Chapter 7

Does obesity along with major depression or anxiety lead to higher use of health care and costs? A 6-year follow-up study

Yeshambel T. Nigatu
Ute Bültmann
Robert A. Schoevers
Brenda W.J.H. Penninx
Sijmen A. Reijneveld

Submitted
ABSTRACT

**Objectives:** We examined the longitudinal associations of obesity, major depression (MD)/anxiety, and their combination with health care utilization (HCU) and costs.

**Methods:** We collected longitudinal data (2004-2013) among N=2706 persons from an ongoing cohort study, the Netherlands Study of Depression and Anxiety at baseline and 2-, 4, and 6-year follow-up. Obesity was defined as having a body mass index of ≥ 30kg/m$^2$, and abdominal obesity was defined as a waist circumference of ≥102 for males and ≥ 88 cm for females. MD and anxiety were assessed with the Composite International Diagnostic Interview. HCU concerned reported primary and specialized care visits, and hospitalizations and costs. We used generalized estimating equations for longitudinal modeling.

**Results:** Obesity and abdominal obesity were longitudinally associated with an increased risk of primary care visits and hospitalizations 2 years later over 6-year follow-up. MD/anxiety was longitudinally only associated with primary care visits. The combination of obesity and MD/anxiety was associated with an increased risk of primary and specialty care visits, and of hospitalizations, odds ratios (95%-confidence intervals): 1.83 (1.44; 2.34), 1.31 (1.06; 1.61) and 1.79 (1.40; 2.29), but the relative excess risks due to interaction were non-significant. The primary and specialty care costs were higher in persons with obesity and MD/anxiety, mean cost ratios = 1.56 (1.27; 1.91) vs 1.36 (1.15; 1.61) than in persons without these conditions.

**Conclusions:** Obesity along with MD/anxiety leads to higher use of care and costs over time. Integrated obesity and depression management efforts may help to reduce the overall health care use and costs.
INTRODUCTION

Obesity is the major contributing cause of type 2 diabetes, coronary artery disease, stroke, gallbladder disease, musculoskeletal disorders, and certain cancers, as well as all-cause mortality (1-3). Obesity is consistently associated with increased health care utilization (HCU) such as primary and specialized care, and hospitalizations, imposing large and increasing health care costs on society (4-6). Bertakis et al showed that obesity (BMI≥30) and severe obesity (BMI > 40) have been associated with a 50% and 100% increase in per capita health care costs, respectively (4,5).

MD and anxiety are also major public health problems and are associated with a number of physical conditions, such as cardiovascular diseases, type 2 diabetes and cancer, among others (3,7). Vogelzangs et al showed that persons with current MD/anxiety disorders were 1.37, 3.54, 4.96 and 4.75 times more likely to have stroke, coronary heart disease, angina pectoris and myocardial infarction compared to those without MD/anxiety, respectively (7). It has also been estimated that one in three adult primary care patients has a full or subclinical depressive disorder (8-10).

Evidence is growing that obesity and MD/anxiety often co-occur and are inter-related (11-18). The potential vicious cycle between these two conditions is assumed to be centered around inflammation (19), since both obese and depressed persons exhibit increased inflammatory markers, such as C-Reactive Protein (CRP), interleukin (IL)-6, and Tumor Necrosis Factor (TNF)-alpha (19-21). These inflammatory markers are found to be associated with an increased risk of chronic diseases (19). Obesity and MD/anxiety also share pleiotropic genes, and it seems that they might have a common etiology which make them valuable to examine (14,17,22-24). This suggests that obesity and MD/anxiety exacerbate each other through a common pathway, i.e. inflammation or genetic susceptibility thereby increase chronic diseases morbidity. Thus, we expect that persons with both obesity and MD/anxiety have markedly increased HCU and associated costs compared to persons with either of the condition alone. This leads to a hypothesis that the joint association of obesity and MD/anxiety is stronger than the sum of their separate associations regarding HCU and health care costs. Therefore, the main objective of the present study is to examine the separate and joint longitudinal associations of obesity and MD/anxiety with risks of increased HCU and costs over time.
METHODS

Study design and population

Data were derived from an ongoing longitudinal cohort study, the Netherlands Study of Depression and Anxiety (NESDA). NESDA examines the etiology, course, and consequences of depressive and anxiety disorders (25). A total of N=2,981 persons were included, aged 18 through 65 years recruited from the community, general practice and secondary care. Exclusion criteria were 1) a primary clinical diagnosis of another psychiatric disorder (i.e. psychotic disorder, obsessive-compulsive disorder, bipolar disorder, or severe addiction disorder), and 2) not being fluent in Dutch. From the original cohort of N=2981 subjects, we included N=2706 persons with complete data on the variables of interest at baseline.

After baseline measurement (2004-2007), extensive face-to-face and questionnaire-based assessments at 2-year (2006-2009), 4-year (2008-2013) and 6-year (2010-2013) follow-up were conducted. The loss to follow-up (i.e. not having at least one follow-up) was 19%, and was associated with lower educational status and occurrence of depressive/anxiety disorders, but not with age, gender, household income and obesity.

The NESDA study protocol was approved by the Ethical Review Board of the VU University Medical Center and subsequently by local review boards of each participating center. After full verbal and written information about the study, written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Measurements

General and abdominal obesity

We assessed general obesity with the body mass index (BMI), calculated from body weight (kg) and height (m) measured at each wave. Participants were classified into two BMI categories according to the standard international classification of the World Health Organization (WHO): non-obese < 30 kg/m², and obese ≥ 30.0 kg/m². Abdominal obesity was defined as having a waist circumference (WC) of ≥102 cm for males and ≥88 cm for females (26,27).
**Major depression and anxiety**

Major depression and anxiety were assessed using the Composite International Diagnostic Interview (CIDI), version 2.1, at each wave. The CIDI is a highly reliable and valid structured clinical interview and diagnoses according to definitions and criteria of the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (28). The interview was conducted by CIDI-trained interviewers (e.g. graduate students in psychology) under the supervision of clinicians. As remitted MD/anxiety is not associated with obesity (29), current MD/anxiety was dichotomized into individuals who were diagnosed positive and negative for the DSM-IV criteria of MD/anxiety in the past six months (30).

**Health care utilization**

Health care utilization (HCU) concerned outpatient visits to primary and specialty care, and hospitalizations at each wave. This information was assessed by the Trimbos/iMTA questionnaire on healthcare consumption and illness (Tic-P) (31). The following questions were used to assess outpatient and inpatient visits for this study: 1) ‘Did you have contact with your physician in the last six months?’ If yes, ‘how many times have you been contacted your physician during the last six months? And were any of these contacts related to mental health problems (yes/no)?’ 2) ‘Did you have any contact with a medical specialist in a general hospital in the last six months? If yes, how many contacts did you have with a medical specialist in the last six months?’ 3) ‘Have you been admitted to a hospital in the last 6 months?’

Health care costs for outpatient visits were calculated by multiplying the number of General practitioner (GP) contacts/visits by €29, and of specialty care visits by €75 (32). The recall period of the questions was 6 months, and the annualized costs were calculated by multiplying the estimated costs by two. All costs are expressed in Euro (€). As the number of participants admitted to a hospital > 1 was very few during 6 months, we did not calculate the hospitalization costs. We assumed that primary and specialty care costs can be used as a proxy for hospitalization costs.
**Statistical analyses**

Data were analyzed in four steps. First, we described the baseline sample characteristics by obesity and/or MD/anxiety status. Second, we examined the separate longitudinal associations of general obesity $t_x$, abdominal obesity $t_x$, and MD/anxiety $t_x$ with HCU $t_{x+1}$ using GEE (Generalized Estimating Equations) binary logistic regression (33,34), with $t_x$ being a given wave and $t_{x+1}$ being the next wave. All analyses were adjusted for age and gender. We also adjusted for any potential relationship between age and the determinants and outcome by including age and age-squared in the models. We checked interactions between obesity and/or MD/anxiety × gender and obesity and/or MD/anxiety × time by entering the interaction terms in the gender or time-adjusted models for the outcome variable.

Third, we examined whether the joint association of obesity $t_x$ and MD/anxiety $t_x$ with HCU $t_{x+1}$ is stronger than the sum of separate associations of obesity and MD/anxiety with HCU. We created a 4-category variable, non-obese and non-depressed, obese, depressed/anxiety, and both obese and depressed/anxiety. If obesity was present, then $i=1$ otherwise $i=0$. If MD/anxiety disorders was present, then $j=1$ otherwise $j=0$. Then, $OR_{ij}$ represented the OR in both obese and depressed/anxiety category $i$, $j$. The three OR estimates [(i.e.$OR_{11}$, $OR_{10}$, $OR_{01}$), and $OR_{00}$ (reference category)] were computed from GEE analyses. The RERI was used to assess the additional risk due to joint exposures of obesity and MD/anxiety compared to the sum of the separate risks for obesity and MD/anxiety regarding higher HCU. Relative excess risk due to interaction (RERI) was defined as:

$$RERI = OR_{11} - OR_{10} - OR_{01} + 1 \quad (35,36).$$

A positive interaction of obesity and MD/anxiety with HCU is reflected by a RERI >0, while a RERI < 0, represents a negative interaction of obesity and MD/anxiety; RERI=0 indicates that there is no interaction (additivity) in the association of obesity and MD/anxiety with HCU. Confidence intervals (CIs) for the RERI were calculated using covariances of parameter estimates from GEE models (35,36).

Fourth, we examined the separate and joint associations of obesity $t_x$ and MD/anxiety $t_x$ with health care costs 2 years later during a 6 year follow-up using GEE-time lag models. Given the skewed nature of the health care costs for primary and specialty care variables, we used GEE with a log-link function and a gamma distribution (37). GEE gamma regression model results should therefore be interpreted in terms of proportional or multiplicative differences (38,39). For instance, In Table 3, $188/148=1.27$, 128
indicates that obese persons have 1.27 times higher increase in primary care costs compared to their non-obese counterparts, which is equivalent to 27% increase in costs for obese persons.

All statistical analyses were performed using SPSS version 22.0. Effects were considered significant when P<0.05.
RESULTS

Characteristics of the sample

Table 1 shows the baseline characteristics of N=2706 subjects by obesity and/or MD/anxiety status. At baseline, the prevalences of general obesity and abdominal obesity, and MD/anxiety were 16%, 35% and 57%, respectively. The median (interquartile range, IQR) number of primary and speciality care visits during 6 months were 2 (1 to 3) and 0 (0 to 1), respectively. The annual health care costs (€) associated with primary and speciality care by obesity and/or MD/anxiety status are depicted in Table 1.

Separate associations of obesity and MD/anxiety with HCU

Longitudinal associations were found between general and abdominal obesity at t_x and primary care visits at t_{x+1} (OR (95%-confidence interval, CI)): 1.44 (1.21; 1.70) and 1.38 (1.22; 1.57), specialized care visits at t_{x+1} OR=1.24 (1.07; 1.45) and 1.27 (1.13; 1.43), and hospitalizations at t_{x+1} OR=1.66 (1.39; 1.98) and 1.75 (1.52; 2.02), respectively. Adjustment for age and gender slightly attenuated the associations but these remained statistically significant except for specialty care visits (Table 2). General and abdominal obesity at t_x were not associated with primary care visits due to mental problems at t_{x+1} with OR=1.17 (0.96; 1.42) and 1.05 (0.90; 1.23), respectively.

We also found a longitudinal association between MD/anxiety at t_x and primary care visits at t_{x+1} OR=1.35 (1.20; 1.52). Adjustment for age and gender slightly attenuated the association, but remained statistically significant. However, MD/anxiety at t_x was not associated with specialty care visits and hospitalizations at t_{x+1} (Table 2).
Table 1 Baseline characteristics of sample and HCU and costs by obesity and major depression/anxiety status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total population (N=2706)</th>
<th>Non-obese and no MD/anxiety (N=1000)</th>
<th>Obese without MD/anxiety (N=170)</th>
<th>MD/anxiety without obesity (N=1262)</th>
<th>Both obese and MD/anxiety (N=274)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, ± SD)</td>
<td>41.8 (13.0)</td>
<td>41.7 (13.9)</td>
<td>47.7 (12.6)</td>
<td>40.5 (12.2)</td>
<td>44.7 (11.2)</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Women, (%)</td>
<td>65.5</td>
<td>64.8</td>
<td>65.9</td>
<td>65.8</td>
<td>66.8</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Educational status, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>5.9</td>
<td>3.2</td>
<td>8.8</td>
<td>6.1</td>
<td>13.1</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>57.8</td>
<td>51.6</td>
<td>60.0</td>
<td>59.9</td>
<td>69.7</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>36.3</td>
<td>45.2</td>
<td>31.2</td>
<td>34.0</td>
<td>17.2</td>
<td></td>
</tr>
<tr>
<td>Abdominal obesity, (%)</td>
<td>35.1</td>
<td>23.0</td>
<td>95.9</td>
<td>23.1</td>
<td>96.7</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Health care use and costs (€)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary care visits * , (%)</td>
<td>83.4</td>
<td>74.2</td>
<td>80.0</td>
<td>89.2</td>
<td>92.7</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Visits because of mental problem, (%)</td>
<td>38.1</td>
<td>10.1</td>
<td>10.6</td>
<td>59.4</td>
<td>59.9</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Specialty care visits, (%)</td>
<td>34.3</td>
<td>31.9</td>
<td>35.3</td>
<td>34.9</td>
<td>39.8</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Hospitalizations, (%)</td>
<td>6.3</td>
<td>5.3</td>
<td>7.6</td>
<td>6.3</td>
<td>9.5</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td>Primary care costs (€), mean (SD)</td>
<td>158.4 (185.8)</td>
<td>103.0 (112.1)</td>
<td>124.9 (123.2)</td>
<td>185.9 (198.1)</td>
<td>254.9 (283.7)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Specialty care costs (€), mean (SD)</td>
<td>147.3 (355.6)</td>
<td>121.8 (317.7)</td>
<td>175.6 (368.5)</td>
<td>153.1 (370.0)</td>
<td>196.5 (402.0)</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Note. * all visits to doctor, telephonic consultations, and visits of the physician at respondents’ home; ANOVA for continuous variables and chi-square for categorical variables.
Table 2: The longitudinal separate and joint associations of obesity $t_x$, major depression/anxiety $t_x$, and their combination with health care use $t_{x+1}$

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Health care utilization</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Primary care visits</td>
<td>Visits due to mental problem</td>
<td>Specialist visits</td>
<td>Hospitalizations</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>OR (95%CI)</td>
<td>aOR* (95%CI)</td>
<td>OR (95%CI)</td>
<td>aOR* (95%CI)</td>
<td>OR (95%CI)</td>
<td>aOR* (95%CI)</td>
</tr>
<tr>
<td>Non-obese</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Obesity (BMI≥30kg/m2)</td>
<td>1.44 (1.21; 1.70)</td>
<td>1.36 (1.15; 1.61)</td>
<td>1.17 (0.96; 1.42)</td>
<td>1.17 (0.96; 1.42)</td>
<td>1.24 (1.07; 1.45)</td>
<td>1.15 (0.98; 1.34)</td>
<td>1.66 (1.39; 1.98)</td>
</tr>
<tr>
<td>No abdominal obesity</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Abdominal obesity b</td>
<td>1.38 (1.22; 1.57)</td>
<td>1.24 (1.09; 1.42)</td>
<td>1.05 (0.90; 1.23)</td>
<td>1.05 (0.90; 1.23)</td>
<td>1.27 (1.13; 1.43)</td>
<td>1.10 (0.99; 1.22)</td>
<td>1.75 (1.52; 2.02)</td>
</tr>
<tr>
<td>No depression/anxiety</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Major depression/anxiety</td>
<td>1.35 (1.20; 1.52)</td>
<td>1.35 (1.20; 1.52)</td>
<td>2.36 (2.03; 2.74)</td>
<td>2.31 (1.99; 2.68)</td>
<td>1.09 (0.99; 1.21)</td>
<td>1.01 (0.91; 1.13)</td>
<td>1.12 (0.98; 1.28)</td>
</tr>
<tr>
<td>General obesity &amp; MD/anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-obese and non-depressed</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Obesity (BMI≥30kg/m2)</td>
<td>1.43 (1.15; 1.78)</td>
<td>1.35 (1.08; 1.68)</td>
<td>1.25 (0.94; 1.66)</td>
<td>1.25 (0.94; 1.66)</td>
<td>1.21 (1.00; 1.47)</td>
<td>1.11 (0.91; 1.34)</td>
<td>1.70 (1.35; 2.12)</td>
</tr>
<tr>
<td>Major depression/anxiety</td>
<td>1.35 (1.19; 1.53)</td>
<td>1.35 (1.19; 1.54)</td>
<td>2.41 (2.04; 2.84)</td>
<td>2.35 (1.99; 2.78)</td>
<td>1.09 (0.97; 1.22)</td>
<td>1.09 (0.97; 1.23)</td>
<td>1.15 (0.99; 1.34)</td>
</tr>
<tr>
<td>Both obese and depressed/anxious</td>
<td>1.92 (1.51; 2.45)</td>
<td>1.83 (1.44; 2.34)</td>
<td>2.62 (2.01; 3.41)</td>
<td>2.55 (1.95; 3.33)</td>
<td>1.40 (1.13; 1.72)</td>
<td>1.31 (1.06; 1.61)</td>
<td>1.84 (1.44; 2.36)</td>
</tr>
<tr>
<td>Abdominal obesity and MD/anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-obese and non-depressed</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Abdominal obesity b</td>
<td>1.46 (1.23; 1.70)</td>
<td>1.29 (1.09; 1.52)</td>
<td>1.26 (1.01; 1.56)</td>
<td>1.26 (1.01; 1.58)</td>
<td>1.26 (1.09; 1.46)</td>
<td>1.07 (0.92; 1.24)</td>
<td>1.77 (1.47; 2.12)</td>
</tr>
<tr>
<td>Major depression/anxiety</td>
<td>1.41 (1.22; 1.62)</td>
<td>1.40 (1.21; 1.62)</td>
<td>2.67 (2.21; 3.23)</td>
<td>2.61 (2.15; 3.16)</td>
<td>1.09 (0.96; 1.25)</td>
<td>1.09 (0.95; 1.24)</td>
<td>1.16 (0.97; 1.39)</td>
</tr>
<tr>
<td>Both obese and depressed/anxious</td>
<td>1.79 (1.50; 2.15)</td>
<td>1.62 (1.35; 1.95)</td>
<td>2.42 (1.95; 3.01)</td>
<td>2.36 (1.89; 2.94)</td>
<td>1.40 (1.20; 1.64)</td>
<td>1.22 (1.04; 1.43)</td>
<td>1.99 (1.64; 2.42)</td>
</tr>
</tbody>
</table>

Note. OR: Odds ratio; *Adjusted for age, age-squared and gender; MD: major depression; b: Waist circumference (WC) ≥ 102 cm for male and 88cm for female; Bold figures reflect statistically significant estimates ($p<0.05$).
Joint associations of obesity and MD/anxiety with HCU

Longitudinal associations were found between obesity and MD/anxiety at t_x and primary- and specialty care visits, and hospitalizations at t_{x+1} with OR (95%-CI)=1.92 (1.51; 2.45), 1.40 (1.13; 1.72 and 1.84 (1.44; 2.36), compared to non-obese and non-depressed/anxious persons respectively (Table 2). The relative excess risks due to interaction (RERI (95%-CI)) between obesity and MD/anxiety on primary care visits, specialty care visits, and hospitalizations were: 0.15 (-0.38, 0.68), 0.10 (-0.24, 0.43), and 0.00 (-0.53, 0.53), respectively (Figure 1). Similarly, the combinations of abdominal obesity and MD/anxiety at t_x with an increased risk of primary and specialty care visits and hospitalizations at t_{x+1}, OR=1.79 (1.50; 2.15), 1.40 (1.20; 1.64 and 1.99 (1.64; 2.42), respectively (Table 2).

The separate and joint associations of obesity and MD/anxiety with health care costs

Table 3 shows the predicted 2-year subsequent health care costs for primary and specialty care by obesity and/or MD/anxiety status during 6-year follow-up. Obese persons had 27% and 25% higher increase in primary and specialty care costs 2 years later compared to their non-obese counterparts, respectively (Table 3). Persons with MD/anxiety had 24% higher increase in primary care costs compared to those without MD/anxiety (Table 3), but not associated with an increase in specialty care costs.

Obesity along with MD/anxiety at t_x was longitudinally associated with an increase in primary and specialty care costs at t_{x+1}, mean cost ratio (95%-CI) =1.56 (1.27, 1.91) and 1.36 (1.15, 1.61) compared to non-obese and non-depressed/anxiety, respectively (Table 3), with a RERI=0.17 (-0.16; 0.51) and -0.11 (-0.46, 0.23), respectively.
Table 3: The longitudinal associations of obesity t,x, major depression/anxiety t,x, and their combination with primary and specialty care costs (€) t+1 6-year follow-up

<table>
<thead>
<tr>
<th>Obesity and/or MD/anxiety</th>
<th>Primary care costs (€)</th>
<th>Specialist care costs (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated marginal means (SE)</td>
<td>Mean cost ratios&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Non-obese</td>
<td>148.6 (2.7)</td>
<td>Reference</td>
</tr>
<tr>
<td>Obesity (BMI≥30kg/m2)</td>
<td>188.2 (12.2)**</td>
<td>1.27 (1.11; 1.44)</td>
</tr>
<tr>
<td>No abdominal obesity</td>
<td>142.4 (2.6)</td>
<td>Reference</td>
</tr>
<tr>
<td>Abdominal obesity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>176.3 (6.8)***</td>
<td>1.24 (1.14; 1.34)</td>
</tr>
<tr>
<td>No major depression/anxiety</td>
<td>142.7 (3.1)</td>
<td>Reference</td>
</tr>
<tr>
<td>Major depression/anxiety</td>
<td>172.7 (5.6)</td>
<td>1.21 (1.13; 1.30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Obesity and MD/anxiety</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obese and non-depressed</td>
<td>137.1 (3.0)ref</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
<td>685.5 (29.2)ref</td>
<td>1 (Reference)</td>
<td>1 (Reference)</td>
</tr>
<tr>
<td>Obesity (BMI≥30kg/m2)</td>
<td>164.5 (9.9)**</td>
<td>1.20 (1.06; 1.36)</td>
<td>1.17 (1.03; 1.33)</td>
<td>899.8 (84.1)*</td>
<td>1.31 (1.07; 1.61)</td>
<td>1.28 (1.04; 1.58)</td>
</tr>
<tr>
<td>Major depression/anxiety</td>
<td>162.9 (4.4)***</td>
<td>1.19 (1.11; 1.27)</td>
<td>1.18 (1.11; 1.26)</td>
<td>795.2 (57.8)</td>
<td>1.16 (0.99; 1.36)</td>
<td>1.15 (0.99; 1.34)</td>
</tr>
<tr>
<td>Both obese and depressed/anxious</td>
<td>213.9 (21.7)***</td>
<td>1.56 (1.27; 1.91)</td>
<td>1.51 (1.25; 1.83)</td>
<td>932.0 (70.5)**</td>
<td>1.36 (1.15; 1.61)</td>
<td>1.31 (1.11; 1.55)</td>
</tr>
</tbody>
</table>

| Abdominal obesity and MD/anxiety |                         |                          |                                |                          |                          |                                |
| Non-obese and non-depressed | 132.7 (3.0)ref       | 1 (Reference)            | 1 (Reference)                  | 623.8 (27.1)ref         | 1 (Reference)            | 1 (Reference)                  |
| Abdominal obesity<sup>b</sup> | 155.1 (6.0)**         | 1.17 (1.07; 1.27)        | 1.12 (1.03; 1.23)              | 881.2 (58.7)            | 1.41 (1.21; 1.65)        | 1.38 (1.16; 1.63)              |
| Major depression/anxiety  | 154.2 (4.3)***        | 1.16 (1.08; 1.25)        | 1.16 (1.08; 1.24)              | 747.2 (83.6)***         | 1.20 (0.96; 1.50)        | 1.19 (0.96; 1.48)              |
| Both obese and depressed/anxious | 201.2 (12.0)***     | 1.52 (1.34; 1.72)        | 1.45 (1.29; 1.63)              | 917.4 (58.8)***         | 1.47 (1.26; 1.71)        | 1.42 (1.21; 1.66)              |

Note. <sup>a</sup>mean cost ratios between exposed and non-exposed groups with 95% confidence intervals; MD; major depression <sup>b</sup>Adjusted for age and gender; <sup>c</sup>Waist circumference (WC) ≥ 102 cm for male and 88 cm for female; Bold figures reflect statistically significant estimates (p<0.05). **; P<0.01; ***: P<0.001.
Figure 1: Cumulative risk of health care use associated with the separate and joint exposures to obesity and major depression/anxiety: Netherlands Study of Depression and Anxiety, 2004–2013.

a) Primary care visits

- Non-obese and non-depressed/anxiety
- Obese
- Major depression/anxiety
- Obese and depressed/anxiety

b) Speciality care visits

- Non-obese and non-depressed
- Obesity
- Major depression/anxiety
- Obesity and major depression/anxiety
c) Hospitalizations

Odds ratios

- Non-obese and non-depressed/anxiety
- Obese
- Major depression/anxiety
- Obese and depressed/anxiety
DISCUSSION

In this 6-year longitudinal study, we examined the associations of obesity, MD/anxiety and their combination with risks of increased HCU and costs during the subsequent two years. Obesity was associated with an increased risk of all types of care except visits due to mental problems. MD/anxiety was associated with an increased risk of primary care visits, but not specialty care visits and hospitalizations. The joint association of obesity and MD/anxiety with higher HCU and costs was slightly larger than would have been expected on the additive scale, but this increase was not statistically significant. This refutes the hypothesis that the joint association of obesity and MD/anxiety with higher HCU is larger than the sum of their separate associations.

We found that obesity along with MD/anxiety was significantly associated with an increased use of all types of care, and was slightly larger than would have been expected on the additive scale. For joint exposures of obesity and MD/anxiety, the additional risk of a primary care visit was 92%, while the risk attributable to obesity and MD/anxiety was 78% (43% to obesity and 35% to MD/anxiety), leading to a RERI=0.15 (Figure 1a). Similarly, the RERIs for specialty care visit and hospitalizations were 0.10 and 0.00 (Figures 1b and 1c), respectively. Although obesity along with MD/anxiety tends to increase the use of care and costs beyond additive effects, the additional risks were not statistically different. An explanation why the RERIs are not statistically significant may be that the interaction between obesity and MD/anxiety needs more time to lead to more than additive effects. This may be due to having the benign phenotype of obesity, i.e. metabolically healthy obesity (MHO) because these phenotypes are transitional states prone to changes in their metabolic status, and have increased risks for adverse health outcomes when follow-ups longer than 10 years are considered (40). Another explanation is that there is also a tendency that patients with MD/anxiety show clinical recovery over time even though residual symptoms of depression or anxiety often persist (41,42). Another, more pragmatic explanation why the RERI is not significant is the rather small sample size for the subgroup analysis of obesity and major depression status categories with HCU.

Another important finding is that persons with obesity alone and depression/anxiety alone differ in use of care and associated costs. Obesity alone (BMI≥30) was longitudinally associated with an increased risk of primary and specialty care visits, and hospitalizations, which is in line with earlier studies (4-6,43-48). This is
explained by the fact that obesity is related causally to serious medical illnesses, in which excess body weight increases the risk of the development of several chronic conditions. However, obesity was not associated with primary care visits due to mental problems during follow-up. This gives an insight that the physiological effects of obesity is more likely to increase HCU and costs compared to its psychological effect (i.e. psychological complaints).

We found that persons with MD/anxiety alone had a higher risk of primary care visits and costs, but not specialty care visits and hospitalizations. In line with our finding, Luppa et al showed that depressed persons have an increased HCU and costs compared to non-depressed once (49). In fact, use of health care among depressed persons can be partly explained by age (e.g. older age) and the severity of depression (e.g. suicidal thoughts), decreased quality of life and higher co-morbidity of medical conditions (10)(49). As presented in this study, the risks of increased use of specialty and inpatient care were significantly higher in persons with MD/anxiety and obesity compared to those with MD/anxiety alone. A possible explanation is that obesity is a state of chronic low grade inflammation, which may exacerbate the psychological and/or physiological effects of depression thereby increasing HCU (19,20,50). Another explanation may be that the greater frequency of specialty care visits among obese adults, and the direct consequence of both obesity and MD/anxiety on the development of chronic conditions such as type II diabetes, coronary heart disease, cerebrovascular disease, certain types of cancer (51,52). Overall, we observed that the joint exposures of obesity and MD/anxiety lead to higher HCU and costs compared to either of the conditions alone.

**Strengths and limitations**

The major strength of our study is its prospective design. We were able to examine longitudinal associations of obesity and MD/anxiety at one point in time with HCU and costs 2 years later over a 6-year follow-up period by using time-lag models (i.e., the temporal association was maintained). This supports assumptions on causality, though not conclusive ones. Moreover, we used psychiatric interviews to diagnose MD/anxiety instead of self-reports as often used before. We assessed obesity using two anthropometric measurements i.e. BMI and WC, as many researchers have been criticizing the BMI for its inadequate reflection of body composition, which does not differentiate
between fat mass and lean body mass, or between abdominal adiposity and general fatness.

We have to keep some limitations in mind. First, the NESDA study is a representative sample of a population with common mental disorders (i.e. depressive and anxiety disorders). Because of this, a rather large proportion of the participants had prevalent depressive or anxiety disorders, implying that non-depressed obese subjects may be underrepresented. Nevertheless, we expect that the resulting study cohort is representative and generalizable to other settings in high-income countries because the prevalence of obesity in our study (16%) is comparable with that in the Dutch population, and within the range of the WHO European region prevalence (10-30%). Another limitation with respect to the outcome might be that the health care use information was based upon self-report, and may have been biased by depressive or anxiety symptoms. The estimated costs appeared smaller because we included major categories of health care services such as primary and specialty care costs, which could still be used as a proxy for hospitalizations costs.

**Implications and conclusions of the study**

Obesity and MD/anxiety are major burdens for the patient, physicians and the society. We showed that obesity and MD/anxiety are separately and jointly associated with an increased risk of HCU and costs, though they differ in use of across categories of health care. If the RERI for primary and specialty care is confirmed in future studies, the joint associations may have public health implications. Intervening on obesity may be more beneficial for individuals with MD/anxiety compared with those without MD/anxiety regarding the risks of primary and specialty care visits and associated costs. Moreover, persons with MD/anxiety consume more primary care resources than other categories of health care (i.e. specialty care and inpatient care). Therefore, careful consideration and maybe monitoring depressive symptoms and a more restraint use of antidepressants with the greatest weight stimulating effects seems to be needed in primary care. Future studies should focus on whether it is possible to manage obesity and MD/anxiety synergistically regarding morbidity, excess use of care and costs.

In conclusion, our study suggests that obesity and MD/anxiety impose a significant burden for HCU and costs. Obesity and MD/anxiety are separately and jointly associated
with risks of HCU and costs. The costs associated with both obesity and MD/anxiety are spread across a range of outpatient health services. This study point to the necessity of special intervention for these high risk groups (i.e. obese and depressed individuals).
REFERENCES


