Fetal and Childhood Exposure to Parental Tobacco Smoking and Arterial Health at Age 10 Years

Giulietta S. Monasso[1,2], Janine F. Felix[1,2], Romy Gaillard[1,2], and Vincent W.V. Jaddoe[1,2]

BACKGROUND
Exposure to parental tobacco smoking during fetal life and childhood is associated with adverse cardiovascular health outcomes. It is not known whether these adverse parental lifestyle exposures are also associated with changes in the structure and function of the carotid arteries in children aged 10 years.

METHODS
In a population-based prospective cohort study among 4,639 healthy children, we examined the associations of fetal exposure to maternal (no, first trimester only, continued), paternal (no, yes), and combined parental tobacco smoking (nonsmoking parents, mother only, father only, both parents smoked) with carotid intima-media thickness and distensibility at 10 years. We also assessed the associations of exposure to any parental tobacco smoking at ages 6 and 10 years with these outcomes.

RESULTS
Compared with no exposure, fetal exposure to continued maternal smoking was not associated with carotid intima-media thickness (−0.04 standard deviation score (SDS); 95% confidence interval (CI): −0.13, 0.05); and distensibility (0 SDS, 95% CI: −0.09, 0.09) at age 10 years. Fetal exposure to two smoking parents was also not associated with carotid intima-media thickness (−0.07 SDS, 95% CI: −0.16, 0.02) and distensibility (0 SDS, 95% CI: −0.09, 0.10) at this age. Exposure to any parental smoking during childhood also was not associated with these outcomes at age 10 years.

CONCLUSIONS
Exposure to parental tobacco smoking during fetal life and childhood was not associated with markers of arterial health in children aged 10 years. Prevention strategies aiming at minimizing smoke exposure later in life are still relevant regarding arterial health.

Keywords: blood pressure; child; cardiovascular disease; distensibility; epidemiology; hypertension; intima-media thickness; smoking

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Fetal tobacco smoke exposure is an important modifiable risk factor for a wide range of negative health outcomes in the offspring's life.[1] It is strongly related to adverse birth outcomes, such as low birth weight and preterm birth, and adverse cardiovascular outcomes in childhood.[2–5] Fetal tobacco smoke exposure is also associated with higher risks of hypertension and type 2 diabetes in adulthood.[6,7] Further, passive tobacco smoke exposure during childhood is a major health concern.[8,9]

In adults, a number of previous observational studies linked tobacco smoking to arterial health. It seems that active and passive tobacco smoking are associated with higher carotid intima-media thickness, a measure of arteriopathy, and with its progression.[10–14] Conversely, previous observational studies in adults reported inconsistent associations of active smoking or smoking intensity with arterial distensibility, a measure of elasticity.[15–19] Less is known about potential associations of tobacco smoke exposure in early life with arterial health in adulthood.[13,20–22] Relating tobacco smoke exposure to arterial health in children might reveal a critical period and thus gives clues about the etiology of vascular disease. Previously, a meta-analysis among 909 healthy school-age children from three observational studies reported no significant association of fetal exposure to maternal smoking with higher carotid intima-media thickness.[23] Conversely, a small population-based cohort study among 259 healthy children aged 5 years reported that fetal exposure to maternal smoking was associated with lower carotid distensibility, with an additive effect of paternal smoking.[24] To the best of our knowledge, no previous studies assessed the relative

Correspondence: Vincent W.V. Jaddoe (jaddoe@erasmusmc.nl)

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[1]The Generation R Study Group, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands; [2]Department of Pediatrics, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands.

importance of passive tobacco smoke exposure at different developmental stages in a child's life in relation to carotid intima-media thickness and distensibility at age 10 years. This could be important from an etiological perspective.

We examined the associations of exposure to maternal, paternal, and parental smoking during fetal life, as well as at ages 6 and 10 years, with carotid intima-media thickness and carotid distensibility at age 10 years. We hypothesized that passive tobacco smoke exposure during early life is associated with higher carotid intima-media thickness and lower carotid distensibility at school age.

MATERIALS AND METHODS

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life onwards in the city of Rotterdam, the Netherlands.[25] The Medical Ethical Committee of the Erasmus MC, University Medical Center in Rotterdam, approved the study (MEC 198.782/2001/31). Pregnant women living in Rotterdam and with an expected delivery date between April 2002 and January 2006 were eligible to participate. Written informed consent was obtained for all participants. **Supplementary Figure S1** shows a flowchart of the study population. For the current study, information on any exposure to parental smoking during fetal life (n = 4,166), and/or age 6 (n = 3,594), and/or at age 10 years (n = 4,017) was available for 4,639 unique singleton children with carotid artery ultrasound data measured at a median age of 9.7 years (95% range: 9.4, 10.5).

Parental smoking

As described previously, we prospectively obtained information on maternal tobacco smoking during pregnancy through questionnaires.[26] These questionnaires were sent from inclusion onwards, which were aimed at early pregnancy, but for some mothers (n = 402/4,639; 9.5%), this was when their child was born. Therefore, mothers reported either prospectively or retrospectively on tobacco smoking behavior and cigarette dosage, in six cigarette dosage categories ranging from <1 to ≥20 cigarettes per day, at gestational ages <18 weeks (early pregnancy), 18–25 weeks (mid-pregnancy), and ≥25 weeks (late pregnancy). For the current study, we constructed one variable describing maternal smoking behavior based on these questionnaires: nonsmoker (reference); smoked until pregnancy was known; and continued smoking (smoked in second and/or third trimester). To examine any dose effects, we restricted the analyses to children born to mothers who continued smoking during pregnancy, in order to take into account cumulative dose as well. Numbers of children per maternal smoking dose category were <1 (n = 79), 1–2 (n = 62), 3–4 (n = 113), 5–9 (n = 145), 10–19 (n = 87), and ≥20 (n = 12). We recategorized this variable into children of high-dose smoking mother (≥5 cigarettes per day) and children of low-dose smoking mother (<5 cigarettes per day, *reference*). This cutoff dosage was chosen as the number of children exposed to even higher dosages was too small for meaningful analyses. Mothers also reported on periconceptional paternal smoking behavior (no/yes). Previous analyses showed a good agreement of maternal report with paternal self-report.[5] For childhood exposure to parental smoking, we constructed two variables describing maternal smoking behavior in children aged 6 and age 10 years, respectively. The same approach was used for paternal smoking behavior in childhood. At age 6 years, information about both maternal and paternal smoking at home (no/yes) was obtained from a questionnaire sent to the parent that was most involved in the care of the child. At age 10 years, both parents reported the following question: "Have you ever smoked?" (No; Yes, but I do not smoke anymore; Yes, I still smoke now). For this study, we recategorized the first two categories into no smoking. To further examine cumulative dose effects of passive tobacco smoke exposure, we also created a variable for parental smoking during pregnancy, at the ages of 6 and 10 years: no parental smoking (reference), any maternal smoking only, paternal smoking only, both parents smoked at any time.

Common carotid artery intima-media thickness and distensibility

As described in detail previously, we measured common carotid artery intima-media thickness and distensibility using the Logiq E9 (GE Medical Systems, Wauwatosa, WI) device.[27] Subsequent offline analyses were performed using the application Carotid Studio (Cardiovascular Suite (Quipu srl, Pisa, Italy)). Carotid intima-media thickness was computed at the far wall as the average distance between lumen-intima and media-adventitia borders. The distensibility coefficient, or distensibility, was defined as the relative change in lumen area during systole for a given peripheral pressure change. We assessed peripheral blood pressure at the right brachial artery four times with the validated automatic sphygmomanometer Datascope Accutorr Plus (Paramus, NJ).[28] The lumen diameter of the carotid artery was computed as the average distance between the far and near media-adventitia interfaces, for each frame of the acquired image sequence. Distension was calculated as the difference between the maximal (diastolic) and minimal (systolic) lumen diameters. The average distension and diameter values were used to compute the average carotid distensibility. We used the overall mean carotid intima-media thickness (mm) and carotid distensibility ($kPa^{-1} \times 10^{-3}$) as outcomes of interest. In a reproducibility study, the interobserver and intraobserver intraclass correlation coefficients were >0.85.[27]

Covariates

Potential confounders were selected based on previous literature, and by constructing a directed acyclic diagram (**Supplementary Figure S2**).[25] We also tested their associations with carotid intima-media thickness and distensibility (**Supplementary Table S1**). We obtained information on maternal covariates and child ethnicity from the first questionnaires at enrollment. Mothers reported their

age, highest completed educational level (recategorized into lower than college and college or higher), and prepregnancy body mass index. Ethnicity was included as it might be associated with carotid intima-media thickness.[29] From midwife and hospital records, we obtained information on child sex. Information on breastfeeding (no versus any) was obtained from postnatal questionnaires. Breastfeeding was included as it has been associated with childhood carotid intima-media thickness and as tobacco metabolites are readily available in breast milk.[30] At ages 6 and 10 years, we measured children's height and weight without shoes or heavy clothing, from which we calculated body mass index (kg/m^2) and subsequently sex- and age-adjusted standard deviation scores (SDS), based on Dutch reference growth charts (Growth Analyzer 4.0, Dutch Growth Research Foundation). We also categorized body mass index into underweight, normal weight, and overweight/obesity, based on the International Obesity Task Force cutoffs.[31]

Statistical analysis

First, we performed a nonresponse analysis by comparing characteristics of children with information on any exposure to parental tobacco smoking during fetal life or childhood, with and without carotid artery ultrasound data, using Student's *t*-tests, Mann–Whitney tests, and Chi-square tests. Second, we examined the associations of fetal and childhood exposure to maternal, paternal, and combined parental tobacco smoking with carotid intima-media thickness and distensibility, using multiple linear regression models. To compare effect estimates, we analyzed both outcomes in SDSs, after natural log transformation of carotid distensibility to obtain a normal distribution. Basic models were adjusted for sex and age at outcome measurement. Confounder models were additionally adjusted for maternal age, education and prepregnancy body mass index, child ethnicity, and breastfeeding. These models were not adjusted for child birth weight, body mass index, and mean arterial pressure, which we considered as potential mediators. We tested for interactions between parental smoking and child ethnicity, sex and body mass index SDS at outcome measurement in relation to both outcomes in the basic model, as these characteristics have been associated with carotid intima-media thickness and distensibility in children.[29,32] As multiple of the interaction terms were significant ($P < 0.05$), we also performed exploratory analyses restricted to a subgroup of children from Dutch ancestry ($n = 2{,}762$), which was the largest ethnic group, and analyses stratified on sex, birth complications (defined as children born at gestational age <37 weeks and/or small for gestational age, $n = 388$), and body mass index category (normal weight (*reference*) versus overweight/obesity)). We used multiple imputations for covariates with missing values, using the Markov Chain Monte Carlo method. We created five datasets and report pooled regression coefficients.[33] We took into account multiple testing by correcting for two outcomes, thus considering $P < 0.05/2 = 0.025$ significant. Statistical analyses were performed using the Statistical Package of Social Sciences version 25.0 for Windows (SPSS IBM, Chicago, IL).

RESULTS

Subject characteristics

Table 1 shows that 15.1% and 43.1% of children had been exposed to continued maternal smoking and paternal smoking during fetal life, respectively. Further, up to 20% of all children were exposed to any parental smoking during childhood. At age 10 years, the mean carotid intima-media thickness was 0.46 (0.04 SD) mm and the median carotid distensibility was 55.8 (95% range 37.3, 85.3) kPa^{-1} × 10^{-3}. **Supplementary Table S2** shows subject characteristics after imputation. The nonresponse analysis suggested that, as compared to children with carotid artery ultrasound data, children without outcomes were more frequently exposed to parental smoking during fetal life and tended to have younger, lower educated mothers (**Supplementary Table S3**). Also, nonincluded children were more frequently boys of non-European ancestry.

Exposure to parental tobacco smoking and arterial health at age 10 years

Table 2 shows that before and after adjustment for confounders, fetal tobacco smoke exposure from both maternal and paternal sources was not associated with carotid intima-media thickness and distensibility at school age. Exposure to paternal tobacco smoking at childhood age of 6 years was associated with lower childhood carotid intima-media thickness at age 10 years in the basic and confounder models for both paternal smoking and combined parental smoking (**Table 3**). Only the association for combined parental smoking remained significant after adjustment for multiple testing (−0.19 SDS (0.04 mm), 95% confidence interval: −0.35, −0.03). In the basic model, exposure to paternal tobacco smoking at age 10 years was associated with lower carotid distensibility at the same age. This association attenuated into nonsignificance after adjustment for confounders and multiple testing (**Table 3**).

Secondary analyses

Among children of mothers who continued smoking during pregnancy, maternal daily cigarette dose was not associated with child carotid intima-media thickness and carotid distensibility at age 10 years (**Table 2**). Among Dutch children only, we also observed no associations of fetal or childhood exposure to parental tobacco smoking with carotid intima-media thickness and distensibility at age 10 years (**Supplementary Tables S4 and S5**). After stratification on sex, we did not observe associations of parental smoking with childhood markers of arterial health after multiple testing adjustments (**Supplementary Tables S6 and S7**). Also, our results were similar for children with and without preterm birth or low birth weight (**Supplementary Tables S8 and S9**). In analyses stratified on childhood body mass index category, we observed that exposure to paternal smoking at age 6 years was associated with lower carotid intima-media thickness at age 10 years among children with normal weight. This finding was not significant after correction for multiple testing (**Supplementary Tables S10 and S11**).

Table 1. Subject characteristics (n = 4,639)[a]

Pregnancy characteristics	
Maternal age, mean (SD), years	31.0 (4.9)
Maternal educational level	
No, primary, secondary, *n* (%)	2,189 (50.6)
College or higher, *n* (%)	2,141 (49.4)
Maternal prepregnancy body mass index, median (95% range), kg/m^2	22.6 (18.1, 34.7)
Maternal smoking during pregnancy[b]	
No, *n* (%)	3,180 (76.3)
Yes, until pregnancy was known, *n* (%)	359 (8.6)
Yes, continued[c], *n* (%)	627 (15.1)
<5 cigarettes per day, *n* (%)	254(51.0)
≥5 cigarettes per day, *n* (%)	244 (49.0)
Paternal smoking during pregnancy	
No, *n* (%)	2,190 (56.9)
Yes, *n* (%)	1,661 (43.1)
Birth and infant characteristics	
Gestational age, median (95% range), weeks	40.1 (35.4, 42.3)
Sex	
Boy, *n* (%)	2,315(49.9)
Girl, *n* (%)	2,324 (50.1)
Birth weight, mean (SD), kg	3.42 (0.57)
Ethnicity	
European, *n* (%)	3,114 (67.9)
Dutch, *n* (%)	2,762
Non-Dutch, *n* (%)	352
Non-European, *n* (%)	1,471 (32.1)
Breastfeeding	
No, *n* (%)	276 (7.4%)
Yes, *n* (%)	3,435 (92.6%)
Childhood characteristics	
Maternal smoking at child age 6 years	
No, *n* (%)	3,343 (93.0)
Yes, *n* (%)	251 (7.0)
Paternal smoking at child age 6 years	
No, *n* (%)	3,274 (91.8)
Yes, *n* (%)	291 (8.2)
Maternal smoking at child age 10 years	
No, *n* (%)	3,424 (85.2)
Yes, *n* (%)	593 (14.8)
Paternal smoking at age 10 years	
No, *n* (%)	2,488 (80.6)
Yes, *n* (%)	599 (19.4)
Age at visit, median (95% range), years	9.7 (9.4, 10.5)
Body mass index, median (95% range), kg/m^2	17.0 (14.0, 24.7)
Underweight, *n* (%)	321 (6.9)
Normal weight, *n* (%)	3,462 (74.9)
Overweight, *n* (%)	840 (18.2)
Common carotid artery intima-media thickness, mean (SD), mm	0.46 (0.04)
Common carotid artery distensibility[d], median (95% range), kPa^{-1} × 10^{-3}	55.8 (37.3, 85.3)

Abbreviations: SD, standard deviation; SDS, standard deviation score.

[a] Based on observed, not imputed data. Missing data: maternal age, *n* = 0; maternal educational level, *n* = 309; maternal body mass index, *n* = 1,049; maternal smoking during pregnancy, *n* = 473; paternal smoking during pregnancy, n=788; parental smoking during pregnancy, n=850; gestational age at birth, *n* = 30; sex, *n* = 0; birth weight, *n* = 8; ethnicity, *n* = 54; breastfeeding, *n* = 928; maternal smoking at child age 6 years, *n* = 1,045; paternal smoking at child age 6 years, *n* = 1,074; parental smoking at age 6 years, *n* = 1,076; maternal smoking at child age 10 years, *n* = 622; paternal smoking at child age 10 years, *n* = 1552; parental smoking at age 10 years, *n* = 1,638; child age, *n* = 0, child body mass index, *n* = 16; carotid intima-media thickness, *n* = 0; carotid distensibility, *n* = 167.

[b] Available for 498 of 627 mothers who continued smoking during pregnancy.

[c] A subgroup of 2,762 children was from Dutch ethnic background and used for exploratory sensitivity analyses.

[d] Shown are original, nonnatural log-transformed values.

DISCUSSION

In this population-based prospective cohort study, we observed no consistent associations of exposure to parental tobacco smoking during fetal life and childhood with carotid intima-media thickness and carotid distensibility in healthy children aged 10 years.

Fetal and childhood tobacco smoke exposure is an important risk factor for a wide range of adverse health outcomes throughout life.[2–9] In adults, previous observational studies reported associations of tobacco smoke exposure from fetal life onwards with carotid intima-media thickness and distensibility, although not consistently.[10–22] Few studies reported associations of exposure to parental smoking during fetal life or childhood with carotid intima-media thickness and distensibility in children. These studies, with smoke exposure levels ranging from 6% up to 33% of children, were relatively small, focused on adolescents or children with overweight.[23,24,34–36] To identify any time-dependent associations, we examined passive tobacco smoke exposure at three developmental stages in a child's life in relation to carotid intima-media thickness and distensibility at age 10 years. We hypothesized that fetal and childhood exposure to parental tobacco smoking is associated with higher carotid intima-media thickness and lower distensibility at age 10 years.

We observed that exposure to maternal or paternal smoking during fetal life was not associated with carotid intima-media thickness and distensibility at the age of 10 years. For carotid intima-media thickness, our null finding for maternal smoking is in line with the results from

Table 2. Associations of fetal exposure to parental tobacco smoking with carotid intima-media thickness and distensibility at age 10 years[a].

	Difference in SDS (95% confidence interval)			
	Carotid intima-media thickness		Carotid distensibility	
	n = 4,639		*n* = 4,472	
	Basic model	Confounder model	Basic model	Confounder model
Maternal smoking (*n* = 4,166)				
No (*n* = 3,180)	Reference	Reference	Reference	Reference
Until pregnancy was known (*n* = 359)	0.00 (−0.11, 0.11)	0.01 (−0.10, 0.12)	−0.03 (−0.15, 0.08)	−0.03 (−0.15, 0.08)
Continued (*n* = 627)	−0.04 (−0.13, 0.04)	−0.04 (−0.13, 0.05)	−0.02 (−0.11, 0.07)	−0.00 (−0.09, 0.09)
<5 cigarettes/day (*n* = 254)	Reference	Reference	Reference	Reference
≥5 cigarettes/day (*n* = 244)	−0.02 (−0.18, 0.15)	0.01 (−0.16, 0.18)	0.10 (−0.09, 0.28)	0.09 (−0.09, 0.27)
Paternal smoking (*n* = 3,851)				
No (*n* = 2,190)	Reference	Reference	Reference	Reference
Yes (*n* = 1,661)	−0.06 (−0.12, 0.01)	−0.06(−0.13, 0.00)	−0.03 (−0.09, 0.04)	−0.02 (−0.08, 0.05)
Parental smoking (*n* = 3,789)				
No (*n* = 1,896)	Reference	Reference	Reference	Reference
Mother only (*n* = 247)	0.08 (−0.06, 0.21)	0.07 (−0.06, 0.20)	−0.07 −0.21, 0.06)	−0.07 (−0.20, 0.07)
Father only (*n* = 1,014)	−0.05 (−0.13, 0.03)	−0.06 (−0.13, 0.02)	−0.05 (−0.12, 0.03)	−0.04 (−0.12, 0.04)
Both (*n* = 632)	−0.07 (−0.16, 0.02)	−0.07 (−0.16, 0.02)	−0.02 (−0.11, 0.07)	0.00 (−0.09, 0.10)

[a] Regression coefficients are linear regression coefficients and represent the change in standard deviation score (SDS) carotid artery intima-media thickness (0.04 mm) and natural log-transformed distensibility (0.021 = 12.4 kPa^{-1} × 10), respectively, as compared with the reference group. Basic models were adjusted for child sex and age at outcome measurement. Confounder models were additionally adjusted for child ethnicity, maternal age, maternal education, maternal prepregnancy body mass index, and breastfeeding.

a previous meta-analysis among healthy 909 children aged 5–9 years from three observational studies (**Supplementary Table S12**).[23] Contrary to us, a previous smaller Dutch study reported that fetal exposure to maternal smoking was associated with lower carotid distensibility in 259 healthy children aged 5 years, with an additive but not independent effect of paternal smoking.[24] This different finding seems not explained by the exposure level to any maternal smoking, which was four-fold higher in our study, nor by the general characteristics of the participants. Potentially, changes in carotid distensibility in relation to fetal smoke exposure are not persistent across childhood, which may explain why we observed no associations in our older study population. Thus, results from our large population-based cohort study do not support the hypothesis that fetal exposure to parental tobacco smoking is associated with carotid intima-media thickness and distensibility at age 10 years.

We also observed that exposure to maternal and paternal smoking at the ages of 6 and 10 years was not consistently associated with carotid intima-media thickness and distensibility at age 10 years. Three previous studies assessed the associations of passive smoke exposure during childhood with carotid intima-media thickness and distensibility in adolescents.[34–36] A Finnish study embedded in a randomized trial to prevent childhood exposure to cardiovascular risk factors reported that passive smoke exposure from school age onwards, assessed by serum cotinine concentrations, was associated with higher carotid and aortic intima-media thickness in 494 nonsmoking adolescents aged 13 years.[36] This inconsistency with our larger study might be related to the different ages at which the carotid artery was assessed, differences between their Scandinavian and our Dutch population, or the fact that we obtained smoking behavior from questionnaires rather than cotinine measurements. Yet, as in our study, the exposure to cigarette smoking was moderate in the Finish study.[36] In line with our null findings for carotid distensibility, a cross-sectional study, embedded in the same Finnish trial, reported that passive smoke exposure during childhood was associated with aortic but not carotid distensibility in 386 adolescents aged 11 years.[35] The same discrepancy between the aorta and carotid artery was observed in a cross-sectional hospital-based study from the United States among 298 nonsmoking adolescents aged 13 years and predominantly with overweight, with self-reported secondhand smoke exposure.[34] This suggests that the aorta might be more or earlier prone to functional changes than the carotid arteries.[37] Thus, our findings do not support the hypothesis that childhood exposure to parental tobacco smoking is associated with carotid intima-media thickness and distensibility in healthy children aged 10 years from a large population-based cohort study.

Our null findings in school-aged children may be interpreted in several ways. First, in children, higher intima-media thickness and lower distensibility may reflect physiological remodeling of the arterial wall in response to growth, rather than pathological structural and functional changes in response to adverse lifestyle exposures such as tobacco smoke.[38,39] Otherwise, it could be that associations of passive tobacco smoke exposure during the earliest phase of life with carotid intima-media

Table 3. Associations of childhood exposure to parental tobacco smoking with carotid intima-media thickness and distensibility at age 10 years[a]

	Differencein SDS (95% confidence interval)			
	Carotid intima-media thickness		Carotid distensibility	
	n = 4,639		*n* = 4,472	
	Basic model	Confounder model	Basic model	Confounder model
Age 6 years				
Maternal smoking (*n* = 3,594)				
No (*n* = 3,343)	Reference	Reference	Reference	Reference
Yes (*n* = 251)	−0.05 (−0.17, 0.08)	−0.04 (−0.17, 0.09)	−0.05 (−0.18, 0.08)	−0.03 (−0.16, 0.11)
Paternal smoking (*n* = 3,565)				
No (*n* = 3,274)	Reference	Reference	Reference	Reference
Yes (*n* = 291)	−0.14 (−0.26, −0.03)*	−0.14 (−0.26, -0.02)*	−0.07 (−0.19, 0.05)	−0.04 (−0.17, 0.08)
Parental smoking (*n* = 3,563)				
Both nonsmoking (*n* = 3,163)	Reference	Reference	Reference	Reference
Maternal smoking (*n* = 109)	−0.03 (−0.22, 0.16)	−0.03 (−0.22, 0.16)	−0.00 (−0.19, 0.19)	0.02 (−0.17, 0.21)
Paternal smoking (*n* = 162)	−0.19 (−0.35, −0.03)*	−0.19 (−0.35, −0.03)**	−0.03 (−0.19, 0.13)	−0.01 (−0.17, 0.16)
Both smoking (*n* = 129)	−0.09 (−0.26, 0.09)	−0.07 (−0.25, 0.10)	−0.12 (−0.30, 0.06)	−0.09 (−0.27, 0.09)
Age 9 years				
Maternal smoking (*n* = 4,017)				
No (*n* = 3,424)	Reference	Reference	Reference	Reference
Yes (*n* = 593)	−0.06 (−0.15, 0.02)	−0.05 (−0.14, 0.04)	−0.04 (−0.13, 0.05)	−0.02 (−0.11, 0.07)
Paternal smoking (n = 3,087)				
No (*n* = 2,488)	Reference	Reference	Reference	Reference
Yes (*n* = 599)	−0.03 (−0.12, 0.06)	−0.02 (−0.11, 0.07)	−0.07 (−0.16, 0.02)	−0.05 (−0.14, 0.04)
Parental smoking (*n* = 3,001)				
Both nonsmoking (*n* = 2,238)	Reference	Reference	Reference	Reference
Maternal smoking (*n* = 186)	−0.13 (−0.28, 0.02)	−0.13 (−0.28, 0.02)	−0.05 (−0.20, 0.10)	−0.03 (−0.19, 0.12)
Paternal smoking (*n* = 401)	−0.01 (−0.12, 0.09)	−0.01 (−0.11, 0.10)	−0.11 (−0.22, -0.00)*	−0.10 (−0.20, 0.01)
Both smoking (*n* = 176)	−0.11 (−0.26, 0.05)	−0.08 (−0.24, 0.07)	−0.03 (−0.19, 0.12)	−0.00 (−0.16, 0.15)

[a] Regression coefficients are linear regression coefficients and represent the change in standard deviation score (SDS) carotid artery intima-media thickness (0.04 mm) and natural log-transformed distensibility (0.021 = 12.4 kPa^{-1} × 10), respectively, as compared with the reference group. Basic models were adjusted for child sex and age at outcome measurement. Confounder models were additionally adjusted for child ethnicity, maternal age, maternal education, maternal prepregnancy body mass index, and breastfeeding.

*$p < 0.05$.

** $p < 0.025$, the p-value we considered significant after multiple testing correction for two outcomes.

thickness and distensibility are either transient or appear at older ages. Further, our relatively healthy and affluent study population may have prevented the detection of associations. Although comparable with other Western cohort studies,[2] the prevalence and dose of parental smoking were relatively low. As we categorized tobacco smoking in the current study, lower doses may have masked, if any, potentially biologically relevant effects of higher doses. Further, we had limited power to examine dose effects of maternal smoking during pregnancy. Last, the variation in carotid artery measurements in our population was limited as well. Thus, associations may be observed among more diverse populations in terms of socioeconomic status and health.

A main general strength of this study is its implementation in an observational prospective birth cohort. We had detailed information on parental smoking behavior from preconception onwards available, as well as carotid artery ultrasound data. We performed power calculations and estimated to be able to detect a difference of 0.077 SD, based on $n = 7{,}000$ and 25% exposed, and alpha = 5% and beta = 20%.[25] Due to missing values, the power for the current study may be lower than originally calculated, but it was still much higher as compared to previous studies in children, with an up to 10-fold smaller sample size. This study also had limitations. In total, 8% of children that participated in the Generation R Study at birth had no information on parental smoking available. This may have introduced selection bias, although

it is difficult to quantify its extent. Further, the nonresponse analysis suggested selection toward a healthier more affluent population of European ancestry, which might have biased the observed effect estimates and limited the generalizability of our null findings to the general population. As we previously observed associations of other exposures with the same outcomes, it seems that the lack of variation in the outcomes does not explain the null findings.[27,40] Further, we assessed parental smoking behavior via questionnaires. Parents may have underreported their smoking behavior, which may have led to the underestimation of the associations. Also, we calibrated carotid distensibility to brachial blood pressure, which will have shifted the calculated distensibility to higher values. We dichotomized breastfeeding into no versus any breastfeeding, the latter comprising any duration up to 1 year. This may have limited the precision. Last, although we had data on important potential confounders, we cannot exclude residual confounding, as in any observational study. This might also explain why we observed some inconsistent associations between exposure to paternal smoking in childhood and carotid intima-media thickness at age 10 years. Our findings do not provide support for the hypothesis that exposure to parental smoking during fetal life and childhood is associated with carotid intima-media thickness and carotid distensibility in healthy school-age children. Prevention strategies aiming at minimizing smoke exposure later in life could still be relevant regarding vascular and other health outcomes.

SUPPLEMENTARY MATERIAL

Supplementary materials are available at *American Journal of Hypertension* (http://ajh.oxfordjournals.org).

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DISCLOSURE

No conflict of interest to declare

DATA AVAILABILITY

All further relevant data supporting the key findings of this study are available within the article and its Supplementary Information files or from the corresponding author upon reasonable request and subject to the Generation R data access procedures.

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