



Mediators in the effect of maternal alcohol consumption and cigarette smoking on cardiometabolic risk factors in 10–14-year-old adolescents

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Abstract

Aim To identify potential mediators of the development of cardiometabolic risk factors in adolescents exposed to cigarette smoking and alcohol *in utero*.

Methods A total of 307 adolescents aged 10–14 years who were enrolled in urban schools in Cape Town, South Africa, were evaluated. Anthropometric measurements, lipid profiles and blood pressure measurements were obtained from 307 adolescents aged 10–14 years in a low-socioeconomic community. Statistical analysis included nonparametric tests, as most of the data were not normally distributed. Mediation analyses were conducted via linear regression and the PROCESS Macros models.

Results Maternal cigarette smoking during pregnancy had a significant direct effect on childhood SBP after adjusting for covariates. However, the indirect effect of BMI on SBP was significant, suggesting a 1-unit increase in BMI leading to a 1.38 mmHg increase in SBP. In addition, BW was not associated with adolescent SBP. Moreover, adolescent BMI mediated the effect of maternal cigarette smoking on overweight/obesity, rather than the direct effect of maternal cigarette smoking. Additionally, BW was significantly and positively associated with BMI but not with adolescent overweight/obesity in this cohort. Maternal smoking was also directly associated with low HDL cholesterol in boys only.

Conclusion BMI was identified as the main mediator in the effect of maternal smoking on adolescent SBP, overweight and obesity. Moreover, *in utero* exposure was not significantly associated with higher BMI or higher BP measurements, obesity or overweight. Cardiometabolic risk in terms of higher BMI/overweight and obesity was lower than those with no exposure.

Keywords Mediators · Maternal tobacco smoking · Alcohol consumption · BMI · Cholesterol · Cardiovascular risk · Blood pressure

Introduction

Adolescents from low socioeconomic backgrounds are at a heightened risk of developing cardiometabolic disorders as they age, with several key mediators influencing this risk (Psaltopoulou et al. 2017; De Smidt et al. 2021; Cajachagua-Torres et al. 2022; Dolley et al. 2022; Hartel et al. 2023; Liu et al. 2025). For example, lower socioeconomic status (SES) relates to poor health behaviour, more financial stress, lower

education levels and lack of healthcare, therefore leading to poorer health outcomes (Doom et al. 2017). In addition, women aged 25–29 years, with lower SES, food insufficiency, unplanned pregnancies, diagnosed with depression, anxiety or suicide ideation, who experience difficult life events or partner violence, particularly in South Africa, are at risk of smoking tobacco and using alcohol or other drugs during pregnancy (Harrison and Sidebottom 2009; Onah et al. 2016; Petersen-Williams et al. 2018; Brink et al. 2022). For example, 18% of women reportedly consumed alcohol or drug use during pregnancy (Onah et al. 2016). In a similar low-income setting in Cape Town, 36.6% of women smoked cigarettes and drank alcohol, 17.5% smoked cigarettes, and 16.7% drank alcohol during pregnancy (Brink et al. 2022). As a result, adolescents exposed to high levels of maternal smoking have lower BW, higher triglycerides,

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elevated systolic blood pressure (SBP) and an increased risk of cardiometabolic clustering such as android fat mass, SBP or diastolic blood pressure (DBP), triglycerides, HDL cholesterol and insulin ≥ 75 th percentile by the age of 10 (Horta et al. 2011; Odendaal et al. 2020; Cajachagua-Torres et al. 2022). Childhood adversity, poverty and SES during adolescence are also significantly associated with cardiovascular disease (CVD) risk in young adulthood (Doom et al. 2017). For example, persistent socioeconomic disadvantage correlates with poorer cardiometabolic profiles, including obesity, fatty liver, hypertension and a higher risk of heart disease, by age 50 (Doom et al. 2017; Vahtera et al. 2018).

Overall, from infancy through adolescence, multiple maternal, environmental and behavioural factors contribute to the increased risk of early development of cardiometabolic disorders in children and adolescents (Viikari et al. 2014; Onah et al. 2016; Stevens et al. 2018; Rauschert et al. 2019; Odendaal et al. 2020; De Smidt et al. 2021). In recent studies, maternal smoking and alcohol use during pregnancy are particularly prevalent among vulnerable women in low-income peri-urban settings (Onah et al. 2016; Odendaal et al. 2020). Therefore, we aim to identify potential mediators of the development of cardiometabolic risk factors in adolescents exposed to cigarette smoking and alcohol *in utero* in a low-income urban population. Secondly, to determine whether *in utero* exposure to these teratogens, cigarette smoking and alcohol, had a greater influence in developing cardiometabolic risk factors compared to conventional risk factors during adolescence.

Methodology

The study used a cross-sectional cohort design, which included mothers and their children aged 10–14 years in Bishop Lavis, South Africa, a low socioeconomic population. The study was conducted between January 2022 and August 2024 and investigated the impact of exposure to alcohol and cigarette smoking during pregnancy on cardiometabolic risk factors and identified potential mediation pathways. A two-stage stratified random cluster sampling method was used to randomly select 307 participants from four schools. Sample size was determined using a general power calculation for comparison groups with a desired power of 0.90. The methods used in this study to obtain anthropometric measurements, lipid profiles and blood pressure have been described in our previous publication (Hartel et al. 2025). Briefly, a research-generated questionnaire was used to retrospectively gather data from both mother and child, self-reported alcohol and tobacco use during pregnancy, birth weights (BW), exposure to second-hand smoke (SHS) and self-reported health conditions.

For statistical analysis, data was analysed using the Statistical Package for the Social Sciences (SPSS)® version 30. A detailed description of our statistical analysis can also be found in our previous publication (Hartel et al. 2025). Nonparametric tests were employed, as most of the data were not normally distributed (Shapiro–Wilk test). Statistical significance was inferred via Spearman's rank correlations, Kruskal–Wallis *H* tests, and Mann–Whitney *U* tests for inferential statistics, with a two-tailed *p* value < 0.05 and $p < 0.01$. The means and standard deviations were used in the nonparametric tests and were reported in tables to facilitate comparisons with existing studies.

To determine the primary mediator, we used linear regression and the PROCESS Macros SPSS add-on (Mackinnon et al. 2010). Firstly, to identify significant relationships between teratogen exposure and cardiometabolic outcomes, Spearman's rank correlations were used. Secondly, after controlling for confounders, PROCESS Macros was utilized to examine the direct and indirect effects of the independent factors on the dependent/outcome variables. In the mediation analysis for indirect pathways, cardiovascular measurements were analysed as continuous variables, as they increase the statistical power of the analysis by utilizing all available data points and provide more clarity on the direction of associations. Five thousand bootstrap samples with 95% CIs were chosen for bootstrapped confidence intervals (CIs). Owing to the low prevalence's found, overweight or obesity were grouped together in the mediation analysis for direct pathways, and elevated or high SBP and DBP. Potential covariates were selected on the basis of previous literature (Juonala et al. 2009; Lamotte et al. 2011; Kable et al. 2023; Jukic et al. 2024). For direct pathways, using binomial logistic regression models, when analysing elevated BP and hypertension, we adjusted for: *birthweight* (BW): pre-pregnancy weight, BMI, current smoking; *Low HDL cholesterol*: Waist circumference(WC), BMI, Physical activity(PA), refined carbohydrate intake; *High LDL cholesterol*: BMI, saturated fat intake, PA; *Elevated triglycerides*: BMI, WC, refined carbohydrate intake, PA; *Overweight/obesity*: BW, sex, maternal pre-pregnancy weight; *Abdominal obesity*: BW, BMI, age, sex, maternal pre-pregnancy weight.

Results

The study cohort included 307 mother–adolescent pairs divided into four groups according to maternal health behaviour during pregnancy: control group ($n = 105$): mothers who did not report any cigarette or alcohol use, nicotine-exposed group ($n = 115$): mothers who reported cigarette smoking only, dual-exposed group ($n = 73$): mothers who reported both cigarette smoking and alcohol use, and the alcohol-exposed group ($n = 14$): mothers who reported

Table 1 Characteristics of the study participants

	No exposure <i>N</i> = 105 (34.20%)	Nicotine exposed <i>N</i> = 115 (37.46%)	Dual exposed <i>N</i> = 73 (23.78%)	Alcohol exposed <i>N</i> = 14 (4.56%)	Kruskal–Wallis <i>H</i> test <i>P</i> value
Maternal characteristics	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Maternal age at birth, years ($\bar{x} \pm$ SD)	27.65 \pm 7.71	25.96 \pm 8.19	27.86 \pm 7.45	31.62 \pm 15.84	0.248
Maternal pre-pregnancy weight, kg ($\bar{x} \pm$ SD)	68.19 \pm 17.53	59.31 \pm 17.62*	52.18 \pm 22.76**	59.4 \pm 10.78	< 0.001**
Exclusive breastfeeding duration (months)	25.00 \pm 23.43	22.39 \pm 23.55	18.30 \pm 18.98	16.23 \pm 14.79	0.308
Birth characteristics					
Birthweight(g)	3266.92 \pm 876.35	3049.10 \pm 563.41	2724.77 \pm 979.02	3290.00 \pm 56.57	0.023*
LBW < 2500 g (%)	11 (10.5%)	15 (13.0%)	14 (19.2%)	2 (14.3%)	-
Gestational age (weeks)	38.37 \pm 2.62	38.60 \pm 2.54	38.15 \pm 3.03	38.75 \pm 4.29	-
Preterm < 36 weeks (%)	8 (7.6%)	9 (7.8%)	9 (12.3%)	1 (7.1%)	-
Adolescent characteristics					
Age (years) ($\bar{x} \pm$ SD)	11.5 \pm 1.23	11.59 \pm 1.46	11.77 \pm 1.1	11.71 \pm 1.77	-
Physically inactive, %	91(85.8%)	93(80.87%)	62(84.93%)	14(100%)	-
Self-reported smoking, %	5(5.4%)	8(8.2%)	8(11.9%)	5(38.5%)	-
Serum cotinine levels (μ g/l)	120.77 \pm 93.17	65.76 \pm 68.96	84.88 \pm 63.69	250 \pm 0.00 [#]	0.172
Self-reported alcohol consumption, %	1(4.3%)	1(1.0%)	2(3.0%)	0(0%)	-

* statistically significant differences < 0.05; ** statistically significant differences < 0.01. *LBW* Low birth weight. # Only one case, therefore no standard deviation reported

alcohol use only (Table 1). Compared with smoking mothers ($U = 59.31 \pm 17.62$ kg, $p < 0.05$) and non-smoking mothers ($U = 68.19 \pm 17.53$ kg), mothers who smoked cigarettes and consumed alcohol during pregnancy, the dual group, had significantly lower estimated pre-pregnancy weights ($U = 52.18 \pm 22.76$ kg, $p < 0.01$). Furthermore, newborns in the dual exposed group were, on average, 379.89 g smaller ($p < 0.05$) than nonexposed newborns were ($p < 0.01$), but this difference became insignificant after a Bonferroni correction ($p = 0.053$). Similarly, newborns in the nicotine-exposed group were, on average, 298.16 g smaller ($p < 0.05$) and were born 9.8 weeks earlier than nonexposed newborns ($p < 0.01$) but also lost significance after a Bonferroni correction ($p = 0.117$) (Table 1). In addition, self-reported smoking was most prevalent in adolescents exposed to both maternal cigarette smoking and alcohol (11.9%) and alcohol only (38.5%).

Furthermore, cardiometabolic risk factors were more prevalent in girls as 22% were classified as abdominally obese, 28.1% had dyslipidaemia, 13.1% were overweight, 9.2% were obese, 12.6% had elevated SBP, 9.3% had elevated DBP and 13.1% were hypertensive (stage 1 and stage 2) compared to their male counterparts. However, only 4.1% of girls had elevated non-fasting glucose. In boys, 15.3% had abdominal obesity, 8.8% were overweight, 8.8% were obese, 8.0% had elevated SBP, 6.4% had elevated DBP and 9.6% were hypertensive (Stage 1 and 2). only 3.4% had elevated non-fasting glucose, and 23.3% had dyslipidaemia.

Table 2 shows the cardiometabolic measurements of 10–14-year-old adolescents. The adolescents in the control group had the highest prevalence rates of overweight (18.3%) and obesity (13.3%). However, when comparing BMI, no significant differences were found across exposure groups. Moreover, no significant differences in body length were observed across the exposure groups. Regarding weight, female adolescents in the control ($U = 23.83 \pm 11.00$ mm) and dual-exposed groups ($U = 42.01 \pm 13.56$ cm) weighed significantly more compared to boys. Also, girls in the control ($U = 45.05 \pm 12.78$ cm) and dual-exposed groups ($U = 20.44 \pm 10.44$ mm) had significantly higher SSFT compared to boys. In addition, Table 2 presents the anthropometric measurements, such as the SSFT, WC, DBP, triglycerides, non-fasting blood glucose and LDL cholesterol, which were not significantly different between the control group and exposure groups. However, SBP was significantly greater in the nicotine-exposed group ($U = 117.92 \pm 14.29$ mmHg, $p < 0.01$) and the dual-exposed group ($U = 115.25 \pm 14.99$ mmHg, $p < 0.05$) than in the control group ($U = 110 \pm 11.98$ mmHg), as shown in Table 2. In addition, HDL cholesterol was significantly lower in the nicotine-exposed group than in the control group ($U = 1.67 \pm 0.79$ mmol/L, $p < 0.05$).

We also compared all cardiometabolic measures in girls and boys separately across the exposure groups (Table 2). Girls in the control group had significantly higher anthropometric, adiposity and blood pressure measures, compared to boys. No significant differences were observed in cholesterol

Table 2 Cardiometabolic measurements in 10–14-year-old adolescents according to sex and in utero exposure group

	No exposure		Nicotine exposed		Dual exposed		Alcohol exposed	
	Male vs female adolescents	<i>p</i> value	Male vs female adolescents	<i>p</i> value	Male vs female adolescents	<i>p</i> value	Male vs female adolescents	<i>p</i> value
	mean (SD)		mean (SD)		mean (SD)		mean (SD)	
	<i>N</i> = 41	<i>N</i> = 65	<i>N</i> = 52	<i>N</i> = 63	<i>N</i> = 29	<i>N</i> = 44	<i>N</i> = 3	<i>N</i> = 11
Weight	39.71 ± 11.26	45.05 ± 12.78	38.77 ± 10.31	38.44 ± 8.45	37.44 ± 11.09	42.01 ± 13.56	37.97 ± 6.60	39.08 ± 10.13
Height	146.60 ± 8.94	146.29 ± 20.45	145.71 ± 10.03	146.73 ± 9.21	144.99 ± 8.47	147.01 ± 8.71	145.02 ± 14.75	145.65 ± 11.97
BMI	18.24 ± 3.90	20.42 ± 4.70	18.09 ± 3.72	17.77 ± 3.389	17.57 ± 5.7	19.19 ± 4.91	18.03 ± 1.25	18.07 ± 2.11
WC	63.87 ± 9.47	65.43 ± 11.89	62.68 ± 8.24	61.28 ± 6.31	62.39 ± 10.87	64.00 ± 10.11	57.97 ± 5.62	61.35 ± 5.02
SSFT	18.56 ± 9.82	23.83 ± 11.00	18.51 ± 8.06	17.93 ± 6.74	16.03 ± 9.25	20.44 ± 10.44	15.00 ± 4.49	18.29 ± 6.78
SBP	106.90 ± 10.56	112.46 ± 13.05	117.921 ± 14.29	118.05 ± 12.85	117.36 ± 14.89	113.86 ± 15.06	113.33 ± 15.50	111.93 ± 11.61
DBP	65.82 ± 8.58	68.79 ± 8.52	71.16 ± 12.71	71.17 ± 11.24	68.49 ± 10.48	67.25 ± 8.38	62.33 ± 5.24	67.49 ± 8.59
MAP	79.51 ± 8.38	83.81 ± 9.00	86.75 ± 12.19	86.79 ± 10.79	84.78 ± 10.86	82.79 ± 9.66	79.33 ± 7.62	82.30 ± 9.23
HR	82.38 ± 13.05	90.43 ± 16.36	87.93 ± 13.93	89.79 ± 14.71	81.69 ± 11.79	88.52 ± 14.28	94.67 ± 17.62	84.76 ± 11.35
TC	6.49 ± 3.41	6.56 ± 3.53	4.91 ± 2.94	5.02 ± 3.01	6.48 ± 3.62	5.92 ± 3.48	7.77 ± 4.49	5.39 ± 3.31
LDL	2.00 ± 1.33	2.04 ± 1.23	1.96 ± 1.33	2.08 ± 1.49	2.24 ± 1.69	1.91 ± 1.00	1.83 ± 0.93	1.78 ± 0.64
HDL	2.08 ± 0.91	2.08 ± 0.98	1.67 ± 0.79	1.70 ± 0.82	2.15 ± 0.89	1.94 ± 0.92	2.58 ± 0.92	1.91 ± 0.83
Trig	1.67 ± 1.29	1.62 ± 1.4	1.22 ± 0.94	1.16 ± 0.88	1.49 ± 1.35	1.39 ± 0.75	1.59 ± 1.14	1.01 ± 0.57
NFBG	5.34 ± 0.59	5.26 ± 1.17	5.35 ± 0.85	5.30 ± 0.79	5.44 ± 0.81	5.30 ± 0.95	5.40 ± 0.85	5.00 ± 1.03

* statistically significant differences < 0.05; ** statistically significant differences < 0.01; *BMI* body mass index, *WC* waist circumference, *SSFT* sum of skinfold thickness, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *HR* heart rate, *TC* total cholesterol, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol, *Trig* triglycerides, *NFBG* non-fasting blood glucose

and non-fasting glucose levels across sex. Supplementary Table 1 shows the correlations between demographic characteristics, maternal behaviours and adolescent cardiometabolic measurements.

Table 3 presents the direct pathways in the mediation models, explaining the direct relationship between teratogen exposure during pregnancy and cardiometabolic risk factors in male and female adolescents. In the model, elevated or high SBP/DBP was combined as a variable to ensure a good fit for the model. Male adolescents exposed to maternal smoking were 6.09 times more likely to have low HDL cholesterol, after the adjustment for covariates (OR 6.090, 95% CI 1.447–25.622, $p=0.014$). The significant association between maternal smoking and overweight/obesity suggested a reduced odds of overweight or obesity in girls (OR 0.280, 95% CI 0.082–0.954, $p=0.042$) (Table 3).

In Fig. 1, the first model revealed that the direct effect of maternal cigarette smoking during pregnancy on childhood SBP was statistically significant ($b=7.8593$, $SE=2.4603$, $t=3.1944$, $p=0.0017$, CI [2.9972, 12.7215]), and remained significant after adjusting for the child's current smoking, second-hand smoke exposure, family history of CVD, age, birthweight, BMI, physical activity, breastfeeding duration and gestational hypertension and diabetes. In addition, the

effect of cigarette smoking during pregnancy on childhood BMI was significant ($b=-1.0790$, $SE=0.4821$, $t=-2.2382$, $p=0.0259$), but this effect became borderline insignificant after adjusting for the child's current smoking, second-hand smoke exposure, sex, birthweight, mother's education level and total minutes of moderate-high PA ($b=-1.3074$, $SE=0.7630$, $t=-1.7136$, $p=0.0631$). However, the indirect effect of BMI on SBP was significant, with a point estimate of $b=1.3892$ ($p=0.0001$) and a 95% bootstrap CI of [0.7903, 1.9693], suggesting that a 1-unit increase in BMI may lead to a 1.38 mmHg increase in SBP even after adjusting for the child's current smoking, second-hand smoke exposure, sex, birthweight, mother's education level, maternal smoking and alcohol use during pregnancy, and total minutes of moderate-high PA (Fig. 1). On the other hand, smoking during pregnancy had a significant direct effect on BW ($b=-335.564$, $SE=93,9464$, $t=-3.5719$, $p=0.0001$), suggesting a decrease of 335.56 g in BW resulting from maternal smoking. However, this difference was lost after adjustment for GA and maternal pre-pregnancy weight ($b=-335.564$, $SE=93.9464$, $t=-3.5719$, $p=0.0001$). In addition, BW was not associated with adolescent SBP ($b=-261.4357$, $SE=142.8085$, $t=-1.8307$, $p=0.696$) (Fig. 1).

Table 3 Unstandardized estimates for mediation models: Direct pathways

Maternal smoking (MS) and cardiometabolic risk factors	Male adolescents (N = 125)				Female adolescents (N = 182)			
	Included in analysis	P- value	OR	95%CI	Included in analysis	P- value	OR	95%CI
MS → Elevated or high SBP/DBP (> 90 percentile)	$n=42$	0.486	0.486	0.355–8.809	$n=78$	0.228	2.058	0.637–6.648
MS → Hypertension (> 95 percentile)	$n=42$	0.233	4.213	0.395–44.874	$n=78$	0.161	2.667	0.676–10.530
MS → Low HDL	$n=102$	0.014*	6.094	1.447–25.662	$n=132$	0.215	0.788	0.713–4.480
MS → High LDL	$n=106$	0.616	0.644	0.116–3.583	$n=157$	0.231	2.347	0.581–9.490
MS → High Triglycerides	$n=102$	0.195	0.232	0.025–2.119	$n=152$	0.545	0.591	0.108–3.246
MS → Overweight/Obesity	$n=45$	0.852	0.855	0.165–4.431	$n=80$	0.042*	0.280	0.082–0.954
MS → Abdominal obesity	$n=45$	-	-	-	$n=77$	0.141	0.174	0.017–1.787
Maternal smoking & alcohol (MSA) and cardiometabolic risk factors	Included in analysis	P- value	OR	95%CI	Included in analysis	P- value	OR	95%CI
MSA → Elevated or high SBP/DBP (> 90 percentile)	$n=43$	0.550	0.638	0.146–2.792	$n=77$	0.857	0.893	0.261–3.061
MSA → Hypertension (> 95 percentile)	$n=43$	0.879	1.145	0.200–6.543	$n=77$	0.653	1.380	0.340–5.605
MSA → Low HDL	$n=82$	-	-	-	$n=153$	0.534	0.724	0.261–2.003
MSA → High LDL	$n=106$	0.341	2.177	0.439–10.807	$n=106$	0.354	0.366	0.044–3.068
MSA → High Triglycerides	$n=102$	0.836	1.205	0.206–7.057	$n=152$	-	-	-
MSA → Overweight/Obesity	$n=45$	0.803	0.790	0.123–5.054	$n=80$	0.449	1.608	0.4700–5.493
MSA → Abdominal obesity	$n=45$	-	-	-	$n=77$	0.438	2.092	0.324–13.489

Binary logistic regression used for categorical variables. * Significance level $p<0.05$. —OR for cardiometabolic risk factor was estimated as 0 ($p=.998$), due to complete separation in the data, where no cases of the outcome were observed in a particular group. # No odds predicted, therefore no 95% CI reported. Adjusted for maternal pre-pregnancy weight, birthweight, saturated fat intake, physical inactivity, BMI, SSFT, WC, second-hand smoke exposure, and self-reported smoking, education level, occupation status, household income, where applicable

Fig. 1 Mediation analysis summary with unstandardized coefficients (b) Cigarette smoking during pregnancy \rightarrow BMI/birthweight \rightarrow average systolic blood pressure. X Independent variable, Y Dependent/Outcome variable, M Potential mediator. Solid lines indicate direct paths. Dashed lines indicate direct paths that involve a mediator

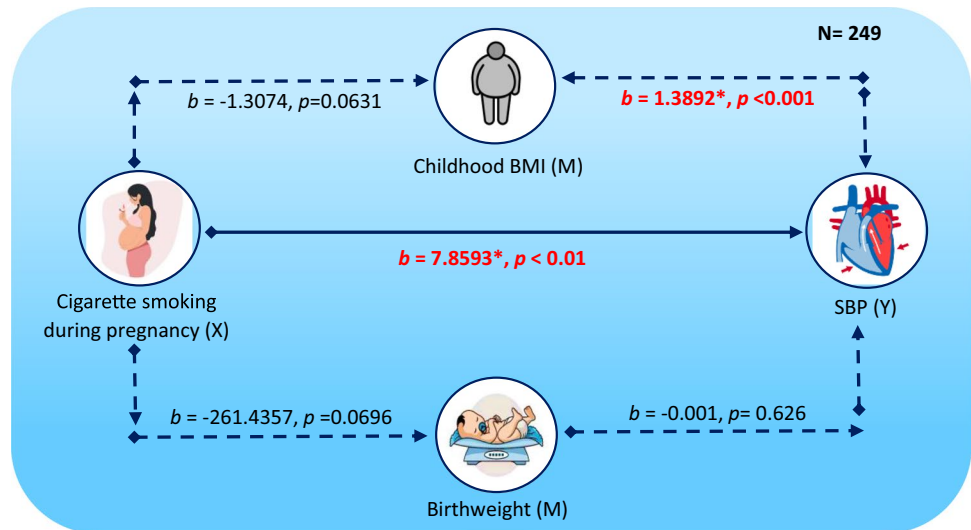
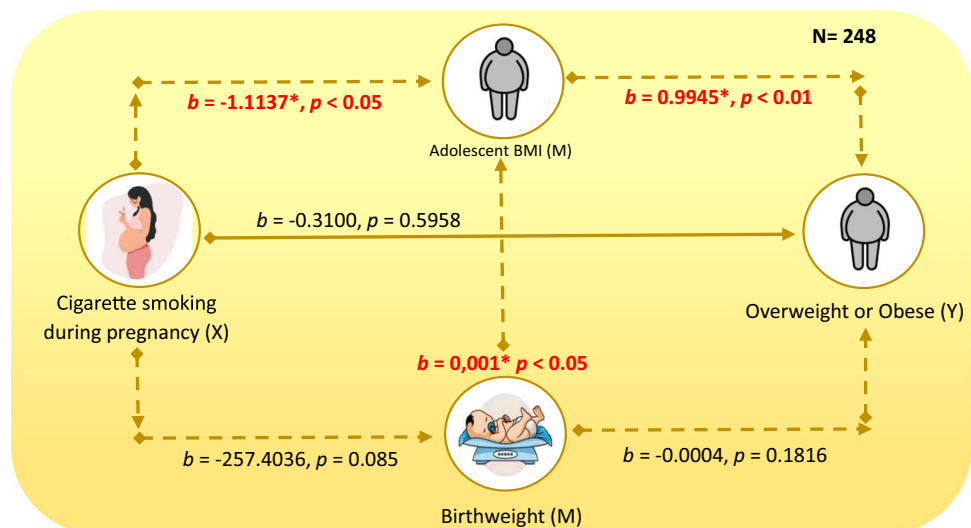


Fig. 2 Mediation analysis summary with unstandardized coefficients (b) Cigarette smoking during pregnancy \rightarrow BMI/birthweight \rightarrow overweight/obesity. X Independent variable, Y Dependent/Outcome variable, M Potential mediator. Solid lines indicate direct paths. Dashed lines indicate direct paths that involve a mediator

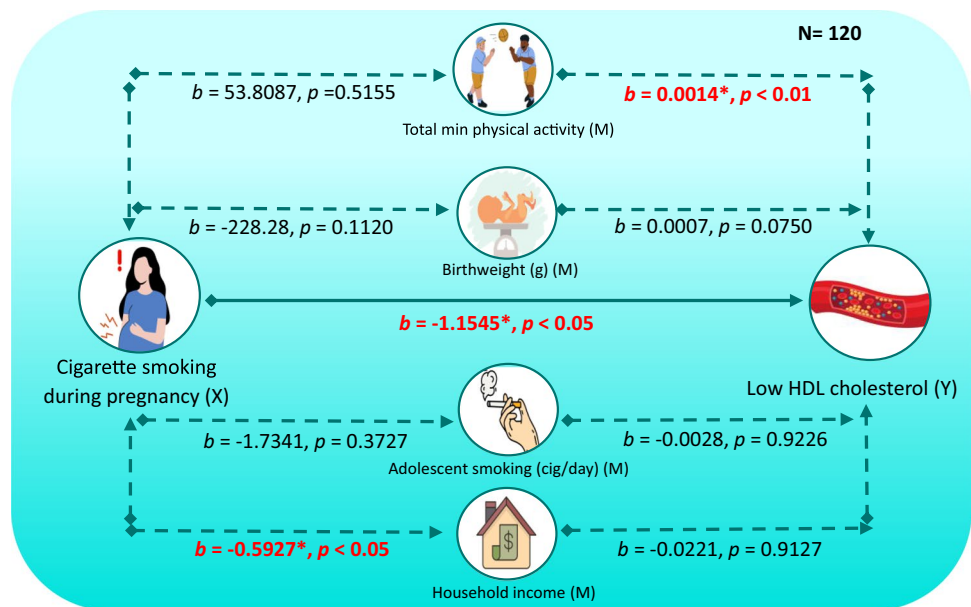


In the second model (Fig. 2), maternal cigarette smoking during pregnancy had no direct effect on adolescent overweight or obesity, but rather adolescent BMI mediated the effect of maternal cigarette smoking on overweight/obesity, therefore having an indirect effect with a point estimate of $b = -0.9955$ ($p < 0.01$) and a 95% bootstrapped CI of $[-183.8902, 11.8324]$ after adjustment for maternal pregestational weight and GA. Moreover, maternal cigarette smoking was not associated with BW after adjustment for maternal pregnancy weight and GA ($b = -257.4036$, $SE = 148.1558$, $t = -1.7374$, $p = 0.0850$). However, BW was significantly associated with BMI ($b = 0.001$, $SE = 0.000$, $t = 1.976$, $p = 0.049$) but not with adolescent overweight/obesity (Fig. 2).

In the third mediation model (Fig. 3), maternal cigarette smoking during pregnancy had a direct effect on adolescent HDL-cholesterol, with a point estimate of $b = -1.1545$

($SE = 0.5796$, $t = -1.9919$, $p < 0.05$) and a 95% bootstrapped CI of $[-2.2906, -0.0185]$ after adjustment for age, weight, height and SSFT. However, no effect was observed in the mediation model when examining boys and girls separately. Moreover, low HDL cholesterol was not associated with the following mediators: recalled birthweight ($b = 0.0007$, $SE = 0.0004$, $t = 1.7805$, $p = 0.0750$), adolescent cigarette smoking ($b = -0.0028$, $SE = 0.0292$, $t = -0.972$, $p = 0.9226$) and household income ($b = -0.0221$, $SE = 0.2013$, $t = -0.1097$, $p = 0.9127$), except for total minutes of physical activity/week ($b = -257.4036$, $SE = 148.1558$, $t = -1.7374$, $p = 0.0850$). Although, maternal smoking was significantly associated with household income, and total minutes of physical activity was associated with low HDL cholesterol (Fig. 3).

Fig. 3 Mediation analysis summary with unstandardized coefficients (b) Cigarette smoking during pregnancy \rightarrow Total min physical activity/birthweight/Adolescent smoking (cig/day)/Household income \rightarrow Low HDL (boys). X Independent variable, Y Dependent/Outcome variable, M Potential mediator. Solid lines indicate direct paths. Dashed lines indicate direct paths that involve a mediator



Discussion

Mediators of BMI and obesity

The study aimed to identify potential mediators in the development of cardiometabolic risk factors in adolescents exposed to cigarette smoking and alcohol *in utero*. We observed that exposure to maternal smoking was significantly associated with a lower BMI in adolescence, generally due to maternal smoking being significantly associated with LBW, resulting in a smaller BMI, as observed in this study. Although there is substantial evidence that maternal smoking is a significant predictor of childhood obesity (Ng and Zelikoff 2007; Suzuki et al. 2009; Behl et al. 2013; Rayfield et al. 2016), in our cohort, we observed that maternal cigarette smoking had no significant direct effect on adolescent overweight/obesity, but rather BMI mediated the effect of maternal smoking on overweight/obesity in adolescents. Interestingly, in the direct pathway analysis, female adolescents had a significantly lower likelihood (OR 0.280) of being overweight. This suggests that adolescents exposed to maternal smoking will likely be born with a lower BW and may have a lower childhood or adolescent BMI. On the other hand, in the dual exposed group, girls had significantly higher BMI and SSFT measures compared to boys, suggesting that girls have higher adiposity levels at this age. However, using BMI as an isolated measure has its limitations as it cannot differentiate between muscle mass and fat mass (Cota et al. 2021). Therefore, regardless of BMI, normal weight adolescents with higher body fat percentage present with insulin resistance, dyslipidemia, low-grade inflammation and oxidative stress which may lead to cardiovascular disease (CVD) (Cota et al. 2021). Previous studies have also

shown that adolescents who experience poverty between birth and 2 years old were 1.66 times more likely to become obese, with low income being associated with higher adult BMI (Lee et al. 2014). Therefore, it is worth noting that they may develop obesity if they have experienced catch-up growth or accelerated weight gain during adolescence due to puberty, remain physically inactive or consume high-caloric diets as they contribute to the accumulation of adipose tissue (Lee et al. 2014; Munthali et al. 2017; Modjadji and Madiba 2019; Cota et al. 2021; Vidal et al. 2023).

Therefore, adolescents from low socioeconomic communities exposed to teratogens *in utero*, born at a lower BW, who notably were not clinically obese, may only develop obesity later in life, as the prevalence of overweight/obesity was moderately prevalent in the adolescent stage. Particularly, girls at this age exposed to teratogens may not be at risk at this age as they had less skinfold thickness and smaller BMIs compared to girls with no exposure. However, development of overweight/obesity in the exposed girls needs close monitoring and possibly tracked into young adulthood as their risk increases as they experience puberty and aging (Power et al. 2003). Although obesity was not noticeable in young adolescence, obesity is highly prevalent in young adults in low socioeconomic populations, emphasizing the need to identify and actively monitor high risk individuals in low-income settings, even those with normal weight phenotype as they age, because normal weight adolescents tend to be less physically fit, relating to fat accumulation, diabetes and metabolic syndrome (Cota et al. 2021).

Furthermore, a systematic review suggests that accelerated growth may have a major influence on the development of cardiometabolic risk factors later in life, rather than low BW alone (Kelishadi et al. 2015). This may be the case in

lower socioeconomic communities such as Bishop Lavis as children are generally thinner or stunted compared to children with no exposure, a representation of the thin-fat phenotype (Modjadji and Madiba 2019). Despite this, the low prevalence of cardiometabolic risk factors in this cohort may be attributed to higher consumption of fruits and vegetables (provided at school feeding schemes), lower consumption of takeaways and sweets and no access to a vehicle, therefore having more time spent participating in PA; possibly having a protective effect against metabolic syndrome, compared to adolescents with no exposure (You and Choo 2016). Despite the persistent undernutrition in children in both rural and urban settings in South Africa, there remains an increase in obesity at a population level (Modjadji and Madiba 2019). Modjadji and Madiba (2019) suggest that the coexistence of childhood undernutrition and maternal obesity observed in the same communities and common in households with low-income and high unemployment rates may be attributed to consumption of energy-dense foods, leading to obesity in adults but not providing sufficient nutrient density to children, leading to stunting and undernutrition (Modjadji and Madiba 2019).

Mediators of blood pressure

Moreover, SBP, particularly in boys, was significantly greater in the nicotine-exposed group and the dual-exposed group, similar to previous studies (Ayer et al. 2011; Stevens et al. 2018; Mourino et al. 2023). Our mediation analysis also revealed a statistically significant and direct effect of maternal smoking on adolescent SBP, but not with DBP. These findings are consistent with a recent meta-analysis showing that maternal smoking increases SBP rather than DBP in children and adolescents (Mourino et al. 2023). Mourino and colleagues suggested that foetal growth restriction as a result of teratogen exposure may lead to altered elastin synthesis and, therefore, a gradual loss of elastin with age, which may result in reduced distensibility and increased SBP. Furthermore, BMI also affects adolescent SBP and suggests that a 1-unit increase in BMI may lead to a 1.38 mmHg increase in SBP even after adjusting for covariates. Another study reported an increased risk for prehypertension in adolescents, particularly those with an increased BMI (Arnold et al. 2019). Apart from screen time, a cross-sectional study also reported that 60.3% of the risk of developing metabolic syndrome was explained by adolescent BMI (Lee et al. 2016). Therefore, monitoring BMI during childhood and adolescence can help prevent the development of elevated BP; however, BP should also be monitored in children with teratogen exposure, as they can present with normal weight but have subclinical signs of cardiometabolic risk (Mourino et al. 2023).

Mediators of cholesterol

In this study, we demonstrated a significant and independent relationship between maternal smoking and low HDL-cholesterol in male adolescents. This significant association has been reported in previous paediatric studies at the age of 8 years old (Ayer et al. 2011) and 5–19 years old (Jaddoe et al. 2008) and 7–12 years old (Vidal et al. 2023), and this association remained significant when examining each trimester (Ayer et al. 2011). In the direct pathway analysis, we found that boys exposed to maternal smoking were 6.09 times more likely to have low HDL-cholesterol, after the adjustment for covariates, similar to previous studies (Ayer et al. 2011; Akison et al. 2019; Weeks et al. 2020). The current findings may be contextualized at a molecular level, as a previous study found methylation of three CpG sites of the aryl hydrocarbon receptor repressor (AHR) gene at birth to be a significant mediator of HDL cholesterol in 7–12-year-old children, indicating a mediating effect years later (Vidal et al. 2023). Therefore, further studies need to explore potential persistent epigenetic changes regarding disruption in genes responsible for HDL production. Although the effect of low HDL-cholesterol on atherosclerotic risk is uncertain in younger ages, adult studies suggests that changes in HDL-cholesterol as small as 0.026 mmol/L can reduce the risk of coronary heart disease by 2–3% (Ayer et al. 2011). Lastly, we also observed that cigarette smoking frequency was significantly correlated with duration of smoking and alcohol use during pregnancy, and smoking duration was significantly correlated with alcohol duration.

The strengths of this study include the use of a fairly large sample for a comparative study. The study design minimized the influence of external factors by using inclusion and exclusion criteria and adjusting for multiple confounding variables during the statistical analysis. It is also possible that these exposures in addition to conventional risk factors have not manifested long enough to develop cardiometabolic risk factors in this population, thus minimizing the odds of cardiometabolic risk. Limitations of this study included the possibility of recall bias: under- or overestimations with recall of maternal smoking and drinking habits. Lastly, using isolated BMI may have limitations as it does not measure muscle and fat mass.

Conclusion

In conclusion, increased BMI may be the main mediator in the development of elevated SBP in adolescents from low socioeconomic communities. This emphasizes that girls exposed to cigarette smoking and alcohol use *in utero*, whether born small or large, can prevent the development of cardiometabolic risk by managing their weight as they

age. Maternal smoking also increased the odds of low HDL-cholesterol in boys. Further research in the field should be carried out in low socioeconomic populations to further investigate the effects of teratogens on cardiometabolic risk factors in adolescents and monitor them as they age as these studies remain rare.

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Author contributions Conceptualization of the work, TH, JDS, AO; data collection, TH, JDS; data analysis and interpretation, TH; drafting the article, TH; editing and revision of the article, TH, JDS. All authors read and approved the manuscript prior to submission.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Biomedical Research Ethics Committee of the University of the Western Cape (Ethics Reference Number: BM21/9/16).

Consent to participate Informed consent was obtained from all participants involved in the study. Written consent was obtained from both woman and child before they participated in the study.

Consent for publication Consent was obtained from both woman and child to publish the data as anonymised.

Conflicts of interest The authors declare no conflict of interest.

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