### It is illegal to post this copyrighted PDF on any website. Major Depressive Disorder, Antidepressant Use, and Subsequent 2-Year Weight Change Patterns in the Netherlands Study of Depression and Anxiety

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### ABSTRACT

**Background:** Although depression and obesity are bidirectionally associated, little is known about weight changes following major depressive disorder (MDD). This study compared 2-year weight changes between patients with current MDD (cMDD), patients with remitted MDD (rMDD), and healthy controls. Additionally, we examined the relationship between antidepressant medication use and 2-year weight change.

**Method:** Data from 2,542 adults aged 18–65 y were sourced from the Netherlands Study of Depression and Anxiety. Data were collected at baseline and after 2, 4, and 6 years (September 2004–April 2013). Depression status (*DSM-IV* criteria for MDD) was established with the Composite International Diagnostic Interview. Subsequent 2-year weight changes were categorized as weight loss (> 5% loss), weight stable (within 5% weight loss or gain), and weight gain (> 5% gain). The association of depression status with subsequent weight change, with weight stable as reference category, was studied by combining all repeated measurements in a mixed multinomial logistical regression model.

**Results:** cMDD, but not rMDD, was significantly associated with both weight gain and weight loss over a 2-year period after adjustment for covariates (odds ratio [OR] = 1.67; 95% confidence interval [CI], 1.37-2.03; P < .001; and OR = 1.27; 95% CI 1.01-1.61; P = .045, respectively). Antidepressant use was associated with weight gain (SSRIs: OR = 1.26; 95% CI, 1.05-1.52; other antidepressants: OR = 1.36; 95% CI, 1.00-1.84; P < .05 for both), but not after considering depression status. Compared to cMDD patients who lost weight, those who gained weight had lower initial weight, were younger, had more comorbid anxiety disorders, and reported poorer quality of mood and reduced appetite as depressive symptoms.

**Conclusions:** Compared to controls, cMDD participants have greater odds of either gaining or losing weight over a 2-year period, regardless of antidepressant use.

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\*Corresponding author: Deborah Gibson-Smith, MSc, GGZ inGeest, A.J. Ernststraat 1187, 1081 HL, Amsterdam, The Netherlands (d.gibson-smith@ggzingeest.nl). **M** ajor depressive disorder (MDD) and obesity are 2 major causes of disability-adjusted life-years worldwide.<sup>1,2</sup> Given the huge impact these 2 disorders have on society, understanding the causes of depression and obesity is of importance. Depression and obesity have been linked cross-sectionally.<sup>3</sup> Additionally, depression and obesity are also related longitudinally, in both directions, indicating that obesity is related to the onset of depression and vice versa.<sup>4</sup> However, according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) diagnostic criteria for MDD,<sup>5</sup> both recent weight gain and weight loss are symptoms of depression. Therefore, both subsequent weight gains and weight losses could be expected in depressed individuals.

Although many studies have examined the relationship between depression and obesity or weight gain, only a few longitudinal studies, to our knowledge, have discriminated between weight gain and weight loss by using weight change categories (ie, comparing weight gain and weight loss to stable weight).<sup>6-10</sup> These studies have obtained mixed results: 3 studies<sup>6,7,10</sup> found a significant association of depressive symptoms with both weight loss and weight gain, while the other 2 studies<sup>8,9</sup> found an association only with weight gain. These studies used measures of depressive symptoms as opposed to a clinical definition of depressive disorder, and they mostly relied on self-reported weight. Furthermore, the potential influence of antidepressants on weight change was not taken into account, despite the fact that certain antidepressants have been associated with weight gain.<sup>11–13</sup> Preventing weight gain or loss as a result of depression is important, as weight changes can lead to further physiological complications, such as diabetes or cardiovascular disease in the case of weight gain<sup>14,15</sup> and frailty in the case of weight loss.<sup>16</sup>

Accordingly, the aim of this study was to compare weight gain and weight loss over 3 sequential, 2-year time periods between patients with clinically diagnosed current MDD (cMDD), patients with remitted MDD (rMDD), and healthy controls. We also investigated the association between antidepressant medication use and weight gain independently and in conjunction with depression status. Finally, to explore why some depressed patients gain weight while others lose weight, we compared general demographic and health characteristics and depressive symptom profiles between depressed patients who gained versus lost weight.

# Weight loss and weight gain are both undesirable Weight loss and weight gain are both undesirable

- Weight loss and weight gain are both undesirable conditions associated with major depressive disorder (MDD); however, evidence of longitudinal weight changes after MDD is lacking.
  - Patients with MDD have a greater chance of gaining or losing weight over a 2-year period compared to mentally healthy individuals.
  - The gain in weight is not related to antidepressant use.

#### METHOD

The data were sourced from the Netherlands Study of Depression and Anxiety (NESDA), which is an ongoing longitudinal cohort study designed to investigate the course trajectories and consequences of depression and anxiety. The study comprised 2,981 participants aged 18-65 years. Participants were recruited between September 2004-February 2007 in 3 different regions from the general population, general practices, and mental health organizations. General exclusion criteria were an inability to speak Dutch and a primary diagnosis of psychotic, obsessive-compulsive, bipolar, or severe addiction disorder. Follow-up interviews were performed after 2, 4, and 6 years (until April 2013). Participants attended 4-hour in-depth interviews that included a psychiatric diagnostic interview and anthropometric, biological, and lifestyle measurements. At follow-up, 86.8%, 80.1%, and 75.7% of the baseline participants were successfully retained. All participants completed written consent forms, and the research protocol was approved by the ethical committees of the participating universities. Further details of NESDA can be found in Penninx et al.<sup>17</sup>

#### **Study Sample**

We selected participants with a diagnosis of cMDD or rMDD along with controls with no history of depressive or anxiety disorders (n = 2,577). Participants who were pregnant at baseline (n = 15), had hyperthyroidism (self-reported, n = 17), were anorexic (self-reported, n = 1), or had no baseline weight assessment (n = 2) were excluded, leaving 2,542 participants at baseline. Data were collected every 2 years over a period of 6 years, and the repeated measurements were combined, resulting in a total of 5,390 observations (2,049, 1,745, and 1,596 observations for each 2-year period, respectively (see Supplementary eFigure 1).

#### Depression

At each assessment, MDD as classified by *DSM-IV* criteria was established with the Composite International Diagnostic Interview (CIDI, lifetime version 2.1 WHO), an instrument with a high test-retest reliability and high validity for anxious and depressed patients.<sup>18–20</sup> The interviews were carried out by specially trained research assistants. At baseline, participants were classified in 3 groups with regard to MDD status: cMDD (MDD within the previous 6 months; n = 1,101), rMDD (lifetime history of MDD, but not in the past 6 months; n = 798), and healthy controls (no lifetime

history of depression or anxiety; n = 643). Additionally, depression severity was assessed with the Inventory of Depressive Symptomatology (IDS)<sup>21</sup> in all participants.

#### Antidepressants

Antidepressant use was assessed at baseline and follow-up interviews by asking participants to bring the packaging from all drugs used in the past month. These were classified according to the Anatomic Therapeutic Chemical (ATC) classification.<sup>21,22</sup> Antidepressants used for more than 50% of the time in the last month were grouped according to type and/or suspected effect on weight gain as follows: tricyclic antidepressants (TCAs) (ATC code: N06AA), selective serotonin reuptake inhibitors (SSRIs) (ATC code: N06AB), and other antidepressants, 92% of which were mirtazapine (ATC code: N06AX11) and venlafaxine (ATC code: N06AX16), along with ATC codes N06AF, N06AG, and other N06AX.

#### **Two-Year Weight Change**

Body weight was measured by trained clinical research staff at all interviews. Participants who were unable to attend one of the participating centers were interviewed at home, which meant that in some cases (<1%) weight was self-reported. Weight changes were calculated for each of the three 2-year intervals. In line with other studies,<sup>7,9</sup> the definition of our main weight change outcome was based on >5% change in weight over a 2-year period from starting weight. Thus, weight change was categorized as weight loss (>5% weight loss), weight stable (within 5% weight loss or gain), and weight gain (>5% weight gain). As a secondary outcome, we created weight change categories based on change in absolute weight of >5 kg over the 2-year intervals to see whether another definition of weight change would give comparable results for the association with depression.

#### Covariates

Based on findings from other studies,<sup>7</sup> the following demographic and health-related variables were assessed at all interviews and included as potentially confounding variables: sex, age, partner status, years of education, initial body weight, smoking status (current, never, former), alcohol intake, and the number of self-reported chronic illnesses. Alcohol intake was measured using the Alcohol Use Disorder Identification Test,<sup>23</sup> and participants were divided into nondrinkers, moderate drinkers (1–14 units/ week), and heavy drinkers (>14 units/week) for both sexes. The number of self-reported chronic illnesses included heart disease, stroke, hyperthyroidism, hypothyroidism, diabetes, rheumatism, arthritis, cancer, hypertension, intestinal disorders, liver disease, allergies, and neurologic problems.

#### **Statistical Analysis**

Descriptive statistics were calculated to evaluate the frequency, mean, and distribution of all variables according to year of follow-up. Observations for participants who reported being pregnant (for follow-up measurements) and

### It is illegal to post this copyrighted PDF on any website. Table 1. Patient Characteristics, Depression Status, Antidepressant Use, and 2-Year Weight

Changes at the Assessment Interviews<sup>a</sup>

<u> </u>	Developer	V/2	V 4	Maran C
Channe attaniation	Baseline	Year 2	Year 4	Year 6
	(N = 2,542)	(N = 2,207)	(N = 2,056)	(N = 1,935)
Male	853 (33.6)	749 (33.9)	693 (33.7)	654 (33.8)
Age, mean (SD), y	41.7 (13.0)	44.0 (13.0)	45.9 (13.1)	47.7 (13.0)
With partner	1,764 (69.4)	1,605 (72.7)	1,496 (72.8)	1,438 (74.3)
North European ancestry	2,410 (94.8)	2,111 (95.7)	1,965 (95.6)	1,860 (96.1)
Physical activity, MET min/wk $\times$ 10 <sup>-3</sup> , mean (SD)	3.81 (3.22)	4.08 (3.42)	3.87 (3.37)	3.97 (3.47)
Current smoker	993 (39.1)	724 (32.8)	643 (31.3)	547 (28.3)
Alcohol drinks/wk <sup>b</sup>				
Less than 1	817 (32.6)	696 (32.9)	659 (34.9)	597 (32.8)
1–14	1,271 (50.8)	1,098 (51.9)	1,000 (52.9)	971 (53.4)
More than 14	416 (16.6)	323 (15.3)	231 (12.2)	250 (13.8)
No. of chronic diseases, mean (SD)	0.90 (1.07)	0.71 (0.93)	0.74 (0.96)	0.73 (0.94)
Antidepressant users				
Tricyclic antidepressants	70 (2.8)	64 (2.9)	54 (2.6)	55 (2.8)
SSRI	461 (18.1)	318 (14.4)	264 (12.8)	235 (12.1)
Other antidepressants	152 (6.0)	127 (5.8)	110 (5.4)	101 (5.2)
Mirtazapine	43 (1.7)	34 (1.5)	32 (1.6)	27 (1.4)
Venlafaxine	103 (4.1)	85 (3.9)	59 (2.9)	59 (3.0)
Other antidepressants	10 (0.4)	9 (0.4)	19 (0.9)	17 (0.9)
Depression status				
Controls	643 (25.3)	564 (22.2)	499 (19.6)	466 (18.3)
Remitted major depressive disorder	798 (31.4)	1,123 (44.2)	1,165 (45.8)	1,140 (44.8)
Current major depressive disorder	1,101 (43.3)	520 (20.5)	392 (15.4)	329 (12.9)
Weight, median (IQR), kg	74.0 (22.0)	75.0 (22.0)	76.0 (22.0)	77.0 (23.0)
2-year change in weight, mean (SD), kg <sup>c</sup>		0.84 (5.0)	0.98 (4.9)	0.02 (5.0)
2-year change in weight (categories) <sup>c</sup>				
Weight stable		1,328 (60.2)	1,186 (57.7)	1,153 (59.6)
Weight loss		255 (11.6)	190 (9.2)	216 (11.2)
Weight gain		480 (21.7)	381 (18.5)	238 (12.3)

<sup>a</sup>Unless otherwise indicated.

<sup>b</sup>Total is less than number participating in follow-up measurement due to missing data.

<sup>c</sup>Weight change between preceding and current measurement.

Abbreviations: IQR = interquartile range, MET = metabolic equivalent total units, SD = standard deviation,

SSRI = selective serotonin reuptake inhibitor.

those with missing data for depression status or weight were removed for the measurement period concerned.

To account for correlation due to multiple observations of each individual participant, all of the 2-year observations were combined into a multinomial logistic mixed model using 2-year weight change categories (loss, gain, stable) as the dependent variable and depression status (cMDD, rMDD, and control) as the independent variable. Odds ratios were established using weight stable controls as the reference category.

An adjusted analysis was also performed that included age, partner status, weight, smoking status, alcohol intake, and number of chronic diseases as time-variant variables and sex and years of education as time-invariant variables (baseline values). In addition, in the unadjusted model, possible interactions with age, sex, education, and initial body mass index (BMI) categories were investigated.

To study the association between antidepressant medication use and weight change, a second analysis was performed with antidepressant medication classes (TCA, SSRI, other antidepressants) entered as independent, timevariant variables. This was done with and without adjustment for other covariates. In a final analysis, the combined effect of depression status and antidepressant use was assessed. All analyses were repeated using an absolute definition (5-kg gain or loss) of weight change. Finally, in order to investigate the long-term association of depression status with weight change, the association between baseline depression status and 6-year weight change categories (baseline to 6-year follow-up) was studied.

We further explored the sociodemographic and healthrelated differences between the group of cMDD patients who gained versus lost > 5% of weight. Participants who had multiple successive cMDD episodes with fluctuating weight change trajectories (ie, successively first gaining then losing weight or vice versa; 11.5%) were excluded from this analysis. For the remaining cMDD participants, the characteristics at the start of the first 2-year weight change were used. As a first step, odds ratios of weight gain were calculated in a binary univariable logistic regression model for all sociodemographic characteristics. Subsequently, the symptom profile difference between depressed patients who gained weight and those who lost weight was explored using a (backward) stepwise regression analysis (P=.05) incorporating all individual 30 IDS items.

Statistical significance was set at P < .05. The multinomial logistic mixed model analyses were conducted using MLWin version 2.3 and all other analyses in SPSS 20 (SPSS Inc, Chicago, Illinois).

#### RESULTS

Table 1 shows the distribution of study characteristics per follow-up for participants. The median weight at baseline

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Figure 1. Distribution of Participants With Weight Gain/Weight Loss/Stable Weight According to Depression Status in Combination With Antidepressant Use (total of 5,390 observations)



was 74 kg, which increased by a median of 1 kg per 2 years. The majority of participants (with complete weight data) were classified as stable in weight (67.7%) between all 2-year follow-up measurements, with 12.1% of participants losing and 20.2% gaining weight (Table 1). Just under half of depressed participants were using antidepressant medication during the course of the study, SSRIs being the most commonly used.

Figure 1 illustrates the distribution of weight change categories according to depression status and antidepressant use. When all of the observations were pooled together, the proportion of those who gained weight and those who lost weight was larger for all cMDD subgroups (ie, cMDD with and without antidepressant medication) compared to controls. This was particularly true for SSRI users: 32% of the SSRI users gained weight compared to only 17% of the controls.

Stratification for gender, age, education level, or BMI categories was not required, as none of the interaction terms between depression status and these variables were found to be significantly associated with weight changes. The crude mixed model multinomial logistical regression showed that, compared to controls, participants with cMDD were significantly more likely to gain >5% of their body weight over a 2-year period than remain weight stable (odds ratio [OR] = 1.95; 95% confidence interval [CI], 1.62–2.34) (Table 2). This relationship remained, albeit with a smaller effect size, after adjustment for confounding variables (OR = 1.67; 95% CI, 1.37-2.03). Additionally, currently depressed participants were more likely to lose weight than remain weight stable in comparison to controls, in both crude and fully adjusted models (OR = 1.62; 95% CI, 1.29-2.03; and OR=1.27; 95% CI, 1.01-1.61, respectively). rMDD was not associated with subsequent weight change in any of the models.

Extension of the follow-up period to 6 years using data on 1,691 participants (299 who lost weight, 545 who gained weight, and 847 stable in weight) revealed that participants who were depressed at baseline were more likely to gain weight over the long term (adjusted OR = 1.33; 95% CI, 1.00–1.76), but not to lose weight (adjusted OR = 1.18; 95% CI, 0.83–1.69). Finally, use of weight change categories based on absolute weight change showed similar results to percentage weight change categories (Supplementary eTable 1).

Analysis of antidepressant groups revealed that, after adjustment, use of SSRIs and other antidepressants was significantly associated with weight gain (OR = 1.26; 95% CI, 1.05-1.52; and OR = 1.36; 95% CI, 1.00-1.84, respectively, Table 2) when compared to using no antidepressants. After combining both depressive status and antidepressants medication use into 1 model, cMDD remained significantly associated with both weight gain and weight loss (in both crude and fully adjusted models), but antidepressant medication use no longer significantly predicted weight gain (Table 2).

Post hoc comparison of cMDD patients who gained (n=302) and lost weight (n=151) showed that lower initial weight, being younger, having fewer chronic diseases, and having an anxiety disorder within the last 6 months were associated with weight gain, while being an ex-smoker was associated with weight loss (Table 3). There was no overall difference in depression severity between both patient groups. Exploratory analysis into the differences in depressive symptomatology showed that those who gained weight had significantly more panic/phobic symptoms, a poorer quality of mood, and less aches and pains compared to those who lost weight (Table 4). Additionally, subsequent weight gain was associated with reported reduced appetite and weight loss in the 2 weeks prior to interview.

#### DISCUSSION

Among a sample of 2,542 participants with 5,390 longitudinal observations, we found that a diagnosis of cMDD (6 months recency) was associated with both weight loss (OR=1.27) and weight gain (OR=1.67) over

#### It is illegal to post this copyrighted PDF on any website. Table 2. Association Between Depression and Antidepressant Use Status and 2-Year Weight Change Categories (5,390 observations; N=2,542 participants)

	2-Year Weig	ht Gain (> 5%)ª	2-Year Weight Loss (> 5%) <sup>a</sup>		
	Crude OR (95% Cl)	Fully Adjusted OR <sup>b</sup> (95% CI)	Crude OR (95% Cl)	Fully Adjusted OR <sup>b</sup> (95% CI)	
Analysis 1					
Depression status Controls (no history of MDD) Remitted MDD Current MDD	1.00 (reference) 1.17 (0.99–1.40) 1.95 (1.62–2.34) <sup>c</sup>	1.00 1.11 (0.93–1.34) 1.67 (1.37–2.03) <sup>c</sup>	1.00 (reference) 1.10 (0.89–1.36) 1.62 (1.29–2.03) <sup>c</sup>	1.00 0.94 (0.75–1.16) 1.27 (1.01–1.61) <sup>d</sup>	
Analysis 2					
Antidepressant use Nonusers Tricyclic antidepressants SSRIs Other antidepressants	1.00 (reference) 1.00 (0.64–1.56) 1.35 (1.13–1.62) <sup>e</sup> 1.32 (0.98–1.77)	1.00 0.98 (0.62–1.54) 1.26 (1.05–1.52) <sup>d</sup> 1.36 (1.00–1.84) <sup>d</sup>	1.00 (reference) 1.51 (0.95–2.39) 1.25 (1.00–1.57) <sup>d</sup> 1.10 (0.75–1.62)	1.00 1.20 (0.75–1.92) 1.05 (0.83–1.33) 1.04 (0.70–1.54)	
Analysis 3 (combined model)					
Depression status Controls (no history of MDD) Remitted MDD Current MDD	1.00 (reference) 1.15 (0.96–1.39) 1.90 (1.56–2.31) <sup>c</sup>	1.00 1.09 (0.91–1.31) 1.61 (1.31–1.98) <sup>c</sup>	1.00 (reference) 1.08 (0.87–1.33) 1.57 (1.24–2.00) <sup>c</sup>	1.00 0.94 (0.75–1.17) 1.28 (1.00–1.64) <sup>d</sup>	
Antidepressant use Nonusers	1.00 (reference)	1.00	1.00 (reference)	1.00	
Tricyclic antidepressants SSRIs Other antidepressants	0.82 (0.52–1.27) 1.13 (0.93–1.37) 1.03 (0.76–1.40)	0.86 (0.54–1.36) 1.12 (0.92–1.36) 1.14 (0.84–1.56)	1.31 (0.82–2.89) 1.10 (0.87–1.40) 0.92 (0.21–1.37)	1.12 (0.69–1.81) 0.99 (0.78–1.27) 0.94 (0.63–1.40)	

<sup>a</sup>The reference category is weight stable.

<sup>b</sup>Adjusted for weight at baseline, gender, age, partner status, years of education, alcohol use, smoking status, and number of chronic diseases.

<sup>c</sup>*P* < .001.

<sup>d</sup>P<.05.

<sup>e</sup>P<.01.

Abbreviations: MDD = major depressive disorder, OR = odds ratio, SSRI = selective serotonin reuptake inhibitor.

## Table 3. Comparison of the Characteristics for Patients With Current MDD Who Consistently Gained or Lost Weight Between Waves

	2-Year Weight Loss	2-Year Weight Gain	Univariable Odds Ratio (95% CI)
Characteristic	(n=151)	(n=302)	for Gaining Weight <sup>a</sup>
Male	40 (26.7)	75 (24.8)	1.10 (0.70–1.71)
Age, mean (SD), y	44.1 (13.1)	39.2 (12.2)	0.97 (0.95–0.99) <sup>b</sup>
Education, mean (SD), y	11.6 (3.3)	11.9 (3.1)	1.02 (0.96–1.09)
Partner status, n (%) with partner	91 (60.0)	177 (58.6)	0.93 (0.63–1.39)
Weight, mean (SD), kg	83.3 (17.7)	73.3 (16.5)	0.97 (0.95–0.98) <sup>b</sup>
No. of chronic diseases, mean (SD)	1.16 (1.32)	0.8 (0.95)	0.77 (0.64–0.91) <sup>c</sup>
Alcohol drinks/wk, n (%)			
Less than 1	56 (37.3)	129 (42.7)	1.00 (reference)
1–14	70 (46.0)	138 (45.7)	0.86 (0.56-1.32)
More than 14	25 (16.7)	35 (11.6)	0.61 (0.33–1.11)
Smoking category, n (%)			
Nonsmoker	37 (24.0)	85 (28.1)	1.00 (reference)
Ex-smoker	58 (38.7)	74 (23.5)	0.55 (0.33–0.93) <sup>d</sup>
Current smoker	56 (37.3)	143 (47.4)	1.11 (0.68–1.82)
Antidepressant use, n (%)			
No antidepressant use			1.00 (reference)
Tricyclic antidepressant use	11 (7.3)	12 (4.0)	0.52 (0.22–1.22)
SSRI use	38 (25.3)	103 (34.1)	1.55 (1.00–2.41) <sup>d</sup>
Other antidepressant use	13 (8.7)	33 (10.9)	1.31 (0.66–2.56)
Anxiety, no. of disorders <sup>e</sup> in last 6 mo, mean (SD)	0.87 (0.92)	1.06 (0.94)	1.66 (1.11–2.47) <sup>d</sup>
IDS score, mean (SD)	29.9 (13.0)	30.8 (13.1)	1.07 (0.88–1.30) <sup>f</sup>

<sup>a</sup>Odds ratios are for weight gain in comparison to weight loss.

<sup>c</sup>P<.01.

<sup>d</sup>P<.05.

<sup>e</sup>General anxiety disorder, social phobia, panic disorder, agoraphobia.

<sup>f</sup>Per standard deviation increase.

Abbreviations: IDS = Inventory of Depressive Symptomatology, MDD = major depressive disorder, SD = standard deviation.

<sup>&</sup>lt;sup>b</sup>P<.001.

Table 4. Comparison of Items From the Inventory of Depressive Symptomatology (IDS) for Patients With Current MDD Who Consistently Gained or Lost Weight Between Waves Determined by a (backward) Stepwise Regression Analysis

Individual Depression Symptoms (IDS)	2-Year Weight Loss (n=151)	2-Year Weight Gain (n=302)	Multivariable Odds Ratio (95% CI) for Gaining Weigh
Q10: Poorer quality of mood, mean (SD)	2.21 (1.15)	2.41 (1.25)	1.27 (1.02–1.57) <sup>a</sup>
Q11: Reduced appetite (2 wk previous), n (%)	6 (4.1)	35 (11.9)	2.19 (1.14–4.22) <sup>a</sup>
Q12: Weight loss (2 wk previous), n (%)	15 (10.2)	60 (20.5)	1.27 (1.02–1.57) <sup>a</sup>
Q23: More aches and pains, mean (SD)	2.31 (1.04)	2.08 (1.99)	0.71 (0.55–0.92) <sup>a</sup>
Q25: Increased panic/phobic symptoms, mean (SD)	1.79 (0.99)	1.95 (1.14)	1.35 (1.05–1.71) <sup>a</sup>
<sup>a</sup> P<.05.			

Abbreviations: MDD = major depressive disorder, SD = standard deviation.

2 years compared to controls. Although SSRI and other antidepressant use (mirtazapine and venlafaxine) was independently associated with weight gain, only cMDD remained significantly associated when depression status and antidepressant use were combined in a single model.

Analysis of 6-year weight changes (baseline-year 6) showed that a diagnosis of cMDD increased the odds of gaining weight, albeit with a smaller odds, but not losing weight. As the majority of participants with cMDD at baseline recover before the subsequent follow-up, this could imply that weight loss is a shorter-term phenomenon occurring in the acute MDD phase.

Our finding that depression is associated with future weight gain is congruent with other studies.<sup>6–10</sup> All but 1 of these studies had similar follow-up intervals of 2 or 3 years. Three of these studies<sup>6–8</sup> also found an association between depression and weight loss, although this was restricted to males for 1 study<sup>7</sup> and participants aged over 55 years in another.<sup>6</sup> However, we found larger odds ratios, which could be attributed to the fact that, by using a clinical psychiatric *DSM* definition of depression, our study included more severe cases. Finding weight loss as well as weight gain confirms the heterogeneous nature of MDD. We found no association between rMDD and subsequent weight changes. The few studies into weight changes during remission yield varying results, with some finding weight  $gain^{24-26}$  and others reporting no changes in weight.<sup>27</sup>

Various antidepressants have been associated with weight gain, including TCAs,<sup>13,28</sup> SSRIs, mirtazapine,<sup>29</sup> and venlafaxine.<sup>13</sup> Similar to Patten et al,<sup>13</sup> our study found that SSRIs and other antidepressants (mostly mirtazapine and venlafaxine) were significantly associated with weight gain. However, we found no significant association between TCA use and weight gain. Importantly, when antidepressant use was combined in a model with depression status, only cMDD remained significantly related to weight gain. Although this may suggest that the underlying depressive disorder, rather than antidepressant medication use, accounts for the weight gain, our observational study design cannot completely disaggregate these effects. Evidence to support our finding can be found in a study by Cassano and Fava,<sup>30</sup> whose review of tolerability issues during long-term antidepressant use found evidence that both antidepressant-treated and placebo-treated patients were liable to gain weight. In our study, both nonmedicated depressed subjects and their medicated peers showed similar weight gains. Supporting the fact that both antidepressant use and MDD are associated with subsequent weight gains is a later study by Patten et al.<sup>31</sup> This study found that both clinically diagnosed MDD and antidepressant use remained associated with a modest increase in weight over a 2-year period. The disparity between this study and ours could be due to the use of a continuous measure of weight change by Patten et al<sup>31</sup> versus the categorical measure in our study. However, those treated with antidepressants are generally more severely depressed. Hence, depression severity could have biased the association between antidepressant medication use and weight change.

Exploratory analysis of differences between depressed participants who gained weight with those who lost weight over a 2-year period showed that starting weight was significantly related to future weight changes, with heavier depressed participants being more likely to lose weight and vice versa. Furthermore, cMDD cases who gained weight had more often experienced losses in appetite and weight in the 2 weeks prior to interview. This may partly represent a regression to the mean phenomenon, indicating that weight instability is common among depressed patients. Recent studies showed that depression characterized by atypical symptoms may be a stronger predictor of obesity and weight gain than other subtypes of depression.<sup>26,32</sup> For example, Lasserre et al<sup>26</sup> found that depression with atypical features was prospectively associated with a higher increase in BMI over a 5.5-year period when patients were compared to controls. However, our analysis into individual symptoms showed that none of the atypical symptoms were related to subsequent weight gain but that, instead, some were related to subsequent weight loss. The contrast between these findings could potentially be due to the fact that Lasserre et al had a considerably longer follow-up period and the physical assessments took place a year before the psychiatric diagnosis. Additionally, we found that somatic illnesses and experience of aches and pain were more common among depressed patients who lost weight, further indicating that somatic frailty is more typical in this subgroup. Finally, depressed patients who gained weight had slightly more anxiety disorder and phobic symptoms.

Several possible behavioral, psychological, and biological mechanisms underlying the association between depression and weight changes have been suggested. Biobehavioral risk factors include dietary patterns, physical activity, alcohol consumption, and smoking habits.<sup>33,34</sup> In addition, a study by Konttinen et al<sup>35</sup> found that emotional eating

**It is illegal to post this copy** and physical activity self-efficacy were both independent pathways between depressive symptoms and adiposity. Among physiological mechanisms, long-term activation of the hypothalamic-pituitary-adrenal (HPA) axis, considered a hallmark of depression, may inhibit lipid-mobilizing enzymes through the action of cortisol, resulting in weight gain.<sup>36,37</sup> Studies in aged populations showed hypoactivity of the HPA axis in depressed persons, especially in subjects with frailty, which is characterized by decreased weight.<sup>38</sup> Finally, an up-regulated inflammatory response has been extensively reported in both obesity and depression.<sup>37</sup>

Our study had several strengths. No previous study has simultaneously measured the impact of clinically diagnosed depression and antidepressant use on measured weight changes over time. This study also benefitted from the ability to incorporate several follow-up measurements over a period of 6 years and the inclusion of several timevariant covariates. Some limitations should be listed. First, residual confounding through aspects as social economic status and diet cannot be eliminated. Second, this study could have benefited from systematically recording whether participants were intentionally trying to lose weight, as this would distort the odds of losing weight. Third, it is possible that patients with large weight gains are more likely to discontinue antidepressant treatment thereby reducing the likelihood that antidepressant use is associated with weight gain. Finally, weight was only measured at 2-year intervals, and potential changes within these intervals were unknown.

Monitoring weight in patients diagnosed with MDD is of clinical relevance, as this can lead to further physiological complications such as diabetes and cardiovascular disease<sup>14,15</sup> for those who gain weight and osteoporosis, sarcopenia, and frailty for those who lose weight.<sup>16,39,40</sup> Moreover, weight gain may lead to poor self-image and increased inflammation, which could further exacerbate depressed status.<sup>41</sup> Understanding of the reasons and mechanisms behind weight changes is needed in order to help physicians give better treatment advice, as fear of weight gain in particular is a major reason for drug treatment noncompliance in depressed patients<sup>42</sup> and may contribute to a hesitancy to start with antidepressant treatment.<sup>31</sup>

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# Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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# **Supplementary Material**

- Article Title: Major Depressive Disorder, Antidepressant Use, and Subsequent 2-Year Weight Change Patterns in the Netherlands Study of Depression and Anxiety
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- **DOI Number:** 10.4088/JCP.14m09658

### List of Supplementary Material for the article

- 1. <u>eFigure 1</u> Illustration of the Study Assessments and Data Structure Used for Analysis
- 2. <u>eTable 1</u> Association between Depression and Antidepressant Use Status and 2-Year Absolute (5 kg) Weight Change Categories

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Supplementary figure 1: Illustration of the study assessments and data structure used for analysis. The correlation within persons was taken into account by using mixed model analysis.

Supplementary table 1: Association between depression and antidepressant use status and 2-year absolute (5kg) weight change categories (N observation=5390, N participants=2542)

2-year Weight Gain (>5kg) <sup>a</sup>		2-year Weight Loss (>5kg) <sup>a</sup>	
Weight adjusted OR (95%CI)	Fully adjusted OR <sup>b</sup> (95%CI)	Weight adjusted OR (95%CI)	Fully adjusted OR <sup>b</sup> (95%CI)
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
$1.25(1.03-1.53)^{c}$	1.16 (0.95-1.42)	1.20 (0.95-1.53)	1.03 (0.81-1.32)
1.98 (1.61-2.43) <sup>e</sup>	1.62 (1.31-2.01) <sup>e</sup>	1.84 (1.43-2.37) <sup>e</sup>	1.48 (1.14-1.93) <sup>d</sup>
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1.10 (0.69-1.77)	1.03 (0.63-1.68)	1.74 (1.08-2.80)	1.47 (0.91-2.40)
1.29 (1.06-1.58) <sup>c</sup>	1.16 (0.94-1.42)	1.26 (0.98-1.60) <sup>c</sup>	1.11 (0.86-1.43)
1.42 (1.04-1.95) <sup>c</sup>	1.41 (1.02-1.95) <sup>c</sup>	1.24 (0.84-1.86)	1.25 (0.84-1.88)
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
$1.23(1.01-1.51)^{c}$	1.15 (0.93-1.41)	1.18 (0.92-1.50)	1.02 (0.79-1.31)
1.93 (1.55-2.40) <sup>e</sup>	1.58 (1.26-1.99) <sup>e</sup>	1.77 (1.35-2.32) <sup>e</sup>	1.44 (1.09-1.91) <sup>e</sup>
1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
0.90 (0.56-1.45)	0.91 (0.56-1.49)	1.45 (0.89-2.35)	1.32 (0.81-2.17)
1.07 (0.87-1.32)	1.03 (0.83-1.27)	1.07 (0.83-1.38)	1.02 (0.78-1.32)
1.11 (0.80-1.54)	1.20 (0.85-1.67)	0.99 (0.66-1.51)	1.09 (0.72-1.65)
	2-year Weight Weight adjusted OR (95%CI) 1.00 (reference) 1.25 (1.03-1.53) <sup>c</sup> 1.98 (1.61-2.43) <sup>e</sup> 1.00 (reference) 1.10 (0.69-1.77) 1.29 (1.06-1.58) <sup>c</sup> 1.42 (1.04-1.95) <sup>c</sup> 1.42 (1.04-1.95) <sup>c</sup> 1.93 (1.55-2.40) <sup>e</sup> 1.00 (reference) 0.90 (0.56-1.45) 1.07 (0.87-1.32) 1.11 (0.80-1.54)	2-year Weight Gain (>5kg) <sup>a</sup> Weight adjusted OR (95%CI)Fully adjusted OR <sup>b</sup> (95%CI)1.00 (reference) $1.00$ (reference) $1.25 (1.03-1.53)^{c}$ $1.16 (0.95-1.42)$ $1.98 (1.61-2.43)^{e}$ $1.62 (1.31-2.01)^{e}$ 1.00 (reference) $1.62 (1.31-2.01)^{e}$ $1.00$ (reference) $1.00$ (reference) $1.10 (0.69-1.77)$ $1.03 (0.63-1.68)$ $1.29 (1.06-1.58)^{c}$ $1.16 (0.94-1.42)$ $1.42 (1.04-1.95)^{c}$ $1.41 (1.02-1.95)^{c}$ $1.00$ (reference) $1.5 (0.93-1.41)$ $1.93 (1.55-2.40)^{e}$ $1.58 (1.26-1.99)^{e}$ $1.00$ (reference) $1.00$ (reference) $0.90 (0.56-1.45)$ $0.91 (0.56-1.49)$ $1.07 (0.87-1.32)$ $1.03 (0.83-1.27)$ $1.11 (0.80-1.54)$ $1.20 (0.85-1.67)$	2-year Weight Gain (>5kg) <sup>a</sup> 2-year Weight Qr (95%CI)Weight adjusted OR (95%CI)Fully adjusted OR (95%CI)Weight adjusted OR (95%CI)1.00 (reference) $1.00$ (reference) $1.00$ (reference) $1.25 (1.03-1.53)^c$ $1.16 (0.95-1.42)$ $1.20 (0.95-1.53)$ $1.98 (1.61-2.43)^e$ $1.62 (1.31-2.01)^e$ $1.84 (1.43-2.37)^e$ $1.00$ (reference) $1.00$ (reference) $1.00$ (reference) $1.10 (0.69-1.77)$ $1.03 (0.63-1.68)$ $1.74 (1.08-2.80)$ $1.29 (1.06-1.58)^c$ $1.16 (0.94-1.42)$ $1.26 (0.98-1.60)^c$ $1.42 (1.04-1.95)^c$ $1.41 (1.02-1.95)^c$ $1.24 (0.84-1.86)$ $1.00$ (reference) $1.00$ (reference) $1.00$ (reference) $1.23 (1.01-1.51)^c$ $1.15 (0.93-1.41)$ $1.18 (0.92-1.50)$ $1.93 (1.55-2.40)^e$ $1.58 (1.26-1.99)^e$ $1.77 (1.35-2.32)^e$ $1.00$ (reference) $1.00$ (reference) $1.00$ (reference) $0.90 (0.56-1.45)$ $0.91 (0.56-1.49)$ $1.45 (0.89-2.35)$ $1.07 (0.87-1.32)$ $1.03 (0.83-1.27)$ $1.07 (0.83-1.38)$ $1.11 (0.80-1.54)$ $1.20 (0.85-1.67)$ $0.99 (0.66-1.51)$

Abbreviations: OR, odds ration; MDD, major depressive disorder, SSRI, Selective serotonin reuptake inhibitors <sup>a</sup>The reference category is weight stable <sup>b</sup>Adjusted for weight at baseline, gender, age, partner status, years of education, alcohol use, smoking status and

number of chronic diseases

 $^{\circ}P < 0.05$ 

 $^{d}P < 0.01$ 

 $^{e}P < 0.001$