Cumulative Effect of Depressed Mood and Obesity on Type II Diabetes Incidence: Findings from the MONICA/KORA Cohort Study

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Abstract

Background

Obesity and depression both individually contribute to the risk of Type II Diabetes (T2DM). The extent to which obesity can be set-off by depression is unknown.

Methods

In a sample of 9,340 participants followed for 15.4 years (79,372 person-years) from the prospective MONICA/KORA population-based cohort conducted in Southern Germany, we investigated the impact of obesity, defined as Body Mass Index (BMI) > 30, and depression on the incidence of T2DM using Cox Proportional Hazards Regression.

Results

The relative risk of T2DM was over 6 fold higher among obese participants in comparison to normal weight participants (HR, 6.05; 95% CI 4.82 to 7.59; p < .0001). Nonetheless, among participants with obesity, comorbidity of depression was associated with an additional 2 fold risk T2DM (HR 8.05, 95% CI 5.90-10.98; p<.0001). This finding corresponded to an increase in the 15.4-year absolute risk of T2DM from 15.9 cases per 1000 person-years (py) in participants with obesity but not depression, to 21.4 cases per 1,000 py for participants with obesity and depression. Further analysis of joint effects and Relative Excess Risk due to Interaction disclosed that depressed mood is associated with significantly higher risk of T2DM in participants with obesity, and to a lesser extent in overweight participants, however an association was not found in normal weight participants.

Conclusions

The present investigation discloses that despite the overreaching importance of obesity as a risk factor for T2DM, there is room for depressed mood to add measurable risk prediction.

Introduction

Even though obesity is established as the leading risk factor for the incidence of type II diabetes mellitus (T2DM), inter-individual differences remain unclear (1-3). Many observers may assume the existence of a ceiling effect between obesity and subsequent T2DM, however, obesity can be attenuated by psychosocial factors in a real-world setting. Among the current psychosocial etiologies of T2DM, depression as a risk factor has gained uttermost attention. Meta-analytic evidence has confirmed that depression is associated with a 37-60% increase in the incidence of T2DM, despite concurrent lifestyle and metabolic risk factors (2, 3).

Surprisingly, there is less research on the involvement of depression in the risk of T2DM among obese people, although epidemiological studies have shown that obesity is also a risk factor for depression (4). Hence, a higher prevalence of depression among people with obesity may contribute inconsistently to their subsequent T2DM risk (5, 6). Nevertheless, if a cumulative effect between obesity and depression on the onset of T2DM exists, this effect must also remain robust following adjustment for metabolic risk factors to rule out a healthy obesity paradigm (7).

In the current investigation, we aimed to determine the extent to which depression a contributes to an additionally measureable risk of T2DM among participants with obesity using data from a prospective population-based cohort. We anticipate that improved understanding of psychosocial factors among people with obesity, particularly depression, will help advance identification of patients at risk and development of effective treatment options for T2DM.

Participants and Methods

Data were obtained from 13,426 subjects (30 to 75 years-old) who took part in one of three cross-sectional surveys as part of the Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg (MONICA) project (8). Baseline information was collected in 1984/85, 1989/90, and 1994/95 through standardized interviews conducted by trained medical staff, a self-administered questionnaire, and medical examination. Participants with prevalent diabetes at baseline (n = 573), without information on diabetes status at follow-up (n = 710) or with incomplete data on all co-variables required for the main analyses (n=2,803) were excluded from the study leading to a final study sample of 9,340 participants. A drop-out analysis of excluded participants did not reveal significant age and sex differences in comparison to participants who were included in the study.

Written informed consent was obtained from each study participant and the study was approved by the local ethics committee.

T2DM

T2DM incidence was assessed using GEFU 2008/2009 (General Morbidity Follow-up) within the framework of the Cooperative Health Research in the Region of Augsburg (KORA) (8). Self-reported cases and the date of diagnosis were validated through hospital records or by contact with physicians.

Obesity

Obesity was determined using Body Mass Index (BMI), defined as a person's weight in kilograms divided by the square of her or his height in meters (kg/m^2). Subjects with BMI < 25 were considered to have normal weight, BMI ≥ 25 and < 30 were classified as overweight and BMI ≥ 30 were classified as obese.

Depressed Mood

Depressed mood was categorized dichotomously into categories of "non-depressed mood" (0-10 for men, 0-12 for women) and "depressed mood" (≥10 for men, ≥12 for women)

based on the depression and exhaustion subscale (DEEX) that lead to a scoring range of 0–24 (9). Clinically, the DEEX scale identified symptoms of reduced vitality, weakness and 'vital exhaustion' but without a negative self-concept and feelings of guilt feelings and hence is used as proxy for measuring depression in a large population-based epidemiological study, however is not limited to major depressive disorder.

Metabolic Factors

Metabolic factors consisted of hypertension (systolic/diastolic blood pressure ≥ 140/90 mmHg and/or use of antihypertensive medication), and dyslipidemia (total cholesterol to high-density lipoprotein cholesterol ratio ≥ 5.0).

Lifestyle factors

Lifestyle factors consisted of smoking status (regular or non-smoker), alcohol intake (weekday and weekend consumption of beer, wine and spirits) and physical activity (physically active if person regularly participated in sports in summer and winter and was active for at least 1 hr/week in at least one season (10).

Statistical analyses

Means and proportions of baseline data were computed for participants with depressed mood and non-depressed mood. Baseline differences between categorical variables were tested using the chi-square test and mean differences were assessed using the t-test.

To assess the absolute risk of T2DM, incidence rates of the BMI categories stratified by depressed mood were calculated, and their significance was obtained using Cochran-Armitage Test for trend. The causal interaction of differences between the various absolute risks across the BMI categories and depressed mood as departure from additivity were investigated by testing the incidence rates on the additive scale (11).

The relative risks of T2DM were assessed for each stratum of BMI category and depressed mood with a single reference category (normal weight and without depressed mood) using three subsequent Cox proportional hazards models. Model 1 was adjusted for

age, sex, and survey. Model 2 also included lifestyle factors (smoking, physical inactivity, alcohol consumption). Model 3, considered as the primary model, additionally included metabolic risk factors (hypertension, dyslipidemia). The interaction of the relative risks as an amount of departure from additivity was calculated using the Relative Excess Risk due to Interaction (RERI) (12, 13).

The assumption of proportional hazards was assessed graphically by checking the log (–log (survival)) curves for parallelism. No severe deviations from parallelism were evident. Two-tailed P-values < 0.05 were considered to be statistically significant. All statistical analyses were performed using SAS (v. 9.3, SAS Institute Inc., Cary, NC, USA). The analyses and description in this article followed the STROBE guidelines for observational cohort studies (14).

Results

The present investigation includes 9,340 participants (51.6% men, 48.4% women), among whom 1,732 (18.5%) were obese, 3,816 (37.6%) participants had depressed mood. Additionally, 602 (6.4%) participants suffered from both obesity and depressed mood. After a mean follow up period of 15.4 years (SD ±6.2, 79,372 person years), there were 968 (10.4%) cases of incident T2DM.

The baseline characteristics, displayed in Table 1, showed that participants with depressed mood were more likely to be older, less educated, and less physically active in comparison to participants without depressed mood. However, clear associations between the BMI categories and depressed mood were not found.

Incidence and relative risk of T2DM by depressed mood

The T2DM incidence rate per 1000 person-years (py) was 7.6 cases for participants with depressed mood and 6.0 cases for participants without depressed mood. The relative risk

analysis showed that in Model 1, depressed mood at baseline was associated with a 17% increased incidence of T2DM (HR 1.17; 95% CI 1.03 to 1.33; p =.01) in comparison to participants without depressed mood. Controlling for lifestyle and metabolic factors did not influence this association (model 2: 1.15, 95% CI 1.01-1.30; p=.04, model 3: HR 1.16; 95% CI 1.06 to 1.02; p =.02).

Incidence and relative risk of T2DM by BMI status

The T2DM incidence per 1000 py was 18.0 cases in obese participants, 6.8 cases in overweight participants and 1.8 cases in normal weight participants. The relative risk analysis showed that in Model 1, obese and overweight BMI categories were associated with 7.8 fold increased risk (HR 7.80, 95% CI 6.26-9.73, p<0001) and 2.9 fold increased risk of T2DM (HR 2.92; 95% CI 2.34-3.63, p<0001), respectively. In the additional models, the risk of T2DM in obese participants was attenuated due to adjustment for metabolic risk factors (model 2: HR 7.85; 95% CI 6.30-9.80, p<0001, model 3: HR 6.0; 95% CI 4.80-7.50, p<0001). On the other hand, the risk of T2DM in overweight participants was not largely effected by further adjustments (model 2: HR 2.94; 95% CI 2.36-3.70, p<0001, model 3: HR 2.50; 95% CI 2.00-3.11, p<0001).

Incidence and relative risk of T2DM by BMI status and depressed mood

As shown in Figure 1, the incidence of T2DM according to the BMI categories and depressed mood revealed a substantially increasing trend. In the total population, obese participants with depressed mood had the highest absolute risk of T2DM, followed by obese participants without depressed mood (21.4 vs. 15.9 cases per 1000 py; Cochran-Armitage test: p=.01). On the other hand, overweight participants with depressed mood had slightly higher absolute risk of T2DM than without depressed mood (7.73 vs. 6.28 cases per 1000 py; Cochran-Armitage test: p=.05). Lastly, normal weight participants did not present significant

differences of absolute T2DM risk with or without depressed mood (2.25 vs 1.59; Cochran-Armitage test: p=.11). Additionally, the absolute risk of T2DM for participants obesity and depressed mood indicated an interaction on the additive scale, as their combined effect was larger than the sum of their effects (21.4 vs 17.15).

The relative risks of incident T2DM associated with the joint effect of BMI categories and depressed mood is presented in Table 2. As shown, participants with either obese or overweight BMIs presented a significantly higher risk of developing T2DM irrespective of depressed mood, whereas normal weight participants did not. However, obese and overweight participants presented an even higher risk of T2DM when they also had depressed-mood. This cumulative effect on the risk of T2DM was substantially more pronounced in obese participants; a finding in line with the RERI of 1.68 (95% CI: 0.16-3.30) in obese subjects with depressed mood, in contrast to the RERI of 0.14 (95% CI: -0.50-3.20) in overwight participants with depressed mood. On the other hand, there was no evidence of a significant interaction on the multiplicative scale between obesity and depressed mood (p=0.44). Furthermore, an in-depth analysis focussing on participants with obesity showed that depressed mood is a significant predictor of their T2DM risk; having depressed mood was associated with a 32% higher risk of T2DM among obese participants than not having depressed mood (HR: 1.32, 95% CI 1.08-1.61, p=0.007).

Discussion

In this study, we investigated the impact of obesity and depression on the risk of T2DM, with a focus on the cumulative effect between these two risk factors. Based on our results, three conclusions are supported.

First, there was a significant risk gradient between a higher BMI and incidence of T2DM that was demonstrated in both the absolute and relative risk models; indeed, obesity

increased the relative risk of T2DM by a HR of 6, confirming prior findings (15). Second, the presence of depressed mood was associated with an increased relative risk of T2DM by a HR of 1.16, a finding that also confirms and extends prior studies that demonstrate a link between depression and onset T2DM (2, 3). The most important finding, however, was that despite the relatively lower risk of depression in the total sample in comparison to obesity, there was a significant cumulative effect between these two risk factors. Specifically, the incidence of T2DM in participants with obesity and depressed mood was increased by a HR of 8.05 in comparison to the HR of 6.12 in obese participants without depressed mood.

This cumulative effect between obesity and depression may reflect shared or additive biological pathways that, when combined, lead to detrimental effects. For instance, in a recent review by Milaneschi et al., it is thought that obesity causes inflammation related alterations in the insulin pathway that lead to T2DM (5). This insulin dysregulation also could play a role in the development of depression (16, 17). Our data supports this theory because the effect of depression is most predictive of T2DM in participants within the obese BMI category. On the other hand, normal and overweight participants presumably have lower levels of inflammation, which does not play an additive role in the development of depression. Likewise, the RERI suggested that the joint effect estimated between obesity and depressed mood is greater than the sum of the estimated effects of obesity or depressed mood alone.

The results presented herein confirm a recent study with 919 participants showing a significant interaction between depression, continuous waist-to-hip ratio (WHR) in the risk of diabetes (6). However, this study had several shortcomings as WHR was self-reported, measure of diabetes was not limited to type 2, and confounding metabolic risk factors beyond WHR were not considered. The current study attains to overcome these limitations and additionally extends the findings to the effect of obesity defined by BMI. Thus, we show that body fat percentage as measured by BMI promotes the increased risk of T2DM in depressed

participants independently of fat distribution. This finding is in paralel to purely the intra-abdominal fat stores, which have already been linked to endocrine abnormalities(18). In summary, this finding suggests that the additional effect of depression remains robust in participants with obesity, and is independent of metabolic risk factors.

The present study has limitations that need to be addressed. Patients who might have prediabetes were not removed at baseline, although it has been shown that undiagnosed prediabetes is not significant associated with depression (19). Furthermore, depressed mood was assessed by the DEEX scale, which is among the less rigorous options to assess depressive mood although a recent re-examination of its validity and reliability is promising (9).

Additionally, depressed mood was measured at one time point, however, recurrence rates of depression are thought to be over 85% within a decade of an episode (20). Despite the limitations, depression as a risk factor for T2DM was much more conservative in our study in comparison to similar studies; hence the effects mentioned herein are thought to be robust. Lastly, we have not included possible associations between antidepressants use and obesity because the population using antidepressants was very low; for example, in a follow-up study of 3,184 participants who participated in the S3 survey, only 4% used antidepressant medication (21).

In conclusion, an increase in the level of depressed mood was associated with an escalated risk of T2DM within obese participants in the KORA/MONICA prospective cohort. Hence, the present investigation discloses that despite the overreaching importance of obesity as a risk factor for T2DM, there is still room for depressed mood to add measurable risk

prediction. The departure from risk additivity that was observed in this study implies that among people with obesity, depressed participants would benefit from a greater risk reduction from an intervention (22) .In this way, depression should be included in part of the risk assessment and treatment of obese individuals in clinical settings, particularly by keeping in mind the magnitude of the layered stigma of having both conditions (23).

Declarations of interest: None

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Table 1. Prevalence of baseline characteristics, according to depressed mood, in the MONICA/KORA Cohort (N=9,340).

Baseline Characteristics		Total, N (%)	Non-Depressed Mood (n=5824)	Depressed Mood (n=3516)	*p*
Age (yr.) (SD)		49.13 (11.76)	48.3 (11.8)	50.5 (11.6)	<.0001
Men		4816 (51.6)	3002 (51.56)	1814 (51.6)	.96
Women		4524 (48.4)	2822 (48.5)	1702 (48.4)	
Education (>12 yrs.)		2603 (27.9)	1687 (29.0)	916 (26.1)	.002
BMI	Normal	3360 (36.0)	2117 (36.4)	1243 (35.4)	.003
	Overweight	4248 (45.5)	2577 (44.3)	1671 (47.5)	
	Obese	1732 (18.5)	1130 (19.4)	602 (17.1)	
Hypertension		3642 (39.0)	2225 (38.2)	1417 (40.3)	.04
[3]Dyslipidemia		3001 (32.1)	1828 (31.4)	1173(33.4)	.04
Regular smoking		2424 (26.0)	1502 (25.8)	922 (26.2)	.64
Alcohol intake	None	2466 (28.3)	1619 (27.8)	1025 (29.2)	.34
	[1]Moderate	4134 (44.3)	2588 (44.4)	1546 (44.0)	
	[2]High	2562 (27.4)	1617 (27.8)	945 (26.8)	
Physically active		3911 (41.9)	2613 (44.9)	1298 (36.9)	<.0001

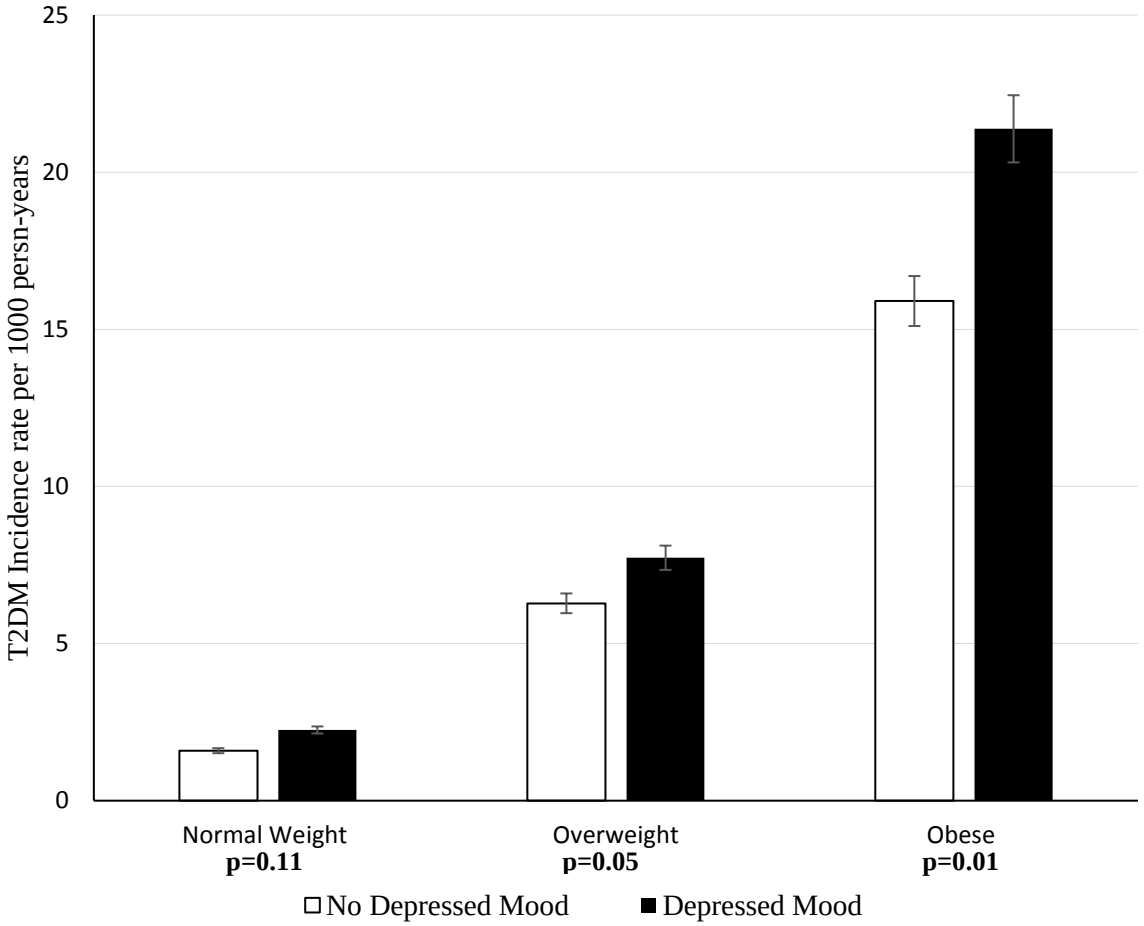
*data represent (N, %) except for age (mean [SD])
[1]Moderate alcohol consumption: 0.1-39.9g/day for men and 0.1-19.9g/day for women, [2]Heavy alcohol consumption: ≥ 40 g/day for men and ≥ 20 g/day for women), [3]Dyslipidemia: ratio of total cholesterol to high-density lipoprotein cholesterol ≥ 5.0

Table 2. Adjusted hazard ratios for T2DM, according to BMI and depressed mood in the MONICA/KORA Cohort (N=9,340).

BMI Groups		Non-Depressed mood (n=5,824) (HR, 95% CI)	Depressed mood (n=3,516) (HR, 95% CI)
Normal Weight (n=3,360)	Model 1	1.00	1.31 (0.90-1.91)
	Model 2	1.00	1.29 (0.90-1.91)
	Model 3	1.00	1.30 (0.90-1.91)
Overweight (n=4,248)	Model 1	3.04 (2.27-4.07)	3.61 (2.68-4.88)
	Model 2	3.07 (2.29-4.11)	3.61 (2.67-4.88)
	Model 3	2.67 (2.00-3.58)	3.11 (2.30-4.21)
Obese (n=1,732)	Model 1	7.89 (5.89-10.57)	10.50 (7.72-14.26)
	Model 2	7.99 (5.96-10.71)	10.35 (7.61-14.10)
	Model 3	6.12 (4.55-8.23)	8.05 (5.90-10.98)

* *P* values <.0001 for overweight and obese BMI groups
ǂParticipants with a normal BMI and no depressed mood serve as the reference group.
Model 1: adjusted for age, sex and survey
Model 2: additionally adjusted for lifestyle risk factors (smoking, alcohol consumption, physical inactivity)
Model 3: additionally adjusted for metabolic risk factors (hypertension, dyslipidemia)

Figure 1. Incidence rates of T2DM, according to categories of BMI and depressed mood (N=9,340).



*The I bars represent 95% CI.
p values show the association of trend between specific BMI category and depressed mood for the incidence of T2DM.
Shown are the unadjusted incidence rates reported per 1000 person-years.