Use of Marginal Structural Models to Examine the Bidirectional Association between Depression and Excess Body Weight

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Abstract

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Background and aims – There is mixed evidence about the bidirectional association between excess body weight (EBW) and depression during adolescence. This study estimated the effects of cumulative depression or excess body weight during early adolescence (age 12-14) on the likelihood of excess body weight or depression during late adolescence (age 17-18). We also examined the effects of depression or excess body weight at a specific time point in adolescence on the likelihood of excess body weight or depression at the subsequent adolescent time point. Effect modification by sex for each association was also examined.

Design: We conducted a prospective cohort study of youth with repeated measurement. The study sample included 521 adolescents from public middle schools in Seattle, Washington, USA. Measured height and weight from five waves were used to determine BMI percentile based on CDC standards. The child-report version of the Mood and Feelings Questionnaire from five

waves was used to assess depressive symptoms. Marginal structural models (MSMs) with stabilized inverse probability weighting (SIPW) that accounted for both time-varying and fixed covariates were used to estimate the strength of associations between excess body weight and depression.

Result: The prevalence of EBW ranged from 23.43% to 31.45%, and the prevalence of elevated depressive symptoms ranged from 13.36% to 23.71% across time points. Finding from MSM analyses indicated that cumulative elevated depressive symptoms during early adolescence had no statistically significant effect on excess body weight during late adolescence (RR=1.08; 95% CI: 0.72, 1.62; p-value=0.70). Similarly, findings from MSM analyses indicated that cumulative EBW during early adolescence had no statistically significant effect on elevated depressive symptoms during late adolescence (RR=1.01; 95% CI: 0.66, 1.53; p-value=0.98). Likewise, MSM analyses indicated that there was no statistically significant lagged effect of elevated depressive symptoms on EBW at the subsequent time point during adolescence (RR=1.17; 95% CI: 0.88, 1.55; p-value=0.27). There was also no statistically significant lagged effect of EBW on elevated depressive symptoms at the subsequent time point during adolescence (RR=1.13; 0.85, 1.51; P-value=0.39). Sex did not modify any of these observed associations (interaction p-value > 0.05).

Conclusion: We found no statistically significant bidirectional cumulative or lagged association between overweight and depression in adolescence, and sex did not modify the associations.

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Chapter 1: INTRODUCTION

Adolescence is a period during which significant advances in physical, psychological, and social development are underway (1). Depression and excess body weight (EBW) are public health concerns threatening the health of a significant proportion of U.S. adolescents (2–7). Adolescent depression is prevalent (7,8,9) with as many as 20% of today's teens affected (8). Untreated depressive disorders are associated with addiction, self-injury, reckless or risky behavior, poor school performance, and socialization and physical health problems (9,10). About 20% of teenagers seriously contemplate suicide, and about 8% of them make suicide attempts. Risk of suicidal ideation and attempt are higher among teenagers with depressive disorders (11–13).

Similarly, EBW is an independent risk factor of health-related morbidity and mortality throughout the life course, including type 2 diabetes mellitus, cardiovascular diseases (e.g., high blood pressure and stroke), dyslipidemia, and cancer, among others (4,5,14,15). Among youth, overweight and obesity (5), also known as excess body weight (EBW) collectively, are defined as age and sex-specific percentiles of body mass index (BMI) at or above the 85th percentile and 95th percentile, respectively (5). In 2017, EBW was present among 30.4% of grade 9-12 youth in the USA (16).

Depression can contribute to the development of excess body weight through mechanisms that include elevated levels of the stress hormone cortisol, increased appetite, physical inactivity, withdrawal from usual recreational and social activities, poor eating habits, sleep disorder, and medication use (17–19). Conversely, in addition to poor health, people with EBW often experience adverse psychosocial consequences including functional impairment (limitations in carrying out daily activities) (20), stigmatization, poor body image, low self-esteem, and unsuccessful frequent dieting (16,20–22) - all of which are directly or indirectly associated with depression (5,22–24).

This suggests that a bi-directional association between depression and EBW among adolescents is plausible.

However, available evidence on this bidirectional association between depression and excess body weight is inconsistent. Investigators, including members of our team, have reported positive (depression causes overweight) (25), sex-specific (depression causes overweight only in females) (24,31), null (no association between depression and overweight) (27), or negative (BMI is inversely related to early adulthood depressive symptoms) (26) statistical associations. A recent meta-analysis of 13 longitudinal studies reported that depressed adolescents had a 1.7 (95% CI: 1.40, 2.07) times increased risk of being obese, while obese adolescents had 1.4 (95% CI: 1.16, 1.70) times increased risk of being depressed (2). This meta-analysis included several articles which mainly studied the effect of adolescent depression or psychological distress on overweight in early adulthood and vice versa (28–32).

Most prior longitudinal studies used two time-point assessments to examine the association between EBW and depression (28,29,31,32). However, taking multiple repeated measurements of exposures has additional advantages – it would enable us to examine the effect of the sum of depression or EBW in multiple assessment periods during early adolescence, i.e., cumulative exposure, on EBW or depression in late adolescence. However, when employing repeated measurements, controlling for confounding becomes more challenging.

Few prior studies have used repeated measures (30,33), and all of which applied conventional regression methods that did not account for time-varying covariates. While estimating the bidirectional causal effect of depression and EBW using repeated measures over time, both EBW and depression during early adolescence can be treated as time-varying exposures. Depression status at one wave may influence the odds of depression and body weight in the next wave, and

body weight at one wave may influence the odds of depression and body weight in the next wave. Confounders like substance use and puberty status are time-varying, too. Both depression and body weight could also affect these time-varying confounders, which complicate the estimates of the association between depression and EBW. In these cases, using conventional regression methods that statistically control for the confounding is inappropriate because, over time, the confounder plays both the role of intermediate and confounder of the exposure effect on outcome (34). Thus, without appropriate adjustment, the results can be biased.

In the presence of time-varying exposures, statistical approaches such as marginal structural models (MSM) (35–37) are more appropriate than the conventional regression methods. These models can reduce bias under situations when i) there exists a time-varying confounder that is a predictor of, or a risk factor for, the outcome of interest as well as the exposure, and (ii) past exposure history predicts subsequent level of the confounders (35,36,38,39). MSMs use inverse probability weights (IPWs), where weights are the inverse of the predicted probability of one's observed exposure according to time-varying and time-fixed covariates. The IPWs are used to re-weight the study sample. In the weighted sample, higher weight is assigned to underrepresented subjects, while lower weight is given to those overrepresented for their observed level of exposure. This creates a "pseudo-population," in which, similar to that of randomization in a randomized trial, the exposure is no longer associated with measured confounders (36,37,40). Using the weighted sample, one can estimate the unconfounded average causal effect of the exposure without the inclusion of time-varying confounders in the final statistical model (37,41).

Hence, we attempted to fill this existing literature gap by using MSM to investigate the potential bidirectional causal association between elevated depressive symptoms and EBW among adolescents at multiple time points over the course of middle school and high school. To our

knowledge, this is the first study to examine potential reciprocal, time-varying, and cumulative effects between depression and EBW during adolescence, using repeated measurements and MSM.

There is evidence that the association between depression and EBW may differ by sex (24,31). Studies have shown that depressed females have a significantly higher BMI than nondepressed females (24,31, 42), while depressed males have a significantly lower BMI than nondepressed males (42). Therefore, examining the role of gender in the relationship between depression and EBW is worth considering.

The study had four aims.

Aim 1: Examine the effects of cumulative elevated depressive symptoms during early adolescence (age 12-14) on the likelihood of excess body weight during late adolescence (age 18)

Aim 2: Examine the effects of cumulative EBW during early adolescence (age 12-14) on the likelihood of elevated depressive symptoms in late adolescence

Aim 3: Examine the lagged effect of elevated depressive symptoms at a specific timepoint in adolescence on the likelihood of EBW at the subsequent adolescent timepoint.

Aim 4: Examine the lagged effect of EBW at a specific timepoint in adolescence on the likelihood of elevated depressive symptoms at the subsequent adolescent timepoint.

Furthermore, we investigated whether sex modified the associations.

Chapter 2: METHODS

2.1. Study setting and study population

We used data from the Developmental Pathways Project (DPP) (43), a community based prospective cohort study of adolescents aimed to examine why some adolescents have good emotional health, while others develop depression and disruptive behavior problems during their middle school and high school years. The study methods have been described in previous articles (41,42). Briefly, enrollment began in 2001 and continued through 2004. Students were recruited from four public middle schools which were selected to represent the ethnic/racial (60% non-white) and socioeconomic (33% living below the federal poverty line) diversity of students enrolled in the Seattle Public School District, Seattle, WA. A total of 521 adolescents and their families participated in this study. About 52.4% were males, and 49% were European Americans, 28.5% African Americans, 18.6% Asian Americans, and 4.4% Native Americans. About 10% were Hispanics. One third were living below the federal poverty line.

Two-stage sampling was conducted. In the first stage, universal screening for depression and conduct problems was carried out in 6th-grade classrooms in the middle schools. In the second stage sampling for the longitudinal study students with elevated depressive and conduct problems (>0.5 sd above the sample mean) were oversampled (43). Study sample weights were developed to account for disproportionate sampling during enrollment based on initial mental health status and sampling fractions utilized to represent the school district student population (sex, race, ethnicity, and school program). Seven assessments were conducted between sixth and twelfth grade (from 12 years to 18 years of age). Baseline assessment was conducted at 6th grade, and follow-up assessments were conducted at 6-, 12-, 18-, 24-, 36-, and 72-months after baseline.

In the current study, we used data from baseline and 6-, 18-, 24-, and 72-months follow-up assessments. There was a 79-85% completion rate during early adolescent follow-ups; 90.4% of the participants completed the late adolescent follow-up interview.

The University of Washington Institutional Review Board approved DPP study protocols, and consent was obtained from both students and parents/guardians.

2.2. Measurement of depression and excess body weight

Depression: The child-report version of the Mood and Feelings Questionnaire (MFQ-C) (44,45) was used to measure adolescent depression at all assessments. The MFQ-C (46,47) is a 33-item measure which queries youth about how they have been feeling or acting within the past two weeks. Response options were 0 ("not true"), 1 ("sometimes"), or 2 ("true"). Studies suggest that MFQ-C is a valid measure of depression among children and adolescents (44,45).

The total MFQ score ranged between 0 and 66, and the distribution was positively skewed to the right. Constructing inverse probability weights for non-normally distributed continuous exposures can lead to biased estimation in MSM (48). We then categorized MFQ-C scores into two groups – less than 15 (0) and 15 and above (1) because this cut off point reflected a 0.5 standard deviation elevation above the sample mean in the first stage of DPP sampling and had been used to select adolescents with elevated depression screening scores for study participation (42,43).

Cumulative elevated depressive symptoms score was defined as the count of elevated depressive symptoms scores in 7^{th} and 8^{th} grade (in 6-, 18-, and 24-month assessments). We excluded the baseline elevated depressive symptom from cumulative depressive symptoms count because we had no prior measurement of time-varying confounders. Hence, cumulative elevated depressive

symptoms has four potential values: 0 (never had elevated depression symptoms in three assessment periods), 1 (had elevated depression symptoms in only one of the three assessment periods), 2 (had elevated depression symptoms in two of the three assessment periods), and 3 (had elevated depression symptoms in all three assessment periods).

Excess Body Weight (EBW): EBW was defined using CDC standard age and sex-specific percentiles of BMI – calculated from weight and height (5): Scale measured weight and height were measured in the baseline, 6-, 18-, 24-, and 72-month follow-up interviews. As mentioned by Rhew et al. (42), a direct measurements of weight and height of respondents were obtained at the end of in-home interviews using a standardized procedure. Shoes were removed, and any outer layers of clothing and heavy items were removed from pockets before weight measurements were taken. Weight was then measured using an electronic scale of uniform brand and model and recorded by the interviewer to the nearest half pound. For height measurements, participants were asked to stand on a hard floor surface with their backs to a bare wall against which a tape measure had been extended; and height was recorded. All measured values were rounded to the nearest inch or pound. Values were first converted to the metric system, and then BMI was computed dividing weight in kilograms by height in meters squared (kg/m^2) (49). For this study, BMI for children and teens was expressed as a percentile. During growth and development, weight and height change, and thus, interpretation of a child's BMI must be relative to other children of the same sex and age (49,50). CDC standard BMI percentiles are based on U.S. children who participated in national surveys conducted from 1963-65 to 1988-94 (49,50). According to CDC (5), for children and teens of the same age and sex, overweight was defined as a BMI at or above the 85th percentile and below the 95th percentile, while obesity was defined as BMI at or above the 95th percentile (5). BMI percentile at or above the 5th

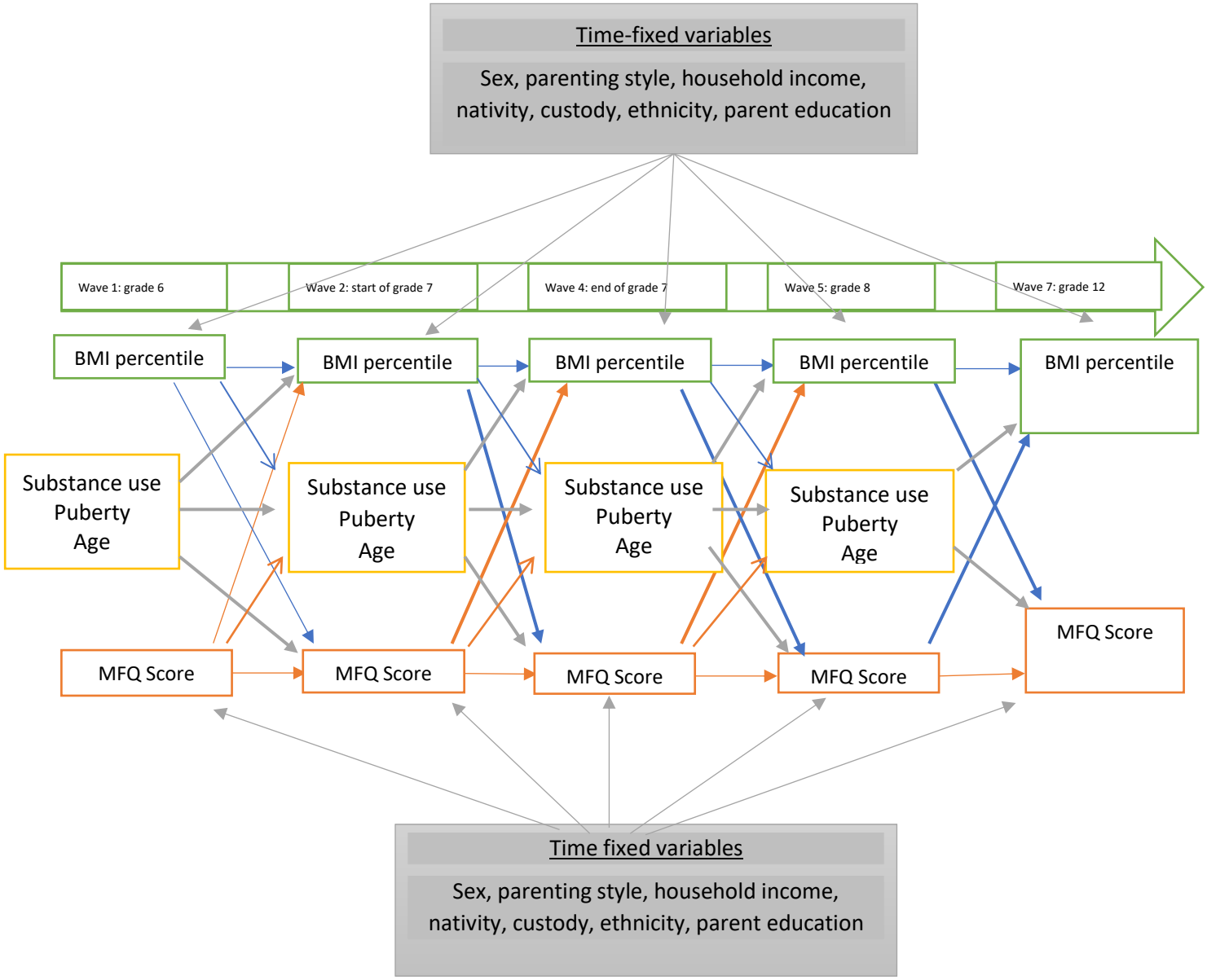
percentile and below the 85th percentile was normal, and BMI percentile below 5th percentile was underweight. For analyses involving EBW, we dichotomized BMI percentile into no-EBW (<85%) and excess body weight (≥ 85).

Cumulative EBW was defined as the sum of times the youth was at EBW during 7th and 8th grade (in 6-, 18-, and 24-month assessments). It has four potential categories 0 (never had EBW in three of the waves), 1 (EBW in only one of the three waves), 2 (EBW in two of the three waves), and 3 (EBW in all three of the waves).

2.3. Covariates

Variables that had been shown in the literature to be associated with both depression and overweight were considered for inclusion into models for calculating the inverse probability weights to control for confounding. The following variables were treated as time-fixed: custody at baseline (51,52) (both biological parents, one biological parent or others including relatives or unrelated adoptees), nativity of parents (53,54) (immigrants vs. non-immigrants), educational status of parents (55) (high school diploma or less, some college, three years college or above), race/ethnicity (56), (non-Hispanic Black, Hispanic, Non-Hispanic Asian, Non-Hispanic White), sex (57) (male and female), baseline household income (55), and parenting style collected 12 months after baseline (58). Parenting style was based on adolescent-responses to a 24-item parent bonding instrument (PBI) for each parent (59). The original questionnaire was a scale of three responses, “like my mom/dad, somewhat like my mom/dad, and not like my mom/dad.” We summed available questionnaire items for both parents and took the average score to categorize parenting style into tertiles where high scores indicate higher parent-adolescent bonding.

We also used the following variables as time-varying covariates: Current smoking or use of any other drug (60–63) (yes/no), pubertal stages (Tanner $\leq$ 3, and $\geq$4) (64,65), age, elevated depressive symptoms, and EBW. Figure 1 shows Directed Acyclic Graphs (DAGs) on the associations of the covariates.



2.3. Statistical Analysis

To describe the distribution of continuous variables in the study population, we used mean and standard deviation when the distribution was normal, and median and interquartile (IQR) when the distribution was skewed. We used proportions to describe the distribution of categorical variables. Study sample weights were applied in each analysis. We also used graphs, diagrams, and tables to present our results.

2.3.1. Cumulative effects

For Aim 1, the outcome of interest was EBW (yes or no) in late adolescence (12^{th} grade), and the exposure was the cumulative count of elevated depressive symptoms (0 to 3) across the 6^{th} to 8^{th}-grade period.

For Aim 2, the outcome of interest was elevated depressive symptoms (<15 or ≥ 15 MFQ score) in late adolescence (12^{th} grade), and the exposure was the cumulative count of EBW (0 to 3) across the 6^{th} to 8^{th}-grade period.

Our primary analytic approach for examining Aims 1 and 2 was marginal structural modeling, which involved fitting Poisson regression models that applied Stabilized Inverse Probability Weights (SIPW) (37). We could not estimate relative risk using logistic regression, and the odds ratio was not a good option for common (not-rare) outcomes (66). Thus, we used Poisson regression with robust standard errors, which gives a better estimate of relative risk and its confidence interval (67). For comparison, we also ran a "conventional" regression model that only included time-fixed covariates and study sample weights (not the full SIPWs).

2.3.2. Lagged association

MSM was our primary analytic approach to evaluate the lagged association between elevated depressive symptoms and EBW, Aims 3 & 4. As with Aims 1 & 2, we also applied SIPWs to a Poisson regression form of a Generalized Estimating Equations (GEE) model using an independent correlation structure to account for clustering of observations within individuals.

For Aim 3, a model was fitted to examine the causal effect of elevated depressive symptoms at 6-, 18-, and 24-month assessment on EBW at a subsequent assessment period 18-, 24-, and 72-month, respectively, over the course of adolescence.

For Aim 4, a model was fitted to examine the causal effect of EBW at 6-, 18-, and 24-month assessment on elevated depressive symptoms at a subsequent assessment period 18-, 24-, and 72-month, respectively, over the course of adolescence.

Rather than including time-fixed and timevarying potential confounders into the model as conventional regression models do, MSM estimates the effect of an exposure weighted for IPW, in which the exposure is independent of the measured confounders (35,36,38,39).

There are specific steps to fit a MSM.

1. In the first step, we used a logistic regression model to estimate the predicted probability or propensity score of one's observed exposure at each visit. We regressed the exposure of interest at each timepoint on time-varying and time-fixed potential confounders. Time-varying confounders included elevated depressive symptoms, EBW, age, puberty, and substance use measured at the assessment prior to the exposure at a given visit. We then determined the predicted probability or propensity score for each exposure category. For example, when the exposure is elevated depression symptoms, the predicted probability

for the exposed group is the predicted probability of having elevated depression symptoms, ps1, while the predicted probability for the non-exposed group is 1-ps1.

2. Secondly, we calculated the inverse of the predicted probability (i.e., the IPW) for each person's observed exposure status at the 6-month, 18- month, and 24-month study visit. The IPW is calculated by assigning those exposed a group weight of 1/ps1. For those who are not exposed (e.g., non-elevated depression symptoms), their IPW for their exposure status would be 1/(1 – ps1) (68).
3. To improve the precision of the weights, we truncated the IPWs such that extreme values at the tail ends of the distribution were recoded to the value at the 1st and 99th percentile (37,41).
4. We then stabilized the IPW. The IPW, as described above, underestimates the variance of the estimated main effects, and the type I error rate is higher due to the inflated sample size (37,69). On the other hand, the IPWs can be somewhat extreme, and the robust variance estimator using IPW often slightly overestimates the variance of the main effects (37,69). Thus, it is common to stabilize the IPW by adding a numerator to the IPW that is a probability of one's exposure according to time-fixed covariates only. This preserves the sample size of the original data, produces an appropriate estimation of the variance of the main effect, and maintains an appropriate type I error rate (37,69). To stabilize the IPW, we computed the predicted probabilities of exposure at each visit according to only the time fixed covariates as a numerator for the weights. The stabilized weight at each visit was calculated then as the predicted probability according to only time-fixed covariates divided by the IPW calculated above, which was the predicted probability according to both time-fixed and time-varying covariates.

MSM assumes exchangeability, positivity, consistency, and no misspecification of the model (36,37,40) used to estimate the weights.

1. Exchangeability implies the well-known assumption of no unmeasured confounding and is untestable (35–37,69). We did an exhaustive literature search before we commenced the study and included as many potential confounders as possible. Thus, for this study, we believed the time-fixed and -varying confounders considered when creating our weights were sufficient to achieve exchangeability.
2. Positivity is a condition that requires a non-zero positive likelihood of being exposed and unexposed at every level of the confounders in order to estimate the average causal effect in each subset of the population defined by the confounders. If there are no exposed observations at one or more levels of the confounders, there will be a structural zero probability of receiving the exposure, and the positivity assumption is violated. We dropped Native Americans because they were only five, and structural zero is observed for each of the two exposure categories. To make sure that all levels of the confounder were represented at each level of the cumulative depressive symptoms and to avoid structural zeros, covariates such as educational status, ethnicity, custody, and income were regrouped and merged. We also assessed for the region of common support by checking the overlap of the distribution of the predicted probability of exposures by exposure status (68).
3. The third assumption of the potential outcome model is consistency, which will hold when there is a well-defined intervention, i.e., amenability for a specific intervention (36,37,40). People reach EBW for different reasons, for example, diet, exercise, and others. Moreover, for counterfactual comparison, we needed to compare the risks if all

adolescents had had EBW and No EBW during the adolescence period. But the risks if all adolescents had they had EBW versus no EBW is not straightforward. What does it mean if adolescents had no EBW or had EBW? How are we going to make someone unexposed or exposed? Besides, we do not know the specific cause of overweight; we do not have one particular intervention that can be applied to all adolescents in the population to decrease overweight (70). Even though diet and physical activities are the commonly recommended interventions to decrease weight, we are not yet sure whether other interventions would be more effective. The same holds for depression too. Therefore, elevated depression and excess body weight might not be ideal outcomes with "a well-defined intervention" for assuming the potential outcome model, but we were aware of this limitation from the outset of the study.

4. Lastly, the correct specification of models is required for both the weights and final models (36,37,40). Our model fulfilled the necessary condition for correct model specification (36,37,40), i.e., the mean of the stable inverse probability weight at each wave was around one.

In order to assess the effect of early adolescence cumulative elevated depressive symptoms on late adolescent overweight, and the effect of early adolescence cumulative EBW on late adolescence elevated depressive symptoms, the product of 6-, 18-, and 24-month assessment SIPWs were used to create a single SIPW reflecting the inverse probability of one's observed depression/overweight history during adolescence (37,41). We then multiplied the single SIPW by the study sampling weight to create the final SIPW, so that applying this weight enabled us to generalize findings to the greater Seattle public school district population. The final SIPWs were

then applied to Poisson regression models with robust standard errors for Aims 1 and 2. Time-fixed covariates were also added to the weighted model to further increase precision.

To assess differences in the effects of cumulative elevated depressive symptoms, additional models included an interaction between cumulative depressive symptoms and sex, and similarly, an additional interaction model between EBW and sex was included to assess sex differences in the effects of EBW on depressive symptoms.

To understand the influence of the time-varying covariates, we ran models that were only weighted according to the sampling weights rather than the full IPWs and adjusted only for time-fixed covariates

A substantial portion of the data was missing, and complete case analysis would have resulted in a considerable loss in sample size and power. Multiple imputations by chained equations (MICE) were used which ran a series of regression models for each missing variable conditional upon other specified variables. In addition to covariates of the current study (custody, income, education, sex, and race/ethnicity), auxiliary variables such as family size and depression and conduct status at enrollment were also included. We imputed the data 20 times, and the final MSMs were fitted in each dataset. Pooled parameter estimates and their standard errors were calculated according to Rubin's rules to account for the between- and within-imputation variance (68,69). We employed one single imputation model to obtain imputed values for exposures and outcomes. In the imputation model, we specified the appropriate distributions for each of the variables in the model (e.g., dichotomous, continuous, count). For the imputations to produce plausible values, we restricted BMI percentile potential values to 0-100 and MFQ score potentival values to 0-66. In the presence of missing data, the multiple imputation approach

should yield unbiased estimates assuming data are missing at random (MAR). MAR assumes that missingness may be related to fully observed variables, but not to unmeasured variables (72). The proportion of measured height missed was 16.2 % in wave 1, 26.9% in wave 2, 30.7% in wave 4, 28.6% in wave 5, and 9.98% in wave 7. Similarly, the proportion of measured weight missed was 1.7% in wave 1, 28.0% in wave 2, 30.9% in wave 4, 29.37% in wave 5, and 10.36% in wave 7. The proportion of MFQ missed was 7.29% in wave 1, 9.02% in wave 2, 15.74% in wave 4 a, 14.0% in wave 5, and 9.4% in wave 7.

A p-value of <.05 and 95% confidence interval that did not overlap 1 were used to determine statistical significance. R version 3.5.1 and STATA version 14 statistical software were used for analyses.

Chapter 3: RESULTS

4.1. Description of excess body weight and elevated depressive symptoms

The median BMI percentile ranged from 68.00 to 72.27 across the study assessments. The prevalence of EBW ranged from 23.43% to 31.45%. Regarding the cumulative EBW during early adolescence, 59.30% never had EBW, 9.00% had EBW only in one of the assessment periods, 11.83% had EBW in two of the assessment periods, and 19.80% of adolescents had EBW at three assessment periods [Table 1].

The median BMI percentile was higher for girls than boy adolescents in all the assessment periods but the first (Figure 2). The median BMI in all the study assessments was higher for adolescents whose MFQ was $\geq$15 [Figure 3].

The median MFQ score ranged from 8.51 to 10.51 out of 66. The prevalence of elevated depressive symptoms ranged from 13.36% to 23.71% across follow-up periods [Table 1]. Regarding the cumulative elevated depressive symptoms during 6-, 18-, and 24-month of assessment periods, 66.43% had never had elevated depressive symptoms, 20.92% had elevated depressive symptoms in one of the assessment periods, 7.50% had elevated depressive symptoms in two of the assessment periods, and 5.18% had elevated depressive symptoms in three of the assessment periods.

The median MFQ score was higher among females except at wave 1, in which male adolescents had higher median MFQ score than their female counterparts [Figure 4]. The median MFQ scores were higher for males, both EBW and No-EBW weight, at wave five and seven [Figure 5].

About 28.94% of adolescents who had elevated depressive symptoms during all three study assessment periods had EBW during late adolescence. And, 25.86% of adolescents who had EBW in three of the assessment periods during early adolescence had elevated depressive symptoms in late adolescence [Figure 6].

4.2. Stable inverse probability weight characteristics and positivity

The mean (sd) of the SIPW computed to examine the effect of elevated depressive symptoms on EBW was 1.02 (0.48) in the 6-month assessment, 0.99 (0.28) in the 18-month assessment, and 0.99 (0.27) in the 24-month assessment.

The mean (sd) of the SIPW computed to examine the effect of EBW on elevated depressive symptoms was 1.01 (0.180) in the 6-month assessment, 1.00 (0.12) in the 18-month assessment, and 1.00 (0.10) in the 24-month assessment.

All levels of the confounders were represented at each level of the cumulative depressive symptoms [Table 2]. There was also an overlap in the distribution of the predicted probability of elevated depressive symptoms, the region of common support, at 6-, 18-, and 24-month assessment periods by elevated depressive symptom status [Figure 7].

Likewise, all levels of the confounders were represented at each level of the cumulative EBW [Table 3]. There was also an overlap of the distribution of the predicted probability of EBW, the region of common support, at 6-, 18-, and 24-month assessment periods by EBW status [Figure 8].

4.3. Cumulative effects

Results for Aim 1: We fitted multivariable Poisson regression without the SIPW and then the MSM with SIPW. A multivariable Poisson regression adjusted for time-fixed covariates indicated cumulative elevated depressive symptoms during early adolescence (12 to 14 years of age) had no statistically significant effect on EBW during late adolescence (17-18 years of age) (RR=1.15; 95% CI: 0.97, 1.37; p-value=0.11). MSM analyses also revealed a similar finding but with a relatively lower estimate and larger standard error (wider confidence interval) (RR=1.08; 95% CI: 0.72, 1.62; p-value=0.70) [Table 4]. Also, this association was not modified by sex (interaction p-value = 0.58).

Results for Aim 2: A multivariable Poisson regression adjusted for time-fixed covariates indicated that there was no statistically significant effect of cumulative EBW during early adolescence (12 to 14 years of age) on elevated depressive symptoms during late adolescence (18 years of age) (RR=1.04; 95% CI: 0.87, 1.22, p-value=0.69). MSM analyses also revealed a similar finding but had a larger standard error (wider confidence interval; RR=1.01; 95% CI: 0.66 1.53; p-value=0.98) [Table 5]. Also, there was no effect modification of this association by sex (interaction p-value = 0.24).

4.4. Lagged effects

Evaluating the lagged association, we fitted multivariable Poisson regression and MSM models. The Poisson regression was weighted for sampling weight but not for SIPW, fitted in GEE, and adjusted for time-fixed covariates. The MSMs were weighted for both the study sampling weight and SIPW.

Results for Aim 3: The multivariable Poisson regression revealed a statistically significant lagged effect of elevated depressive symptoms on EBW at the subsequent time point during adolescence. For elevated depressive symptoms during a specific 6-, 18-, 24-month assessment there was a 33.3% (RR=1.33; 95% CI: 1.07, 1.66; p-value = 0.01) increased likelihood of EBW during 18-, 24-, and 72-month follow-up periods, respectively. This positive association, however, was not revealed by MSM analyses. The MSM finding indicated that there was no statistically significant effect of elevated depressive symptoms on EBW at the subsequent time point during adolescence (RR=1.17; 95% CI: 0.88, 1.55; p-value=0.27) [Table 4], and this effect was not modified by sex, p-value=0.45.

Results for Aim 4: Adjusted for time-fixed covariates, the multivariable Poisson regression indicated that EBW during 6-, 18-, and 24-month assessment had no statistically significant effect on elevated depressive symptoms at 18-, 24-, and 72-month follow-up periods, respectively (RR=1.23; 95% CI: 0.92, 1.64; p-value=0.17). Similarly, MSM analyses showed no statistically significant lagged effect of EBW on elevated depressive symptoms at the subsequent time point during adolescence (RR=1.13; 0.85, 1.51; P-value=0.39) [Table 5]. There was no effect modification of this association by sex, p-value=0.53.

Chapter 4: DISCUSSION

Using marginal structural models, our cohort study revealed that there is no statistically significant prospective association between elevated depressive symptoms and EBW in either direction. The null finding held when we examined the effects of cumulative exposure during early adolescence on outcome in late adolescence or conducted a lagged analysis over multiple intervals.Multivariable Poisson regression analyses yielded a null result for the lagged effect of EBW on later elevated depression symptoms but yielded a statistically significant lagged effect of elevated depressive symptoms on EBW. Elevated depression symptoms at one time point associated with a 33.3% increase in the risk of EBW at the prior time point. The literature shows mixed evidence from longitudinal studies (1,20), about the bidirectional association between depression and EBW. Previous studies found no statistically significant association (27), inverse association (26), a positive association (25), and sex-specific positive association (74). Nonetheless, there are two recent articles, one systematic review (73) and one meta-analysis (2), that investigated and asserted this bidirectional association of depression and obesity. The meta-analysis reported that depressed adolescents had 1.7 (RR 1.70, 95% CI: 1.40, 2.07) times increased risk of being obese, while obese adolescents had 1.40 (RR 1.40, 95% CI: 1.16, 1.70) times increased risk of being depressed (2). The studies included in the review and meta-analysis were different from this present study in two primary ways: i) they included articles focused on broader developmental periods than our study, and ii) there were differences in how depression and overweight were ascertained. The systematic review compiled longitudinal and cross-sectional studies conducted on children and adolescents, and thus, it is difficult to conclude if the finding holds only to the adolescent population (73). The meta-analyses included articles which mainly studied the effect of adolescence depression or psychological distress and overweight on early

adulthood overweight and depression, respectively (28–32). This included a range of ages beyond the adolescence years, which could contribute to why their conclusions differed from our study results. Also, depression was ascertained differently. Some were based on depressive symptoms (5/13 articles) or others clinical diagnosis (8/13 articles) (2). In regards to body mass, some articles calculated BMI using self-report (6/13), and others measured (7/8) height and weight (2). Multiple methodological differences, including the developmental period under study, whether the study design was cross-sectional or cohort, whether the sample was from community or clinical settings, the sample size, the type of statistical analyses conducted, the ways exposure and outcomes were measured (self-report/measured, symptoms/diagnoses) and operationalized (continuous, binary, ordinal), whether the study focused on two-time points or repeated measurements, and the covariates taken into account, could explain why our results differed from those of the systematic review and the meta-analysis.

A prospective cohort study of 9347 adolescents in grade 7 through grade 12 who completed in-home interviews for the National Longitudinal Study of Adolescents (NLSA) in the US found that depressed adolescents were at increased risk (odds ratio: 2.05; 95% CI:1.18,3.56) for the development and persistence of obesity during adolescence (75). Even though this study focuses on the same developmental period as our study does, the two studies have other substantial methodologic differences. First, the NLSA used self-reported height and weight, and evidence showed that an association between depression and EBW depends on method of measurement (42). Members of our team have reported a statistically significant association between depression and overweight using self-reported height and weight but found a null association using measured height and weight (42). This indicates that differential misclassification of self-reported height and weight by depression status could be an explanation for the observed association, which is not an

issue in our study because we used measured height and weight. Second, the NLSA outcome of interest was obesity, ≥95 BMI percentile while ours is EBW, ≥ 85 BMI percentile. Third, they used two-point assessment periods and could not use an analytical approach that would account for time-varying covariates. Using a similar analytic approach (without considering time-varying covariates), our multivariable Poisson regression adjusted for time-fixed covariates indicated that adolescents who had elevated depressive symptoms in a specific time point in adolescence had a 33.3% (RR=1.33; 95% CI: 1.07, 1.66) increased likelihood of EBW at the subsequent time point during adolescence. However, after we weighted our exposure for EBW, elevated depressive symptoms, puberty, and substance use measured at the assessment period prior to exposure, the estimate decreased, and the inference changed – we found no significant association.

There are plausible explanations of why the null association between depression and EBW could be the true inference. First, the nature of adolescence could be one factor; adolescents gain weight and increase appetite for non-psychological related factors (76) such as physiological (hormonal changes during puberty favors gaining weight) and behavioral (physical activity) processes while also promoting weight loss and decreased appetite (58,66). Pubertal changes in pituitary growth hormone, the gonadal hormones, the stress response, and leptin may also drive physical growth and weight gain, especially body fat gain in females and muscle mass gain in males (76–79).

Secondly, this absence of association between depression and excess body weight could be because of the varying effect of depression on different individuals. There is marked heterogeneity in how depression affects appetite; some gain weight while others lose weight. Evidence showed that about 48% of adult depressed patients exhibit depression-related decreases in appetite, while about 35% exhibit depression-related increases in appetite (80). The body weight-increasing effect

of depression on individuals with increased appetite could be nullified by its body weight-decreasing effect among individuals who had decreased appetite.

Our study had several advantages, including that it was a prospective cohort study with repeated measurements that could capture the episodic nature of depression during the adolescent period. Depression was measured using a questionnaire that has been well-validated in adolescent samples, and body weight and height were measured using a standard protocol. We were able to examine the effect of early adolescent cumulative and lagged depression on excess body weight, and vice versa. We also used MSM that improves causal inference and minimizes the collider bias that could be introduced by the conventional regression method (81,82). MSM allowed us to control for a number of time-varying and time fixed covariates. Time-varying covariates included previous levels of depression, bodyweight, puberty, age, and substance use. Even though the inference was the same, assessing the effect of elevated depressive symptoms on EBW, the non-weighted models had relatively higher point estimates than the weighted estimates from MSM. Without adjusting for the time-varying covariates, in the conventional, non-weighted model, it was found that the elevated depressive symptoms had a significant lagged effect on EBW on the subsequent wave of assessment, while the MSM model revealed no association. This showed that findings without considering the time-varying covariates could be misleading. However, the MSM estimates had wider confidence intervals than the multivariable regressions.

This study had limitations. Because of the limited statistical power due to small sample size and non-clinical sample, we could not use clinically meaningful cutoff points for MFQ score, and this could have contributed to the null association we found between elevated depressive symptoms and EBW in this study.

The study assessment periods had inconsistent time intervals, which could have an impact on our study for the lagged analyses. The study was conducted among public school students and may not be generalizable to private school attenders. This study was also conducted in a student population sample, and the findings might not be generalizable to patients in health facilities.

Chapter 5: CONCLUSION

We found no bidirectional cumulative or lagged associations between depression and excess body weight. The null findings did not differ by sex. Future studies should use larger samples that would include more adolescents with clinical levels of depressive symptoms. They should also use repeated measurements and apply MSMs to account for the time-varying nature of depression and EBW. Future studies should investigate whether there is an identifiable subgroup of depressed adolescents at risk for overweight or whether particular depressive symptoms are associated with overweight.

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Tables and figures

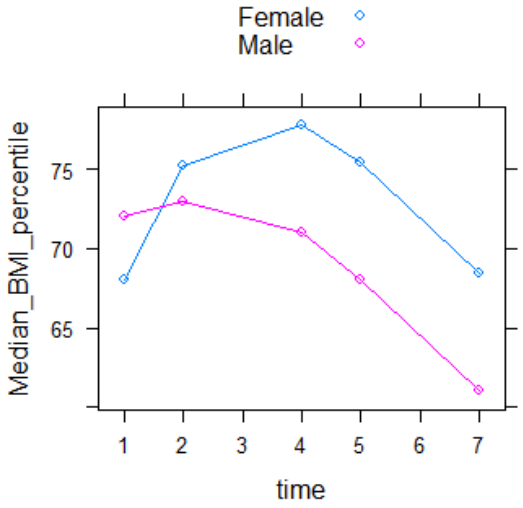

Figure 2: Median BMI percentile during the five study assessment periods (baseline, 6-,18-, 24-, and 72-month) by sex

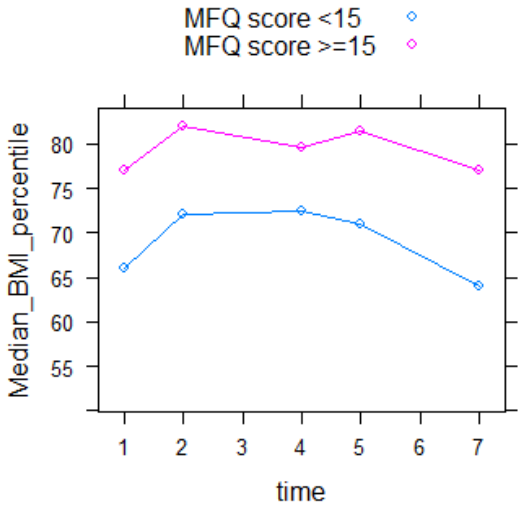

Figure 3: Median BMI percentile during the five study assessment periods (baseline, 6-,18-, 24-, and 72-month) by depression (MFQ>=15)

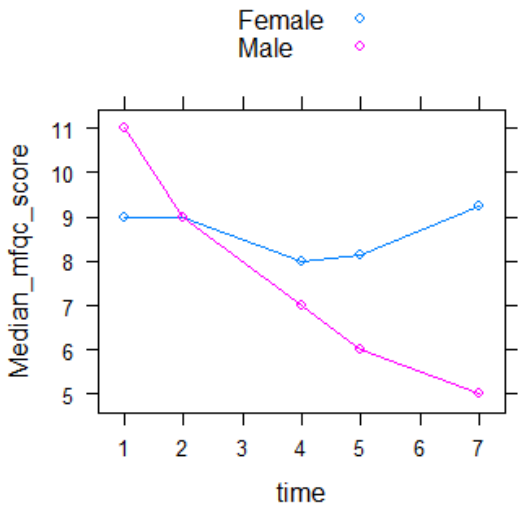

Figure 4: Median MFQ-C score during the five study assessments (baseline, 6-,18-, 24-, and 72-month) by sex

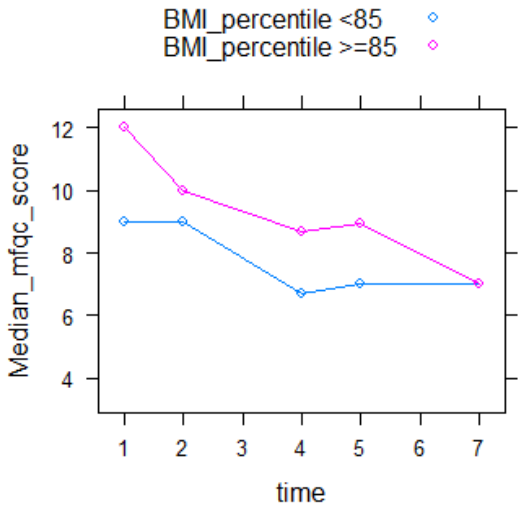

Figure 5: Median MFQ score during the five study assessment periods (baseline, 6-,18-, 24-, and 72-month) by excess body weigh at each time-point.

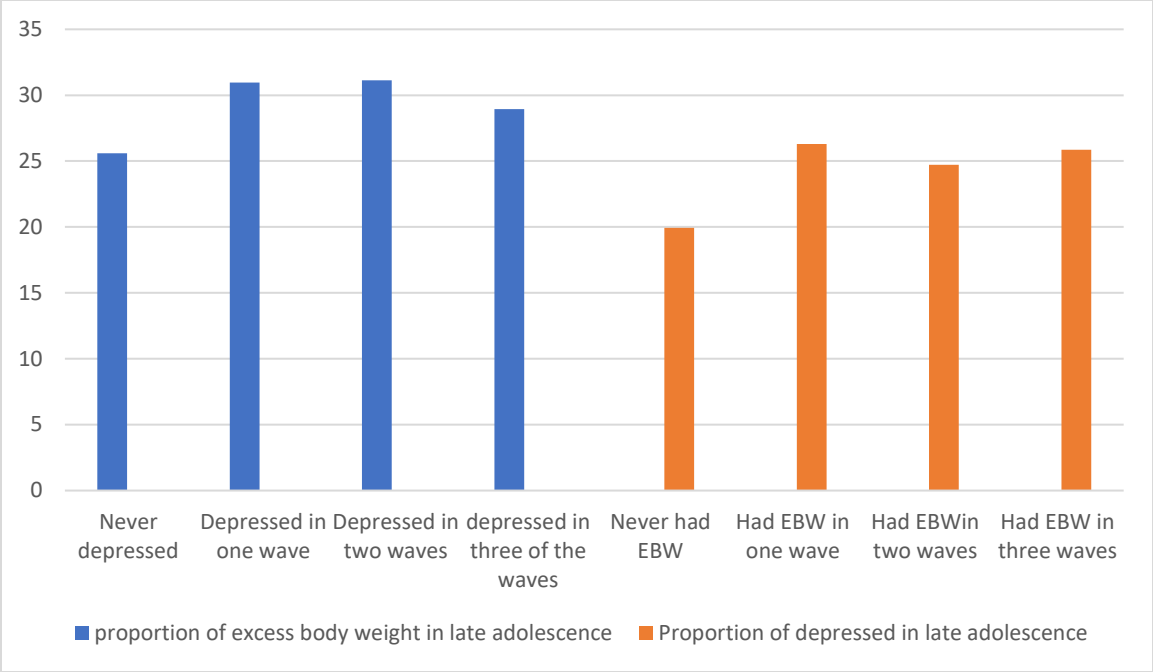

Figure 6: Proportion of EBW in late adolescence by cumulative elevated depressive symptoms score and the proportion of elevated depressive symptoms score in late adolescence by cumulative EBW

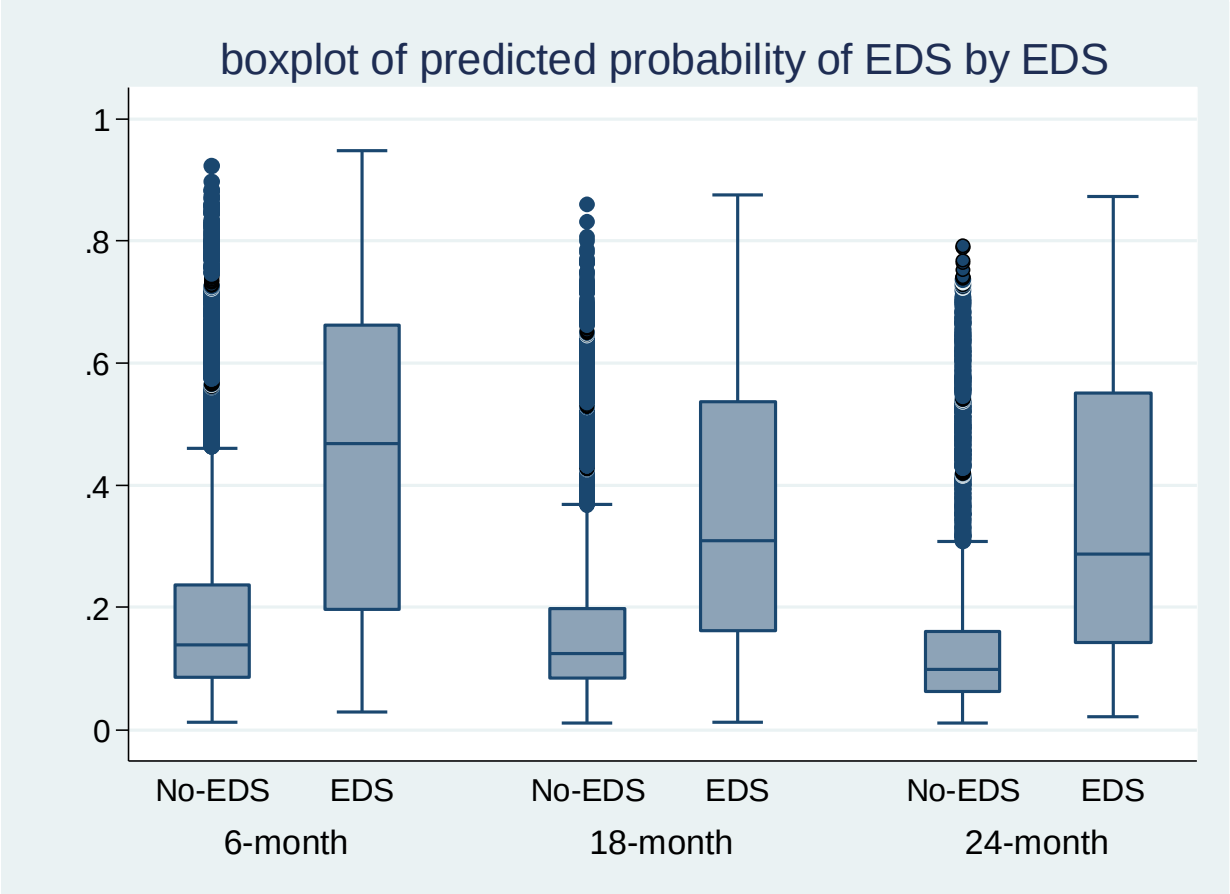

Figure 7: Predicted probability of Elevated Depressive Symptoms (EDS) by EDS at 6-, 18-, and 24-month assessment period

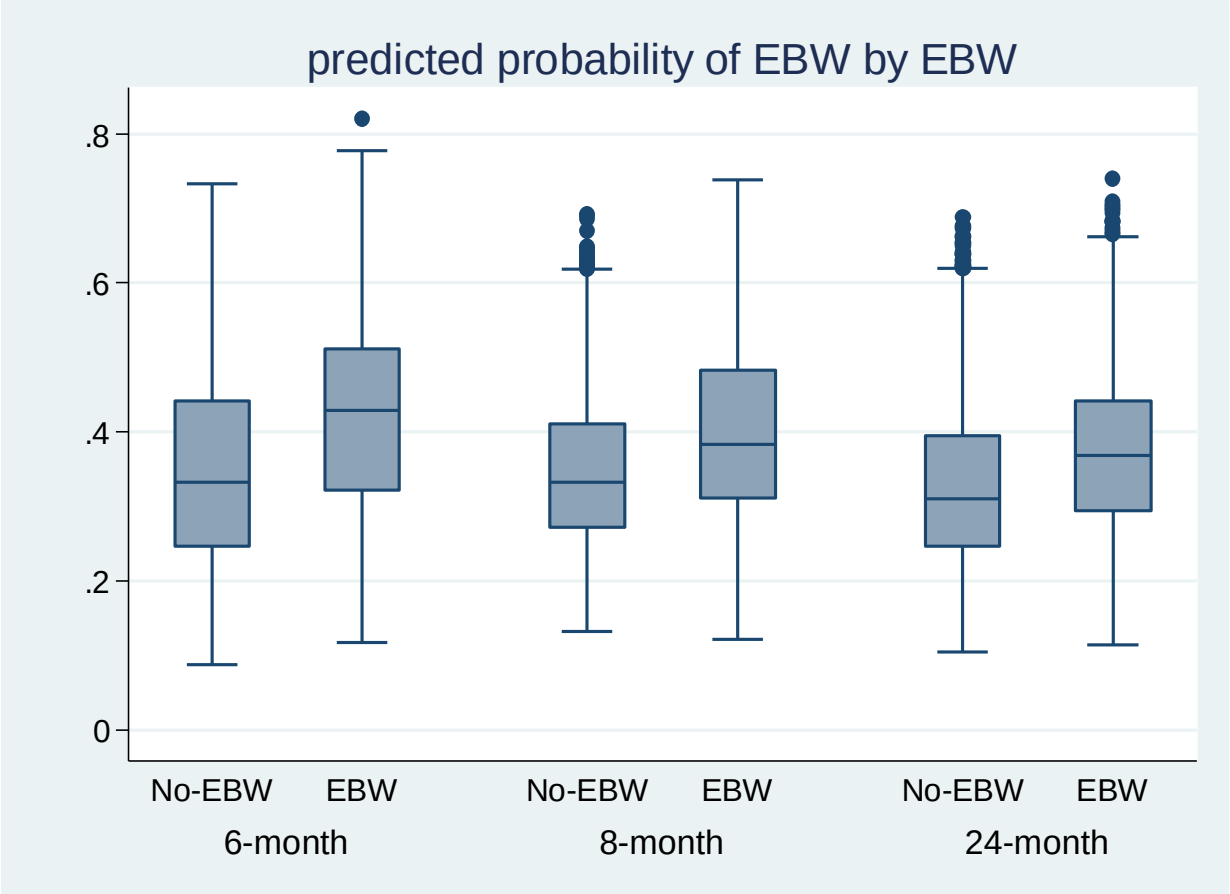

Figure 8: Predicted probability of Excess Body Weight (EBW) by EBW at 6-, 18-, and 24-month assessment period

Table 1: Descriptive statistics for depression, overweight, and obese at baseline, 6-, 18-, 24-, and 72-month assessment (n=516).

	Wave 1	Wave 2	Wave 4	Wave 5	Wave 7
Median BMI percentile (n)	68.00	73.38	71.80	72.27	65.24
Excess body weight %	23.43	30.89	31.45	29.51	29.71
Median MFQ score(n)	10.51	10.19	8.98	8.51	9.77
Elevated depressive symptom score ≥15	23.71	20.68	16.68	13.36	21.02
Elevated depressive symptom score ≥20	11.94	12.29	6.93	6.38	11.57

Table 2: Proportion of EBW in late adolescence by the cumulative elevated depressive symptoms during early adolescence for each potential confounder.

	Cumulative elevated depressive symptoms			
Variables	**0**	**1**	**2**	**3**
Female sex	59.19	24.11	9.62	7.08
Parent Education				
High school or lower	47.62	30.41	13.95	8.02
Some college	60.31	24.46	9.00	6.23
AAs and above[1]	74.88	14.90	6.66	3.56
Custody				
Both biological parents	69.64	18.66	8.84	2.86
One biological parent or adoptees	49.77	28.57	11.10	10.55
Nativity of Parents:				
Immigrant	58.04	25.77	11.07	5.12
Born in US	65.76	19.74	8.45	6.04
Race/ethnicity				
Asian or Hispanic	56.89	23.86	14.91	4.33
Black	55.40	27.81	7.34	9.45
White	74.94	15.59	5.85	3.63
Household Income				
<35,000	48.22	30.77	11.34	9.68
35,000-50,000	66.15	18.92	8.66	6.26
≥50,000	71.86	17.11	8.53	2.50
Parenting Behavior Inventory				
Tertile 1	57.10	21.32	13.81	7.77
Tertile 2	67.18	21.64	6.13	5.05
Tertile 3	66.00	24.64	6.60	2.76

Table 3: Proportion of late adolescent elevated depressive symptoms by cumulative EBW during early adolescence for each potential confounder.

	Cumulative EBW[1]			
	0	**1**	**2**	**3**
Variables				
Female sex	49.88	13.86	13.73	22.53
Parent Education				
High school or lower	50.25	13.90	12.64	23.21
Some college	47.79	9.77	11.43	31.01
AAs and above[1]	61.38	11.65	10.73	16.24
Custody				
Both biological parents	59.39	9.70	9.42	21.50
One biological parent or adoptees	46.73	15.03	15.31	22.93
Nativity of Parents:				
Immigrant	51.72	14.41	13.18	20.69
Born in US	56.14	9.98	10.30	23.51
Race/ethnicity				
Asian or Hispanic	52.77	12.31	12.59	22.33
Black	74.94	15.59	5.85	3.63
White	64.74	7.82	7.64	19.80
Household Income				
<35,000	46.53	16.23	14.97	22.27
35,000-50,000	47.31	7.07	14.47	31.16
≥50,000	62.27	10.18	8.00	19.55
Parenting Behavior Inventory				
Tertile 1	58.97	12.75	11.13	17.15
Tertile 2	51.48	9.62	9.82	29.08
Tertile 3	49.74	13.05	14.48	22.72

[1]EBW=Excess body weight

Table 4: Effect of cumulative and lagged Depression on overweight/obesity (n=516)

Aim	Variable	Non-weighted Relative Risk (95% CI)	[1]Multivariable Adjusted Relative Risk (ARR, 95% CI)	Weighted Relative Risk (RRw=95% CI)
	EDS[2]			
Cumulative effect	Cumulative EDS	**1.19 (1.00, 1.40)[3]**	1.15 (0.97, 1.37)	1.08 (0.72, 1.62)
Lagged effect	Depressed	**1.42 (1.14, 1.77)[3]**	**1.33 (1.07, 1.66)[3]**	1.18 (0.90, 1.55)

[1]Multivariable AA: Adjusted for time-fixed covariates
[2]EDS= Elevated depressive symptoms
[3]Statistically significant at P-value <0.05

Table 5: Effect of cumulative and lagged EBW on depression (n=516)

Aim	Variable	Non-weighted Relative Risk (95% CI)	[1]Multivariable Adjusted Relative Risk (ARR, 95% CI)	Weighted Relative Risk (RRw=95% CI)
Cumulative effect	Cumulative EBW	1.06 (0.90, 1.24)	1.04(0.87, 1.22)	1.01 (0.66, 1.53)
Lagged	No-EBW	1		1
	EBW	1.34 (1.00, 1.78)[2]	1.23 (0.92, 1.64)	1.13 (0.85, 1.51)

[1]Multivariable regression: Adjusted for time-fixed covariates
[2]Statistically significant at P-value <0.05