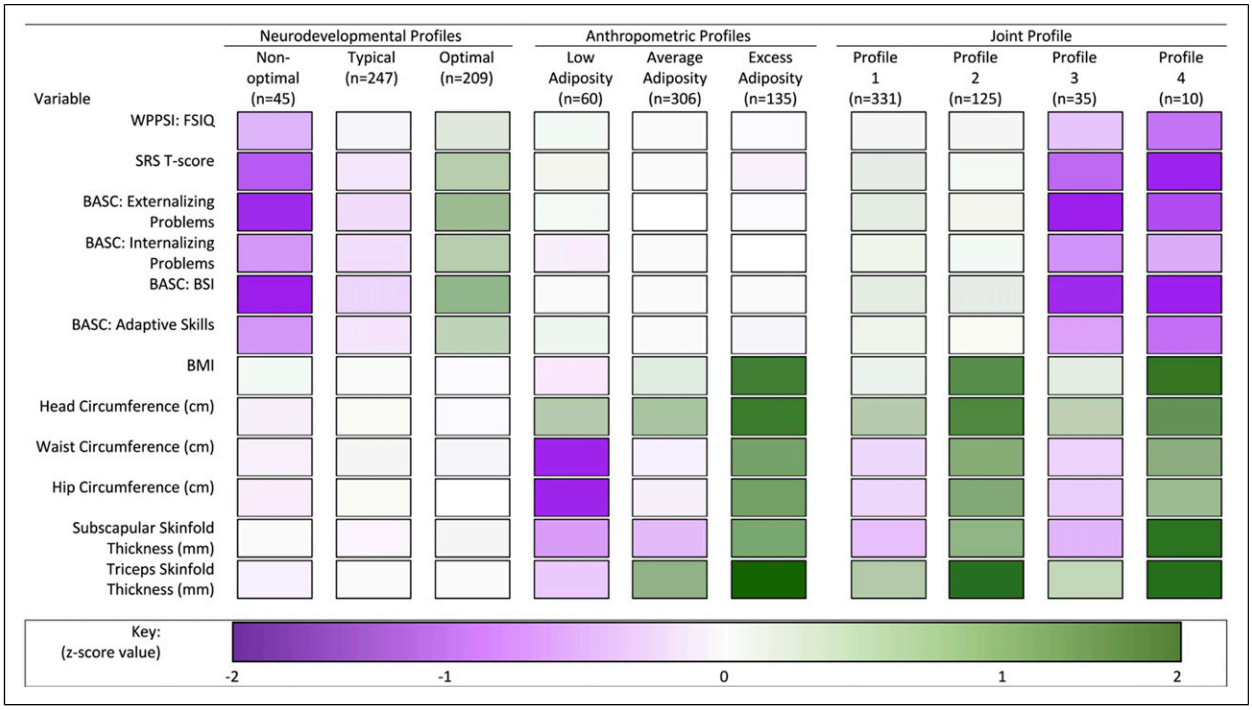

Figure 2. Heat map of mean z-scores of individual health outcomes for neurodevelopmental and anthropometric classes and joint phenotypic profiles among MIREC study participants. For neurodevelopmental outcomes: Non-optimal: (n=45) are characterized by lower cognitive abilities and more problem behaviors, Typical: (n=247) are characterized by average scores on all neurodevelopmental assessments, and Optimal: (n=209) are characterized by higher cognitive abilities and less behavior problems. Note, z-scores of selected outcomes (SRS T-scores, BASC: Externalizing Problems, BASC: Internalizing Problems, BASC: Behavioral Symptoms Index) were reverse scored so the direct of the scores would be the same across all neurodevelopmental outcomes. For example, lower WPPSI FSIQ scores indicate lower cognitive abilities, and reverse scored SRS T-scores indicate more autism related traits. For Anthropometric outcomes: Low Adiposity: (n=60) are characterized be less adiposity, Average Adiposity: (n=306) are characterized by average or medium adiposity, Excess Adiposity: (n=135) are characterized by increased adiposity. Phenotypic Profile 1 (n=331) is characterized by Optimal or Typical Neurodevelopmental Profiles and Low or Average Adiposity Anthropometric Profiles. Phenotypic Profile 2 (n=125) is characterized by Optimal or Typical Neurodevelopmental Profiles and Excess Adiposity Anthropometric Profiles. Phenotypic Profile 3 (n=35) is characterized by Non-typical Neurodevelopmental Profiles and Low or Average Adiposity Anthropometric Profiles. Phenotypic Profile 4 (n=10) is characterized by Non-Optimal Neurodevelopmental Profiles and Excess Adiposity Anthropometric Profiles.

were specific to neurodevelopment (e.g., caregiving environment) or anthropometry (e.g., pre-pregnancy BMI).

While patterns of multimorbidity have previously been studied in children, relatively little research has evaluated neurodevelopment and anthropometry together. One study explored the co-occurrence of 57 chronic morbidities, and found children with complex medical conditions could be classified into four groups within the domains of oncology, neurodevelopment, congenital and perinatal, and respiratory conditions.[4] Another study observed that children with many co-occurring conditions, identified as medical conditions resulting in pediatric intensive care unit hospitalization, are at an increased risk of developing mental health related illnesses, such as post-traumatic stress disorder.[50] Thus, multimorbidity in early childhood may be a risk factor for development of adverse health later in life.

The observation that child neurodevelopmental and anthropometric outcomes overlap is not novel. However, the findings of this study support that phenotypic profiles are a method to consider when assessing multiple health outcomes. Indeed, this is consistent with clinical recommendations recognizing the overlap of symptomatology across psychiatric diagnoses,[6–8] a single-outcome-at-a-time approach does not account for the frequency of co-occurring health outcomes and the reality of child health status. Additionally, from an etiologic perspective, there is reason to consider comprehensive measures of health outcomes rather than individual outcomes, given how the same environmental exposures are associated with multiple child outcomes. For example, gestational phthalate levels have been associated with both atypical neurodevelopment[51–54] and childhood obesity.[55] Finally, other fields have explored statistical approaches to capturing multiple, overlapping

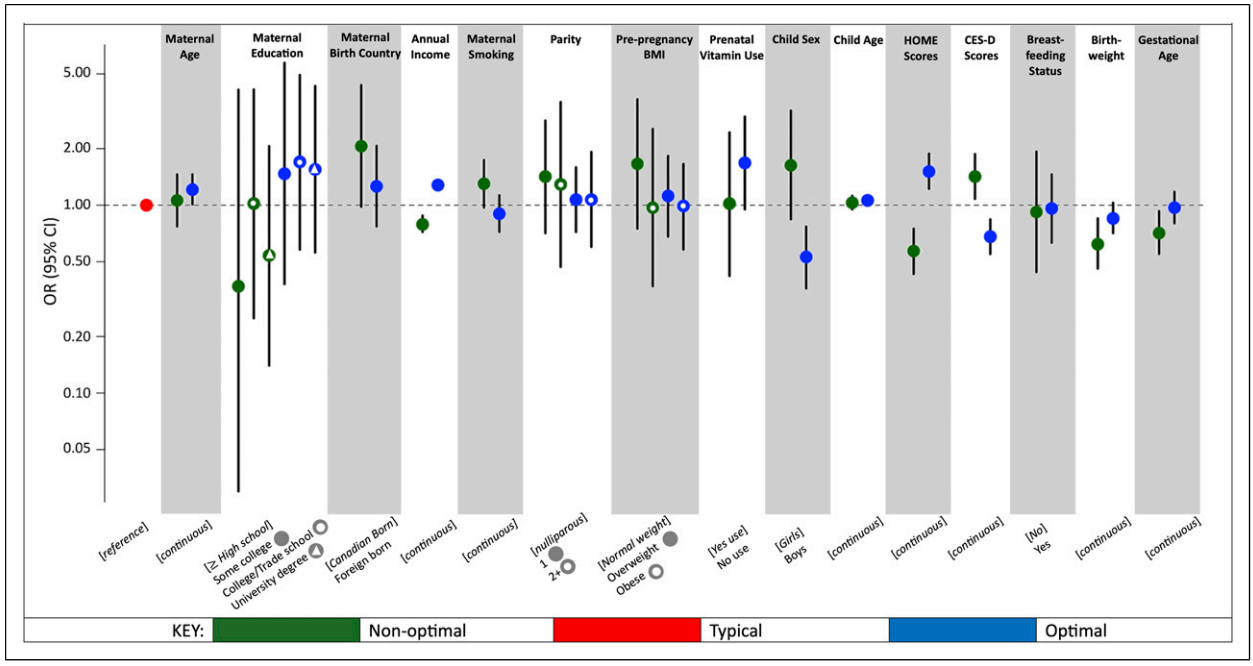

Figure 3. Bivariate associations of maternal and child sociodemographic and perinatal covariates with neurodevelopmental profiles among MIREC Study participants. Odds ratios and 95% confidence intervals for the association between individual covariates and class assignment are displayed for neurodevelopmental profiles on the left column, and anthropometric profiles on the right column. The Medium Scores class (Neurodevelopmental Profile) serves as the reference group. For individual, categorical covariates, the category displayed in brackets and is italicized serves as the reference category. Note, the x-axis is displayed on the log scale. For neurodevelopmental outcomes: Non-optimal: (n=45) are characterized by lower cognitive abilities and more problem behaviors, Typical: (n=247) are characterized by average scores on all neurodevelopmental assessments, and Optimal: (n=209) are characterized by higher cognitive abilities and less behavior problems. Note, the following variables are scaled by the standard deviation: maternal age (SD: 4.5), annual income ($25,750), HOME scores (4.4), CES-D scores (4.3), birthweight in grams (518), and gestational age at the time of delivery (1.6). Maternal smoking status based on $\log_{10}$-transformed plasma cotinine concentrations from the first trimester of pregnancy. Breastfeeding status is defined as those who did breastfeed exclusively for at least 6 months compared to those who did not.

factors, such as chemical mixtures analyses in environmental health. Thus, this work serves as a proof-of-concept, and future work may consider evaluating "mixtures" of health outcomes as a method to more accurately capture child health status.

Unique to our study, we identified neurodevelopmental and anthropometric profiles, and considered joint phenotypic profiles. Given the understanding that neurodevelopmental features overlap,[2,3] we anticipated high correlations among neurodevelopmental assessments. While our dimension reduction approach to classifying neurodevelopment was not specific to children with diagnosed neurodevelopmental disorders, our findings support prior work emphasizing the need to consider continuous behavioral and cognitive features to characterize presentations of neurodevelopment to better reflect the diversity of neurophenotypes that may not be captured by specific diagnoses.[9]

Similar to our findings, others have reported high correlations among multiple anthropometric measures, such as BMI and waist circumference.[56] Given the high correlations among anthropometric measures and dual x-ray absorptiometry (gold standard adiposity measure) it is reasonable to consider these measures as valid and reliable assessments of adiposity in children.[56] Further, multiple measures of excess adiposity have been implicated as risk factors for cardiometabolic outcomes.[57]

These results suggest that previously identified characteristics associated with individual child health outcomes are also associated with profiles of neurodevelopment and anthropometry. For example, we found that higher annual household income was associated with optimal profiles of neurodevelopment and adiposity. Prior work evaluating childhood multimorbidity found that lower socioeconomic position was predictive of co-occurring child health outcomes.[4] Socioeconomic position is also related to factors associated with health promotion, such as access to healthcare or psychosocial stress.[58] We also observed that boys were less likely to be classified into the Optimal neurodevelopmental profile, consistent with prior work

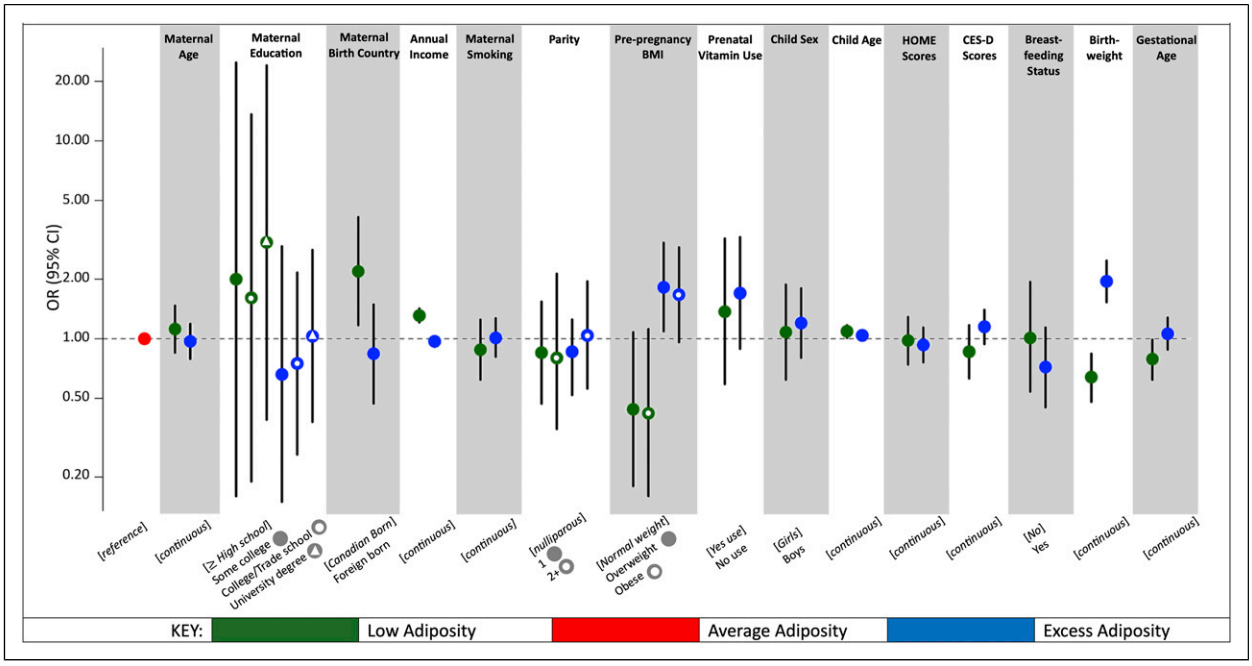

Figure 4. Bivariate associations of maternal and child sociodemographic and perinatal covariates with anthropometric profiles among MIREC Study participants. Odds ratios and 95% confidence intervals for the association between individual covariates and class assignment are displayed for neurodevelopmental profiles on the left column, and anthropometric profiles on the right column. The Medium Scores class (Anthropometric Profiles: Average Adiposity) serves as the reference group. For individual, categorical covariates, the category displayed in brackets and is italicized serves as the reference category. Note, the x-axis is displayed on the log scale. For Anthropometric outcomes: Low Adiposity: (n=60) are characterized be less adiposity, Average Adiposity: (n=306) are characterized by average or medium adiposity, and Excess Adiposity: (n=135) are characterized by increased adiposity. Note, the following variables are scaled by the standard deviation: maternal age (SD: 4.5), annual income ($25,750), HOME scores (4.4), CES-D scores (4.3), birthweight in grams (518), and gestational age at the time of delivery (1.6). Maternal smoking status based on $\log_{10}$-transformed plasma cotinine concentrations from the first trimester of pregnancy. Breastfeeding status is defined as those who did breastfeed exclusively for at least 6 months compared to those who did not.

suggesting sex-specific differences in neurodevelopment[59] Additionally, child caregiving environment and maternal depressive symptoms were associated with child neurodevelopment profiles, but not adiposity profiles. Consistent with previous research, we found that higher-quality caregiving environment was associated with optimal child neurodevelopment.[60] We also found that maternal depressive symptoms may be an indicator of atypical child neurodevelopment, which can be due to genetic predisposition to psychopathology or differential reporting among mothers with more depressive symptoms.[61]

For child anthropometric profiles, pre-pregnancy BMI was predictive of child adiposity status. This was expected given previously established relations between parent and child BMI.[62] Given the strong relation between maternal and child BMI, future work could consider more proximal factors (i.e., dietary patterns within families and current maternal BMI) of parental adiposity on child anthropometry. Consistent with prior work, we also identified birthweight as a predictor of child adiposity.[63] Associations between birthweight and anthropometric profiles do not substantially differ when adjusting for gestational age, suggesting that birthweight independently measures aspects of infant size associated with later life risk of excess adiposity.

This study has several strengths. First, we used a pan-Canadian study with rich phenotyping data, as well as prospectively collected maternal, reproductive, and child characteristics. In addition, with ongoing mid-childhood and adolescent follow-up, we can investigate how these profiles predict child health in the future. Second, we used dimension-reduction techniques to classify child health considering both neurodevelopment and anthropometry, allowing us to describe the relations between multiple child health measures.

Our study has some limitations. First, we only considered the co-occurrence of neurodevelopment and anthropometry; we did not examine other domains of child health. Additionally, we selected variables as predictors for profiles of child health outcomes based on prior literature and data availability. While these are not comprehensive of all possible predictors, future work may consider other

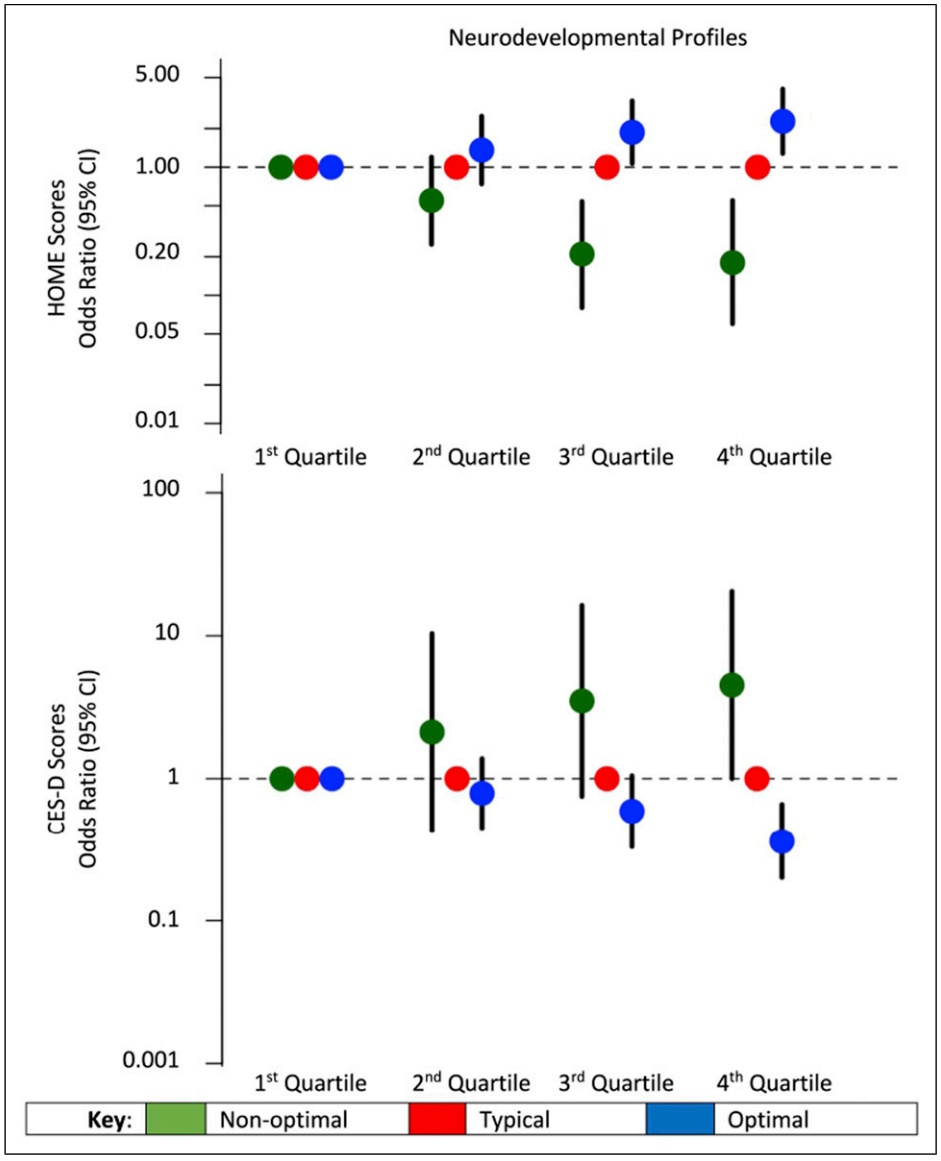

Figure 5. Associations between increasing quartiles of HOME and CES-D scores with neurodevelopmental profiles among MIREC Study participants. For HOME scores, the lowest quartile (lowest scores for caregiving environment) serves as the reference group, with increasing quartiles indicting an increase in the caregiving environment. For CES-D scores, the lowest quartile (lowest scores for maternal depressive symptoms) serves as the reference group, with increasing quartiles indicating an increase in maternal depressive symptoms. Note, the y-axis is displayed on the log scale. For neurodevelopmental profiles, the Typical class serves as the reference group. Non-optimal: (n=45) are characterized by lower cognitive abilities and more problem behaviors, Typical: (n=247) are characterized by average scores on all neurodevelopmental assessments, and Optimal: (n=209) are characterized by higher cognitive abilities and less behavior problems.

prevalent pediatric health conditions and predictors of child health. Second, children in the MIREC Study are generally of higher socioeconomic position and healthy, evidenced by a small proportion of children with less optimal measures. This limits our ability to identify those who may be more vulnerable to the effects of multimorbidity. Further, all class assignments derived using LPA were determined based off the individual outcomes within this cohort (not clinically meaningful cut-points) and may not be representative to those in other samples. A requirement of LPA is that all participants must have complete outcome data. As a result, we excluded roughly 18% of participants who participated in the neurodevelopmental arm of the age 3 follow up. While study sample characteristics off our analytic sample were similar to those of the larger MIREC sample,[19] selection bias is possible. In addition, the MIREC study was

based in one country, Canada, which may limit the external validity of our study to other regions.

Third, it is possible that misclassification occurred among the outcome measures. For example, neurodevelopmental assessments completed by caregivers (i.e., the SRS and BASC), as opposed to teachers or childcare providers, may be less likely to identify the presence of certain child behaviors. In addition, young children may not fully exhibit internalizing behaviors, contributing to less reliable assessments at younger ages.

Fourth, to satisfy the assumptions of LPA, we excluded ~18% of children who participated in the age 3-year follow-up, but had incomplete neurodevelopmental and anthropometric data. However, distributions of study sample characteristics were similar among those in the analytic sample compared to those who were eligible for participation at age 3-years, reducing concerns for selection bias. Despite using data from a large cohort study, we are still limited in sample size. Results pertaining to these groups (i.e., Non-optimal neurodevelopmental profile [n=45]) should be interpreted with caution.

Fifth, while LPA as a dimension reduction approach offers more flexibility in cluster assignment relative to 'hard clustering' techniques (i.e., K-means clustering), there is uncertainty in latent class assignment which could induce bias. When we corrected for uncertainty in latent class assignment, we identified that the direction of this bias is attenuation (versus strengthening).[48]

These data indicate that children exhibit distinct profiles of co-occurring neurodevelopmental and anthropometric health outcomes. Relatively few children in this cohort had both non-optimal neurodevelopment and anthropometry. These neurodevelopmental and anthropometric profiles were associated with some socioeconomic, maternal, and child characteristics. Future work should consider characterizing the phenome to quantify the potential impact of environmental and lifestyle characteristics on multimorbid child health outcomes.

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Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Karl T. Kelsey is a founder and scientific advisor to Cellintech, which had no role in this research. Dr. Joseph M. Braun served as an expert witness in litigation related to perfluorooctanonic acid contamination in drinking water in New Hampshire. No other authors report any conflicts of interest.

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Ethical statement

Ethical approval

The MIREC Study was approved by the Research Ethics Board of Health Canada, and all participating study sites' ethics review committees. The Health Canada and Public Health Agency of Canada Research Ethics Board Protocol Number: **REB-2006-027H**

Informed consent

All mothers provided informed consent for themselves and their participating children.

Consent for publication

Not applicable, only de-identified group level data was used for these analyses.

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Supplemental Material

Supplemental material for this article is available online.

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Appendix

Abbreviations

BASC-2:	Behavioral Assessment System for Children
BSI:	Behavioral Symptoms Index
CES-D:	Center for Epidemiologic Studies Depression scale
CI:	Confidence Interval
DSM:	Diagnostic and Statistical Manual of Mental Disorders
FSIQ:	Full Scale Intelligence Quotient
HOME:	Home Observation for Measurement of the Environment Inventory
LPA:	Latent Profile Analysis
MIREC:	Maternal-Infant Research on Environmental Chemicals Study
OR:	Odds Ratio
PCA:	Principal Component Analyses
SD:	Standard Deviation
SRS-2:	Social Responsiveness Scale
US:	United States
WHO:	World Health Organization
WPPSI-III:	Wechsler Preschool and Primary Scale of Intelligence