Journal of Developmental Origins of Health and Disease

www.cambridge.org/doh

Association of urinary polycyclic aromatic hydrocarbons and obesity in children aged 3–18: Canadian Health Measures Survey 2009–2015

Tracey Bushnik[1], Suzy L. Wong[1], Alison C. Holloway[2] and Errol M. Thomson[3]

[1]Health Analysis Division, Statistics Canada, Ottawa, Canada, [2]Department of Obstetrics and Gynecology, McMaster University, Hamilton, Canada and [3]Environmental Health Science and Research Bureau, Health Canada, Ottawa, Canada

Original Article

Cite this article: Bushnik T, Wong SL, Holloway AC, and Thomson EM. (2020) Association of urinary polycyclic aromatic hydrocarbons and obesity in children aged 3–18: Canadian Health Measures Survey 2009–2015. *Journal of Developmental Origins of Health and Disease* **11**: 623–631. doi: 10.1017/S2040174419000825

Received: 26 February 2019
Revised: 1 November 2019
Accepted: 3 November 2019
First published online: 6 December 2019

Keywords:
polycyclic aromatic hydrocarbons; children; obesity; biomonitoring; urinary metabolites

Address for correspondence:
Errol Thomson, Environmental Health Science and Research, Bureau, Health Canada, 0802B Tunney's Pasture, Ottawa, Ontario, K1A 0K9, Canada.
Email: errol.thomson@canada.ca

Abstract

Polycyclic aromatic hydrocarbons (PAHs) may contribute to obesity. Childhood obesity is a strong predictor of adult obesity and morbidity; however, the relationship between PAHs and obesity in young children (e.g., aged 3–5) has not been studied. We examined the association between urinary PAH metabolites and measures of obesity in children. We analyzed data from 3667 children aged 3–18 years who participated in the Canadian Health Measures Survey (CHMS, 2009–2015). We ran separate multivariable linear models to estimate the association between quartiles of PAH metabolites and each of body mass index (BMI) percentile, waist circumference (WC), and waist-to-height ratio (WHtR) in the total population, as well as in the age subgroups 3–5, 6–11, and 12–18, adjusting for age, sex, ethnicity, education, income quintile, diet, creatinine, and exposure to environmental tobacco smoke. A multinomial logistic regression model estimated adjusted odds ratios for risk of central obesity. BMI, WC, and WHtR were positively associated with total PAH and naphthalene metabolites in the total population aged 3–18 and in age groups 6–11 and 12–18. In 3–5 year olds, WHtR, but not BMI, was significantly associated with total PAH, naphthalene, and phenanthrene metabolites. Overall, those in the highest quartile for naphthalene or total PAH metabolites had three times greater odds of having central obesity compared with those in the lowest quartile. Urinary PAH metabolites are associated with WHtR, an indicator of central obesity and predictor of health risks associated with obesity, in children as young as 3–5.

Introduction

Obesity is a serious global public health challenge representing one of the leading causes of morbidity, mortality, and health care expenditure worldwide.[1,2] The global age-standardized prevalence of obesity in children increased more than eight-fold between 1975 and 2016; in 2016, there were 124 million children aged 5–19 worldwide who were obese.[3] The consequences of childhood obesity are extensive and include multiple medical, social, and psychological comorbidities.[4,5] Moreover, there is considerable evidence to demonstrate that obesity in children persists into adulthood, with obese children being more than five times more likely to be obese as adults than nonobese children [pooled relative risk 5.21, 95% CI 4.50–6.02].[6]

Although the rise in obesity rates has historically been thought to be largely driven by increased caloric intake and insufficient physical activity, there is mounting evidence that exposure to synthetic chemicals in our environment, called obesogens, plays an important role in the global obesity epidemic.[7] Moreover, studies suggest that exposures that occur during early life may have profound life-long impacts on body weight homeostasis.[8] To date, epidemiological studies have shown an association between exposure to environmental chemicals including pesticides, phthalates, flame retardants, bisphenol A, and polycyclic aromatic hydrocarbons (PAHs) and an increased risk of obesity.[8–12]

PAHs have long been pollutants of concern as known human carcinogens, and more recently because of mounting evidence of endocrine disrupting action. PAHs are mainly generated by incomplete combustion of organic materials and are ubiquitous in the environment; routes of exposure include inhalation, ingestion, and skin absorption. Metabolism of PAHs produces hydroxylated PAHs, which have estrogen-like structure and properties.[13] Experimental work has demonstrated that exposure to benzo[a]pyrene, the most well-studied PAH, increases fat mass and leads to weight gain.[14] PAHs may also alter serotonin signaling and impact feeding behaviours,[15] as well as limit lipolysis directly through incorporation into adipocytes.[16] PAHs have been shown to activate early growth response genes and bind to peroxisome proliferator-activated receptors in cell culture systems,[17] suggesting potential pathways beyond aryl

CAMBRIDGE UNIVERSITY PRESS

hydrocarbon receptor binding by which PAHs could mediate impacts on a variety of biological systems, including lipid homeostasis and adipogenesis.[18]

There is some, albeit limited, evidence to suggest a link between PAH exposure and obesity in children aged 6–19 years.[19–21] Interestingly, this association was stronger in the younger (i.e., 6–11 years of age) children versus adolescents (i.e., 12–19 years of age).[20] However, despite longitudinal data suggesting that body weight from 2 to 6 years old is the most critical for prediction and realization of adult overweight,[22] the evaluation of the association between PAH levels and obesity in children younger than 6 years old has not been determined. In the present study, we used data from the Canadian Health Measures Survey (CHMS, 2009–2015) to examine the association between urinary PAH metabolites and obesity in children aged 3–18 years.

Methods

Data source

The data are from the second (2009–2011), third (2012–2013), and fourth (2014–2015) cycles of the CHMS. The CHMS is an ongoing survey designed to provide comprehensive direct health measures at the national level and collects information from community-dwelling individuals. Full-time members of the Canadian Armed Forces and people living on reserves or in other Aboriginal settlements, in institutions, and in some remote regions are excluded (collectively representing approximately 3% of the Canadian population). The CHMS involves an in-person household interview and a subsequent visit to a mobile examination center (MEC). The household interview gathers general demographic and socioeconomic data and detailed health, nutrition, and lifestyle information. At the MEC, blood and urine are collected and direct physical measurements are taken, including height, weight, and waist circumference (WC). Detailed information about the CHMS is available online.[23–25]

Cycles 2–4 collected information for the substances of interest from people aged 3–79; the overall response rates were 55.5%, 51.7%, and 53.7%, respectively, resulting in 6395, 5785, and 5794 respondents. Participants in one cycle were not eligible to participate in other cycles. The three cycles combined had a total of 4445 respondents aged 3–18. For the present study, 551 respondents were excluded because of missing values for at least one of the PAH metabolites of interest, 21 were then excluded because of missing values for one of the outcomes, and a further 206 were excluded because of missing values for at least one of the covariates, leaving an analytical sample size of 3667. Comparison of the characteristics of in-scope respondents who were not retained (NR) in the analysis to those who were retained (R) in the analysis revealed only minor differences. In the NR group, there was a slightly higher proportion of people aged 12–18 (NR = 51%, R = 45%), they were slightly more likely to be male (NR = 54%, R = 51%) or to eat fruits or vegetables fewer than five times per day (NR = 73%, R = 68%), and had a higher average WC (NR = 69 cm, R = 67 cm).

Measures

PAH metabolites

For the analysis of the PAH metabolites, urine samples were hydrolyzed using β-glucuronidase enzymatic solution and extracted with an organic solvent at neutral pH. The extracts were evaporated, derivatized with *N*-methyl-*N*-(trimethylsilyl)-trifluoroacetamide, and analyzed using an Agilent 7890 gas chromatograph coupled with an Agilent 7000B triple-quad tandem mass spectrometer operating in electron impact ionization mode. Analytes were quantified using multiple reaction monitoring. Further information about the laboratory analysis of the PAH metabolites and the quality control measures used in cycles 2–4 of the CHMS is available online.[26–28] Limits of detection (LOD) for all metabolites included in this study are presented in Supplementary Table S1. Those below the LOD were assigned a value equal to the highest detection limit of all three cycles, divided by the square root of 2. For this study, the following groups of PAH metabolites were derived: fluorene (FLUO; sum of 2-hydroxyfluorene, 3-hydroxyfluorene, and 9-hydroxyfluorene); naphthalene (NAP; sum of 1-hydroxynaphthalene and 2-hydroxynaphthalene); phenanthrene (PHEN; sum of 1-hydroxyphenanthrene, 2-hydroxyphenanthrene, 3-hydroxyphenanthrene, 4-hydroxyphenanthrene, and 9-hydroxyphenanthrene); and pyrene (PYR; 1-hydroxypyrene). Total PAH was the sum of all groups by their molarity. Quartile ranges were as follows: NAP (μg/l) Q1: ≤2.88; Q2: 2.88–5.14; Q3: 5.14–9.30; Q4: >9.30. FLUO (μg/l) Q1: ≤0.26; Q2: 0.26–0.44; Q3: 0.44–0.70; Q4: >0.70. PHEN (μg/l) Q1: <0.18; Q2: 0.18–0.31; Q3: 0.31–0.52; Q4: >0.52. PYR (μg/l) Q1: ≤0.06; Q2: 0.06–0.11; Q3: 0.11–0.19; Q4: >0.19. Total PAH (nmol/l) Q1: ≤24.52; Q2: 24.52–42.08; Q3: 42.08–73.35; Q4: >73.35. Note that 3-hydroxybenzo(a) pyrene, 2-hydroxychrysene, 3-hydroxychrysene, 4-hydroxychrysene, 6-hydroxychrysene, and 3-hydroxyfluoranthene were also assessed, but as the percent below LOD exceeded 98% for each, they were excluded from the study.

Creatinine

Creatinine was measured in urine using the colorimetric end-point Jaffe method. An alkaline solution of sodium picrate reacts with creatinine in urine to form a red Janovski complex using Microgenics DRI® Creatinine-Detect® reagents (#917). The absorbance was read at 505 nm on a Hitachi 917 chemistry autoanalyzer. The LOD was 4.0 mg/dl in cycle 2 and 5.0 mg/dl in cycles 3 and 4.[26–28]

Cotinine

Free cotinine was measured in urine and recovered by solid-phase extraction in a 96-well plate format on an automated robotic workstation.[29] The LOD was 1 μg/l in cycle 2 and 1.1 μg/l in cycles 3 and 4.[26–28]

Height

Height was measured to the nearest 0.1 cm using a ProScale M150 digital stadiometer (Accurate Technology Inc., Fletcher, NC, USA).

Weight

Weight was measured to the nearest 0.1 kg with a Mettler Toledo VLC with Panther Plus terminal scale (Mettler Toledo Canada, Mississauga, Canada).

Waist circumference

WC was measured to the nearest 0.1 cm, directly on the landmarked skin with a flexible, inelastic measuring tape with a tension meter attached. In keeping with the NIH protocol (NIH, 2000), the measure was taken at the highest point of the iliac crest.

Waist-to-height ratio

Waist-to-height ratio (WHtR) is a measure of fat distribution and primarily identifies those with abdominal obesity.[30,31] It was

https://doi.org/10.1017/S2040174419000825 Published online by Cambridge University Press

calculated as measured WC in centimeters divided by measured height in centimeters.

Body mass index percentile

Body mass index (BMI) was calculated as measured weight in kilograms divided by measured height in meters squared (kg/m^2). BMI percentile was derived from the respondent's BMI-for-age-and-sex *Z*-score, based on a set of cutoffs specified by the World Health Organization.[32]

Central obesity

Central obesity categories corresponded to: not at risk (ratio of waist to height below 0.50), at risk (ratio of waist to height from 0.50 to less than 0.55), and high probability (ratio of waist to height at or above 0.55).[33]

Covariates

We controlled for the following potential confounders of the association between PAHs and obesity: ethnicity, education, income, diet, and exposure to environmental tobacco smoke (ETS). White or nonwhite ethnicity was based on respondents' answer to which racial or cultural group they belong. Highest level of household education was defined as less than secondary school graduation, secondary school graduation, or higher. Household income ($n = 1176$ cases were imputed[23–25]) was adjusted for household size and was categorized according to lowest household income quintile versus above the lowest quintile. Diet quality was captured through reported fruit and vegetable consumption[34] and was categorized as less than five times per day versus five or more times per day. This was derived from the sum of the frequency of daily consumption of 100% fruit juices; fruit; tomatoes or tomato sauce (excluding tomato paste, ketchup, or pizza sauce); lettuce or green leafy salad; potatoes (including baked, boiled, mashed, or in potato salad, but excluding sweet potatoes); and spinach, mustard greens, or collards (excluding kale); and "other" types of vegetables, excluding those already mentioned. ETS exposure categories were derived from measured urinary cotinine. The not exposed category included those whose cotinine level fell below the LOD. The low, medium, and high ETS exposure categories were based on weighted tertiles among those whose cotinine level was above the LOD.

Statistical analysis

Descriptive statistics were used to examine the characteristics of the study population. Each group of PAH metabolites and total PAH was categorized into quartiles based on the weighted distribution in the study population. Multivariable linear models were run separately to estimate the association between each group of PAHs (in quartiles) and total PAH metabolites (in quartiles), with BMI percentile, WC, and WHtR, respectively, adjusting for age, sex, ethnicity, education, income quintile, diet, creatinine, ETS exposure, and cycle of CHMS. These models were run for the entire study population and stratified by age group (3–5, 6–11, and 12–18 years). *Beta* coefficients and predicted marginals (referred to as model-adjusted means) were estimated, and the linear trend in these means across each group of PAH metabolites was tested. A multinomial logistic regression model estimated adjusted odds ratios (ORs) for risk of central obesity and high probability of central obesity (each compared with no risk of central obesity) in association with each group of PAH metabolites and total PAH metabolites. Like other studies that have examined PAHs and anthropometric measures,[20,21] urinary creatinine was included as an independent variable in all models to account for variation in dilution in spot urinary samples. Because three cycles of data were pooled for this analysis, all models included a CHMS cycle indicator. The CHMS sample design of collection sites selected within regions results in a limited number of degrees of freedom available for variance estimation.[23–25] For this study, 35 degrees of freedom were available and specified in all procedure statements. The multinomial regression could not be run separately by age group due to this limited number of degrees of freedom. To further account for the survey's complex sampling design, all analyses were weighted using the combined CHMS survey weight generated for cycles 2–4, and variance estimation and significance testing based on Satterthwaite statistics were done using the replicate weights generated by Statistics Canada.[23–25,35] Confidence intervals (95%) and *P*-values were presented for all model estimates. The data were analyzed with SAS 9.3 and SAS-Callable SUDAAN 11.0. The code used to conduct analyses is provided in Supplementary Table S2.

Results

Characteristics of the full study population aged 3–18 and according to age group are presented in Table 1. The study population was 51% male, and 85% came from households with higher than secondary school graduation. The proportion of individuals eating fruits and vegetables fewer than five times per day was highest in the 12–18 age group. On the basis of cotinine levels, 83% of the study population was not exposed to ETS, with a higher proportion of those aged 3–5 and 6–11 not exposed compared with those aged 12–18 (86% and 87% vs. 78%). On average, the population was just above the 60th BMI percentile for age and sex, had an average WHtR of 0.47, and 23% were at risk of or had a high probability of central obesity (i.e., WHtR >= 0.50). NAP metabolites accounted for the bulk of total PAH metabolites, and mean levels of all PAH metabolites increased with age.

We assessed three measures of obesity: two previously assessed for ages 6–19 in relation to urinary PAHs, BMI, and WC,[20,21] and one not previously assessed WHtR. After covariate adjustment, BMI percentile for age and sex increased monotonically across quartiles of NAP and total PAH metabolites in the full population of 3–18 year olds (Supplementary Table S3). On average, those in the highest quartile for the NAP metabolites had a predicted BMI percentile of 66th compared with 56th for those in the lowest quartile (Fig. 1). This positive gradient was observed for the 6–11 and 12–18 age groups, separately, but not for those aged 3–5. There was very little difference in BMI percentile across quartiles of FLUO, PHEN, and PYR metabolites.

WC increased monotonically across the NAP metabolites and total PAH metabolites for the total population and for each age group after covariate adjustment (Supplementary Table S4). WC varied little across the other metabolites. On average, there was a positive linear trend ($P < 0.01$) in predicted WC across the NAP and total PAH metabolites for all age groups (Fig. 2).

Like WC, after covariate adjustment WHtR increased monotonically across quartiles of NAP metabolites and total PAH metabolites for the total population and each age group (Supplementary Table S5) with a corresponding positive linear trend in average predicted WHtR (Fig. 3). Unlike the other outcomes, WHtR also increased across quartiles of PHEN metabolites for those aged 3–5 and those aged 6–11. Among the total population, those in the highest quartile for NAP and total PAH

https://doi.org/10.1017/S2040174419000825 Published online by Cambridge University Press

Table 1. Characteristics, by age group, household population aged 3–18, 2007–2015

	Ages 3–18		Ages 3–5		Ages 6–11		Ages 12–18	
	n	Weighted estimate % or mean	*n*	Weighted estimate % or mean	*n*	Weighted estimate % or mean	*n*	Weighted estimate % or mean
Total	3667	100.0	1242	100.0	1320	100.0	1105	100.0
Sex								
Male	1825	50.8	610	50.5	668	51.7	547	50.1
Female	1842	49.2	632	49.5	652	48.3	558	49.9
Ethnicity								
White	2559	65.4	858	65.4	922	65.6	779	65.3
Nonwhite	1108	34.6	384	34.6	398	34.4	326	34.8
Highest level of household education								
Less than secondary school graduation	118	3.5	43	5.0	46	4.0	29	2.4
Secondary school graduation	360	11.6	108	9.4	133	12.1	119	12.1
Higher than secondary school graduation	3189	84.9	1091	85.5	1141	83.9	957	85.4
Income quintile adjusted for household size								
Lowest (first)	633	19.8	219	24.2	231	20.5	183	17.4
Not lowest (second–fifth)	3034	80.2	1023	75.8	1089	79.5	922	82.6
Diet quality								
Fruits/vegetables five or more times per day	1324	32.4	535	36.7	473	36.1	316	27.7
Fruits/vegetables less than five times per day	2343	67.6	707	63.3	847	63.9	789	72.3
ETS exposure category								
Not exposed	3122	83.0	1087	85.6	1155	87.4	880	78.4
Low exposure	226	6.1	81	8.7	69	5.3	76	5.7
Medium exposure	188	5.4	54	4.2	72	5.8	62	5.7
High exposure	131	5.5	20	1.6	24	1.5	87	10.3
Body mass index percentile	3667	61.5	1242	61.7	1320	60.2	1105	62.4
Waist circumference (cm)	3667	66.9	1242	51.6	1320	62.1	1105	76.9
Ratio of waist to height (WHtR)	3667	0.47	1242	0.49	1320	0.46	1105	0.46
Central obesity								
Not at risk	2757	76.7	852	69.1	1050	80.2	855	76.7
At risk	590	13.3	319	24.3	151	10.2	120	11.5
High probability	320	10.0	71	6.5	119	9.6	130	11.7
NAP metabolites (μg/l)	3667	5.21	1242	4.61	1320	4.56	1105	6.11
FLUO metabolites (μg/l)	3667	0.43	1242	0.34	1320	0.40	1105	0.51
PHEN metabolites (μg/l)	3667	0.32	1242	0.26	1320	0.29	1105	0.37
PYR metabolites (μg/l)	3667	0.11	1242	0.10	1320	0.10	1105	0.12
Total PAH (nmol/l)	3667	42.45	1242	37.04	1320	37.25	1105	49.88
Urinary creatinine (mg/dl)	3667	118.7	1242	64.4	1320	97.2	1105	157.8

ETS, environmental tobacco smoke; FLUO, fluorine; LOD, limits of detection; NAP, naphthalene; PAH, polycyclic aromatic hydrocarbon; PHEN, phenanthrene; PYR, pyrene; WCH, waist to height.
Source: Combined 2009–2011, 2012–2013, and 2014–2015 Canadian Health Measures Survey.
PAH means are geomeans.
BMI percentile values are based on WHO growth reference values specific to sex and age in months.
Central obesity categories correspond to: not at risk (ratio of waist to height below 0.50), at risk (ratio of waist to height from 0.50 to less than 0.55), and high probability (ratio of waist to height at or above 0.55).
ETS exposure category based on measured the urinary cotinine values. Not exposed: below the LOD (<1.1 ng/ml), low exposure (1.1–5 ng/ml), medium exposure (>5–24 ng/ml), and high exposure (>24 ng/ml).

https://doi.org/10.1017/S2040174419000825 Published online by Cambridge University Press

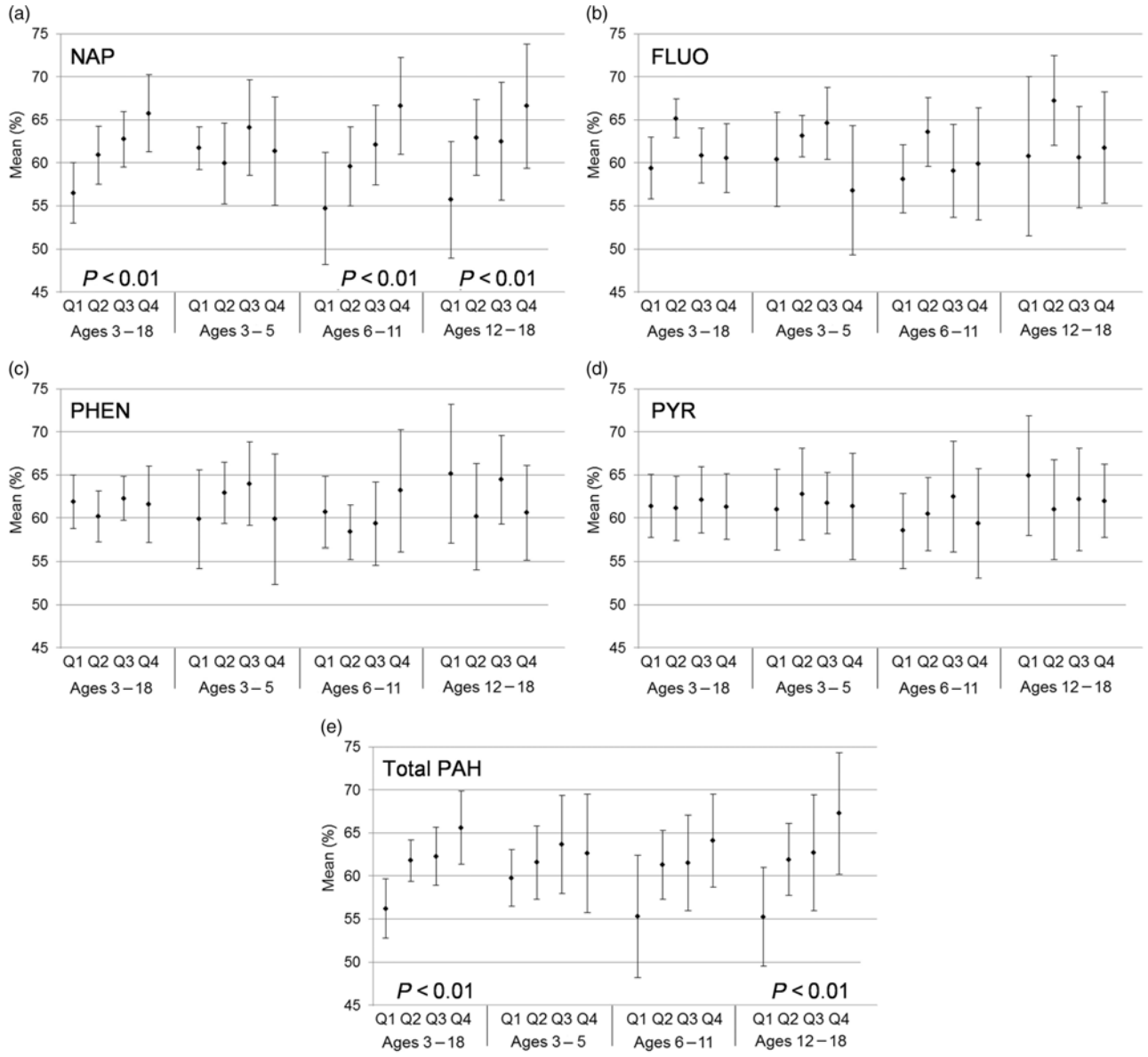

Fig. 1. Multivariable linear regression association between BMI percentile and quartiles of urinary levels of PAH metabolites, by age group, household population aged 3–18, 2007–2015. Model-adjusted means and 95% confidence intervals are presented for each PAH quartile. The *P*-value is based on the *t*-statistic from the test of linear trend in means with a positive gradient across a given set of PAH quartiles.

metabolites had three times greater odds of having central obesity versus no central obesity compared with those in the lowest quartile (Table 2). The results also suggest a potential monotonic increase in the odds of having central obesity versus having no risk across the quartiles of PHEN metabolites.

Discussion

In utero and early-life exposures may be critical determinants of later onset disease, including metabolic syndrome and obesity.[8,12,36,37] As these appear to represent windows of vulnerability to environmental exposures with long-term consequences, there is considerable interest in assessing risks associated with exposure to contaminants to which the population is widely exposed. We show for the first time that urinary PAH metabolites are associated with WHtR, a proxy for central adipose tissue and predictive indicator of health risks associated with obesity, in children as young as 3–5 years old. These associations were independent of exposure to ETS and robust to control for a variety of covariates. The findings build upon previous work reporting associations between urinary PAH metabolites and obesity in children aged 6–19,[19–21] and contribute to the literature highlighting young children as a population of concern.

Childhood obesity is associated with increased risk of morbidity and mortality in adulthood from cardiovascular disease, hypertension, and type 2 diabetes and carries substantial societal and economic implications.[5,38] Importantly, many of the cardiometabolic risk factors for obesity-related comorbidities (i.e., dyslipidemia, elevated blood pressure, and impaired glucose tolerance) are evident in overweight and obese children.[39,40] While BMI is a widely accepted measure of obesity, there has been increasing interest in WHtR, a marker of central obesity, including evidence that it may

https://doi.org/10.1017/S2040174419000825 Published online by Cambridge University Press

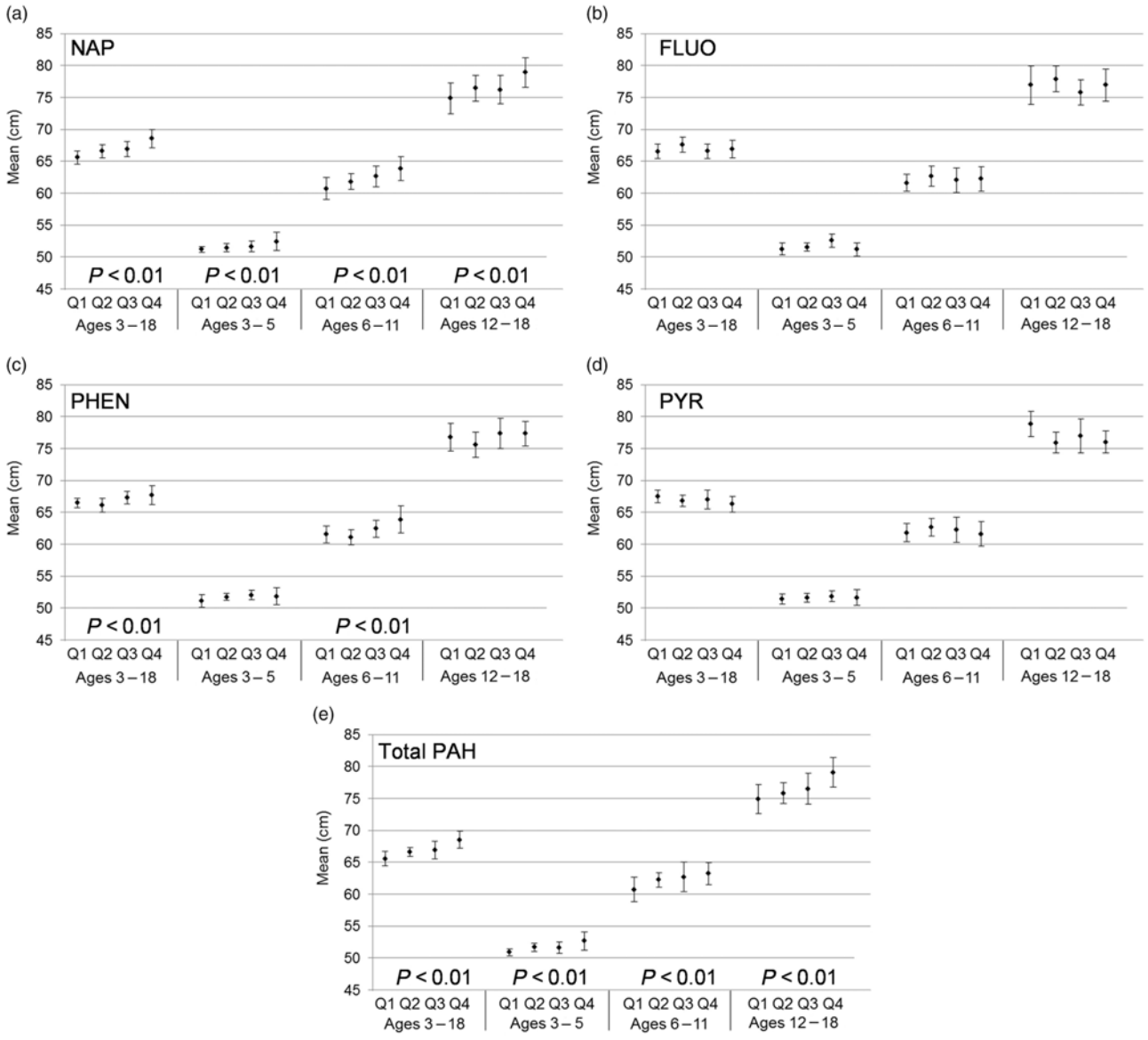

Fig. 2. Multivariable linear regression association between waist circumference (cm) and quartiles of urinary levels of PAH metabolites, by age group, household population aged 3–18, 2007–2015. Model-adjusted means and 95% confidence intervals are presented for each PAH quartile. The *P*-value is based on the *t*-statistic from the test of linear trend in means with a positive gradient across a given set of PAH quartiles.

be a better indicator of whole body fat and visceral adipose tissue,[41] as well as a better predictor of cardiometabolic risk,[30,42] when compared to BMI or WC. Indeed, a recent meta-analysis covering 300,000 adults showed that WHtR was a significantly better predictor of adverse cardiometabolic outcomes than WC and BMI in both sexes.[42] Results from a number of studies support use of WHtR in children, with some indicating that it outperforms BMI as an indicator of cardiometabolic risk.[43–46] To our knowledge, WHtR has not been previously assessed in relation to urinary PAH metabolites. Our data, which show stronger associations between urinary PAH metabolites and WHtR in children aged 3–5 than were seen for BMI or WC alone, suggest that WHtR may be a more sensitive indicator of potential obesogenic effects in a pediatric population.

Children may be more vulnerable to environmental contaminants for a number of reasons: potential greater exposure because of behavioral patterns and proximity to pollutant sources, greater body burden per unit body mass, and the potential for higher sensitivity due to developmental stage. In a study using data from the National Health and Nutrition Examination Survey (NHANES), significantly higher levels of urinary PAH metabolites were observed in children aged 6–11 compared to 12–19 and adults,[47] consistent with a greater body burden in younger children. Intake of NAP, normalized by subject mass, has been calculated to be over five times higher for a 10-kg child compared to a 70-kg adult.[48] Effects of exposure to PAHs may start prenatally, as suggested by associations between maternal PAH exposure and childhood obesity.[49] Urinary PAH metabolites are associated with higher levels of markers of inflammation and oxidative stress during pregnancy,[50] indicating potential systemic impacts of PAH exposure that could impact pregnancy and development. Emerging evidence that PAHs may alter levels of reproductive hormones in umbilical cord sera[51] provides a further link between maternal exposures and potential prenatal impacts. Thus associations observed in early childhood could possibly reflect effects of both prenatal and postnatal exposures.

https://doi.org/10.1017/S2040174419000825 Published online by Cambridge University Press

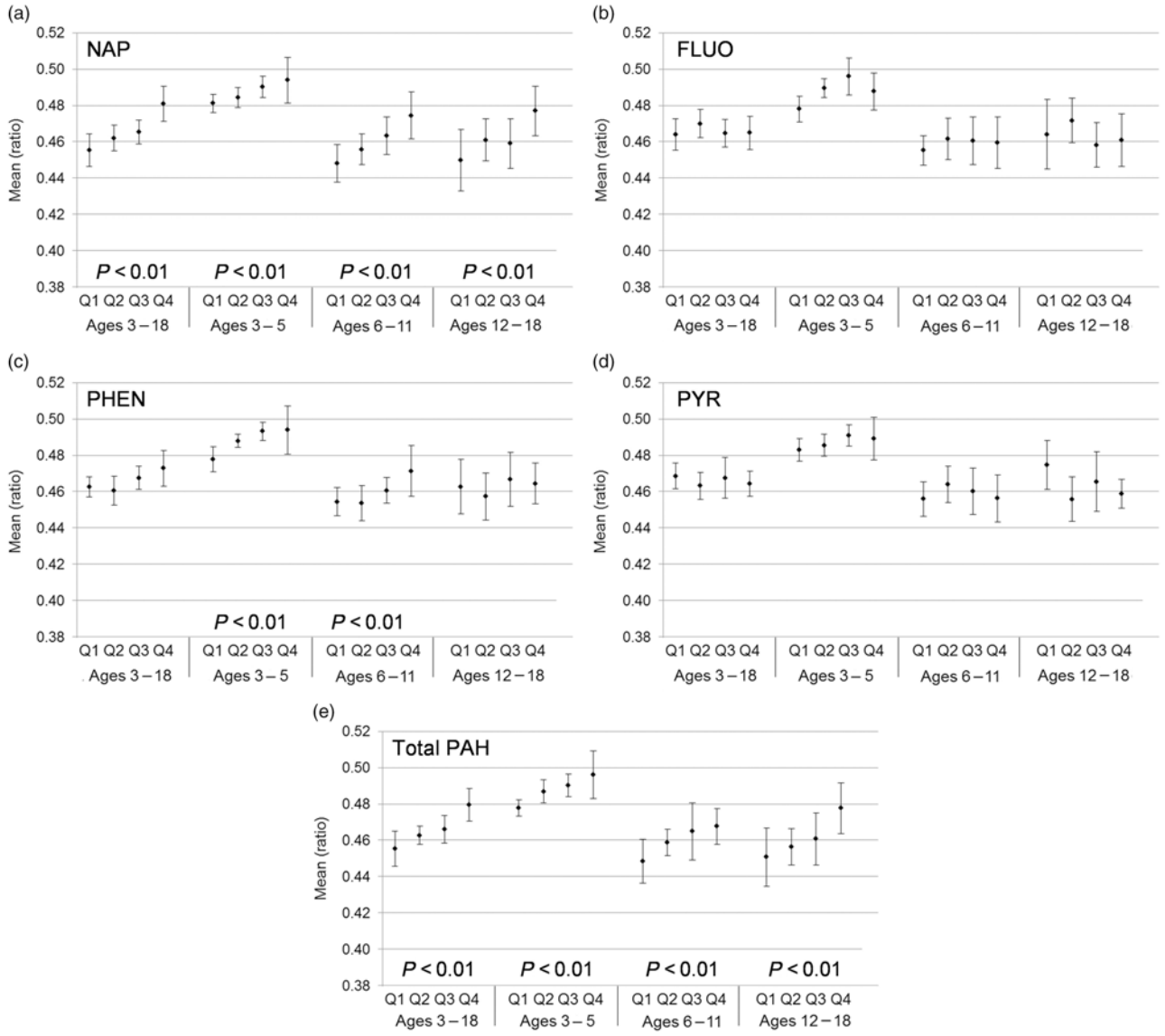

Fig. 3. Multivariable linear regression association between ratio of waist circumference to height and quartiles of urinary levels of PAH metabolites, by age group, household population aged 3–18, 2007–2015. Model-adjusted means and 95% confidence intervals are presented for each PAH quartile. The *P*-value is based on the *t*-statistic from the test of linear trend in means with a positive gradient across a given set of PAH quartiles.

In line with previous studies, measures of obesity were most strongly associated with NAP and total PAH metabolites.[20,21] NAP metabolites comprise the bulk of total urinary PAH metabolites. Given the abundance of NAP, and the fact that it exists almost entirely in the gas phase, NAP metabolites have been proposed to serve as surrogates for exposure to airborne PAHs.[52] Urinary PAH metabolites correspond well with even relatively low levels in ambient air pollution, indicating that they can serve as biomarkers of exposure.[53] While the majority of significant positive associations were with NAP metabolites, consistent with inhalation exposures, in 3–5 year olds, WHtR was also significantly associated with PHEN and to a lesser extent FLUO, where dietary exposure cannot be discounted.[47,54] Importantly, the association between urinary PAH metabolites and obesity measures remained after adjusting for exposure to ETS, suggesting a more generalized effect of environmental and dietary exposures. Air pollution has itself been associated with increased prevalence of cardiometabolic risk factors.[55,56]

Strengths of the present population-based study include the inclusion of 3–5 year olds, extending the evaluation of associations with PAH metabolites to a younger and possibly more sensitive population with significant exposure to PAHs. We assessed several measures of obesity, including WHtR, which had not previously been assessed in relation to PAH metabolites. The CHMS included a rich covariate dataset enabling adjustment for potential confounders such as diet and ETS exposure. A significant limitation is the cross-sectional nature of the data, which precludes determination of the directionality of effects. Urinary PAH metabolites were only assessed a single time, and thus, it is possible that proximal exposures mask long-term trends from chronic exposure that might be more relevant to long-term biological effects. However, a recent study in New York City showed that repeated measure of urinary PAH metabolites exhibited overall variation of less than 5%.[57] As in any population study, other unmeasured factors may influence or drive the association between PAH metabolites and obesity; these include other air pollutants that

https://doi.org/10.1017/S2040174419000825 Published online by Cambridge University Press

Table 2. Odds ratios (95% CI) from multinomial logistic regression models of association between quartiles of urinary levels of PAH metabolites and risk of central obesity and high probability of central obesity versus not at risk of central obesity, household population aged 3–18, 2007–2015

	At risk of central obesity versus not at risk	95% CI		High probability of central obesity versus not at risk	95% CI	
		From	To		From	To
Ages 3–18						
NAP metabolites						
Q1	Ref	...	...	Ref	...	...
Q2	0.80	0.52	1.23	1.66	0.89	3.10
Q3	1.11	0.66	1.88	1.48	0.73	3.00
Q4	1.23	0.69	2.19	3.15	1.56	6.34
FLUO metabolites						
Q1	Ref	...	...	Ref	...	...
Q2	1.47	1.12	1.93	1.41	0.68	2.91
Q3	1.04	0.72	1.52	1.10	0.59	2.06
Q4	0.98	0.56	1.71	1.33	0.65	2.75
PHEN metabolites						
Q1	Ref	...	...	Ref	...	...
Q2	0.96	0.62	1.49	1.15	0.66	2.00
Q3	1.19	0.77	1.82	1.36	0.70	2.62
Q4	1.26	0.70	2.26	1.89	1.00	3.58
PYR metabolites						
Q1	Ref	...	...	Ref	...	...
Q2	0.95	0.66	1.38	0.91	0.62	1.34
Q3	0.91	0.59	1.41	0.96	0.44	2.07
Q4	1.01	0.63	1.61	0.73	0.46	1.15
Total PAH						
Q1	Ref	...	...	Ref	...	...
Q2	0.94	0.60	1.47	1.47	0.69	3.13
Q3	1.08	0.63	1.86	1.91	1.06	3.47
Q4	1.21	0.68	2.16	2.94	1.39	6.19

CHMS, Canadian Health Measures Survey; ETS, environmental tobacco smoke; FLUO, fluorine; LOD, limits of detection; NAP, naphthalene; PAH, polycyclic aromatic hydrocarbon; PHEN, phenanthrene; PYR, pyrene.
Source: Combined 2009–2011, 2012–2013, and 2014–2015 Canadian Health Measures Survey. Not at risk of central obesity = ratio of waist circumference to height <0.50, at risk of central obesity = 0.50≤ ratio of waist circumference to height <0.55, high probability of central obesity = ratio of waist circumference to height ≥0.55.
Models adjusted for age (continuous), sex, education, diet, creatinine, ETS exposure category (two-level), and cycle of CHMS.
ETS exposure category based on the measured urinary cotinine values. Not exposed: below the LOD (<1.1 ng/ml) and exposed (1.1 ng/ml or higher).

may co-vary with PAH exposure. Moreover, PAHs that may co-vary with those assessed here[47] but whose metabolites were not present in measurable quantities in urine (e.g., 3-hydroxybenzo(a) pyrene, 2-hydroxychrysene, 3-hydroxychrysene, 4-hydroxychrysene, 6-hydroxychrysene, 3-hydroxyfluoranthene) could nevertheless have biologically relevant effects. Limited sample sizes prevented us from assessing whether ETS exposure level was an effect modifier of the association between PAH metabolites and our measures of obesity. However, analyses conducted in the subpopulation not exposed to ETS (as assessed by cotinine) showed clearly that effects of NAP and total PAH metabolites were not dependent upon ETS exposure (Supplementary Table S6).

Conclusions

In summary, we found that urinary PAH metabolites were associated with measures of obesity in children as young as 3–5 years. While there is considerable interest in evaluating the potential role of early-life exposures in disease, PAHs and air pollution more broadly remain understudied risk factors for later-life obesity and its associated comorbidities. Given the potential importance of such exposures, further research is warranted to examine potential obesogenic and endocrine disrupting effects of PAHs in infants and young children.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/S2040174419000825.

Acknowledgements. Thank you to Alain Filiatreault for assistance with preparation of figures.

Financial support. This work was supported by Statistics Canada and Health Canada. Funding sources had no involvement in study design; collection, analysis, and interpretation of data, nor the writing of the publication.

Conflicts of interest. None.

References

1. Lehnert T, Sonntag D, Konnopka A, Riedel-Heller S, Konig HH. Economic costs of overweight and obesity. *Best Pract Res Clin Endocrinol Metab*. 2013; 27, 105–115.
2. World Health Organisation (WHO). Obesity and Overweight. Fact Sheet, 2018. World Health Organisation, Geneva, Switzerland. http://www.who.int/mediacentre/factsheets/fs311/en/.
3. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128-9 million children, adolescents, and adults.NCD Risk Factor Collaboration (NCD-RisC). *Lancet*. 2017; 390(10113), 2627–2642. doi: 10.1016/S0140-6736(17)32129-3. Epub. 2017.
4. Rankin J, Matthews L, Cobley S, *et al.* Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. *Adolesc Health Med Ther*. 2016; 7, 125–146.
5. Reinehr T. Long-term effects of adolescent obesity: time to act. *Nat Rev Endocrinol*. 2018; 14, 183–188.
6. Simmonds M, Burch J, Llewellyn A, *et al.* The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: a systematic review and meta-analysis. *Health Technol Assess*. 2015; 19, 1–336.
7. Heindel JJ, Blumberg B. Environmental obesogens: mechanisms and controversies. *Annu Rev Pharmacol Toxicol*. 2019; 59, 89–106.
8. La Merrill M, Birnbaum LS. Childhood obesity and environmental chemicals. *Mt Sinai J Med*. 2011; 78, 22–48.
9. Hu H, Kan H, Kearney GD, Xu X. Associations between exposure to polycyclic aromatic hydrocarbons and glucose homeostasis as well as metabolic syndrome in nondiabetic adults. *Sci Total Environ*. 2015; 505, 56–64.
10. Ranciere F, Lyons JG, Loh VH, *et al.* Bisphenol A and the risk of cardiometabolic disorders: a systematic review with meta-analysis of the epidemiological evidence. *Environ Health*. 2015; 14, 46.
11. James-Todd TM, Huang T, Seely EW, Saxena AR. The association between phthalates and metabolic syndrome: the National health and nutrition examination Survey 2001-2010. *Environ Health*. 2016; 15, 52.
12. De Long NE, Holloway AC. Early-life chemical exposures and risk of metabolic syndrome. *Diabetes Metab Syndr Obes*. 2017; 10, 101–109.

13. Schultz TW, Sinks GD. Xenoestrogenic gene expression: structural features of active polycyclic aromatic hydrocarbons. *Environ Toxicol Chem*. 2002; 21, 783–786.
14. Irigaray P, Ogier V, Jacquenet S, *et al.* Benzo[a]pyrene impairs beta-adrenergic stimulation of adipose tissue lipolysis and causes weight gain in mice. A novel molecular mechanism of toxicity for a common food pollutant. *FEBS J*. 2006; 273, 1362–1372.
15. Stephanou P, Konstandi M, Pappas P, Marselos M. Alterations in central monoaminergic neurotransmission induced by polycyclic aromatic hydrocarbons in rats. *Eur J Drug Metab Pharmacokinet*. 1998; 23, 475–481.
16. Irigaray P, Lacomme S, Mejean L, Belpomme D. Ex vivo study of incorporation into adipocytes and lipolysis-inhibition effect of polycyclic aromatic hydrocarbons. *Toxicol Lett*. 2009; 187, 35–39.
17. Kim JH, Yamaguchi K, Lee SH, *et al.* Evaluation of polycyclic aromatic hydrocarbons in the activation of early growth response-1 and peroxisome proliferator activated receptors. *Toxicol Sci*. 2005; 85, 585–593.
18. Grun F, Blumberg B. Environmental obesogens: organotins and endocrine disruption via nuclear receptor signaling. *Endocrinology*. 2006; 147, S50–S55.
19. Poursafa P, Dadvand P, Amin MM, *et al.* Association of polycyclic aromatic hydrocarbons with cardiometabolic risk factors and obesity in children. *Environ Int*. 2018; 118, 203–210.
20. Scinicariello F, Buser MC. Urinary polycyclic aromatic hydrocarbons and childhood obesity: NHANES (2001-2006). *Environ Health Perspect*. 2014; 122, 299–303.
21. Kim HW, Kam S, Lee DH. Synergistic interaction between polycyclic aromatic hydrocarbons and environmental tobacco smoke on the risk of obesity in children and adolescents: the U.S. National health and nutrition examination Survey 2003-2008. *Environ Res*. 2014; 135, 354–360.
22. de Kroon ML, Renders CM, van Wouwe JP, van BS, Hirasing RA. The terneuzen birth cohort: BMI changes between 2 and 6 years correlate strongest with adult overweight. *PLoS One*. 2010; 5, e9155.
23. Statistics Canada. Canadian Health Measures Survey (CHMS) Data User Guide: Cycle 2, November 2012. Available at http://www23.statcan.gc.ca/imdb-bmdi/documents/5071_D4_T9_V1-eng.htm, 2012.
24. Statistics Canada. Canadian Health Measures Survey (CHMS) Data User Guide: Cycle 3, November 2014. Available at http://www.statcan.gc.ca, 2014.
25. Statistics Canada. Canadian Health Measures Survey (CHMS) Data User Guide: Cycle 4, October 2017. Available at http://www.statcan.gc.ca, 2017.
26. Health Canada. Second Report on Human Biomonitoring of Environmental Chemicals in Canada:Results of the Canadian Health Measures Survey Cycle 2 (2009-2011) (Health Canada, Catalogue H128-1/10/601-1E-PDF) Ottawa: Minister of Health, 2013.
27. Health Canada. Third Report on Human Biomonitoring of Environmental Chemicals in Canada:Results of the Canadian Health Measures Survey Cycle 3 (2012-2013) (Health Canada, Catalogue H128-1/10/601-2E-PDF) Ottawa: Minister of Health, 2015.
28. Health Canada. Fourth Report on Human Biomonitoring of Environmental Chemicals in Canada:Results of the Canadian Health Measures Survey Cycle 4 (2014-2015) (Health Canada, Catalogue H128-1/10/601-4E-PDF) Ottawa: Minister of Health, 2017.
29. Institut national de santé publique du Québec. *Analytical Method for the Determination of Cotinine in Urine by HPLC-MS-MS Robotic Workstation Method (C-550), Condensed version for CHMS*, 2009. Québec:Institut national de santé publique du Québec.
30. Browning LM, Hsieh SD, Ashwell M. A systematic review of waist-to-height ratio as a screening tool for the prediction of cardiovascular disease and diabetes: 0.5 could be a suitable global boundary value. *Nutr Res Rev*. 2010; 23, 247–269.
31. Ashwell M, Lejeune S, McPherson K. Ratio of waist circumference to height may be better indicator of need for weight management. *BMJ*. 1996; 312, 377.
32. de Onis M, Onyango AW, Borghi E, *et al.* Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007; 85, 660–667.
33. Mehta SK. Waist circumference to height ratio in children and adolescents. *Clin Pediatr (Phila)*. 2015; 54, 652–658.
34. Garriguet D. Diet quality in Canada. *Health Rep*. 20(3); 2009, 41–52.
35. Statistics Canada. Instructions for combining multiple cycles of Canadian Health Measures Survey (CHMS) data, 2017. Available at http://www.statcan.gc.ca.
36. Legler J, Hamers T, van Eck van der Sluijs-van de Bor M. *et al.* The OBELIX project: early life exposure to endocrine disruptors and obesity. *Am J Clin Nutr*. 2011; 94, 1933S–1938S.
37. de Kroon ML, van de Bor M. Obesogenic effects of endocrine disruptors, what do we know from animal and human studies? *Environ Int*. 2014; 70, 15–24.
38. Grant-Guimaraes J, Feinstein R, Laber E, Kosoy J. Childhood overweight and obesity. *Gastroenterol Clin North Am*. 2016; 45, 715–728.
39. Anderson LN, Lebovic G, Hamilton J, *et al.* Body mass index, waist circumference, and the clustering of cardiometabolic risk factors in early childhood. *Paediatr Perinat Epidemiol*. 2016; 30, 160–170.
40. Ali O, Cerjak D, Kent JW, *et al.* Obesity, central adiposity and cardiometabolic risk factors in children and adolescents: a family-based study. *Pediatr Obes*. 2014; 9, e58–e62.
41. Swainson MG, Batterham AM, Tsakirides C, Rutherford ZH, Hind K. Prediction of whole-body fat percentage and visceral adipose tissue mass from five anthropometric variables. *PLoS One*. 2017; 12, e0177175.
42. Ashwell M, Gunn P, Gibson S. Waist-to-height ratio is a better screening tool than waist circumference and BMI for adult cardiometabolic risk factors: systematic review and meta-analysis. *Obes Rev*. 2012; 13, 275–286.
43. Nambiar S, Truby H, Davies PS, Baxter K. Use of the waist-height ratio to predict metabolic syndrome in obese children and adolescents. *J Paediatr Child Health*. 2013; 49, E281–E287.
44. Khoury M, Manlhiot C, McCrindle BW. Role of the waist/height ratio in the cardiometabolic risk assessment of children classified by body mass index. *J Am Coll Cardiol*. 2013; 62, 742–751.
45. Mokha JS, Srinivasan SR, Dasmahapatra P, *et al.* Utility of waist-to-height ratio in assessing the status of central obesity and related cardiometabolic risk profile among normal weight and overweight/obese children: the Bogalusa Heart Study. *BMC Pediatr*. 2010; 10, 73.
46. Graves L, Garnett SP, Cowell CT, *et al.* Waist-to-height ratio and cardiometabolic risk factors in adolescence: findings from a prospective birth cohort. *Pediatr Obes*. 2014; 9, 327–338.
47. Li Z, Sandau CD, Romanoff LC, *et al.* Concentration and profile of 22 urinary polycyclic aromatic hydrocarbon metabolites in the US population. *Environ Res*. 2008; 107, 320–331.
48. Preuss R, Angerer J, Drexler H. Naphthalene–an environmental and occupational toxicant. *Int Arch Occup Environ Health*. 2003; 76, 556–576.
49. Rundle A, Hoepner L, Hassoun A, *et al.* Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy. *Am J Epidemiol*. 2012; 175, 1163–1172.
50. Ferguson KK, McElrath TF, Pace GG, *et al.* Urinary polycyclic aromatic hydrocarbon metabolite associations with biomarkers of inflammation, angiogenesis, and oxidative stress in pregnant women. *Environ Sci Technol*. 2017; 51, 4652–4660.
51. Yin S, Tang M, Chen F, Li T, Liu W. Environmental exposure to polycyclic aromatic hydrocarbons (PAHs): the correlation with and impact on reproductive hormones in umbilical cord serum. *Environ Pollut*. 2017; 220, 1429–1437.
52. Rappaport SM, Waidyanatha S, Serdar B. Naphthalene and its biomarkers as measures of occupational exposure to polycyclic aromatic hydrocarbons. *J Environ Monit*. 2004; 6, 413–416.
53. Castano-Vinyals G, D'Errico A, Malats N, Kogevinas M. Biomarkers of exposure to polycyclic aromatic hydrocarbons from environmental air pollution. *Occup Environ Med*. 2004; 61, e12.
54. Ramesh A, Walker SA, Hood DB, *et al.* Bioavailability and risk assessment of orally ingested polycyclic aromatic hydrocarbons. *Int J Toxicol*. 2004; 23, 301–333.
55. Yang BY, Qian ZM, Li S, *et al.* Long-term exposure to ambient air pollution (including PM1) and metabolic syndrome: the 33 Communities Chinese Health Study (33CCHS). *Environ Res*. 2018; 164, 204–211.
56. Poursafa P, Mansourian M, Motlagh ME, Ardalan G, Kelishadi R. Is air quality index associated with cardiometabolic risk factors in adolescents? The CASPIAN-III Study. *Environ Res*. 2014; 134, 105–109.
57. Jung KH, Liu B, Lovinsky-Desir S, *et al.* Time trends of polycyclic aromatic hydrocarbon exposure in New York City from 2001 to 2012: assessed by repeat air and urine samples. *Environ Res*. 2014; 131, 95–103.

https://doi.org/10.1017/S2040174419000825 Published online by Cambridge University Press