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Impact of parental smoking on adipokine profiles and cardiometabolic risk factors in Chinese children

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HIGHLIGHTS

- Parental smoking exposure was not only associated with adiposity, but also with unfavorable adipokine profiles.
- Parental smoking exposure was associated with metabolic syndrome and its components in Chinese children.
- Alterations in adipokine levels might mediate the relation between passive smoking and cardiometabolic disorders in children.

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ABSTRACT

Background and aims: The mechanisms by which passive smoking leads to cardiometabolic risks, and the tissues involved still require elucidation. We aimed to evaluate the association of parental smoking exposure (PSE) with the secretion of adipocyte-derived hormones and cardiometabolic risk factors in Chinese children.
Methods: We included 3150 school children aged 6-18 years from the Beijing Child and Adolescent Metabolic Syndrome (BCAMS) study. Data on PSE and potential confounders were collected. Six adipokines related to insulin resistance and metabolic syndrome (MetS) were measured.
Results: PSE was reported in nearly two-thirds of the children. After adjusting for covariates, including age, sex, pubertal stages, lifestyle factors, and family history, PSE was independently associated with increases of 39.2% in leptin and 3.9% in retinol binding protein-4 and decreases of 11.4% in fibroblast growth factor 21 and 4.6% in adiponectin levels ($p < 0.05$ for all), plus risks for central obesity (OR 1.59, 95% CI 1.33–1.90), elevated blood pressure (1.22, 1.02–1.46) and MetS (1.43, 1.11–1.85). However, the associations of PSE with hypertension and MetS were abolished when adjusted for adiposity parameters or the above-mentioned adipokine profiles.
Conclusions: PSE was associated with dysregulation of adipokine levels, which might mediate the development of MetS in early life.

1. Introduction

The alarming increase in the prevalence of obesity, particular childhood obesity, and the coexistent disorders in the metabolic syndrome (MetS), such as hyperglycemia and hypertension, has reached epidemic proportions [1]. Meanwhile, exposure to secondhand smoke, now a serious global problem, was reported to be another important modifiable factor in addition to unhealthy diet, sedentary lifestyle and insufficient sleep, associated with obesity and cardiometabolic disorders [2–4]. The Global Burden of Disease study recently showed that 55.9% adolescents were exposed to secondhand smoke in 68 low-income and middle-income countries [5]. In China, the biggest tobacco producing and consuming country of the world, about 182 million children are exposed to secondhand smoke everyday, according to data

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from the International Tobacco Control Policy Evaluation Project in China (ITC China Project) [6]. Primarily exposed to parental tobacco smoking, children are particularly vulnerable to secondhand smoke exposure, whose detrimental consequences may track into their adult life [2,7]. Several previous studies showed that parental smoking exposure (PSE) was associated with childhood obesity, and MetS components including abnormal lipid profiles, elevated blood pressure and impaired glucose regulation [8–12], the mechanisms by which passive smoking leads to these cardiometabolic disorders and the tissues involved, however, remain unclear, and studies on the Chinese population are scarce.

Currently, adipose tissue is regarded as a dynamic endocrine organ releasing a host of molecules that are generally referred to as adipokines [13], which are involved in energy expenditure, inflammatory response and cardiometabolic homeostasis [14]. One hypothesis is that the association of secondhand smoke exposure with cardiometabolic risk may be mediated through adiposity [8,12,15,16], particularly via the adverse effects on the endocrine function of the adipose tissue [17]. To date, albeit with limited data, observational studies have provided evidence for an association between exposure to secondhand smoke and dysregulation of adipokines, as two inflammation-related adipokines, leptin and adiponectin, are altered with secondhand smoke exposure [18,19]. However, other adipokines related to cardiometabolic disease, such as retinol binding protein 4 (RBP4) [13,20], fibroblast growth factor 21 (FGF21) [21], resistin [13] and osteonectin [22], have not yet been systematically investigated in this regard. Therefore, leveraging the large cohort of Beijing Children and Adolescents Metabolic Syndrome (BCAMS) study [23], we aimed to evaluate the association between PSE, adiposity, adipokine profiles including leptin, resistin, adiponectin, FGF21, osteonectin and RBP4, as well as the MetS and its components in Chinese school children.

2. Materials and methods

2.1. Study population

Subjects were from the BCAMS study (Supplementary Fig. S1), which is a longitudinal cohort study of cardiovascular risk factors since childhood. The study protocol has been reported in detail elsewhere [23] and is registered at www.clinicaltrails.gov (NCT03421444). In brief, in 2004 a population-based survey was conducted in the Beijing area with a representative sample of children and adolescents (n = 19,593, 50% boys). Approximately 4500 were identified as being at elevated risk for MetS due to the presence of at least one of the following risk factors: overweight defined by body mass index (BMI) ≥ 85th percentile; blood pressures > 90th percentile, total cholesterol (TC) ≥ 5.2 mmol/L, triglyceride (TG) ≥ 1.7 mmol/L or fasting plasma glucose (FPG) ≥ 5.6 mmol/L based on finger capillary blood tests. These high MetS risk subjects, together with a reference sample of 1095 healthy children, were further invited to undergo medical examinations for verification based on venipuncture blood samples. After excluding children who actively smoked (i.e. answered "Yes" to the question whether they had smoked one or more cigarettes during the 6 months before the interview), 3150 subjects had complete data and were finally included in the current study. Signed informed consent was obtained from participants and/or their parents/guardians. The BCAMS study was approved by the Ethics Committee at the Capital Institute of Pediatrics in Beijing.

2.2. Clinical and anthropometric measurements

Subjects' height, weight, waist circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured according to our standard protocol [23]. BMI was calculated as weight divided by height squared, BMI z-score was calculated by age and gender according to the standards of the Centers for Disease Control and Prevention 2000. Body fat mass percentage (FAT%) was assessed by bioelectrical impedance analysis (BIA, TANITA TBF-300 A). Pubertal development was assessed by two pediatricians of the same gender as the child and pubertal status was scored by Tanner Stage from breast development in girls and testicular volume in boys.

Information on lifestyle, socioeconomic factors (parents' education and employment status), family history (diabetes, hypertension, dyslipidemia) and parents' weight and height were obtained by questionnaire [24]. Activity (≥3 times/week) and inactivity (< 3 times/week) were assessed by their frequency of participating in extracurricular physical activities (cycling, hiking, running, swimming, etc.) for at least 30 min each time. Diet score was used to evaluate dietary quality [25].

2.3. Laboratory measurements

Blood samples collected after an overnight (≥10 h) fast were analyzed for concentrations of FPG, TG, TC, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), leptin, resistin, adiponectin, FGF21, osteonectin and RBP4. Serum leptin and adiponectin were measured by an enzyme-linked immunosorbent assay (ELISA) which was developed and performed centrally in the National Health Committee Key Laboratory of Endocrinology in Peking Union Medical College Hospital. The intra- and inter-assay CVs for leptin were < 7.4% and < 9.3% [25], and < 5.4% and < 8.5% for adiponectin [26], respectively. Resistin and FGF21 were measured by using the ELISA kit (Phoenix Pharmaceuticals). The intra and inter-assay CVs were < 5.2% and < 10.1% for resistin [23], and < 6.0% and < 8.6% for FGF21, respectively [27]. RBP4 was measured by ELISA kits (R&D Systems) with intra- and inter-assay CVs of 6.2% and 8.5% [20]. For measurement of osteonectin, we have established a sandwich ELISA system with the intra- and inter-assay CVs of 5.2% and 9.1% [28]. All samples were assayed blind in duplicate.

2.4. Exposure to parental smoking

The parental smoking status data was self-reported by participants and/or their parents/guardians as they were asked whether father and/or mother smoked. The corresponding answers were "Neither", "Father only", "Mother only" and "Both". Due to the small proportion of subjects with maternal smoking (2.5%), we classified the sample into two groups by PSE: children with at least one parent reporting smoking and children with no exposure to parental smoking.

2.5. Definition of metabolic syndrome

A modified ATPIII criteria for MetS was employed in this study, in which MetS was defined by the presence of greater than or equal to three of the following five components [23]: (1) central obesity defined as waist circumference ≥ 90th percentile for age and gender (established based on the BCAMS study); (2) elevated blood pressure defined as SBP/DBP ≥ 90th percentile for age, sex and height (according to the BCAMS study); (3) elevated TG defined as TG ≥ 1.24 mmol/L, equal to the 90th percentile of the reference population; (4) reduced HDL-C defined as ≤ 1.03 mmol/L, equivalent to 5th percentile of the reference population; (5) hyperglycemia defined as FPG ≥ 5.6 mmol/L. According to the Working Group for Obesity in China [29], we used age- and sex-specific BMI percentiles to define overweight (85th) and obesity (95th) for children and adolescents.

2.6. Statistical analysis

Values were expressed as means (standard deviation), median (interquartile range), percentage (%) or mean ± standard error as appropriate. All skewed distributions were natural log (ln)-transformed

Table 1
Characteristics stratified by parental smoking status.

	Non-exposed (n = 1108)	Parental smoking (n = 2042)	*p*
Age (y)	11.7 (3.1)	12.0 (3.1)	**0.008**
Boys, n (%)	576 (52.0)	1001 (49.0)	0.112
Birthweight (kg)	3.35 (0.53)	3.35 (0.52)	0.758
Tanner stage, n (%)			**0.016**
I	358 (33.4)	623 (31.4)	
II	159 (14.8)	282 (14.2)	
III	196 (18.3)	318 (16.0)	
IV	262 (24.4)	499 (25.2)	
V	98 (9.1)	260 (13.1)	
Body weight status, n (%)			< **0.001**
Normal weight	610 (55.3)	847 (41.7)	
Overweigh	184 (16.7)	397 (19.5)	
Obesity	310 (28.1)	789 (38.8)	
Urban, n (%)	798 (72.0)	1217 (59.6)	< **0.001**
Lifestyle factors			
Daily sleeping hours (h)	8.5 (1.2)	8.5 (1.2)	0.531
Diet scores	36.5 (4.5)	35.4 (4.9)	< **0.001**
Activity (≥3 times/week), n (%)	619 (56.9)	1126 (56.0)	0.610
Socioeconomic factors			
Father's education ≥ university, n (%)	331 (30.3)	340 (16.8)	< **0.001**
Mother's education ≥ university, n (%)	223 (20.4)	276 (13.6)	< **0.001**
Unemployment father, n (%)	34 (3.1)	104 (5.2)	**0.007**
Unemployment mother, n (%)	95 (8.8)	189 (9.5)	0.570
Family history			
Any parents has diabetes, n (%)	28 (2.5)	89 (4.4)	**0.009**
Any parents has hypertension, n (%)	126 (11.4)	240 (11.8)	0.750
Any parents has dyslipidemia, n (%)	90 (8.1)	141 (6.9)	0.211
Father's BMI (kg/m^2)	25.13 (3.20)	24.92 (3.26)	0.086
Mother's BMI (kg/m^2)	22.92 (3.35)	23.47 (3.47)	< **0.001**
Adiposity-related anthropometric indices			
BMI (kg/m^2)	21.01 (4.74)	22.40 (4.97)	< **0.001**
BMI z-score	0.65 (1.22)	0.94 (1.17)	< **0.001**
waist circumference (cm)	70.3 (12.5)	73.5 (13.2)	< **0.001**
FAT%	22.86 (8.31)	25.36 (8.57)	< **0.001**
Adipokine profiles			
Leptin (ng/ml)	4.79 (1.52–11.04)	7.04 (2.39–15.83)	< **0.001**
Adiponectin (ug/ml)	11.71 (7.92–17.14)	11.05 (7.32–15.58)	**0.011**
RBP4 (μg/ml)	32.18 (26.05–39.72)	32.87 (27.62–39.97)	**0.001**
FGF21 (pg/ml)	601.50 (264.00–1538.50)	547.50 (249.00–1353.00)	**0.034**
Resistin (ng/ml)	14.58 (10.44–21.24)	14.83 (10.70–21.46)	0.841
Osteonectin (μg/ml)	1.05 (0.78–1.44)	1.02 (0.78–1.41)	0.623
Metabolic indices			
SBP (mm Hg)	106 (14)	109 (14)	< **0.001**
DBP (mm Hg)	66 (10)	69 (10)	< **0.001**
TG (mmol/L)	0.86 (0.63–1.20)	0.91 (0.67–1.24)	**0.020**
TC (mmol/L)	4.11 (0.81)	4.09 (0.79)	0.545
LDL-C (mmol/L)	2.53 (0.74)	2.56 (0.72)	0.283
HDL-C (mmol/L)	1.43 (0.33)	1.39 (0.32)	< **0.001**
Fasting glucose (mmol/L)	5.0 (0.5)	5.1 (0.5)	**0.002**
MetS components			
Central obesity, n (%)	301 (27.3)	769 (37.9)	< **0.001**
Elevated BP, n (%)	280 (25.3)	634 (31.1)	< **0.001**
Reduced HDL-C, n (%)	97 (8.8)	223 (10.9)	0.055
Elevated TG, n (%)	249 (22.5)	512 (25.1)	0.104
Hyperglycemia, n (%)	111 (10.1)	259 (12.7)	**0.028**
MetS, n (%)	104 (9.5)	282 (14.0)	< **0.001**

BMI, body mass index; BMI z-score: standardized by age and gender; FAT%, fat mass percentage; RBP4, retinol binding protein 4; FGF21, fibroblast growth factor 21; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; BP, blood pressure; MetS, metabolic syndrome. Values displayed as mean (standard deviation), median (interquartile range) or number (%). Values in bold are significant at $p < 0.05$.

for the analyses. Two sample t tests were applied to compare continuous variables. Differences among categorical variables were evaluated using chi-square test. Rank sum test was used for ranked data. Covariance analysis was applied to test the associations of secondhand smoking status with adiposity-related anthropometric indices, adipokines and cardiometabolic risk factors. Coefficient estimates of log (ln)-transformed adipokines were converted to the original scale and interpreted as relative differences (in percentages) in comparison to the reference category [30]. Binary logistic regression models were used to estimate the odds ratios (OR) for MetS and its components. For all statistical analyses, a two-tailed p value < 0.05 was considered statistically significant. Analyses were performed with the Statistical Package for Social Science (SPSS) 24.0.

3. Results

3.1. Study subjects

The characteristics of subjects stratified by parental smoking status are summarized in Table 1. There were 2042 (64.8%) children exposed

Table 2
Adjusted adiposity parameters and adipokine levels between different parental smoking status groups.

	Non-exposed	Parental smoking	*p*
BMI (kg/m^2)	21.13 ± 0.13	22.25 ± 0.10	< **0.001**
BMI z-score	0.65 ± 0.03	0.93 ± 0.03	< **0.001**
Waist circumference (cm)	70.3 ± 0.3	73.1 ± 0.2	< **0.001**
FAT%	23.30 ± 0.25	25.18 ± 0.18	< **0.001**
Leptin (ng/ml)[a]	1.41 ± 0.04	1.74 ± 0.03	< **0.001**
Adiponectin (μg/ml)[a]	2.42 ± 0.02	2.38 ± 0.01	**0.036**
RBP4 (μg/ml)[a]	3.45 ± 0.01	3.49 ± 0.01	**0.006**
FGF21 (pg/ml)[a]	6.51 ± 0.04	6.39 ± 0.03	**0.023**
Resistin (ng/ml)[a]	2.72 ± 0.02	2.73 ± 0.01	0.891
Osteonectin (μg/ml)[a]	0.04 ± 0.02	0.06 ± 0.01	0.596

BMI, body mass index; BMI z-score: standardized by age and gender according; FAT%, fat mass percentage; RBP4, retinol binding protein 4; FGF21, fibroblast growth factor 21.
Analysis of covariance controlled for age, sex, Tanner stage, residence, diet scores, parents' education (highest education level in parents defined by either parent), parents' BMI and family history (diabetes).
Data are expressed as the mean ± standard error.
Values in bold are significant at $p < 0.05$.
[a] Skewed distributions were natural logarithmically transformed.

to parental smoking. The mean ages of the two groups were 12.0 and 11.7 years, respectively ($p < 0.05$). The proportions of boys in two groups were roughly equivalent ($p > 0.05$). The exposed group was older, with more overweight and obesity, unhealthier diet, family history of diabetes and lower socioeconomic status (all $p < 0.05$). No relationships of tobacco exposure with sleep and exercise were observed (all $p > 0.05$).

3.2. Parental smoking, adiposity-related anthropometric indices, and adipokine profiles

Children with PSE were strongly associated with elevated BMI, BMI z-score, waist circumference and FAT% (all $p < 0.001$) (Table 1). In adjusted analyses, as shown in Table 2, additional adjustments for age, sex, Tanner stage, residence, diet scores, parents' education, parents' BMI and family history didn't change the associations between PSE and adiposity-related anthropometric indices. With respect to adipokines (Table 2 and Fig. 1), PSE resulted in a 39.2% increase (percent difference converted to original scale) in leptin, a 11.4% decrease in FGF21, a 4.6% decrease in adiponectin and a 3.9% increase in RBP4 levels, with adjustment for age, sex, Tanner stage, residence, diet scores, parents' education, parents' BMI and family history (all $p < 0.05$). There was no significant difference in resistin and osteonectin levels between the two groups (all $p > 0.05$). However, after further adjustment for BMI (Fig. 1), only the difference in leptin levels between the two groups remained significant (percent difference 8.6%, $p = 0.017$) but was markedly attenuated.

3.3. Parental smoking and metabolic characteristics

Compared to the non-exposed group, PSE children had increased SBP, DBP, TG, FPG and decreased HDL-C (all $p < 0.05$) (Table 1). The prevalence of MetS was 14% in children exposed to parental smoking versus 9.5% in those not exposed ($p < 0.001$). Exposed children had more frequent central obesity, elevated blood pressure and hyperglycemia compared to the non-exposed (all $p < 0.05$).

In adjusted analyses (Supplementary Table S1), SBP and DBP were still positively associated with PSE in the model which adjusted for age, sex, Tanner stage, residence, diet scores, parents' education, parents' BMI and family history, whilst FPG ($p = 0.065$) and HDL-C ($p = 0.062$) were borderline significant. When further adjusting for BMI, however, all associations were abolished (all $p > 0.05$). In sensitivity analysis, adjustment of waist circumference, or FAT%, or above-mentioned adipokines instead of BMI did not change the results (data not shown).

In multiple logistic regression (Table 3) when controlling for age, sex and Tanner stage, PSE was significantly associated with central obesity (OR 1.63, 95% CI 1.38–1.92, $p < 0.001$), elevated blood pressure (OR 1.33, 95% CI 1.13–1.58, $p = 0.001$), hyperglycemia (OR 1.30, 95% CI 1.02–1.66, $p = 0.032$) and higher risk of MetS (OR 1.55, 95% CI 1.21–1.98, $p < 0.001$), but not with altered lipids. After further adjustment for residence, lifestyle, socioeconomical factors and family history, associations of PSE with central obesity (OR 1.59, 95% CI 1.33–1.90, $p < 0.001$), elevated blood pressure (OR 1.22, 95% CI 1.02–1.46, $p = 0.028$) and MetS (OR 1.43, 95% CI 1.11–1.85, $p = 0.006$) were still significant (all $p < 0.05$), whilst attenuated with additional adjustment for BMI (all $p > 0.05$). Again, the finding was unchanged when adjusted for adiposity by including waist circumference (data not shown) or FAT%, or the above-mentioned adipokine profiles instead of BMI as a covariate.

4. Discussion

Although increasing evidence suggests an association between PSE and obesity in childhood, studies including adipokine biomarkers to elucidate such relationship are scarce. Based on this large BCAMS study of Chinese children, we investigated the association of PSE with a series of promising adipokines, and we found that PSE was not only associated with adiposity, but also with unfavorable adipokine profiles including increased leptin and RBP4 as well as decreased adiponectin and FGF21 levels. These are in part due to the increased adiposity, but the elevated levels of leptin remained, even when adjusted for BMI. In addition, we demonstrated the associations of PSE with hypertension and MetS in Chinese children, which were not confounded by age, sex, puberty, dietary habits, socioeconomic factors, parents' BMI and family history. Notably, these associations no longer held with additional adjustment for adiposity-related anthropometric indices or adipokines, suggesting that impaired function of adipose tissue, especially alterations in adipokines levels, might mediate the relation between passive smoking and cardiometabolic disorders in children.

As expected, our study confirmed previous findings that PSE was correlated with offspring adiposity, where BMI was adopted as the main adiposity indicator [2,8,31]. It should be acknowledged that BMI does not reflect body fat distribution; therefore we also assessed the FAT% (a supplementary estimate of total adiposity) and waist circumference (a recommended marker of abdominal adiposity). The consistent findings when using different anthropometric indices reinforced the conclusion that PSE was positively associated with offspring adiposity.

Many adipokines are pro-inflammatory but a subset has anti-inflammatory functions such as adiponectin. Importantly, the imbalance of pro- and anti-inflammatory adipokines caused by excess adiposity, contributes to metabolic dysfunction [13]. In the current study, we selected six inflammation-related adipokines and found associations between PSE and adipokine profiles. In addition, controlling for these adipokines removed the association of PSE and clinical manifestation of multiple cardiometabolic disorders.

Among the six adipokines we studied, leptin and adiponectin, as classic pro- and anti-inflammatory adipokines, were the two most studied in literature. Notably, in line with the previous studies [18,32], we found that childhood tobacco smoke exposure was associated with elevated leptin and reduced adiponectin. In a study of 990 Swedish children, participants exposed to secondhand smoke exhibited a 27% increase in leptin levels (comparable with our 39.2%), while no significant difference in adiponectin levels was observed [30]. However, although observational studies showed discrepancies, available experimental studies indicated that nicotine could increase leptin levels [33] and reduce the expression of adiponectin [34]. Therefore, exposure to parental smoking may cause the dysregulation of leptin and adiponectin, which may subsequently lead to metabolic disorders.

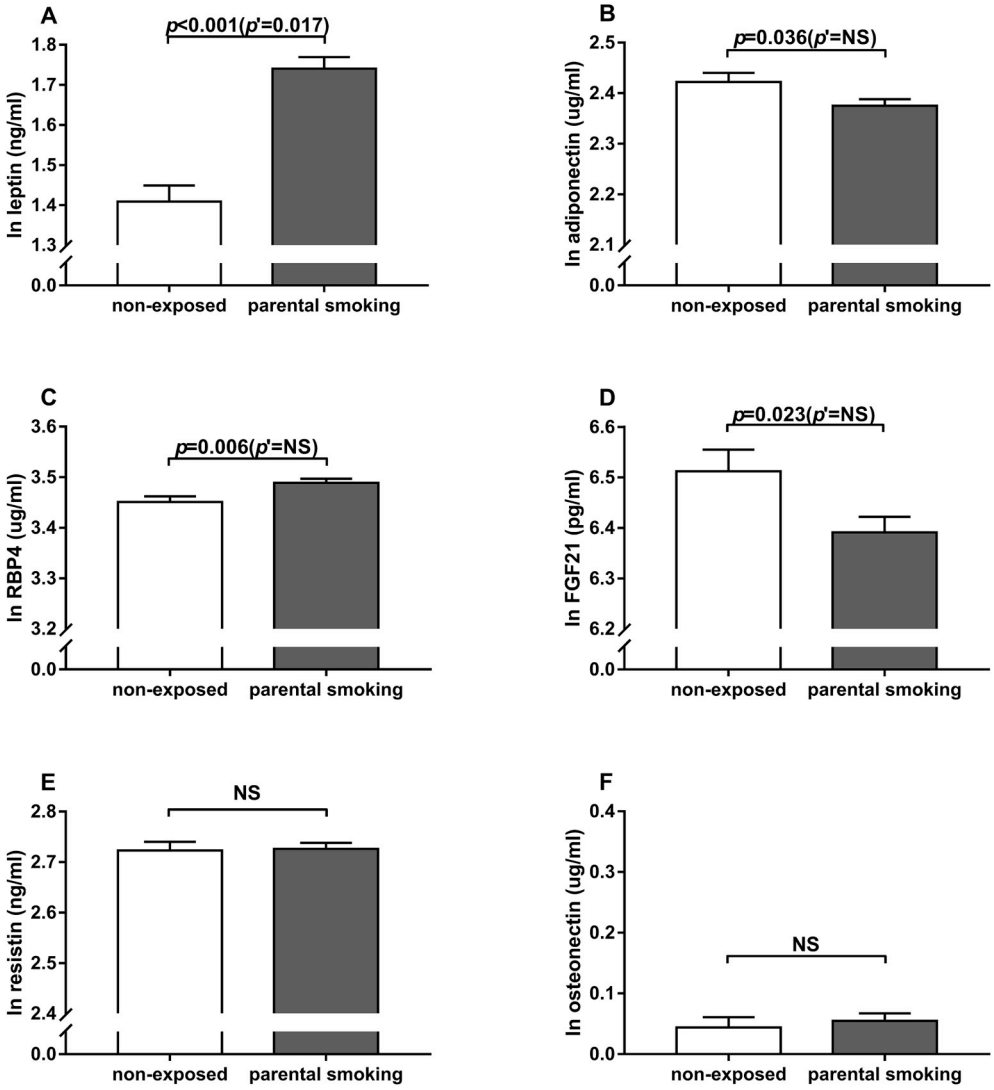

Fig. 1. Adjusted levels of adipokines between different parental smoking status groups.
Data were natural logarithmically transformed and expressed as mean with standard error. All *p* values were adjusted for age, sex, Tanner stage, residence, diet scores, parents' education (highest education level in parents defined by either parent), parents' BMI and family history (diabetes); *p*' values were further adjusted for BMI. (A) The parental smoking group was associated with increased leptin compared with the non-exposed group. (B) The parental smoking group had lower adiponectin levels than the non-exposed group, and the difference was attenuated with further adjustment for BMI. (C) The parental smoking group was associated with increased RBP4 levels compared with the non-exposed group, and the association was attenuated with further adjustment for BMI. (D) The difference in FGF21 levels between the two groups was attenuated after controlling for BMI. (E and F) Resistin and osteonectin levels were not significantly different (NS) between the two groups.
RBP4, retinol binding protein 4; FGF21, fibroblast growth factor 21.

Table 3
Adjusted associations between parental smoking status and metabolic syndrome and its components.

	Model 1		Model 2		Model 2 + BMI		Model 2 + FAT%		Model 2 + adipokine profiles[a]	
	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*	OR (95%CI)	*p*
Central obesity	1.63 (1.38–1.92)	< **0.001**	1.59 (1.33–1.90)	< **0.001**	–	–	–	–	–	–
Elevated BP	1.33 (1.13–1.58)	**0.001**	1.22 (1.02–1.46)	**0.028**	1.00 (0.83–1.21)	0.988	1.07 (0.89–1.29)	0.472	1.06 (0.87–1.29)	0.550
Reduced HDL-C	1.23 (0.95–1.60)	0.115	1.16 (0.88–1.53)	0.283	0.99 (0.75–1.31)	0.941	1.04 (0.79–1.38)	0.771	1.08 (0.80–1.45)	0.626
Elevated TG	1.31 (0.95–1.35)	0.172	1.09 (0.91–1.32)	0.350	0.93 (0.77–1.13)	0.466	0.99 (0.82–1.20)	0.911	0.85 (0.69–1.05)	0.138
Hyperglycemia	1.30 (1.02–1.66)	**0.032**	1.17 (0.92–1.51)	0.204	1.14 (0.89–1.47)	0.310	1.15 (0.89–1.48)	0.281	1.16 (0.89–1.52)	0.262
MetS	1.55 (1.21–1.98)	< **0.001**	1.43 (1.11–1.85)	**0.006**	1.02 (0.76–1.37)	0.879	1.21 (0.92–1.59)	0.183	1.05 (0.79–1.40)	0.735

HDL-C, high-density lipoprotein cholesterol; BP, blood pressure; TG, triglyceride; MetS, metabolic syndrome.
Model 1: adjusted for age, sex, Tanner stage.
Model 2: adjusted for age, sex, Tanner stage, residence, diet scores, parents' education (highest education level in parents defined by either parent), parents' BMI and family history (diabetes).
Values in bold are significant at $p < 0.05$.
[a] Adipokine profiles include leptin, adiponectin, FGF21 and RBP4. Adipokine levels were natural logarithmically transformed for analyses.

Like leptin, RBP4 and resistin generally exhibit pro-inflammatory properties. RBP4, highly expressed in adipose and liver, enhances the expression of phosphoenolpyruvate carboxykinase to elevate hepatic glucose production and attenuates insulin signalling to impair muscle glucose uptake [13]. It is therefore a known biomarker of insulin resistance and MetS [13,20]. In line with our previous finding that active smoking increased RBP4 levels in adults [35], the present study showed that PSE was also associated with increased RBP4 levels in children. Thus, increased RBP-4 concentrations may serve as a novel link between smoking and insulin resistance, and MetS. Resistin may activate suppressor of cytokine signaling 3 (SOCS3) to modulate glucose metabolism and inhibit insulin signalling, promoting inflammation and insulin resistance [13]. A previous study in adults showed that smoking men had higher resistin levels, and nicotine increased resistin through

activation of the KATP channel [36]. However, we did not find a strong link between PSE and circulating resistin levels among children. Given the poor knowledge of these associations, our findings underscore the need for further studies to elucidate the associations.

In contrast to previous work on leptin, adiponectin, resistin and RBP-4, FGF21 and osteonectin have not yet been reported in previous research of PSE. FGF21 represses inflammation, promotes fatty acid oxidation, increases glucose uptake, reduces serum glucagon, improves insulin sensitivity and protects against MetS [21]. The adipokine osteonectin also plays a key role in adipose tissue inflammation and related metabolic diseases [22]. In the present study, we found that children exposed to parental smoking had lower FGF21 levels than controls, but no significant difference in osteonectin levels was observed. More studies are needed to confirm these observations.

In line with previous studies in children [9,31], we demonstrated the association of passive smoking with MetS in Chinese children. As for the components of MetS, except for lipids, either central obesity, elevated blood pressure or hyperglycemia showed association with PSE in the present study. However, previous studies showed discrepancies in blood pressures [10,31], lipids [7,31] and fasting glucose [31,37]. Different levels of adjusted cofounders, racial difference and small sample sizes with less power might contribute to these discrepancies. Besides, it should be noted that sex differences might also account for the inconsistent results, as we found the adverse effects of tobacco exposure were greater in boys than in girls (Supplementary Table S2). However, the mechanism involved is unclear and further studies are warranted to elucidate these sex-related differences.

Interestingly, associations between PSE and cardiometabolic factors were all attenuated when additional adjustment for adiposity-related anthropometric indices or adipokine profiles was made, implying that association between tobacco exposure and cardiometabolic disorders might be causally linked through excess adiposity and concomitant adipokine profiles. Moreover, previous adult studies and animal studies also provided support for our results [15,16,38]. It is noteworthy that the dysregulated adipokines, as biomarkers for pathophysiological changes, may initiate cardiovascular disorders in early life. Multiple behavioral and environmental factors including passive smoking might impact the cardiometabolic risk through dysregulation of adipokines. Our study indicated that identifying children with abnormal adipokines followed by early preventive strategies could be of particular significance to lower future cardiovascular risk [21].

China has the largest number of smokers in the world. However, according to data from the ITC China Project, there has been limited progress in tobacco control over the last decade [6,39]. Our study adds evidence on the potential adverse health effects of tobacco, suggesting that there is an urgent need for implementing strong national smoke-free laws to reduce the detrimental effects of tobacco exposure, not only on smokers themselves, but also on passive smokers, especially children.

The current study benefits from a large, well-characterized cohort of individuals, with a wealth of phenotypic information collected according to a standardized protocol. We were able to examine a wide array of cardiometabolic outcomes, controlling for many potential confounding factors, while the large sample size enabled sufficient power for statistical inference. Moreover, we systematically analyzed six inflammation related adipokines, contributing to a better understanding of the potential pathways by which tobacco exposure causes cardiometabolic disorders. Nevertheless, there are several limitations to the study. First, our self-reported exposure lacked detailed information to quantify the accumulative exposure that may cause bias and limit precision of the exposure measurement. Although the metabolites of nicotine were proposed to quantify the exposure, lack of a unified standard may lead to incomparable results [38,40]. Second, we did not distinguish prenatal from postnatal exposure. As individuals generally start smoking at an early age, it is unlikely that smoking parents stopped smoking after giving birth to their children. Third, while the sample size was large, there were not enough subjects to separately examine maternal smoking as it was rare in this sample. Moreover, parents' weight and height were recorded through self-report questionnaires rather than by laboratory examination, and this may have influenced the accuracy of the data. Lastly, the associations were examined in cross-sectional settings, which is not sufficient to establish causality, and future longitudinal studies are necessary to clarify the current findings.

In conclusion, in this Chinse cohort, we found PSE was not only associated with fat storage, but also with alteration in plasma adipokines, including increased leptin and RBP4, as well as decreased adiponectin and FGF21, which might explain the association of PSE and high MetS risk among the children. Our study provides novel insights into passive smoking and cardiometabolic dysfunction in youth, and emphasizes the urgency of adopting and implementing complete smoking bans.

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CRediT authorship contribution statement

Yu Li: Investigation, Formal analysis, Writing - original draft, Visualization. **Dongmei Wang:** Investigation. **Yuhan Wang:** Investigation. **Yanglu Zhao:** Formal analysis, Writing - review & editing. **Lanwen Han:** Investigation. **Ling Zhong:** Investigation. **Qian Zhang:** Investigation. **John R. Speakman:** Data curation, Writing - review & editing. **Ming Li:** Investigation, Data curation, Writing - review & editing. **Shan Gao:** Conceptualization, Investigation.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2020.03.023.

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