Chapter 5

The Longitudinal Joint Effect of Obesity and Major Depression on Work Performance Impairment

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ABSTRACT

Objectives: We examined the longitudinal effect of obesity, major depression (MD) and their combination on work performance impairment (WPI).

Methods: We collected longitudinal data (2004-2013) on 1726 paid employees selected from the Netherlands Study of Depression and Anxiety at baseline and 2-, 4-, and 6-year follow-up. We defined obesity with body mass index and waist circumference. We diagnosed major depression with the composite international diagnostic interview (CIDI 2.1). We assessed work performance impairment with a questionnaire for costs associated with illness. We used generalized estimating equations for modeling, and estimated interaction on the additive scale.

Results: Obesity, abdominal obesity and major depression were longitudinally associated with increased risk of high WPI. The combinations of obesity and major depression, and of abdominal obesity and major depression were associated with increased risk of high WPI, odds ratios (95%-confidence intervals): 2.36 (1.61; 3.44) and 1.88 (1.40; 2.53), respectively, but the relative excess risks due to interaction were non-significant.

Conclusions: The longitudinal joint effect of obesity and major depression on high WPI implies that intervening on obesity may be more beneficial for individuals with major depression than those without regarding risk of high WPI, if confirmed in a large, representative sample.
INTRODUCTION

Obesity and major depression are major public health problems, posing enormous challenges in the decades to come (1,2). Both obesity and MD increase the risk of adverse health outcomes, such as diabetes II, cardiovascular diseases, premature death and disability (1,2). Major depression is even expected to be one of the top leading causes of disability adjusted life years by 2030 in high-income countries (1). In the European Union area, the costs of depression were estimated at 92 billion Euro in 2010, with lost productivity due to absenteeism (being off work due to sickness) and presenteeism (being present at work while ill) representing over 50% of all costs related to depression (3). It has been shown that a broad range of occupational health problems including depression is strongly associated with obesity, making obesity a prevailing problem in the working population (4-6). Previous studies that examined obesity in working populations are mainly focused on absenteeism (7,8), less is known about productivity loss at work due to obesity.

Both obesity and major depression can impair work performance. Work performance impairment (WPI) refers to productivity loss at work due to health problems. WPI is an increasing problem in aging workforces and has enormous cost implications for individuals, companies and society as a whole (9,10). Earlier, cross-sectional studies showed that major depression is associated with high WPI (11,12). Higher body weight and an excess of visceral fat are also associated with productivity loss (5-7). However, it is not known whether obesity and major depression jointly affect high WPI and if the risk of major depression on high WPI further increases in obese individuals or not.

There are 3 main reasons to examine their interaction or joint effect on WPI. First, obesity and depression are bidirectionally related, and neither obesity nor major depression fully precedes the other regarding the effect of WPI (i.e., no sole mediation). Then, it would be interesting to examine the joint effect of these two risk factors on high WPI and to estimate to what extent their joint effect differs from the sum of their separate effects on high WPI. Second, obesity and major depression share around 12 to 20% pleiotropic genes, and it seems that they might have a common etiology which make them valuable to examine (13-17). Third, both obesity and depression are associated with a global burden of disease and disability (1,2). In terms of their effects on the risk of high
WPI, obesity and major depression may interact thereby augmenting or reducing the effect of one another. If obesity and major depression exacerbate a common pathway, we expect to observe a substantially elevated risk of WPI in people with both exposures.

The interaction between 2 exposures of interest on a certain outcome can best be measured by statistical interaction on the additive scale using measures such as the relative excess risk due to interaction (RERI) and attributable proportion (AP) (18,19). A statistical interaction on the additive scale is more relevant to disease prevention and workplace health promotion programs in vulnerable workers than an interaction on the multiplicative scale, which is relevant in disease etiology (18). For example, if the joint effect of obesity and major depression surpasses the sum of their separate effects, then a reduction of either obesity or major depression would also reduce the risk of the other factor regarding high WPI. In terms of clinical decision making, then someone with major depression can reduce his/her risk regarding high WPI even more by losing weight than someone without major depression.

The main objective of the present study was to examine the longitudinal separate and joint effects of obesity and major depression on WPI. We used the RERI and AP as measures to test the hypothesis that the joint effect of obesity and major depression on high WPI is larger than the sum of the separate effects of obesity and major depression on high WPI. To our knowledge, there is no study to date that investigated this hypothesis.
METHODS

Study design and population

We derived data (2004-2013) from an ongoing longitudinal cohort study, the Netherlands Study of Depression and Anxiety (NESDA). This study examines the etiology, course, and consequences of depressive and anxiety disorders (20). A total of N=2,981 persons were included, aged 18 through 65 years, with a current depressive or anxiety disorder, with subthreshold symptoms, and controls without lifetime diagnoses of depressive or anxiety disorder. Recruitment took place in the community, primary care, 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. 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.

Out of the NESDA population (N=2981), we selected 1726 respondents who had a paid job for 8 or more hours per week at baseline. We took this cutoff because the employee should have been at work at least 1 day a week to be able to report the WPI information and to be consistent with previous NESDA studies (11-12). This constituted the final study sample. After the baseline measurement, we conducted extensive face-to-face and questionnaire-based assessments were conducted at 2-year, 4-year and 6-year follow-up. The loss to follow-up regarding WPI measurements (availability of less than two measurements) was 27% and was associated with higher age, lower educational status, depressive disorder, but not with gender, weight status and anxiety disorder.

Measurements

General and abdominal obesity

We assessed general obesity with the body mass index (BMI; weight in kilograms divided by the square of height in meters). We calculated BMI from body weight (kg) and height (m) measured at baseline (t0), at 2-year (t1), 4-year (t2) and 6-year (t3) follow-up. We classified the participants into two BMI categories according to the standard international classification of the World Health Organization (WHO): non-obese < 30 kg/m², and obese
We defined abdominal obesity as having a waist circumference (WC) of \( \geq 102 \text{ cm} \) and \( \geq 88 \text{ cm} \) for males and females, respectively (21, 22).

**Major depression**

We assessed major depression by the Composite International Diagnostic Interview (CIDI 2.1), a highly reliable and valid instrument for assessing depressive and anxiety disorders. The CIDI is a 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) (23). The CIDI contains questions directly corresponding to the symptoms of axis I psychiatric disorders listed in the DSM-IV. It translates the criteria of DSM-IV into questions that can be readily and reliably answered by the general population.

Participants were diagnosed at baseline \((t_0)\), at 2-year \((t_1)\), 4-year \((t_2)\) and 6-year \((t_3)\) follow-up. The interview was conducted by CIDI-trained interviewers (e.g. graduate students in psychology) under the supervision of clinicians. As remitted major depression was not associated with obesity (24), we dichotomized current major depression into individuals who were diagnosed positive and negative for the DSM-IV criteria of major depression in the past six months (25).

**Work performance impairment**

We measured work performance impairment (WPI) with the Trimbos/Institute for Medical Technology Assessment Questionnaire for Costs Associated with Psychiatric Illness (26). We used the following questions/items to assess WPI: ‘On how many days in the last six months have you been working while hindered by health problems?’ and ‘How efficient have you been working on the days that you were at work but were also hindered by health problems?’ (11). The scores range between 0 (inefficient) and 1 (efficient). We computed WPI with the following formula, in which a higher rate indicates more impairment.

\[
\text{WPI} = \frac{\text{\# days hindered during last half year} \times (1 - \text{efficiency}) \times \text{\# working hours per day}}{\text{\# working hours per week}}
\]

For example, the WPI rate of someone working 8 hours per day, 40 hours a week, who reported 25 days hindered, and a score of 0.8 at the efficiency scale, is \(25 \times (1-0.8) \times 8/40 = 1\). The variable ranged from 0 to 39 and did not meet normality assumptions.
Therefore, we dichotomized WPI (low; high) by taking the highest quartile (> 1.60) as cutoff point (11).

**Covariates**
Covariates concerned sociodemographic characteristics (age, gender, educational status and working hours). Age was used as a continuous variable. Educational level was categorized into low (primary and lower secondary education), middle (higher secondary education) and high (tertiary or higher education). Anxiety disorders were assessed by the CIDI 2.1 and defined as having a diagnosis of anxiety disorders at least once during their lifetime.

**Statistical analysis**
We analyzed data in 3 steps. First, we described the characteristics of the cohort using means and proportions by obesity and major depression status.

Second, we examined the separate effects of general obesity, abdominal obesity and major depression on high WPI using Generalized Estimating Equations (GEE). GEE allows correlated observations over time and missing values at different measurement points (27). We used an exchangeable correlation structure to take within subject dependencies into account. In this structure the correlations between subsequent measurements were assumed to be the same, irrespective of the length of the time interval. The goodness of fit was checked by Quasi likelihood under Independence model Criterion (QIC) in time-lag models. In these models, the value of the outcome WPI at \( t_{x+1} \) \((x = 0, 1, \ldots)\) was longitudinally associated with obesity or/and major depression at time-point \( t_x \) over 6-years (28). The odds ratios (OR) resulting from GEE logistic regression analyses can be interpreted as the longitudinal relationships between the predictors (obesity or depression or their combination) with high WPI (28). All analyses were adjusted for age, gender and educational status. We adjusted for any potential relationship between age and the determinants and outcome by including age and age-squared in the models. Interactions between obesity and major depression x gender and obesity and major depression x time were checked by entering the centered interaction terms in the gender or time-adjusted models for the outcome variable.
Third, we examined whether the joint effect of obesity and major depression on high WPI is larger than the sum of separate effects of obesity and major depression on high WPI. We created a 4-category variable, non-obese and non-depressed, obese, depressed, and both obese and depressed. If obesity is present, then \(i=1\) otherwise \(i=0\). If major depression is present, then \(j=1\) otherwise \(j=0\). Then, \(OR_{ij}\) represented the OR in both obese and depressed category \(i, j\). The three OR estimates [(i.e.\(OR_{11}\), \(OR_{10}\), \(OR_{01}\), and \(OR_{00}\) (reference category))] were computed from the GEE analyses. We assumed that obesity and major depression modify each other regarding the risk of high WPI, and that neither of them fully precedes the other. We also assumed that the effects of both exposures on high WPI were unconfounded. The presence of interactions on the additive scale was assessed by using the RERI and the AP. RERI was defined as: \(RERI=OR_{11}-OR_{10}-OR_{01}+1\), and \(AP=RERI/\ OR_{11}\). CIs for the RERI and AP were calculated using Andersson et al.’s algorithm with covariances of parameter estimates from GEE models \((18,19)\). A positive interaction of obesity and major depression with high WPI is reflected by a RERI or AP >0, while a RERI or AP < 0, represents a negative interaction of obesity and major depression; RERI or AP=0 indicates that there is no interaction (additivity) in the association of obesity and major depression with WPI. The presence of interaction on the multiplicative scale was assessed by including the product term (obesity x major depression) in the obesity and major depression adjusted model, and defined as \(OR_{11}/\ OR_{10}\times OR_{01}\), which reflects whether the joint effect of obesity and major depression was larger than the product of the separate effects of obesity and major depression on high WPI.

All statistical analyses were performed using SPSS version 20.0. Effects were considered significant when 95%-CI of OR and RERI did not contain one and zero, respectively.
RESULTS

Characteristics of the sample

Table 1 shows the baseline characteristics of the 1,726 respondents by obesity and major depression status. At baseline, the prevalences of general obesity and abdominal obesity were 14% and 32%, respectively. A total of 555 employees (32%) was diagnosed with major depression in the past six months. The prevalences of general and abdominal obesity in participants with major depression were 18% and 34%, respectively. Out of those participants diagnosed with major depression, 72% were diagnosed with anxiety disorder at least once during their lifetime. Most workers (80%) were white collar (non-manual) workers. High WPI at baseline was significantly correlated with WPI at 2-year (kappa, \( k = 0.20 \)), 4-year (\( k = 0.18 \)) and at 6-year (\( k = 0.13 \)) follow-up (\( p < 0.001 \)), indicating stability of WPI over time.

Table 1: Baseline characteristics of sample by obesity and major depression status:
Netherlands study of depression and anxiety, 2004-2007

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total population (N=1726)</th>
<th>Non-obese and no MD (n=1024)</th>
<th>Obese without MD (n=147)</th>
<th>MD without obesity (n=457)</th>
<th>Both obesity and MD (n=98)</th>
<th>ANOVA/ ( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>41.0 (11.7)</td>
<td>40.7 (11.9)</td>
<td>46.5 (11.0)</td>
<td>39.4 (11.3)</td>
<td>43.3 (10.0)</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Females, (%)</td>
<td>64.6</td>
<td>64.6</td>
<td>59.2</td>
<td>68.1</td>
<td>57.1</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Educational status, (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4.2</td>
<td>2.6</td>
<td>7.5</td>
<td>5.5</td>
<td>10.2</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Middle</td>
<td>53.1</td>
<td>47.8</td>
<td>62.6</td>
<td>57.8</td>
<td>73.5</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>42.7</td>
<td>49.6</td>
<td>29.9</td>
<td>36.8</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>Working hours, mean (SD)</td>
<td>31.1 (10.7)</td>
<td>30.8 (10.1)</td>
<td>33.1 (13.5)</td>
<td>30.8 (10.5)</td>
<td>32.5 (12.9)</td>
<td>( p &lt; 0.05 )</td>
</tr>
<tr>
<td>Abdominal obesity(^a), (%)</td>
<td>31.7</td>
<td>21.7</td>
<td>95.2</td>
<td>20.1</td>
<td>95.9</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>Anxiety disorder, (%)</td>
<td>55.8</td>
<td>47.9</td>
<td>49.0</td>
<td>71.6</td>
<td>75.5</td>
<td>( p &lt; 0.001 )</td>
</tr>
<tr>
<td>High WPI, (%)</td>
<td>24.7</td>
<td>14.9</td>
<td>24.5</td>
<td>42.2</td>
<td>44.9</td>
<td>( p &lt; 0.001 )</td>
</tr>
</tbody>
</table>

\(^a\): Waist circumference (WC) \( \geq 102 \text{ cm for male and 88 cm for female} \); MD: major depression; Obesity (BMI \( \geq 30 \text{kg/m}^2 \)); WPI: work performance impairment
Longitudinal relationship between obesity and WPI

We found longitudinal associations between general and abdominal obesity at tᵩ and high WPI at tᵩ₊₁ (OR (95%-confidence interval, CI)): = 1.45 (1.16; 1.80) and 1.34 (1.12; 1.59), respectively. Adjustment for age, gender and educational status slightly attenuated the estimates for the longitudinal association between general and abdominal obesity and high WPI (Table 2). No significant interactions between gender x obesity and time x obesity on high WPI were found.

Table 2: The longitudinal relation between obesity at tᵩ and major depression at tᵩ with high WPI at tᵩ₊₁: Netherlands study of depression and anxiety, 2004-2013

<table>
<thead>
<tr>
<th>Predictors</th>
<th>'High work performance impairment (WPI)</th>
<th>OR (95%-CI)</th>
<th>aORᵇ (95%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-obese</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Obesity (BMI≥30kg/m²)</td>
<td>1.45 (1.16; 1.80)</td>
<td>1.35 (1.08; 1.69)</td>
<td></td>
</tr>
<tr>
<td>No abdominal obesity</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Abdominal obesityᵃ</td>
<td>1.34 (1.12; 1.59)</td>
<td>1.23 (1.03; 1.48)</td>
<td></td>
</tr>
<tr>
<td>No major depression</td>
<td>Reference</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Major depression</td>
<td>1.66 (1.38; 2.00)</td>
<td>1.63 (1.35; 1.96)</td>
<td></td>
</tr>
</tbody>
</table>

OR: Odds ratio; 95%-CI: 95%-confidence interval;ᵇ Adjusted for age, gender and educational status.ᵃ Waist circumference (WC) ≥ 102 cm for male and 88cm for female;ᵇ reference: low WPI. **Bold figures** reflect statistically significant estimates (p<0.05)

Longitudinal relationship between major depression and WPI

We found a longitudinal association between major depression at tᵩ and high WPI at tᵩ₊₁ OR = 1.66 (1.38; 2.00). After adjustment for age, gender and educational status, the association attenuated but remained statistically significant (Table 2). No significant interactions between gender x major depression, and time x major depression on high WPI were found.

Longitudinal joint effect of obesity and major depression on WPI

We found a longitudinal joint association of general obesity and major depression at tᵩ and high WPI at tᵩ₊₁ was found as compared to non-obese and non-depressed counterparts OR = 2.57 (1.77; 3.74) (Table 3). After adjustment for age, gender and
educational status, the association attenuated but remained statistically significant OR=2.36 (1.61; 3.44). The joint association of general obesity and major depression on high WPI was additive RERI= 0.57 (-0.46; 1.60) and AP= 0.22 (-0.11; 0.55). The interaction on the multiplicative scale was OR=1.15 (0.71; 1.85) (Table 3 and Figure 1). Similarly, the joint association of abdominal obesity and major depression on high WPI was additive RERI= -0.09 (-0.46; 0.61) and AP= -0.04 (-0.39; 0.30). The interaction on the multiplicative scale was OR=0.84 (0.57; 1.24).

Table 3: The longitudinal separate and joint associations of obesity tₓ and major depression tₓ with high WPI tₓ+1: Netherlands study of depression and anxiety, 2004-2013

| Predictors                          | High work performance impairment (WPI) |  |  |  |
|-------------------------------------|----------------------------------------|------------------|----------|------------------|----------|
|                                     |                                        | OR (95%-CI)      | aOR (95%-CI) | RERI (95%-CI)⁵  | OR (95%-CI)⁶  |
| General obesity and major depression|                                        |                  |            |                  |          |
| Non-obese and non-depressed         | Reference                              | Reference        | Reference  | Reference        | Reference  |
| Obesity (BMI≥30kg/m²)               | 1.39 (1.07; 1.80)                      | 1.31 (1.01; 1.70) |  |                  |          |
| Major depression                    | 1.62 (1.31; 1.99)                      | 1.59 (1.29; 1.96) |  |                  |          |
| Both obese and depressed            | 2.57 (1.77; 3.74)                      | 2.36 (1.61; 3.44) | 0.57 (-0.46; 1.60) | 1.15 (0.71; 1.85) |          |
| Abdominal obesity and major depression|                                      |                  |            |                  |          |
| Non-obese and non-depressed         | Reference                              | Reference        | Reference  | Reference        | Reference  |
| Abdominal obesity                   | 1.39 (1.14; 1.70)                      | 1.29 (1.05; 1.58) |  |                  |          |
| Major depression                    | 1.77 (1.40; 2.24)                      | 1.74 (1.37; 2.20) |  |                  |          |
| Both obese and depressed            | 2.07 (1.55; 2.78)                      | 1.88 (1.40; 2.53) | -0.09 (-0.79; 0.61) | 0.84 (0.57; 1.24) |          |

OR: Odds ratio; 95%-CI: 95%-confidence interval; RERI: Relative excess risk due to interaction; ⁵ adjusted for age, gender and educational status at baseline. ⁶ Waist circumference (WC) ≥ 102 cm for male and 88cm for female; ⁷ reference: low WPI. ⁸ departure from additivity; RERI=OR₁₁−OR₀₀−OR₀₁+1= 2.57-1.62-1.39=0.57. ⁹ Departure from multiplicativity; OR₁₁/ OR₀₀ OR₀₁=2.57/1.62*1.39=1.15. Bold figures reflect statistically significant estimates (p<0.05)
Figure 1: Cumulative risk of high work performance impairment associated with the separate and joint exposures to obesity and major depression: Netherlands study of depression and anxiety, 2004-2013
DISCUSSION
To our best knowledge, this is the first study examining the longitudinal effects of general and abdominal obesity, major depression and their combination on high WPI over 6-year follow-up. Obesity and major depression were independently associated with an increased risk of high WPI. Moreover, the combination of obesity and major depression was also associated with an increased risk of high WPI. The interactions between obesity and major depression on high WPI on the additive and the multiplicative scale were in the expected direction (i.e. positive interaction), but not statistically significant. This refutes the hypothesis that the joint effect of obesity and major depression on high WPI is larger than the sum of the separate effects of obesity and major depression on high WPI.

Our finding that obesity was longitudinally associated with an increased risk of high WPI is consistent with a nationwide prospective cohort study in the US (29). That study found that obesity among employed women was associated with more self-reported work limitations when compared with normal-weight employed women (29). Dutch and Swedish studies also found associations of obesity with high productivity loss at work and work impairment (30-32). These findings across countries suggest that obesity is a global public and occupational health problem with a strong relationship with WPI.

The finding that major depression was longitudinally associated with an increased risk of high WPI confirms conclusions of a systematic review (33) that showed a robust relationship between depressive disorders and work limitations. Several other studies have also reported consistent findings regarding the association of major depression and productivity loss at work (12,34-37). However, another Dutch study, the Netherlands Mental Health Survey and Incidence Study (NEMESIS), found no association between major depression/anxiety and impaired work performance (34). Possible explanations for this discrepancy are the differences in sampling and in assessment of major depression between the NEMESIS and NESDA cohort studies. NEMESIS comprised a representative sample of the general population, while NESDA included individuals with anxiety and depressive disorders from the community, primary and secondary healthcare (20). The prevalence of depression in the NEMESIS study was lower (5.2%) and concerned at average milder cases compared to NESDA (34). This might also be due to the different DSM versions that were used to assess major depression. The NEMESIS study used DSM-
Ill, while NESDA used the updated version, DSM-IV. In the DSM-IV, a clinical significance criterion for depression has been included that requires the depressive symptoms to cause clinically significant impairment in social activities, or occupational or other functioning (23).

We found that the observed joint effect of obesity and major depression on high WPI was slightly larger than would have been expected on the additive scale. For the joint exposures obesity and major depression, the additional risk of high WPI was 157%, while the risk attributable to obesity and major depression was 101% (39% to obesity and 62% to major depression), leading to a RERI=0.57. However, the RERI was not statistically significant. A possible explanation for the non-significant interaction between obesity and major depression on high WPI is that there is a tendency that patients with major depression or anxiety show clinical recovery over time even though residual symptoms of depression or anxiety often persist (38,39). This characteristic of major depression might influence the interaction effect on high WPI. It has also been shown that obesity is more strongly associated with more severe and chronic forms of major depression as opposed to a current and a broader diagnosis of major depression (25,40). Moreover, the interplay between obesity and major depression may need more time to lead to an actual interaction effect beyond additive effects. 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 WPI.

It is possible that major depression shares genetic and complex biologic etiologic substrates with obesity (13, 41, 42), which could explain the observed joint effect of obesity and major depression on high WPI (i.e. positive direction on the additive and multiplicative scale). For instance, gene-environment interactions may have activated the hypothalamic-pituitary-adrenal axis, which subsequently has led to depression and aggravation of obesity. Moreover, the alteration of neurotransmitters’ function and hormonal disturbances play an important role in the development and maintenance of both obesity and depressive disorders (41,42). Obesity and major depression are also independent risk factors for chronic conditions such as cardiovascular diseases, diabetes, and musculoskeletal disorders (1,2). These mechanisms and comorbidities could explain the observed joint effect of obesity and major depression on high WPI in our study population.
Strengths and limitations

The major strength of our study is its prospective design. We were able to examine longitudinal associations of obesity and major depression at one point in time with high WPI two years later over a 6-year follow-up period 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 major depression 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 estimated interactions on additive and multiplicative scales.

We should also 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). Due to this, a rather large proportion of the participants had prevalent depressive or anxiety disorders, implying that non-depressed obese employees 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 (14%) is comparable with that in the Dutch population (12%) (44), and within the range of the WHO European region prevalence (10-30%) (1). Furthermore, large-scale epidemiological studies have shown that the prevalence of both depression and anxiety disorders in the Netherlands is in the range of other high income countries such as the US, Germany or Canada (45). The structure of the Dutch Health Care System is also comparable to that of several other European countries (e.g. UK, Germany) in which the general practitioner serves as the gatekeeper. In NESDA, 50% of the participants were recruited via general practices.

Another limitation with respect to the outcome might be that the WPI measure which was based upon self-report and not on employer-reported data may have been biased by depressive or anxiety symptoms. However, it has been shown that self-reported decreased work performance is highly correlated with employer payroll records (43). Finally, we used the number of days the respondent worked while hindered by health problems to compute WPI. It is not known explicitly whether the impairment was caused by depressive or anxiety disorders or by any other specific disease.
**Implications of the study**

The findings demonstrate that obesity and major depression are important public and occupational health problems. Both obesity and major depression are separately and jointly associated with an increased risk of high WPI. Probably, more severe and/or recurrent forms of major depression might further increase the risk of high WPI in obese employees, as obesity is more strongly associated with recurrent or chronic depression than single or short episodes of major depression (40). If the RERI is confirmed in further studies, the joint effect of obesity and major depression on high WPI could have public and occupational health implications. Intervening on obesity may be more beneficial for individuals with major depression compared to those without major depression regarding the risk of high WPI. Hence, further research is needed to reexamine the joint effect of obesity and major depression in relation to high WPI in larger sample sizes and in the general population.

**Conclusions**

In conclusion, our study suggests that there is a longitudinal relationship of obesity, abdominal obesity and major depression with an increased risk of high WPI. The longitudinal joint effect of obesity and major depression on high WPI implies that intervening on obesity may be more beneficial for individuals with major depression compared with those without major depression regarding the risk of high WPI, if confirmed in a large representative sample.
REFERENCES


