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ORIGINAL RESEARCH

Maternal Smoking Intensity During Pregnancy and Early Adolescent Cardiovascular Health

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BACKGROUND: The adverse cardiovascular effects of smoking are well established. We aimed to investigate the less well-understood effects of pregnancy smoke exposure on offspring cardiovascular health in early adolescence.

METHODS AND RESULTS: Data were drawn from the nationally representative Longitudinal Study of Australian Children's Child Health CheckPoint. Mothers reported mean daily cigarettes smoked in each trimester (≤10 versus >10/day), and smoking cessation during pregnancy. Blood pressure, pulse wave velocity, carotid intima-media thickness, and retinal microvascular parameters were measured in early adolescence (mean 11.5 years). Hypertension was defined as systolic blood pressure ≥120 or diastolic blood pressure ≥80 mm Hg. 187 (11.8%) of 1582 women (mean age 30.7±0.2 years), smoked during pregnancy, of whom 143 (76.5%) smoked throughout pregnancy, and 58 (31.0%) smoked >10 cigarettes/day. Compared with those born to nonsmoking mothers, the odds of hypertension in early adolescence were 1.44 (95% CI, 1.01–2.06) if mothers ever smoked, 1.99 (1.22–3.24) if mothers smoked >10 cigarettes/day, and 1.64 (1.11–2.42) if mothers smoked throughout pregnancy There was limited evidence of associations between smoking throughout pregnancy and other cardiovascular measures. Offspring of mothers who stopped smoking during pregnancy and nonsmokers had similar cardiovascular measures, apart from hypertension.

CONCLUSIONS: Offspring of mothers who smoked in pregnancy have increased risks of hypertension in adolescence, with increased risk with greater exposure intensity and duration. Mothers who stopped smoking during pregnancy had offspring with similar cardiovascular health to those born to nonsmokers. Our findings underscore the importance of specific strategies to stop maternal smoking before conception and during pregnancy.

Key Words: adolescent ■ blood pressure ■ carotid intima-media thickness ■ maternal smoking ■ pulse wave velocity ■ retinal microvascular parameters

According to a systematic review and meta-analysis published in 2018, the prevalence of smoking during pregnancy is estimated to be 1.7% globally, ranging from 0.8% in the African region to 8.1% in the European region.[1] From an Australian cross-sectional survey in 2021, approximately 8.7% of mothers reported smoking at some point during their pregnancy, even higher than the global prevalence, highlighting a major public health issue.[2]

Nicotine crosses the placenta into fetal circulation and may also accumulate in the amniotic fluid, which binds to endogenous nicotinic acetylcholine receptors and potentially affects the developing endocrine, immunological, respiratory, and cardiovascular systems.[3]

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CLINICAL PERSPECTIVE

What Is New?

- In this study of 1582 pairs of Australian mother–child dyads, 11.8% of mothers had a history of smoking during pregnancy; compared with offspring of mothers who did not smoke in pregnancy, offspring of mothers who smoked in any trimester during pregnancy, smoked >10 cigarettes per day during pregnancy, or smoked throughout pregnancy, had higher blood pressure and increased risk of hypertension at early adolescence.
- There was a trend of more cigarettes or smoking throughout pregnancy with poorer blood pressure.
- If mothers stopped smoking in any trimester during pregnancy, offspring had similar cardiovascular health to nonsmoking-exposed offspring in early adolescence.

What Are the Clinical Implications?

- We found that adverse associations with child cardiovascular health were mitigated in offspring whose mothers stopped smoking during pregnancy, highlighting the potential impact of interventions specifically targeting smoking before and during pregnancy to reduce potential long-term adverse cardiovascular effects on offspring.

Nonstandard Abbreviations and Acronyms

cIMT	carotid intima-media thickness
CRAE	central retinal arteriolar equivalent
CRVE	central retinal venular equivalent
PWV	pulse wave velocity
SEP	socioeconomic position

Smoking during pregnancy has been strongly associated with a range of pregnancy complications (eg, ectopic pregnancy, placental abruption, and preeclampsia), and adverse outcomes in offspring (eg, congenital anomalies, preterm birth, perinatal death, and low birthweight).[4–6] The adverse effects of pregnancy smoking extend into childhood.[6] For example, maternal smoking increases the risk of offspring childhood overweight and obesity, bronchial asthma, and respiratory tract infections.[6–8]

There is a relative scarcity of evidence regarding longer-term associations between maternal smoking and offspring cardiovascular health outcomes. A history of maternal smoking has been associated with children with greater carotid intima-media thickness (cIMT), increments in diastolic blood pressure (DBP), and greater carotid-femoral pulse wave velocity (PWV), compared with those with nonsmoking mothers.[9,10] Most studies only compare childhood cardiovascular health outcomes between smoking and nonsmoking mothers[6] and more granular analyses, including the number of cigarettes and effects of mothers stopping smoking during pregnancy, which would guide public health interventions, are lacking. Thus, our hypothesis was that (1) the offspring's risk of having adverse cardiovascular profiles would be higher in those whose mothers smoked more cigarettes during pregnancy, and (2) the offspring's risk would be lower in those whose mothers stopped smoking at any time during pregnancy.

We aimed to investigate the extent to which maternal smoking status and intensity during pregnancy affected the cardiovascular health of offspring in early adolescence using data from a population-derived longitudinal cohort.

METHODS

Data Sharing

Data described in the article, code book, and analytic code will be available upon request pending application and approval of a data-sharing agreement.

Study Design and Participants

Data were drawn from the LSAC (Longitudinal Study of Australian Children) and its cross-sectional physical health and biospecimens module, the Child Health CheckPoint (CheckPoint) study. All data and materials have been made publicly available on the LSAC website and can be accessed at https://growingupinaustralia.gov.au/. Detailed information about LSAC study design and participant recruitment is described previously.[11,12] In brief, a population-representative sample of offspring aged 0 to 1 year was recruited into LSAC's Birth cohort, with data collection continued biennially since 2004. The response rate of the first invitation in 2004 was 57.2% (n=5107), of which 73.7% (n=3764) were retained to wave 6 in 2014.

At wave 6, interviewers invited all contactable families (n=3513) to consent to share their contact details with the CheckPoint team. Children aged 11 to 12 years were invited to attend an assessment with their primary caregiver. The CheckPoint study provided physical health measures and collected biosamples in participated families in 2015 to 2016. Details of CheckPoint study design have been described previously.[13,14]

The CheckPoint study was approved by The Royal Children's Hospital Melbourne Human Research Ethics

Committee (33225D) and the Australian Institute of Family Studies Ethics Committee. A parent or guardian provided written consent for their own and their child's participation in the study, and children provided assent for each measure.

Exposure: Maternal Smoking Collected at LSAC Wave 1

At wave 1 in 2004, LSAC recruited 5107 infants aged 0 to 1 years from the Australian universal health care system, using a 2-stage randomized sampling design to recruit a sample representative of the Australian birth population at the time. The LSAC team collected information through face-to-face structured interviews with children's caregivers (98.6% were the child's biological mother). The team asked if mothers smoked cigarettes during pregnancy (Yes/No). Additionally, the team asked about how many cigarettes the woman smoked per day in each trimester. Maternal smoking during pregnancy was categorized for further analysis based on status (nonsmokers versus ever smoked during pregnancy), intensity (throughout pregnancy average daily cigarettes smoked ≤10 versus >10), and cessation during pregnancy (smoking cessation at any point during pregnancy versus smoking throughout pregnancy).

Outcomes: Child Cardiovascular Measures in Early Adolescence

At LSAC's CheckPoint wave, offspring underwent a series of measures including BP, PWV, cIMT, and retinal vascular parameters. The protocol, reliability, and details of each measurement have been previously described.[15–17] Following 7 minutes in the supine position at rest, systolic BP (SBP), DBP, and PWV were measured via SphygmoCor XCEL (AtCor Medical, Australia) at the brachial artery up to 3 times, with mean values reported. The mean arterial blood pressure (MAP) was calculated as 1/3 of SBP plus 2/3 of DBP. PWV was calculated as the ratio of the distance traveled by the pulse wave and the time delay between the waveforms (m/s). Higher values indicate faster PWV and greater arterial stiffness. Carotid artery images were obtained via a B-mode ultrasound machine (Vivid-I, GE Healthcare, Chicago, IL). The right carotid artery was measured as participants lay supine with their head turned 45° to the left to expose the right side of the neck. The cIMT was analyzed using Carotid Analyzer (Coralville, IA). cIMT (μm) is defined as the distance from the lumen-intima interface to the media-adventitia interface. Higher values are suggested to be indicative of early atherosclerosis.[18] In a darkened room, without mydriasis, 2 digital photographs focusing on the optic disc were taken of each eye via retinal camera (45° no-mydriatic Canon CR-DGi, Tokyo, Japan). Right eye fundus photographs were preferentially selected for scoring by experienced graders using the Singapore I Vessel Assessment (SIVA, version 3.0, Singapore Eye Research Institute, Singapore) software. Central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE) were calculated. A lower CRAE value indicates narrowed arterioles and a higher CRVE value indicates widened venules, both reflective of more adverse retinal microvasculature.[19] We excluded some data due to poor quality images or inability to measure at the assessment center. In the analysis, participants with data on at least 1 exposure and 1 of the 5 outcomes were included in the analysis sample.

Covariates

At LSAC wave 1, data on maternal age at pregnancy, gestational age, mode of delivery, child birthweight, alcohol exposure during pregnancy, household income, current or most recent occupation of each parent, and highest educational qualification of each parent were obtained via face-to-face interviews. A composite family socioeconomic position (SEP) score[20]: each component was scaled and an unweighted average was calculated and standardized within wave 1 to have a mean of 0 and an SD of 1. A higher score indicates a more advantaged SEP. Child age at CheckPoint was calculated to the nearest week using the date of birth, which was imported from Medicare Australia's database at the time of LSAC enrolment, and the date of assessment. Sex was imported from Medicare, along with the date of birth. In CheckPoint, child height and weight were measured in light clothing and without shoes or socks. Body mass index (BMI, kg/m^2) was calculated as weight (kg) divided by height (m) squared and then BMI were transformed to age- and gender-adjusted BMI *Z* scores using the US Centers for Disease Control and Prevention growth reference charts.[21]

Statistical Analysis

Comparisons of characteristics between smokers and nonsmokers were analyzed by Student's *t* test, nonparametric comparison test, or χ^2-test when applicable. In all our analyses, we incorporated survey weights to account for the intricate multilevel sampling design of LSAC and made adjustments for nonresponse and attrition across the 6 waves of data collection. The average daily cigarette smoked reported by mothers was skewed (range 0–45, median=0, skewness=5). Thus, we treated this as a categorical variable. We performed associations in the following steps: (1) to examine associations of maternal smoking during pregnancy and continuous offspring cardiovascular

measures; and (2) to examine associations of maternal smoking during pregnancy and categorized cardiovascular outcomes in offspring; hypertension (SBP≥120 or DBP≥80 mm Hg),[22] high PWV (at or above the age-, sex-, and heart-rate specific 90th percentile of PWV),[23,24] high CIMT (values ≥90th percentile for sex, age, and study population specific),[25] generalized retinal arteriolar narrowing, and generalized retinal venular dilatation (the lowest and highest 20th percentile of the study population distributions of CRAE and CRVE, respectively).[26] In all regressions, we applied both unadjusted and adjusted models. We adjusted for major prespecified confounders, maternal age, family SEP, and child sex, defined using a direct acyclic graph (Figure S1). In sensitivity analysis, models were further adjusted for (1) alcohol exposure and paternal smoking, which may have a bidirectional relationship with the exposures; (2) mediators lying on the causal pathway, mothers' postnatal smoking status, child birthweight, gestational age, mode of delivery and BMI *Z* score at follow-up and (3) interactions between maternal smoking exposures with maternal age, child sex, alcohol exposure, and paternal smoking were investigated. All statistical analyses were performed in

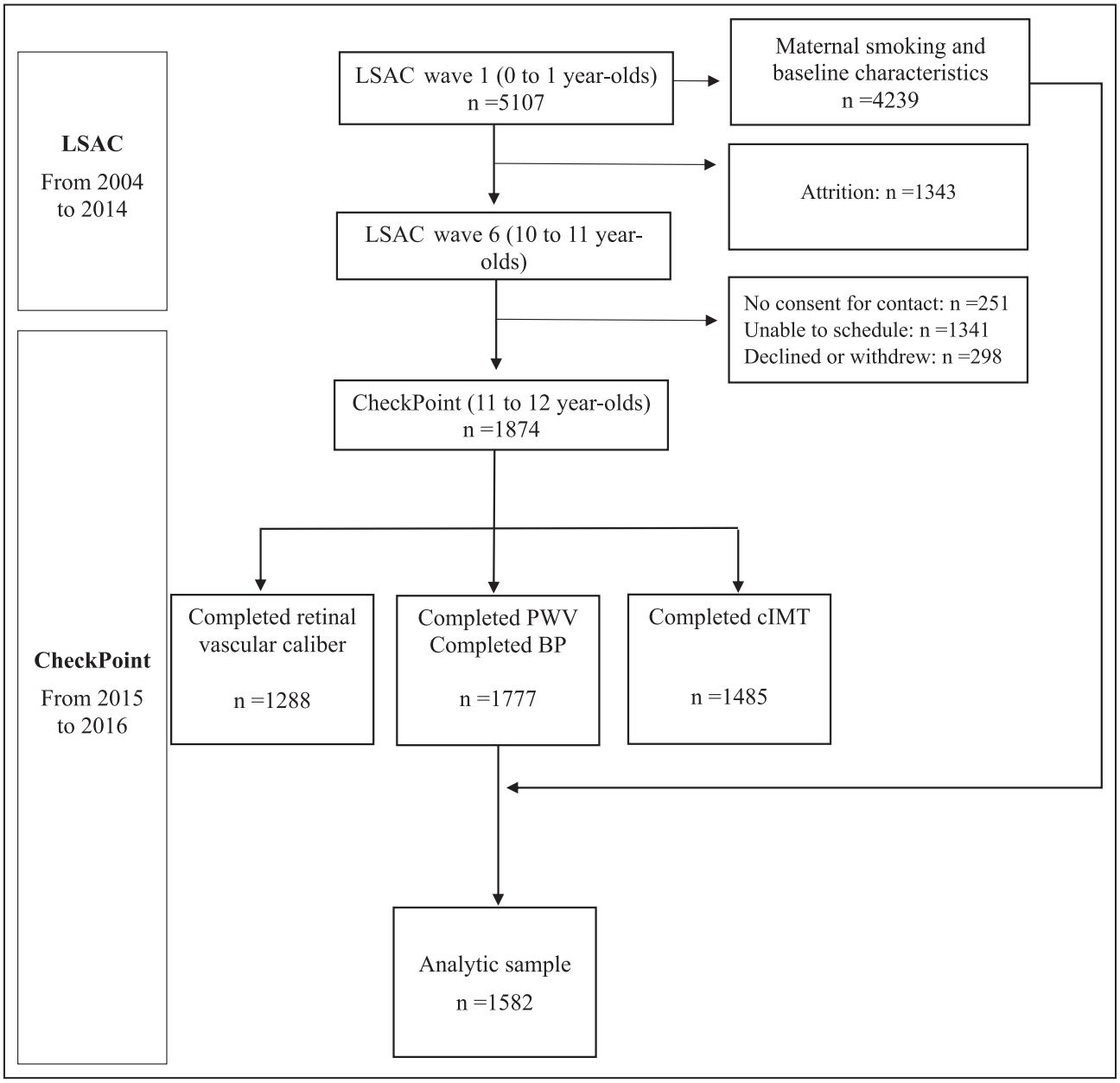

Figure 1. Participant flow chart.
BP indicates blood pressure; CheckPoint, the Child Health CheckPoint study; cIMT, carotid intima-media thickness; LSAC, Longitudinal Study of Australian Children; and PWV, pulse wave velocity.

Stata 17.0 SE (StataCrop LP, TX), and the results were presented with estimates (β or odds ratio [OR]) and 95% CIs. Two-tailed *P* values were reported.

RESULTS

Of the 1874 offspring participating in CheckPoint, 1582 had data available on at least 1 exposure and 1 outcome (Figure 1). Sample characteristics of the analytic sample were presented in Table 1. The mean age of pregnant women was 30.7 (SD 0.2) years. The mean offspring age was 11.5 (SD 0.0) years and approximately 49% were girls. Of 1582 women, 187 (11.8%) reported smoked during pregnancy, of whom 143 (76.5%) smoked throughout pregnancy, and 58 (31.0%) smoked >10 cigarettes/day. Throughout pregnancy, the average number of cigarettes smoked daily ranged from 0 to 45. Mothers who smoked were younger, had lower family SEP, and had a higher rate of alcohol exposure during pregnancy compared with those who never smoked during pregnancy (Table S1).

Compared with offspring born to nonsmoking mothers, those born to mothers who had ever smoked in any trimester had higher SBP and MAP in both unadjusted and adjusted models (Table 2). For example, in the adjusted model, compared with offspring of mothers who did not smoke, offspring of mothers who had ever smoked during pregnancy had a 2.07 mm Hg (95% CI, 0.29–3.84) and 1.44 mm Hg (0.22–2.66) increments in SBP and MAP, respectively. In logistic regression models with categorical cardiovascular measures, offspring born to mothers who had ever smoked in any trimester had 1.44 (1.01–2.06) times risk of developing hypertension at 11 to 12 years of age than those mothers who never smoked during pregnancy (Table 2). There was limited evidence of associations between maternal smoking during pregnancy and other cardiovascular health measures (ie, PWV, cIMT, CRAE, CRVE) in early adolescence.

We further examined maternal smoking intensity and offspring cardiovascular health. Compared with offspring born to nonsmoking mothers, those born to mothers who smoked >10 cigarettes daily during pregnancy had higher SBP, DBP, and MAP in unadjusted and adjusted models. (Table 3). There was evidence of a dose–response of smoking intensity and offspring SBP, DBP, and MAP (*P*-for-trend <0.05). Similarly, in logistic models with categorical cardiovascular measures (Table S2, Figure 2), compared with offspring born to nonsmoking mothers, the odds of having hypertension were 2.19 (1.37–3.49) if mothers smoked >10 cigarettes/day. These odds attenuated slightly to 1.99 (1.22–3.24) but remained after adjustment (Figure 2). Maternal smoking intensity was not associated with other child cardiovascular measures (ie, PWV, cIMT, CRAE, or CRVE) in early adolescence.

Table 1. Sample Characteristics of Analytic Sample (n=1582)

Variables	Weighted Mean±SD/%	Nonweighted Mean±SD/%
Mothers		
Age at pregnancy, y	30.7 (0.2)	31.4 (4.7)
Family socioeconomic status	0.04 (0.04)	0.32 (0.95)
Ever smoked during pregnancy		
No	82.8	88.2
Yes	17.2	11.8
In smokers, average daily cigarettes during pregnancy (median, range)*	0 (0–45)	0 (0–28)
Smoked in first trimester		
No	82.8	88.6
≤10 cigarettes	14.8	7.8
>10 cigarettes	2.4	3.6
Smoked in second trimester		
No	82.8	90.0
≤10 cigarettes	14.8	6.8
>10 cigarettes	2.4	3.2
Smoked in third trimester		
No	83.7	90.4
≤10 cigarettes	13.9	6.5
>10 cigarettes	2.4	3.1
Smoking degree over pregnancy		
No smoking	82.8	90.5
All trimesters ≤10 cigarettes	14.8	5.7
Smoked >10 cigarettes in any trimester	2.4	3.8
Continuously smoked during pregnancy from first to third trimester	16.3	9.3
Children		
Age, y	11.5 (0.0)	11.5 (0.5)
Sex (female%)	49.0	49.5
Pulse wave velocity, m/s	4.5 (0.0)	4.5 (0.6)
Carotid intima-media thickness, μm	583.3 (1.76)	581.0 (47.3)
Systolic blood pressure, mm Hg	108.5 (0.3)	108.0 (7.9)
Diastolic blood pressure, mm Hg	62.6 (0.2)	62.5 (5.8)
Retinal arteriolar caliber, μm	144.9 (0.4)	144.9 (11.4)
Retinal venular caliber, μm	208.7 (0.4)	208.4 (15.0)

*The average daily cigarettes smoking is skewed, so median and range were reported.

Maternal smoking cessation during pregnancy was not associated with differences in offspring cardiovascular measures (Table 3). There was some evidence of increased SBP, DBP, and MAP among mothers who smoked throughout pregnancy (*P*-for-trend <0.05). For example, in the full adjustment, offspring born to mothers smoked throughout pregnancy had 2.54 mm Hg (0.54–4.53), 1.46 mm Hg (0.21–2.71), and 1.82 mm Hg

Table 2. Associations of Maternal Smoking (Nonsmoker vs Ever Smoked During Pregnancy) and Child Cardiovascular Health Measures

Continuous cardiovascular measures	Ever smoked in any trimester		Adverse cardiovascular measures	Ever smoked in any trimester	
	Model 1	Model 2		Model 1	Model 2
	β (95% CI)	β (95% CI)		OR (95% CI)	OR (95% CI)
PWV	0.05 (−0.04 to 0.15)	0.03 (−0.07 to 0.12)	High PWV	0.86 (0.49 to 1.51)	0.75 (0.42 to 1.32)
cIMT	2.74 (−8.72 to 14.20)	−2.06 (−14.21 to 10.10)	High CIMT	1.26 (0.82 to 1.94)	0.88 (0.55 to 1.40)
SBP	2.56 (0.90 to 4.23)*	2.07 (0.29 to 3.84)*	Hypertension	1.58 (1.14 to 2.18)*	1.44 (1.01 to 2.06)*
DBP	1.19 (0.02 to 2.36)*	1.13 (−0.02 to 2.29)			
MAP	1.65 (0.45 to 2.84)*	1.44 (0.22 to 2.66)*			
CRAE	−0.78 (−3.32 to 1.75)	−0.59 (−3.16 to 1.99)	Generalized arteriolar narrowing	1.17 (0.65 to 2.13)	1.13 (0.60 to 2.14)
CRVE	−0.00 (−3.57 to 3.57)	0.26 (−3.44 to 3.95)	Generalize venular widening	0.77 (0.42 to 1.41)	0.83 (0.45 to 1.53)

Model 1: unadjusted model. Model 2: adjusted for maternal age, family socioeconomic status, and child sex. Definitions: High PWV (at or above the age-, sex-, and heart-rate specific 90th percentile of PWV); high cIMT (values ≥90th percentile for sex, age, and study population specific; pediatric hypertension) (SBP≥120 or DBP≥80 mm Hg); generalized retinal arteriolar narrowing (the lowest 20th percentile of the study population distribution of CRAE), and generalized retinal venular dilatation (the highest 20th percentile of study population distribution of CRVE). CIMT indicates carotid intima-media thickness; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; OR, odds ratio; PWV, pulse wave velocity; and SBP, systolic blood pressure.

*P-value <0.05.

(0.48–3.16) increments in SBP, DBP, and MAP, respectively (Table 3), and a 64% increased risk (1.11–2.42) of developing hypertension, compared with offspring born to nonsmoking mothers (Table S2, Figure 2).

In sensitivity analyses (Tables S3 through S11), all linear and logistic regression models were further adjusted for alcohol exposure during pregnancy, paternal smoking, maternal postnatal smoking, gestational age, child birthweight, mode of delivery, and BMI Z scores at follow-up. The association of ever smoked during pregnancy and offspring BP approached the null after further adjusting for paternal smoking, except that the further adjustment did not affect the associations between smoking intensity or smoking continuously during pregnancy with offspring blood pressure. There were no interactions between smoking exposures (ie, ever smoked, smoking intensity, or smoking cessation) with maternal age, child sex, alcohol exposure during pregnancy, and paternal smoking (data not shown).

DISCUSSION

In this study of 1582 pairs of Australian mother–child dyads, 11.8% of mothers had a history of smoking during pregnancy. In addition, compared with offspring of mothers who did not smoke in pregnancy, offspring of mothers who smoked in any trimester during pregnancy, smoked >10 cigarettes per day during pregnancy, or smoked throughout pregnancy had higher BP and increased risk of hypertension at early adolescence. We note a trend of more cigarettes or smoking throughout pregnancy associated with poorer BP in offspring. These associations remained evident after sensitivity analyses. We observed some evidence of adverse offspring cardiovascular health outcomes in PWV, cIMT, and CRAE among mothers who smoked.

Globally, the prevalence of smoking during pregnancy was estimated to be 1.7%, ranging from 0.8% in the African region to 8.1% in the European region.[1] In our study, we found that Australian women exhibited a high prevalence of smoking during pregnancy, with 11.8% reporting smoking histories during pregnancy. Among these, 76.5% continued smoking throughout pregnancy. Despite well-documented short-term effects, few studies explore the long-term impact of maternal smoking on child cardiovascular health.[4,6,27]

Our study aligns with existing literature regarding maternal smoking and its impact on offspring hypertension across the life course. In the Dutch Generation R study (n=4109), offspring exposed to continued smoking during pregnancy (≥5 cigarettes per day) had higher SBP (mean difference, 0.15 Standardized Deviation Score [7.9 mm Hg] [95% CI, 0.03–0.26]) at a mean age of 9.8 years.[28] A European cohort with similar age offspring reported analogous findings that maternal smoking beyond 12 weeks of gestation was associated with over 2-fold increased likelihood of offspring hypertension (OR, 2.20 [95% CI, 1.09–4.42]) at 11 years.[29] In the Nurses' Health Study II and the Nurses' Mothers' Cohort involving 33 086 nurses, maternal smoking of ≥15 cigarettes/d during pregnancy was associated with an increased incidence of hypertension in the female offspring at a mean age of 34 years (RR, 1.19 [95% CI, 1.09–1.29]), compared with nonsmoking mothers.[30] Our study of offspring aged 11

Table 3. Linear Regression Models of Maternal Smoking Intensity and Smoking Cessation During Pregnancy and Child Cardiovascular (With Nonsmokers as Reference Group)

Cardiovascular measures	Model 1							Model 2						
	Nonsmokers	Smoked≤10 cigarettes/day (n=129)		Smoked>10 cigarettes/day (n=58)		*P*-for-trend		Nonsmokers	Smoking cessation at any point during pregnancy (n=35)		Smoking throughout pregnancy (n=143)		*P*-for-trend	
		Model 1	Model 2	Model 1	Model 2				Model 1	Model 2	Model 1	Model 2		
		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	Model 1	Model 2		β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	Model 1	Mode 2
Pulse wave velocity	Ref	0.00 (−0.11 to 0.12)	−0.03 (−0.15 to 0.09)	0.16 (−0.03 to 0.34)	0.14 (−0.05 to 0.32)	0.25	0.32	Ref	−0.03 (−0.24 to 0.18)	−0.05 (−0.27 to 0.16)	0.09 (−0.02 to 0.2)	0.07 (−0.04 to 0.18)	0.29	0.44
Carotid intima-media thickness	Ref	−0.89 (−13.48 to 11.71)	−5.63 (−18.82 to 7.55)	10.05 (−12.71 to 32.81)	5.16 (−18.02 to 28.33)	0.68	0.62	Ref	−2.14 (−26.32 to 22.04)	−7.48 (−32.06 to 17.1)	3.7 (−9.36 to 16.77)	−1.06 (−14.69 to 12.58)	0.84	0.83
Systolic blood pressure	Ref	1.61 (−0.15 to 3.36)	1.13 (−0.72 to 2.98)	4.42 (1.26 to 7.57)*	3.89 (0.7 to 7.07)*	0.01*	0.04*	Ref	0.89 (−2.4 to 4.17)	0.5 (−2.85 to 3.84)	3.06 (1.15 to 4.96)*	2.54 (0.54 to 4.53)*	<0.01*	0.04*
Diastolic blood pressure	Ref	0.48 (−0.98 to 1.94)	0.45 (−0.96 to 1.87)	2.56 (0.67 to 4.45)*	2.46 (0.59 to 4.33)*	0.03*	0.03*	Ref	0 (−3.15 to 3.15)	−0.01 (−3.05 to 3.02)	1.52 (0.25 to 2.78)*	1.46 (0.21 to 2.71)*	0.06	0.07
Mean arterial pressure	Ref	0.86 (−0.54 to 2.26)	0.68 (−0.72 to 2.07)	3.18 (1.09 to 5.27)*	2.94 (0.85 to 5.02)*	<0.01*	0.02*	Ref	0.29 (−2.68 to 3.27)	0.16 (−2.76 to 3.07)	2.03 (0.71 to 3.35)*	1.82 (0.48 to 3.16)*	0.01*	0.03*
Central retinal arteriolar equivalent	Ref	0.1 (−3.12 to 3.32)	0.46 (−2.69 to 3.6)	−2.67 (−5.96 to 0.62)	−2.82 (−6.27 to 0.63)	0.27	0.23	Ref	−0.56 (−7.6 to 6.48)	−0.08 (−6.29 to 6.13)	−1.14 (−3.75 to 1.46)	−1.03 (−3.72 to 1.66)	0.69	0.75
Central retinal venular equivalent	Ref	1.24 (−3.29 to 5.77)	1.64 (−2.87 to 6.15)	−2.66 (−7.38 to 2.06)	−2.7 (−7.65 to 2.24)	0.45	0.24	Ref	4.41 (−8.53 to 17.35)	4.87 (−7.45 to 17.2)	−0.73 (−4.18 to 2.73)	−0.54 (−4.17 to 3.09)	0.72	0.69

Model 1: unadjusted analysis. Model 2: adjusted for maternal age, family socioeconomic status, and child sex.
**P*-values <0.05.

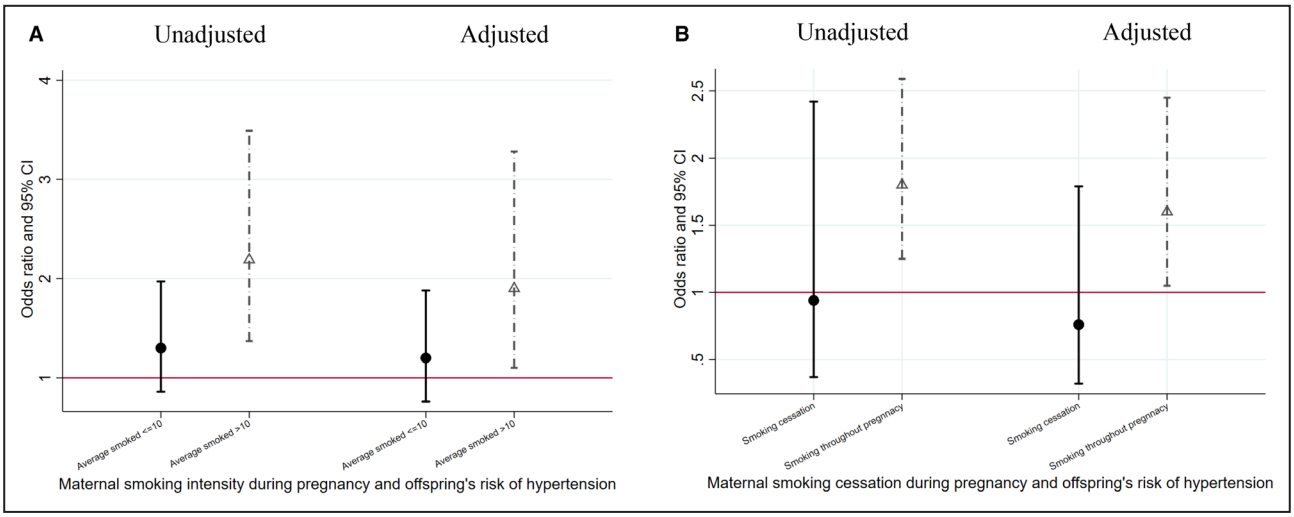

Figure 2. Maternal smoking conditions with offspring risk of hypertension at age 11 to 12 years.
A, Maternal smoking intensity during pregnancy; **B**, Maternal smoking cessation and smoking throughout pregnancy.

to 12 years showed that any maternal smoking during pregnancy was associated with elevated BP and an increased risk of hypertension in early adolescence. Furthermore, mothers who smoked >10 cigarettes/day during pregnancy were associated with a 2-fold risk of hypertension in their offspring at 11 to 12 years. Given the strong tracking of BP from childhood to adulthood,[31] our findings suggest that early exposure to maternal smoking may contribute to long-term hypertension and adverse cardiovascular risk.

It has been reported that stopping smoking in the first trimester, especially before 15 weeks of gestation, reduces the risk of preterm birth and small-for-gestational-age infants.[32] We found that smoking cessation at any point of pregnancy was not associated with differences in child cardiovascular measures compared with those who never smoked. However, if the mother smoked throughout pregnancy, the offspring had an increased risk of hypertension compared with those who never smoked. Stopping smoking during pregnancy is considered particularly challenging because of physical and psychological addiction; for example, nicotine metabolism increases during pregnancy, leading to stronger experience in both cravings and withdrawal symptoms for pregnant women when quitting.[33] Therefore, it may be easier to target women before conception with smoking cessation interventions to prevent potential future harm to their offspring.

In our study, we did not see associations between maternal smoking exposures and PWV, cIMT or retinal vascular parameters in this relatively healthy population. Studies with offspring aged 5 to 6 years have reported associations between maternal smoking exposure during pregnancy and offspring higher cIMT and PWV.[9,10] However, in older offspring (age 10 years) in the same cohort, there were no associations of maternal smoking exposure during pregnancy and offspring cIMT.[34] This could be due to the attenuation effect of maternal smoking during pregnancy by postnatal growth and exposure to other risk factors.

Strengths and Limitations

Our study has several strengths. We included extensive cardiovascular measures within the same individuals, characterizing both functional (ie, BP, PWV) and structural (ie, cIMT, retinal arteriolar/venular caliber) parameters, which have each been associated with subsequent cardiovascular disease in adults.[35–37] We investigated the same associations using data from the same equipment and protocols in offspring, thereby minimizing differences in analysis, measurement, batch, and confounding structures. We collected maternal smoking in detail, including mean daily exposure, and cigarettes smoked in each trimester, allowing us to ascertain if mothers continued or stopped smoking during pregnancy, as well as smoking intensity. Last but not least, we adjusted for potential confounding factors in the models, and these had limited influence on the associations of maternal smoking exposure and offspring BP. This demonstrates an independent effect of maternal smoking on BP that other factors may not explain.

We acknowledge several limitations. Cigarette smoking was self-reported postnatally and may have been subject to recall bias or social pressure to underreport. The majority of respondents were women; only 70% of fathers had smoking data. This limited our ability to examine the influence of paternal or parental smoking on child cardiovascular health as the sample sizes in sensitivity analysis were modest. Our cohort contains 90% White families (1346/1497), which

highlights smoking issues among White families. We did not collect mothers' medical histories at baseline, which may lead to residual bias. We recommend that future researchers extend our study by testing if effects replicate among other population groups or when adjusting for medical history. Due to attrition and the inherent recruitment bias of most cohorts, the CheckPoint sample had higher family SEP than the originally recruited LSAC sample and the Australian population. According to the 2021 Australian report, smoking during pregnancy is more common among those with low family SEP, and disadvantaged women are less likely to stop smoking during pregnancy.[2] Therefore, we used sample weighting to partly address this issue. There was no evidence of associations between other cardiovascular phenotypic assessments with maternal smoking, which may reflect in part the limited power. Further studies with larger sample sizes and a longer follow-up are warranted. Passive smoking is a well-recognized risk factor for the development of cardiovascular disease, especially in the offspring exposed to the parental smoking environment.[38]

Clinical Implications

Maternal smoking is a modifiable risk factor for a compromised intrauterine environment, and there is broad evidence of its deleterious effects on offspring health.[6] Although there were no data quantifying the economic impact of smoking exposure-induced cardiovascular consequences in offspring, it has been estimated in England that maternal smoking in pregnancy was associated with higher primary care, prescription and hospital in-patient episode rates; and the total health care cost of a smoking mother's child was £91.18 at age 1 and £221.80 at age 5 years.[39] A simulation result showed that a 5% reduction in smoking during pregnancy would correspond to a potential median cost savings of $150 533 from emergency department visits of mothers and infants in the United States.[40] Smoking cessation programs during pregnancy were conducted in different countries, and most were cost effective.[41] For example, there was strong clinical-trial evidence that counseling can significantly increase rates of smoking cessation if delivered at a sufficient intensity.[33] We found the adverse effects on child cardiovascular health were mitigated after stopping smoking during pregnancy, highlighting the potential impact of interventions specifically targeting smoking before and during pregnancy to reduce potential long-term adverse cardiovascular effects on offspring.

CONCLUSIONS

We report that offspring of mothers who smoked in any trimester during pregnancy had higher blood pressure and greater risk of hypertension in early adolescence than nonexposed offspring, with evidence of a dose–response effect. If mothers stopped smoking at any point during pregnancy, their offspring's cardiovascular measures were not different from those who never smoked. Population strategies should focus on maternal smoking prevention before pregnancy, in addition to continuing health promotion during and after pregnancy.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S11
Figure S1

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