Body Composition in Adolescents During Treatment With Selective Serotonin Reuptake Inhibitors

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abstract

OBJECTIVES: To examine the independent contribution of major depressive disorder (MDD), generalized anxiety disorder (GAD), and selective serotonin reuptake inhibitors (SSRIs) to changes in body composition in older adolescents.

METHODS: Medically healthy 15- to 20-year-olds who were unmedicated or within 1 month of starting an SSRI were prospectively followed. Psychiatric functioning and medication treatment were assessed monthly. Body Mass Index (BMI) was measured every 4 months. Every 8 months, a whole-body dual-energy radiograph absorptiometry scan was obtained to determine lean BMI, fat mass index, and visceral fat mass. Linear mixed effects regression analysis examined associations between MDD, GAD, and SSRI use variables and body composition measures.

RESULTS: Over 1.51 ± 0.76 years of follow-up, 264 participants contributed 805 observations. After adjusting for age, sex, physical activity, dietary intake, and time in the study, MDD severity was inversely associated, prospectively, with BMI, fat mass index, and lean BMI *z* scores, whereas cumulative SSRI treatment duration and dose were positively associated with these outcomes. GAD severity and diagnosis were not significantly associated with any body composition outcome. Moreover, citalopram and escitalopram were most strongly associated with the increase in all body composition measures, including visceral fat mass, whereas the associations with fluoxetine were somewhat weaker. Sertraline was not different from no SSRI treatment.

CONCLUSIONS: Depression severity was associated with a decrease in measures of body composition in older adolescents over a mean of 1.5 years, whereas SSRI treatment was positively associated with these outcomes, with differential effects across treatment groups.

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WHAT'S KNOWN ON THIS SUBJECT: Depression and obesity are bidirectionally associated. This comorbidity compounds the morbidity associated with both conditions. However, the confounding effect of psychotropic agents has not been thoroughly investigated.

WHAT THIS STUDY ADDS: This longitudinal study found that a diagnosis of depression was not independently associated with weight gain. However, citalopram and escitalopram, but not sertraline, were associated with an increase in both adiposity and lean mass. Fluoxetine fell in between.

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Obesity and major depressive disorder (MDD) are bidirectionally associated.[1–4] Dysregulation of the hypothalamo-pituitary-adrenal axis, other endocrinologic abnormalities, autonomic nervous system dysfunction, subclinical inflammation, and lifestyle factors have all been implicated.[5,6] Furthermore, most psychotropic agents cause weight gain.[4,7] However, longitudinal studies examining the association between obesity and MDD either failed to account for psychopharmacology or did not examine measures of adiposity beyond BMI (ie, body fat and visceral adiposity).[8,9]

To disentangle the contribution of MDD from that of psychotropic agents to longitudinal changes in body composition, we used data collected in a 2-year prospective study examining the skeletal effects of selective serotonin reuptake inhibitors (SSRIs) in older adolescents.[10] We expected that both MDD and the use of SSRIs would be independently associated with increased adiposity. Given the high comorbidity between MDD and generalized anxiety disorder (GAD), we further investigated whether GAD is independently associated with adiposity.

METHODS

Participants

Fifteen- to twenty-year-old participants were recruited in this observational study.[10] Enrollment was restricted to individuals not taking psychotropic agents or those who were within 1 month of starting an SSRI. Treatment with psychotropic agents other than SSRIs during the 2 years before study entry led to exclusion, with the exception of use of benzodiazepines, trazodone, α_2-agonists, or psychostimulants (dose stable for 2 months, $n = 3$). Other exclusionary criteria included the presence of an eating disorder, substance dependence, pregnancy, significant medical or surgical history, the chronic use of medications potentially affecting bone metabolism, or plans to move out of the state within a year.

Procedures

The local institutional review board approved the study and informed consent and assent were obtained. Participants completed the baseline visit and returned for a follow-up visit every 4 months for up to 2 years. Between in-person visits, they were contacted by phone monthly.

At all encounters, participants were queried about their medical history and medication use. Adherence was based on self-report and pharmacy records. At every in-person visit, the Inventory of Depressive Symptomatology (IDS),[11] the Beck Depression Inventory (BDI-II),[12] the Beck Anxiety Inventory (BAI),[13] and the modified version of the Physical Activity Questionnaire for Adolescents[14] were obtained. In addition, height and weight were measured according to standard procedures.[10] Grip strength was measured using a Jamar Plus hand dynamometer (model number: 12-0604; Patterson Medical, Bolingbrook, IL) as described previously.[10]

At study entry and annually thereafter, participants completed the full-length Block Food Frequency Questionnaire (FFQ 2005.1; NutritionQuest.com, Berkeley, CA). This was used to compute the Healthy Eating Index (http://epi.grants.cancer.gov/hei/tools.html), a measure of conformance to the dietary guidelines we used to account for the possible contribution of dietary factors to changes in body composition. However, because dietary intake was assessed yearly but a dual-energy radiograph absorptiometry (DXA) scan was obtained every 8 months, dietary data were available only for 57.3% of the visits.

At study entry and every 8 months, a whole-body DXA scan was obtained using a Hologic QDR DELPHI-4500A unit or a Hologic Discovery A unit (Hologic, Inc, Bedford, MA). The 2 DXA units were cross-calibrated and daily quality-control scans were performed.[10] The Hologic software (APEX 4.0.1/13.4.1) determined total body less head lean and fat mass. The package also includes an automated algorithm to estimate visceral adipose tissue mass (VFat), (grams).[15] For some scans, manual adjustment of the regions of interest was necessary, as recommended by the manufacturer.

Clinical diagnoses, which were based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR),[16] incorporated information from the review of medical records and the self- and researcher-completed symptom rating scales, the Diagnostic Interview Schedule for Children,[17] and an unstructured interview by a child psychiatrist. The severity of MDD and GAD was quantified for each week over the study period by using the Longitudinal Interval Follow-up Evaluation,[18] modified for use with adolescents (A-LIFE).[10,19]

Statistical Analysis

BMI was computed as weight/height^2 (kg/m^2), lean BMI (LBMI) as lean mass/height^2 (kg/m^2), and fat mass index (FMI) as fat mass/height^2 (kg/m^2) and age- and sex-specific z scores were generated.[20,21]

To capture the change in the BDI-II and BAI, the mean score over the interim visits, up to and including the score at the visit when a DXA scan was obtained, was used as the predictor variable in the relevant models.

Differences across participants taking SSRIs at study entry versus those who were not were evaluated

using Student's *t* test for continuous variables and χ^2 test for categorical variables.

The association between MDD, GAD, and SSRIs on the one hand and each body composition measure (BMI *z* score, FMI *z* score, LBMI *z* score, and VFat) on the other was examined by using a linear mixed effects regression.[22] Different indices of MDD and GAD were used, including DSM-IV-TR–based diagnoses as well as scale scores (Table 4). SSRI treatment was characterized in terms of duration of use and dose, accounting for adherence. Given that SSRI adherence was missing for only 2.6% of all observations, the expectation-maximization (EM) algorithm was used to impute the missing values.[23] All models included adjustment for age (years) at study entry, sex, and level of physical activity (Table 4). Because neither energy intake (kilocalories) nor the Healthy Eating Index (mean 60.5 ± 12.2, range: 32.6–92.6) significantly contributed to any of the models (all *P* values > 0.40), they were excluded. Height (centimeters) was also included in the VFat analysis to account for differences in body size. Participant-specific random intercepts and slopes were used with an unstructured covariance matrix. Duration of study participation was the time metric in the analysis. Maximum likelihood methods were used for estimation, which yielded unbiased estimates under the assumption that the missing data mechanism is ignorable.[24] The covariates of interest were analyzed as time-dependent covariates and decomposed into a between-subject and a within-subject component.[25] The former represents a cross-sectional effect, whereas the latter represents an individual slope effect.

All hypothesis tests were 2-tailed with a significance level of $P < .05$, and analyses used procedures from SAS version 9.4 for Windows (SAS Institute Inc, Cary, NC).

TABLE 1 Baseline Demographic and Clinical Characteristics of the Participants as a Group and Split on the Basis of SSRI Use at Study Entry (Mean ± SD, Unless Noted Otherwise)

Variable	Total Sample	No SSRI Group	SSRI Group	*P*
	N = 264	*n* = 137	*n* = 127	
Age, y	18.9 ± 1.6	19.0 ± 1.5	18.8 ± 1.7	>.40
Female subjects, *n* (%)	159 (60)	76 (55)	83 (65)	>.10
Race, *n* (%)				>.30
White	233 (88)	119 (87)	114 (90)	
African American	12 (5)	5 (4)	7 (6)	
Asian	15 (6)	11 (8)	4 (3)	
American Indian	4 (2)	2 (1)	2 (2)	
Hispanic, *n* (%)	22 (8)	11 (8)	11 (9)	>.80
BMI	24.3 ± 4.7	24.2 ± 4.4	24.4 ± 5.0	>.60
BMI *z* score	0.43 ± 0.93	0.40 ± 1.00	0.46 ± 0.90	>.50
LBMI *z* score	−0.53 ± 0.93	−0.53 ± 0.94	−0.52 ± 0.91	>.90
FMI *z* score	0.25 ± 0.73	0.23 ± 0.73	0.28 ± 0.72	>.50
Vfat, g	249 ± 125	245 ± 117	254 ± 133	>.50
Physical activity score[a]	2.2 ± 0.8	2.3 ± 0.8	2.2 ± 0.8	>.30
Estimated daily caloric intake, kcal	1762 ± 941	1715 ± 816	1814 ± 1064	>.40
Cigarette use, *n* (%)	41 (16)	16 (12)	25 (20)	<.08
Alcohol use, *n* (%)	183 (69)	95 (69)	88 (69)	>.90
Psychiatric Characteristics				
MDD at study entry, *n* (%)				<.0001
Symptomatic	131 (50)	29 (21)	102 (80)	
In full remission	42 (16)	27 (20)	15 (12)	
Never	91 (34)	81 (59)	10 (8)	
MDD at study end, *n* (%)				<.0001
Symptomatic	79 (30)	23 (17)	56 (44)	
In full remission	108 (41)	44 (32)	64 (50)	
Never	77 (29)	70 (51)	7 (6)	
Percent time meeting full MDE criteria[b]	25.2 ± 31.8	12.1 ± 25.7	39.4 ± 31.2	<.0001
IDS score	13.9 ± 10.8	7.9 ± 8.1	20.3 ± 9.5	<.0001
BDI-II score	11.1 ± 10.5	5.7 ± 6.5	16.9 ± 10.8	<.0001
GAD at study entry, *n* (%)	73 (28)	23 (17)	50 (39)	<.0001
Percent time meeting GAD criteria[b]	40.3 ± 38.8	25.4 ± 34.1	56.4 ± 37.3	<.0001
BAI score	8.3 ± 8.6	4.4 ± 5.0	12.6 ± 9.6	<.0001
SSRI use at study end, *n* (%)	71 (27)	2 (1)	69 (54)	<.0001
Duration of SSRI use, y	0.42 ± 0.67	0.02 ± 0.18	0.85 ± 0.73	<.0001

BDI-II, Beck Depression Inventory (Second Edition).

[a] Physical activity score 1 = low, 5 = high.

[b] Percent time meeting full MDE or GAD criteria captures the percentage of weeks in which the participant met DSM-IV-TR criteria for a major depressive episode or generalized anxiety disorder, based on the Longitudinal Interview Follow-up Evaluation for Adolescents (A-LIFE).

RESULTS

Participants

A total of 279 participants enrolled in the study and provided 850 observations. After exclusions for psychosis and bipolar disorder, the timing of SSRI use, having a genetic condition or substance use disorder, and missing depression data, 264 adolescents with 805 observations were eligible for the analysis. As would be expected, participants in the SSRI group were more likely to have MDD and GAD and to score higher on all measures related to these disorders (Table 1). They were also less likely to complete the study (61% vs 80%, $P = .0007$). This difference was also reflected in the duration of study participation (1.4 ± 0.9 years vs 1.6 ± 0.7 years, Student's *t* test = 2.14, $P < .04$).

SSRI Treatment and Change in BMI *z* Score

On average, the BMI *z* score did not significantly change across the entire sample over the course of the study (Tables 2 and 3). After controlling for the standard covariates, the scores on the IDS and BAI were inversely

associated with changes in BMI *z* scores, whereas the duration of exposure to SSRIs and the cumulative dose during the interim period between DXA scans were positively associated with the changes in BMI *z* scores (Table 4). When both the IDS score and cumulative SSRI dose were concurrently entered in the model, both remained significantly associated with changes in BMI *z* scores, but in opposite directions (within-subject effect β = −.006, SE = 0.002, $P < .002$ and within-subject effect β = .120, SE = 0.044, $P < .007$, respectively). In contrast, when both the BAI score and the cumulative SSRI dose were concurrently entered in the model, only the latter was significantly associated with a change in BMI *z* scores (within-subject effect β = .132, SE = 0.044, $P < .003$).

SSRI Treatment and Body Composition

Next, we examined whether MDD, GAD, or SSRI treatment differentially affect the body's composition. Both FMI and LBMI *z* scores significantly increased over the study period (Tables 2 and 3). After adjusting for the standard covariates, the duration of use and the dose of SSRIs were both positively associated with increased FMI and LBMI *z* scores (Table 4). This association remained significant after accounting for the effect of the IDS score, which was negatively associated with these outcomes (for FMI *z* score: within-subject IDS score effect β = −.003, SE = 0.001, $P < .03$ and within-subject SSRI dose effect β = .089, SE = 0.035, $P < .02$; for LBMI *z* score: within-subject IDS score effect β = −.005, SE = 0.002, $P < .007$ and within-subject SSRI dose effect β = .093, SE = 0.041, $P < .03$). When the models predicting FMI and LBMI *z* scores were also adjusted for LBMI and FMI *z* scores, respectively, the within-subject SSRI effect became nonsignificant, suggesting that the increase in the 2 indices was proportional.

When both the BAI score and the cumulative SSRI dose given during the interim period between DXA scans were concurrently entered in the model, only the latter was significantly associated with change in FMI and LBMI *z* scores (within-subject effect β = .093, SE = 0.035, $P < .009$ and within-subject effect β = .103, SE = 0.041, $P < .02$, respectively).

To test whether the observed increase in LBMI *z* score was indeed because of an increase in muscle mass, we examined the prospective effect of SSRI use on grip strength. After adjusting for age ($P > .80$), sex ($P < .0001$), height ($P < .0001$), and time in the study ($P < .0001$), neither the within-subject effect of duration of SSRI treatment nor its between-subject effect was significantly associated with grip strength (β = −3.59, SE = 3.09, $P = .2463$ and β = −1.54, SE = 0.84, $P = .0688$, respectively).

SSRI Treatment and Visceral Adiposity

VFat also significantly increased over the course of the study (Tables 2 and 3). After adjusting for the standard covariates, plus height, SSRI treatment was positively associated, albeit not significantly, with an increase in visceral fat mass (Table 4).

SSRI Treatment and Height

Both height and height *z* score increased during the study (Tables 2 and 3). After adjusting for the standard covariates, SSRI treatment duration, but not the IDS score ($P > .60$), was inversely associated with change in height *z* score (within-subject effect β = −.041, SE = 0.021, $P < .05$).

TABLE 2 Change Between Baseline and Final Visit in Anthropometric and Body Composition Variables Across the Entire Sample (Mean ± SD, Median [Interquartile Range])

	Mean ± SD	Median (IQR)	Signed Rank S	*P*
Wt, kg	1.95 ± 6.29	0.55 (5.30)	4938.5	<.0001
Wt percentile	1.2 ± 10.5	0.0 (8.1)	1973.5	<.03
Wt *z* score	0.05 ± 0.38	0.00 (0.39)	2353.5	<.01
BMI	0.58 ± 2.16	0.05 (1.81)	4244.5	<.0001
BMI percentile	0.9 ± 12.5	0.0 (9.0)	1284.5	>.10
BMI *z* score	0.04 ± 0.42	0.00 (0.40)	1575.5	<.09
FMI *z* score	0.04 ± 0.35	0.00 (0.32)	2167.5	<.02
LBMI *z* score	0.11 ± 0.39	0.01 (0.46)	3297	<.0001
Visceral fat, g	8.4 ± 72.8	0.0 (50.1)	2066.5	<.03
Height, cm	0.4 ± 0.9	0.1 (0.9)	5442.5	<.0001
Height percentile	0.5 ± 3.8	0.0 (3.0)	1506.5	<.10
Height *z* score	0.02 ± 0.13	0.00 (0.13)	1968.5	<.03

IQR, interquartile range.

TABLE 3 Spearman's Correlation Coefficients Between Baseline and Change in Anthropometric and Body Composition Variables Across the Entire Sample

	Weight *z* Score (*P*)	BMI *z* Score (*P*)	LBMI *z* Score (*P*)	FMI *z* Score (*P*)	VFat, g (*P*)	Height *z* Score (*P*)
Wt *z* score change	−0.15 (<.02)	−0.11 (<.07)	−0.08 (>.20)	−0.09 (.10)	−0.09 (>.10)	−0.14 (<.02)
BMI *z* score change	−0.17 (<.006)	−0.15 (<.02)	−0.11 (<.08)	−0.12 (.05)	−0.11 (<.07)	−0.10 (<.10)
LBMI *z* score change	−0.03 (>.60)	−0.02 (>.70)	−0.11 (<.08)	0.06 (.30)	0.08 (>.10)	−0.05 (>.40)
FMI *z* score change	−0.24 (<.0001)	−0.20 (=.0009)	−0.12 (<.06)	−0.22 (=.0003)	−0.20 (=.0009)	−0.15 (<.02)
Vfat change, g	−0.13 (< .04)	−0.09 (>.10)	−0.05 (>.40)	−0.11 (<.08)	−0.22 (=.0003)	−0.10 (<.09)
Height *z* score change	−0.09 (>.10)	−0.09 (>.10)	−0.07 (>.20)	−0.08 (>.10)	−0.03 (>.60)	−0.08 (>.20)

z score refers to age-sex–specific *z* score.

TABLE 4 Parameter Estimates (SEs) for Depression-, SSRI-, and Anxiety-Related Variables From Linear Mixed Effects Regression Analysis Models for Age-Sex–Specific BMI, FMI, and LBMI *z* scores and for VFat (grams)

	BMI *z* Score	FMI *z* Score	LBMI *z* Score	VFat
Depression				
Current depression status, continuous	−0.010 (0.010)	−0.008 (0.008)	−0.013 (0.009)	−0.99 (1.53)
Depression trend, continuous	−0.073 (0.075)	−0.020 (0.057)	−0.130 (0.072)**	−3.64 (9.70)
Weeks in MDE, within-subject effect	−0.000 (0.002)	0.001 (0.001)	0.001 (0.001)	−0.43 (0.24)**
Weeks in MDE, between-subject effect	−0.008 (0.007)	−0.003 (0.005)	−0.006 (0.006)	−0.09 (0.85)
Mean BDI-II score, within-subject effect	−0.001 (0.002)	−0.001 (0.002)	−0.002 (0.002)	−0.16 (0.36)
Mean BDI-II score, between-subject effect	−0.006 (0.007)	−0.002 (0.005)	−0.008 (0.007)	−0.21 (0.91)
IDS score, within-subject effect	−0.007 (0.002)*	−0.004 (0.001)*	−0.005 (0.002)*	−0.38 (0.30)
IDS score, between-subject effect	−0.007 (0.007)	−0.005 (0.005)	−0.008 (0.006)	−0.69 (0.86)
SSRI use				
SSRI indicator	0.056 (0.041)	0.051 (0.033)	0.032 (0.039)	11.38 (6.55)**
SSRI use, within-subject effect	0.222 (0.073)*	0.151 (0.058)*	0.241 (0.069)*	15.17 (11.80)
SSRI use, between-subject effect	1.097 (0.387)*	0.920 (0.291)*	0.974 (0.379)*	128.76 (49.79)*
SSRI dose, within-subject effect	0.140 (0.043)*	0.100 (0.035)*	0.108 (0.041)*	12.58 (7.11)**
SSRI dose, between-subject effect	0.319 (0.222)	0.256 (0.167)	0.322 (0.217)	27.40 (28.59)
Anxiety				
Weeks with GAD, within-subject effect	−0.002 (0.001)**	−0.001 (0.001)	−0.002 (0.001)**	−0.33 (0.17)**
Weeks with GAD, between-subject effect	−0.001 (0.005)	−0.001 (0.004)	0.003 (0.005)	0.05 (0.64)
Mean BAI score, within-subject effect	−0.005 (0.002)*	−0.004 (0.002)*	−0.004 (0.002)	−0.55 (0.39)
Mean BAI score, between-subject effect	0.001 (0.008)	0.003 (0.006)	−0.003 (0.008)	−0.04 (1.10)

The base model included the following "standard covariates": baseline age, sex, physical activity, and time in the study (in addition to height, for the VFat models). All models included the standard covariates in addition to the predictor specified in each model. Current depression status included: 0 = never depressed, 1 = full remission, 2 = remitting, 3 = partial remission, 4 = relapse, 5 = MDE. Depression trend reflects whether over the course of the study, the clinical course was one of improvement (1), decline (2), or no symptoms (0). Weeks in MDE and weeks in GAD reflect the percentage of weeks in which the participant met DSM-IV-TR criteria for a MDE or GAD, on the basis of the Longitudinal Interview Follow-up Evaluation for Adolescents (A-LIFE). SSRI use reflects aggregate use between visits, in years. SSRI dose reflects the cumulative dose of SSRI taken by participants. Both SSRI use and dose were adjusted for adherence as captured by self-report and pharmacy records.

* $P < .05$.

** $P < .10$.

Sex Effect

Next, we examined the interaction effect between sex and SSRI-related variables. There was no evidence for a sex difference in the effect of SSRI treatment duration on LBMI and height *z* scores or VFat (all *P* values > .10). In contrast, male participants showed a larger increase than female participants in BMI and FMI *z* scores over a more extended SSRI treatment period (β = .31, SE = 0.12, $P < .01$ and β = .23, SE = 0.10, $P < .02$, respectively).

Differences Between Individual Drugs

Given that the majority of SSRI-treated participants used 1 of 4 drugs (Table 5), a categorical variable was created to denote which drug, including no use of a drug, that each participant received. Citalopram and escitalopram were grouped together and participants taking other drugs (eg, paroxetine) were excluded, given their small number.

TABLE 5 Number (%) of Participants on Individual Drugs Across Different Research Visits

	Citalopram or Escitalopram	Fluoxetine	Sertraline	No SSRI
Study entry[a]	51 (19)	36 (14)	36 (14)	137 (52)
Visit 8 mo	17 (10)	19 (11)	18 (10)	124 (79)
Visit 16 mo	8 (6)	8 (6)	11 (8)	118 (81)
Visit 24 mo	9 (5)	7 (4)	14 (8)	150 (83)

[a] Four participants were on paroxetine at study entry.

The previous models were rerun with this new SSRI-type variable to determine if differences between individual agents existed. After controlling for the standard covariates (and height for VFat), significant differences emerged (Table 6). Citalopram and escitalopram were associated with the largest increases in body composition measures compared with no SSRI treatment, whereas sertraline was associated with no significant change and fluoxetine's effect was intermediate.

DISCUSSION

To our knowledge, this is the first longitudinal study to examine the independent effect of MDD, GAD, and SSRI treatment on body composition changes in older adolescents. In contrast to our prediction, some MDD measures were inversely correlated with changes in body composition and GAD did not exert a measurable independent effect. In contrast, SSRI treatment predicted an increase in all outcomes. This effect appeared to vary among individual agents.

A large and growing number of studies have found MDD to be associated with increased adiposity.[26] In fact, using the baseline data from this same sample, we found an interaction effect between MDD and weight, whereby overweight or obese individuals with MDD had

TABLE 6 Differences in the Parameter Estimates (SEs) for SSRI Type From Linear Mixed Effects Regression Analysis Models for Body Composition Measures

	BMI *z* Score	FMI *z* Score	LBMI *z* Score	VFat	Height *z* Score
Citalopram versus no SSRI slope	0.24 (0.06)***	0.20 (0.05)***	0.21 (0.05)***	34.9 (9.9)***	−0.03 (0.02)
Fluoxetine versus no SSRI slope	0.14 (0.07)**	0.13 (0.06)**	0.13 (0.06)**	29.6 (11.3)**	−0.04 (0.02)*
Sertraline versus no SSRI slope	0.04 (0.06)	0.05 (0.04)	0.05 (0.05)	8.6 (9.0)	−0.01 (0.02)
Citalopram versus sertraline slope	0.20 (0.08)**	0.15 (0.06)**	0.17 (0.07)**	26.3 (12.5)**	−0.02 (0.03)
Fluoxetine versus sertraline slope	0.10 (0.08)	0.08 (0.07)	0.08 (0.08)	21.1 (13.7)	−0.03 (0.03)
Citalopram versus fluoxetine slope	0.10 (0.09)	0.07 (0.07)	0.08 (0.08)	5.3 (14.1)	0.01 (0.03)

Citalopram group included participants on citalopram or escitalopram.
* $P < .10$.
** $P < .05$.
*** $P < .0005$.

more visceral and subcutaneous fat.[27] More importantly, despite some inconsistencies, longitudinal studies have generally found that MDD predicts the development of obesity over time, regardless of age, sex, or racial and ethnic background.[1,8,28]

When MDD was categorically defined in our sample (ie, as defined in the DSM-IV-TR), it failed to predict changes in BMI *z* score. Even when we divided the participants on the basis of their trend of change in symptoms over the study course (ie, no change, improving toward remission, etc), we again found no association. Only the score on the researcher-completed IDS reached statistical significance, and this was actually in a direction opposite to our prediction: namely, a more severe depression was associated with weight loss. MDD may be associated with increased or decreased appetite and weight.[29] In fact, other researchers have shown that considering patients' symptoms is important in examining the association between MDD and weight gain.[8] Oftentimes, increased appetite in MDD is associated with the atypical subtype. However, the prevalence of MDD with atypical features in our participants was low,[27] perhaps explaining the inverse association between MDD and depression that we observed.

Most prospective studies examining the association of MDD and obesity did not thoroughly account for psychotropic use.[30–34] This is a critical shortcoming, given their potential to cause weight gain.[8,9,35,36] In addition, even studies that assessed psychopharmacology did so often in a cursory way (eg, querying the patient about use in 6-month intervals or in the 2–4 weeks before the study visit, etc).[8,37–42] If depression severity is associated with weight gain and with likelihood of psychotropic use, and if antidepressants cause weight gain, then detailed assessment of treatment is necessary to disentangle one from the other.

In fact, both duration of SSRI use as well as the cumulative dose were positively associated with the body composition measures, which suggests that the effect may be dose-dependent. Of course, SSRI use may be an index of psychopathology severity (ie, more severe cases are prescribed SSRIs) and, therefore, what might appear as an association between SSRI use and weight gain is merely an association between severe MDD or GAD and weight gain (ie, confounding by indication). However, it is important to note that being prescribed an SSRI was not by itself a significant predictor (Table 4). This is also consistent with the lack of a significant association between depression trends and changes in adiposity measures. Finally, when each of the 2 depression indices were entered in the models concurrently with SSRI use, both remained significant and were associated with the outcomes in an inverse direction.

Although the clinical utility of BMI is well established,[20] it fails to distinguish between lean mass, an index of physical fitness, and fat mass, a cardiovascular risk factor.[43] Thus, taking advantage of the availability of DXA scans in our study, we examined fat and lean mass separately. To our surprise, SSRI use was positively associated with both outcome variables in a similar manner. When we specifically focused on VFat, the association with SSRI use remained positive, albeit weaker. This suggests that over extended periods of use, SSRIs will cause an overall increase in BMI, comprising an increase in both fat and lean mass. Importantly, this is also associated with an increase in VFat, which is particularly detrimental to health.[44] Notably, this association cannot be attributed to lifestyle factors, such as physical activity or dietary factors, or to differences in body size (in the case of VFat), which we accounted for. It may be due to a drug-induced increase in sympathetic nervous system activity,[45] as has been shown recently in mice treated chronically with fluoxetine, although the same was not true for citalopram.[46]

DXA-based measurement of lean body mass is indirectly determined by subtracting bone and fat mass from overall mass. Thus, it comprises muscle and water mass.[47] Given that grip strength did not significantly increase during SSRI treatment, it is likely that the increase in lean body mass primarily reflects an increase

in water volume. This is possible given that SSRIs have been associated with the syndrome of inappropriate antidiuretic hormone secretion.[48] In addition, our participants had a low LBMI *z* score, although their BMI was greater than normal (Table 1). Thus, there may have been some increase in muscle mass to carry the additional (fat) weight associated with the initiation of SSRIs. Of note, LBMI *z* score was also less than average in the Iowa Bone Development Study (mean ∼ −0.3; T.L. Burns, PhD, personal communication, 2017), suggesting this may be due, at least in part, to differences in calibration across Hologic imaging units for whole body scans.

The set of primary analyses combined all SSRIs together to optimize sample size. However, when the most commonly used SSRIs were compared, citalopram or escitalopram were associated with the largest increase in body composition measures, whereas sertraline was no different from no SSRI treatment. Fluoxetine, on the other hand, was associated with significant increases, albeit of smaller magnitude. The citalopram and escitalopram results are consistent with findings from the Treatment of Resistant Depression in Adolescence (TORDIA) study in which citalopram and paroxetine showed a larger increase in BMI over 24 weeks when compared with fluoxetine and venlafaxine.[9] However, the magnitude of change we observed was larger likely because our follow-up period was nearly 3 times as long as that in the TORDIA study and because, by design, our participants had not taken psychotropic agents for at least 2 years before study entry. This also likely explains why fluoxetine was associated with weight gain in this study but not in the TORDIA study.

Finally, although the participants grew only by 0.4 cm during the study period, which is to be expected given their age, SSRI use was still found to negatively impact longitudinal growth. Notably, the largest association was with fluoxetine (Table 6), consistent with findings from an intermediate-term randomized clinical trial.[49] Additionally, SSRIs have been reported to disrupt hormonal signaling, decreasing longitudinal growth.[50] This finding needs replication in younger individuals, for whom the implications could be more significant given their potential to grow.

This study's novel findings should be considered in light of its limitations. First, although the sample is relatively sizeable given the detailed assessment, the study may have still been underpowered to detect a significant effect of MDD or GAD (categorically defined), independently of SSRI use. Notably, however, most estimates in the models suggested an inverse association with the outcome measures. Similarly, a larger sample could have allowed stratifying the analyses by sex, race, and ethnicity in a randomized placebo-controlled design. Furthermore, although we attempted to track symptom severity and medication adherence closely, these variables are difficult to capture accurately over extended periods of time.[51] Finally, we documented dietary information and physical activity on the basis of self-report, a method with known shortcomings. Future studies could make use of state-of-the-art methods to collect such information in real time. They could also directly measure muscle mass as well as serum sodium and osmolality to more thoroughly examine the effect of SSRIs on muscle mass.

CONCLUSIONS

In this longitudinal study of older adolescents, depression severity was associated with a reduction in weight over time, whereas SSRI use was associated with an increase in weight over time. This was particularly true for citalopram, escitalopram, and fluoxetine, which is notable given that fluoxetine and escitalopram are the only 2 drugs approved for treatment of MDD in youth, with the latter being favored in medically-ill adolescents given its low propensity to cause drug-drug interactions. Importantly, this led to an increase in VFat, which may account for the elevated incidence of cardiovascular disease observed in patients with MDD. The reason for sex-related differences in the treatment effect on body composition warrants further investigation. Future research should also explore mechanisms as well as interventions to attenuate these treatment effects.

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ABBREVIATIONS

BAI: Beck Anxiety Inventory
DSM-IV-TR: *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*
DXA: dual-energy radiograph absorptiometry
FMI: fat mass index
GAD: generalized anxiety disorder
IDS: Inventory of Depressive Symptomatology
LBMI: lean BMI
MDD: major depressive disorder
MDE: major depressive episode
SSRI: selective serotonin reuptake inhibitors
TORDIA: Treatment of Resistant Depression in Adolescence
VFat: visceral adipose tissue mass

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