Journal of Developmental Origins of Health and Disease

www.cambridge.org/doh

Involuntary tobacco smoke exposures from conception to 18 years increase midlife cardiometabolic disease risk: a 40-year longitudinal study

Zhongzheng Niu[1], Lina Mu[1], Stephen L. Buka[2], Eric B. Loucks[2], Meng Wang[1,3,4], Lili Tian[5] and Xiaozhong Wen[6]

[1]Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, The State University of New York at Buffalo, Buffalo, NY, USA; [2]Department of Epidemiology, Brown University School of Public Health, Providence, RI, USA; [3]RENEW Institute, The State University of New York at Buffalo, Buffalo, NY, USA; [4]Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington, Seattle, WA, USA; [5]Department of Biostatistics, School of Public Health and Health Professions, The State University of New York at Buffalo, Buffalo, NY, USA and [6]Division of Behavioral Medicine, Department of Pediatrics, Jacobs School of Medicine and Biomedical Sciences, The State University of New York at Buffalo, Buffalo, NY, USA

Original Article

Cite this article: Niu Z, Mu L, Buka SL, Loucks EB, Wang M, Tian L, and Wen X. (2023) Involuntary tobacco smoke exposures from conception to 18 years increase midlife cardiometabolic disease risk: a 40-year longitudinal study. *Journal of Developmental Origins of Health and Disease* **14**: 689–698. doi: 10.1017/S2040174423000375

Received: 23 June 2023
Revised: 29 October 2023
Accepted: 29 November 2023
First published online: 8 January 2024

Keywords:
Maternal smoking; involuntary smoke; environmental tobacco smoke; cardiometabolic disease; hypertension; diabetes; Collaborative Perinatal Project; DOHaD

Corresponding author:
Xiaozhong Wen;
Email: xiaozhongwen@hotmail.com

Abstract

Few population studies have sufficient follow-up period to examine early-life exposures with later life diseases. A critical question is whether involuntary exposure to tobacco smoke from conception to adulthood increases the risk of cardiometabolic diseases (CMD) in midlife. In the Collaborative Perinatal Project, serum-validated maternal smoking during pregnancy (MSP) was assessed in the 1960s. At a mean age of 39 years, 1623 offspring were followed-up for the age at first physician-diagnoses of any CMDs, including diabetes, heart disease, hypertension, or hyperlipidemia. Detailed information on their exposure to environmental tobacco smoke (ETS) in childhood and adolescence was collected with a validated questionnaire. Cox regression was used to examine associations of *in utero* exposure to MSP and exposure to ETS from birth to 18 years with lifetime incidence of CMD, adjusting for potential confounders. We calculated midlife cumulative incidences of hyperlipidemia (25.2%), hypertension (14.9%), diabetes (3.9%), and heart disease (1.5%). Lifetime risk of hypertension increased by the 2nd -trimester exposure to MSP (adjusted hazard ratio: 1.29, 95% confidence interval: 1.01–1.65), ETS in childhood (1.11, 0.99–1.23) and adolescence (1.22, 1.04–1.44). Lifetime risk of diabetes increased by joint exposures to MSP and ETS in childhood (1.23, 1.01–1.50) or adolescence (1.47, 1.02–2.10). These associations were stronger in males than females, in never-daily smokers than lifetime ever smokers. In conclusion, early-life involuntary exposure to tobacco smoke increases midlife risk of hypertension and diabetes in midlife.

Introduction

Heart disease, stroke, and diabetes, together known as cardiometabolic disease (CMD), cause 18 million deaths in the globe each year, more than any other causes.[1] Although CMD is mainly diagnosed in a later life, cumulating evidence has suggested that its disease process initiates in early life.[2,3] This early initiation has also been associated with various early-life environmental exposures.[4] Of particular interests are involuntary exposures to tobacco smoke, including *in utero* exposure to maternal smoking during pregnancy (MSP) and environmental tobacco smoke (ETS) exposure after birth.[5] *In utero* exposure to MSP has been associated with low birth weight, childhood obesity, and decreased kidney volume, while ETS exposure after birth may further potentiate the risk of diabetes and hypertension.[6–10] However, there is little research directly linking early-life involuntary exposure to tobacco smoke with later-life CMD, mostly due to the challenge of long follow-up.[5,11] In addition, MSP and ETS are correlated, because mothers who smoked during pregnancy are likely to continue smoking after delivery and thus expose the offspring to ETS, generating a "double-hit".[12] However, whether early-life exposure to the "double-hit" of both MSP and ETS may have additive effect on CMD remains unknown.

We *a prior* selected sex and offspring's own smoking as potential effect modifiers. Previous studies have suggested sex differences in the susceptibility of exposure to maternal stressors during pregnancy where females were more likely to be protected by estrogens and earlier linear growth compared to males.[13] In addition, cardiovascular responses to maternal stressors during pregnancy (e.g., undernutrition) and early-life stressors (emotional and physical stimuli) differ by sex, where males had higher resting vascular resistance while females had higher cardiac sympathetic activation.[14] Moreover, risk of midlife CMD is also higher in males than females.[15]

Similarly, one's own smoking has been an established risk factor for CMD.[15,16] Thus, we also stratified the analyses by adult smoking status to explore potentially different pathways with or without adult smoking.

We analyzed data from a 40-year longitudinal study, the New England Family Study (NEFS), that collected detailed information on MSP in the 1960s and then followed the adult offspring in the 2000s for CMD occurrence and a detailed history of ETS exposure from birth to 18 years.[17,18] Although the prevalence of smoking was much higher in the 1960s (over 50%) compared to the present (about 10%),[19] the biological mechanism underlying the association of early-life involuntary exposure to smoking with midlife CMD risk should not change with time substantively, and therefore findings based on this historical cohort remain relevant, especially to test the developmental origins of health and disease (DOHaD) hypotheses. We hypothesized that (1) the risk of CMD increased with *in utero* exposure to MSP and early-life exposure to ETS, and (2) the increased risk could be more striking when exposed both *in utero* and in early life, among males or active smokers.

Methods

Study population

Participants were offspring born to mothers who were enrolled at two New England sites (Boston, MA and Providence, RI, total $N = 15{,}721$) of the Collaborative Perinatal Project (CPP) from 1959 to 1966. The CPP was a multicenter, national-wide birth cohort study ($N = 55{,}908$) on prenatal and perinatal factors of children's health.[18] Detailed information on mothers' health and behaviors was collected, including their smoking habits in each trimester of pregnancy. In 2001–2004, a follow-up project, the New England Family Study (NEFS), randomly selected 4579 adult offspring born to mothers of the CPP to fill a screening questionnaire, among whom 3121 mailed back the questionnaire. Eventually, 1674 finished the follow-up questionnaire and 1623 with complete information made to the final analytical sample. Compared to the remaining unselected 11,142 who were also born to mothers of CPP at New England sites, the final analytical sample had similar distributions of maternal smoking and other key covariates, such as maternal age at delivery.[17,20] There is a higher proportion of female offspring in the NEFS than in the original cohort, possibly due to a lower response rate in males than in females, as has been seen in other studies.[21] All participants provided informed consent at enrollment. The study was reviewed by Institutional Review Boards at Harvard School of Public Health, Brown University, and University at Buffalo.

Maternal smoking during pregnancy

At each prenatal visit, mothers reported whether they smoked cigarettes since the last visit and, if so, the average number of cigarettes smoked per day. For women enrolled in the second (49.4%) or third (18.6%) trimester, their smoking behaviors before enrollment were imputed using the information collected from the earliest prenatal visits. A validation study demonstrated strong agreement (Kappa = 0.83) between serum cotinine and self-reported smoking in a subsample of the CPP participants.[22] We converted the number of cigarettes to packs (1 pack = 20 cigarettes) in each trimester as the trimester-specific quantity of *in utero* exposure to MSP and then averaged over the three trimesters as the whole pregnancy exposure in further analyses.

Environmental tobacco smoke exposure

At the adult follow-up telephone interview, trained staff used a questionnaire to assess each participant's exposure to ETS in early life. The questionnaire had similar questions for two periods: birth to 10 years (childhood) and 11–18 years (adolescence). Participants answered if they lived together with the following potential caretakers: the biological mother, biological father, other female, and other male caregivers, in each year from birth to 18 years. If they lived together, participants further answered 'Did your (fill in type of caretaker) ever smoke (cigarettes, pipes, cigars) in your home for a year or longer? If YES, how old were you then. (circle all ages that apply, from birth to 1, then each year from 1 to 18).' Participants also answered 'About how many CIGARETTES did your (fill in type of caretaker) smoke per day, on average? (1 pack = 20 cigarettes). (Selection from None, 0.5, 1, 1.5, 2 or more packs); During these years that your (fill in type of caretaker) smoked in the home, about how many hours per day were you exposed to his/her smoke, on average? (Fill in exact hours).'. The questionnaire also included other questions to help the participant to recall each smoker's behavior: if family photos from childhood/adolescence often showed the smoker's smoking, and in which situations the smoker smoked when the participant was around (e.g., during meals and while driving). In addition to the four possible caregivers listed above, a fifth smoker's smoking behavior and the relationship with the participant were asked in a similar manner, but the information was not included in the analyses because very few participants (<1%) reported a fifth smoker. Because the pack of smoked cigarettes and the hour of exposure to each smoker were asked for the whole periods in childhood and adolescence, we calculated the average ETS exposure quantity (hour-pack) from each caregiver in each of these two periods using the following formula: ETS quantity = (number of years smoked in the home * average pack per day smoked * hours per day exposed)/year in the period. We then combined the ETS quantity in hour-packs/day across all caregivers as the final ETS exposure in childhood and adolescence, respectively. Retrospective recalling of childhood and adolescence exposure to ETS has been widely used in life course studies, with high agreement in the status, duration, and severity of ETS exposure between participants' recall and the responses from their surrogates (e.g., parents).[23] In addition, the questions that we used have been validated and recommended to assess ETS exposure in this field.[24]

Cardiometabolic disease

At the adult follow-up, participants filled a questionnaire on their health status and medical history. Participants were asked if a doctor had ever told them that they had any of the following CMDs: high blood pressure (hypertension), high cholesterol (hypercholesterolemia), stroke, heart attack, angina, congestive heart failure, or diabetes. Considering the severity of the diseases and the small number of cases, we combined stroke, heart attack, angina, coronary heart disease, and congestive heart failure into one group named "heart disease". For hypertension and diabetes, a second question was asked about whether the condition was only diagnosed during pregnancy. Pregnancy-induced hypertension and gestational diabetes were not considered as CMD diagnoses in current analyses. If a CMD was reported, further questions were asked on the age at the first diagnosis and current medication use.

Covariates

In the CPP, mothers reported their race and perinatal characteristics, including age at prenatal enrollment (year), education (<9th,

https://doi.org/10.1017/S2040174423000375 Published online by Cambridge University Press

10th–12th, and >12th grades), marital status (married/other), and parity. We calculated their pre-pregnancy body mass index (BMI, Kg/m^2) using self-reported pre-pregnancy weight and height at prenatal visits in the original CPP. Birth weight (grams) and gestational duration (weeks) were obtained from birth records. At the adult follow-up, the offspring participants reported their age, race, and current active smoking status (yes/no).

Statistical analyses

We used frequencies and proportions to describe the distributions of categorical variables and Chi-squared tests to compare the distribution of categorical variables by maternal smoking status during pregnancy (yes/no). We used the exact probability test to compare the lifetime incidence rates of CMD by maternal smoking status during pregnancy.[25] The potentially non-linear relationship between MSP or ETS exposure and CMD risk was tested by incorporating a spline term of exposure for the risk of CMD in a generalized additive model. Given none of the spline terms reached statistical significance (Supplemental Table S1), we treated MSP or ETS as a continuous variable. We used Cox proportional hazards regression models to estimate the hazard ratios (HRs) and 95% confidence interval (CI) for incident hypertension, hypercholesterolemia, diabetes, and heart disease by each pack/day increment of *in utero* exposure to MSP and by each hour-pack/day increment in ETS exposure in childhood and adolescence. Survival time was based on the duration from birth to the age at the first health-professional diagnosis or age at the adult follow-up if none of these conditions was diagnosed. For ETS exposure, the reported HRs were scaled for an interquartile-range increase in hour-pack/day among those with exposure to facilitate interpretation, i.e., 9.8 hour-pack/day for childhood ETS exposure and 8.0 hour-pack/day for adolescence ETS exposure. To avoid reverse causality, CMD cases that were diagnosed before 18 years were excluded from the analyses ($N = 24$ for hypercholesterolemia, 17 for hypertension, and 7 for diabetes). No cases of heart disease occurred before 18 years. We checked the proportional hazards assumption by testing the statistical significance of the exposures' interactions with the survival time.

The analyses included a set of potential confounders based on the literature review and the hypothesized causal structure analyses using directed acyclic graphs (Supplemental Figures S1–S2).[26] Different sets of confounders have been identified according to the exposure period. A general set of confounders was adjusted for all exposure periods, including study site, maternal age, race, education, marital status, offspring's sex and race. For *in utero* MSP exposure, pre-pregnancy BMI and parity were further adjusted. For ETS exposures in childhood or adolescence, maternal smoking during the whole pregnancy (average pack/day) and birth weight were further adjusted; and for ETS exposure in adolescence, both *in utero* MSP exposure over the whole pregnancy and ETS exposure in childhood were further adjusted. We deemed offspring current smoking as a potential mediator on the path from exposure to outcome, therefore we did not adjust for adult current smoking, which could underestimate the total effect.

In addition to adjusting for *in utero* exposure in the analyses of childhood and adolescent exposure, we also estimated the potential effect modification of *in utero* exposure. Specifically, we calculated the *P*-value for the product term of *in utero* exposure during the whole pregnancy (pack/day) and ETS exposure (hour-pack/day) in childhood and adolescence. We further calculated the stratum-specific hazard ratio of childhood and adolescent ETS exposure by maternal smoking status during pregnancy (yes/no).

We *a priori* selected two potential effect modifiers, i.e., offspring's sex and own active smoking behavior, giving their important roles in the CMD risk.[27] Specifically, we calculated the P-value for interaction between sex and *in utero*, childhood, or adolescence exposure; and estimated the stratum-specific hazard ratio by offspring sex (male/female). Similarly, we calculated the stratum-specific hazard ratio by offspring's smoking status (ever/never-daily smoking).

For the sensitivity analyses to assess the potential dose-response relationship, we restricted the analytic sample by excluding those without MSP/ETS exposure in each period.

All analyses were conducted in SAS 9.4 (Cary, NC).

Results

As shown in Table 1, mothers were enrolled at an average age of 25 years (SD 5.8). Most of the mothers were White (86.4%), had 10th–12th-grade education (63.7%), were married (89.9%), and had normal BMI (18.5–25 Kg/m^2, 73.4%). The median daily cigarette consumption was 3.0 cigarettes in the first trimester and increased to 3.5 and 3.8 cigarettes in the second and the third trimester, respectively. The prevalence of low birth weight (<2500 g) and preterm birth (<37 weeks) were 8.1% and 7.9%, respectively. The offspring were exposed to ETS for a median of 4.0 (Q1, Q3: 0.3, 10.0) hour-packs/day in childhood and 2.0 (Q1, Q3: 0, 7.5) hour-packs/day in adolescence. Offspring were followed-up at an average age of 39.1 years (SD: 1.9), 40.7% of them were males, and 50.2% were daily smokers. Detailed descriptions and histograms of MSP/ETS exposures are shown in Supplemental Figure S3.

As shown in Table 2, risk for hypertension significantly increased by 1.29 times (adjusted HR [aHR], 95% CI: 1.01–1.65) for each pack increment of *in utero* exposure to MSP in the second trimester. The increased risk was similar in the first (aHR: 1.27, 95% CI: 0.99–1.63) and the third (aHR: 1.23, 95% CI: 0.96–1.28) trimester, although not significant. *In utero* exposure to MSP in each trimester was also associated with increased risk of diabetes, although not significantly. There is no significant association of *in utero* exposure to MSP in each trimester with hypercholesterolemia or heart disease.

Interquartile range increment of one hour-pack/day in exposure to ETS in childhood (aHR: 1.11, 95% CI: 0.99–1.23) and adolescence (aHR: 1.22, 95% CI: 1.04–1.44) were both associated with hypertension, even after adjusting for *in utero* exposure to MSP and earlier ETS exposure (for adolescence) (Table 3). When stratified by *in utero* exposure to MSP, risk of hypertension by both childhood and adolescent ETS exposure remained significant only in those with *in utero* MSP exposure, although the *P*-value for interaction was >0.05. Risk of diabetes significantly increased with both childhood (aHR: 1.23, 95% CI: 1.01–1.50) and adolescence (aHR: 1.47, 95% CI: 1.02–2.10) ETS exposure among those with joint *in utero* exposure to MSP.

In sensitivity analyses in a subsample with any exposure to MSP and ETS (excluding unexposed participants), there was no meaningful changes in the main effect estimation for the association of MSP or ETS exposure with CMD risk (Supplemental Table S2).

There is a significant interaction between sex and both *in utero* exposure to MSP and childhood ETS exposure with the risk of hypertension (Table 4). For sex-specific analysis, associations of *in utero* exposure to MSP, childhood and adolescent ETS with hypertension were more striking in males than females. No

https://doi.org/10.1017/S2040174423000375 Published online by Cambridge University Press

Table 1. Maternal and offspring characteristics in 1623 participants of the NEFS study

Characteristics	Overall *N* (%)
Overall	1,623
Maternal characteristics	
Site	
Boston	858 (52.9)
Providence	765 (47.1)
Maternal age at delivery (year), Mean (SD)	25.0 (5.8)
Maternal race/ethnicity	
White	1,403 (86.4)
African American	208 (12.8)
Others	12 (0.7)
Maternal education	
2–9 grades	392 (24.2)
10–12 grades	1,033 (63.6)
>12 grades	198 (12.2)
Maternal marital status – married	1,459 (89.9)
Maternal pre-pregnancy BMI groups	
Undernutrition	125 (7.7)
Normal	1,191 (73.4)
Overweight/obese	307 (18.9)
Parity	
0	357 (22.0)
1	381 (23.5)
≥2	885 (54.5)
Maternal smoking during pregnancy (average cig/day), median (Q1, Q3)	
Whole pregnancy	3.6 (0.0, 17.4)
1st trimester	3.0 (0.0, 17.0)
2nd trimester	3.5 (0.0, 17.5)
3rd trimester	3.8 (0.0, 18.6)
Offspring characteristics	
Birth weight categories	
<2500 g	131 (8.1)
2500–4000 g	1,377 (84.8)
>4000 g	115 (7.1)
Gestational duration categories	
<37 weeks	128 (7.9)
37–42 weeks	1,354 (83.4)
>42 weeks	141 (8.7)
Offspring sex – male	661 (40.7)
Offspring race – white	1,352 (83.3)
ETS exposure (average hour-pack/day), median (Q1, Q3)	
0–18 years	3.5 (0.5, 9.2)
Childhood (0–10 years)	4.0 (0.3, 10.0)
Adolescence (11–18 years)	2.0 (0.0, 7.5)
Age at adult follow-up, Mean (SD)	39.1 (1.9)
Ever daily smoker	815 (50.2)

significant sex differences in the associations were observed for other CMDs.

There is a significant interaction between adult offspring's own smoking status (ever/never-daily smoking) and both *in utero* exposures to MSP and ETS exposure with the risk of diabetes (Table 5). Among never-daily smokers, both *in utero* exposure to MSP in the first (aHR: 2.23, 95% CI: 1.18–4.22) or the second (aHR: 2.35, 95% CI: 1.24–4.47) trimester and ETS exposure in childhood (aHR: 1.38, 95% CI: 1.12–1.71) or adolescence (aHR: 1.45, 95% CI: 1.01–2.08) were associated with increased risk of diabetes. The associations with CMDs were all non-significant among ever-daily smokers.

Discussion

In a 40-year longitudinal cohort, we found involuntary exposures to tobacco smoke from conception to adolescence were associated with increased risk of hypertension in midlife. The risk of hypertension was even higher, and the risk of diabetes was also increased with joint exposure to both *in utero* MSP and childhood/adolescent ETS. Such associations were overall stronger among males than females and among never-daily smokers than ever-daily smokers. We did not find any significant association of early-life involuntary exposure to tobacco smoke with midlife hyperlipidemia or heart disease.

Our findings on the association of *in utero* exposure to MSP with increased risk of hypertension in adulthood were consistent with some previous studies,[6,28] but not all of them.[29,30] A meta-analysis that combined four previous studies found high study heterogeneity ($I^2 > 95\%$, $P < 0.0001$) and a non-significant combined association, suggesting critical roles of study design (prospective vs. retrospective) and exposure assessment accuracy in elucidating the association of *in utero* exposure to MSP with adult hypertension.[30] Our study provides important contribution in this aspect given our prospective collection of MSP, which was not likely to be biased by offspring's health outcomes decades later. We also found the point estimates were generally comparable across the three trimesters of pregnancy, suggesting the whole pregnancy could be important for the association of maternal smoking with future risk of hypertension in offspring. Note in our 1960s pregnancy cohort, only a small proportion (<5%) of mothers changed smoking behavior over pregnancy. Research using recent cohorts in which more women quit smoking at various gestational weeks is needed to further examine whether sensitive windows exist.

The risk of hypertension also increased with exposure to ETS postnatally from birth to 18 years. In previous studies with postnatal ETS exposure,[10,31] *in utero* exposure status was often unknown. Because pregnant women who smoked during pregnancy were likely to continue smoking after giving birth,

https://doi.org/10.1017/S2040174423000375 Published online by Cambridge University Press

Table 2. Cox regression model for associations of *in utero* exposure to maternal smoking with adult cardiometabolic disease

Exposure periods	Hyperlipidemia	Hypertension	Diabetes	Heart disease
N case	409	241	49	24
Person year	60,661	61,458	62,931	63,362
Lifetime incidence rate (per 1000 person-year)	6.74	3.92	0.78	0.38
1st-trimester exposure to maternal smoking, per pack/day				
Unadjusted HR (95% CI)	1.06 (0.88–1.28)	1.21 (0.95–1.53)	1.31 (0.78–2.20)	0.97 (0.45–2.10)
Adjusted HR (95% CI)	1.03 (0.85–1.24)	1.27 (0.99–1.63)	1.25 (0.74–2.13)	0.92 (0.42–2.05)
2nd-trimester exposure to maternal smoking, per pack/day				
Unadjusted model	1.10 (0.92–1.32)	1.22 (0.97–1.55)	1.34 (0.80–2.24)	0.95 (0.44–2.05)
Adjusted model	1.07 (0.88–1.29)	1.29 (1.01–1.65)	1.30 (0.77–2.20)	0.91 (0.41–2.01)
3rd-trimester exposure to maternal smoking, per pack/day				
Unadjusted model	1.10 (0.92–1.33)	1.16 (0.91–1.48)	1.13 (0.65–1.97)	0.90 (0.41–1.98)
Adjusted model	1.08 (0.89–1.30)	1.23 (0.96–1.58)	1.10 (0.62–1.94)	0.88 (0.38–2.02)
Whole pregnancy exposure to maternal smoking, per pack/day				
Unadjusted model	1.09 (0.90–1.32)	1.20 (0.94–1.53)	1.27 (0.74–2.18)	0.94 (0.43–2.06)
Adjusted model	1.06 (0.87–1.28)	1.27 (0.99–1.64)	1.23 (0.71–2.13)	0.90 (0.40–2.05)

HRs measure the effect of a single pack/day increase in maternal smoking during pregnancy on the hazard of adult cardiometabolic disease. Adjusted HR were controlled for study site, maternal age, race, education, marital status, pre-pregnancy BMI, parity, offspring's sex and race.

children exposed to *in utero* maternal smoking were also more likely to be exposed to postnatal ETS. *In utero* exposure could potentially confound the association of postnatal ETS exposure with adult hypertension risk. In the present study, we first adjusted for *in utero* exposure to maternal smoking when postnatal ETS was the main exposure and found no meaningful changes in the point estimate of the association between ETS and CMD. Further, when the analyses on postnatal ETS were stratified by *in utero* exposure, the increased risk of hypertension mostly remained among offspring with *in utero* exposure but not among those without. These findings suggested the importance of accounting for earlier exposure when assessing the effect of postnatal ETS exposure.

In addition to hypertension, the risk of diabetes also increased when the offspring were jointly exposed to *in utero* maternal smoking and postnatal ETS. To the best of our knowledge, we are the first to report such a possible synergetic effect, although the individual effect has been reported previously.[29,32] Two previous studies reported association of *in utero* exposure to maternal smoking with the increased risk of diabetes (including type 2 and gestational diabetes).[29,32] Another two studies showed early-life ETS exposure was associated with risk factors of diabetes, including higher BMI and increased risk of obesity.[11,33] Other than hypertension and diabetes, we also found a non-significantly increased risk of heart disease with ETS exposure in male adolescents, likely because the number of heart disease was small. Nevertheless, our findings were consistent with previous retrospective studies that reported associations of childhood or adolescence ETS exposures with increased carotid artery intima-media thickness,[34] brachial artery flow-mediated dilatation,[32] carotid atherosclerotic plaque,[10] and risk of CHD and stroke.[35]

We found offspring's sex could modify the association of *in utero* and postnatal ETS exposure with CMD. One possible explanation for this sex difference could be the protective effects of hormones and the healthier lifestyle in the female.[36] We also found offspring's own lifetime daily smoking status modified the association of *in utero* and postnatal ETS exposure with midlife risk of hypertension and diabetes. Although adult smoking could be a mediator on the path from MSP/ETS exposure to midlife CMD, our findings on the significant associations among never-daily smokers suggest the underlying mechanisms may be independent of adult smoking. This is also supported by the insignificant associations among ever daily smokers. Another possible explanation for such effect modification is that smokers were less likely to participate research studies,[37] especially those with CMD. Therefore, interpretation of our findings among smokers should take extra caution.

A few plausible mechanisms may explain the association of *in utero* exposure to maternal smoking with adult hypertension, such as upregulated maternal blood pressure tone, nicotine and other harmful substances, placental dysfunction that induce oxidative stress, inflammation, arterial endothelium injury, and epigenetic modification.[38–40] Similarly, early-life exposure to ETS may potentiate the vulnerability of children because children have a higher respiration rate relative to body size than adults, partially developed detoxification mechanisms, and sensitive cardiovascular and endocrine system development during the rapid growth period.[5,41]

Cumulative evidence has suggested that a small disturbance of the cardiovascular system in early life could be amplified over time and subsequently accelerate the development of cardiovascular disease in later life.[42,43] Therefore, protecting children from involuntary tobacco smoke is an important primordial prevention strategy of cardiovascular disease. Banning smoking in public places mitigates ETS in the general population,[44] but studies also reported an increasing trend of ETS exposure in children, possibly because their parents switched to smoking more at home.[45,46] Other intervention strategies such as parental smoking cessation, smoke-free home, and indoor air filtration warrant consideration.[47,48]

https://doi.org/10.1017/S2040174423000375 Published online by Cambridge University Press

Table 3. Cox regression model for associations of childhood and adolescence exposure to ETS with adult cardiometabolic disease

Exposure periods	Hyperlipidemia	Hypertension	Diabetes	Heart disease
Total sample (N = 1623)				
N case	409	241	49	24
Person year	60,661	61,458	62,931	63,362
Lifetime incidence rate (per 1000 person-year)	6.74	3.92	0.78	0.38
Childhood (0–10 years) exposure to ETS[a]				
Unadjusted HR (95% CI)	1.08 (0.99–1.16)	1.10 (0.99–1.21)	1.23 (1.03–1.47)	1.19 (0.91–1.54)
Adjusted HR (95% CI)	1.07 (0.98–1.17)	1.11 (0.99–1.23)	1.18 (0.97–1.45)	1.16 (0.88–1.52)
Adolescence (11–18 years) exposure to ETS[a]				
Unadjusted HR (95% CI)	1.08 (1.00–1.18)	1.16 (1.05–1.28)	1.31 (1.12–1.53)	1.28 (1.03–1.60)
Adjusted HR (95% CI)	1.05 (0.92–1.20)	1.22 (1.04–1.44)	1.35 (0.98–1.86)	1.44 (0.94–2.20)
Offspring without in utero exposure (N = 660)				
N case	158	83	13	9
Person year	24,694	25,043	25,613	25,783
Lifetime incidence rate (per 1000 person-year)	6.40	3.31	0.51	0.35
Childhood (0–10 years) exposure to ETS[a]				
Unadjusted HR (95% CI)	1.18 (0.88–1.58)	1.07 (0.70–1.62)	0.19 (0.02–2.00)	1.84 (0.78–4.34)
Adjusted HR (95% CI)	1.18 (0.88–1.59)	1.16 (0.77–1.74)	0.16 (0.02–1.81)	1.65 (0.69–3.98)
Adolescence (11–18 years) exposure to ETS[a]				
Unadjusted HR (95% CI)	1.11 (0.90–1.36)	1.08 (0.80–1.45)	0.01 (0.00–6.05)	1.63 (1.06–2.52)
Adjusted HR (95% CI)	1.10 (0.88–1.37)	1.17 (0.86–1.58)	0.01 (0.00–5.96)	1.59 (0.96–2.64)
Offspring with in utero exposure (N = 963)				
N case	235	141	30	15
Person year	35,967	36,415	37,318	37,579
Lifetime incidence rate (per 1000 person-year)	6.53	3.87	0.80	0.40
Childhood (0–10 years) exposure to ETS[a]				
Unadjusted HR (95% CI)	1.07 (0.98–1.18)	1.10 (0.98–1.23)	1.24 (1.03–1.49)	1.10 (0.79–1.54)
Adjusted HR (95% CI)	1.05 (0.95–1.16)	1.12 (1.00–1.25)	1.23 (1.01–1.50)	1.10 (0.78–1.56)
Adolescence (11–18 years) exposure to ETS[a]				
Unadjusted HR (95% CI)	1.07 (0.97–1.19)	1.17 (1.05–1.30)	1.33 (1.14–1.55)	1.10 (0.77–1.58)
Adjusted HR (95% CI)	1.02 (0.87–1.19)	1.24 (1.03–1.49)	1.47 (1.02–2.10)	1.08 (0.64–1.84)
*P-interaction**				
Childhood (0–10 years)	0.21	0.91	*0.07*	*0.08*
Adolescence (11–18 years)	0.71	0.55	0.12	0.27

Adjusted HR were controlled for study site, maternal age, race, education, marital status, maternal smoking during pregnancy (average pack/day), offspring's sex, race and birth weight; For ETS exposure in adolescence, ETS exposure in childhood was additionally adjusted.

**P*-interaction tests the significance of the product term of ETS with maternal smoking during the whole pregnancy (yes/no).

[a]HRs measure the effect of an IQR increase in daily exposure to ETS on the hazard of adult cardiometabolic disease (IQR = 9.8 hour-packs/day for ETS exposure in childhood, 8.0 in adolescence).

This study was strengthened by a comprehensive measure of involuntary tobacco smoke exposure from conception to 18 years and the longitudinal follow-up. This study had several potential limitations. As reported previously, female offspring were over-represented in the adult follow-up, thus could introduce a potential collider bias.[20] However, controlling sex as a confounder and stratification analyses by sex could potentially reduce this bias. Information on maternal smoking during pregnancy was self-reported, although measurement error was unlikely to differ by midlife CMDs substantially. Information on ETS exposure was recalled by the adult offspring, thus recall bias might exist given they were aware of their CMD diagnoses. This is a common limitation among life course studies. Prior publications indicated that use of recommended questions and survey methods could

https://doi.org/10.1017/S2040174423000375 Published online by Cambridge University Press

Table 4. Sex-stratified associations of early-life exposure to *in utero* maternal smoking or ETS with adult cardiometabolic disease

Exposure periods	Hyperlipidemia	Hypertension	Diabetes	Heart disease
Among female offspring (N = 962)				
N case	210	98	26	14
Person year	35,982	36,705	37,185	37,456
Lifetime incidence rate (per 1000 person-year)	5.84	2.67	0.70	0.37
1st-trimester exposure to maternal smoking[a]	1.17 (0.89–1.54)	1.03 (0.66–1.60)	1.19 (0.56–2.53)	0.61 (0.17–2.23)
2nd-trimester exposure to maternal smoking[a]	1.22 (0.93–1.59)	1.03 (0.66–1.60)	1.22 (0.58–2.58)	0.61 (0.17–2.20)
3rd-trimester exposure to maternal smoking[a]	1.18 (0.89–1.56)	0.99 (0.63–1.54)	0.97 (0.43–2.18)	0.68 (0.20–2.38)
Whole pregnancy exposure to maternal smoking[a]	1.20 (0.90–1.58)	1.01 (0.65–1.59)	1.13 (0.52–2.48)	0.62 (0.17–2.27)
Childhood (0–10 years) exposure to ETS[a]	1.10 (0.99–1.22)	1.00 (0.84–1.19)	1.10 (0.82–1.46)	1.19 (0.85–1.65)
Adolescence (11–18 years) exposure to ETS[a]	1.08 (0.92–1.26)	1.17 (0.95–1.44)	1.25 (0.85–1.86)	1.17 (0.68–2.02)
Among male offspring (N = 661)				
N case	183	126	17	10
Person year	24,679	24,753	25,746	25,906
Lifetime incidence rate (per 1000 person-year)	7.42	5.09	0.66	0.39
1st-trimester exposure to maternal smoking[a]	0.93 (0.69–1.26)	1.57 (1.12–2.20)	1.50 (0.67–3.37)	1.59 (0.50–5.11)
2nd-trimester exposure to maternal smoking[a]	0.95 (0.71–1.29)	1.55 (1.11–2.18)	1.60 (0.71–3.60)	1.55 (0.48–5.01)
3rd-trimester exposure to maternal smoking[a]	1.00 (0.74–1.36)	1.48 (1.04–2.10)	1.40 (0.60–3.27)	1.29 (0.37–4.45)
Whole pregnancy exposure to maternal smoking[a]	0.96 (0.71–1.30)	1.56 (1.10–2.20)	1.52 (0.66–3.51)	1.49 (0.44–5.04)
Childhood (0–10 years) exposure to ETS[a]	0.97 (0.82–1.14)	1.24 (1.08–1.41)	1.30 (0.99–1.72)	1.05 (0.58–1.92)
Adolescence (11–18 years) exposure to ETS[a]	0.95 (0.78–1.15)	1.27 (1.04–1.54)	1.45 (0.98–2.14)	1.39 (0.79–2.44)
P-interaction				
1st-trimester exposure to maternal smoking[a]	0.22	0.06	0.52	0.15
2nd-trimester exposure to maternal smoking[a]	0.16	0.09	0.48	0.15
3rd-trimester exposure to maternal smoking[a]	0.33	0.12	0.42	0.26
Whole pregnancy exposure to maternal smoking[a]	0.22	0.08	0.47	0.17
Childhood (0–10 years) exposure to ETS[a]	0.10	0.03	0.36	0.94
Adolescence (11–18 years) exposure to ETS[a]	0.14	0.28	0.39	0.29

All models were adjusted for study site, maternal age, race, education, marital status, offspring's race; for intrauterine exposures, pre-pregnancy BMI, parity were also adjusted; for ETS, maternal smoking during pregnancy (average pack/day) and birthweight, were adjusted; and for ETS exposure in adolescence, ETS exposure in childhood was additionally adjusted.
[a]HRs measure the effect of a single pack increase in maternal smoking during pregnancy or an IQR increase in daily exposure to ETS on the hazard of adult cardiometabolic disease (IQR = 9.8 hour-packs/day for ETS exposure in childhood, 8.0 in adolescence).

yield reasonably accurate information on ETS exposure years and the number of exposure pack-years.[24] Our questionnaire utilized these recommended questions and there were additional efforts such as using family photos to facilitate participants to recall early-life exposure. CMD status and age at first diagnosis were self-reported and thus subject to measurement errors. Previous validation studies suggested an acceptable level of reliability of self-reported CMD outcomes in the US population.[49,50] Residual confounding might exist given potential measurement errors in some controlled confounders such as time-varying socioeconomic status. Shared environment could affect both MSP/EST and offspring CMD risk. Although we have adjusted key factors that could reflect some aspects of home and neighborhood environment (e.g., study site, education, age, marital status, race), residual confounding by other factors such as physical activity and diet was not adjusted. We did not adjust for multiple comparisons given that our analyses were hypothesis-driven.[51] Thus, we could not rule out the possibility of false positive results. Although the overall sample size was fairly large, the number of CMD cases was modest, given the relatively young age (~40s) of adult offspring.

Conclusion

In summary, we found *in utero* exposure to maternal smoking during pregnancy as well as exposure to ETS in childhood and adolescence might increase midlife risk of hypertension. In addition, joint exposure to both maternal smoking during pregnancy and ETS in childhood and adolescence might increase the risk of diabetes. Males and never-daily smokers seemed to have even higher risk of midlife CMD if they were exposed to tobacco smoke in early life. Future studies are needed to replicate our findings.

https://doi.org/10.1017/S2040174423000375 Published online by Cambridge University Press

Table 5. Offspring smoking-stratified associations of early-life exposure to *in utero* maternal smoking or childhood/adolescence ETS with adult cardiometabolic disease

Exposure periods	Hyperlipidemia	Hypertension	Diabetes	Heart disease
Never-daily smoker (N = 808)				
N case	171	118	21	12
Person year	30,345	30,696	31,431	31,549
Lifetime incidence rate (per 1000 person-year)	5.64	3.84	0.67	0.38
1st-trimester exposure to maternal smoking[a]	1.04 (0.77–1.41)	1.37 (0.96–1.95)	2.23 (1.18–4.22)	0.72 (0.19–2.63)
2nd-trimester exposure to maternal smoking[a]	1.11 (0.82–1.50)	1.35 (0.95–1.92)	2.35 (1.24–4.47)	0.71 (0.19–2.64)
3rd-trimester exposure to maternal smoking[a]	1.06 (0.77–1.44)	1.41 (0.97–2.04)	1.92 (0.92–4.02)	0.90 (0.25–3.19)
Whole pregnancy exposure to maternal smoking[a]	1.07 (0.78–1.46)	1.39 (0.96–2.00)	2.27 (1.13–4.56)	0.77 (0.21–2.82)
Childhood (0–10 years) exposure to ETS[a]	1.00 (0.86–1.15)	1.16 (1.00–1.33)	1.38 (1.12–1.71)	1.26 (0.86–1.86)
Adolescence (11–18 years) exposure to ETS[a]	1.00 (0.84–1.19)	1.21 (1.01–1.46)	1.45 (1.01–2.08)	1.26 (0.77–2.08)
Ever daily smokers (N = 815)				
N case	222	106	22	12
Person year	30,316	30,762	31,500	31,813
Lifetime incidence rate (per 1000 person-year)	7.32	3.45	0.70	0.38
1st-trimester exposure to maternal smoking[a]	1.09 (0.83–1.44)	1.28 (0.85–1.92)	0.46 (0.16–1.37)	1.29 (0.41–4.10)
2nd-trimester exposure to maternal smoking[a]	1.09 (0.83–1.43)	1.28 (0.85–1.92)	0.50 (0.18–1.43)	1.25 (0.40–3.94)
3rd-trimester exposure to maternal smoking[a]	1.14 (0.87–1.50)	1.10 (0.73–1.66)	0.53 (0.19–1.48)	0.94 (0.27–3.19)
Whole pregnancy exposure to maternal smoking[a]	1.11 (0.84–1.47)	1.22 (0.81–1.85)	0.49 (0.17–1.42)	1.16 (0.35–3.84)
Childhood (0–10 years) exposure to ETS[a]	1.09 (0.97–1.23)	1.09 (0.93–1.27)	0.74 (0.42–1.30)	1.05 (0.65–1.68)
Adolescence (11–18 years) exposure to ETS[a]	1.06 (0.90–1.25)	1.24 (0.99–1.55)	0.86 (0.47–1.60)	1.20 (0.65–2.23)
P-interaction				
1st-trimester exposure to maternal smoking[a]	0.76	0.65	0.01	0.34
2nd-trimester exposure to maternal smoking[a]	0.48	0.53	0.01	0.35
3rd-trimester exposure to maternal smoking[a]	0.72	0.20	0.02	0.70
Whole pregnancy exposure to maternal smoking[a]	0.65	0.42	0.01	0.43
Childhood (0–10 years) exposure to ETS[a]	0.63	0.64	0.03	0.56
Adolescence (11–18 years) exposure to ETS[a]	0.96	0.64	0.07	0.69

All models were adjusted for study site, maternal age, race, education, marital status, offspring's sex, race, and age at adult follow-up; for intrauterine exposures, pre-pregnancy BMI, parity, birth weight category, preterm, or post-term were also adjusted; for ETS, maternal smoking during pregnancy (average pack/day) and birth weight were also adjusted; and for ETS exposure in adolescence, ETS exposure in childhood was additionally adjusted.

[a]HRs measure the effect of a single pack increase in maternal smoking during pregnancy or an IQR increase in daily exposure to ETS on the hazard of adult cardiometabolic disease (IQR = 9.8 hour-packs/day for ETS exposure in childhood, 8.0 in adolescence).

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2040174423000375

Acknowledgments. This work was supported by the American Heart Association (AHA) pre-doctoral fellowship awarded to Zhongzheng Niu (Grant number: 20PRE35120245). We acknowledge the participants and other collaborators from the Early Determinant of Health Study and the New England Family Study. Dr. Wen's time effort was supported through the Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (HHS) under R40MC31880 entitled "Socioeconomic disparities in early origins of childhood obesity and body mass index trajectories"; Clinical and Translational Science Award Pilot Study support from National Center for Advancing Translational Sciences, National Institutes of Health (NIH) grant UL1TR001412; and R21 exploratory research support from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH grant R21HD091515 (all awarded to Xiaozhong Wen). The information, content and/or conclusions are those of the author and should not be construed as the official position or policy of, nor should any endorsements be inferred by AHA, NIH, HRSA, HHS or the US Government. The sponsors had no role in writing the manuscript or the decision to submit it for publication.

Author contribution. Zhongzheng Niu: Conceptualization, Methodology, Software, Formal analysis, Data Curation, Writing – Original Draft, Review & Edit; Lina Mu: Conceptualization, Methodology, Writing – Review & Edit, Supervision; Stephen L. Buka: Conceptualization, Methodology, Writing – Review & Edit; Eric B. Loucks: Conceptualization, Methodology, Writing – Review & Edit; Meng Wang: Conceptualization, Methodology, Writing – Review & Edit; Lili Tian: Conceptualization, Methodology, Writing – Review & Edit; Xiaozhong Wen: Conceptualization, Methodology, Writing – Review & Edit, Supervision.

Financial support. All authors have no financial relationships relevant to this article to disclose.

Competing interests. All authors have no conflicts of interest to disclose.

Ethical standard. The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the institutional committees (UB IRB).

References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet*. 2020; 396(10258), 1204–1222. DOI: 10.1016/S0140-6736(20)30925-9.
2. Ross R, Glomset JA. The pathogenesis of atherosclerosis (first of two parts). *N Engl J Med*. 1976; 295(7), 369–377. DOI: 10.1056/nejm197608122950707.
3. Ross R, Glomset JA. The pathogenesis of atherosclerosis (second of two parts). *N Engl J Med*. 1976; 295(8), 420–425. DOI: 10.1056/nejm197608192950805.
4. Bateson P, Barker D, Clutton-Brock T, *et al.* Developmental plasticity and human health. *Nature*. 2004; 430(6998), 419–421. DOI: 10.1038/nature02725.
5. Raghuveer G, White DA, Hayman LL, *et al.* Cardiovascular consequences of childhood secondhand tobacco smoke exposure: prevailing evidence, burden, and racial and socioeconomic disparities: a scientific statement from the American Heart Association. *Circulation*. 2016; 134(16), e336–e359. DOI: 10.1161/CIR.0000000000000443.
6. de Jonge LL, Harris HR, Rich-Edwards JW, *et al.* Parental smoking in pregnancy and the risks of adult-onset hypertension. *Hypertension*. 2013; 61(2), 494–500. DOI: 10.1161/HYPERTENSIONAHA.111.200907.
7. Mayer C, Joseph KS. Fetal growth: a review of terms, concepts and issues relevant to obstetrics. *Ultrasound Obstet Gynecol*. 2013; 41(2), 136–145. DOI: 10.1002/uog.11204.
8. Taal HR, Geelhoed JJ, Steegers EA, *et al.* Maternal smoking during pregnancy and kidney volume in the offspring: the Generation R Study. *Pediatr Nephrol*. 2011; 26(8), 1275–1283. DOI: 10.1007/s00467-011-1848-3.
9. Niu Z, Xie C, Wen X, *et al.* Placenta mediates the association between maternal second-hand smoke exposure during pregnancy and small for gestational age. *Placenta*. 2015; 36(8), 876–880. DOI: 10.1016/j.placenta.2015.05.005.
10. West HW, Juonala M, Gall SL, *et al.* Exposure to parental smoking in childhood is associated with increased risk of carotid atherosclerotic plaque in adulthood: the Cardiovascular Risk in Young Finns Study. *Circulation*. 2015; 131(14), 1239–1246. DOI: 10.1161/CIRCULATIONAHA.114.013485.
11. McConnell R, Shen E, Gilliland FD, *et al.* A longitudinal cohort study of body mass index and childhood exposure to secondhand tobacco smoke and air pollution: the Southern California Children's Health Study. *Environ Health Perspect*. 2015; 123(4), 360–366. DOI: 10.1289/ehp.1307031.
12. Tong VT, Dietz PM, Morrow B, *et al.* Trends in smoking before, during, and after pregnancy–Pregnancy Risk Assessment Monitoring System, United States, 40 sites, 2000-2010. *MMWR Surveill Summ*. 2013; 62(6), 1–19.
13. Osmond C, Barker DJ, Winter PD, *et al.* Early growth and death from cardiovascular disease in women. *BMJ*. 1993; 307(6918), 1519–1524. DOI: 10.1136/bmj.307.6918.1519.
14. Jones A, Beda A, Osmond C, *et al.* Sex-specific programming of cardiovascular physiology in children. *Eur Heart J*. 2008; 29(17), 2164–2170. DOI: 10.1093/eurheartj/ehn292.
15. Virani SS, Alonso A, Aparicio HJ, *et al.* Heart disease and stroke statistics-2021 update: a report from the American Heart Association. *Circulation*. 2021; 143(8), e254–e743. DOI: 10.1161/CIR.0000000000000950.
16. Benjamin EJ, Muntner P, Alonso A, *et al.* Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*. 2019; 139(10), e56–e528. DOI: 10.1161/CIR.0000000000000659.
17. Gilman SE, Martin LT, Abrams DB, *et al.* Educational attainment and cigarette smoking: a causal association? *Int J Epidemiol*. 2008; 37(3), 615–624. DOI: 10.1093/ije/dym250.
18. Niswander KR, Gordon M. *The Women and Their Pregnancies: The Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke*, 1972. National Institute of Health, Bethesda, MD.
19. Cornelius ME, Loretan CG, Jamal A, *et al.* Tobacco product use among adults - United States, 2021. *MMWR Morb Mortal Wkly Rep*. 2023; 72(18), 475–483. DOI: 10.15585/mmwr.mm7218a1.
20. Paradis AD, Shenassa ED, Papandonatos GD, *et al.* Maternal smoking during pregnancy and offspring antisocial behaviour: findings from a longitudinal investigation of discordant siblings. *J Epidemiol Commun Health*. 2017; 71(9), 889–896. DOI: 10.1136/jech-2016-208511.
21. Otufowora A, Liu Y, Young II H. Sex differences in willingness to participate in research based on study risk level among a community sample of African Americans in North Central Florida. *J Immigr Minor Health*. 2021; 23(1), 19–25. DOI: 10.1007/s10903-020-01015-4.
22. Klebanoff MA, Levine RJ, Clemens JD, *et al.* Serum cotinine concentration and self-reported smoking during pregnancy. *Am J Epidemiol*. 1998; 148(3), 259–262. DOI: 10.1093/oxfordjournals.aje.a009633.
23. Cummings KM, Markello SJ, Mahoney MC, *et al.* Measurement of lifetime exposure to passive smoke. *Am J Epidemiol*. 1989; 130(1), 122–132. DOI: 10.1093/oxfordjournals.aje.a115303.
24. Avila-Tang E, Elf JL, Cummings KM, *et al.* Assessing secondhand smoke exposure with reported measures. *Tob Control*. 2013; 22(3), 156–163. DOI: 10.1136/tobaccocontrol-2011-050296.
25. Martin DO, Austin H. Exact estimates for a rate ratio. *Epidemiology*. 1996; 7(1), 29–33. DOI: 10.1097/00001648-199601000-00006.
26. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999; 10(1), 37–48.
27. Arnett DK, Blumenthal RS, Albert MA, *et al.* 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019; 140(11), e563–e595. DOI: 10.1161/CIR.0000000000000677.
28. Cupul-Uicab LA, Skjaerven R, Haug K, *et al.* In utero exposure to maternal tobacco smoke and subsequent obesity, hypertension, and gestational diabetes among women in the MoBa cohort. *Environ Health Perspect*. 2012; 120(3), 355–360. DOI: 10.1289/ehp.1103789.
29. Dior UP, Lawrence GM, Sitlani C, *et al.* Parental smoking during pregnancy and offspring cardio-metabolic risk factors at ages 17 and 32. *Atherosclerosis*. 2014; 235(2), 430–437. DOI: 10.1016/j.atherosclerosis.2014.05.937.
30. Kataria Y, Gaewsky L, Ellervik C. Prenatal smoking exposure and cardio-metabolic risk factors in adulthood: a general population study and a meta-analysis. *Int J Obes (Lond)*. 2019; 43(4), 763–773. DOI: 10.1038/s41366-018-0206-y.
31. Gall S, Huynh QL, Magnussen CG, *et al.* Exposure to parental smoking in childhood or adolescence is associated with increased carotid intima-media thickness in young adults: evidence from the Cardiovascular Risk in Young Finns study and the Childhood Determinants of Adult Health Study. *Eur Heart J*. 2014; 35(36), 2484–2491. DOI: 10.1093/eurheartj/ehu049.
32. Juonala M, Magnussen CG, Venn A, *et al.* Parental smoking in childhood and brachial artery flow-mediated dilatation in young adults: the Cardiovascular Risk in Young Finns study and the Childhood Determinants of Adult Health study. *Arterioscler Thromb Vasc Biol*. 2012; 32(4), 1024–1031. DOI: 10.1161/ATVBAHA.111.243261.
33. Jaakkola JM, Rovio SP, Pahkala K, *et al.* Childhood exposure to parental smoking and life-course overweight and central obesity. *Ann Med*. 2021; 53(1), 208–216. DOI: 10.1080/07853890.2020.1853215.
34. Chen W, Yun M, Fernandez C, *et al.* Secondhand smoke exposure is associated with increased carotid artery intima-media thickness: the Bogalusa Heart Study. *Atherosclerosis*. 2015; 240(2), 374–379. DOI: 10.1016/j.atherosclerosis.2015.04.002.
35. Pistilli M, Howard VJ, Safford MM, *et al.* Association of secondhand tobacco smoke exposure during childhood on adult cardiovascular disease risk among never-smokers. *Ann Epidemiol*. 2019; 32, 28–34 e1. DOI: 10.1016/j.annepidem.2019.01.012.
36. Salerni S, Di Francescomarino S, Cadeddu C, *et al.* The different role of sex hormones on female cardiovascular physiology and function: not only oestrogens. *Eur J Clin Invest*. 2015; 45(6), 634–645. DOI: 10.1111/eci.12447.

https://doi.org/10.1017/S2040174423000375 Published online by Cambridge University Press

37. Seltzer CC, Bosse R, Garvey AJ. Mail survey response by smoking status. *Am J Epidemiol*. 1974; 100(6), 453–457. DOI: 10.1093/oxfordjournals.aje.a112057.
38. Geelhoed JJ, El Marroun H, Verburg BO, *et al.* Maternal smoking during pregnancy, fetal arterial resistance adaptations and cardiovascular function in childhood. *BJOG Int J Obstet Gynaecol*. 2011; 118(6), 755–762. DOI: 10.1111/j.1471-0528.2011.02900.x.
39. Reijnders IF, Mulders A, van der Windt M, *et al.* The impact of periconceptional maternal lifestyle on clinical features and biomarkers of placental development and function: a systematic review. *Hum Reprod Update*. 2019; 25(1), 72–94. DOI: 10.1093/humupd/dmy037.
40. Rogers JM. Smoking and pregnancy: epigenetics and developmental origins of the metabolic syndrome. *Birth Defects Res*. 2019; 111(17), 1259–1269. DOI: 10.1002/bdr2.1550.
41. Groner JA, Huang H, Nagaraja H, *et al.* Secondhand smoke exposure and endothelial stress in children and adolescents. *Acad Pediatr*. 2015; 15(1), 54–60. DOI: 10.1016/j.acap.2014.09.003.
42. Allen NB, Siddique J, Wilkins JT, *et al.* Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. *JAMA*. 2014; 311(5), 490–497. DOI: 10.1001/jama.2013.285122.
43. Kishi S, Teixido-Tura G, Ning H, *et al.* Cumulative blood pressure in early adulthood and cardiac dysfunction in middle age: the CARDIA study. *J Am Coll Cardiol*. 2015; 65(25), 2679–2687. DOI: 10.1016/j.jacc.2015.04.042.
44. Frazer K, Callinan JE, McHugh J, *et al.* Legislative smoking bans for reducing harms from secondhand smoke exposure, smoking prevalence and tobacco consumption. *Cochrane Database Syst Rev*. 2016; 2, CD005992. DOI: 10.1002/14651858.CD005992.pub3.
45. Ho SY, Wang MP, Lo WS, *et al.* Comprehensive smoke-free legislation and displacement of smoking into the homes of young children in Hong Kong. *Tob Control*. 2010; 19(2), 129–133. DOI: 10.1136/tc.2009.032003.
46. Homa DM, Neff LJ, King BA, *et al.* Vital signs: disparities in nonsmokers' exposure to secondhand smoke–United States, 1999-2012. *MMWR Morb Mortal Wkly Rep*. 2015; 64(4), 103–108.
47. Rice JL, Brigham E, Dineen R, *et al.* The feasibility of an air purifier and secondhand smoke education intervention in homes of inner city pregnant women and infants living with a smoker. *Environ Res*. 2018; 160, 524–530. DOI: 10.1016/j.envres.2017.10.020.
48. Wen X, Eiden RD, Justicia-Linde FE, *et al.* Reducing fetal origins of childhood obesity through maternal smoking cessation during pregnancy: an intervention study. *Int J Obes (Lond)*. 2019; 43(7), 1435–1439. DOI: 10.1038/s41366-018-0267-y.
49. Barr EL, Tonkin AM, Welborn TA, *et al.* Validity of self-reported cardiovascular disease events in comparison to medical record adjudication and a statewide hospital morbidity database: the AusDiab study. *Intern Med J*. 2009; 39(1), 49–53. DOI: 10.1111/j.1445-5994.2008.01864.x.
50. Bergmann MM, Byers T, Freedman DS, *et al.* Validity of self-reported diagnoses leading to hospitalization: a comparison of self-reports with hospital records in a prospective study of American adults. *Am J Epidemiol*. 1998; 147(10), 969–977. DOI: 10.1093/oxfordjournals.aje.a009387.
51. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology*. 1990; 1(1), 43–46.

https://doi.org/10.1017/S2040174423000375 Published online by Cambridge University Press