Original Investigation

Depression With Atypical Features and Increase in Obesity, Body Mass Index, Waist Circumference, and Fat Mass

A Prospective, Population-Based Study

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IMPORTANCE Depression and obesity are 2 prevalent disorders that have been repeatedly shown to be associated. However, the mechanisms and temporal sequence underlying this association are poorly understood.

OBJECTIVE To determine whether the subtypes of major depressive disorder (MDD; melancholic, atypical, combined, or unspecified) are predictive of adiposity in terms of the incidence of obesity and changes in body mass index (calculated as weight in kilograms divided by height in meters squared), waist circumference, and fat mass.

DESIGN, SETTING, AND PARTICIPANTS This prospective population-based cohort study, CoLaus (Cohorte Lausannoise)/PsyCoLaus (Psychiatric arm of the CoLaus Study), with 5.5 years of follow-up included 3054 randomly selected residents (mean age, 49.7 years; 53.1% were women) of the city of Lausanne, Switzerland (according to the civil register), aged 35 to 66 years in 2003, who accepted the physical and psychiatric baseline and physical follow-up evaluations.

EXPOSURES Depression subtypes according to the *DSM-IV*. Diagnostic criteria at baseline and follow-up, as well as sociodemographic characteristics, lifestyle (alcohol and tobacco use and physical activity), and medication, were elicited using the semistructured Diagnostic Interview for Genetic Studies.

MAIN OUTCOMES AND MEASURES Changes in body mass index, waist circumference, and fat mass during the follow-up period, in percentage of the baseline value, and the incidence of obesity during the follow-up period among nonobese participants at baseline. Weight, height, waist circumference, and body fat (bioimpedance) were measured at baseline and follow-up by trained field interviewers.

RESULTS Only participants with the atypical subtype of MDD at baseline revealed a higher increase in adiposity during follow-up than participants without MDD. The associations between this MDD subtype and body mass index (β = 3.19; 95% CI, 1.50-4.88), incidence of obesity (odds ratio, 3.75; 95% CI, 1.24-11.35), waist circumference in both sexes (β = 2.44; 95% CI, 0.21-4.66), and fat mass in men (β = 16.36; 95% CI, 4.81-27.92) remained significant after adjustments for a wide range of possible cofounding.

CONCLUSIONS AND RELEVANCE The atypical subtype of MDD is a strong predictor of obesity. This emphasizes the need to identify individuals with this subtype of MDD in both clinical and research settings. Therapeutic measures to diminish the consequences of increased appetite during depressive episodes with atypical features are advocated.

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Major depressive disorder (MDD) is among the diseases with the greatest public health impact worldwide[1] and confers an approximately 50% elevated mortality of various causes.[2] Obesity represents another major burden for public health and is also associated with elevated mortality.[3] Moreover, both depression and obesity are associated with various chronic diseases such as diabetes mellitus, hypertension, dyslipidemia, cancer, and respiratory and osteoarticular diseases.[4-9] Obesity could also be one explanation for the approximately doubled risk for cardiovascular disease (CVD)[10] and cerebrovascular diseases and the excess mortality among depressed individuals.[2] Accordingly, gaining a better understanding of the mechanisms underlying the association between MDD and obesity is of high clinical and scientific relevance.

Although cross-sectional studies have consistently documented a strong association between obesity and depressive disorders or depressive symptoms,[11] the direction of this association and its underlying mechanisms are still poorly understood. Prospective studies have revealed contradictory findings regarding the sequence of onset of depression and obesity.[12,13] These inconsistent results could be due to the large heterogeneity of depression as well as to methodologic variance across studies including sample selection, the length of follow-up, and the assessment of depression and obesity. A major limitation of previous prospective studies, which also likely contributes to inconsistent findings, was the use of inaccurate measures. A recent review of population-based studies on the prospective association between obesity and depression could only identify 3 of 15 studies that included measured weight and height as well as direct diagnostic interviews to elicit standardized criteria for depression.[13] However, these 3 studies were restricted to adolescents and did not provide evidence showing an association between depression before the age of 15 years and obesity in young adulthood. The other studies used self-reported weight and height or assessed depressive symptoms using rating scales, which generally do not allow characterization into depression subtypes and do not take into account the frequent occurrence of comorbid mental disorders or past psychopathology.

Because of the large heterogeneity of depression in terms of symptom manifestations, course, and response to pharmacologic treatment,[14,15] studying subtypes of depression is likely to be a more promising approach than studying depression as a whole with respect to cardiovascular risk. Four studies that subdivided depression according to the presence or absence of atypical features, such as increased appetite and hypersomnia during depressive episodes, showed that participants with these features had a higher body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) than other individuals with depression or those who had never been depressed.[16-19] However, the cross-sectional design of 3 of these studies[16,17,19] impeded drawing conclusions regarding the direction of causality, whereas the population-based prospective Zurich Cohort Study revealed a trend for a positive association between atypical depression and the average rate of weight gain over 20 years.[18] Moreover, most of the previous studies assessing the association between depression and obesity were restricted to BMI as an adiposity measure, although recent data suggest that waist circumference is more strongly associated with the risk for CVD than BMI[20] and that body fat percentage could be an independent risk factor for mortality.[21]

Accordingly, the aims of the present study were to assess the prospective associations between MDD subtypes, including melancholic, atypical, combined, and unspecified, and the subsequent change of adiposity in terms of BMI, waist circumference, and fat mass, or the incidence of obesity, in a population-based prospective cohort using a standardized diagnostic interview and anthropometric measures.

Methods

Participants

The data of the present article stemmed from CoLaus (Cohorte Lausannoise)/PsyCoLaus (Psychiatric arm of the Cohorte Lausannoise),[22,23] cohort studies designed to prospectively study mental disorders and cardiovascular risk factors in the general population. The sample was randomly selected from the residents of the city of Lausanne, Switzerland, in 2003, according to the civil register. Sixty-seven percent of the 35- to 66-year-old participants (n = 5535) who underwent the physical examination between 2003 and 2006 also accepted the psychiatric evaluation, which resulted in a sample of 3719 individuals.[23] Participants with a diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, or eating disorders at the psychiatric baseline evaluation (n = 159) were excluded from the present analyses because these disorders are likely associated with changes in adiposity. Among the remaining individuals who had undergone the psychiatric baseline evaluation, 3054 also took part in the physical follow-up evaluation, whereas 42 individuals had died during the follow-up interval and 464 were not available for the physical examination, resulting in a participation rate of 87% among the survivors. The mean (SD) duration of the follow-up was 5.5 (0.4) years. Compared with those who participated at follow-up, nonparticipants were more likely to be men, have lower socioeconomic status, be smokers, have a higher alcohol consumption, be less physically active, meet criteria for obesity, and live alone at the baseline evaluation.

The institutional ethics committee of the University of Lausanne approved the CoLaus study (approvals 16/03 and 33/09) and subsequently the PsyCoLaus study (approvals 134/05 and 239/09). All participants signed a written informed consent after having received a detailed description of the goal and funding of the study.

Assessments

The physical measures were taken in identical ways at the baseline and follow-up visits. Participants had to have fasted for at least 8 hours and abstained from strenuous physical activity for 12 hours before the examination. Weight and height were measured in participants standing without shoes in light indoor clothes. Weight was measured in kilograms to the nearest 100 g and height was measured to the nearest 5 mm. Obe-

sity was defined as a BMI of greater than or equal to 30. Waist circumference was measured with a nonstretchable tape over the unclothed abdomen at the narrowest point between the lowest rib and the iliac crest. Two measures were made and the mean value was used for analyses. Fat mass was assessed by electrical bioelectrical bioimpedance[24] using the Bodystat 1500 analyzer.

In addition, information on sociodemographic characteristics, current medication, and health-related behaviors, including smoking, alcohol consumption, and physical activity, was collected through a standardized interview. White origin was defined as having both parents and grandparents born in a restricted list of countries (available from the authors). Socioeconomic status was assessed using the Hollingshead scale.[25] Alcohol consumption was considered to be low if participants drank between 1 and 13 units per week and high if they drank 14 or more units per week. Participants were considered physically active if they reported physical activity for at least 20 minutes twice a week.

Diagnostic information on mental disorders at baseline and follow-up was collected using the French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS).[26,27] The DIGS was completed with anxiety disorder sections of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version.[28] Psychiatric diagnoses were assigned according to the *DSM-IV*.[29] The criteria for atypical features according to the *DSM-IV* requires mood reactivity and at least 2 of the following 4 symptoms: (1) increased appetite or significant weight gain, (2) hypersomnia, (3) leaden paralysis, and (4) a long-standing pattern of interpersonal rejection sensitivity. Because weight change was an outcome variable, we only applied the appetite part of the criterion, which requires either increased appetite or weight gain. For the melancholic features specifier, the *DSM-IV* requires either a loss of energy or a lack of mood reactivity and 3 of the following 5 symptoms: (1) depression regularly worse in the morning, (2) early morning awakening, (3) psychomotor retardation or agitation, (4) decreased appetite (we did not consider weight loss as a criterion), and (5) excessive guilt. We could not take into account the criterion "distinct quality of depressed mood" because it was not assessed in the DIGS. Major depressive disorder was subdivided according to the history of atypical or melancholic features into 4 subtypes: (1) MDD with atypical features only, (2) MDD with melancholic features only, (3) combined MDD with atypical and melancholic features simultaneously or during distinct episodes, and (4) unspecified MDD with neither atypical nor melancholic features. For individuals who refused the DIGS interview at follow-up (19%), MDD status at follow-up was assessed using the Center for Epidemiologic Studies Depression scale. A score of 19 or higher was considered an indicator of the presence of a major depressive episode (MDE).[30,31] Interviewers were required to be psychologists, who were trained over a 2-month period. Each interview and diagnostic assignment was reviewed by an experienced senior psychologist.

Statistical Analysis

Analyses were performed using the Statistical Analysis System version 9.2 for Windows (SAS). Associations between MDD status and continuous adiposity variables (BMI, waist circumference, and fat mass) were established at baseline using robust rather than multiple regression models because the residuals did not reveal a normal distribution. The association between MDD status and obesity was assessed using logistic regression. Similar serially adjusted models were used to determine the associations between depression status at baseline and changes of continuous variables (calculated in percentage of the baseline value) or the incidence of obesity during follow-up. The choice of the covariates in the models was determined by the findings of previous studies that suggested potential associations of these covariates with both MDD and adiposity variables. The first model (model 1) was adjusted for sociodemographic characteristics (sex, age, socioeconomic status, ethnicity, and living alone). The second model (model 2) was further adjusted for the effects of comorbid anxiety disorders or drug dependence, treatment with antidepressants or drugs possibly inducing weight gain (a list and the way in which it was extracted is provided in the eTable in the Supplement) and health-related behavioral characteristics (physical activity, alcohol consumption, and smoking status) at baseline. The third model (model 3) was also adjusted for the presence of an MDE during the follow-up to assure that a measured association was attributable to depression status at baseline and not to new episodes that occurred during the follow-up. When the association between MDD and the incidence of obesity was assessed, all models were also adjusted for baseline BMI. We found a significant interaction between sex and depression status to affect the body fat percentage (sex by current atypical MDD: $P = .04$ and $P = .006$ in models 1 and 2, respectively). Accordingly, data regarding this outcome were analyzed separately for women and men.

Results

Table 1 provides the sample description for all participants according to the MDD status. At baseline, 7.6% of the participants met criteria for current MDD and 36.7% reported at least 1 remitted MDE in the past. Among the participants with MDD, approximately 10% revealed atypical and melancholic episodes (combined), 14% had atypical episodes, 29% had melancholic episodes, and 48% had unspecified episodes. Among depressed participants taking antidepressant medication at baseline, approximately 75% reported taking selective serotonin or serotonin-norepinephrine reuptake inhibitors and less than 10% a tricyclic or tetracyclic drug.

The mean (SD) BMI of the whole sample at baseline was 25.3 (4.3) (mean [SD], 24.6 [4.7] in women and 26.2 [3.7] in men). **Table 2** presents the baseline BMI of the sample and the change of the BMI in percentage during the follow-up in function of the baseline depression status. Participants with current or remitted atypical MDD as well as those with the current combined MDD subtype revealed a higher BMI at baseline than individuals who had never been depressed. During the follow-up, the BMI of the whole sample increased by 2.6% (SD, 6.7%). After adjustment for sociodemographic characteristics (model 1), participants meeting the criteria for current atypical MDD

Table 1. Characteristics of Participants at Baseline

Characteristic	All Participants	MDD Status								
		Current				Remitted				
		Atypical	Melancholic	Combined	Unspecified	Atypical	Melancholic	Combined	Unspecified	No MDD
Total No.	3054	48	55	31	97	140	323	104	554	1702
Women, %	53.1	66.7	72.7	74.2	54.6	72.9	68.1	69.2	61.4	43.4
Age, mean (SD), y	49.7 (8.8)	50.1 (8.0)	49.1 (8.1)	50.2 (9.2)	48.2 (7.9)	48.0 (8.9)	49.3 (8.8)	49.3 (9.2)	49.0 (8.9)	50.2 (8.8)
SES, mean (SD)[a]	3.4 (1.3)	2.9 (1.3)	3.1 (1.3)	2.7 (1.2)	3.3 (1.3)	3.6 (1.2)	3.4 (1.3)	3.5 (1.3)	3.5 (1.2)	3.4 (1.3)
Nonwhite, %	8.0	6.3	9.1	9.7	14.4	7.9	8.4	8.7	7.9	7.5
Living alone, %	23.2	14.6	34.5	22.6	22.7	33.6	29.4	28.8	28.3	19.1
Anxiety disorders, %[b]	17.4	35.4	32.7	25.8	21.6	21.4	25.7	31.7	22.0	11.7
Smoking status, %										
Former	32.6	31.3	21.8	29.0	30.9	30.0	33.1	28.8	34.3	33.0
Current	27.3	22.9	41.8	29.0	30.9	28.6	27.2	35.6	31.8	24.6
Alcohol intake, %[c]										
Low	58.8	62.5	50.9	41.9	51.5	65.7	60.1	62.5	60.3	58.1
High	16.0	10.4	14.5	19.4	14.4	7.9	11.1	12.5	14.3	18.6
Substance dependence, %[d]	2.5	2.1	0.0	3.2	3.1	0.7	3.7	3.8	2.9	2.2
Physically active, %[e]	56.5	35.4	38.2	35.5	44.3	59.3	62.8	56.7	57.9	56.9
Antidepressant use, %	7.5	22.9	20.0	16.1	20.6	18.6	16.7	22.1	7.4	2.2
Weight gain–inducing drug use, %	14.4	31.3	12.7	25.8	21.6	20.7	21.4	30.8	16.6	9.8
Age at MDD onset, mean (SD), y	NA	33.6 (16.7)	35.9 (13.4)	32.3 (14.0)	35.2 (13.9)	32.7 (13.1)	31.3 (12.1)	29.4 (12.2)	33.7 (12.7)	NA
Time spent in episodes, mean (SD), wk	NA	398.2 (524.8)	252.5 (232.2)	364.2 (516.2)	352.0 (437.9)	136.2 (207.9)	155.1 (257.8)	191.3 (364.7)	121.1 (230.7)	NA
MDE during follow-up, %[f]	15.9	23.4	30.8	24.1	26.9	29.9	26.4	32.4	19.9	9.0

Abbreviations: MDD, major depressive disorder; MDE, major depressive episode; SES, socioeconomic status.

[a] Hollingshead Four-Factor Index of Social Status (5 is the highest status).

[b] Generalized anxiety disorder, social phobia, panic disorder, or agoraphobia.

[c] Number of drinks per week: low = 1-13 and high = 14 or more.

[d] Lifetime dependence on cocaine, heroin, stimulant, sedative, or hallucinogen.

[e] Physically active more than 20 minutes twice a week.

[f] Information on 2942 participants.

and, to a lesser degree, those who met criteria for remitted atypical episodes or remitted melancholic episodes at baseline had a higher BMI increase than participants who had never been depressed. These differences in BMI increase remained statistically significant after additional adjustment for comorbid anxiety or drug dependence, lifestyle characteristics (physical activity, alcohol consumption, and smoking) and medication use (antidepressants and drugs potentially inducing weight gain) at baseline (model 2) and additional adjustment for the presence of an MDE during the follow-up (model 3). In contrast to the participants with atypical MDD, those with remitted melancholic episodes did not reveal a higher BMI than those who had never been depressed at baseline (Table 2) or follow-up (mean [SD], 26.0 [4.5] and 25.7 [4.8], respectively; $\beta = 0.17$; 95% CI, −0.37 to 0.60).

During follow-up, the proportion of participants meeting criteria for obesity increased from 12.4% to 15.5%. At baseline, only participants with remitted atypical MDD revealed a significantly higher prevalence of obesity than those who had never been depressed (**Table 3**). Among participants who were not obese at baseline, current atypical MDD strongly increased the odds for being obese at the follow-up visit regardless of the number of variables for which the models were adjusted (Table 3). Similarly, remitted melancholic MDD predicted an increased risk for obesity after adjustment for potential confounders (models 2 and 3). However, the prevalence of obesity in participants with remitted melancholic MDD did not significantly differ from that of participants who had never been depressed at baseline (Table 3) or follow-up (mean [SD], 13.9% [1.9%] and 15.8% [0.9%], respectively; odds ratio [OR], 0.94; 95% CI, 0.66-1.33).

The mean (SD) waist circumference of the participants was 87.6 (13.0) cm. Participants with current or remitted atypical

Table 2. BMI at Baseline and BMI Change During Follow-up by Depression Status

	BMI at Baseline(n = 3054)		BMI Change, % of the Baseline Value			
				β (95% CI)		
Depression Status	Mean (SD)	β (95% CI)[a]	% (SD)	Model 1(n = 3024)[b]	Model 2(n = 3024)[c]	Model 3(n = 2917)[d]
Current MDD						
Atypical	26.8 (4.1)	1.77 (0.71 to 2.82)[e]	4.3 (7.7)	2.86 (1.19 to 4.53)[f]	3.03 (1.35 to 4.71)[f]	3.19 (1.50 to 4.88)[f]
Melancholic	25.4 (5.2)	0.16 (−0.83 to 1.15)	3.6 (7.1)	0.51 (−1.05 to 2.07)	0.53 (−1.04 to 2.10)	0.91 (−0.70 to 2.52)
Combined	26.3 (4.2)	1.41 (0.11 to 2.72)[g]	2.0 (8.5)	1.18 (−0.87 to 3.22)	1.46 (−0.59 to 3.50)	2.07 (−0.03 to 4.18)
Unspecified	25.1 (4.5)	0.02 (−0.73 to 0.77)	2.5 (7.0)	0.28 (−0.90 to 1.46)	0.41 (−0.78 to 1.60)	0.43 (−0.78 to 1.63)
Remitted MDD						
Atypical	26.4 (5.2)	1.14 (0.50 to 1.78)[f]	3.2 (8.2)	1.12 (0.12 to 2.12)[g]	1.28 (0.28 to 2.29)[g]	1.18 (0.16 to 2.20)[g]
Melancholic	24.8 (4.8)	−0.31 (−0.75 to 0.13)	4.0 (7.7)	1.20 (0.50 to 1.89)[f]	1.36 (0.65 to 2.07)[f]	1.43 (0.71 to 2.16)[f]
Combined	25.1 (3.9)	0.13 (−0.60 to 0.86)	2.1 (6.5)	0.16 (−0.98 to 1.31)	0.34 (−0.82 to 1.50)	0.49 (−0.68 to 1.66)
Unspecified	24.8 (4.1)	−0.23 (−0.59 to 0.13)	2.6 (6.7)	0.14 (−0.42 to 0.70)	0.17 (−0.39 to 0.74)	0.23 (−0.34 to 0.80)
No MDD	25.5 (4.2)	0 [Reference]	2.2 (6.2)	0 [Reference]	0 [Reference]	0 [Reference]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MDD, major depressive disorder.

[a] Robust regression adjusted for age and sex.

[b] Model 1: robust regression adjusted for age, sex, socioeconomic status, ethnicity, living alone, and length of follow-up.

[c] Model 2: model 1 and adjusted for physical activity, smoking habit, alcohol use, drug dependence, anxiety disorders, antidepressant use, and weight-increasing drug use.

[d] Model 3: model 2 and adjusted for the presence of major depressive episode during follow-up.

[e] $P < .01$.

[f] $P < .001$.

[g] $P < .05$.

Table 3. Obesity at Baseline and Incidence of Obesity During Follow-up by Depression Status at Baseline Incidence of Obesity During Follow-up According to Depression Status at Baseline

	Obesity at Baseline(n = 3054)		Incidence of Obesity During Follow-up			
				OR (95% CI)		
Depression Status	%	OR (95% CI)[a]	%	Model 1(n = 2674)[b]	Model 2(n = 2674)[c]	Model 3(n = 2580)[d]
Current MDD						
Atypical	14.6	1.23 (0.54-2.79)	17.1	3.58 (1.25-10.25)[e]	3.66 (1.23-10.95)[e]	3.75 (1.24-11.35)[e]
Melancholic	16.4	1.49 (0.71-3.11)	8.7	2.53 (0.60-10.61)	2.80 (0.67-11.74)	3.20 (0.75-13.64)
Combined	19.4	1.73 (0.69-4.32)	4.0	0.63 (0.07-5.67)	0.80 (0.09-7.04)	0.78 (0.09-7.05)
Unspecified	13.4	1.16 (0.63-2.13)	1.2	0.19 (0.02-1.55)	0.18 (0.02-1.47)	0.18 (0.02-1.50)
Remitted MDD						
Atypical	20.0	0.69 (0.34-1.39)	8.9	1.53 (0.65-3.58)	1.73 (0.72-4.15)	1.88 (0.77-4.55)
Melancholic	10.5	1.98 (1.26-3.10)[f]	5.9	1.82 (0.94-3.55)	2.03 (1.03-4.02)[e]	2.11 (1.04-4.29)[e]
Combined	8.7	0.86 (0.58-1.27)	5.3	0.98 (0.32-3.07)	0.99 (0.32-3.07)	1.06 (0.34-3.32)
Unspecified	9.4	0.75 (0.54-1.04)	4.0	0.93 (0.51-1.67)	0.92 (0.50-1.67)	1.04 (0.57-1.92)
No MDD	13.0	1 [Reference]	5.1	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: MDD, major depressive disorder; OR, odds ratio.

[a] Adjusted for age and sex.

[b] Model 1: logistic regression adjusted for age, sex, socioeconomic status, ethnicity, baseline body mass index, and length of follow-up.

[c] Model 2: model 1 and adjusted for physical activity, smoking habit, alcohol use, substance dependence, living alone, anxiety disorders, antidepressant use, and weight-increasing drug use.

[d] Model 3: model 2 and adjusted for presence of major depressive episode during follow-up.

[e] $P < .05$.

[f] $P < .01$.

MDD had a larger waist circumference than individuals who had never been depressed (**Table 4**). The waist circumference increased by 4.6% (8.3%) during the follow-up. Again, the presence of atypical MDD at baseline predicted elevated waist increase during the follow-up regardless of the number of variables for which we adjusted (Table 4).

The mean (SD) fat mass percentage was 33.0% (7.9%) in women and 22.7% (7.5%) in men at baseline. The fat mass was higher in women with current or remitted atypical MDD than in women who had never been depressed (**Table 5**). Similarly, men with remitted atypical MDD had an elevated fat mass at baseline. Depression status at baseline was only predictive of the increase of body fat percentage in men. Men presenting with a current atypical MDD at baseline revealed an elevated increase of body fat at follow-up.

Table 4. Waist Circumference at Baseline and Waist Circumference Change During Follow-up by Depression at Baseline

	Waist at Baseline, cm(n = 3054)		Waist Change, % of the Baseline Value			
				β (95% CI)		
Depression Status	Mean (SD)	β (95% CI)[a]	% (SD)	Model 1(n = 2988)[b]	Model 2(n = 2988)[c]	Model 3(n = 2883)[d]
Current MDD						
Atypical	89.8 (11.8)	4.52 (1.53 to 7.51)[e]	6.8 (8.2)	2.31 (0.14 to 4.49)[f]	2.39 (0.20 to 4.58)[f]	2.44 (0.21 to 4.66)[f]
Melancholic	85.5 (14.6)	0.42 (−2.38 to 3.23)	5.4 (8.5)	0.55 (−1.46 to 2.57)	0.42 (−1.61 to 2.46)	0.51 (−1.59 to 2.61)
Combined	87.8 (10.6)	3.27 (−0.44 to 6.97)	4.2 (9.1)	−0.43 (−3.09 to 2.23)	−0.32 (−2.99 to 2.35)	0.12 (−2.64 to 2.89)
Unspecified	87.1 (13.0)	0.41 (−1.73 to 2.54)	5.5 (9.3)	1.09 (−0.45 to 2.63)	1.18 (−0.38 to 2.73)	1.04 (−0.55 to 2.64)
Remitted MDD						
Atypical	88.7 (14.5)	3.52 (1.71 to 5.33)[g]	5.5 (9.1)	0.9 (−0.42 to 2.21)	1.01 (−0.31 to 2.34)	0.86 (−0.49 to 2.21)
Melancholic	85.1 (13.9)	−0.64 (−1.89 to 0.61)	6.1 (9.9)	0.75 (−0.16 to 1.66)	0.81 (−0.12 to 1.74)	0.92 (−0.03 to 1.87)
Combined	85.6 (12.2)	0.65 (−1.42 to 2.72)	5.2 (9.2)	−0.34 (−1.83 to 1.15)	−0.31 (−1.82 to 1.20)	−0.14 (−1.67 to 1.40)
Unspecified	85.4 (12.2)	−0.74 (−1.75 to 0.27)	4.6 (8.3)	−0.03 (−0.77 to 0.70)	−0.09 (−0.83 to 0.65)	−0.12 (−0.88 to 0.64)
No MDD	88.8 (12.9)	0 [Reference]	4.0 (7.6)	0 [Reference]	0 [Reference]	0 [Reference]

Abbreviation: MDD, major depressive disorder.

[a] Robust regression adjusted for age.

[b] Model 1: robust regression adjusted for age, sex, socioeconomic status, ethnicity, living alone, and length of follow-up.

[c] Model 2: model 1 and adjusted for physical activity, smoking habit, alcohol use, drug dependence, anxiety disorders, antidepressant use, and weight-increasing drug use.

[d] Model 3: model 2 and adjusted for presence of major depressive episode during follow-up.

[e] $P < .01$.

[f] $P < .05$.

[g] $P < .001$.

Discussion

To our knowledge, the present study is the first to assess the prospective associations between subtypes of MDD and the subsequent changes in adiposity in the general population. The most salient findings were that (1) MDD with atypical features is prospectively associated over a 5.5-year period with a higher increase in adiposity in terms of BMI, incidence of obesity, and waist circumference in both sexes as well as fat mass in men. (2) The higher increase of adiposity in individuals with MDD with atypical features is not explained by potential confounders including sociodemographic and lifestyle characteristics, comorbid mental disorders, antidepressant medication, or other potentially weight-increasing medications. And (3) the elevated BMI increase in individuals with MDD with atypical features is not a temporary phenomenon but persists after the remission of the depressive episode and is not attributable to new episodes.

The results of the present study should be considered in the context of several limitations. First, the interval of approximately 1 year between the physical and the psychiatric baseline evaluations entailed the risk for misclassifying current episodes at the physical baseline visit as remitted depressive episodes, which could have led to an overestimation of the effect of remitted episodes on adiposity. Second, in 19% of participants who refused the diagnostic interview at the follow-up visit, the occurrence of a depressive episode during the follow-up period needed to be determined using a depression scale rather than a diagnostic interview. However, it is unlikely that this limitation introduced a differential bias because participation at the interview did not differ across diagnostic groups. Third, participants and nonparticipants at the physical follow-up differed with respect to sociodemographic and behavioral characteristics, suggesting that individuals with a less healthy lifestyle were less likely to participate. Nonetheless, because only 13% of the initial sample did not participate at the follow-up, it is unlikely that nonparticipation introduced a substantial bias. Fourth, the data of the present study were based on an urban sample in Switzerland. However, although the particular features of the sample are likely to affect the prevalence estimates of diseases, it is less likely that they significantly affect the assessed prospective associations between depression subtypes and adiposity. Fifth, our assessment of physical activity only partially reflected daily activity and energy expenditure.

The observed strong association between the atypical subtype of MDD and an increased BMI and waist circumference confirms findings from previous cross-sectional research[16,17,19] and is compatible with the results of a longitudinal study with multiple assessments between ages 20 and 40 years.[18] As the association between MDD and adiposity was almost exclusively restricted to MDD with atypical features in our study, it is not surprising that the ORs of developing obesity for individuals with this subtype (OR, 2.41) was much higher than that of the association between the overall diagnosis of depression and obesity according to a recent meta-analysis of longitudinal studies (OR, 1.59).[12] The discrepant results from previous studies, which did not assess specific MDD subtypes, could be attributable to variance in the proportion of the atypical subtype. This is probably also true for the inconsistent results of previous research regarding waist circumference. Indeed, previous cross-sectional studies, which did not subtype depression, yielded 2 positive[32,33] and 2 negative[34,35] findings. In addition, 1 prospective study based on a 5-year follow-up documented a positive association between current de-

Table 5. Fat Mass at Baseline and Fat Mass Change During Follow-up by Depression Status at Baseline

	Body Fat Mass at Baseline, %		Fat Mass Change, % of the Baseline Value			
				β (95% CI)		
Depression Status	Mean (SD)	β (95% CI)[a]	% (SD)	Model 1[b]	Model 2[c]	Model 3[d]
Women, No.		1604		1324	1324	1281
Current MDD						
Atypical	36.8 (7.8)	3.58 (1.10 to 6.07)[e]	11.0 (17.3)	1.05 (−5.44 to 7.53)	0.52 (−6.03 to 7.06)	0.72 (−6.06 to 7.50)
Melancholic	33.6 (8.1)	1.30 (−0.94 to 3.53)	9.3 (23.1)	−3.91 (−9.49 to 1.67)	−3.49 (−9.15 to 2.17)	−2.84 (−8.76 to 3.08)
Combined	35.2 (7.8)	2.69 (−0.22 to 5.60)	11.9 (27.3)	4.26 (−3.19 to 11.71)	4.72 (−2.78 to 12.22)	4.46 (−3.35 to 12.28)
Unspecified	32.2 (7.0)	0.41 (−1.55 to 2.37)	7.3 (17.6)	−0.91 (−6.00 to 4.18)	0.14 (−5.01 to 5.29)	0.73 (−4.62 to 6.09)
Remitted MDD						
Atypical	34.9 (8.2)	2.45 (0.99 to 3.92)[e]	6.0 (20.1)	−0.96 (−4.58 to 2.65)	−0.63 (−4.27 to 3.02)	−0.45 (−4.18 to 3.28)
Melancholic	32.1 (7.9)	−0.31 (−1.38 to 0.76)	12.2 (26.2)	0.56 (−2.06 to 3.19)	0.87 (−1.80 to 3.54)	0.93 (−1.83 to 3.70)
Combined	33.5 (7.8)	1.12 (−0.58 to 2.82)	15.4 (72.6)	−0.68 (−4.93 to 3.57)	−0.6 (−4.94 to 3.73)	0.01 (−4.46 to 4.49)
Unspecified	32.5 (7.9)	−0.18 (−1.08 to 0.73)	12.6 (51.8)	−1.1 (−3.37 to 1.18)	−1.17 (−3.46 to 1.13)	−0.87 (−3.24 to 1.49)
No MDD	32.9 (7.9)	0 [Reference]	12.6 (41.6)	0 [Reference]	0 [Reference]	0 [Reference]
Men, No.		1423		1221	1221	1178
Current MDD						
Atypical	23.5 (6.0)	0.47 (−1.98 to 2.93)	30.7 (36.5)	15.87 (4.45 to 27.28)[e]	16.55 (5.06 to 28.04)[e]	16.36 (4.81 to 27.92)[e]
Melancholic	23.4 (6.3)	1.24 (−1.30 to 3.77)	18.2 (20.4)	5.85 (−4.64 to 16.33)	6.43 (−4.07 to 16.94)	8.06 (−2.99 to 19.11)
Combined	26.6 (7.0)	2.75 (−0.71 to 6.21)	2.7 (18.3)	−6.11 (−20.34 to 8.11)	−6.76 (−20.95 to 7.43)	−9.23 (−24.74 to 6.29)
Unspecified	22.9 (5.8)	0.33 (−1.17 to 1.83)	12.4 (19.8)	2.43 (−3.72 to 8.57)	3.36 (−2.82 to 9.55)	2.61 (−3.74 to 8.97)
Remitted MDD						
Atypical	23.6 (6.7)	1.66 (0.05 to 3.27)[f]	11.6 (22.2)	0.67 (−5.82 to 7.15)	2.02 (−4.64 to 8.69)	1.97 (−4.85 to 8.78)
Melancholic	22.3 (6.0)	−0.24 (−1.25 to 0.77)	16.6 (27.3)	3.15 (−1.07 to 7.38)	4.11 (−0.20 to 8.41)	3.28 (−1.21 to 7.76)
Combined	22.2 (4.6)	0.06 (−1.69 to 1.81)	8.5 (24.2)	−0.33 (−7.53 to 6.87)	0.40 (−6.90 to 7.70)	0.01 (−7.37 to 7.39)
Unspecified	21.9 (5.1)	−0.34 (−1.09 to 0.40)	12.4 (23.3)	0.84 (−2.27 to 3.95)	1.07 (−2.06 to 4.21)	0.90 (−2.32 to 4.13)
No MDD	22.8 (5.7)	0 [Reference]	10.5 (23.0)	0 [Reference]	0 [Reference]	0 [Reference]

Abbreviation: MDD, major depressive disorder.

[a] Robust regression adjusted for age.

[b] Model 1: robust regression adjusted for age, sex, socioeconomic status, ethnicity, living alone, and length of follow-up.

[c] Model 2: model 1 and adjusted for physical activity, smoking habit, alcohol use, drug dependence, anxiety disorders, antidepressant use, and weight-increasing drug use.

[d] Model 3: model 2 and adjusted for the presence of major depressive episode during follow-up.

[e] $P < .01$.

[f] $P < .05$.

pression and visceral fat increase but not with waist circumference increase.[36] The finding of a stronger association of the atypical MDD subtype with adiposity in current than in remitted depressed participants in our study was attributable to the higher degree of severity of current disorders. Indeed, individuals who were depressed at baseline were more likely to experienced long-lasting or highly recurrent depressive episodes, which was reflected by the significantly longer time they had spent in episodes than participants with remitted depression.

Interestingly, participants with remitted melancholic depression, who typically have decreased appetite during depressive episodes, also gained more weight and had a higher incidence of obesity during the follow-up period than those who had never been depressed. However, these participants did not reveal a higher BMI or a higher prevalence of obesity at the follow-up than those who had never been depressed as their low baseline measures aligned themselves to those of individuals who had never been depressed across time. The weight gain of these participants likely reflected the compensation of the weight loss that occurred during the previous depressive episode.

Conclusions

The present study provides additional insight into the complex relationship between atypical depression and adiposity by demonstrating that the high comorbidity between this depression subtype and obesity is not simply attributable to the occurrence of atypical depressive symptoms in already obese individuals, but to a strong prospective association between the atypical MDD subtype and adiposity. Moreover, this finding strongly advocates the subtyping of the heterogeneous depression diagnosis in future research.[37] As suggested by previous research, specific depression subtypes are likely associated with different biological correlates and with differential pathways to cardiovascular risk.[37] Although it is plau-

sible that increased appetite during depressive episodes with atypical features can lead to temporary weight gain, our finding of persistently elevated BMI increase after a follow-up period of more than 5 years, even in individuals with remitted episodes, supports a potential obesity-related pathway from atypical depression to CVD and other chronic diseases related to obesity. Mechanisms that could link depression and obesity include adipokine, pro-inflammatory dysregulation, alterations in the hypothalamic-pituitary-adrenal axis,[38,39] weight-increasing effects of psychotropic medication, lifestyle factors (poor nutrition and physical inactivity[40]), and psychological factors such as emotional eating and beliefs about one's inability to maintain physical activity behaviors in depressed individuals.[41] Other research also suggests the potential involvement of genetic determinants, such as the *FTO* gene, which has been shown to selectively favor weight gain in depressed individuals.[42] This gene could also be associated with the atypical depression subtype.[43] Another study supports a specific association between the atypical depression subtype and elevated inflammatory markers, which are well known to be associated with obesity, whereas hypercortisolemia was linked to the melancholic subtype.[37] Our results do not support a significant role of medication or physical exercise in the prospective association between atypical depression and adiposity, whereas the role of the hypothalamic-pituitary-adrenal axis, adipokines, and inflammatory processes in this association still needs to be determined in longitudinal research.

For the clinician, the atypical subtype deserves particular attention because this subtype is a strong predictor of adiposity. Accordingly, the screening of atypical features and, in particular, increased appetite in individuals with depression is crucial. The prescription of appetite-stimulating medication should be avoided in these patients and dietary measures during depressive episodes with atypical features are advocated. Clinical studies need to determine to what degree the timely and appropriate treatment of depressive episodes with atypical features can prevent an increase of adiposity during and after such episodes and thereby reduce the long-term risk for CVD and other chronic diseases related to obesity.

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REFERENCES

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010 [published correction appears in *Lancet*. 2013;381(9867):628]. *Lancet*. 2012;380(9859):2163-2196.

2. Cuijpers P, Vogelzangs N, Twisk J, Kleiboer A, Li J, Penninx BW. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry*. 2014;171(4):453-462.

3. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006;355(8):763-778.

4. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA*. 1999;282(16):1523-1529.

5. Field AE, Coakley EH, Must A, et al. Impact of overweight on the risk of developing common chronic diseases during a 10-year period. *Arch Intern Med*. 2001;161(13):1581-1586.

6. Clarke DM, Currie KC. Depression, anxiety and their relationship with chronic diseases: a review of the epidemiology, risk and treatment evidence. *Med J Aust*. 2009;190(7)(suppl):S54-S60.

7. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. *Psychol Med*. 2010;40(11):1797-1810.

8. Nabi H, Chastang JF, Lefèvre T, et al. Trajectories of depressive episodes and hypertension over 24 years: the Whitehall II prospective cohort study. *Hypertension*. 2011;57(4):710-716.

9. van Reedt Dortland AK, Giltay EJ, van Veen T, Zitman FG, Penninx BW. Longitudinal relationship of depressive and anxiety symptoms with dyslipidemia and abdominal obesity. *Psychosom Med*. 2013;75(1):83-89.

10. Van der Kooy K, van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. *Int J Geriatr Psychiatry*. 2007;22(7):613-626.

11. de Wit L, Luppino F, van Straten A, Penninx B, Zitman F, Cuijpers P. Depression and obesity: a meta-analysis of community-based studies. *Psychiatry Res*. 2010;178(2):230-235.

12. Luppino FS, de Wit LM, Bouvy PF, et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220-229.

13. Faith MS, Butryn M, Wadden TA, Fabricatore A, Nguyen AM, Heymsfield SB. Evidence for prospective associations among depression and obesity in population-based studies. *Obes Rev*. 2011;12(5):e438-e453.

14. Antonijevic IA. Depressive disorders: is it time to endorse different pathophysiologies? *Psychoneuroendocrinology*. 2006;31(1):1-15.

15. Ghaemi SN, Vöhringer PA. The heterogeneity of depression: an old debate renewed. *Acta Psychiatr Scand*. 2011;124(6):497.

16. Lamers F, de Jonge P, Nolen WA, et al. Identifying depressive subtypes in a large cohort study: results from the Netherlands Study of Depression and Anxiety (NESDA). *J Clin Psychiatry*. 2010;71(12):1582-1589.

17. Levitan RD, Davis C, Kaplan AS, Arenovich T, Phillips DI, Ravindran AV. Obesity comorbidity in unipolar major depressive disorder: refining the core phenotype. *J Clin Psychiatry*. 2012;73(8):1119-1124.

18. Hasler G, Pine DS, Gamma A, et al. The associations between psychopathology and being overweight: a 20-year prospective study. *Psychol Med*. 2004;34(6):1047-1057.

19. Glaus J, Vandeleur C, Gholam-Rezaee M, et al. Atypical depression and alcohol misuse are related to the cardiovascular risk in the general population. *Acta Psychiatr Scand*. 2012;128(4):282-293.

20. van Dijk SB, Takken T, Prinsen EC, Wittink H. Different anthropometric adiposity measures and their association with cardiovascular disease risk factors: a meta-analysis. *Neth Heart J*. 2012;20(5):208-218.

21. Bigaard J, Frederiksen K, Tjønneland A, et al. Body fat and fat-free mass and all-cause mortality. *Obes Res*. 2004;12(7):1042-1049.

22. Firmann M, Mayor V, Vidal PM, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. *BMC Cardiovasc Disord*. 2008;8:6.

23. Preisig M, Waeber G, Vollenweider P, et al. The PsyCoLaus study: methodology and characteristics of the sample of a population-based survey on psychiatric disorders and their association with genetic and cardiovascular risk factors. *BMC Psychiatry*. 2009;9:9.

24. Jebb SA, Siervo M, Murgatroyd PR, Evans S, Frühbeck G, Prentice AM. Validity of the leg-to-leg bioimpedance to estimate changes in body fat during weight loss and regain in overweight women: a comparison with multi-compartment models. *Int J Obes (Lond)*. 2007;31(5):756-762.

25. Hollingshead AB. *Four factor Index of Social Status*. New Haven, CT: Yale University Press; 1975.

26. Nurnberger JI Jr, Blehar MC, Kaufmann CA, et al; NIMH Genetics Initiative. Diagnostic Interview for Genetic Studies: rationale, unique features, and training. *Arch Gen Psychiatry*. 1994;51(11):849-859, discussion 863-864.

27. Preisig M, Fenton BT, Matthey ML, Berney A, Ferrero F. Diagnostic Interview for Genetic Studies (DIGS): inter-rater and test-retest reliability of the French version. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(4):174-179.

28. Endicott J, Spitzer RL. A diagnostic interview: the Schedule for Affective Disorders and Schizophrenia. *Arch Gen Psychiatry*. 1978;35(7):837-844.

29. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. 4th ed, text revision*. Washington, DC: American Psychiatric Association; 2000.

30. Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Meas*. 1977;1(3):385-401.

31. Morin AJ, Moullec G, Maïano C, Layet L, Just JL, Ninot G. Psychometric properties of the Center for Epidemiologic Studies Depression Scale (CES-D) in French clinical and nonclinical adults. *Rev Epidemiol Sante Publique*. 2011;59(5):327-340.

32. Marijnissen RM, Bus BA, Holewijn S, et al. Depressive symptom clusters are differentially associated with general and visceral obesity. *J Am Geriatr Soc*. 2011;59(1):67-72.

33. Williams LJ, Pasco JA, Henry MJ, et al. Lifetime psychiatric disorders and body composition: a population-based study. *J Affect Disord*. 2009;118(1-3):173-179.

34. Hach I, Ruhl UE, Klotsche J, Klose M, Jacobi F. Associations between waist circumference and depressive disorders. *J Affect Disord*. 2006;92(2-3):305-308.

35. Keddie AM. Associations between severe obesity and depression: results from the National Health and Nutrition Examination Survey, 2005-2006. *Prev Chronic Dis*. 2011;8(3):A57.

36. Vogelzangs N, Kritchevsky SB, Beekman AT, et al. Depressive symptoms and change in abdominal obesity in older persons. *Arch Gen Psychiatry*. 2008;65(12):1386-1393.

37. Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol Psychiatry*. 2013;18(6):692-699.

38. Taylor VH, Macqueen GM. The role of adipokines in understanding the associations between obesity and depression. *J Obes*. 2010;pii:748048.

39. Hryhorczuk C, Sharma S, Fulton SE. Metabolic disturbances connecting obesity and depression. *Front Neurosci*. 2013;7:177.

40. Paz-Filho G, Licinio J, Wong ML. Pathophysiological basis of cardiovascular disease and depression: a chicken-and-egg dilemma. *Rev Bras Psiquiatr*. 2010;32(2):181-191.

41. Konttinen H, Silventoinen K, Sarlio-Lähteenkorva S, Männistö S, Haukkala A. Emotional eating and physical activity self-efficacy as pathways in the association between depressive symptoms and adiposity indicators. *Am J Clin Nutr*. 2010;92(5):1031-1039.

42. Rivera M, Cohen-Woods S, Kapur K, et al. Depressive disorder moderates the effect of the FTO gene on body mass index. *Mol Psychiatry*. 2012;17(6):604-611.

43. Milaneschi Y, Lamers F, Mbarek H, Hottenga JJ, Boomsma DI, Penninx BW. The effect of FTO rs9939609 on major depression differs across MDD subtypes [published online February 4, 2014]. *Mol Psychiatry*. doi:10.1038/mp.2014.4.