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Depression, its co-morbidities and treatment, and childhood body mass index trajectories

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Abstract

Objective—No prior studies have evaluated depression diagnoses and cumulative antidepressant use in relation to longitudinal body mass index (BMI) trajectories in a population-representative sample.

Methods—We used electronic health record data from 105,163 children ages 8 to 18 years with 314,648 BMI values. Depression diagnoses were evaluated as ever vs. never, cumulative number of encounters with diagnoses, and total duration of diagnoses. Antidepressants were evaluated as months of use. Associations were evaluated with diagnoses alone, antidepressants alone, and then together, adjusting for covariates.

Results—A total of 6,172 (5.9%) and 10,628 (10.1%) children had a diagnosis of depression or received antidepressant treatment, respectively. At all ages, children receiving Medical Assistance (30.9%) were more likely to be treated with antidepressants. Depression diagnosis and antidepressant use were all independently and positively associated with BMI trajectories; associations were stronger with longer durations of diagnosis and treatment. Among children who received 12 or more months of antidepressants (vs. none), the mean (95% CI) weight gain at 18 years associated with antidepressant use (all classes) was 2.10 (1.76–2.45) kg.

Conclusions—Depression and antidepressant use were both independently associated with increasing BMIs over time, suggesting an important unintended consequence of healthcare to the obesity epidemic.

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Keywords

childhood obesity; longitudinal; depression; antidepressants; body mass index

INTRODUCTION

Obesity and depression are both common in children and have increased in prevalence over the past decades [1], with depression prevalence now estimated as 2–3% for children and 4–8% for adolescents [2, 3]. The cumulative incidence of major depressive disorder during adolescence ranges from 15% to 20%, comparable to the lifetime prevalence in adults [3]. Depression during adolescence is more common in girls and sex differences persist throughout adulthood [4]. Sex differences are also present for obesity [5]. Since antidepressant use has risen nearly 400% since 1988, at a time when obesity rates have doubled, a recent review of epidemiologic, clinical, and preclinical evidence hypothesized that this may be a contributory factor in the obesity epidemic [6].

Depression, depressive symptoms, and other psychological co-morbidities frequently co-exist with obesity, most often reported in cross-sectional studies [7–9]. There are likely complex bidirectional associations between obesity, depressive symptoms, and psychiatric diagnoses; obesity increases the risk of developing depression and depression can accentuate weight gain [10–12]. Most studies in children have focused on whether obesity was associated with depressive symptoms measured psychometrically. Fewer studies have evaluated whether diagnosed depression was associated with weight gain in children; of these, there are none that have used both objective diagnoses of depression and tried to disentangle depression from its treatment.

The role of psychotropic medications can be difficult to discern given the bidirectional links between depression and weight gain. Some antidepressants have been associated with weight gain, especially in adults [13], and others with weight loss, with different propensities by medication classes. In short-term studies mainly in adults, tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors were associated with weight gain, while selective serotonin reuptake inhibitors (SSRIs) and bupropion were associated with weight loss [14–17]. A recent review of six randomized controlled trials concluded that SSRIs and serotonin-norepinephrine reuptake inhibitors (SNRIs) did not cause weight gain and may lead to improvements in weight status over the short-term, but studies were limited to 8–32 weeks of follow-up [10] so there is uncertainty about longer-term impacts. SSRIs are the most prescribed medication class for pediatric depression, generalized anxiety disorder, and obsessive compulsive disorder [10, 18] and may be associated with weight gain [6].

To our knowledge, no prior studies have evaluated depression diagnoses and cumulative antidepressant use in relation to body mass index (BMI) trajectories in children and adolescents in a large, representative sample of a general regional population. We have been interested in possible healthcare system contributions to the childhood obesity epidemic [19, 20]. We now present an analysis with another important class of pharmaceuticals.

METHODS

Study population and design

The study population and design have been previously reported [19, 20]. In brief, we used electronic health records (EHR) from primary care patients of the Geisinger Clinic, who are representative of the general population in their 37-county region of Pennsylvania [21]. For the present analysis we started with 163,820 children and adolescents previously reported [19, 20], but after examining antidepressant use by age, we limited the study population to those aged 8 to 18 years (percentages who received antidepressants at age 5, 6, and 7 years were 0.51%, 0.87%, and 1.40%, respectively). Subjects had to have at least one BMI in that age range and contact with the health system before the first modeled BMI, leaving 105,163 children with 314,648 BMI measurements under study.

Data collection and variable creation

EHR data were available on sociodemographics, encounters (inpatient, outpatient, emergency), vital signs, laboratory tests, procedures, and medications [19, 20]. Orders and encounters have an associated date and were accompanied by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnostic codes. These data were used to identify dates, counts, and durations of depression diagnoses and psychotropic medication orders.

Depression diagnoses, obtained from encounters (outpatient, inpatient, emergency) and medication orders (the diagnosis is linked to the order), were identified using previously reported methods [19, 22] with ICD-9 codes 296.2 (major depressive disorder, single episode, excluding 296.26 [in full remission]); 296.3x (major depressive disorder, recurrent episode, excluding 296.36 [in full remission]); 298.0 (depressive type psychosis); 300.4 (dysthymic disorder); 309.0 (adjustment disorder with depressed mood); 309.1 (prolonged depressive reaction); and 311 (depressive disorder, not elsewhere classified). Antidepressant use was identified with medication orders classified using the Medi-Span Therapeutic Classification System and the 14-digit Generic Product Identifier (GPI) that identified drug group (e.g., antidepressants), class (e.g., TCAs), and name (e.g., amitriptyline). To derive cumulative counts of antidepressant use, only one order was counted per month. For the cumulative month counts it was assumed that the refill orders accompanying antidepressant orders were all completely used. Antidepressant use was first evaluated combining all classes, then repeated separating SSRIs and TCAs from all other classes.

Several co-morbidities and general health measures were evaluated as ever vs. never diagnosed. These included diabetes mellitus, identified by ICD-9 codes 250.0–250.3, 250.8, 250.9, and 250.4–250.7 from encounters and medication orders; asthma, identified by ICD-9 493.x; and number of hospitalizations (0, 1, 2, or 3+) for non-mental health conditions, as a general indicator of overall health. Because anxiety disorders are often co-morbid with depression, and concern that ICD-9 codes were not precisely used to distinguish the two, we repeated analyses counting anxiety (ICD-9 300.0x) and depression diagnoses together. Other psychotropic medication use was identified using previously reported methods for stimulants [19] and anti-anxiety agents were identified by drug group.

Data analysis

The goals of the analysis were to evaluate independent and joint associations of depression diagnoses and antidepressant use with BMI trajectories over time, and by antidepressant class (separately comparing SSRIs and TCAs to all other agents), while controlling for other psychiatric diagnoses and other psychotropic medication use. Specification of models and model building were similar to those previously reported [19, 20].

In longitudinal studies of childhood growth, there are several options for analysis, including untransformed BMI, BMI percentiles, or BMI z-scores. We modeled untransformed BMI values, because when modeling trajectories of change, this measure yields estimates that are more interpretable, precise, and sensitive to factors that alter change [19, 20, 23]. SAS (SAS Institute, Cary, NC) and Stata (Stata Corp, College Station, TX) were used for analysis. We used mixed effects linear regression models with BMI as the dependent variable to model growth curve trajectories of BMI by age. Models included fixed-effects terms for age (centered), age², and age³, sex, race/ethnicity (African American, Hispanic, other, white), and Medical Assistance (a surrogate for family socioeconomic status). Random effects, allowed to covary via an unstructured covariance matrix, included subject-specific intercepts and coefficients for age and age². To allow differences in BMI trajectories by demographic characteristics, models included cross-products of sex and Medical Assistance with all three age terms as fixed effects, and of race/ethnicity with age and age².

Depression diagnosis was modeled in three ways, as ever vs. never, cumulative count of depression diagnoses (1, 2, 3–5, 6+), and total duration from first to last depression diagnosis (0, 0.1–5.9, 6–18.9, 19–35.9, and 36+ months). These different methods of evaluating diagnostic history were relevant to the accuracy of the diagnosis, the severity of the depression, and the utilization of care. **Antidepressant use** was modeled as cumulative number of months of prescribing (1, 2–4, 5–11, and 12+); each order was assumed to represent one month of treatment. Models were first fitted with one form of diagnosis or treatment alone, and then together. Cross-products of diagnosis and antidepressant variables with age, age², and age³ were included to evaluate whether associations differed by age (allowing for non-linearity). The magnitudes of the associations were calculated as previously reported [19, 20]. Extensive diagnostics were completed on all final models [19, 20].

RESULTS

Description of children, depression diagnoses, and antidepressant use

There were approximately equal numbers of boys and girls, a majority was white, the average age at baseline was 12 years, almost 6,200 children had at least one diagnosis of depression, and over 10,600 children had received antidepressants before their last BMI (Table 1). Compared to children treated with antidepressants with a depression diagnosis, those treated without a diagnosis were more likely to be boys (48.3% vs. 33.0%), younger at initiation of treatment (13.2 vs. 14.8 years), and treated for a shorter duration (8.0 vs. 10.9 months) (all p-values < 0.001). Among children who received antidepressants, the average age of first order was almost 14 years and these children were treated for an average of 9

months (Table 1). There were between 25,809 and 34,573 BMIs for each age year. The proportion of children with a depression diagnosis increased from 0.6% to 3.0% to 11.5% at ages 8, 13, and 18 years, respectively; and the proportion on antidepressants similarly increased from 2.4% to 7.2% to 16.6% at the same ages. Among children treated with antidepressants, there were 630 children at age 8 years with a mean (SD) of 7.0 (9.1) months of treatment; this increased to 4327 children at age 18 years with a mean (SD) of 10.3 (12.3) months of treatment. At all ages, children who were receiving Medical Assistance (representing 30.9% of BMIs) were 2.0–2.5 times more likely to be treated with antidepressants.

Evaluation of all antidepressant orders up to the last BMI for each child in the analysis revealed that 50.2% of all orders was accounted for by three agents (citalopram [19.3% of orders], fluoxetine [15.8%], sertraline [15.2%]) and 75.8% of orders with three additional agents (amitriptyline [10.0%], paroxetine [8.6%], bupropion [7.0%]). The most commonly prescribed class was SSRIs (64.1% of orders), followed by tricyclics (14.7%) and bupropion. Children commonly had a history of both SSRI and other antidepressant use; among 7,494 children with an SSRI order, 27.0% had other antidepressant orders for a mean (SD) of 7.1 (9.4) months; and among the 5,160 children with a non-SSRI antidepressant order, 39.3% had SSRI orders for a mean (SD) of 9.6 (10.8) months. Of the children ever prescribed an antidepressant, 28.4% had also been prescribed a stimulant and 17.6% an anti-anxiety medication.

Associations of depression diagnoses with BMI trajectories

At the average age (12.3 years at baseline), children with at least one depression diagnosis had a higher average BMI than children without such a diagnosis (Table 2, **model 1a**) and this association strengthened among children at older ages (i.e., the cross-products of diagnosis with age). This association was also present when depression diagnosis was examined as the duration of depression diagnosis, with a monotonic trend of increasing beta coefficients across categories of increasing duration (Table 2, **model 1b**) with no evidence of effect modification by age. Finally, depression diagnoses were modeled as the cumulative count of encounters with a depression diagnosis, with a trend of increasing BMIs with increasing numbers of depression diagnoses (Table 2, **model 1c**) with little evidence of effect modification by age (Table 2, **model 1d**).

Associations of antidepressant use with BMI trajectories

Antidepressant use was associated with BMI, most apparent among children with 5–11 and 12 or more months of use (Table 3, **model 2a**). The significant age cross-products indicated that this association was stronger among older children. When depression diagnosis (ever vs. never) was added to this model, antidepressant associations were slightly attenuated but still present and depression diagnosis was independently associated with BMI (Table 3, **model 2b**, and Figure). The age cross-products indicated that there was effect modification of the depression diagnosis association by age (Table 3, **model 2c**, p-value for all three age cross-products as a group = 0.01). Finally, when depression diagnosis was added to model 2a as duration of diagnosis, both antidepressant use and duration of depression diagnosis were independently associated with BMI with evidence of larger associations as both increased

across their categories (Table 3, **model 2d**). There was no evidence of effect modification by age of depression diagnosis duration in model 2d (results not shown), and no evidence that the associations of diagnosis with BMI were modified by antidepressant treatment (results not shown). The magnitude of the antidepressant association was large; for example (model 2b), on average, among children who received 12+ months (vs. none) of antidepressant treatment, the mean (95% CI) extra weight at 18 years associated with antidepressant use (all classes combined) was 2.10 (1.76–2.45) kg. When model 2b was restricted to children with normal BMIs (< 75th percentile, 2000 CDC growth charts) at baseline (52,183 children with 156,587 BMIs), antidepressant associations were stronger and more dose-responsive and the depression diagnosis term was no longer significant. Specifically, associations (beta, SE, p-value) by duration were, for 1 month (0.126, 0.049, 0.011), 2–4 months (0.201, 0.048, < 0.0001), 5–11 months (0.452, 0.045, < 0.0001), and 12+ months (0.548, 0.054, < 0.0001).

Evaluation of anxiety diagnoses, other medical conditions, and by drug group

When anxiety diagnoses were included in the counting of depression diagnoses, in model 1a, the diagnosis association declined to 0.195 ($p < 0.001$) from 0.297 (in Table 2) when anxiety diagnoses were not included. This was also the case for model 1b; main effect associations of diagnosis durations declined by approximately 30 to 50% for each duration category; and for models 1c and 1d, although the magnitude of the decline in associations was not as large as for model 1b (results not shown). For models 2b, 2c, and 2d, the main effect association of depression diagnosis when anxiety diagnoses were included was reduced by approximately 50%, but the antidepressant duration associations strengthened. For example, for model 2b, when anxiety diagnoses were included for identification of depression, the diagnosis association declined to beta = 0.050 ($p = 0.06$), but the antidepressant treatment association betas for 1, 2–4, 5–11, and 12+ months increased to 0.213, 0.150, 0.369, and 0.500, respectively (all p-values < 0.001).

Inclusion of diabetes (ever vs. never) did not substantively change associations. Asthma (ever vs. never) was associated with higher BMI at the average age ($p < 0.0005$) but did not substantively change associations. Associations and inferences were unchanged after adjustment for counts of non-mental health hospitalizations.

The association of SSRI use with average BMI (Table 4, **model 3a**, “SSRIs only”) at the average age was stronger than for all antidepressants combined and there was some evidence that associations were larger at older ages (e.g., cross-products with age³); the mean extra weight at 18 years associated with SSRIs was 2.53 (2.12–2.93) kg. In contrast, there were no consistent associations when all other antidepressant classes were combined after removal of SSRIs (Table 4, **model 3b**, “All others”), either alone or when added to the SSRI model (results not shown). Because TCAs were not commonly used to treat depression in the studied children (TCA orders were most often accompanied by headache, migraine, or other psychiatric diagnosis codes), model 2b was repeated in two ways. First, after removal of TCAs from antidepressant duration counting, antidepressant associations (beta coefficients) strengthened, for 1, 2–4, 5–11, and 12+ months to 0.236, 0.221, 0.427, and 0.602, respectively (all $p < 0.001$). Second, when the antidepressant duration counting included only TCAs and no other antidepressants, TCAs were not associated with BMI; beta

coefficients for 1, 2–4, 5–11, and 12+ months were -0.065 , -0.102 , 0.053 , and 0.090 , respectively (all $p > 0.20$).

When stimulant use duration was added to the SSRI model, it demonstrated strong dose-effect relations previously reported [19], but depression inferences did not change. When anti-anxiety agents were added to the all combined antidepressants model (model 2a), there were no substantive changes in associations or inferences for depression diagnosis or treatment (results not shown).

DISCUSSION

In a large, longitudinal, population-based study of children and adolescents aged 8–18 years, we discerned clear evidence that depression itself as well as its treatment were each independently associated with BMI trajectories over time. The longer the duration of diagnosis and treatment, the larger were the associations. On a population level, the magnitude of the antidepressant association with weight gain was substantial; a shift in the distribution of BMIs by a mean of over 2 kg likely represents many more overweight and obese children in the tail of the distribution. Associations were robust to control for a number of confounding variables, as well as to adjustment for other medical and psychiatric diagnoses and other psychotropic agent treatments. Notably, associations were stronger for SSRIs, the most commonly prescribed class of agents. Finally, antidepressants were more than twice as commonly prescribed for children of families with low socioeconomic status (identified with Medical Assistance for health insurance compared to those who never used Medical Assistance).

Antidepressant and other psychotropic medication use have increased in recent decades in the U.S. [6, 19]. Using NHANES data, use of antidepressants in the past month among adolescents 12–17 years of age, during three time periods 1988–94, 1999–2004, and 2005–10 increased from 0.5% to 3.7% to 3.1%, respectively. During the same time periods, ADHD medication use increased from 0.2% to 3.3% to 3.9%; and any psychotropic medication use from 1.3% to 6.8% to 6.6%. Over this time span, there was a five-fold increase in any psychotropic medication use, driven by a six-fold increase in antidepressants and 19-fold increase in ADHD medications (http://www.cdc.gov/nchs/ppt/nchs2012/SS-22_JONAS.pdf). Some have hypothesized that this escalation of antidepressant use may be contributing to the obesity epidemic [6].

There have been few studies on medication use by obesity or overweight status; even fewer employed longitudinal designs, but the implied interest was differential healthcare utilization by obesity status, including through mental health outcomes. However, other evidence suggests that overweight and obese children were more likely to be on medication; in a Canadian study, overweight and obese children were 59% more likely to take any prescription medication in the last month, and 34% more likely for nervous system medication, most of which were analgesics but 12–14% were psychotropics [24, 25].

Prior studies of weight gain associated with SSRIs in adolescents have provided inconsistent evidence. In a study using EHR data, adolescents were overweight at baseline and were

prescribed antidepressants for a depression diagnosis ($n = 255$); those prescribed SSRIs ($n = 194$) had an increase in BMI z-scores, but fewer than 25 children each were prescribed other classes [26]. In a cohort of children of low income families treated with psychotropics and later diagnosed with bipolar disorder, SNRI and heterocyclic compounds (but not SSRIs) were associated with an increased odds of obesity diagnosed in adolescence [27]. Four different SSRIs used to treat panic disorder in adults were each associated with significant increases in body weight [28].

A recent review of the bidirectional associations of obesity and depression [7] reported that most studies have evaluated weight as a predictor of depression; only two studies evaluated depression as predictor of weight. The authors concluded that the majority of longitudinal studies did not provide evidence that depressive symptoms in childhood or adolescence were a risk factor for obesity in later life, but two studies suggested there may be an association only in female adolescents. In contrast, several longitudinal studies have reported an association between childhood or young adult depression diagnosis and adult BMI or risk of obesity [29–34].

There are many studies that suggest our findings are biologically plausible. There are strong links between stress, depression, and obesity and complex pathways and feedbacks among obesity, depression, antidepressant treatment, eating behaviors, and physical activity behaviors [6]. Physical inactivity and binge eating are common behaviors to cope with depressive symptoms [35, 36]. Dysregulation of stress-response systems is a key element of the shared biology of obesity and depression [37]. High glycemic index foods and an overall diet with a high glycemic load have been implicated in the regulation of mood and body weight in cross-sectional studies but prospective studies are conflicting [38, 39].

Our study had several limitations. Our analysis was longitudinal, but observational, so there remains the potential for uncontrolled endogeneity. There is also the potential for confounding by indication, and that the different BMI trajectory risk profiles are due to a combination of the diagnosis and the treatment for different subgroups of children with different types of depression. Treatment guidelines recommend that antidepressant selection be tailored to depression subtypes and severity [40]. We did not observe complete childhood trajectories, but rather a portion of childhood typically spanning 3–5 years for each child. We would have missed diagnoses and treatments before children entered care and those provided outside of the healthcare system. Finally, we were unable to determine adherence to prescribed medications recorded in the EHR, resulting in possible over-estimation of medication exposure. We believe most of these are likely to bias our results towards the null and to reduce the magnitude of the observed associations.

CONCLUSION

Depression diagnosis and its treatment were each independently associated with BMI trajectories in a large sample of children and adolescents representing the general population in a large region of Pennsylvania. Depression diagnosis and antidepressant treatment may identify a population of children who are particularly vulnerable to increases in BMI over time and who are in need of careful monitoring to try to prevent weight gain. The

associations suggest that antidepressant treatment may be an important contributor to weight gain, but the study design does not allow causal conclusions regarding the relative importance of diagnosis or treatment.

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What is already known about this subject?

- Depression, depressive symptoms, and other psychological co-morbidities frequently co-exist with obesity, most often reported in cross-sectional studies
- Antidepressant use has increased dramatically in the past few decades
- No prior studies have tried to disentangle depression diagnoses from cumulative antidepressant use in relation to longitudinal body mass index (BMI) trajectories in a population-representative sample of children with years of follow-up

What does this study add?

- Using electronic health records, depression diagnosis and its treatment were each independently associated with BMI trajectories in a large sample of children and adolescents representing the general population in a large region of Pennsylvania
- The longer the duration of diagnosis and treatment, the larger were the associations
- On a population level, the magnitude of the antidepressant association with weight gain was substantial; a shift in the distribution of BMIs by a mean of over 2 kg likely represents many more overweight and obese children in the tail of the BMI distribution

Figure.

BMI trajectories (predicted values from regression model with modeled lines) by duration of antidepressant use (all classes) from model 2b in Table 3, adjusting for depression diagnosis and covariates. The predicted BMI values were from the fixed portion of the model using observed population means as values for other variables.

Table 1

Description of 105,163 children in analysis, 8 to 18 years of age.

Variable	Value
Sex, female, %	50.5
Race/ethnicity, %	
White	93.2
African-American	4.1
Hispanic	0.8
Other and missing	1.9
Age at baseline, years, mean (SD)	12.3 (3.4)
Age at last BMI, years, mean (SD)	14.9 (3.4)
Duration from first to last BMI, years, mean (SD)	2.5 (2.7)
BMI at baseline, kg/m ² , mean (SD)	21.5 (5.5)
BMI, last, kg/m ² , mean (SD)	23.4 (5.9)
BMI in analysis per child, n (%)	
1	33,872 (32.2)
2	21,793 (20.7)
3	15,496 (14.7)
4	11,221 (10.7)
5–7	17,866 (17.0)
8+	4,915 (4.7)
Children with depression diagnosis before <u>first</u> BMI, n (%)	2,108 (2.0)
Age at first depression diagnosis, years, mean (SD)	14.7 (2.8)
Children with depression diagnosis before <u>last</u> BMI, n (%)	6,172 (5.9)
Children with depression diagnoses by category, n (%)	
No depression diagnosis	98,991 (94.1)
1 diagnosis	2,483 (2.4)
2 diagnoses	1,037 (1.0)
3–5 diagnoses	1,388 (1.3)
6+ diagnoses	1,264 (1.2)
Depression diagnoses, cumulative encounters, all children, n (%)	0.24 (1.77)
Depression diagnoses, cumulative encounters, among children with at least one depression diagnosis, n (%)	4.13 (6.12)
Children who received antidepressants, n (%)	10,628 (10.1)
Age at first antidepressant order, years, mean (SD)	13.9 (3.3)

Variable	Value
Antidepressant orders before last BMI, cumulative months, all children, mean (SD)	0.9 (4.7)
Antidepressant orders before last BMI, cumulative months, among children who received antidepressants, mean (SD)	9.2 (12.0)
Children by cumulative antidepressant orders groups, n (%)	
None	94,535 (89.9)
1 month	2,351 (2.2)
2–4 months	2,301 (2.2)
5–11 months	3,279 (3.1)
12+ months	2,697 (2.6)

Table 2

Evaluation of associations of depression diagnoses with BMI trajectories among 105,163 children ages 8–18 years with 314,648 BMI observations

Variable	Model 1a Beta (SE)	Model 1b Beta (SE)	Model 1c Beta (SE)	Model 1d Beta (SE)
Depression diagnosis before BMI _i	0.297 (0.040) ***			
Cross-product with age	−0.010 (0.016)			
Cross-product with age ²	−0.007 (0.003) *			
Cross-product with age ³	0.002 (0.0008) *			
Duration of diagnosis before BMI _i				
< 6 mo		0.285 (0.052) ***		
6 mo to 1.5 y		0.398 (0.057) ***		
1.5 y to 3 y		0.478 (0.071) ***		
> 3 y		0.523 (0.097) ***		
Depression diagnosis counts				
1 diagnosis			0.248 (0.035) ***	0.294 (0.050) ***
By age				0.0001 (0.022)
By age ²				−0.005 (0.004)
By age ³				−0.0001 (0.001)
2 diagnoses			0.117 (0.050) *	0.252 (0.079) **
By age				−0.055 (0.036)
By age ²				−0.016 (0.008) *
By age ³				0.004 (0.002) *
3–5 diagnoses			0.316 (0.046) ***	0.368 (0.076) ***
By age				0.006 (0.033)
By age ²				−0.009 (0.008)
By age ³				0.001 (0.002)
6+ diagnoses			0.530 (0.060) ***	0.556 (0.099) ***
By age				0.011 (0.040)
By age ²				−0.031 (0.010) **
By age ³				0.007 (0.002) **

[†] Models controlled for age (centered), age², age³, sex and age and age² cross-products, race/ethnicity and age and age² cross-products, and Medical Assistance and age and age² cross-products as described in the Methods.

P-values:

p < 0.001;

**
0.001 p < 0.01;

*
0.01 p < 0.05

Table 3

Evaluation of associations of antidepressant use, without and with adjustment for depression diagnosis, with BMI trajectories among 105,163 children ages 8–18 years with 314,648 BMI observations

Variable	Model 2a Beta (SE)	Model 2b Beta (SE)	Model 2c Beta (SE)	Model 2d Beta (SE)
Antidepressant duration category				
1 month	0.225 (0.047) ***	0.205 (0.048) ***	0.193 (0.048) ***	0.210 (0.048) ***
2–4 months	0.168 (0.046) ***	0.139 (0.047) **	0.121 (0.047) **	0.145 (0.046) **
5–11 months	0.390 (0.042) ***	0.356 (0.043) ***	0.335 (0.044) ***	0.352 (0.043) ***
12+ months	0.521 (0.055) ***	0.487 (0.077) ***	0.469 (0.056) ***	0.474 (0.056) ***
Cross-products with age				
1 month	0.034 (0.022)	0.031 (0.022)	0.036 (0.022)	0.031 (0.022)
2–4 months	0.090 (0.021) ***	0.086 (0.021) ***	0.092 (0.021) ***	0.086 (0.021) ***
5–11 months	0.025 (0.018)	0.020 (0.018)	0.030 (0.019)	0.019 (0.018)
12+ months	0.030 (0.021)	0.025 (0.021)	0.036 (0.022)	0.022 (0.021)
Cross-products with age ²				
1 month	−0.002 (0.004)	−0.002 (0.004)	−0.001 (0.004)	−0.025 (0.004)
2–4 months	−0.004 (0.004)	−0.004 (0.004)	−0.002 (0.004)	−0.004 (0.004)
5–11 months	−0.011 (0.003) **	−0.011 (0.003) **	−0.009 (0.003) *	−0.011 (0.003) **
12+ months	−0.004 (0.004)	−0.004 (0.004)	−0.002 (0.004)	−0.004 (0.004)
Cross-products with age ³				
1 month	−0.001 (0.001)	−0.001 (0.001)	−0.001 (0.001)	−0.001 (0.001)
2–4 months	−0.003 (0.001) **	−0.003 (0.001) **	−0.003 (0.001) **	−0.003 (0.001) **
5–11 months	0.002 (0.001) *	0.002 (0.001) *	0.002 (0.0009)	0.002 (0.0009) *
12+ months	0.002 (0.001) *	0.003 (0.001) *	0.002 (0.001) *	0.003 (0.001) *
Depression diagnosis before BMI _i		0.103 (0.031) **	0.195 (0.042) ***	
Cross-product with age			−0.036 (0.018) *	
Cross-product with age ²			−0.007 (0.003) *	
Cross-product with age ³			0.001 (0.0009)	
Duration of diagnosis before BMI _i				
< 6 mo				0.073 (0.034) *
6 mo to 1.5 y				0.125 (0.038) **
1.5 y to 3 y				0.169 (0.046) ***
> 3 y				0.163 (0.065) *

[†] Models controlled for age (centered), age², age³, sex and age and age² cross-products, race/ethnicity and age and age² cross-products, and Medical Assistance and age and age² cross-products as described in the Methods.

P-values:

 $p < 0.001$;

**

 $0.001 \quad p < 0.01$;

*

 $0.01 \quad p < 0.05$

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Table 4

Evaluation of associations of SSRIs and all other antidepressants with BMI trajectories among 105,163 children ages 8–18 years with 314,648 BMI observations (two separate models)

Variable	Model 3a SSRIs only Beta (SE)	Model 3b All Others Only Beta (SE)
Antidepressant duration category		
1 month	0.288 (0.057) ***	0.105 (0.063)
2–4 months	0.235 (0.058) ***	0.048 (0.063)
5–11 months	0.500 (0.050) ***	0.123 (0.063)
12+ months	0.771 (0.066) ***	0.111 (0.093)
Cross-products with age		
1 month	0.055 (0.027) *	0.049 (0.028)
2–4 months	0.026 (0.026)	0.118 (0.028) ***
5–11 months	−0.015 (0.021)	0.098 (0.027) ***
12+ months	−0.031 (0.025)	0.098 (0.035) **
Cross-products with age ²		
1 month	−0.0004 (0.005)	−0.0004 (0.005)
2–4 months	−0.002 (0.005)	−0.0003 (0.005)
5–11 months	−0.012 (0.004) **	−0.008 (0.005)
12+ months	−0.009 (0.005)	0.004 (0.007)
Cross-products with age ³		
1 month	−0.003 (0.001) *	−0.0007 (0.001)
2–4 months	−0.002 (0.001)	−0.002 (0.001)
5–11 months	0.003 (0.001) **	−0.002 (0.001)
12+ months	0.006 (0.001) ***	−0.002 (0.002)

[†]Models controlled for age (centered), age², age³, sex and age and age² cross-products, race/ethnicity and age and age² cross-products, and Medical Assistance and age and age² cross-products as described in the Methods.

P-values:

p < 0.001;

**
0.001 p < 0.01;

*
0.01 p < 0.05