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Adolescent BMI trajectory and associations with adult metabolic syndrome and offspring obesity

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Abstract

Objective: This study examined the association of adolescent BMI trajectory with adult metabolic syndrome (MetSyn) and with intergenerational obesity.

Methods: This study used data from the National Heart, Lung, and Blood Institute (NHLBI) Growth and Health Study (1987–1997). Data from the 20-year follow-up (2016–2019) study were included from the original participants ($N = 624$) and their children ($N = 645$). Adolescent BMI trajectories were identified using latent trajectory modeling. Mediation analysis using logistic regression models was performed to estimate confounder-adjusted odds ratios (OR) and 95% CI between adolescent BMI trajectory and adult MetSyn. Using similar methods, the association between BMI trajectory and offspring obesity was examined.

Results: Latent trajectory modeling identified four patterns: "weight loss then gain" ($N = 62$); "persistently normal" ($N = 374$); "persistently high BMI" ($N = 127$); and "weight gain then loss" ($N = 61$). Women who had a persistently high BMI trajectory had twice the odds of having children who met the definition for obesity compared with the persistently normal group, adjusting for adult BMI (OR: 2.76; 95% CI: 1.39–5.46). None of the trajectory groups was associated with adult MetSyn compared with the persistently normal group.

Conclusions: Intermittent adolescent obesity may not confer MetSyn risk during adulthood. However, maternal adolescent BMI trajectories that are persistently high may increase the odds of intergenerational obesity among offspring.

INTRODUCTION

Obesity can track throughout childhood, and that predicts a greater incidence of adulthood obesity [1, 2]. It is possible that obesity during childhood can also confer risk of metabolic disease in adulthood or risk of obesity in one's offspring [1–4]. Metabolic syndrome (MetSyn) is defined by the National Heart, Lung, and Blood Institute (NHLBI) as the name for a cluster of conditions that raises the risk for heart disease, diabetes, stroke, and other metabolic health issues [5]. The prevalence of MetSyn has been on the rise in the United States. As of 2016, an estimated 35% of American adults met the criteria for MetSyn [6, 7].

The relationship between adolescent obesity and incident MetSyn in adulthood has been a source of conflict in the literature. Some authors have found that adults who had obesity as an adolescent have an increased risk of developing metabolic conditions such as diabetes, cardiovascular disease, or MetSyn in adulthood compared with those who did not have obesity in adolescence [4, 8–10]. However, others have argued that adolescent obesity is not an independent risk factor for MetSyn in adulthood and that, rather, a sustained high body mass index (BMI) that extends into adulthood confers a risk, pointing out that childhood obesity and metabolic health are significantly and positively associated in studies that have failed to control for BMI in

adulthood. However, in studies that have adjusted for adulthood BMI, the association becomes reversed [9–11]. Because adolescence is an important developmental period of weight gain and weight fluctuation, it may be normal and not pathological to have periods of high BMI. In contrast, persistent obesity may be driving adulthood risk [12]. This is an important distinction to make so that interventions do not end up creating harm by enforcing dieting and weight restrictions during this time. Furthermore, failing to address current weight status suggests that this relationship between adolescent obesity and metabolic health diagnosis could be biased [11, 13, 14]. This discord represents a gap in the literature regarding the long-term effects of adolescent BMI trajectory on metabolic health. This study examined trajectory of weight during adolescence as a more meaningful predictor of adult risk and offspring risk for obesity.

Many studies have shown that maternal gestational weight, gestational weight gain, and parental BMI are key risk factors for negative childhood health and childhood obesity [15–19]. However, little is known about the extent to which a mother's adolescent BMI trajectory may influence adiposity in her children. This study seeks to fill these gaps using the well-characterized National Institutes of Health (NIH) NHLBI Growth and Health Study (NGHS), a longitudinal observational study that followed White and Black girls from ages 9 to 10 years until 19 to 20 years.

In the current analysis, we explored the relationship between adolescent BMI trajectory and incident MetSyn in adulthood using latent trajectory modeling (LTM) and logistic regression. The association between adolescent BMI trajectory and offspring BMI was also estimated. We hypothesized that patterns of BMI consistent with those maintaining a high BMI throughout adolescence would be reflected in higher odds of MetSyn during adulthood than those whose trajectories indicated a healthier BMI maintenance. We also hypothesized that offspring whose mother's adolescent BMI trajectories were persistently at the highest BMI levels throughout adolescence would have higher odds of meeting the criteria for child BMI > 95th percentile.

Study Importance

What is already known?

- It is possible that obesity during childhood can also confer risk of metabolic disease in adulthood or risk of obesity in one's children.
- The relationship between adolescent obesity and incident metabolic syndrome (MetSyn) in adulthood has been a source of conflict in the literature.
- Little is known about the extent to which a mother's adolescent BMI trajectory may influence adiposity in her children.

What does this study add?

- Intermittent adolescent obesity does not appear to confer health risk during adulthood or to offspring.
- Persistently high adolescent BMI trajectories among mothers confer risk of intergenerational transmission of obesity among children.
- The results suggest that having persistently high BMI levels throughout adolescence increases the odds of meeting the criteria for MetSyn in adulthood; however, this association was found to be mostly mediated by adult BMI status.

How might these results change the direction of research or the focus of clinical practice?

- Our findings imply that adolescence is not a developmental stage when having a high BMI preordains an elevated risk for MetSyn. Rather, only through a sustained high body mass into adulthood does MetSyn become a risk.

METHODS

The NGHS is a prospective cohort study designed to investigate racial/ethnic differences in cardiometabolic risk factors and outcomes. The study began in 1987, with annual examinations concluding in 1997 [20]. Over that period, 2379 adolescent girls aged 9 to 10 years were recruited from three sites: Richmond, California; Washington, DC; and Cincinnati, Ohio [20, 21]. Slightly more than half of the cohort was African American. Eligibility included being noninstitutionalized and having at least one parent or caretaker. If a girl's family planned on moving away within 12 months of enrollment, the girl was ineligible to join the study.

The follow-up study was initiated in 2016 with the goal of recontacting the full California NGHS cohort nearly 30 years after the original date of enrollment. Responses were received from 624 of the original 887 participants, now aged 36 to 43 years, and 645 of the participants' biological children, aged between 2 and 17 years. The follow-up collected anthropometric data, blood pressure (BP), and behavioral and eating questionnaires, as well as biological samples from the original participants and their children.

The original NGHS study and the follow-up study received approval from the University of California, Berkeley Committee for Protection of Human Subjects (CPHS # 2013-11-5774). The study was performed according to the guidelines of the Declaration of Helsinki. Written consent from the participants was obtained by study staff. The data used in this secondary analysis were deidentified before analysis.

Data

The California NGHS historic, follow-up, and offspring longitudinal data were included in this analysis. The historic study collected

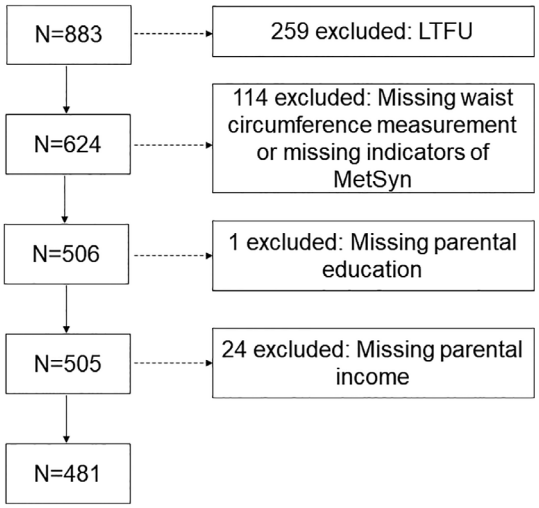

FIGURE 1 Flow diagram of adult population removal due to LTFU or missing values. Total $N = 481$ adult participants for final MetSyn analysis. Abbreviations: LTFU, loss to follow-up; MetSyn, metabolic syndrome

demographic, anthropometric, nutritional, and psychological data at yearly clinic visits in Richmond, California ($N = 887$). This analysis included only those who also participated in the follow-up study ($N = 624$). Baseline characteristics were compared between those who were retained in the study against those who were lost to follow-up. In total, 143 of the 624 adult participants were removed from the analysis because of missingness. A total of 118 adults were missing the outcome of interest. One was removed because of missing parental education values, and 24 adults were removed because of missing values in the parental income covariate. Figure 1 presents a flow diagram of participant removal.

Exposure: BMI trajectory in adolescence

The historic study group was aged 9 to 10 years and was followed for 10 years. To account for standard growth experienced during adolescence, the raw BMI values (weight in kilograms divided by height in meters squared) from the historic cohort were converted to BMI *z* scores using the Centers for Disease Control and Prevention (CDC) 2000 BMI-for-age growth charts [22, 23]. We used LTM to create homogeneous classes from the historic cohort participants' standardized BMI *z* scores while allowing for random effects in respect to individual measurements over the course of the 10-year study period [24, 25]. Previous literature that used this trajectory modeling technique to model BMI over time had most commonly used three to four grouping classifications of BMI [19, 26, 27]. Following the framework published by Lennon et al., we created an initial random-effects model, after which we selected the optimum number of classes that best fit the data, with an additional requirement that each class must contain at least 5% of the study population [24].

An unrestricted random-effects model with quadratic form was selected to identify the classes, allowing for a model of increasing and decreasing BMI over time to be classified. As Lennon et al. did, we used the Bayesian information criterion (BIC) to select the number of groupings that best fit the data [24]. The BIC is a measure of model fit based on the likelihood function with a penalty factor for the number of parameters included (here, groups), somewhat analogous to the adjusted R^2 measure from a linear regression model. The penalty requires the additional fit gained from more complex models to more than compensate the cost of estimating additional parameters. Across a comparison of several candidate models, the one with the lowest BIC has the superior fit [28]. Various models that included one to seven subgroups were compared. We found that models that contained four and five subgroups ($k = 4$, $k = 5$) had the lowest BIC, suggesting that these models fit the data best. A model with four trajectories was chosen over the model with five trajectories because the fifth subgrouping had only 24 observations less than 4% of the study population.

Outcome: MetSyn in adulthood

Participants of the follow-up study, now aged 36 to 43 years, visited their local LabCorp site to submit biological data. We created a dichotomous variable indicating whether an adult participant met the International Diabetes Federation (IDF) standard criteria for MetSyn. IDF MetSyn criteria require that woman have central obesity defined by ethnicity-specific waist circumference (WC) cut points and two of the following: triglycerides ≥ 150 mg/dL; high-density lipoprotein < 50 mg/dL; BP ≥ 130/85 mm Hg; or fasting blood glucose ≥ 100 mg/dL [29–31]. Of the 624 women in the follow-up study, 258 were missing a combination of anthropometric or blood draw laboratory results. As a result, researchers were unable to assign them a value for presence of MetSyn.

To help alleviate the missing values, we reviewed the provided health data of those with WC values who were missing values for MetSyn diagnosis by IDF criteria ($n = 144$). These 144 women were dichotomized into groups with WC > 88 cm (35 in; $n = 107$) or ≤ 88 cm ($n = 37$). Those with high WC were further reviewed for possible MetSyn. If participants had indicated that they were on medication for BP, diabetes, or heart disease, or if they were diagnosed with a chronic metabolic condition such as high BP, high cholesterol, heart disease, or diabetes, it was assumed that they would have met the cutoffs for one of the metabolic measurements in the IDF criteria for MetSyn diagnosis. Furthermore, if participants had also been on either two or more of the described medications or had obesity (class II or III), they were assumed to have met a second criterion for diagnosis. Using this method allowed us to recover 145 participants. After removal of missing data, the final sample size of the original cohort used in analysis was 481 adults. Analysis of participants who were missing data revealed that they were similar to those with complete data. However, there was a difference in adult BMI, with the average BMI for those missing outcome data being slightly lower (mean = 29.8) than from the analytic sample (mean = 32.1).

Outcome: offspring childhood obesity

To account for standard growth expected during adolescence for the offspring, aged between 2 and 17 years, the raw BMI scores from the follow-up offspring cohort were converted to BMI percentiles using the CDC 2000 BMI-for-age growth charts [22, 23]. A dichotomous variable was created indicating whether the offspring would be considered at risk to have obesity by the CDC standard of having ≥ 95th percentile [32].

Covariates

We used a directed acyclic graph to encode assumptions about the relationships among exposure, outcome, and potential confounders of interest [33]. Covariates considered as confounders included participant race (Black; Non-Hispanic White), adolescent parental income (<$10,000; $10,000–$19,999; $20,000–$39,999; $40,000+), and parental education (high school or less; some college; college graduate +). For the offspring data analysis, the previous covariates were included in addition to parental smoking history (never smoked; formerly smoked; currently smoking) and age of offspring at clinic visit.

Statistical methods

Summary statistics were computed by comparing the four BMI trajectory classes and MetSyn in adulthood as well as comparing trajectory class and offspring obesity risk (Tables 1 and 2). Multivariable logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) for the associations of each BMI trajectory with dichotomous metabolic health outcomes, compared with the "persistently normal" BMI trajectory. The model included the covariates described in the previous section to control for potential confounding. The offspring data contained participants who were siblings, potentially violating the independence of observation assumption; therefore, we used an equivalent generalized estimating equation (GEE) model, with the offspring data clustered on the mother with an exchangeable correlation structure. Additionally, some of the variables in both the adult follow-up data set and the offspring data set were missing. The adult data were analyzed using a complete-case analysis, whereas the missing offspring data were addressed using multiple imputation methods.

Multiple imputation

A total of 165 offspring were unable to have their height and weight accurately measured by clinic staff. To account for the missing data, their BMI data was imputed using multiple imputation methods. We used multiple imputation packages in R (version 4.1.1): MI and MItools [34, 35]. Multiple imputation methods have been used previously to deal with missing data and have been found to yield similar results to complete-case analysis so long as the predictors of missingness were included [36, 37]. A data set was created containing important predictors related to the missing BMI variable in the offspring data set.

TABLE 1 Distribution of covariates of participants in adulthood (age 36–43 years) stratified by BMI trajectory classification in the NGHS California cohort ($n = 624$)

	Weight loss then gain	Persistently normal	Persistently high BMI	Weight gain then loss
Number of adult participants (%)	62 (10)	374 (60)	127 (20)	61 (10)
Race, *n* (%)				
White	38 (12)	199 (63)	50 (16)	30 (10)
African American or Black	24 (12)	175 (57)	77 (25)	31 (10)
Adult participant parental education, *n* (%)				
High school or less	8 (6)	76 (57)	35 (26)	14 (11)
Some college	33 (11)	169 (58)	63 (22)	26 (9)
College graduate or more	21 (11)	129 (64)	29 (14)	20 (10)
Adult participant parental income, *n* (%)				
<$10,000	4 (4)	63 (56)	30 (27)	15 (13)
$10,000–$19,999	10 (9)	60 (55)	30 (28)	9 (8)
$20,000–$39,999	23 (13)	109 (63)	30 (17)	11 (6)
$40,000+	21 (10)	129 (64)	29 (14)	24 (12)
Adult BMI category at follow-up, *n* (%)				
Normal weight	11 (8)	107 (75)	2 (1)	25 (17)
Overweight	11 (11)	110 (69)	12 (8)	21 (13)
Obesity	32 (10)	153 (50)	111 (25)	15 (5)
Outcome, *n* (%)				
MetSyn	2 (5)	21 (51)	16 (39)	2 (5)

Abbreviations: MetSyn, metabolic syndrome; NGHS, National Heart, Lung, and Blood Institute Growth and Health Study.

These predictors were age, height, weight, race, general health, and gender. For the purposes of the imputation, the variables age, height, weight, and BMI were treated as positive continuous variables, and general health, a self-reported measurement of the child's general well-being, was treated as an ordered categorical variable. Last, race was treated as an unordered categorical variable.

To check for bias, a qualitative sensitivity analysis was performed to observe major differences in magnitude and direction of the ORs produced between the pooled multiple imputation data and a complete-case analysis. After comparison, the major difference between the original data sets and the imputed data was that the analysis of the imputed data yielded a narrower range of CIs; the magnitude and direction of our associations remained similar between data sets. The imputed data were used for the analysis, and the pooled ORs and 95% CIs for the nonimputed data are reported in Table 4.

Mediation analysis of adult BMI

Previous work has suggested that the association between adolescent obesity and MetSyn in adulthood was mediated by participant BMI status in adulthood. To explore this in our data, we employed the Medflex package in R and followed the methods to use the package published by Lange et al. in 2017 [38, 39]. This method uses an imputation-based approach by generating a second exposure variable that is set to the

TABLE 2 Distribution of biological offspring characteristics and maternal covariates stratified by maternal BMI adolescent trajectory classification in the NGHS California cohort ($n = 645$ biological offspring)

	Weight loss then gain	Persistently normal	Persistently high BMI	Weight gain then loss
N (%)	62 (10)	408 (63)	106 (16)	69 (11)
Offspring characteristics				
Sex, *n* (%)				
Female	36 (58)	201 (49)	50 (47)	37 (54)
Male	26 (42)	207 (51)	56 (53)	32 (46)
Obesity, *n* (%)				
Childhood obesity	14 (23)	73 (18)	35 (33)	13 (19)
Childhood overweight	5 (8)	53 (13)	20 (19)	5 (7)
Childhood normal	27 (44)	178 (44)	24 (23)	24 (35)
Childhood underweight	1 (2)	6 (1)	1 (1)	2 (3)
Maternal characteristics				
Race, *n* (%)				
White	38 (61)	221 (54)	40 (38)	30 (43)
African American or Black	24 (39)	187 (46)	66 (62)	39 (57)
Parental education, *n* (%)				
High school or less	10 (16)	90 (22)	19 (18)	20 (29)
Some college	32 (52)	189 (46)	58 (55)	31 (45)
College grad or more	20 (32)	129 (32)	29 (27)	18 (26)
Parental income, *n* (%)				
<$10,000	4 (6)	81 (20)	25 (24)	17 (25)
$10,000–$19,999	16 (26)	69 (17)	24 (23)	11 (16)
$20,000–$39,999	21 (34)	116 (28)	28 (26)	15 (22)
$40,000+	21 (34)	142 (35)	29 (27)	26 (38)
Smoking status, *n* (%)				
No, I have never smoked	30 (48)	244 (60)	56 (53)	42 (61)
Yes, but I am not currently smoking	20 (32)	105 (26)	39 (37)	12 (17)
Yes, I currently smoke	12 (19)	59 (14)	11 (10)	15 (22)
Mother's BMI at follow-up, *n* (%)				
Normal weight	14 (23)	119 (29)	1 (1)	27 (39)
Overweight	18 (29)	113 (28)	7 (7)	23 (33)
Obesity	30 (48)	177 (43)	98 (92)	19 (28)

Abbreviation: NGHS, National Heart, Lung, and Blood Institute Growth and Health Study.

opposite value of the observed exposure. This allowed us to measure the unobserved nested counterfactual based on the outcome mean [39]. A generalized linear model was used to estimate the association of our exposure and outcome with the adult BMI mediator, the natural indirect effect, and the effect without the adult BMI mediator, i.e., the natural direct effect. CIs were calculated using robust standard errors based on sandwich estimates to offset the downward bias of the default generalized linear model standard error caused by the uncertainty inherent to weight prediction of our estimated mediator model [39]. The offspring data required a modification of the mediation analysis methods described by Lange, Vansteelandt, and Bekaert in 2012 [40]. A GEE logistic regression model was used to estimate the effect of adolescent growth trajectory on the mediator of interest, i.e., adult BMI. This model was then used to predict a weight by dividing the predicted value from the observed growth trajectory from the possible three other growth trajectory classifications. We then used a GEE logistic regression clustered on the mother. We controlled for the observed exposure, the possible exposure, and our covariates and weighted the model using the value computed earlier.

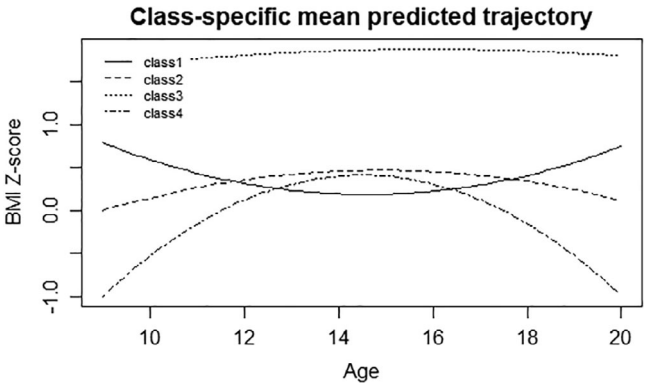

FIGURE 2 Graphical representation of age and BMI *z* score grouped by the classification produced by the model. Class 1, "weight loss then gain," shows participants who lost weight as teenagers and then gained again in early adulthood. Class 2, "persistently normal BMI," indicates those with a normal BMI throughout their adolescence. Class 3, "persistently high BMI," indicates those with persistently high BMI values throughout adolescence. Class 4, "weight gain then loss," illustrates participants who were underweight, gained weight, and then lost weight in young adulthood.

RESULTS

Figure 2 describes the four groupings that resulted from the LTM performed on the adolescent girls from the original NGHS who were available for follow-up ($N = 624$). Class 1, with 10% of the sample, represents participants with BMI in the overweight range in early adolescence, ages 9 and 10 years, which dropped into a normal range as teenagers and then rose again in early adulthood ("weight loss then gain" trajectory). Class 2, the largest group, with 60% of the sample, represents participants with normal BMI throughout their adolescence ("persistently normal BMI"). This class was used as the referent group in the logistic regression. Class 3, with 20% of the sample, represents participants whose BMI values were > 85th percentile throughout adolescence ("persistently high BMI"). Class 4, with 10% of the sample, represents participants who were underweight in early adolescence, ages 9 to 10 years, and whose weight rose toward normal weight and then dropped back down in young adulthood ("weight gain then loss" trajectory).

Table 1 presents the distribution of adult participants across the four BMI trajectory classifications. For participants in class 2, who maintained a persistently normal BMI in adolescence, there was a lower proportion of adults whose BMI indicated that they had obesity than those who had been in class 3, i.e., those who had persistently high BMI in adolescence. A slight majority of those in class 2 were White with parents who were college graduates or higher.

Table 2 presents the distribution of offspring across the four maternal BMI trajectory classifications. A slightly lower percentage of male offspring had mothers who fell into the class 1 BMI trajectory, i.e., those who started at a higher BMI in childhood and then decreased BMI in later adolescence. However, a slightly lower percentage of female offspring had mothers in class 2, i.e., those who had persistently normal BMI, and class 3, i.e., those who had persistently high BMI. Among the offspring, the greatest percentage of those who met the age- and sex-adjusted criteria for obesity had mothers in class 3 (46.2%; 49/106). A majority of offspring had mothers whose BMI indicated that they had obesity at time of recruitment ($n = 324$; 50.2%).

Among the adult participants, women whose BMI trajectory was persistently high in adolescence had 3.08 (95% CI: 1.15–8.25) times the odds of meeting the criteria for MetSyn in adulthood than those who had a normal BMI throughout adolescence, adjusting for confounders previously mentioned (Table 3). Mediation analysis found that the high BMI trajectory throughout adolescence had an imprecise direct association with MetSyn (OR: 1.43; 95% CI: 0.74–2.78) after controlling for confounders. The indirect effect through adulthood BMI resulted in a precise risk estimate (OR: 2.15; 95% CI: 1.56–2.97) after controlling for confounders.

Table 4 shows a comparison of results from an analysis of maternal BMI trajectory on adolescent offspring BMI using logistic regression analysis on imputed and complete-case data. This showed that the results were similar in magnitude, direction, and level of statistical significance among the complete-case analysis. Table 5 presents the analysis of maternal BMI trajectory during adolescence on offspring BMI, which found that maternal BMI trajectory class 3 (persistently high BMI) was associated with 2.76 (95% CI: 1.39–5.46) greater odds of their offspring being at the 95th percentile for BMI as children compared with maternal class 2 (normal BMI trajectory), holding other covariates constant. After performing mediation analysis on the data, we found that the high BMI trajectory throughout adolescence still had a direct association with our outcome (OR: 2.76; 95% CI: 1.41–5.40) after controlling for confounders. The indirect effect through adult BMI had a null estimate (OR: 1.00; 95% CI: 0.99–1.01).

TABLE 3 NDE, NIE, and TE ORs for the mediation analysis performed for the adult populations regarding the association between BMI trajectory class (exposure) and odds of being diagnosed with MetSyn (outcome), with respect to adult BMI category (mediator; $N = 481$)

	NDE OR (95% CI)	NIE OR (95% CI)	TE OR (95% CI)
Persistently normal	REF	REF	REF
Weight loss then gain	0.87 (0.32–2.4)	1.31 (0.97–1.76)	1.14 (0.31–4.22)
Persistently high	1.43 (0.74–2.78)	2.15 (1.56–2.97)	3.08 (1.15–8.25)
Weight gain then loss	0.83 (0.24–2.88)	0.71 (0.42–1.18)	0.58 (0.10–3.39)

Note: Adjusted for race, parental education, parental income, and BMI at follow-up.
Abbreviations: MetSyn, metabolic syndrome; NDE, natural direct effect; NIE, natural indirect effect; OR, odds ratio; REF, reference; TE, total effect.

TABLE 4 Comparison of the reported TE ORs from a pooled analysis of imputed data ($n = 645$) and a complete-case analysis of the unimputed data ($n = 460$)

	TE OR (95% CI)[a]	TE OR (95% CI)[b]
Persistently normal	REF	REF
Weight loss then gain	1.48 (0.69–3.21)	1.12 (0.41–3.05)
Persistently high	2.76 (1.39–5.46)	2.68 (1.41–5.09)
Weight gain then loss	1.30 (0.49–3.44)	1.42 (0.59–3.41)

Note: Results shown for the multivariable logistic regression using a generalized estimating equation performed for the mediation analysis of offspring populations regarding the association between BMI trajectory class and odds of having obesity between age 2 and 17 years. Adjusted for age, race, maternal BMI at follow-up visit, parental education, parental income, and smoking status.
Abbreviations: OR, odds ratio; REF, reference; TE, total effect.
[a]Pooled analysis of imputed data ($N = 645$).
[b]Unimputed data set ($n = 460$).

DISCUSSION

Our goal was to assess the relationship between BMI trajectory over the course of adolescence measured in the historic data collection and metabolic health in adulthood, as well as the intergenerational effects on BMI of the biological children. Our initial estimates suggested that mothers whose adolescent BMI trajectory was maintained at a high level had increased odds of meeting the criteria for MetSyn in adulthood when compared with women classified as having BMI levels considered normal throughout adolescence. However, mediation analysis supported the theory that high body mass throughout adolescence was largely associated with meeting the MetSyn criteria through high adult BMI. To our knowledge, this is the first study that used LTM to produce adolescent BMI trajectories and measure the associations with MetSyn in adulthood. Our subsequent analysis of the offspring cohort found that having a mother whose BMI trajectory was at the highest BMI levels throughout adolescence was associated with significantly greater odds of being at the 95th percentile for BMI as children compared with having a mother whose BMI was classified as normal throughout adolescence. This relationship held in the mediation analysis, suggesting that the association between offspring BMI and parental adolescent BMI trajectory was not mediated by parental adult BMI.

Previous findings have shown that associations between adolescent BMI and MetSyn attenuate after adjusting for BMI in adulthood [9–11]. Our study's findings add to the existing literature, which has suggested that having a BMI trajectory at the highest BMI level in adolescence was associated with having statistically nonsignificant increased odds of being diagnosed with MetSyn in adulthood [4, 8–11, 13, 14]. Our findings imply that adolescence is not a developmental stage when having a high BMI preordains an elevated risk for MetSyn. Rather, only through a sustained high body mass into adulthood does MetSyn become a risk. As a result, we would suggest the adult BMI is truly a mediator between adolescent BMI trajectory and MetSyn.

TABLE 5 NDE, NIE, and TE ORs for the mediation analysis performed for the imputed offspring populations regarding the association between BMI trajectory class and odds of having obesity with respect to parental adult BMI ($N = 645$)

	NDE OR (95% CI)	NIE OR (95% CI)	TE OR (95% CI)
Persistently normal	REF	REF	REF
Weight loss then gain	1.49 (0.69–3.20)	1.00 (1.00–1.00)	1.48 (0.69–3.21)
Persistently high	2.76 (1.41–5.40)	1.01 (0.99–1.01)	2.76 (1.39–5.46)
Weight gain then loss	1.30 (0.49–3.42)	1.00 (1.00–1.00)	1.30 (0.49–3.44)

Note: Adjusted for age, race, maternal BMI at follow-up, parental education, parental income, and smoking status.
Abbreviations: NDE, natural direct effect; NIE, natural indirect effect; OR, odds ratio; REF, reference; TE, total effect.

This study also investigated the effect that maternal adolescent BMI trajectory had on BMI of the biological children of these women. Our findings suggest that children whose biological mother's BMI trajectories were at the highest BMI level throughout adolescence may be at risk of having BMI > 95th percentile during childhood, regardless of their mother's current BMI. These findings are similar to the literature, which has suggested that maternal weight and obesity can have an adverse effect on the health of biological children and which has presented results suggesting that a persistently high adolescent BMI trajectory does influence the odds of obesity in biological children [15–19].

To our knowledge, this is the first study that assessed the association between BMI trajectory of the mother and the intergenerational

effect it may have on offspring BMI using LTM. Our findings are strengthened by the inclusion of height and weight measurements taken during the yearly clinic visits of the historic study to compare against the height and weight measurements taken in the 30-year follow-up study.

This study is not without limitations. As an observational cohort study, our results may be biased by uncontrolled confounders, which make it harder to estimate the true causal effect [41]. Although mediation analysis showed that adult BMI did not mediate the association between parental adolescent BMI trajectory and offspring obesity, that does not mean that this association was not confounded by a variable not captured in the study. Intergenerational effects are complex, and the true cause of the association may not have been captured in this analysis. Nutrition, genetic, and lifestyle factors could affect the relationship [42–45].

There was substantial missing data in our study, especially in relation to maternal metabolic health, maternal WC, and offspring BMI variables. To address missingness in our data sets, we used multiple imputation methods or attempted to recover missing outcomes using medical indicators. However, this approach is less statistically efficient than having a larger sample size, and validity of imputation relies on the assumption that the data were missing at random; therefore, future studies should investigate BMI trajectory outcomes in larger samples. Reduced participation could contribute to the wide CIs seen in the exponentiated ORs from the logistic regression because there were a limited number of participants who fell into the parabolic-shaped BMI trajectories, which may have biased the results. We should also note that the methods of analysis employed in this study are parametric in nature, which is heavily influenced by our causal model. As such, incorrect specification of our statistical models could heavily bias our results. It is important to note that this study population was restricted to women of African American and White racial descent growing up in the Richmond, California, area when classifying BMI trajectory. As a result, this study's findings may not be generalizable to male individuals, individuals who are from other racial/ethnic groups, or individuals raised in other areas of the United States.

CONCLUSION

In summary, we identified BMI trajectories using LTM, categorizing participant BMI throughout adolescence to get a more robust assessment of exposure to obesity during adolescence. The results initially suggest that having the highest BMI levels consistently throughout adolescence increases the odds of meeting the criteria for MetSyn in adulthood. However, this association was found to be mostly mediated by the participants' adult BMI status at follow-up. It is critical to examine the mediating influence of adult BMI because our study suggests that adolescent weight gain and even persistent obesity without developing adult obesity are not strong risk factors for poor adult metabolic health.

Second, the biological children of those same women have increased odds of having obesity as children. The result of this analysis underlines the continued need for nutrition education and weight maintenance programs before and throughout adolescence. Future studies looking to perform longitudinal analysis on the effects of adolescent BMI trajectory on adult MetSyn diseases should consider the possible mediating influence of adult BMI.O

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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