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RESEARCH ARTICLE

Prenatal Substance Exposure and Obesity: Trajectories of Tri-Ponderal Mass Index in Early Adolescence

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Introduction: The long-term impact of prenatal substance exposure on obesity remains inconclusive. Few studies have explored the trajectories of tri-ponderal mass index, despite its greater accuracy and reliability in assessing adolescent adiposity. The aim of this study was to examine adiposity trajectories assessed by tri-ponderal mass index from preadolescence age to early adolescence and the influence of prenatal substance exposure on these patterns.

Methods: This study used data from the Adolescent Brain Cognitive Development study (Release 5.1), an ongoing longitudinal study on child development. Data were collected between 2016 and 2021. A total of 7,881 children with data across 5 waves were included. Prenatal substance exposure (tobacco, alcohol, caffeine, marijuana) was reported by mothers. Latent growth mixture modeling was conducted to identify tri-ponderal mass index trajectories, followed by multinomial logistic regression to examine the role of prenatal substance exposure, controlling for covariates. All analyses were conducted in 2024.

Results: Three trajectories emerged: stable tri-ponderal mass index (86.6%), increasing tri-ponderal mass index (12.5%), and decreasing tri-ponderal mass index (0.9%). The risk of increasing tri-ponderal mass index was associated with prenatal tobacco and caffeine exposure, showing dose-dependent effects. Tobacco exposure both before and after awareness of pregnancy increased the risk, with no significant benefit from cessation. Prenatal exposure to multiple substances further elevated the risk of increasing tri-ponderal mass index.

Conclusions: Obesity risk can originate prenatally. The long-term impact of prenatal substance exposure on adiposity development during adolescence highlights the need for preconception and prenatal health interventions to reduce obesity risk in offspring.

INTRODUCTION

Over the past 4 decades, obesity rates have doubled in over 70 countries and increased in most others.[1] Childhood and adolescent obesity is rising rapidly, posing immediate health risks and increasing the likelihood of persistence into adulthood with severe long-term consequences.[2,3] Globally, the number of adolescents and young adults (aged 15–24 years) with obesity reached 80.6 million in 2021, having tripled since 1990, and is expected to rise substantially by 2050.[4] Therefore, understanding the developmental

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trajectory of adiposity during adolescence is crucial for effective prevention and intervention.

Obesity results from complex interactions among genetic, environmental, and behavioral factors. Prenatal substance exposure (PSE), including tobacco (prenatal tobacco exposure [PTE]), alcohol (prenatal alcohol exposure [PAE]), caffeine (prenatal caffeine exposure [PCE]), and marijuana (prenatal marijuana exposure [PME]), has been linked to adverse offspring outcomes[5,6] The developmental origins of health and disease hypothesis suggests that early environmental exposures can have lasting health effects,[7] emphasizing the need to examine PSE in obesity research. For instance, maternal smoking may impair fetal growth through altered placental function, oxidative stress, and epigenetic modifications.[8]

Despite evidence linking PSE to offspring health, its long-term impact on adiposity development remains unclear. Most studies assess obesity at a single time point, failing to capture dynamic body composition changes, leading to inconsistent findings. The effects of PAE on adiposity vary across studies.[9,10] In addition, evidence regarding PCE is mixed. Whereas a prior study found associations with lower child height but not increased obesity risk,[11] others reported dose-dependent links between higher caffeine intake and excess weight gain from infancy through childhood.[12] PME has been linked to small-for-gestational-age birth and low birth weight, followed by rapid postnatal weight gain and increased adiposity in childhood,[13] although findings on its long-term effects into adolescence remain limited. Inconsistencies across studies may stem from differences in exposure levels, timing (e.g., cessation after pregnancy awareness), and postnatal substance use.[14,15] Moreover, many prior studies have focused on single substances, overlooking cumulative effects despite frequent polysubstance use among pregnant women.[16]

BMI is widely used to assess obesity but may not be accurate for adolescence owing to hormonal shifts and growth spurts. The tri-ponderal mass index (TMI), defined as weight divided by height cubed, has been proposed as a more stable alternative.[17,18] Unlike BMI, TMI accounts for growth-related body proportion changes and performs better in estimating body fat percentage, particularly during puberty. It also allows for more reliable international comparisons because it is independent of national weight distributions. Although prior studies using models that assume no within-group variance identified similar BMI trajectory patterns,[19,20] early adolescence is characterized by complex growth dynamics, suggesting potential within-group heterogeneity.

Longitudinal research using TMI to examine adiposity development remains scarce, and the role of PSE as an early-life risk factor for adolescent obesity is not well understood. Therefore, this study addressed these gaps by investigating the influence of PSE on adiposity trajectories over time, with 3 key objectives: (1) identifying distinct TMI trajectories over 4 years from preadolescence to early adolescence; (2) assessing associations between these trajectories and PTE, PAE, PCE, and PME, expecting effects to vary by substance type and amount; and (3) evaluating the impact of exposure timing, status changes, and polysubstance use, hypothesizing stronger effects for multiple exposures than for single-substance exposure.

METHODS

Study Sample

The Adolescent Brain Cognitive Development (ABCD) Study (Release 5.1) included data from 11,868 children aged 9–10 years enrolled between 2016 and 2018 (https://abcdstudy.org). The study employed a school-based, stratified probability sampling approach across 21 research sites to ensure demographic representativeness. It includes annual follow-up assessments across multiple domains, including brain imaging, cognitive functioning, physical health, and psychosocial development. Further details regarding the study protocol are available in the original source.[21] For this study, individuals with complete anthropometric measurement data were included, which are available for 11,856 participants at baseline (Year 0); 11,137 at the 1-year follow-up (Year 1); 9,151 at the 2-year follow-up (Year 2); 3,777 at the 3-year follow-up (Year 3); and 4,178 at the 4-year follow-up (Year 4). The study adhered to the guidelines proposed by the STROBE.[22]

The sample for this study was obtained on the basis of multiple exclusion criteria, as detailed in Appendix Material (available online) and outlined in the flowchart (Appendix Figure 1, available online). The final sample consisted of 7,881 children. Of these, 7,877 children were available at Year 0; 7,690 at Year 1; 6,318 at Year 2; 2,596 at Year 3; and 2,860 at Year 4.

The data from the ABCD Study are held in the National Institute of Mental Health Data Archive. The ABCD Study is responsible for obtaining participant consent and assent, with protocols approved by a centralized IRB at the University of California, San Diego.[23]

Measures

Height and weight were measured twice (or thrice if discrepancies existed) by trained researchers to minimize measurement error. The average height (in.) and weight (lbs.), measured in light clothing and stocking feet at each wave, were converted to TMI using the formula

weight (kg)/height (m).[3] In this study, the conversion was (weight [lbs.]/2.205)/(height [in.]/39.370).[3]

Data on past or current eating disorders (Year 2 and Year 4) and medications affecting food intake (across all waves) were collected. Lactational substance exposure and childhood substance use were treated as confounders. Demographic variables—including age, sex, race, pubertal stage, birth weight, maternal age at childbirth, and maternal education (as a socioeconomic indicator)—were controlled for in the analysis (Appendix Material, available online, provides details).

At the baseline of the ABCD Study, the Developmental History Questionnaire was used to inquire about the use of specific substances during pregnancy, including tobacco (PTE); alcohol (PAE); caffeine (PCE); marijuana (PME); and other substances such as cocaine, heroin, and oxycodone.[24] PTE, PAE, and PME were coded dichotomously (yes/no) on the basis of responses to items asking whether the mother used the substance during pregnancy either before or after pregnancy recognition. Regarding PCE, the mothers were asked to respond to the categorical question *Did you/biological mother have any caffeine during pregnancy (from conception until delivery)?* The response options were *nonuse, at least once a day* (daily use), *less than once a day but more than once a week* (weekly use), and *less than once a week* (monthly use).

The amount of substance use was measured by asking about the daily frequency of smoking and marijuana use, the maximum number of alcoholic drinks consumed in 1 sitting, average weekly alcohol intake, and weekly caffeine consumption (calculated from daily intake × 7 and monthly intake/4.33).

Moreover, if any prenatal use of tobacco, alcohol, or marijuana played a role, the exposures before and after awareness of pregnancy were compared. These were further divided into nonuse (no consumption before or after knowing about the pregnancy), abstain (consumption before but not after knowing about the pregnancy), and consistent use (consumption both before and after knowing about the pregnancy). In addition, prenatal exposure levels were classified into 4 categories: nonexposure, monoexposure (using 1 substance), dual-exposure (using 2 substances), and polyexposure (using more than 2 substances). Detailed patterns of substance combinations are presented in Appendix Table 1 (available online).

Statistical Analysis

TMI trajectories were modeled using adjusted TMI Z-scores, which were derived by regressing background variables on TMI and calculating standardized residuals ($Z=[V-V_0]/RMSE$, where V=observed TMI, V_0=predicted value, and RMSE is the root mean square error).

A single-class growth curve model was first performed to assess overall TMI development. Latent growth mixture modeling (LGMM) was then conducted to identify subpopulations with different TMI growth patterns. Solutions with 2−5 classes were tested. As a potential alternative model, latent class growth models assuming no within-class variances were also performed. The modeling employed robust maximum likelihood estimation for mixture model analysis, using 500 random starts and 20 initial iterations to optimize global solutions and stabilize parameter estimation. Details on the modeling procedures, missing data treatment, and model fit criteria are provided in the Appendix (available online).

Group differences across TMI trajectories were assessed using chi-square tests for categorical variables and either 1-way ANOVA (with Student−Newman−Keuls posthoc tests) or Kruskal−Wallis tests for continuous variables, depending on variance assumptions. Multinomial logistic regression analysis was conducted to examine the effect of PSE (independent variable) on TMI trajectories (dependent variable), controlling for demographics and relevant confounders.

Descriptive statistics and attrition analysis were performed in IBM SPSS 29. All modeling was conducted using Mplus 8.3 software.[25] Additional statistical analyses and figure generation were completed in R (Version 4.4.1).

RESULTS

Table 1 presents sample characteristics and PSE across 5 waves, including missing data, because cases with missing values on key predictors were not excluded. The final sample included 3,978 boys and 3,903 girls. At baseline (Year 0), 99.5% of participants were aged either 9 or 10 years. Key demographics remained stable across the waves. Although attrition occurred, most participants had sufficient data for reliable modeling (Appendix Material, available online).

Both linear and quadratic growth curve models fit the data well, with the quadratic model providing a better fit (Appendix Material and Appendix Table 2, available online). Although overall TMI levels remained stable, significant variance existed in baseline levels and slopes. Model fit with equal error variances confirmed reliability for identifying growth patterns. The single-class model is illustrated in Appendix Figure 2 (available online).

Fit indices (Appendix Table 3, available online) of LGMM favored the quadratic over the linear model. Both the 4- and 5-class models included multiple small-sized classes, indicating uneven class distribution and

Table 1. Characteristics and Prenatal Substance Exposures of Sample Available at Each Wave

Variables	Year 0 (*n*=7,877)	Year 1 (*n*=7,690)	Year 2 (*n*=6,318)	Year 3 (*n*=2,596)	Year 4 (*n*=2,860)	*p*-value
Sex						0.820
Males	3,976 (50.5%)	3,874 (50.4%)	3,227 (51.1%)	1,328 (51.2%)	1,469 (51.4%)	
Females	3,901 (49.5%)	3,816 (49.6%)	3,091 (48.9%)	1,268 (48.8%)	1,391 (48.6%)	
Race						**<0.001**
White	4,182 (53.1%)	4,119 (53.6%)	3,521 (55.7%)	1,421 (54.7%)	1,641 (57.4%)	
Black	1,116 (14.2%)	1,064 (13.8%)	829 (13.1%)	365 (14.1%)	308 (10.8%)	
Hispanic	1,647 (20.9%)	1,592 (20.7%)	1,239 (19.6%)	493 (19.0%)	584 (20.4%)	
Asian	151 (1.9%)	149 (1.9%)	113 (1.8%)	40 (1.5%)	52 (1.8%)	
Other	781 (9.9%)	766 (10.0%)	616 (9.7%)	277 (10.7%)	275 (9.6%)	
Age, years (baseline)	9.48 (0.51)	9.48 (0.51)	9.48 (0.51)	9.46 (0.50)	9.51 (0.50)	**0.002**[a]
Puberty	2.56 (0.74)	2.55 (0.74)	2.57 (0.73)	2.57 (0.74)	2.68 (0.70)	**<0.001**[b]
Birth weight (lbs.)	6.58 (1.46)	6.58 (1.46)	6.55 (1.47)	6.53 (1.48)	6.53 (1.50)	0.279[b]
ME	16.67 (2.73)	16.70 (2.72)	16.76 (2.64)	16.73 (2.64)	16.85 (2.62)	0.069[a]
MAC	29.52 (6.11)	29.57 (6.07)	29.58 (6.07)	29.49 (5.94)	29.77 (5.99)	0.393[b]
PSE						
Tobacco	935 (12.0%)	906 (11.9%)	745 (11.9%)	330 (12.8%)	306 (10.8%)	0.252
Missingness	58 (0.7%)	58 (0.8%)	49 (0.8%)	15 (0.6%)	21 (0.7%)	
Alcohol	1,906 (25.2%)	1,872 (25.3%)	1,537 (25.3%)	623 (25.0%)	703 (25.5%)	0.991
Missingness	304 (3.9%)	301 (3.9%)	251 (4.0%)	101 (3.9%)	108 (3.8%)	
Caffeine						0.857
Daily	1,824 (24.4%)	1,779 (24.4%)	1,503 (25.0%)	583 (23.5%)	689 (25.2%)	
Weekly	1,480 (19.8%)	1,449 (19.9%)	1,198 (19.9%)	507 (20.5%)	559 (20.5%)	
Monthly	1,192 (16.0%)	1,167 (16.0%)	974 (16.2%)	426 (17.2%)	424 (15.5%)	
Missingness	406 (5.2%)	394 (5.1%)	308 (4.9%)	117 (4.5%)	127 (4.4%)	
Marijuana	394 (5.0%)	382 (5.0%)	301 (4.8%)	125 (4.9%)	103 (3.6%)	**0.037**
Missingness	72 (0.9%)	71 (0.9%)	55 (0.9%)	23 (0.9%)	27 (0.9%)	

Note: Boldface indicates statistical significance ($p<0.05$).
Values are presented as *n* (%) or mean (SD). Puberty: Mean score derived from parent- and child-reported Pubertal Development Scale stages; higher scores indicate more advanced pubertal development. ME level is presented as a continuous variable on the basis of a 29-point ordinal scale.
[a]Kruskal–Wallis test.
[b]One-way ANOVA.
MAC, maternal age at childbirth; ME, maternal education; PSE, prenatal substance exposure.

potential overfitting. In addition, the Lo–Mendell–Rubin test became nonsignificant for the 4-class (p=0.058) and 5-class (p=0.124) solutions. On the basis of a combination of statistical criteria, model parsimony, and interpretability, the 3-class model was selected.

Figure 1 presents LGMM-estimated TMI trajectories and observed individual trajectories within each class. Groups were named on the basis of developmental patterns: stable TMI (n=6,827; 86.6%) showed consistent levels, increasing TMI (n=987; 12.5%) showed upward trends, and decreasing TMI (n=67; 0.9%) declined over time. Random effect parameters are detailed in Appendix Table 4 (available online). Model consistency across sample sizes supported full information maximum likelihood reliability (Appendix Figures 3 and 4, available online). Despite the decline in TMI, individuals in the decreasing TMI group exhibited a significant increase in weight over the 4-year period (mean increase=42.73 lbs., SD=24.58; t[25]=8.86, p<0.001), suggesting a disproportionate gain in height relative to weight. In addition, an analysis mapping each TMI trajectory group onto Centers for Disease Control and Prevention–defined sex- and age-specific BMI categories (normal weight, overweight, obesity) at baseline is provided in Appendix (available online).

The stable TMI group had more White and fewer Black and Hispanic children than other groups. The decreasing TMI group had higher birth weights, whereas the stable TMI group had higher maternal education. The increasing TMI group had higher rates of marijuana and tobacco exposure during breastfeeding, whereas lactational caffeine exposure was more common in the stable TMI group (Table 2).

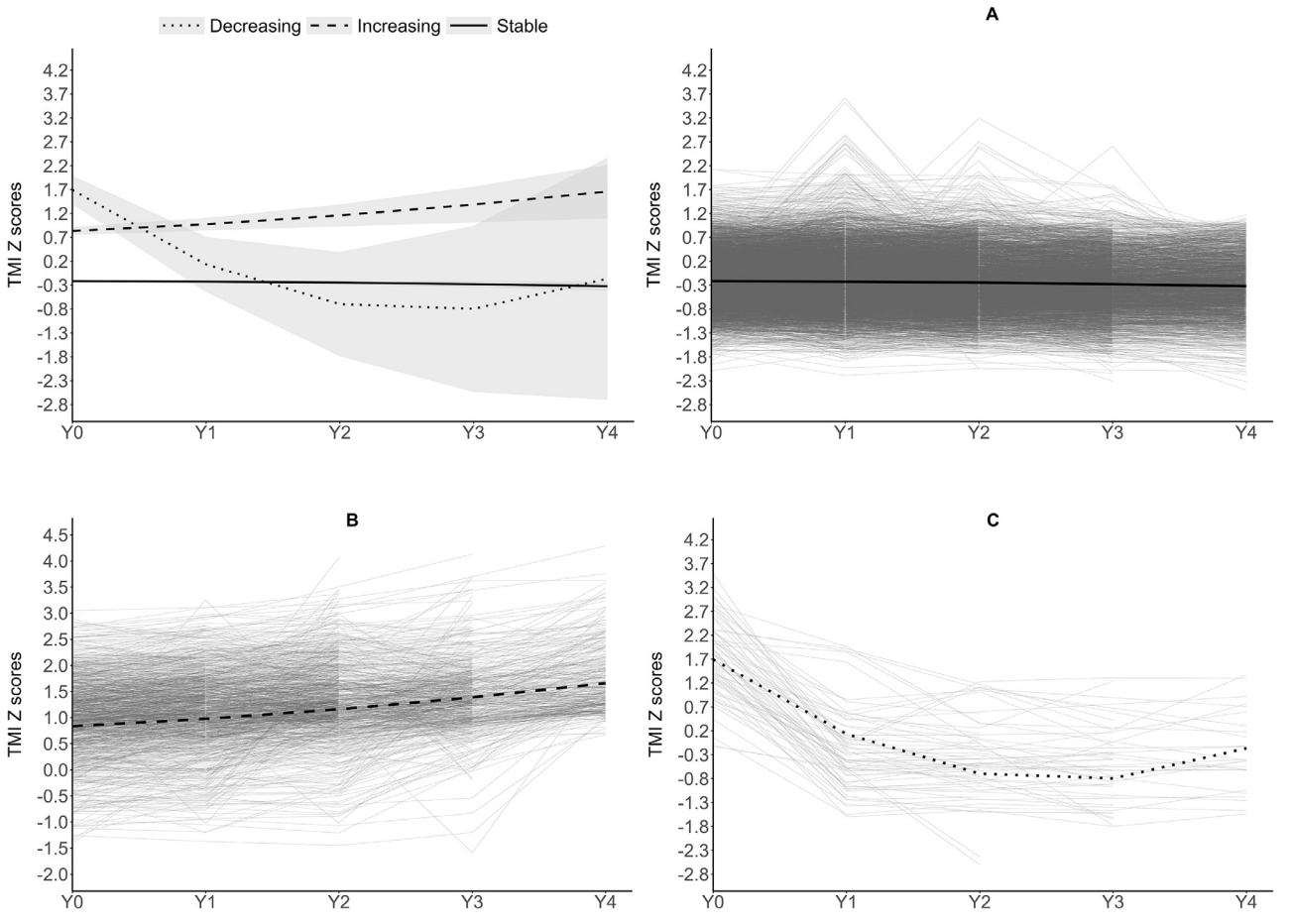

Figure 1. TMI trajectory patterns based on latent growth mixture modeling (shaded bands: 95% CIs), with observed individual trajectories within each group. (A) Stable TMI. (B) Increasing TMI. (C) Decreasing TMI.
TMI, tri-ponderal mass index.

Single time-point analyses showed that TMI correlated positively with PTE and PME, correlated negatively with PAE, and was unrelated to PCE (Appendix Figure 5, available online). PTE was less prevalent in the stable TMI group, whereas daily PCE was more frequent in the increasing TMI group. Polyexposure was also more common in the increasing TMI group (Table 2).

Figure 2 illustrates ORs and 95% CIs for PSE effects on TMI trajectories, controlling for confounders. As indicated in the upper panel, PTE and daily/weekly caffeine consumption increased the likelihood of belonging to the increasing TMI group (ORs=1.53, 1.39, and 1.38, respectively). PAE showed a marginal association with decreasing TMI (p=0.060).

As shown in Figure 2, higher maternal daily tobacco (OR=1.06) and weekly caffeine use (OR=1.01) were linked to a greater likelihood of increasing TMI (middle panel). Tobacco use both before (OR=1.55) and after (OR=1.51) pregnancy awareness significantly predicted increasing TMI, with a persistent risk for those who quit after becoming aware of their pregnancy (OR=1.47). Polyexposure further elevated risk (OR=1.70) (lower panel).

DISCUSSION

To the authors' knowledge, this is the first longitudinal study to examine the impact of PSE on adiposity development in early adolescence using TMI. Three distinct TMI trajectories over 4 years were identified using LGMM: stable TMI, increasing TMI, and decreasing TMI. After adjusting for confounders, prenatal tobacco and caffeine exposure (PTE and PCE) were significantly linked to the increasing TMI trajectory, highlighting the enduring impact of maternal substance use on obesity risk in offspring.

A large majority of participants had a stable TMI, whereas slightly more than one tenth had a consistently increasing TMI, and about 1% had a decreasing TMI. Children in the increasing TMI group exhibited higher

Table 2. Group Comparisons for Variables Between TMI Trajectory Groups

Variables	Stable TMI	Increasing TMI	Decreasing TMI	*p*-value
Sex				0.274
Males	3,427 (50.2%)	512 (51.9%)	39 (58.2%)	
Females	3,400 (49.8%)	475 (48.1%)	28 (41.8%)	
Race				**<0.001**
White	3,720 (54.5%)	440 (44.6%)	24 (35.8%)	
Black	910 (13.3%)	193 (19.6%)	14 (20.9%)	
Hispanic	1,392 (20.4%)	240 (24.3%)	16 (23.9%)	
Asian	133 (1.9%)	15 (1.5%)	3 (4.5%)	
Other	672 (9.8%)	99 (10.0%)	10 (14.9%)	
Age, years (baseline)	9.47 (0.51)	9.49 (0.50)	9.54 (0.50)	0.467[a]
Puberty	2.55 (0.73)	2.61 (0.79)	2.69 (0.73)	**<0.001**[b]
Birth weight (lbs.)	6.56 (1.46)	6.65 (1.48)	7.06 (1.22)	**<0.001**[b]
ME	16.77 (2.71)	16.02 (2.76)	15.76 (3.05)	**<0.001**[b]
MAC	29.61 (6.11)	28.93 (6.02)	29.22 (6.68)	**<0.001**[b]
Childhood substance use				
Tobacco	196 (2.9%)	31 (3.1%)	4 (6.0%)	0.299
Alcohol	2,280 (33.4%)	293 (29.7%)	17 (25.4%)	**0.029**
Caffeine	5,056 (74.1%)	780 (79.0%)	57 (85.1%)	**<0.001**
Early substance exposure				
Tobacco				
Lactational (*n*=7,881)	93 (1.4%)	27 (2.7%)	1 (1.5%)	**0.008**
Prenatal (*n*=7,823)	747 (11.0%)	178 (18.1%)	10 (14.9%)	**<0.001**
Alcohol				
Lactational (*n*=7,881)	591 (8.7%)	51 (5.2%)	5 (7.5%)	**<0.001**
Prenatal (*n*=7,577)	1,670 (25.5%)	215 (22.5%)	21 (31.3%)	0.069
Caffeine				
Lactational (*n*=7,881)	2,146 (31.4%)	248 (25.1%)	15 (22.4%)	**<0.001**
Prenatal (*n*=7,475)				**0.034**
Daily	1,559 (24.1%)	256 (27.5%)	10 (15.9%)	
Weekly	1,271 (19.6%)	198 (21.3%)	11 (17.5%)	
Monthly	1,053 (16.2%)	129 (13.9%)	10 (15.9%)	
Marijuana				
Lactational (*n*=7,879)	46 (0.7%)	16 (1.6%)	0 (0.0%)	**0.014**
Prenatal (*n*=7,809)	325 (4.8%)	63 (6.5%)	6 (9.0%)	**0.030**
Prenatal exposure level				**<0.001**
Monoexposure	2,702 (43.4%)	386 (42.7%)	20 (31.7%)	
Dual-exposure	1,211 (19.4%)	168 (18.6%)	18 (28.6%)	
Polyexposure	354 (5.7%)	84 (9.3%)[1]	3 (4.8%)	

Note: Boldface indicates statistical significance ($p<0.05$).
Values are presented as *n* (%) or mean (SD). Puberty: Mean score derived from parent- and child-reported Pubertal Development Scale stages; higher scores indicate more advanced pubertal development. ME level is presented as a continuous variable on the basis of a 29-point ordinal scale.
[a]Kruskal–Wallis test.
[b]One-way ANOVA.
MAC, maternal age at childbirth; ME, maternal education; TMI, tri-ponderal mass index.

baseline TMI levels than those in the stable TMI group, suggesting that weight gain may have already begun prior to adolescence. According to baseline BMI categories, the increasing and decreasing TMI groups were predominantly composed of children with overweight and obesity, whereas the stable TMI group largely comprised children with normal weight.

PTE emerged as a robust predictor of increasing TMI, supporting prior findings that smoking during pregnancy elevates childhood overweight risk.[26] Consistent with previous research, this study highlighted that early tobacco exposure was associated with later obesity extending into early adolescence, with higher amounts of daily smoking indicating an increased risk of TMI

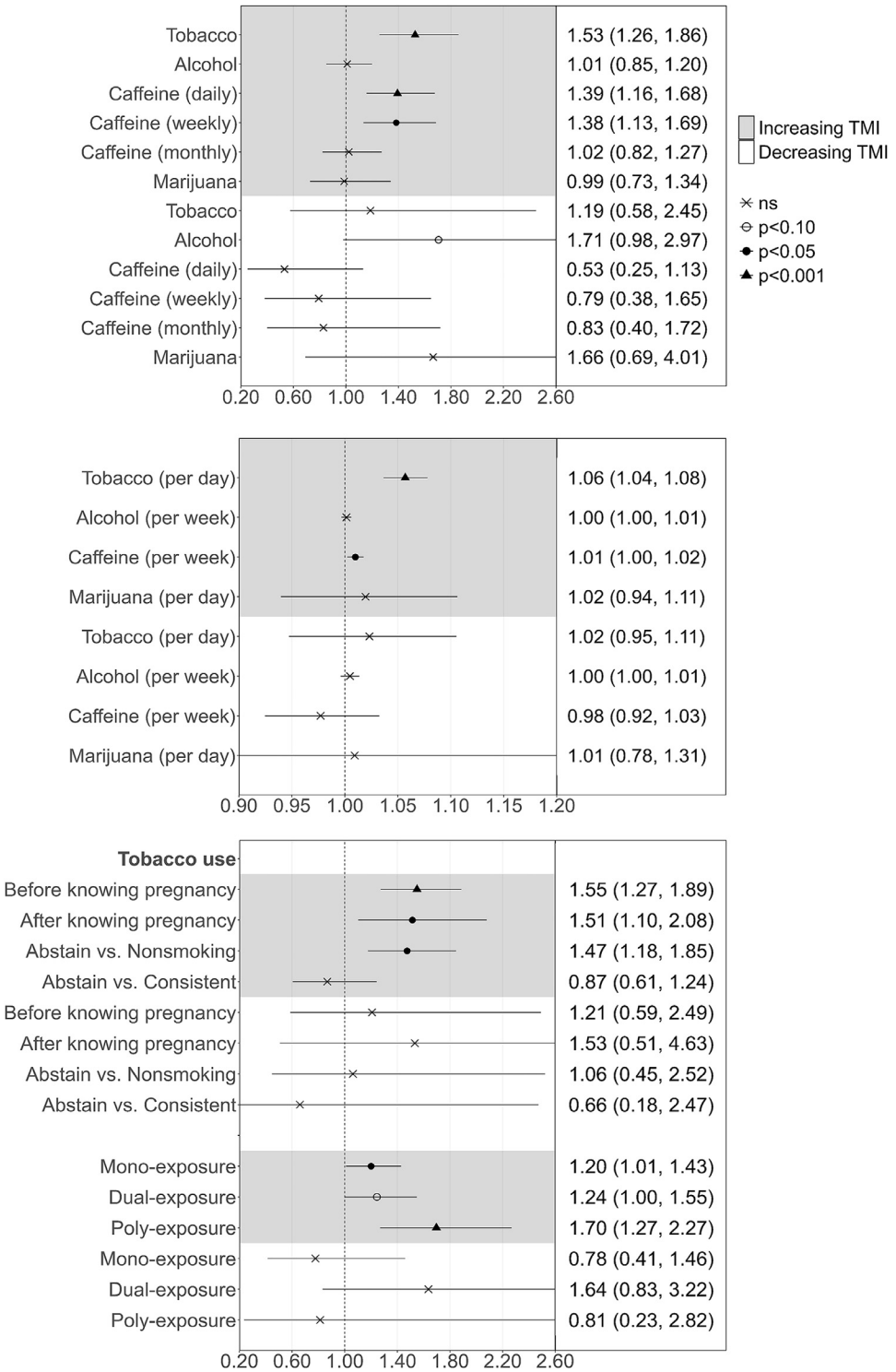

Figure 2. ORs for prenatal substance exposure predicting TMI trajectories (reference group: stable TMI).

Note: Upper panel displays prenatal exposure (0=no, 1=yes) for each substance. Middle panel displays the amount of substance used (daily for tobacco/marijuana, weekly for alcohol/caffeine). Lower panel displays tobacco exposure timing (before versus after pregnancy awareness) and prenatal substance exposure levels. Monoexposure denotes using 1 substance. Dual-exposure denotes using 2 substances. Polyexposure denotes using more than 2 substances.

growth during early adolescence. The effect may be explained by several mechanisms, including oxidative stress, changes in placental function, alterations in central nervous system regulation of energy balance, increased sensitivity to obesogenic diets, and reduced physical activity.[8,27]

Notably, PTE both before and after awareness of pregnancy played a role in predicting an increase in TMI, underscoring the importance of early gestational exposure. Mothers who quit smoking after becoming aware of their pregnancy did not show significant improvement in their children's adiposity outcomes, compared with those who continued smoking. Most previous research on smoking cessation has focused on infants or preschool children. For instance, mothers who stop smoking by the third month of pregnancy tended to have infants with birth weights similar to those of nonsmoking mothers.[28] A recent meta-analysis further indicated that children of mothers who quit smoking during pregnancy still had a significantly higher risk of overweight and obesity than those of nonsmoking mothers,[29] partially supporting the current findings. This underscores the need for preconception and early pregnancy interventions because cessation after pregnancy awareness may not fully mitigate adverse effects.

The long-term effects of PCE on the risk of obesity in children remain understudied.[12] Supporting the growing body of evidence, both daily and weekly PCEs were found to be associated with increasing TMI in early adolescence, with a modest dose−response effect. Although mechanisms are not fully clear, proposed pathways involve alterations in brain structure, reward sensitivity, and glucose metabolism.[30−33] Hence, according to the findings, current guidelines on caffeine consumption during pregnancy warrant reevaluation.

In addition, PAE showed a trend toward an association with decreasing TMI. Although TMI declined, individuals in this group gained substantial weight over time. This high-early, catch-down pattern may reflect early adiposity surplus followed by constrained anabolic changes during puberty. Ethanol-related impairments in placental angiogenesis, insulin growth hormone signaling, and mitochondrial function may blunt anabolic growth.[34,35] Consistently, prior research has reported reduced pubertal lean- and bone-mass accretion in children with PAE.[36,37] Regarding marijuana exposure, it was less common in the stable TMI group but did not predict TMI changes after adjustment. Although animal studies suggest that the endocannabinoid system may influence metabolic programming,[38] human evidence remains limited and inconsistent, possibly owing to lower exposure intensity, timing variability, and complex biological and lifestyle interactions.[13,39]

Although not all PSEs significantly predisposed children to an increase in TMI during early adolescence, multiple exposures amplified the odds of increasing TMI, which is particularly noteworthy. In real-world scenarios, prenatal exposure to multiple substances is common.[16,40] However, the cumulative and potential synergistic effects of multiple substance exposures on adiposity development remain largely unexplored.

Limitations

Some limitations to this study should be acknowledged. First, the retrospective self-reported data on PSE are susceptible to recall or reporting biases. Second, the decreasing TMI group was small, raising concerns about overfitting. Although this group represented a small proportion of the sample, the absolute size (n=67) allowed for estimation and parameter instability. Although sensitivity analyses supported model robustness, results related to this group should be considered exploratory. Third, information relevant to maternal substance use such as maternal prepregnancy BMI, dietary patterns during pregnancy, and paternal substance use were unavailable, potentially resulting in residual confounding and limiting causal inference. Fourth, PCE lacked precise timing information, precluding identification of critical windows. More granular exposure data would improve future research. Fifth, unlike direct methods such as dual-energy X-ray absorptiometry, TMI does not distinguish fat from lean mass, which may attenuate exposure−adiposity associations. However, it remains a practical and reliable alternative for large-scale longitudinal studies where direct body composition measures are not feasible. Sixth, the decreasing number of participants across waves may have introduced bias in trajectory estimation. However, most participants had sufficient data for reliable modeling. Finally, this study spanned 4 years; longer-term follow-up is needed to determine whether these trajectories persist into late adolescence and to clarify their potential implications for chronic disease risk later in life.

CONCLUSIONS

This study provides supportive evidence that PSE, particularly to tobacco and caffeine, plays a potential long-term role in increasing adiposity from preadolescence to early adolescence. By addressing a critical gap in understanding the determinants of body fat development during this period, the study reinforces the importance of early-life influences on later growth and underscore the necessity of a substance-free pregnancy. These findings suggest that obesity prevention efforts should begin as early as the prenatal stage to mitigate long-term risks.

Future research is needed to further elucidate the mechanisms driving these associations, such as neurocognitive pathways, and to develop targeted interventions that reduce the lasting impact of PSE on offspring health.

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CREDIT AUTHOR STATEMENT

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SUPPLEMENTAL MATERIAL

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