Parental Smoking and Vascular Damage in Their 5-year-old Children

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WHAT'S KNOWN ON THIS SUBJECT: Smoking during pregnancy has been related to thicker carotid intima media thickness in young adults, and this was also shown in neonates.

WHAT THIS STUDY ADDS: This study is the first to show that the effect of smoking during pregnancy on the vasculature of children is (still) visible at the age of 5 years. Pregnancy appears to be the critical period for this damage to occur.

abstract

FREE

BACKGROUND: The relation between smoke exposure in early life, the prenatal period in particular, and the vascular development of young children is largely unknown.

METHODS: Data from the birth cohort participating in the WHISTLER-Cardio study were used to relate the smoking of parents during pregnancy to subsequent vascular properties in their children. In 259 participating children who turned 5 years of age, parental smoking data were updated and children's carotid artery intima-media thickness (CIMT) and arterial wall distensibility were measured by using ultrasonography.

RESULTS: Children of mothers who had smoked throughout pregnancy had 18.8 μm thicker CIMT (95% confidence interval [CI] 1.1, 36.5, P = .04) and 15% lower distensibility (95% CI −0.3, −0.02, P = .02) after adjustment for child's age, maternal age, gender, and breastfeeding. The associations were not found in children of mothers who had not smoked in pregnancy but had smoked thereafter. The associations were strongest if both parents had smoked during pregnancy, with 27.7 μm thicker CIMT (95% CI 0.2, 55.3) and 21% lower distensibility (95% CI −0.4, −0.03).

CONCLUSION: Exposure of children to parental tobacco smoke during pregnancy affects their arterial structure and function in early life. *Pediatrics* 2012;129:45–54

Autopsy studies have shown that active smoking at a young age promotes the development of fibrous plaques and fatty streaks as precursors of atherosclerosis in aortas and coronary arteries.[1] Young adult smokers have thicker and stiffer arterial walls.[2,3]

Among the many adverse effects of parental smoking is the propensity of children to start smoking. However, passive exposure to tobacco smoke in families has also been associated with thicker arterial walls in young adults,[4] with attenuated endothelial function in prepubertal children[5] and in newborns.[6]

It is unknown if later life vascular damage occurs through smoking-induced adverse cardiovascular risk factor levels, or whether there are direct effects and if there are particular periods of tobacco smoke exposure that are critical in children's vascular development. In a previous study, we found that parental smoking is associated with vascular damage in young adult offspring, but also that maternal smoking in pregnancy might be specifically implicated.[4] However, in that study, 28 years had elapsed between pregnancy and the measurement of vascular outcome, and information bias and confounding, specifically by spouse and offspring smoking, could not be fully ruled out.[7] Therefore, we were inconclusive about whether pregnancy was a critical period.

To overcome these limitations, we used a new prospective study (WHISTLER-Cardio) within an ongoing population-based birth cohort study.[8] Parental smoking behavior in pregnancy was measured shortly after birth by questionnaire, and at the child's age of 5 years. Children's vascular characteristics were measured by using noninvasive ultrasound scanning at age 5 years, along with extensive cardiovascular risk factor profiling. With this design, we attempted to reduce smoking recall bias to a minimum, avoid confounding by active offspring smoking, and optimally account for other confounders.

Our research question was whether parental smoking in pregnancy is associated with nonsmoking children's arterial wall structure and function.

METHODS

Study Design and Study Population

The current study is part of the WHeezing Illnesses STudy LEidsche Rijn (WHISTLER), a large prospective population-based birth cohort study, initiated in December 2001 and still ongoing. Study design and rationale were described in detail elsewhere.[8] In brief, healthy infants born in Leidsche Rijn, a residential area near the city of Utrecht, were enrolled (currently >2000) at the age of 2 weeks. In November 2007 the study was extended for cardiovascular research questions (WHISTLER-Cardio). All children who had reached the age of 5 years were invited according to the last-known telephone number and address, for a second, follow-up visit (until September 2009, n = 511). Of these, 75 of 511 (15%) subjects were lost to follow-up because of incorrect telephone numbers and nonresponse despite mailing or incorrect address. One hundred eighteen declined to take part, and 318 (73%) were willing to participate. Vascular measurements were performed in 264 subjects. The WHISTLER-Cardio study was approved by the pediatric Medical Ethical Committee of the University Medical Center Utrecht. Written informed parental consent was obtained.

Neonatal Visit

When eligible children were 4 weeks of age, parents visited our outpatient clinic. Infants' anthropometry was assessed, and lung function measurement was performed (described elsewhere). Information with regard to pre-, peri-, and postnatal factors was obtained by a parental questionnaire.[9] Data on parental characteristics were obtained from the linked database of the Utrecht Health Project, a large health-monitoring study in Leidsche Rijn.[10]

Follow-up Visit

Children were reinvited at the clinic at the age of 5 years. Anthropometrics and vascular characteristics were measured.

Determinant Measurement

During the neonatal visit, mothers filled in a questionnaire. Questions included: Did you smoke during the pregnancy? (yes/no); how many cigarettes per day did you on average smoke in the first half of your pregnancy?; how many cigarettes per day did you on average smoke in the second half of your pregnancy? Smoking during pregnancy was defined as smoking a minimum of 1 cigarette per day during the entire pregnancy (data complete for 98.5%, 260/264). Nonsmoking mothers in pregnancy and early quitters (n = 6) were pooled as a group in the analysis. This was considered justified because early quitting, contrary to continued smoking in pregnancy, was shown not to lower endothelial nitric oxide in the fetal vascular bed, so that early quitting prevents reductions of fetal vasodilatory capacity.[11] Two mothers who reported to smoke only during the second half of pregnancy were excluded.

During the follow-up visit, an average of 5 years later, the following questions were asked by questionnaire to both parents: Do you currently smoke? (yes/no); what do you smoke and how much (cigarettes/day, cigars/week,

packs of pipe tobacco/week)? Data on current smoking of mothers and fathers was complete for 233 of 264 (88.3%). Questions with regard to smoke exposure of the child, included: Is your child daily exposed to smoke ("yes," "not anymore," "no never")?; if yes, how many hours a day (on average) is your child in a smoky room (0, 0–1, 1–2, 2–3, 4–6, >6 hours)?

Outcome Measurement

Vascular conditions of the right common carotid artery were studied ultrasonographically by using high-resolution echo-tracking technology (Art.laboratory, Esaote, Italy) including a 128 radiofrequency line multi-array, with a L10-5 40-mm linear array transducer. Rough radiofrequency data were analyzed online, and 6-second cine loops were stored without compression (120 Mbytes) for offline analysis. This novel technology gives access to all major mechanical parameters for 4-cm arterial segments: diastolic diameter *d*, the change in diameter as function of time (distension), and carotid artery intima-media thickness (CIMT). CIMT and diameter were measured with 2.1-μm resolution, and distension was measured with 1.7-μm resolution.[12] Both measurements were repeated a maximum of 4 times. Measurements were performed with subjects in a supine position, after at least 10 minutes of resting. One investigator (C.C.G.), blinded to data on smoking and confounders, performed all measurements. Figure 1 shows a video still of the CIMT measurement. Coefficients of variation based on measurements by one observer in 10 subjects on 2 different occasions for distension, CIMT, and diameter were 7.1%, 4.3%, and 2.4%, respectively.

During ultrasonography, blood pressure (BP) was recorded twice at the brachial artery by using a semi-automatic oscillometric device (DINAMAP; Critikon, Tampa, FL). Both values were averaged to estimate common carotid artery local pulse pressure, assuming mean arterial pressure minus diastolic BP constant throughout the large artery tree. Averages of CIMT, diameter, and distension over every session per individual were used to assess the elastic properties of the carotid artery, including cross-sectional distensibility (DC) and the elastic modulus (EM). See formulas and units in the appendix.

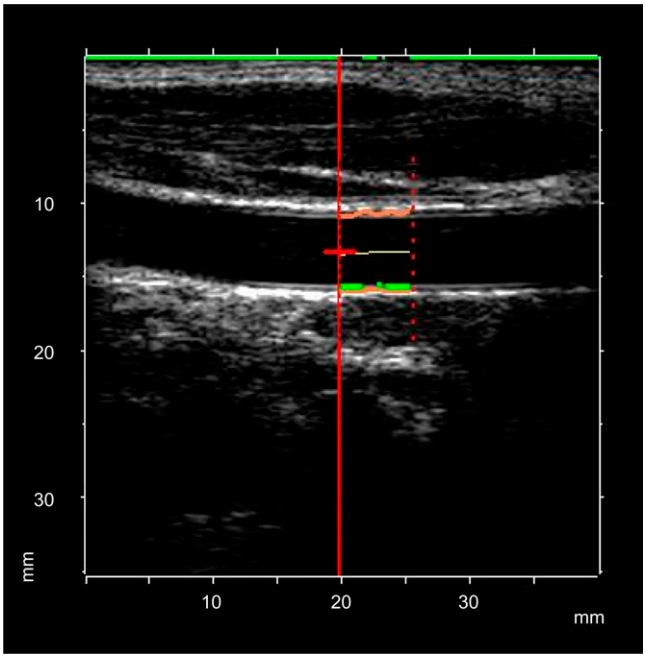

FIGURE 1
Video still from the CIMT measurement. In this longitudinal view of the common carotid artery, diameter and intima-media thickness on the far wall (thin white lining) is automatically detected and measured.

CIMT and distension measurements were successfully assessed in 258 of 264 subjects (97.7%) and 237 (89.8%) subjects, respectively. In 13 of 237 cases DC could not be calculated (BP was not measured during distension measurement). Vascular measurements took approximately 30 minutes to complete, while children could watch their favorite motion pictures.

The current study pertains to the 259 subjects with data of smoking during pregnancy available and vascular outcome measured at the age of 5 years.

Confounding and Explanatory Factors

In the analysis, infant feeding and maternal age were considered possible confounders because of their putative relation with determinant and outcome. Socioeconomic status is associated with maternal smoking and breast-feeding rates,[13,14] whereas breast-feeding was shown to be beneficial to the adult vasculature,[15] although this has not yet been confirmed.[16,17] Mothers who smoke during pregnancy are usually younger, but higher maternal age has been associated with offspring BP, a determinant of vascular condition.[18]

Maternal smoking in pregnancy yields lower birth weight newborns,[19] and is suggested to increase the risk for obesity.[20] To see if associations between parental smoking and offspring's vascular characteristics would be explained through offspring's growth trajectory, we calculated *z*-scores of BMI at birth, the first visit, and at age 5 years. For each child, we calculated

differences in *z*-scores at various time intervals and entered these in the models.

Furthermore, the associations were adjusted for current smoke exposure of the child, (dichotomized as "yes" and "not anymore or no never").

Data Analysis

For descriptive purposes and for evaluation of possible confounding, means and variance measures of parent and child characteristics at several time intervals were calculated by smoking of mothers during pregnancy. Baseline characteristics (neonatal visit and before) of nonparticipants (including those lost to follow-up) were compared with participants of the follow-up visit at age 5 years using the Student *t* test or χ^2 tests whenever appropriate.

For further analysis, CIMT, wall distensibility, and EM were used as dependent variables. Because a skewed distribution according to the Kolmogorov-Smirnov test with Lilliefors significance correction ($P = .001$ and $P < .001$, respectively), the latter two were natural log-transformed to normalize distributions.

First, to assess whether smoking during pregnancy was a critical period, vascular characteristics of children with persistently nonsmoking mothers (pregnancy no, currently no) were compared with children with exclusively postnatal maternal smoke exposure (pregnancy no, currently yes) and children with both pre- and postnatal maternal smoke exposure (pregnancy yes, currently yes), by using general linear modeling.

Second, vascular characteristics were analyzed, by using linear regression, by persistent maternal smoking in pregnancy, with separate confounder adjustment, adjustment for current smoke exposure of the child, and growth trajectory.

Third, categories of numbers of cigarettes (none, below the median of 5 cigarettes, above the median of 5 cigarettes smoked per day during pregnancy by the mother) were used for dose-response evaluation.

Finally, vascular characteristics were analyzed by paternal and maternal smoking during pregnancy, compared with the both nonsmoking parents category. Separate vascular characteristics were used as dependent variables and the different categories of parental smoking behavior as independent variables. Confounders were entered as covariates.

All results are expressed as regression coefficients with 95% confidence intervals and *P* values. Statistical significance was considered reached at $P_{2\text{-sided}} < 0.05$. All analyses were performed with SPSS version 17.0 for Windows.

RESULTS

Overall, mean CIMT was 383.8 μm (SD, 33.2), the median of distensibility was 95.5 per MPa (minimum 50, maximum 227 per MPa). No statistically significant differences were observed at birth between the characteristics of children of smoking and nonsmoking mothers

TABLE 1 Baseline Characteristics of WHISTLER Children and Their Parents by Maternal Smoking During Pregnancy

	Smoking Exposure Category		*P*
	Smoking No ($n = 244$)	Smoking Yes ($n = 15$)	
WHISTLER children at birth			
Gender (% males)	43.0	53.3	.43
Birth wt (g)	3493.4 (501.5)	3447.1 (626.8)	.73
Birth length (cm)	50.9 (2.5)	50.1 (3.5)	.29
Gestational age (wk)	39.5 (1.4)	39.4 (1.4)	.84
Mothers age (y)	32.1 (3.6)	31.3 (3.1)	.37
WHISTLER neonatal visit			
Age first visit (wk)	4.6 (1.3)	4.4 (1.2)	.59
Body wt (g)	4278.7 (625.3)	4266.2 (514.9)	.94
Length (cm)	54.3 (2.3)	53.5 (1.9)	.23
Nutrition (%)			
Breastfeeding	58.6	26.7	.01
Bottle-feeding	23.4	26.7	
Breast- and bottle-feeding	18.0	46.7	
WHISTLER follow-up age 5 y			
Age (y)	5.4 (0.3)	5.5 (0.3)	.49
Body wt (kg)	20.1 (2.8)	22.2 (3.4)	.01
Body height (cm)	114.8 (5.0)	115.2 (3.8)	.75
Systolic blood pressure (mm|Hg)	106.0 (7.8)	109.1 (7.9)	.13
Diastolic blood pressure (mm|Hg)	55.4 (7.0)	54.2 (5.6)	.50
Carotid end-diastolic diameter (μm)	5395.0 (400.5)	5416.5 (445.2)	.85
Current smoke exposure, n (% yes)	9 (3.8)	6 (40)	<.001
Mothers			
Ethnicity (% white)	79.5	88.9	.49
Body wt (kg)	70.9 (11.0)	74.0 (14.7)	.41
Body height (cm)	170.0 (6.6)	168.5 (7.1)	.49
Current smoking, n (%)	16 (7.4)	11 (84.6)	<.001
Fathers			
Body wt (kg)	85.4 (12.0)	90.4 (10.8)	.25
Body height (cm)	183.2 (7.5)	181.7 (6.2)	.58
Smoking during pregnancy, n (%)	28 (14.4)	6 (54.5)	<.001
Current smoking, n (%)	33 (15.3)	6 (46.2)	.004
Socioeconomic status (%)			
Low education (primary school)	6.9	0	
Middle education (secondary school)	37.9	77.8	.06
High education (tertiary school)	55.2	22.2	

Values are means (SD), unless otherwise indicated.

during pregnancy, but children of smoking mothers were lighter and shorter, and mothers were slightly younger. They were breastfed less often. At age 5 years, they had higher body weight. There was a clear association between reported current smoking habits of both parents and maternal smoking during pregnancy. Smoking of mothers during pregnancy was associated with smoking of fathers during pregnancy (Table 1).

Table 2 shows that nonparticipating infants had slightly lower gestational age, and they were breastfed less often, and had lighter and shorter mothers than participants.

To distinguish between pre- and postnatal exposure effects, Fig 2 shows, with children of 198 persistently nonsmoking mothers as a reference, that children of 16 women who did not smoke in pregnancy but did smoke currently had no differences in CIMT (−0.05 μm, 95% CI −16.6, 16.5), distensibility (0.05 natural log of DC [LnDC], 95% CI −0.07, 0.2), and EM (−0.10 LnEM, 95% CI −0.2, 0.04). By contrast, children of mothers who had smoked both in pregnancy and in the postnatal period (n = 11) had a thicker CIMT (23.3 μm, 95% CI 3.6, 43.0) and 19% ($1 - e^{-0.21}$) lower distensibility (95% CI −0.4, −0.1). The group of mothers who smoked in pregnancy but not currently was too small for meaningful analysis. EM was not significantly related to maternal smoke exposure. For further analysis, we only evaluated CIMT and DC as outcome measures.

For evaluation of pregnancy exposure specifically, Table 3 shows that children exposed to maternal smoking in pregnancy had 18.8 μm thicker CIMT and 15% ($1 - e^{-0.16}$) lower arterial distensibility than nonexposed offspring (model 1).

With regard to growth, the exposed children were somewhat lighter but much shorter at birth, with growth showing an upward shift through the distribution during the first years of life. The association of smoking during pregnancy and CIMT (Table 3, model 2) was abolished after adjustment for growth pattern. If daily smoke exposure of the child (yes/no) was taken into account, the associations did not change (not shown).

Figure 3 shows the relation between increasing number of cigarettes per day smoked by mothers in pregnancy and higher CIMT (Fig 3A) and a statistically significant trend with lower mean arterial distensibility (Fig 3B).

Figure 4 shows separate contributions to the effects on children's vascular characteristics of paternal and maternal smoking during pregnancy. Paternal smoking did not affect vascular outcomes, whereas maternal smoking did. If mothers had smoked during pregnancy, paternal smoking did have an added effect. If both parents had smoked during pregnancy, children had 27.7 μm (95% CI 0.2, 55.3) thicker CIMT and 21% lower distensibility (95% CI −0.4, −0.03). Mothers of smoking couples during pregnancy consumed a similar number of cigarettes per day (median 3.0 versus median 6.0, Mann-Whitney U test; P = .85) as mothers with nonsmoking partners.

TABLE 2 Baseline Characteristics of the Nonresponders Compared With the Participants of the Follow-up Visit at Age 5 y

	Responders (n = 325)	Nonresponders (n = 229)	P
WHISTLER children at birth			
Gender (% males)	46.2	51.5	.21
Birth wt (g)	3516.7 (504.1)	3447.5 (624.7)	.17
Birth length (cm)	50.9 (2.5)	50.6 (2.8)	.21
Gestational age (wk)	39.5 (1.4)	39.2 (1.7)	.04
WHISTLER neonatal visit			
Age first visit (wk)	4.2 (3.3)	4.3 (1.3)	.93
Body wt (kg)	4305.9 (625.7)	4387.8 (725.5)	.18
Length (cm)	54.4 (2.4)	54.3 (2.7)	.72
Infant feeding (%)			
Breastfeeding	57.1	46.9	
Formula-feeding	23.8	29.0	.06
Breast- and formula-feeding	19.0	24.1	
Mothers			
Age at birth child (y)	32.5 (3.8)	32.0 (3.6)	.15
Body wt (kg)	71.1 (11.7)	68.4 (12.0)	.03
Body height (cm)	169.8 (6.5)	168.3 (7.4)	.03
BMI (kg/m^2)	24.7 (3.9)	24.2 (3.9)	.19
Smoking during pregnancy (% yes)	6.3	8.3	.36
Fathers			
Body wt (kg)	85.2 (11.6)	83.4 (11.5)	.13
Body height (cm)	183.2 (7.4)	183.2 (7.9)	.95
BMI (kg/m^2)	25.4 (2.9)	24.8 (3.0)	.09
Socioeconomic status (%)			
Low education (primary school)	6.2	7.9	
Middle education (secondary school)	39.7	39.3	.83
Higher education	54.1	52.9	

Values are means (SD), unless otherwise indicated.

DISCUSSION

Our study shows that tobacco smoke exposure during gestation has structural and functional effects on the vascular wall of young children.

To our knowledge, WHISTLER-Cardio is the first study to report on smoking and arterial characteristics in 5-year-olds. However, some alternative explanations should be considered. Participants had slightly different profiles than

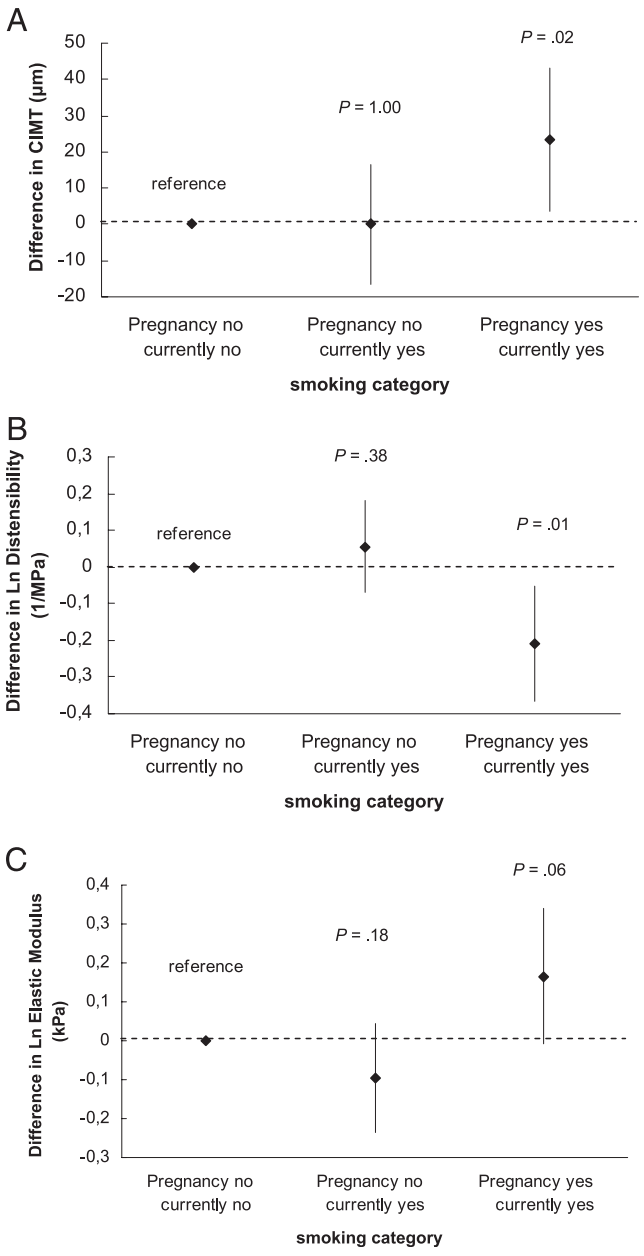

FIGURE 2

Difference in vascular outcome of children by smoking habits of mother in pregnancy and current smoking. Values are linear regression coefficients (95% confidence limits) from general linear models with children's vascular outcomes as dependent variables and indicators of combinations of maternal smoking in pregnancy (yes/no) and current maternal smoking (yes/no) as independent variables. The number of mothers that had smoked in pregnancy but not currently was too small for meaningful analysis.

nonparticipants. That may have had an influence, but could only have biased our finding if smoke exposure in nonresponders were associated with healthier vessels, which we consider unlikely. Because the WHISTLER cohort started some weeks postpartum, we could not measure cotinine at birth for assessment of maternal smoking during pregnancy. Self-reported maternal smoking has shown both low[21] and high[22] correlations to cotinine levels in umbilical cord blood and maternal urine, although cotinine measurements may not be superior to self-report.[23] Nicotine and cotinine as maternal and neonatal hair biomarkers for active smoking were reported promising.[24,25] However, that technology was unknown at the time of the WHISTLER design, and it is not known if measurements at inclusion (weeks postpartum) accurately reflect smoke exposure in pregnancy. Nevertheless, underreporting of smoking cannot be excluded but would most likely mean dilution of the association. Vascular measurements were automated and the ultrasonographer was blinded for other child characteristics. Whereas CIMT and distensibility are acknowledged proxies of cardiovascular disease risk in adulthood,[26] associations between these measures at age 5 and manifest cardiovascular disease in later life are unknown, and can only be assumed. Finally, in accordance with findings from large studies,[27,28] birth weight was lower if mothers had smoked, but our study was not designed to statistically detect these differences.

Only few studies addressed early life smoke exposure and childhood vascular structure and function. A small study indicated thicker aortic intima-media thickness in neonates if mothers smoked during pregnancy. Another study showed attenuated endothelial function in 11-year-olds of smoking mothers.[5] Recently, parental smoking in pregnancy was shown related to fetal arterial resistance and cardiac function at 2 years of age.[29] We show that arterial structure and function in 5-year-old children are adversely affected by smoking of parents.

Studies on early life passive smoking exposure and cardiovascular risk profiles in childhood have shown that smoking is considered a risk factor for childhood[30,31] and adult obesity.[32] In our study, offspring from smoking mothers did indeed have higher body weight at age 5 years. In addition, the

TABLE 3 Relation Between Smoking During Pregnancy and Vascular Characteristics in the 5-Year-Old Children

	CIMT (μm)			Distensibility (LnDC)		
	n	Linear Regression Coefficient (95% CI)	*P*	*n*	Linear Regression Coefficient (95% CI)	*P*
Crude						
No smoking	243	Reference		210	Reference	
Yes, entire pregnancy	15	15.4 (−2.0, 32.9)	.08	14	−0.17 (−0.3, −0.04)	.01
Model 1[a]						
No smoking	243	Reference		210	Reference	
Yes, entire pregnancy	15	18.8 (1.1, 36.5)	.04	14	−0.16 (−0.3, −0.02)	.02
Model 2[b]						
No smoking	214	Reference		188	Reference	
Yes, entire pregnancy	13	12.2 (−6.7, 31.1)	.20	12	−0.15 (−0.3, −0.01)	.03

CIMT, carotid intima-media thickness; LnDC, natural log of distensibility (1/MPa).

[a] Model 1: adjusted for age, gender, maternal age at birth, and breastfeeding.

[b] Model 2: adjusted for difference in *z*-score of BMI between visit at 4 wk after birth and age 5 y.

specific growth pattern of offspring of mothers smoking in pregnancy did partly explain the association with vascular characteristics. Maternal smoking in pregnancy has been shown to be related to a sharper rise in lipids in childhood.[33] Some have found offspring BP to be related to maternal smoking in pregnancy,[34] but not others.[35,36]

Alongside the effects of smoking in pregnancy on early life cardiovascular risk profiles, there may be direct effects as well. Nicotine passes the placenta, and it was shown that cotinine levels in neonates equaled levels of the smoking mothers.[37] Clearly, fetuses are exposed to the many toxic constituents in tobacco smoke consumed by their mothers. It is conceivable that such influences contribute to very early life vascular damage. Maternal smoking in pregnancy induces chronic hypoxia by carbon monoxide and reduces nitric oxide production in the fetal circulation.[29,38] Atherosclerotic changes were seen in the coronaries of fetuses and newborns that died and whose mother smoked in pregnancy.[39] Recently it was shown that maternal smoking leads to different (para) sympathetic control in the offspring, resulting in differences in vascular physiology between smoke-exposed and control infants.[40]

Our findings suggest that both smoking by mothers themselves in pregnancy and exposure to passive smoking could be important, and that more exposure leads to more vascular damage in the offspring. However, the effect of exposure by the father is not clear. Our findings suggest that paternal smoking in pregnancy is important in the case of maternal smoking in pregnancy, but not when mothers did not smoke in pregnancy. Although speculative, it could be that fathers who smoked in pregnancy, did so less in the direct vicinity of more health-concerned nonsmoking mothers, than fathers of couples who both continued smoking in pregnancy. The effect of smoking during pregnancy on offspring vasculature was not clear if mothers smoked during pregnancy and fathers did not, whereas it was clear if both parents smoked. Mothers with smoking partners during pregnancy smoked similar numbers of cigarettes as mothers with nonsmoking partners, which supports the additive role of paternal smoking.

Tobacco smoking, including passive smoking, is known to be one of the most important risk factors for manifest cardiovascular disease.[41,42] Although there is no debate on the ill effects of tobacco smoking on health in general, it is important to know whether there

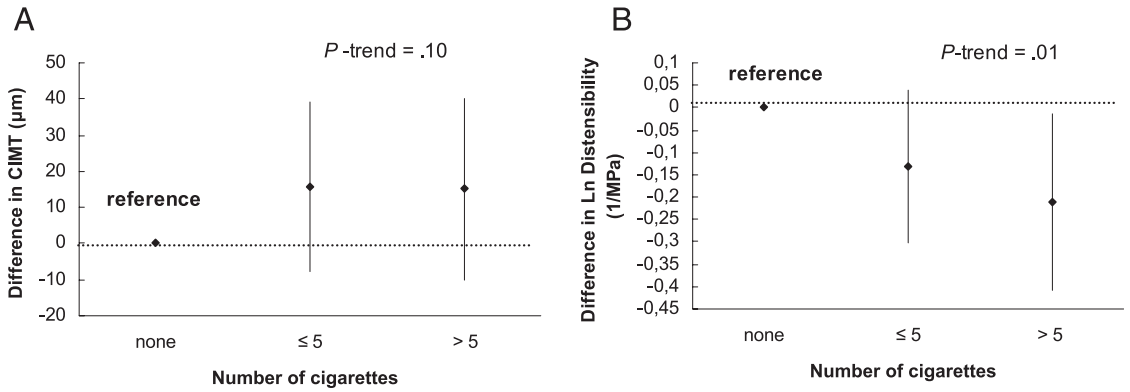

FIGURE 3

Dose of tobacco smoke exposure in pregnancy and difference in CIMT (A) and distensibility (B) in the children. Dose-response relation between number of cigarettes smoked per day by mother in pregnancy (none, below median [5 cigarettes] $n = 8$, and above median, $n = 7$) and CIMT (A) and LnDC (B) in their children. All values are differences compared with the reference (nonsmoking) category and 95% confidence limits.

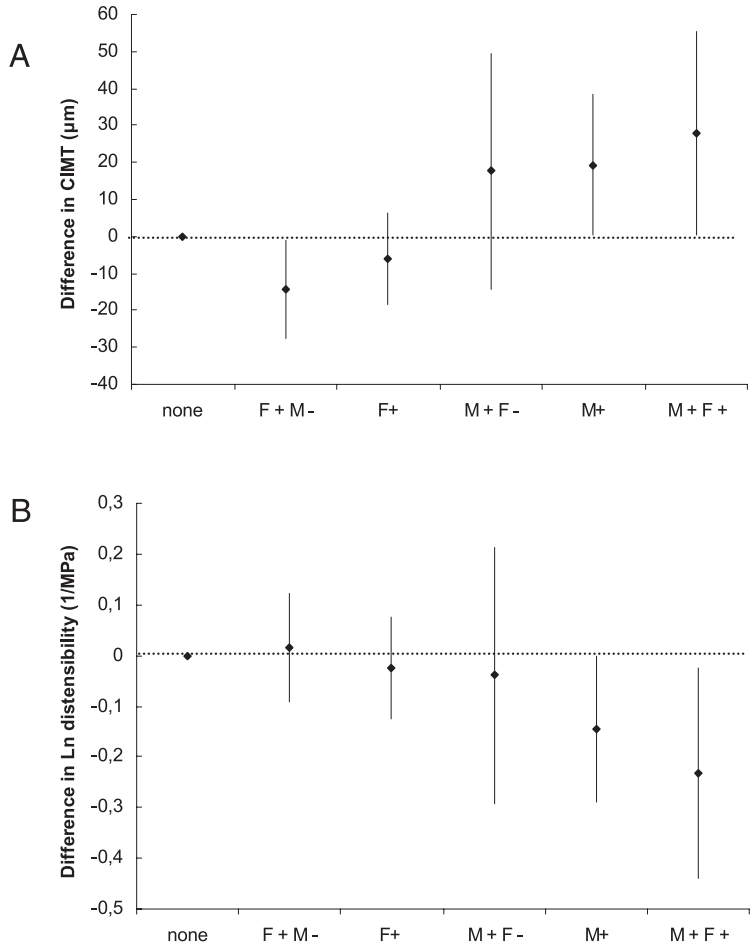

FIGURE 4

Paternal and maternal smoking during pregnancy and vascular outcome in their children. Differences in children's CIMT (A) and Ln distensibility (B) between combinations of maternal and paternal smoking behavior during pregnancy (M+, mother smoked during pregnancy; F+, father smoked during pregnancy) and children's vascular outcome of both nonsmoking parents as the reference category. Each of the combinations (F+M−/none, F+/none, M+F−/none, M+/none, M+F+/none) were separately analyzed. Values are linear regression coefficients (95% confidence limits). All analyses were adjusted for age, gender, breastfeeding, and maternal age.

are particularly vulnerable periods in early life. In our study, smoking in pregnancy explained 0.57 SD of CIMT. There was no association with offspring vasculature if the mother had not smoked in pregnancy but had smoked thereafter. In contrast, clear effects on offspring vasculature were noted from mothers who smoked persistently during pregnancy. Moreover, there was a clear positive trend between the number of cigarettes smoked by mothers in pregnancy and adverse vascular health, a finding that adds to the credibility of gestational smoking being causally related to offspring vascular damage. It is therefore inferred that gestation is a critical period. In view of the early origins of cardiovascular disease, preventive measures against smoking should be specifically directed at the gestational period.

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APPENDIX Equations

Δd (change in carotid diameter)	$d_{systolic} - d$
Δp (carotid pulse pressure)	CF * Δd
CF (conversion factor)	(MAP − DBP)/($d_{mean} - d$)
MAP (mean arterial pressure)	DBP + (SBP − DBP)/3
ΔA (change in arterial cross-sectional area)	$\pi/4 * [(d + \Delta d)^2 - d^2]$
DC	$(\Delta A / A) / \Delta P = (2 \Delta d * d + \Delta d^2) / (\Delta p * d^2)$
EM	(d/IMT) / DC
$d_{systolic}$	mean end-systolic lumen-IMT diameter (mm)
d	mean end-diastolic lumen-IMT diameter (mm)
A	arterial cross-sectional area (mm^2)
DC	distensibility coefficient (1/MPa)
EM	elasticity, Young's modulus (kPa)
IMT	intima-media thickness, end-diastolic (mm)
SBP	systolic blood pressure in brachial artery (mmHg)
DBP	diastolic blood pressure in brachial artery (mmHg)
MAP	mean arterial pressure in brachial artery (mmHg)

HOARDING: *Last week I went to the grocery store to purchase milk, cereal, and fruit. I was heading for the check-out counter when an end-of-aisle display caught my attention. Cans of diced tomatoes, which I use frequently when cooking, were on sale. The sign indicating the price also noted that customers could only purchase three. I wasn't planning on cooking with diced tomatoes soon and I already had quite a stash in the pantry, but this was a good deal. Anyone facing a similar predicament should know that the placement of food items, cost, and even the exact wording of the signage in most large grocery stores have been carefully choreographed by food manufacturers. According to an article in* Time *(The Culture: November 7, 2011), manufacturers have all kinds of tricks to make sure shoppers buy their products and more specifically, buy something that they had not planned on buying. Research has shown that shoppers respond to seemingly small cues. For example, using parquet rather than linoleum floors in a particular aisle conveys a sense of quality and may make shoppers slow. Creating ridges in the floor makes the shopping cart clatter and cause shoppers to instinctively slow. The goal is to make sure the shopper spends as much time as possible looking at the food items. Grocery stores appeal to very primitive human instincts: survival and getting a good deal. While fewer people in the U.S. face food insecurity than most other places in the world, there is a natural tendency to want to make sure there is always enough food. If we can couple that desire with getting a good deal, then dopamine is presumably released and the shopper feels a rush of satisfaction or pleasure. One approach is to place a limit on the number of individual items that can be purchased. The natural tendency for many shoppers is to hoard the maximum amount as if suspicious that there are not any more cans of diced tomatoes in back. Removing the dollar sign from the price helps disconnect the shopper from the economic cost of putting the food item into the cart. So while I pushed the tiniest cart available around the store, carried a specific shopping list, and avoided the stand-up displays, I was no match for the diced tomatoes. Three cans went into the cart. Who knows, maybe there will be a terrible Vermont snowstorm and I will be happy that I have a dozen cans in the basement.*

Noted by WVR, MD

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