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Fat Distribution and Major Depressive Disorder in Late Adolescence

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Abstract

Objective—Substantial evidence exists to indicate bidirectional relationships between obesity and depressive disorders and the importance of fat distribution to this relationship. This analysis used a well-characterized sample of individuals in late adolescence to determine the association between depressive illness and fat distribution.

Method—Medically healthy, 15 to 20 year-olds, one-half of whom had recently begun treatment with a selective serotonin reuptake inhibitor underwent a comprehensive psychiatric evaluation that resulted in diagnostic classification and weekly psychiatric disorder ratings over the prior 4 months, using the Longitudinal Interval Follow-up Evaluation. A whole body scan, using dual x-ray absorptiometry, allowed estimatiions of total body less head (TBLH), total mass, fat mass, and visceral adipose tissue mass (VAT). Assessments occurred between September 2010 and April 2014. linear regression analyses, adjusted for relevant covariates, examined the association between DSM-IV-TR major depressive disorder (MDD) and VAT. These procedures also determined whether significant associations were confined to overweight/obese participants.

Results—The analysis included data from 200 participants (71% females, mean age: 19.0±1.6 years), of whom 128 had current MDD. The presence of MDD was associated with increased fat mass among overweight/obese (Cohen's d=0.79, p<0.002), but not normal weight, participants.

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This was true of both visceral and non-visceral fat mass measures. Accounting for the presence of generalized anxiety disorder did not alter the findings.

Conclusion—In adolescents, relationships between central adiposity and MDD may be confined to those who are overweight/obese. Despite the high co-morbidity of GAD and depressive disorders, only the latter appeared to be significantly associated with central adiposity.

Keywords

Fat distribution; visceral obesity; major depressive disorder; generalized anxiety disorder

Introduction

Studies of both clinic-based[1–6] and community-based[7–11] samples have, with some exceptions,[12–14] demonstrated significant associations between excess body weight and depressive symptoms or disorders. In most reports, central adiposity, whether directly quantified as visceral adipose tissue (VAT),[1, 3, 6–9, 11, 15, 16] or indirectly estimated as a waist-to-hip ratio,[4, 5, 8, 10, 17, 18] accounted for much or all of the relationship between excessive weight and depressive morbidity. Some reports also found that the relationship between VAT and depressive illness was restricted to, or more robust in, overweight/obese individuals.[7] Others found that individual depressive symptoms varied in their tendency to promote weight gain such that the strongest associations with obesity were apparent within depressive subtypes (marked by episodes with hyperphagia and hypersomnia (i.e., atypical depression).[4, 19]

The causal relationship between VAT and depressive illness may well be bidirectional. Depressive illness is likely to promote weight gain when symptoms of fatigue and anhedonia result in decreased activity levels, or when hyperphagia or medication side effects increase food intake. Hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, present in many individuals with major depressive disorder (MDD), may also promote VAT deposition because the effects of increased glucocorticoid release on gluconeogenesis are strongest within VAT.[20] This is illustrated by the finding that obese women with high waist-to-hip ratios exhibit more robust cortisol responses to corticotropin-releasing hormone than do obese women with lower waist-to-hip ratios.[7] In the opposite causal direction, visceral adipocytes produce more cytokines than do subcutaneous ones[21–24] and are thus more likely to promote depressive illness.[5, 12, 25–27]

Accordingly, evidence exists for differing causal models. In one investigation using linear regression analysis, inflammation, as reflected by C-reactive protein (CRP) concentration, appeared to explain how adiposity (i.e., body mass index or BMI) leads to the emergence of depressive symptoms.[28] In another, structural equation modeling suggested that depressive symptoms result in weight accumulation that then activates an inflammatory response.[5]

These findings together suggest that vicious cycles are at play in individuals who are both overweight and suffering from depressive illness. Indeed, a combination of depressive symptoms and high CRP values has been shown to be a substantially stronger predictor of later obesity than either depressive symptoms or high CRP values, individually.[29] This

interplay is, therefore, likely to have significant implications for long-term psychiatric and cardiovascular morbidity and, thus, to comprise a major public health issue.

The relationship between depressive illness and excess weight in adolescence is particularly important because high BMI in this age group increases the risk of obesity in adulthood as much as 45-fold.[30] Moreover, if the association between depressive illness and obesity holds in adolescents, it may have even greater prognostic relevance for long-term physical health than it does in adult populations. This is underscored by the observation in one cohort that depressive symptoms in childhood predicted decreased insulin sensitivity years later, independent of current BMI.[6] However, the cross-sectional studies that have examined links between obesity and depressive illness in this age group have yielded inconsistent results. Some have identified no association,[12, 13, 31] some found an association in one sex but not the other,[4, 27] and some have reported that both boys and girls with a high BMI had more depressive symptoms.[8, 32] Of note, at least some of the variability in the findings may be due to the fact that most, though not all,[8] studies analyzed BMI, a measure that does not distinguish between adipose and lean mass composition.

Prospective studies can better address the direction of causality between depressive illness and excess weight. Most of these have shown that depressive symptoms during late childhood and adolescence predict later obesity[33] particularly in girls.[34, 35] In fact, the relationship between depressive disorders and later obesity appears to be stronger when depression develops earlier in life. Conversely, evidence that obesity portends later depressive illness exists as well.[31, 36–38]

In light of these findings, we utilized data from a well-characterized group of individuals in late adolescence to address the following questions: Is increased adiposity in this age group associated with having MDD and is this association stronger for certain depressive symptoms? If so, how much of this relationship is accounted for by VAT? Does the relationship hold across the full range of BMI or is it largely confined to individuals who are overweight/obese? Finally, is excess VAT significantly associated only with MDD or does this association extend to anxiety disorders?

Methods

Participants

Two-hundred participants, 15 to 20 years old, who were within one month of starting a selective serotonin reuptake inhibitor (SSRI; n=103), or who were taking no psychotropics, were enrolled from outpatient and inpatient clinical settings, as well as by e-mail solicitation and word of mouth, into an ongoing longitudinal observational study examining the skeletal effects of SSRIs. Treatment with other psychotropic medications over the two years prior to study entry led to exclusion, with the exception of benzodiazepines, antihistaminic agents, trazodone, α_2-agonists, mirtazapine, or a stable dose of psychostimulants. Other grounds for exclusion were the presence of eating disorders, substance dependence, pregnancy, significant medical or surgical history, the chronic use of medications potentially affecting bone metabolism (e.g., extended corticosteroid use), or plans to move out of state in the following year. The University of Iowa Institutional Review Board approved the study and

adult participants provided informed consent. The parent/guardian of minor participants provided written informed consent while the minors gave written assent to the study.

Procedures

Trained research coordinators collected demographic and clinical data in an intake assessment battery that included the Inventory for Depressive Symptomatology (IDS).[39] The participants were also queried about their use of alcohol, nicotine, and illicit substances. Subjects completed the physical activity questionnaire for older children, an instrument that quantified physical activity over the preceding week (Crocker et al, 1997) and described their recent food intake with the food frequency questionnaire (FFQ 2005) (NutritionQuest.com).

Trained nursing staff at the Clinical Research Unit of the University of Iowa obtained the anthropometric measurements. Height was measured to the nearest 0.1 cm, using a stadiometer (Holtain Ltd., UK) while standing erect without shoes, and weight was recorded to the nearest 0.1 kg using a digital scale (Scaletronix, Wheaton, IL) while wearing indoor clothes. They were categorized as being obese if their BMI was ≥ 30 kg/m^2 or their age-sex-specific BMI percentile was ≥ 95. The threshold for being underweight was a BMI < 18 kg/m^2 or BMI percentile < 5. The medical records for the year preceding study enrollment were reviewed to extract relevant clinical information, including available anthropometric measurements.

Diagnoses, based on the Diagnostic and Statistical Manual of Mental Disorders,[40] incorporated information from the review of medical records and the self- and researcher-completed symptom rating scales, the NIMH Diagnostic Interview Schedule for Children (DISC-IV),[41] and an unstructured interview by a child psychiatrist (CAC). Parents were not interviewed.

Symptoms of MDD over the four months preceding intake were quantified for each week using the Longitudinal Interval Follow-up Evaluation,[42] modified for use with adolescents (A-LIFE). The A-LIFE is commonly used in longitudinal studies as it allows estimation of both the duration and severity of individual disorders.[43] It identifies change points anchored by memorable dates such as holidays or the beginnings of academic semesters. For mood and anxiety disorders, the A-LIFE Psychiatric Status Rating (PSR) scores range from 1 for no symptoms, to 2 to 4 for varying levels of symptom severity and impairment, and to 5 and 6 for full criteria. Comorbid phenomena, such as substance use disorders, are also scored on a weekly basis on a 3-point Likert scale with 1 reflecting the absence of symptoms and 3 indicating a threshold level. A prior history of the corresponding disorder was not required for the rating to be made, so that sub-threshold symptoms were rated even in the absence of a previous or current full episode.

A whole-body dual energy x-ray absorptiometry (DXA) scan was obtained using a *Hologic Discovery A unit* (Hologic, Inc, Bedford, MA), software package APEX 4.0.1/13.4.1. DXA-based VAT measurements have been validated in adults and shown to be equivalent to measurements obtained using computed tomography.[44] In addition, we found a very strong correlation between DXA-based and magnetic resonance imaging-based VAT volumes in

children and adolescents (r > 0.99, n=4, unpublished data). The Hologic software also determined total body less head (TBLH) mass, lean mass, fat mass, gynoid mass, android mass, and waist circumference. Android and gynoid masures quantified the fat amounts in waist and hip areas, respectively. Daily quality-control scans of the DXA unit are performed with a phantom supplied by the manufacturer.

Data Analysis

Four individuals were excluded from the analysis, two that were diagnosed with a probable psychotic disorder and two that were underweight, Because relationships between adiposity and depressive illness were likely to be more meaningful and robust when depressive symptoms were current. 18 participants who had only a past history of major depressive episodes were excluded. All of these had been in full remission for 3.0±2.5 years.

BMI was computed as weight/height^2 (kg/m^2) and BMI age-sex-specific z scores were generated based on the 2000 Centers for Disease Control and Prevention normative data.[45] Total body less head (TBLH) fat and lean scores were computed as the fat or lean mass minus the mass of the head/height^2 (kg/m^2). Lean body mass index (LBMI) and fat mass index (FMI) age-sex-specific z scores were generated based on the 1999–2004 National Health and Nutrition Examination Survey.[46]

The Student t-test and the chi-square or Fisher's Exact test were used to compare continuous and categorical variables across participants with vs. without MDD. Multivariable linear regression analysis was used to examine the association between MDD and VAT mass, the primary outcome of interest, as well as adiposity-related variables. Adjustments were made for age, sex, and height; the latter accounting for differences related to body frame size.[47] Additionally, in order to examine whether the findings were specific to MDD, the presence of GAD was also included in the model. Further, additional analyses examined the association between adiposity variables and the proportion of weeks during the four months prior to study entry in which MDD ratings indicated meeting diagnostic criteria (i.e., rating of 5 or 6). The presence of reverse vegetative symptoms (hypersomnia or hyperphagia) in the week preceding study entry was taken from the IDS and also examined for its association with increased central adiposity. Because the association between adiposity and depressive illness has been confined to overweight individuals in some studies,[7] we also tested for an interaction effect between the depression measures and the presence or absence of overweight/obesity (referred to as obesity status, henceforward).

Cohen's d effect size was the difference in group-specific least squares means (LS means) divided by the residual of the relevant multivariable linear regression model. All hypothesis tests were two-tailed with a significance level of $p < 0.05$ and analyses utilized procedures from SAS version 9.3 for Windows (SAS Institute Inc., Cary, NC).

Results

Table 1 summarizes the demographic, clinical, and anthropometric characteristics of the sample. As would be expected, female sex, comorbid GAD, and SSRI use were more

prevalent among individuals with MDD. However, no other significant differences between the two MDD groups emerged. One third of the participants were overweight or obese.

Association of MDD and VAT

After adjusting for age (p>0.60), sex (p>0.60), and height (p>0.20), there was a significant interaction effect between obesity status and MDD (p<0.02) whereby no difference in VAT mass was observed within the normal weight group between those with and those without MDD, (p>0.90) but, among overweight/obese individuals, the presence of MDD was associated with a larger VAT mass (difference in LS means= 90.7, 95% confidence interval [CI]: 11.5, 169.8, Cohen's d=0.79, p<0.02). Other fat mass measures also differed significantly by depression status among overweight/obese participants. Further individual adjustments for calorie intake (p=0.90), physical activity (p=0.10), and number of cigarettes smoked each day (p=0.35) did not alter the findings. Cohen's d=0.86 with all three variables in the model. To test the possibility that SSRI exposure had itself affected weight measures we compared the weights of 56 individuals who had been weighed within a month before starting SSRI medication to their weights on study entry. Compared to pretreatment values the age-sex- specific BMI z scores had minimally decreased by study entry (mean difference = −0.07, 95% ci: −0.12, −0.02, p<0.004).

VAT mass, android fat mass, waist circumference, TBLH fat mass, limb fat mass, gynoid fat mass, TBLH lean mass, and BMI z score did not differ by level of reverse vegetative depressive symptoms during the week preceding study entry. For instance, among participants with MDD, those with no hypersomnia or hyperphagia (n=45) had a VAT mass similar to those with at least one of these two symptoms (n=83). Mean VAT mass (kg) values were 0.24±0.15 and 0.28±0.18 (p=0.24), respectively.

Of interest, the zero-order correlations between VAT mass, on the one hand, and both TBLH fat mass and gynoid fat mass (an index of subcutaneous fat), varied by weight category. Correlations were highly significant for overweight/obese individuals (rho=0.74, p<0.0001 and 0.65, p<0.0001) but not for those with normal weights (Spearman's rho=0.16, p=0.06 and 0.05, p>0.50). In contrast, the association between VAT mass and TBLH total mass was more comparable between the two obesity status groups [rho=0.54 (p<0.0001) vs. rho=0.69 (p<0.0001).

Impact of GAD on the Association of MDD and VAT

The above multivariable regression analyses were repeated after accounting for the presence of GAD as this is frequently comorbid with MDD and may itself affect metabolic pathways. Again, among lean participants, the presence of GAD was not related to any of the adiposity variables. However, among the overweight/obese, the presence of GAD was associated with reduced adiposity, except for VAT mass (Table 2). As with MDD, GAD was not associated with lean mass.

Discussion

This study of a group in their late adolescence, enriched for those in a current major depressive episode, showed that MDD in adolescents and young adults who are obese is

associated with greater visceral adiposity. We are unaware of studies, other than the one cited,[7] that considered relationships between body fat distribution and depressive symptoms separately in normal weight and overweight groups. The greater importance of the presence of MDD to fat mass in overweight individuals may be a reflection of the “vicious cycle” posited earlier, perhaps with a threshold effect. If so, adiposity and depressive morbidity may drive each other in at-risk individuals, with increasing intensity as both phenomena worsen. Certainly the earlier findings, together with those described here, indicate that future investigations should separate obese and normal weight individuals as they assess relationships between adiposity and depressive morbidity.

The findings did not support our prediction that relationships between depressive disorder and adiposity would be strongest for measures of visceral fat. However, associations between visceral fat mass and measures of peripheral fat stores were particularly high in the overweight/abuse group and this may have obscured differences in the strengths of the relationships between depressive morbidity and peripheral versus central fat measures.

Though GAD was strongly comorbid with MDD, it was independently associated with adiposity in the overweight/obese group though in the opposite direction from its relation to MDD. Hillman et al.,[8] likewise found positive relationships between BMI measures and depressive symptoms but not trait anxiety. Anderson et al.,[34] found both anxiety and depressive symptoms to be predictive of later obesity, but they did not test both in the same model, and it was thus not possible to isolate the independent contribution of anxiety disorders. Our finding that depressive morbidity, but not that of GAD, was strongly associated with higher amounts of adiposity despite the frequent coexistence of GAD and MDD is intriguing since it implies that a core set of depressive symptoms is at play and that the relationship to fat distribution is not one simply involving psychiatric morbidity in general. In further support of this specificity is another recent report that showed that young women with borderline personality disorder and MDD had higher VAT measures than did healthy controls while those with borderline personality disorder alone did not.[2]

This study’s several strengths include the enrollment of young, unmedicated or only recently medicated participants. Extensive psychiatric assessments included carefully determined diagnoses and week-to-week quantifications of symptom severity for MDD and anxiety disorders. Finally, the DXA scans provided validated adiposity measures that specifically isolate VAT.

Chief among the study’s limitations is its cross-sectional design. The results cannot be used as evidence for causal relationships between excessive body weight and depressive illness in either direction. A two-year follow-up is underway, however. Future analyses will address whether high VAT values increase risks for the onset, persistence, or recurrence of MDD and whether the presence or persistence of depressive illness promotes subsequent VAT deposition.

Longitudinal measures of depressive and anxiety disorder morbidity were limited to the four months that preceded intake because potential inadequacies of memory would have made

morbidity measures over longer periods less dependable. The ongoing prospective phase will allow a substantially longer view of morbidity.

Inclusion criteria limited ages to 15 through 20 so as to avoid the greater flux in growth and metabolism that puberty entails. This, of course, precludes the generalizability of these results to younger adolescents and children. We would argue, though, that these age groups should be studied separately given the differences between them, both in anthropomorphic measures and in the manifestations of depressive illness.

A meta-analysis has shown that relationships between early depressive illness and later obesity are strongest in adolescent depressive disorder.[33] This makes our findings of public health importance because they indicate a particular age period when intervention to lessen eventual cardiovascular morbidity through better weight control might be most useful. Moreover, the possibility that central adiposity promotes the persistence of depressive symptoms in overweight/obese individuals suggests an underlying role for inflammatory mechanisms in the maintenance of depressive disorder and this, in turn, may offer another potential tool in the management of an illness that often results in substantial disability over a lifetime.[48]

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Clinical Points

- The relationship between excess body weight and depressive illness is complex and may differ by the distribution of body fat, age and type of depressive symptoms.
- The results presented here indicate that the likelihood of current major depressive disorder increases with fat quantities in overweight but not normal weight adolescents, regardless of fat distribution.
- In contrast, generalized anxiety disorder does not appear to be associated with increased adiposity despite its high comorbidity with depressive disorder.
- The findings suggest that efforts directed at weight loss may improve control of depressive symptoms, and vice versa, in overweight adolescents and young adults.

Table 1

Demographic and Clinical Characteristics by Lifetime History of MDD

	Total Sample (n=200)	MDD (n=128)	No MDD (n=72)	*p*
Female, n (%)	142 (71)	99 (77)	43 (60)	**<0.01**
Age, years	19.0±1.6	18.9±1.6	19.1±1.4	>0.30
Caucasian, n (%)	175 (88)	112 (88)	63 (88)	>0.90
Hispanic, n (%)	16 (8)	13 (10)	3 (4)	>0.10
Physical Activity Score	2.1±0.8	2.1±0.8	2.2±0.8	>0.50
Calorie Intake, kcal/d	1378±916	1679±870	1,840±988	>0.10
Taking SSRI, n (%)	103 (52)	98 (67)	10 (14)	**<0.0001**
GAD, n (%)	64 (32)	51 (40)	13 (18)	**<0.0001**
Alcohol Abuse, n (%)	24 (12)	14 (11)	10 (14)	>0.50
Cigarette Use, n (%)	30 (15)	18 (14)	12 (17)	>0.60
Cigarettes/day	2.6±4.1	3.1±5.0	1.9±2.2	>0.90
Anthropometric Measurements				
BMI, kg/m^2	24.2±4.8	24.3±4.5	24.2±5.0	>0.40
BMI z score	0.40±0.92	0.39±0.92	0.42±0.93	>0.60
Overweight/Obese, n (%)	65 (33)	36 (28)	29 (40)	***<0.10***
Waist Circumference, cm	89.0±13.0	89.3±12.1	88.8±13.6	>0.50
TBLH Mass, kg	64.6±14.9	64.1±14.5	65.5±15.7	>0.60
TBLH Lean Mass, kg	46.0±9.7	45.1±8.6	47.6±11.3	>0.10
LBMI z score	−0.12±0.85	−0.10±0.84	−0.15±0.88	>0.70
TBLH Fat Mass, kg	18.6±9.5	19.0±9.9	17.9±8.9	>0.50
FMI z score	−0.11±0.87	−0.13±0.90	−0.06±0.83	>0.50
Limb Fat Mass, kg	10.6±4.8	10.8±5.0	10.0±4.5	>0.20
Gynoid Fat Mass, kg	1.3±0.9	1.4±0.9	1.3±0.8	>0.90
Android Fat Mass, kg	3.9±1.6	4.0±1.7	3.7±1.5	>0.30
Visceral Adipose Tissue Mass, kg	0.26±0.15	0.26±0.17	0.26±0.12	>0.40

(mean±sd unless noted otherwise)

MDD: major depressive disorder; SSRI: selective serotonin reuptake inhibitor; GAD: generalized anxiety disorder; BMI: body mass index; TBLH: total body less head; LBMI: lean body mass index; FMI: fat mass index.

Table 2

Fat Distribution Measures[a] and Current Diagnoses: Overweight/Obese Participants[b]

	MDD +	MDD −	Cohen d[c]	GAD +	GAD −	Cohen d[c]
VAT Fat Mass, kg	0.44	0.34	**0.88**	0.37	0.41	0.36
Android Fat Mass, kg	2.3	1.8	**0.86**	2.3	1.8	**0.82**
Waist Circumference, cm	104.3	97.5	**0.81**	97.7	104.2	**0.78**
TBLH Fat Mass, kg	27.7	22.2	**0.94**	21.9	28.1	**1.06**
Limb Fat Mass, kg	14.3	11.9	0.76	11.7	14.6	**0.90**
Gynoid Fat Mass, kg	5.2	4.4	0.75	4.3	5.3	**0.97**
TBLH Lean Mass, kg	53.9	52.5	0.34	52.7	53.7	0.26

[a] Least square means

[b] Significant findings ($p<0.05$) are bolded and marginally significant findings ($p<0.10$) are underlined. MDD: major depressive disorder, GAD: generalized anxiety disorder, VAT: visceral adipose tissue, TBLH: total body less head. Plus and minus signs indicated presence or absence of the disorder

[c] Adjusted for age, sex, and height. The differences between lean individuals with vs. without MDD and with vs. without GAD were not significant.