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Associations between the prenatal environment and cardiovascular risk factors in adolescent girls: Internalizing and externalizing behavior symptoms as mediators

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Abstract

This longitudinal study examines links among adolescent internalizing and externalizing symptoms, the prenatal environment (e.g., nicotine exposure) and pre/perinatal maternal health, and cardiovascular risk factors. Girls (N=262) ages 11–17 reported internalizing and externalizing behaviors and mothers reported about the prenatal environment and maternal health during and 3 months post-pregnancy. Adolescent cardiovascular risk included adiposity, smoking, blood pressure, and salivary C-reactive protein. Internalizing symptoms mediated relations between prenatal exposures/maternal health and adiposity; externalizing symptoms mediated relations between prenatal exposures and adolescent smoking. Healthcare providers who attend to internalizing and externalizing symptoms in girls may ultimately influence cardiovascular health, especially among those with pre/perinatal risk factors.

Cardiovascular disease (CVD) is associated with risk factors beginning in childhood (Williams, 2002) and remains the leading cause of death in the United States (Heron et al., 2009) with one in three adults affected (National Center for Chronic Disease Prevention and Health Promotion, 2011). These rates are expected to rise over the next two decades, with over 40% of adults diagnosed with CVD by 2030, and total costs expected to surpass \$1 trillion annually (Heidenreich et al., 2011). Understanding pediatric factors that contribute to CVD is essential, given the staggering levels of CVD burden. The American Heart Association (AHA) highlighted six childhood risk factors for CVD: lack of physical activity, obesity, type II diabetes, high blood pressure, high cholesterol, and cigarette smoking (Williams, 2002). Recent data also supports the role of inflammation in CVD. Mildly elevated serum C-reactive protein (CRP) is associated with chronic inflammation and considered a unique risk factor for CVD through atherosclerosis (Bisoendial, Boekholdt, Vergeer, Stroes, & Kastelein, 2010; Black, Kushner, & Samols, 2004; Pearson et al., 2003).

This study focuses on four cardiovascular risk factors relevant to adolescence: blood pressure, adiposity, inflammation, and cigarette smoking.

Developmental origins theory (Adair, 2008; Barker, 2007; Gillman, Rifas-Shiman, Berkey, Field, & Colditz, 2003; Whitaker & Dietz, 1998) suggests that gestational health and fetal programming are the origins of adult cardiac and metabolic disease. Consistent with this theory, prenatal and perinatal health plays an important role in shaping later adolescent and adult health and behavior. The evidence supporting this notion is rapidly expanding (for review, see Wang, Walker, Hong, Bartell, & Wang, 2013). For example, a family history of hypertension has been linked to gestational hypertension, and may be a risk factor for hypertension in offspring (Hindmarsh, Bryan, Geary, & Cole, 2010). Prenatal nicotine exposure (Huang, Lee, & Lu, 2006; Power & Jeffries, 2002; Syme et al., 2009) and gestational diabetes (Gillman et al., 2003; Huang et al., 2006; Whitaker & Dietz, 1998) are both associated with increased risk of obesity in childhood and adolescence. A similar pattern among maternal smoking, gestational diabetes, and inflammation (as measured by CRP) has also been identified (Ayer et al., 2011; Patel et al., 2012). These findings further highlight the importance of prenatal care, where monitoring maternal weight gain and glucose, for example, may be important for the prevention of subsequent obesity in offspring (Whitaker & Dietz, 1998). Maternal pre/perinatal smoking have also been linked to adolescent smoking (Abreu-Villaça, Seidler, Tate, Cousins, & Slotkin, 2004; Cornelius, Leech, Goldschmidt, & Day, 2005; diFranza, Aligne, & Weitzman, 2004; Kandel & Urdu, 1999; Kandel, Wu, & Davies, 1994). Taken together, these studies indicate the importance of maternal health and the pre/perinatal environment for subsequent cardiovascular health.

Likewise, the prenatal environment (e.g., prenatal exposure to substances) and maternal health (e.g., gestational diabetes, mental health) have been associated with adolescent internalizing (i.e., anxious, depressive) and externalizing (i.e., disruptive) symptoms. Unlike clinical or psychiatric diagnoses (e.g., depression, Attention Deficit Hyperactivity Disorder), internalizing and externalizing symptoms (which often are seen as part of clinical diagnoses) occur on a continuum. Research has indicated that, compared to children who were not exposed, prenatal smoking is associated with a significant increase in subsequent adolescent internalizing and externalizing symptoms (Ashford, van Lier, Timmermans, Cuijpers, & Koot, 2008; D'Onofrio et al., 2007; Gatzke-Kopp & Beauchaine, 2007). Further, maternal weight gain during pregnancy has been linked to inattentive and hyperactive symptoms (A. Rodriguez et al., 2008) and internalizing (i.e., negative emotionality; Alina Rodriguez, 2010) in school-aged offspring. Postpartum depression has also been linked to emotional and behavior problems in childhood (Murray et al., 1999). Taken together, these studies indicate the importance of maternal health and the pre/perinatal environment for subsequent internalizing and externalizing symptoms and behavior problems in offspring.

A separate literature has established links between adolescent internalizing/externalizing symptoms and cardiovascular health (Dietz & Matthews, 2011; Hastings, Zahn-Waxler, & Usher, 2007; Monk et al., 2001; Suls & Bunde, 2005). In a literature review examining emotionality and cardiovascular disease, Suls & Bunde (2005) report fairly consistent findings to suggest that in previously healthy populations, increased depressive, anxiety, and hostility symptoms were associated with a greater risk of cardiovascular disease. In adults,

anxiety symptoms and comorbid anxiety and depressive symptoms were associated with an increased probability for elevated CRP (Liukkonen et al., 2011). Among youth with hypertension, internalizing symptoms were significantly higher compared to non-hypertensive peers (Lande et al., 2009). and anxiety symptoms increased the likelihood of elevated CRP in adults. Childhood obesity is also associated with internalizing and externalizing behavior symptoms (Anderson, He, Schoppe-Sullivan, & Must, 2010; Mustillo et al., 2003), and internalizing symptoms appear to influence cardiovascular risk differently than externalizing symptoms (Hastings et al., 2007). Taken together, these lines of research indicate an association between increases in internalizing and externalizing symptoms and factors that contribute to cardiovascular health.

Currently, it remains unclear how the prenatal environment and maternal health, internalizing and externalizing symptoms, and cardiovascular health might be inter-related. Associations have been established among all of these factors, but no studies have simultaneously taken each pathway into account when examining associations. As a result, The nature of these relations is unclear. Specifically, it is possible that the prenatal environment and maternal health are predictors of internalizing and externalizing symptoms as well as cardiovascular health, and as a result prenatal/perinatal programming accounts for associations between internalizing/externalizing and cardiovascular health. Alternatively, these constructs may represent a process, whereby pre/perinatal factors predict internalizing and externalizing symptoms, which in turn modify behaviors that contribute to cardiovascular health (i.e., mediation). We hypothesized that internalizing/externalizing symptoms during adolescence would mediate the relationship between the prenatal environment and maternal health and adolescent cardiovascular health risk factors. Based on that hypothesis, this study aims to identify whether in girls a) the prenatal environment and/or maternal health predicts risk factors for adolescent cardiovascular health; b) the prenatal environment/maternal health predicts internalizing/externalizing symptoms during adolescence; c) adolescent internalizing/externalizing symptoms predict risk factors for adolescent cardiovascular health; and d) when all paths are included in the model, adolescent internalizing/externalizing symptoms mediates the relations between the prenatal environment/maternal health and risk factors for adolescent cardiovascular health. Understanding these associations may guide health care providers toward identification of pathways to cardiovascular risk factors in adolescents and points for potential intervention and prevention efforts.

Method

Participants

This study uses secondary data analysis of 262 girls enrolled by age cohort (11, 13, 15, and 17 years) in a cohort- sequential design (Shadish, Cook, & Campbell, 2002). A cohort-sequential design utilizes a set of longitudinal studies (in this case, 4 studies) with each longitudinal study representing a different cohort. Data can then be analyzed either by time of measurement or by age. Recruitment was from the Teen Health Center at Cincinnati Children's Hospital Medical Center (CCHMC) and the surrounding community. CCHMC is located in the United States. The study was funded to examine the effects of depressive

symptoms and smoking on reproductive and bone health [Blinded Citations]. Girls attended on-site visits for three time-points, one year apart (T1-T3). The first visit occurred between December 2003 and October 2007. Exclusion criteria were: 1) pregnancy or breast feeding within 6 months, 2) primary amenorrhea (menarche > 16 years), 3) secondary amenorrhea (< 6 cycles/year; not due to hormonal contraception), 4) body mass index < 1st percentile or weight > 300 pounds (limit for Dual-energy X-ray absorptiometry [DXA] scanner table), 5) medication usage or medical disorder influencing bone health, and 6) psychological disorders impairing comprehension or compliance (e.g., schizophrenia). Approximately 90% of girls were present for at least two time-points. See Table 1 for sample sizes per year.

Procedures

The Institutional Review Board at CCHMC approved the study. Informed consent was obtained from parents; adolescents provided assent. The Clinical Translational Research Center was used for annual visits, where questionnaires and physical examinations were completed.

Measures

Prenatal environment—At T1 (i.e., participant ages 11–17), mothers of girls were asked via questionnaire about the prenatal environment for the target child, and maternal health during and 3 months following pregnancy. Assessment of the prenatal environment included: prenatal care measured as the month in which mothers had their first prenatal visit, and whether mothers ever smoked, drank alcohol, or used illegal drugs during pregnancy. These items were used to create a latent prenatal environment factor that was used as a predictor in subsequent models.

Maternal health—Maternal health included whether mothers reported having high blood pressure, diabetes, or infections during pregnancy, and depression within the first three months postpartum. These items were used to create a latent maternal health factor that was used as a predictor in subsequent models.

Internalizing and externalizing symptoms—At T2 (i.e., participant ages 12–18) internalizing and externalizing symptoms were assessed using adolescent report and items from the validated internalizing and externalizing scales of the Youth Self Report (YSR) (Achenbach, 1991). Response options ranged from 0 (*not true*) to 2 (*very true or often true*). Confirmatory factor analyses (CFA, described below) were conducted for all items in each scale to ensure appropriate latent measurement models were used (see Results for CFA findings).

Adolescent CVD risk factors—At T3 (i.e., participant ages 13–19), the outcomes (CVD risk factors) for this study were adiposity, smoking, blood pressure, and inflammation. Adiposity includes three items. Body mass index (BMI) is a continuous index of body shape and was calculated (weight in kg/height in m²) from the mean of three measures of height using a wall-mounted stadiometer (Holtain Ltd., Crosswell, United Kingdom) and weight using a digital scale (Scaletronix, Carol Stream, IL). Standardized BMI (BMI-Z) is a z-score of a girl's BMI in comparison to normed reference data from the Center for Disease Control

and indicates whether the BMI of a particular girl is similar to the BMI of her same-aged peers (values close to 0) or much higher (positive values) or lower (negative values) than that of her peers (Kuczmarski et al., 2000; Kuczmarski et al., 2002). Finally, percent total body fat was measured by DXA (Hologic QDR4500 bone densitometer, Hologic, Inc., Bedford, MA). DXA scans were analyzed using software release 12.6. Two items were used to assess self-reported adolescent smoking from a smoking questionnaire: ever smoking (i.e., Have you ever smoked a cigarette, even a puff?) and age at which the youth reported smoking initiation. Manual blood pressure with a mercury sphygmomanometer (systolic, diastolic) was assessed twice during annual visits by trained research nurses; the mean of the two measures was used in analyses. Salivary CRP was assessed as a marker of inflammation. Recent studies indicate modest to strong associations between salivary and serum CRP (Ouellet-Morin, Danese, Williams, & Arseneault, 2011; Out, Hall, Granger, Page, & Woods, 2012; Punyadeera, Dimeski, Kostner, Beyerlein, & Cooper-White, 2011). Salivary CRP also appears to discriminate between risk categories for developing CVD as proposed by the AHA (Out et al., 2012), and between patients with acute myocardial infarction and controls (Floriano et al., 2009). Saliva samples were collected using Salivettes® and assayed for CRP using a commercially available immunoassay (Salimetrics, State College, PA) following the manufacturer's recommended protocol. The test volume was 15 µL, with a range of standards from 93.75 to 3000 pg/mL. The assay has a lower limit of sensitivity of 10 pg/mL. Samples were assayed in duplicate and averaged for statistical analyses. Intra- and inter-assay coefficients of variation were less than 10% and 15%, respectively. Covariates (T1) include chronological age, race, and the Hollingshead for socioeconomic status (Hollingshead, 1975).

Statistical Analyses

Structural equation modeling (SEM; Kline, 2005) with full-information maximum likelihood (FIML) estimation was used to estimate latent variables (i.e., using multiple items as indicators of an underlying construct) for the prenatal environment, maternal health, internalizing symptoms, externalizing symptoms, and adiposity. FIML (Kenward & Roger, 1997) was used to arrive at valid parameter estimates under the assumption of ignorable missing data (Hofer & Hoffman, 2007). These methods accommodate missing data and use all available data in the analysis. Mplus 6.1 (Muthen & Muthen, 1998–2012) was used to conduct CFAs (Brown, 2006) to ensure appropriate measurement and modeling of each latent variable. For all models, fit was evaluated using χ^2 significance (non-significance indicating good fit) and when available, comparative fit indices (CFI) .95, root mean square error of approximation (RMSEA) < .06, and standardized root mean residual (SRMR) < .08 to indicate good fit (Hu & Bentler, 1998). In models that included categorical variables (e.g., smoking during pregnancy) only χ^2 fit statistics are available. CRP was non-normally distributed, so log10 transformations of CRP was used. Covariates were included in all analyses and 2-tailed tests of statistical significance ($p < .05$) were used. To examine mediation, structural models tested the following: a) the direct path from the prenatal environment/maternal health to each individual risk factor for cardiovascular health; b) the direct path from the prenatal environment/maternal health to internalizing/externalizing; c) the direct path from internalizing/externalizing to each risk factor for cardiovascular health; and d) the indirect path from the prenatal environment/maternal health to risk factors for

cardiovascular health with a direct path from internalizing/externalizing to risk factors for cardiovascular health (i.e., mediation). To increase our confidence in the findings, we also tested an alternative hypothesis – that adolescent cardiovascular health at T2 mediated relations between the prenatal environment/maternal health and internalizing/externalizing behavior problems at T3. The longitudinal design of this study allows us to test direction in mediating pathways that meet the assumptions of temporal precedence (Shadish et al., 2002). Mediation effects were tested consistent with Baron and Kenny (Baron & Kenny, 1986). Standardized regression coefficients (β) from each model were used to examine the strength of each relationship. These coefficients are adjusted for other paths in the model, and higher absolute values indicate stronger relationships.

Results

Girls were between 11 and 17 years at T1 (Mean age = 14.4 Y, SD = 2.2), and were primarily White (62%) or Black (32%). For the purpose of analysis, those reporting another racial/ethnic group or mixed race were combined with those reporting Black to create a dichotomous White/non-White variable. Means and frequencies of study variables are provided in Table 1.

CFA models

Measurement models for all latent variables were estimated using CFA. The final measurement models are depicted in Figure 1. The model for the prenatal environment had good fit, and consisted of four maternal-reported items: prenatal care and cigarette, alcohol, and illegal drug use during pregnancy (all reported at T1). Maternal health also had good fit, and consisted of four maternal-reported items: gestational diabetes, high blood pressure during pregnancy, infection during pregnancy, and depression within three months of birth (all reported at T1). Internalizing symptoms was estimated using all items from the internalizing subscale of the YSR at T2; only 14 items were significant, and non-significant items were removed from the final model (see Table 2). Similarly, externalizing symptoms was estimated using all items from the externalizing subscale, but only 12 items significantly loaded and remained in the final model (see Table 2). Finally, adiposity was indicated by three items: BMI, BMI-Z, and percent total body fat (all at T3).

The prenatal environment, maternal health, and cardiovascular risk

Regression models were used to estimate the effects of the prenatal environment and maternal health on four risk factors for cardiovascular health outcomes: adiposity, smoking, blood pressure, and salivary CRP (Table 3). The prenatal environment and maternal health were related ($\beta = .24, p = .03$). The prenatal environment significantly predicted smoking, such that exposure to substances and later prenatal care was associated with higher levels of adolescent smoking ($\beta = -0.28$) and an earlier age of initiating smoking ($\beta = -0.20$). Better maternal health was associated with lower adolescent adiposity ($\beta = -0.29$). Neither the prenatal environment or maternal health predicted adolescent systolic or diastolic blood pressure; nor was either predictor related to salivary CRP.

The prenatal environment, maternal health, and internalizing and externalizing symptoms

The effects of the prenatal environment and maternal health on adolescent internalizing and externalizing symptoms were also estimated (Table 3). The prenatal environment significantly predicted internalizing ($\beta = -0.29$) and externalizing ($\beta = -0.27$) symptoms such that better environments were associated with fewer internalizing and externalizing symptoms; maternal health only predicted internalizing symptoms ($\beta = -0.20$), where improved maternal health was associated with fewer internalizing symptoms.

Internalizing and externalizing symptoms and cardiovascular risk

Analyses were conducted estimating the effects of adolescent internalizing and externalizing symptoms on risk factors for cardiovascular health outcomes (Table 4). Higher internalizing symptoms predicted higher adolescent adiposity ($\beta = 0.34$); higher externalizing symptoms predicted smoking ($\beta = -0.11$ – -0.26). Neither internalizing or externalizing symptoms predicted systolic or diastolic blood pressure; nor were internalizing or externalizing related to CRP.

Mediation Models

To examine whether internalizing and externalizing symptoms mediated the pathway from the prenatal environment and maternal health to adolescent adiposity and smoking, two models were estimated: one predicting adiposity, and one predicting smoking. Based on non-significant findings from preliminary models, mediation with blood pressure and CRP were not tested. Further, based on preliminary models, the mediation model tested for smoking included the prenatal environment and externalizing symptoms (Figure 2); the model tested for adiposity included maternal health and internalizing symptoms (Figure 3).

Results suggest confirmation of the hypothesized models for both smoking and adiposity: externalizing symptoms fully mediated the effects of the prenatal environment on adolescent smoking; internalizing symptoms fully mediated the effects of maternal health on adolescent adiposity. Further, there was evidence of significant indirect effects of the prenatal environment on smoking through externalizing symptoms and of maternal health on adolescent adiposity through internalizing symptoms.

To examine an alternate hypothesis, that risk factors for cardiovascular outcomes might be predicting internalizing and externalizing, we tested a model using cardiovascular health at T2 and internalizing and externalizing symptoms at T3. Specifically, one model was estimated using the prenatal environment (T1) to predict externalizing (T3) with smoking as a mediator (T2). A second model used maternal health and the prenatal environment (both T1) to predict internalizing (T3) mediated by adiposity (T2). The results of these models indicated that the prenatal environment predicted adolescent lifetime smoking ($\beta = .10$, $p < .05$) but not age at smoking ($\beta = .05$, $p > .10$), with no significant prediction to externalizing ($ps > .10$). In the second model, only maternal health predicted adiposity ($\beta = -0.30$, $p < .01$) with no significant prediction of internalizing ($ps > .10$). Thus, our initial hypothesis, that the prenatal environment and maternal health operate through internalizing and externalizing to predict risk factors for cardiovascular outcomes, received statistical support, and the alternate hypothesis did not.

Discussion

To our knowledge this is the first study to longitudinally test direct and indirect effects of the prenatal environment, maternal health, and adolescent internalizing and externalizing symptoms on CVD risk factors in adolescent girls. Findings indicate two different pathways to smoking and adiposity – the prenatal environment appears to operate through externalizing symptoms to predict smoking, while the prenatal environment and maternal health operate through internalizing symptoms to predict adiposity in adolescent girls. Interestingly, these processes did not impact blood pressure or salivary CRP in adolescence. These findings are consistent with previous literature on prenatal exposure and internalizing/externalizing symptoms as they impact adolescent smoking (Crone & Reijneveld, 2007; D'Onofrio et al., 2007; diFranza et al., 2004; Gatzke-Kopp & Beauchaine, 2007; Helstrom, Bryan, Hutchinson, Riggs, & Blechman, 2004; Kandel & Urdy, 1999; Kandel et al., 1994) and obesity rates (Adair, 2008; Huang et al., 2006; Pirkola et al., 2010; Power & Jeffries, 2002; Syme et al., 2009; Whitaker & Dietz, 1998), but findings further illuminate a pathway to smoking and increased adiposity that may be amenable to intervention.

It is likely that the processes by which the prenatal environment and maternal health impact smoking and adiposity (i.e., through internalizing and externalizing symptoms) reflects a more complex pathway with additional constructs that could not be included in this secondary analyses. For example, self-regulation has been associated with all the constructs in this model (Chasnoff et al., 1998; Doan, Fuller-Rowell, & Evans, 2012; Novak & Clayton, 2001; Olson et al., 1997; Riggs, Kobayakawa Sakuma, & Pentz, 2007; Wiebe et al., 2009) – it is plausible that the prenatal environment and maternal health impacts adolescent girls' self-regulation, resulting in adolescents that are poorly regulated and display more internalizing and externalizing symptoms as well as engaging in smoking and behaviors that increase adiposity. Research that examines the role of adolescent self-regulation in moderating relations between maternal prenatal health and internalizing and externalizing symptoms may help to elucidate those effects and provide further insight into the processes underlying these findings.

The findings that both the prenatal environment and maternal health were unrelated to blood pressure and CRP were unexpected, but limitations of these measures may be contributing to the lack of significant findings. Blood pressure was not assessed under a stress paradigm, and the majority of youth had blood pressures that were within age norms. Salivary CRP also has limitations. Salivary CRP levels have a systemic origin (Megson, Fitzsimmons, Dharmapatni, & Bartold, 2010; Pradeep, Manjunath, & Kathariya, 2010), but local inflammatory processes and poor oral hygiene may also be important contributors to higher salivary CRP scores, but would not be indicative of cardiovascular risk (Noack et al., 2001; Ouellet-Morin et al., 2011). Thus, the use of salivary CRP to measure *systemic* inflammation and risk for CVD may be limited for individuals with poor oral health. Future studies on salivary CRP should incorporate objective measures of oral health. Further, the use of salivary CRP in children and adolescents is relatively novel and not yet standardized. It may also be the case that the processes tested in this study reflect more static rather than dynamic processes – that is, processes that are relatively stable and unfold over longer periods of time than are reflected by blood pressure or CRP during adolescence.

It is also worth noting that the indicators in the parent study of cardiovascular risk, while consistent with the current literature, were not exhaustive. The recent emphasis on cardiovascular health in the literature, especially during adolescence, has resulted in a broadly-defined and operationalized list of contributing risk factors. For example, weight is known to relate to health outcomes on a continuum, but the emphasis is often placed on categories of overweight or obese; whether a continuous or categorical indicator better represents cardiovascular risk is not clear (Williams, 2002). Similarly, smoking is of clear import for cardiovascular health, but how much primary and/or secondary smoke exposure is needed to increase risk, or whether past versus present smoke exposure is a better indicator of risk is not known (Williams, 2002). Future research should examine this more closely.

Strengths of this study include the use of longitudinal data with constructs assessed at multiple timepoints, and the use of SEM to evaluate complex constructs with multiple indicators while accounting for missing data. Further, this is the first study to examine a multistep process from the prenatal environment and maternal health to cardiovascular risk factors in adolescence using internalizing and externalizing symptoms as mediators. Limitations of the study include the use of secondary data; given that this was not the primary goal of the parent study, additional measures for some constructs may have optimized the analyses. The prenatal environment and maternal health indicators generally focused on constructs relevant to the parent study and thus a comprehensive prenatal history was not determined. Further, prenatal exposure and maternal health were assessed retrospectively (from 10–17 years later) and through maternal report. This is not uncommon in studies of adolescence; for example, the National Longitudinal Study of Adolescent Health (Harris, 2009) and National Longitudinal Surveys of Youth (Bureau of Labor Statistics, 2005) have used similar techniques, and multiple papers have been published with those studies. However, retrospective reports can be inaccurate or biased, and accuracy of maternal reporting could not be validated in this study. Other potentially relevant constructs, including self-regulation and weight for gestational age, were not available. Further, there was a large range in salivary CRP, and salivary CRP is a relatively new approach to measuring inflammation. Finally, the sample only included adolescent girls, so whether or how these processes operate among adolescent boys is not known.

Implications for Practice

The findings from this study speak to the value of considering the impact of psychological factors with physical factors when interacting with adolescent girls in primary care practices or psychological services. Specifically relevant would be identifying potential internalizing and externalizing symptoms in adolescents and monitoring or intervening in order to prevent subsequent development of risk factors for cardiovascular disease later in life. Such interventions may be of particular importance for adolescent girls who have had known exposure prenatally to substances, below optimum prenatal care, or heightened maternal health complications. It appears that these youth would benefit the most from early intervention that addresses internalizing and externalizing behavior symptoms. Notably, the participants in this study represented a normal continuum of internalizing and externalizing symptoms (rather than diagnostic categories) and significant effects still emerged. This

suggests that clinicians should be vigilant of these issues for all adolescent girls, and not just for those meeting clinical criteria for mental health disorders. Healthcare providers who attend to internalizing and externalizing symptoms may ultimately influence cardiovascular health, especially among those with pre/perinatal risk factors.

In conclusion, findings from this study indicate a multi-step process linking the prenatal environment and maternal health to some of the adolescent risk factors for cardiovascular disease, which operate through either internalizing or externalizing symptoms. These findings suggest a window of susceptibility for adult disease, and speak to the importance of maintaining maternal health during and after pregnancy, and in protecting individuals from the prenatal environment to toxins and disease. However, when the window for primary prevention has passed, these findings suggest that treatment addressing adolescent internalizing and externalizing symptoms may be an effective way to influence smoking and adiposity. For youth with known prenatal exposures to substances or whose mothers were less healthy during pregnancy, close monitoring of internalizing and externalizing symptoms during development may be warranted in preventing these costly and burdensome outcomes.

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Figure 1.

Confirmatory Factor Analyses for five latent variables included in subsequent mediation models. Items for the prenatal environment (figure 1a) and maternal health (figure 1b) come from maternal report at Time 1 (T1). Items for internalizing (figure 1c) and externalizing (figure 1d) behaviors come from adolescent report at Time 2 (T2). Items for adiposity (figure 1e) come from clinician measures to calculate BMI and BMI z-score, and from DXA scans for percent body fat at Time 3 (T3). 262 adolescent girls were included in the study. All models met criteria for good fit (i.e., non-significant χ^2 test or CFI > .94, RMSEA < .06, SRMR < .08). * $p < .05$; ** $p < .01$. Abbreviations include Body Mass Index (BMI).

Figure 2.

Externalizing behaviors at Time 2 (T2) mediated the prenatal environment at Time 1 (T1) in predicting age started smoking and amount of smoking, both at time 3 (T3). Standardized beta coefficients provided in figures. Positive coefficients indicate a positive relationship between two variables, negative coefficients indicate negative relationships. Larger absolute values of beta coefficients indicate stronger effects. * $p < .05$; ** $p < .01$. Model Fit: $\chi^2 (63) = 64.64$, $P = .42$. Circles=latent, squares=observed constructs. The prenatal environment is based on maternal report and externalizing and smoking variables are based on adolescent report from 262 girls.

Figure 3.

Internalizing behaviors at Time 2 (T2) mediated the prenatal environment at Time 1 (T1) and maternal health at Time 1 (T1) in predicting adiposity at Time 3 (T3). Standardized beta coefficients provided in figures. Positive coefficients indicate a positive relationship between two variables, negative coefficients indicate negative relationships. Larger absolute values of beta coefficients indicate stronger effects. * $p < .05$; ** $p < .01$. Model Fit: $\chi^2 (63) = 46.94, p = .94$. Circles=latent, squares=observed constructs. The prenatal environment and maternal health are based on maternal report and internalizing variables based on adolescent report from 262 girls. Adiposity based on clinician measures of the 262 adolescent girls.

Table 1

Sample Characteristics and Study Variables of 262 Adolescent Girls

	Mean (SD)	Frequency (%)
<u>Time 1 Variables (n = 262)</u>		
Age (years)	14.35 (2.17)	
Race		162 (62) White 84 (32) Black 16 (6) Other
SES	37.32 (13.67)	
Prenatal environment		
Month started prenatal visits	1.92 (1.35)	
Smoking during pregnancy		61 (24) Yes
Alcohol during pregnancy		31 (12) Yes
Illegal drug use during pregnancy		12 (5) Yes
Maternal health		
High Blood Pressure during pregnancy		27 (11) Yes
Gestational Diabetes		15 (6) Yes
Infection during pregnancy		17 (7) Yes
Maternal Depression		13 (5) Yes
<u>Time 2 Variables (n = 214)</u>		
Internalizing symptoms (t-score)	46.55 (9.24)	
Externalizing symptoms (t-score)	53.30 (8.03)	
Amount Smoked (categories below)	5.29 (2.59)	
Age Tried Smoking (categories below)	3.58 (1.19)	
BMI	24.54 (6.71)	
zBMI	0.70 (1.03)	
% body fat	28.76 (7.74)	
Systolic Blood Pressure (mm/Hg)	101.71 (11.45)	
Diastolic Blood Pressure (mm/Hg)	63.70 (9.43)	
<u>Time 3 Variables (n = 208)</u>		
Internalizing symptoms (t-score)	46.55 (9.26)	
Externalizing symptoms (t-score)	53.30 (8.03)	
Amount Smoked (categories below)	5.59 (2.67)	
Age Tried Smoking (categories below)	1.63 (2.43)	
BMI	25.02 (6.05)	
zBMI	.74 (.93)	
% body fat	29.37 (7.48)	
Systolic Blood Pressure (mm/Hg)	102.02 (8.61)	
Diastolic Blood Pressure (mm/Hg)	62.91 (7.38)	
C-Reactive Protein (pg/mL)	4305.80 (12669.23)	

NOTE: Abbreviations include: Socioeconomic status (SES) based on Hollingshead codes, which range from 0 to 66 and larger number is higher SES; Body Mass Index (BMI); Standardized Body Mass Index (zBMI). Race recoded in all analyses as 0 (White) or 1 (non-White). Month started prenatal visits coded as 0 (first month) to 8 (ninth month) or 9 (no prenatal care). Dichotomous T1 indicators (e.g., smoking during pregnancy)

coded as 1 (yes) or 0 (no). Amount smoked in lifetime coded 0 (never, not even a puff), 1 (1 or more puffs, but never a whole cigarette), 2 (1 cigarette), 3 (2–5 cigarettes), 4 (6–15 cigarettes), 5 (16–25 cigarettes), 6 (26–99 cigarettes), 7 (100 or more cigarettes), 8 (500 or more cigarettes). Age tried smoking coded 0 (8 years or younger), 1 (9–10 years), 2 (11–12 years), 3 (13–14 years), 4 (15–16 years), 5 (17–18 years), 6 (19–20 years), 7 (21 or older). C-Reactive protein was transformed for subsequent analyses (CRP median = 1510.13).

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Table 2

Item loadings for Internalizing and Externalizing Latent Variables

Internalizing			
Item	B	SE	P
1	1.00	0.00	-
2	1.77	0.32	0.00
3	2.26	0.37	0.00
4	1.50	0.26	0.00
5	1.39	0.24	0.00
6	1.50	0.30	0.00
7	1.16	0.29	0.00
8	0.25	0.09	0.01
9	0.80	0.16	0.00
10	0.82	0.23	0.00
11	0.91	0.18	0.00
12	1.09	0.23	0.00
13	0.91	0.24	0.00
14	1.88	0.33	0.00
χ^2 (DF)	129.54 (76)		0.01
CFI	.95		
RMSEA	.06		
SRMR	.04		
Externalizing			
Item	B	SE	P
1	1.00	0.00	-
2	1.07	0.13	0.00
3	1.29	0.15	0.00
4	0.65	0.11	0.00
5	1.04	0.16	0.00
6	0.83	0.12	0.00
7	0.47	0.18	0.01
8	0.89	0.14	0.00
9	0.15	0.04	0.00
10	0.51	0.16	0.00
11	1.13	0.19	0.00
12	0.57	0.10	0.00
χ^2 (DF)	70.32 (54)		0.07
CFI	.97		
RMSEA	.04		
SRMR	.04		

Table 3

Standardized Predictor Loadings for Regression Models Predicting Internalizing, Externalizing, and Cardiovascular Health Outcomes from the Prenatal Environment and Maternal Health, controlling for key covariates.

	Internalizing	Externalizing	Adiposity	Smoke Age	Smoke Amount	Systolic BP	Diastolic BP	CRP
Age	0.15*	0.05	0.37**	0.64**	0.65**	0.21**	0.07	-0.04
SES	0.08	-0.01	-0.21*	-0.08	-0.12*	-0.16*	-0.20**	0.09
Race	-0.06	0.06	0.12**	0.01	-0.08	0.07	0.20**	0.04
Prenatal Environment	-0.29*	-0.27*	-0.03	-0.20*	-0.28**	0.03	0.06	-0.03
Maternal Health	-0.20**	-0.10	-0.29**	0.03	0.01	-0.08	-0.09	-0.10
X ² (DF)	47.21 (63)	46.94 (63)	45.22 (63)	49.27 (63)	49.27 (63)	45.22 (63)	45.22 (63)	44.94 (63)

NOTE: Abbreviations include: Socioeconomic status (SES), C-reactive Protein (CRP). Amount smoked in lifetime coded 0 (never, not even a puff), 1 (1 or more puffs, but never a whole cigarette), 2 (1 cigarette), 3 (2–5 cigarettes), 4 (6–15 cigarettes), 5 (16–25 cigarettes), 6 (26–99 cigarettes), 7 (100 or more cigarettes), 8 (500 or more cigarettes).

* $p < .05$;

** $p < .01$.

Table 4

Standardized Predictor Loadings for Regression Models Predicting Cardiovascular Health Outcomes from Internalizing and Externalizing symptoms, controlling for key covariates.

	Adiposity	Smoke Age	Smoke Amount	Systolic BP	Diastolic BP	CRP
Age	0.35**	0.62**	0.63**	0.18**	0.03	-0.01
SES	-0.25*	-0.12*	-0.16**	-0.19**	-0.22**	0.08
Race	0.13	-0.03	-0.14**	0.06	0.20**	0.06
Internalizing	0.34**	0.07	-0.07	0.13	0.13	-0.06
Externalizing	0.02	0.11*	0.26**	-0.07	-0.11	-0.04
X ² (DF)	703.19 (456)**	653.69 (422)**	653.69 (422)**	648.84 (422)**	648.84 (422)**	661.27 (402)**
CFI	.95	.95	.95	.95	.95	.81
RMSEA	.05	.05	.05	.05	.05	.05
SRMR	.06	.07	.07	.07	.07	.07

NOTE: Abbreviations include: Socioeconomic status (SES), C-reactive Protein (CRP). Amount smoked in lifetime coded 0 (never, not even a puff), 1 (1 or more puffs, but never a whole cigarette), 2 (1 cigarette), 3 (2–5 cigarettes), 4 (6–15 cigarettes), 5 (16–25 cigarettes), 6 (26–99 cigarettes), 7 (100 or more cigarettes), 8 (500 or more cigarettes).

* $p < .05$;

** $p < .01$.