Major Depression Predicts an Increase in Long-Term Body Weight Variability in Young Adults

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Abstract

HASLER, GREGOR, SHMUEL LISSEK, VLADETA AJDACIC, GABRIELLA MILOS, ALEX GAMMA, DOMINIQUE EICH, WULF RÖSSLER, AND JULES ANGST. Major depression predicts an increase in long-term body weight variability in young adults. *Obes Res.* 2005;13: 1991–1998.

Objective: To test the hypothesis that major depression predicts an increase in long-term body weight variability (BWV).

Research Methods and Procedures: This was a prospective community-based single-age cohort study of young adults ($N = 591$) followed between the ages of 19 and 40. Following initial screening, information was derived from six subsequent semistructured diagnostic interviews conducted by mental health professionals. Major depression was diagnosed on the basis of DSM criteria. BWV was defined as the root mean square error of a regression line fitted to each individual's BMI values over time. Multiple regression analysis was used to test the association between major depression and BWV while controlling for potentially confounding variables including antidepressant treatment, eating disorder symptoms, and physical activity. We used random effects models to determine the temporal relationship between repeated measures of major depression and body weight change.

Results: A highly significant positive association between major depression and BWV was found, whereas major depression was not associated with BMI level or BMI trend. Depression severity showed a dose-response-type relationship with the magnitude of BWV. After controlling for potentially confounding variables including antidepressant use, eating disorder symptoms, smoking, and physical activity, major depression remained a significant predictor of BWV ($\beta = 0.13$, $p < 0.001$). Longitudinal analysis revealed a unidirectional association between major depression and a later increase in body weight change rate irrespective of antidepressant medication.

Discussion: Results from this study implicate depression as an important risk factor for increased BWV. Given increasing evidence for a link between major depression and both diabetes and cardiovascular disease, current results encourage further research on depression, BWV, and negative health outcomes.

Key words: body weight changes, major depression, antidepressants, exercise, weight cycling

Introduction

The scientific literature is in disagreement regarding the negative health consequences of weight cycling. Epidemiological research finds fairly consistent associations between increased body weight variability (BWV)[1] and cardiovascular morbidity and mortality (1–5). In contrast, recent studies discuss the weak direct adverse effects of weight cycling on cardiovascular risk factors (6–8). How-

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[1] Nonstandard abbreviations: BWV, body weight variability; SCL-90-R, Symptom Checklist 90-R; SPIKE, Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology; BMI-RMSE, root mean square error; CI, confidence interval; OR, odds ratio.

ever, these and other studies provide growing evidence that increased BWV is associated with health risk factors including elevated weight (7), weight gain (6), android fat distribution (9), smoking (10), and low-grade systemic inflammation (11).

Only a small number of studies have been conducted on BWV and psychopathological factors. Most of them have examined the psychological consequences of weight cycling (1). However, a series of studies in affective disorders suggested that depression precedes and potentially causes relevant long-term weight change. This association appeared to be influenced by BMI and depression severity (12–14) and was found irrespective of a history of pharmacotherapy (15,16). Moreover, other potential predictors of BWV such as eating disorder symptoms and smoking have been associated with affective disorders (17–19). The role of depression, antidepressant treatment, and depression-related psychopathology as potential predictors of BWV has not been systematically examined.

Based on previous reports, we test the hypothesis that major depression is associated with an increase in BWV. Data were derived from a prospective community study of young adults with comprehensive clinical and psychopathological information collected over a 20-year follow-up period.

Research Methods and Procedures

Sample

The Zurich cohort study is comprised of a cohort of 4547 subjects (2201 men and 2346 women) representative of the canton of Zurich in Switzerland, who were assessed in 1978 with the Symptom Checklist 90-R (SCL-90-R) (20) and a questionnaire for sociodemographic data. The study is based on a stratified sample with an overrepresentation of risk cases. To increase the probability of detecting a sufficient number of symptomatic participants, a subsample of 591 subjects (292 men and 299 women) was selected for interview, with two-thirds consisting of high scorers (defined by the 85th percentile or more of the SCL-90-R) and a random sample of those with scores below the 85th percentile. After a complete description of the study to the subjects, written informed consent was obtained from subjects. The screening took place in 1978 when subjects were age 19, the first and second interviews in 1979 and 1981, the third and fourth interviews in 1986 and 1988, the fifth interview in 1993, and the sixth in 1999. We used diagnostic information from all interviews for this study.

Across 20 years, 62.1% of the original sample continued to participate in the study, and the following proportions participated in specific numbers of interviews: 47% in all six interviews, 63% in five interviews, 74% in four interviews, 82% in three interviews, and 91.4% in at least two interviews. Those who had dropped out did not differ significantly from the 1999 participants with regard to their risk status (scoring high vs. scoring low on the SCL-90-R) at study entry and most demographic characteristics (21). The subjects included in this BWV analysis were examined at three or more of the six interviews of the Zurich cohort study ($N = 479$).

Diagnostic Interview

The diagnostic instrument used in the Zurich study was the Structured Psychopathological Interview and Rating of the Social Consequences for Epidemiology (SPIKE), a semistructured instrument that was developed for epidemiological studies (22). Health professionals with extensive clinical training administered the SPIKE in the participants' homes (23). This interview schedule assesses a number of somatic diseases including obesity. In addition, it assesses a wide range of psychiatric disturbances including affective disorders, substance use disorders, and eating disorders. The section on body weight and eating disturbances includes a broad spectrum of weight-related concerns and behaviors. Their assessment has previously been described (19). Demographic variables were assessed in the first interview. Social class was defined according to subjects' occupational status and categorized into four classes (1, college student; 2, employee; 3, worker, apprentice; 4, pupil, unskilled worker).

Diagnostic Definitions

Diagnostic information from all interviews was used. Classification of psychiatric disorders were made by algorithms on the basis of DSM-III-R criteria (major depressive disorder, eating disorders), and DSM-IV criteria (substance abuse/dependence). The essential feature of a DSM major depression is a clinical course characterized by one or more major depressive episodes; such an episode is a period of at least 2 weeks during which there is either depressed mood or the loss of interest or pleasure in nearly all activities and additional depressive symptoms/impairment. Minor depression consists of minor depressive episodes that are identical to major depressive episodes in duration but involve fewer symptoms and less impairment. Depressive symptoms refer to core depressive symptoms (depressed mood, loss of interest) over periods of time of <2 weeks. The SPIKE rating of the diagnostic level of depression was found to have high sensitivity and specificity (0.95 and 0.59, respectively, for major depression and 0.83 and 0.63, respectively, for minor depression). Antidepressant treatment included pharmacological treatments with tricyclic antidepressants, selective serotonin reuptake inhibitors, and benzodiazepines. Only 24.5% of individuals with major depression received antidepressant medication during the study period.

Given the low prevalence of binge eating disorder (DSM IV research criteria) in general-population samples, we used a low threshold for binge eating: at least four binges (i.e.,

eating, in a discrete period of time, an amount of food that is definitely larger than most people would eat, with a sense of lack of control and subsequent distress) over one year were required for binge eating (19); using this definition, binge eating showed a strong effect on weight gain in a previous study (24). None of the subjects in this study met criteria for anorexia nervosa.

BWV

For the Zurich cohort study, height was determined by self-report in 1979, and weight was determined by self-report at each interview. BMI instead of weight was used for analyses because BMI is more correlated with height. BMI variability can be separated into two components: trend over time and variability (weight cycling) over time. To separate the components of BMI variability and BMI trend, we used a simple linear regression model. Each individual's BMI values from interviews in 1979, 1981, 1986, 1988, 1993, and 1999 were regressed on the age at interview. The root mean square error (BMI-RMSE) of this model reflected the SD around the BMI slope and was used to measure the magnitude of weight variability (25). We adjusted all associations with the BMI-RMSE for the number of BMI measures to reduce a potential bias due to missing data. To examine the temporal order between behavioral variables and weight variability, we used the absolute weight change rate between two adjacent interviews as both predictor and outcome variable.

Assessment of Physical Activity

The level of physical activity was assessed in 1979, 1981, and 1986 by interview based on three questions concerning sports activity, walking, and watching television (response categories: 1, less than once a month; 2, at least once a month; 3, at least once a week; 4, more than once a week). The coefficients for the correlations among the three items assessing physical activity levels ranged from 0.02 to 0.11.

Statistical Analysis

Cross-sectional (i.e., over the 20-year study period) analyses were based on a subsample that included all subjects having three or more BMI measures ($N = 479$) because at least three BMI measures were necessary to calculate BWV estimates; diagnostic information was used from all interviews. To test associations between behavioral variables and BWV, we calculated standardized βs from linear regression models that were adjusted for gender, stratified sampling, mean BMI, and number of BMI measures. To examine dose-response type relationships between depression and BWV, we used a four-level variable for maximal depression severity (0, no depressive symptoms; 1, depressive symptoms; 2, minor depression; 3, major depression).

To explore the influence of major depression and possible confounding variables, we first examined the association between BWV and each of these variables separately after controlling for gender, stratified sampling, mean BMI, and number of BMI measures. Based on previous evidence (24,26–29), we selected potentially confounding variables that have been associated with depression and body weight such as eating disorders, weight-related concerns and behaviors, smoking and substance use disorders, physical activity, educational level, and socioeconomic status. None of the subjects had anorexia nervosa; therefore, we included the anorexia-associated symptom of reduced appetite in the analysis. Potentially confounding variables that showed statistically significant associations ($p < 0.05$) with BWV in the initial data exploration were included in the multivariate analysis.

We conducted a number of secondary analyses to test the stability of our results. To evaluate the effect of dropout, we conducted a separate analysis in subjects who had all interviews ($N = 259$) and an analysis on all subjects with three or more interviews ($N = 479$) including the average age at BMI assessments as a covariate and age-by-predictor interactions. To evaluate a potential bias due to extreme BWV values or skewness of the BWV distribution, we conducted analysis with categorical BWV response variables (two proportional odds models with three and four ordered BWV categories as response variable and the same independent variables as in the multiple regression model). Because the variables coding for weight-related treatments might be redundant with BWV, we compared models of BWV with and without the weight treatment variable.

To examine the longitudinal relationship between major depression and weight change rate during different time periods, we assembled data from the whole sample ($N = 591$) in panel format (i.e., multiple records per patient, with one record for each interview) including information on weight change that preceded major depression: between the previous and the diagnostic interview (short-term precedence), between the two adjacent interviews preceding the diagnostic interview (long-term precedence), between the diagnostic interview and the adjacent subsequent interview (short-term subsequent), and between the two adjacent interviews after the diagnostic interview (long-term subsequent). Weight change was calculated as the absolute BMI change rate per year between two interviews. To examine associations between weight change and later major depression (binary outcome variable), we calculated robust estimates of repeated measures by generalized estimating equations (30) with subject as cluster and a first order autoregressive within-cluster correlation structure to account for the correlated outcomes from longitudinal observations on the same subject. To test for associations between major depression and later weight change (continuous outcome variable), we used a random effects model for repeated measures (BMI change rate) with subject as a random effect, subject as cluster, and a first order auto-

Table 1. Associations between BWV* and psychiatric conditions, weight-related behaviors, and demographic variables ($N = 479$)

Diagnosis/symptom	Frequency† (%)	β‡	p
Major depression	37.2	0.14	0.001
Antidepressant medication	13.8	0.10	0.03
Alcohol dependence/abuse	25.1	0.07	0.12
Drug dependence/abuse	12.3	0.01	0.86
Smoking	64.1	0.10	0.02
Overeating	26.1	0.01	0.80
Binge eating (bulimia not included)	10.7	0.08	0.08
Bulimia nervosa	2.5	−0.01	0.90
Appetite perceived as too low	10.3	0.10	0.03
Treatment for weight problems	8.3	0.21	<0.0001
Walking, hiking (four frequency levels)		−0.05	0.25
Sports activity (four frequency levels)		−0.15	0.0006
Watching television (four frequency levels)		0.02	0.63
Female gender	50.1	0.18	<0.0001
Education level (five levels, 1 = lowest level)		−0.10	0.02
Social class (four classes, 1 = lowest class)		−0.05	0.26

* BWV estimated by the SE around the BMI slope, the BMI-RMSE.

† Unweighted cumulative frequency rates ($N = 479$, 100%).

‡ Standardized β adjusted for mean BMI, number of BMI measures, gender, and stratified sampling.

regressive within-cluster correlation structure. These longitudinal models were adjusted for gender, age, BMI at baseline, stratified sampling, antidepressant medication, smoking, treatment for weight problems, sports activity, and educational level. Analyses were conducted using SAS for Windows release 8.02 (SAS Institute Inc., Cary, NC).

Results

The mean of the BMI-RMSE (BWV estimate) was 0.849 (SD = 0.550). The minimal, median, and maximal BMI-RMSE values were 0.031, 0.747, and 4.681, respectively. Mean BMI was correlated with BMI-RMSE ($r = 0.319$, $p < 0.0001$).

Cross-Sectional Associations

Over the 20-year study period, we found a dose-response-type relationship between the maximal severity of depressive psychopathology and BWV when comparing least-squared means adjusted for mean BMI, number of BMI assessments, gender, and stratified sampling. Subjects without depressive symptoms had an adjusted BWV of 0.698 [95% confidence interval (CI), 0.401 to 0.994], subjects with depressive symptoms had an adjusted BWV of 0.701 (95% CI, 0.548 to 0.873), subjects with minor depression had an adjusted BWV of 0.786 (95% CI, 0.717 to 0.854), and subjects with major depression had an adjusted BWV of 0.937 (95% CI, 0.858 to 1.017). This dose-response-type relationship was statistically significant [$F(3,4,6,7) = 5.55$, $p < 0.001$]. There were no differences by adult major depression for mean BMI ($t = 0.91$, $p = 0.37$) or BMI trend/slope ($t = 0.32$, $p = 0.75$).

Table 1 shows that antidepressant treatment was strongly related to major depression [odds ratio (OR) = 4.4, 95% CI 2.5 to 7.7, $p < 0.0001$] and positively associated with BWV, although the association was weaker for antidepressant treatment than for major depression. Substance use disorders were not associated with BWV, but smoking was positively associated with BWV. Among the eating-related variables, only low appetite and treatment for weight problems were positively associated with BWV, whereas overeating, binge eating, and bulimia nervosa were not associated with BWV. A more detailed exploration of the data showed that weight-related concerns including fear of weight gain, permanent weight concerns, frequent weighing, and weight-related behaviors including dieting, intentional vomiting, exercise for weight-control, and taking drugs for weight control were not significantly associated with BWV (data not shown in Table 1). Among the indicators of physical activity, the level of sports activity was clearly negatively associated with BWV. There was a rela-

Table 2. Multivariate associations between BWV* and psychiatric conditions, weight-related behaviors, and demographic variables ($N = 479$)

Variable	β	p
Female gender	0.07	0.17
Stratified sampling (SCL-90-R high scorer)	0.01	0.76
Mean BMI	0.32	<0.0001
Number of BMI measures	0.06	0.20
Major depressive disorder	0.13	0.007
Antidepressant medication	0.04	0.45
Smoking	0.07	0.10
Appetite perceived as too low	0.07	0.10
Treatment for weight problems	0.19	<0.0001
Sports activity (four frequency levels)	−0.13	0.003
Educational level (five frequency levels)	−0.10	0.03

* BWV estimated by the SE around the BMI slope, the BMI-RMSE. $R^2 = 0.28$, adjusted $R^2 = 0.26$ ($p < 0.0001$).

tively strong and positive association between female gender and BWV. Among the demographic variables, the educational level was negatively associated with BWV.

Cross-Sectional Multivariate Associations

We did not find any significant interactions between major depression and gender, antidepressant medication, smoking, low appetite, treatment for weight problems, sports activity, and educational level associated with BWV. Table 2 shows the final multivariate results. Mean BMI was the strongest correlate of BWV. Major depression, treatment of weight problems, sports activity, and education level kept their strength of association with BWV in the multivariate model, whereas female gender, antidepressant treatment, smoking, and low appetite became non-significant correlates of BWV.

Secondary Analyses

Excluding subjects who had not participated in all six interviews led to some minor changes in estimates that did not alter the interpretation of the results. Likewise, including the mean age in the multivariate model did not lead to changes in the results. Ordinal logistic regression models using three and four ordered BWV categories as response variables showed that the proportional odds assumption was met and confirmed the results of the multiple regression model. The exclusion of the potentially BWV-redundant variable, treatment for weight problems, did not change results of the multivariate model of BWV.

Longitudinal Associations

The longitudinal analysis on repeated measures of major depression did not show a relationship between absolute weight change rate and later depression [short term, OR = 0.7 (0.5, 1.1), $p = 0.14$; long term, OR = 1.3 (0.9, 1.9), $p = 0.19$]. As shown in Table 3**,** the longitudinal analysis on repeated measures of absolute weight change rate showed that major depression was related to the short-term subsequent weight change rate during the period between the diagnostic interview and the following adjacent interview irrespective of antidepressant medication. The association did not change when excluding all subjects who received antidepressant medication at any point during the study period. However, major depression was not associated with the long-term weight change rate between the two following adjacent interviews, whereas antidepressant medication was associated with the long-term weight change rate (Table 3).

Discussion

Cross-sectionally (i.e., over the 20-year study period), we found a dose-response-type relationship between the severity of depressive psychopathology and the magnitude of BWV. The multivariate analysis revealed that the major depression-BWV association was independent of antidepressant use, substance use, smoking, physical activity, treatment of weight problems, and demographic variables. Longitudinally, major depression was associated with the short-term rate of body weight change over the following 2 to 5 years irrespective of antidepressant treatment, whereas major depression was not associated with long-term weight change rate (i.e., >5 years after the major depressive episode) or with preceding body weight change rates. Overall, these results are in line with findings from previous studies reporting long-term weight changes in subjects with affective disorders irrespective of a history of pharmacotherapy (12–16). The present study adds to these previous findings that depressive psychopathology shows a dose-response-type relationship with BWV and that major depression is a predictor rather than a consequence of weight change.

Given the relatively strong and consistent association between eating disorder symptoms and major depression (17–19), we hypothesized that eating disorder symptoms such as binge eating, anorexia, or permanent weight concerns were mediators between major depression and increased BWV. Although binge eating was associated with major depression [OR = 1.8 (1.0, 3.1), $p < 0.05$], binge eating was only weakly associated with BWV, and it did not influence the depression-BWV association. Other eating-related problems that were associated with major depression, such as overeating and bulimia nervosa, were not

Table 3. Multivariate longitudinal associations between depression and later body weight change

Variable	*N*	Short-term weight change*		Long-term weight change†	
		β‡	*p*	*β*‡	*p*
Major depressive disorder§	278	0.08	0.005	0.01	0.75
Antidepressant medication§	121	0.00	0.34	0.08	0.009
Smoking§	946	0.01	0.93	0.02	0.72
Treatment for weight problems¶	228	0.17	<0.0001	0.17	<0.0001
Sports activity (four frequency levels)¶		−0.09	0.003	−0.08	0.02
Educational level (five frequency levels)¶		−0.09	0.003	−0.08	0.02

Number of cases refers to the number of repeated measures as used in the analysis (total number of observations = 2702 from 591 subjects).
* Absolute weight change rate (change in BMI per year) between the diagnostic interview and the following adjacent interview (change rate 2 to 6 years after the diagnostic interview).
† Absolute weight change rate (change in BMI per year) between the adjacent interviews following the diagnostic interview (change rate 7 to 11 years after the diagnostic interview).
‡ Standardized β from random effects models on repeated measures (BMI change rate) with subject as random effect, subject as cluster, and a first order autoregressive within-cluster correlation structure. Models were adjusted for baseline BMI, gender, age, and stratified sampling.
§ Time-varying exposure variable preceding the outcome variable.
¶ Time-invariant exposure variable (time-invariant variables and variables that were not measured at each interview).

associated with BWV. In contrast, BWV-associated symptoms including treatment for weight problems and a generally reduced appetite were not associated with major depression, and they did not influence the depression-BWV association. Together, eating disorder symptoms that were examined in the present study did not explain the association between major depression and increased BWV.

Because substance use disorders were not associated with BWV, they appeared to be unlikely mediators of the depression-BWV association. Smoking was associated with major depression [OR = 1.7 (1.2, 2.5), $p < 0.01$], but it did not influence the depression-BWV association, in either the cross-sectional or the longitudinal analysis. The level of sports activity appeared to be an important correlate of BWV, but it was not associated with major depression, and it did not influence the depression-BWV association. The relatively strong and positive association between female gender and BWV disappeared in the multivariate analysis; it seemed to be explained by the highly significant associations between female gender and major depression, treatment for weight problems, and a low frequency of sports activity (data not shown). The educational level was not associated with major depression and appeared to be a relatively independent correlate of BWV.

Appetite and weight change are non-specific symptoms of major depression (31). Moreover, increasing evidence implicates common brain monoamines and peptides in depression and the regulation of food intake or body weight. These monoamines and peptides include serotonin, norepinephrine, dopamine, neuropeptide Y, and corticotropin-releasing hormone (31,32). With respect to metabolic processes, both obesity and depression have been associated with glucose intolerance, insulin resistance, and diabetes (33). As a result, associations between depression and body weight are not surprising. In women, a relatively strong association between depression in childhood and increased weight gain in adulthood has consistently been found (27,34,35). In contrast, evidence for a specific relationship between adult depression and body weight has been less consistent. Although Stunkard et al. (36) found that the direction and extent of weight change was consistent across adult depressive episodes, a more recent longitudinal study did not show any correlation between direction and extent of appetite/weight change across episodes. In line with the latter study, we did not find the direction of weight change to be consistent over time (data not shown), nor did we find an association between major depression and BMI or BMI trend. Therefore, in the present study, the association between adult major depression and increased BWV appeared to be relatively specific.

The longitudinal analysis showed a clear temporal direction between major depression and body weight change. Although major depression was related to later short-term body weight change rate, body weight change rate was not associated with later depression. In line with the cross-sectional analysis, antidepressant treatment did not influ-

ence this directed association. The magnitude of the longitudinal association between depression and weight change was smaller than the cross-sectional association between depression and BWV. The relatively specific association between depression and weight variability (in contrast to weight trend) may explain the difference because the weight change rate as used in the longitudinal analyses included both weight variability and weight trend. Longitudinal associations and dose-response relationships suggest the involvement of causal mechanisms (37); that is, major depression may cause an increase in weight variability. It is important, however, to be aware that even a specific temporal order between two conditions may occur in the absence of any causal relationships between them (38). The finding that antidepressant treatment was associated with later long-term weight change has to be interpreted with caution because it was not based on a specific hypothesis, and we did not find it in the cross-sectional analysis.

This study has several methodological limitations that need to be addressed. Height and weight were assessed by self-report. Recent clinical and epidemiological studies have continued to use self-reported BMI as a primary outcome measure or a main predictor variable, despite the fact that self-reported BMI is measured with some degree of bias (39,40). Studies have continued to use self-reported BMI due to convenience, coupled with the fact that validation studies suggest that such bias is small and unlikely to affect conclusions about associations between BMI and psychopathology (41–43). Overall, studies show that people tend to exaggerate their height and underestimate their weight, which would underestimate BMI. However, a Swiss national survey showed that BMI underreporting depends on age, being minimal in young adults between ages 20 and 40 (44). The interval between the weight measures was too large to detect short-term BWV. There were no data on specific antidepressant drugs available. Additional limitations may reduce the generalization of the results. These include the inclusion of a single age cohort, an attrition rate of 38%, and a sampling method that increased the probability of symptomatic subjects. There are, however, several strengths of this study that render these data suitable to address the questions of this study. Such strengths include the fact that a community-based sample was used, that the study employed a longitudinal design spanning over 20 years, that experienced professionals administered the interviews, and that the results were confirmed by secondary analyses using alternative measures for BWV.

Because major depression is a highly prevalent condition in the general population, the results of this study may well have a relevant public health impact. Given increasing evidence for major depression as a risk factor for diabetes (45) and cardiovascular disease (46), results from the current study warrant further research on the relationships among depressive psychopathology, BWV, and negative health outcomes.

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