Short-term and long-term effects of major depressive disorder subtypes on obesity markers and impact of sex on these associations

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Abstract

Background – Only a few studies with conflicting results have examined the effects of sex on the prospective association between depression and subsequent obesity.

Objective – 1) To simultaneously assess the associations of the subtypes (atypical, melancholic, unspecified) of major depressive disorder (MDD) measured at baseline and subtypes of major depressive episodes (MDE) that emerged during a 5.5-year follow-up with changes in obesity markers (body mass index, waist circumference, fat mass) during this follow-up, and 2) to test the effect of sex on these associations.

Methods – Data from CoLaus|PsyCoLaus, a population-based cohort study including 2702 participants (50.1% women, mean age 49.6 years). Criteria for mental disorders were elicited using semi-structured interviews.

Results – Atypical MDD at baseline and during follow-up were associated with a steeper increase in the three studied obesity markers. Melancholic MDD at baseline was associated with a steeper increase in BMI. Several significant interactions with sex were found indicating higher increase in fat mass in men than in women following melancholic MDD reported at baseline, higher decrease in BMI and fat mass in women than in men related to melancholic MDE emerging during follow-up and higher increase in waist circumference in men than in women following unspecified MDD reported at baseline.

Limitations – Urban sample which may not be representative for the whole population.

Conclusions – Our results further advocate for the specific need of a thorough monitoring of obesity markers in patients with atypical MDD and suggest less favorable obesity marker changes mainly related to melancholic MDE in men.

Keywords – major depressive disorder; subtypes; obesity; metabolic factors; sex differences; longitudinal study

Introduction

Obesity rates are increasing globally (Ng et al., 2014) and major depressive disorders were among the three leading causes of disability in 2017 (GBD 2017 Mortality Collaborators, 2018). These two major public health burdens are not only independently important, but they are also linked. Indeed, meta-analytical findings of prospective studies suggest a bi-directional association between depression, assessed as a whole, or depressive symptoms, and obesity (Luppino et al., 2010; Mannan et al., 2016a, 2016b). However, recent meta-analyses of cross-sectional and prospective data also suggest that not only obesity is associated with depression or depressive symptoms, but also underweight (Byrne et al., 2015; Jung et al., 2017). This potentially U-shaped association between Body Mass Index (BMI) and depression is likely to be attributable to heterogeneity within depression (Byrne et al., 2015). It has been postulated that two major subtypes of MDD are differentially associated with BMI, i.e. atypical depression with obesity and melancholic depression with underweight (Byrne et al., 2015; Milaneschi et al., 2019). Indeed, three cross-sectional studies in adults have provided support for associations between obesity markers and the atypical subtype (Cizza et al., 2012; Glaus et al., 2013; Lamers et al., 2013) or symptoms (Petri et al., 2017) of depression. In two of them (Glaus et al., 2013; Lamers et al., 2013), the atypical subtype fully accounted for the association between depression and obesity markers. Similarly, three cohort studies including ours have also supported a prospective association between the atypical depression subtype and obesity markers among patients (Lamers et al., 2016) and people recruited from the community (Hasler et al., 2004; Lasserre et al., 2014), although two of these studies also found a steeper increase in BMI in people with melancholic depression (Lamers et al., 2016; Lasserre et al., 2014). However, the analyses of these studies did not separately assess the long-term and short-term effects of MDD subtypes on the development of obesity markers, which may vary across subtypes and explain partially inconsistent findings across previous studies. Indeed, as data from the psychiatric follow-up were not yet available, Lasserre et al. 2014 could only adjust for the presence of depressive symptoms according to the CES-D scale for the week prior to the physical follow-up, but not for major depressive episodes (MDE) that had occurred earlier during the 5.5-year follow-up period. Hence, it is possible that the significant effects of atypical and melancholic episodes that occurred prior to baseline were mediated by new depressive episodes that occurred during the follow-up prior to the 1-week period preceding the physical follow-up exam. Given that increase in

appetite is a symptom of atypical depression, this type of episode is likely to predispose to weight gain during episodes. However, after the offset of episodes this temporary weight gain could be followed by weight loss, constantly elevated but stable weight or an ongoing increase in weight. Conversely, as decrease in appetite is a typical symptom of melancholic depression, this subtype is likely to predispose to weight loss during episodes, which could be followed by persistently low weight or regain of weight.

There is a considerable body of research on the potential effect of sex on the association between depression and obesity in adolescents and adults. Indeed, it is well know that sex is associated with both the prevalence of depression and obesity, with a predominance of women with major depressive disorders (MDD) (Hasin et al., 2005) and a predominance of men with obesity in most Western countries (Kanter and Caballero, 2012); e.g. in Switzerland, 51% of men versus 33% of women were obese or overweight in 2017 (OFSP, 2017). However, studies focusing on the effect of sex on the association between depression and obesity have provided inconsistent findings. Most cross-sectional research has supported a stronger association between depressive disorders and obesity in women as compared to men (Andreyeva et al., 2007; Carpenter et al., 2000; de Wit et al., 2010; Keddie, 2011; Pereira-Miranda et al., 2017). Moreover, several longitudinal studies as well as a meta-analysis based on prospective adolescent data have documented a stronger association in adolescent girls (Blaine, 2008; Mannan et al., 2016b). Likewise, two recent studies on adults have found depression to be a stronger predictor of obesity in women (Rajan and Menon, 2017; Vittengl, 2018). In contrast, two meta-analyses of adult data did not support an effect of sex on this association (Blaine, 2008; Luppino et al., 2010).

Given the lack of data on specific short and long-term effects of MDD subtypes on obesity markers as well as the absence of estimates on the sex-effects on these associations, the goals of the present paper were to: 1) simultaneously assess the associations of the subtypes (atypical, melancholic, unspecified) of MDD measured at baseline and subtypes of MDE that emerged during the 5.5-year follow-up with changes in obesity markers (body mass index, waist circumference and fat mass) during this follow-up period in the general population, and 2) test the effect of sex on these associations.

Methods

Sample and design

The present data stem from CoLaus|PsyCoLaus (Firmann et al., 2008; Preisig et al., 2009), a prospective cohort study designed to investigate the prevalence of cardiovascular risk factors and psychiatric disorders in the community and to determine their association (Firmann et al., 2008; Preisig et al., 2009). The cohort was randomly selected from the residents of the city of Lausanne (Switzerland) from 2003 to 2006 according to the civil register. A first follow-up evaluation took place between 2009 and 2013. Among the 5535, 35 to 66 year-old participants of the physical baseline exam, 67% (n=3719) also accepted the psychiatric evaluation (Figure 1). A total of 153 participants with a diagnosis of bipolar or schizoaffective disorder, schizophrenia or eating disorder at baseline were excluded from the present analyses given that these disorders are likely to be associated with metabolic changes. Six subjects with a missing MDD diagnosis at baseline were also excluded. Among the remaining 3560 subjects, 45 died during the follow-up (mean duration 5.5 years, s.d. 0.4 years) and 2702 accepted the physical and psychiatric follow-up evaluations (76.9% participation among survivors). Non-participants at follow-up were more likely than participants to be male (50.8% vs. 46.7%, chisq=4.4, p=0.036), to live alone (27.7% vs. 22.8%, chisq=8.7, p=0.003), to be less physically active (49.9% vs. 56.8%, chisq=12.6, p<0.001), and to be current smokers (32.2% vs. 27.0%, chisq=8.5, p=0.004).

Variables and measures

The physical measures were taken in identical ways at the baseline and follow-up visits. Participants had to fast for at least 8 hours and to have abstained from strenuous physical activity for 12 hours before the exam. Weight and height were measured in participants standing without shoes in light indoor clothes. Weight was measured in kilograms to the nearest 100g using a Seca® scale (Hamburg, Germany). Height was measured to the nearest 5mm using a Seca® gauge (Hamburg, Germany). Obesity was defined as a BMI $\geq$ 30 kg/m^2 according to the World Health Organization guidelines. Waist circumference was measured with a non-stretchable tape over the unclothed abdomen at the narrowest point between the lowest rib and the iliac crest. Two measures were made and the mean value (expressed in centimeters) was

used for analyses. Fat mass was assessed by bioimpedance (Jebb et al., 2007) using the Bodystat® 1500 analyzer (Isle of Man, UK).

In addition, information on socio-demographic characteristics, current medication and health-related behaviors including smoking, alcohol consumption and physical activity was collected through a standardized interview. Socio-economic status (SES) was assessed using the Hollingshead scale (Hollingshead, 1975). Alcohol consumption was defined as the number of drinks per week. Subjects were considered as physically active if they reported leisure time physical exercise activity for at least 20 minutes twice a week. Medication use was subdivided into antidepressant use and weight gain inducing drug use (list extracted from Micromedex ("Micromedex", n.d.) and the Swiss Compendium of Medications (*Compendium Suisse des Médicaments*®, 2010) at both baseline and follow-up assessments. Diagnostic information on mental disorders at baseline and follow-up was collected using the French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994), which revealed excellent inter-rater and fair to good test–retest reliability for mood and substance use (Berney et al., 2002; Preisig et al., 1999). The DIGS was completed with anxiety sections of the French version (Leboyer et al., 1991) of the Schedule for Affective Disorders and Schizophrenia—lifetime and anxiety disorder version (SADS-LA) (Endicott and Spitzer, 1978). Criteria for atypical features include mood reactivity and at least two of the following four symptoms: 1) increased appetite or significant weight gain, 2) hypersomnia, 3) leaden paralysis, and 4) interpersonal rejection sensitivity. In order to avoid potential redundancy with the obesity markers, we only applied the appetite part of the appetite/weight gain criterion. The melancholic features specifier requires either a loss of energy or a lack of mood reactivity and three out of the following five symptoms: 1) depression regularly worse in the morning, 2) early morning awakening, 3) psychomotor retardation or agitation, 4) decreased appetite (we did not consider weight loss as a criterion) and 5) excessive guilt. We could not take into account the criterion "distinct quality of depressed mood" because it was not assessed in the DIGS. MDD was subdivided according to the lifetime history of episodes with atypical or melancholic features into three subtypes (Lasserre et al., 2017): 1) MDD with atypical features only, 2) MDD with melancholic features only, 3) unspecified MDD with neither atypical nor melancholic features or with both atypical and melancholic

features. Participants were interviewed by master-level psychologists who were trained over a one- to two-month period. Each interview and diagnostic assignment was reviewed by an experienced senior psychologist.

The Institutional Ethics' Committee of the University of Lausanne approved the CoLaus|PsyCoLaus study. All participants signed a written informed consent after having received a detailed description of the goal and funding of the study.

Statistical analyses

Analyses were performed using SAS 9.4 for Windows. In order to first assess the effect of sex on the associations of subtypes of MDD at baseline and subtypes of MDE during follow-up with changes in the three measured obesity markers (BMI, waist circumference, body fat mass) during follow-up (difference in obesity marker levels between baseline and follow-up), we tested interactions between sex and subtypes of MDD at baseline and subtypes of MDE during follow-up. We applied robust rather than multiple regression models because the residuals of the dependent variables (obesity markers) were not normally distributed. The subtypes of MDD at baseline and subtypes of MDE during follow-up were simultaneously entered into all models. Participants with missing information on obesity markers at follow-up were excluded from the respective analyses (Figure 1). Models were adjusted for age, ethnicity, length of follow-up, baseline and follow-up factors [living alone, behavioral characteristics (physical activity, smoking status, alcohol intake), medication use (antidepressants and weight gain inducing drugs) and non-mood disorders (anxiety disorders, substance dependence)], MDD remission status at baseline (current vs. remitted), and the corresponding obesity marker at baseline. In case of significant sex by MDD or MDE subtype interactions, we applied separate models by sex for the respective obesity marker change. If there was no interaction, a final model without the interaction terms but with adjustment for sex as a main effect was applied. The models were used to explore the evolution of BMI, waist circumference and body fat mass, in relation to the depression subtypes prior to baseline or during follow-up.

Results

Table 1 presents the characteristics of participants by sex. Except for ethnicity, current smoking at baseline and follow-up, physical activity at follow-up and substance dependence during follow-up, women and men significantly differed on all variables. Women were approximately one year older than men, had a slightly shorter follow-up, were more likely to live alone at baseline and follow-up, were more often physically active at baseline and more frequently reported anxiety disorders, the use of antidepressants or weight gain inducing drugs at baseline and follow-up, a current MDE at baseline, a lifetime history of subtypes of MDD at baseline and the occurrence of subtypes of MDE during follow-up. In addition, women revealed higher body fat mass at baseline and follow-up. In contrast, men were more likely to have been former smokers, to report more substance dependence at baseline and consumption of higher number of alcoholic drinks per week at baseline and follow-up, and to have higher BMI and larger waist circumference at baseline and follow-up.

Table 2 depicts the results from robust regression models that tested interactions between sex and baseline as well as follow-up MDD status regarding change in obesity markers during follow-up in the overall sample. After adjustment for socio-demographic and behavioral characteristics, anxiety disorders and substance dependence, medication use, remission status of MDD at baseline and obesity markers at baseline, we found four significant interactions with sex: 1) regarding change in BMI for melancholic episodes during follow-up, 2) regarding change in waist circumference for a history of unspecified MDD at baseline, and regarding change in body fat mass for 3) melancholic MDD at baseline and for 4) melancholic episodes during follow-up. All four interactions indicated that men with depression had a larger increase or smaller decrease in the respective obesity marker during follow-up than women.

Table 3 provides the results of the robust regression models that assessed the prospective associations between baseline as well as follow-up MDD status and change in obesity markers during follow-up with adjustments for multiple potential confounders. Given significant interactions with sex for analyses regarding changes in all three obesity markers, results were provided for the overall sample (with estimates applying for depression variables that did not interact with sex) as well as separately for women and men (with estimates applying for depression variables that revealed a significant interaction with sex). With

respect to change in BMI there was only a significant interaction with melancholic episodes during follow-up but not with MDD status at baseline. The results of the model with BMI change as the dependent variable revealed that participants with a lifetime history of atypical or melancholic MDD at baseline had a steeper increase of BMI during follow-up than participants with no history of MDD at baseline, independently of the potential occurrence of depressive episodes during follow-up. In addition, independently of the MDD status at baseline, participants who exhibited MDE with atypical features during follow-up revealed a steeper BMI increase during the follow-up. In contrast, women who exhibited melancholic episodes during follow-up presented a smaller increase in BMI during follow-up than those with no depressive episodes during follow-up. Such a reduced increase in BMI during follow-up was not observed in men who exhibited melancholic episodes during follow-up. Within the entire cohort, sex was not associated with change in BMI.

Regarding waist circumference, although according to the previous interaction analysis, men with unspecified MDD at baseline had a significantly higher increase in this obesity marker than women with this MDD subtype at baseline, the sex-specific results showed that neither men nor women with unspecified MDD at baseline differed significantly in the change of this obesity marker from participants with no diagnosis of MDD. Given the absence of interactions with sex for atypical and melancholic MDD, the results for the whole cohort applied for these MDD subtypes with respect to waist circumference. Similarly to the results regarding BMI, both participants with a lifetime history of atypical MDD at baseline or the occurrence of depressive episodes with atypical features during follow-up also had a steeper increase in waist circumference during follow-up. Moreover, in the entire cohort waist circumference increased more in women than in men during follow-up.

Interaction analysis also supported a significant effect of sex on the associations of a lifetime history of melancholic MDD at baseline and the occurrence of this type of episode with increase in body fat mass. Sex-specific results showed that men with a lifetime history of melancholic MDD at baseline had a steeper increase in body fat mass than those without a history of MDD, whereas in women this was not the case. Conversely, only women but not men exhibiting this type of episode during follow-up revealed a significantly reduced increase in body fat mass as compared to those without a history of MDD. Given the absence of other interactions with sex, the results for the whole cohort applied otherwise. Again,

participants with atypical features during follow-up had a steeper increase in body fat mass during follow-up. Within the entire cohort, body fat mass increased more in women than in men during follow-up.

Discussion

The present study is the first to report independent prospective associations of subtypes of MDE occurring both before and during follow-up with changes in obesity markers as well as the role of sex in these associations. Moreover, in contrast to the large majority of previous studies that only assessed BMI, we also included waist circumference and body fat mass as adiposity measures given that recent data suggest that waist circumference is more strongly associated with the risk of cardiovascular diseases than BMI (van Dijk et al., 2012) and body fat percentage could be an independent risk factor for mortality (Bigaard et al., 2004). Our most salient findings were that: 1) atypical MDD both at baseline and during follow-up were independently associated with a steeper increase in obesity markers, and 2) interactions between sex and MDD subtypes regarding obesity marker changes mainly concerned melancholic episodes indicating less favorable changes in BMI and body fat mass during follow-up in men with this type of episodes as compared to women.

Hence, these findings confirm and extend those of previous studies. By assessing the occurrence of depression before and during the follow-up period, we could demonstrate two clearly distinct association patterns of atypical and melancholic MDD with obesity markers. Atypical MDD was not only associated with increase in obesity markers during periods with an occurrence of this type of episode, which is expected given that increase in appetite is an important symptom of this depression subtype, but atypical MDD was also independently associated with an obesity marker increase after the offset of episodes, suggesting a long-lasting metabolic dysregulation. This observation is compatible with longitudinal data of a clinical study conducted in the Netherlands (Lamers et al., 2016) and complements previously reported findings of our own study (Lasserre et al., 2014). In contrast, participants with melancholic episodes during follow-up had a reduced increase in BMI, which is expected given that a decrease in appetite is one of the symptoms of this depression subtype. However, after adjustment for the occurrence of this type of episode during follow-up, melancholic MDD at baseline was associated with an increase in BMI in men and women as well as body fat mass in men during follow-up, suggesting regain of the weight loss after the

offset of episodes. This is in line with evidence showing that in contrast to atypical MDD, an elevated increase in BMI among people with melancholic MDD is a temporary phenomenon that is not associated with elevated BMI in the long run (Glaus et al., 2013; Lamers et al., 2016). The finding of contrary associations of melancholic MDD with BMI in function of current versus remitted status could also explain partially inconsistent findings across previous studies.

Recently, Pistis et al. found evidence for a causal relationship between BMI and the atypical depression symptom increase in appetite according to the Mendelian Randomization approach (Pistis et al., 2021). However, they did not find evidence for a causal relationship between BMI and atypical depression as a whole. Moreover, given the lack of a polygenic risk score that could be used as an instrumental variable for atypical depression, the authors could not test the opposite pathway, atypical depression as a causal factor for increase in obesity markers, which would correspond to the analyses of the present article. Hence, the establishment of a causal relationship between BMI and one of five atypical depression symptoms by Pistis et al. does not preclude a potential causal pathway from atypical depression to increase in obesity markers.

The pathophysiological mechanisms that underlie the association between atypical MDD and obesity are still only partially understood. A series of mechanisms have been postulated that could underlie the link between depression in general and obesity including: 1) poor health behaviors such as poor diet (Mannan et al., 2016a), overeating or binge eating (Faith et al., 2011), physical inactivity (Faith et al., 2011; Mannan et al., 2016a, 2016b), smoking, alcohol or drug use; 2) sleep patterns including sleep difficulties and sleep duration (Faith et al., 2011; Mannan et al., 2016a, 2016b); 3) the effects of antidepressants (Faith et al., 2011; Mannan et al., 2016b); and 4) common genes (Byrne et al., 2015; Mannan et al., 2016a, 2016b) such as the FTO gene (Milaneschi et al., 2014) or polygenic risk scores (Milaneschi et al., 2017). Our results do not provide evidence for a significant role of the measured health behaviors (physical activity, smoking, alcohol consumption), comorbid non-mood disorders or medication in the prospective association between atypical MDD and obesity markers. However, our analyses did not test the role of diet, sleep and circadian rhythm patterns and their potential role on the association between atypical MDD and obesity should be addressed in future longitudinal studies.

Although female sex was associated with a steeper increase of waist circumference and body fat mass in the whole cohort, we found some evidence for an effect of sex on the associations of mainly the melancholic depression subtype with changes in BMI and fat mass. Given that with respect to changes in BMI our observed interaction was restricted to the relatively rare melancholic subtype, it is not surprising that the two meta-analyses of prospective studies in adults (Blaine, 2008; Luppino et al., 2010) did not find evidence for interactions between depression as a whole and sex regarding BMI. However, although we observed four interactions with sex regarding obesity markers, they would not survive Bonferroni correction for multiple testing and could be spurious. Alternatively, the restriction of sex-specific effects mainly to melancholic episodes could indicate less favorable metabolic outcomes in men presenting with this depression subtype as compared to women. Several explanations for potential sex-specific effects in the association between depression and obesity have been suggested. According to a recent American study, prenatal maternal stress during fetal brain development could have differential sex-specific effects on the hypothalamic-pituitary-adrenal axis (HPA-axis) and metabolic functions, leading to potential sex differences in the depression-obesity comorbidity (Goldstein et al., 2016). Moreover, depressed women may release more leptin, which plays a role in inflammation and the development of obesity (Li et al., 2017).

The present study has several limitations. First, the interval of approximately one year between the physical and the psychiatric baseline evaluations entailed the risk of misclassifying current episodes at the physical baseline visit as remitted depressive episodes, which could have led to an overestimation of the effect of remitted episodes on obesity markers. Second, we only studied the role of sex, whereas more recent research highlighted the need to distinguish “sex” (biological characteristics) from “gender” (social roles and behaviors) in clinical research (Schiebinger and Stefanick, 2016). The well-established differences between men and women in cardiovascular diseases may be better explained by gender-related characteristics (Pelletier et al., 2016; Regitz-Zagrosek et al., 2016) than by hormones and other biological differences. Third, participants and non-participants at the physical follow-up differed with respect to socio-demographic and behavioral characteristics suggesting that subjects with a less healthy lifestyle were less likely to participate. Nonetheless, given that only 23.1% of the initial sample did not participate at the follow-up, it is unlikely that non-participation introduced substantial bias in the estimates of associations.

Fourth, our data are based on an urban sample in Switzerland. However, although the particular features of the sample are likely to affect the prevalence estimates of diseases, it is less likely that they significantly affect the assessed prospective associations between depression subtypes and obesity markers (Lasserre et al., 2014). Fifth, analyses did not include the effect of diet or sleep and our assessment of physical activity was restricted to leisure time physical activity, which only partially reflects daily activity and energy expenditure. Sixth, given the absence of a permanent monitoring of obesity markers we could not distinguish the effects of episodes on obesity markers that were present during the duration of the depressive episode from those that were present after the offset of these episodes until the end of the follow-up period.

In conclusion, our results further emphasize the need of paying particular clinical attention to the atypical MDD subtype given that this subtype is a strong predictor of increase in obesity markers not only during depressive episodes but, more importantly for the long-term course, after their offset. A series of cross-sectional and prospective studies have also established links between atypical depression and diabetes (Glaus et al., 2013), fasting glucose (Lamers et al., 2013; Lasserre et al., 2017), triglycerides (Lamers et al., 2013; Vogelzangs et al., 2014) and the metabolic syndrome (Glaus et al., 2013; Lamers et al., 2016, 2013; Lasserre et al., 2017; Takeuchi et al., 2013). All these metabolic conditions can be consequences of overweight and are likely to expose patients with atypical MDD to an elevated long-term risk of cardiovascular diseases. Hence, the screening of atypical features and increased appetite in depressive patients is advocated, appetite-stimulating medication should be avoided and dietary measures are likely to be beneficial for these patients. Conversely, although we found some evidence suggesting less favorable metabolic outcomes in men than in women mainly related to melancholic episodes, these findings need to be further addressed in future studies which may include the more culturally-related measure of gender.

Authorship Contribution Statement

Study concept and design: Preisig, Clair

Acquisition of data: Preisig, Vollenweider

Statistical analysis: Strippoli, Ottino, Gholam, Lasserre

Drafting the manuscript: Ottino

Critical revision of the manuscript: Preisig, Vandeleur, Strippoli, Clair, Gholam, Lasserre, Vollenweider, Marques-Vidal

Study supervision: Clair, Preisig

All authors have approved the final article.

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Declaration of Competing Interest

None.

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Table 1. Characteristics of participants (N = 2702)

	Total (N = 2702)	Men (N = 1262)	Women (N = 1440)	Statistics	p-value
Socio-demographic characteristics					
Age (y), mean (SD)	49.6 (8.8)	49.1 (8.7)	50.1 (8.8)	t=3.0	0.003
Nonwhite, %	7.9	7.8	8.0	χ^2=0.0	0.832
White, %	92.1	92.2	92.0		
Length of follow-up (months), mean (SD)	66.2 (4.9)	66.4 (5.4)	66.0 (4.5)	t=-2.2	0.030
Living alone at baseline, %	22.8	17.7	27.3	χ^2=35.2	<0.001
Not living alone at baseline, %	77.2	82.3	72.7		
Living alone at follow-up, %	26.1	19.4	32.0	χ^2=54.7	<0.001
Not living alone at follow-up, %	73.9	80.6	68.0		
Behavioral factors at baseline					
Physically active [a], %	56.8	53.0	60.1	χ^2=13.9	<0.001
Not physically active, %	43.2	47.0	39.9		
Smoking status, %				χ_2^2=24.1	<0.001
Current	27.0	28.2	26.0		
Former	32.5	36.1	29.3		
Never	40.5	35.7	44.7		
Number of alcoholic drinks per week, mean (SD)	6.8 (8.7)	9.7 (10.5)	4.1 (5.5)	t=-17.7	<0.001
Non-mood disorders at baseline					
Anxiety disorders [c], %	17.4	13.0	21.3	χ^2=31.9	<0.001
No anxiety disorders, %	82.6	87.0	78.7		
Substance dependence [d], %	2.4	4.0	1.1	χ^2=22.9	<0.001
No substance dependence, %	97.6	96.0	98.9		
Medication at baseline					
Antidepressant use, %	8.6	5.8	10.9	χ^2=20.6	<0.001
No antidepressant use, %	91.4	94.2	89.1		
Weight gain inducing drug use, %	15.7	6.9	23.4	χ^2=128.0	<0.001
No weight gain inducing drug use, %	84.3	93.1	76.6		
Behavioral factors at follow-up					
Physically active [a], %	33.4	35.0	31.9	χ^2=2.9	0.090
Not physically active, %	66.6	65.0	68.1		
Current smoking, %	23.0	23.7	22.3	χ_2^2=20.7	<0.001
Former smoking, %	37.1	40.8	33.9		
Never smoking, %	39.9	35.5	43.8		
Number of alcoholic drinks per week, mean (SD)	6.5 (8.2)	9.2 (9.9)	4.0 (5.3)	t=-17.4	<0.001
Non-mood disorders at follow-up					
Anxiety disorders [c], %	6.3	4.4	8.1	χ^2=15.5	<0.001
No anxiety disorders, %	93.7	95.6	91.9		
Substance dependence [d], %	0.3	0.3	0.3	χ^2=0.0	0.852
No substance dependence, %	99.7	99.7	99.7		
Medication at follow-up					
Antidepressant use, %	9.1	6.2	11.6	χ^2=23.9	<0.001

No antidepressant use, %	90.9	93.8	88.4		
Weight gain inducing drug use, %	9.5	3.2	15.1	χ^2=111.6	<0.001
No weight gain inducing drug use, %	90.5	96.8	84.9		
History of MDD at baseline					
Current MDE, %	7.4	5.5	9.1	χ^2=12.3	<0.001
No current MDE, %	92.6	94.5	90.9		
Atypical MDD, %	6.3	3.8	8.5	χ_3^2=143.3	<0.001
Melancholic MDD, %	12.1	8.2	15.5		
Unspecified MDD, %	26.0	20.4	30.9		
None, %	55.7	67.7	45.1		
MDE during follow-up					
Atypical, %	2.7	1.6	3.7	χ_3^2=30.7	<0.001
Melancholic, %	4.1	3.2	4.9		
Unspecified, %	9.1	7.2	10.8		
None, %	84.1	88.1	80.6		
Obesity markers at baseline					
BMI (kg/m^2), mean (SD)	25.3 (4.4)	26.1 (3.7)	24.6 (4.8)	t=-9.1	<0.001
Waist circumference (cm), mean (SD)	87.6 (13.1)	94.2 (10.7)	81.9 (12.2)	t=-27.6	<0.001
Body fat mass (%), mean (SD)	28.1 (8.7)	22.6 (5.7)	33.0 (8.0)	t=37.9	<0.001
Obesity markers at follow-up					
BMI (kg/m^2), mean (SD)	26.0 (4.6)	26.7 (3.9)	25.3 (5.0)	t=-8.3	<0.001
Waist circumference (cm), mean (SD)	91.0 (12.9)	96.2 (11.2)	86.5 (12.7)	t=-20.9	<0.001
Body fat mass (%), mean (SD)	30.1 (8.7)	24.5 (5.7)	35.2 (7.8)	t=37.1	<0.001

Y: years; SD: standard deviation; MDD: Major Depressive Disorder; MDE: Major Depressive Episode; BMI: Body Mass Index.

[a] Physically active more than 20 minutes twice a week.
[b] Number of drinks per week: low = 1-13 and high = 14 or more.
[c] Generalized anxiety disorder, social phobia, panic disorder or agoraphobia.
[d] Lifetime dependence on cocaine, stimulant, sedative or hallucinogen drugs.

Table 2. Interactions between sex and depression status prior to baseline and during follow-up on change in obesity markers during follow-up

	Interactions		
	β[a]	95% CI	p-value
Change in BMI (n=2674)			
History of MDD at baseline			
Atypical MDD x Male sex	0.29	(-0.21,0.79)	0.250
Melancholic MDD x Male sex	0.21	(-0.16,0.57)	0.270
Unspecified MDD x Male sex	0.14	(-0.12,0.40)	0.297
MDE during follow-up			
Atypical MDE x Male sex	-0.32	(-1.07,0.42)	0.398
Melancholic MDE x Male sex	**0.58**	**(0.02,1.15)**	**0.043**
Unspecified MDE x Male sex	0.21	(-0.18,0.60)	0.285
Change in waist circumference (n=2688)			
History of MDD at baseline			
Atypical MDD x Male sex	0.81	(-1.34,2.96)	0.461
Melancholic MDD x Male sex	0.20	(-1.37,1.77)	0.807
Unspecified MDD x Male sex	**1.18**	**(0.04,2.31)**	**0.042**
MDE during follow-up			
Atypical MDE x Male sex	-0.83	(-4.06,2.40)	0.614
Melancholic MDE x Male sex	1.96	(-0.50,4.42)	0.118
Unspecified MDE x Male sex	1.60	(-0.08,3.28)	0.062
Change in body fat mass (n=2246)			
History of MDD status at baseline			
Atypical MDD x Male sex	0.66	(-0.89,2.21)	0.405
Melancholic MDD x Male sex	**1.19**	**(0.07,2.31)**	**0.037**
Unspecified MDD x Male sex	0.25	(-0.56,1.07)	0.544
MDE during follow-up			
Atypical MDE x Male sex	-0.10	(-2.35,2.16)	0.933
Melancholic MDE x Male sex	**1.78**	**(0.03,3.53)**	**0.046**
Unspecified MDE x Male sex	0.69	(-0.52,1.91)	0.264

BMI: Body Mass Index; MDD: Major Depressive Disorder; MDE, Major Depressive Episode; 95CI: 95% confidence interval.

[a] Robust regression models adjusted for age, ethnicity, length of follow-up, baseline and follow-up characteristics (living alone, physical activity, smoking habit, alcohol use, drug dependence, anxiety disorders, antidepressant use, weight-increasing drug use), remission status of depression at baseline and corresponding obesity marker at baseline.

Table 3. Change in obesity markers during follow-up by depression status prior to baseline and during follow-up in the overall sample and by sex

	Change in BMI (n=2674)			Change in waist circumference (n=2688)			Change in body fat mass (n=2246)		
	Crude change mean (SD)	β[a]	95% CI	Crude change mean (SD)	β[a]	95% CI	Crude change mean (SD)	β[a]	95% CI
Overall									
History of MDD at baseline									
Atypical	0.79 (2.43)	**0.35****	**(0.12,0.59)**	4.74 (7.70)	**1.48****	**(0.45,2.50)**	1.96 (6.03)	**0.72**	**(-0.02,1.46)**
Melancholic	0.90 (2.00)	**0.31*****	**(0.13,0.49)**	4.39 (7.85)	**0.35**	**(-0.42,1.12)**	2.75 (5.96)	0.48	(-0.07,1.04)
Unspecified	0.60 (1.77)	**0.03**	**(-0.11,0.17)**	3.65 (6.89)	-0.35	(-0.93,0.24)	2.07 (5.87)	**-0.15**	**(-0.57,0.28)**
None (ref.)	0.56 (1.61)	**0 (ref.)**		3.14 (6.24)	**0 (ref.)**		2.06 (5.64)	**0 (ref.)**	
MDE during follow-up									
Atypical	1.29 (1.90)	**0.62*****	**(0.29,0.96)**	6.42 (7.04)	**2.18****	**(0.74,3.63)**	3.99 (4.50)	**1.27***	**(0.26,2.28)**
Melancholic	0.43 (2.41)	-0.36**	(-0.64,-0.09)	3.72 (7.57)	**-0.21**	**(-1.41,0.98)**	2.12 (6.06)	-0.71	(-1.57,0.15)
Unspecified	0.93 (1.74)	**0.15**	**(-0.04,0.34)**	4.85 (6.35)	**0.55**	**(-0.27,1.38)**	2.57 (6.00)	**-0.02**	**(-0.62,0.58)**
None (ref.)	0.58 (1.72)	**0 (ref.)**		3.28 (6.69)	**0 (ref.)**		2.04 (5.76)	**0 (ref.)**	
Female sex	0.63 (1.96)	**0.03**	**(-0.10,0.15)**	4.69 (7.36)	**0.81****	**(0.22,1.40)**	2.35 (6.62)	**4.30*****	**(3.85,4.76)**
Male sex (ref.)	0.62 (1.51)	**0 (ref.)**		2.19 (5.66)	**0 (ref.)**		1.91 (4.63)	**0 (ref.)**	
Men									
History of MDD at baseline									
Atypical	1.32 (1.31)	0.52*	(0.11,0.92)	4.21 (4.75)	1.85*	(0.23,3.47)	2.83 (5.59)	1.13	(-0.09,2.34)
Melancholic	1.04 (1.69)	0.39**	(0.12,0.67)	2.90 (6.11)	0.31	(-0.79,1.41)	2.94 (4.78)	**1.19****	**(0.37,2.00)**
Unspecified	0.66 (1.52)	0.07	(-0.12,0.27)	2.60 (6.07)	**0.28**	**(-0.49,1.04)**	2.06 (4.48)	-0.19	(-0.77,0.39)
None (ref.)	0.52 (1.47)	0 (ref.)		1.87 (5.50)	0 (ref.)		1.69 (4.59)	0 (ref.)	
MDE during follow-up									
Atypical	1.26 (1.34)	0.39	(-0.19,0.98)	4.75 (5.18)	1.19	(-1.16,3.54)	4.15 (4.42)	1.08	(-0.66,2.82)
Melancholic	0.90 (1.57)	**-0.04**	**(-0.45,0.38)**	3.64 (5.44)	0.61	(-1.08,2.30)	2.09 (5.01)	**0.31**	**(-0.90,1.53)**
Unspecified	0.94 (1.42)	0.29*	(0.00,0.57)	4.14 (5.87)	1.54**	(0.40,2.68)	2.66 (4.15)	0.40	(-0.46,1.26)
None (ref.)	0.58 (1.51)	0 (ref.)		1.94 (5.62)	0 (ref.)		1.81 (4.65)	0 (ref.)	
Women									

History of MDD at baseline									
Atypical	0.58 (2.72)	0.20	(-0.11,0.51)	4.94 (8.57)	1.10	(-0.31,2.50)	1.60 (6.20)	0.48	(-0.53,1.49)
Melancholic	0.83 (2.13)	0.23	(-0.02,0.47)	5.07 (8.45)	0.13	(-0.98,1.23)	2.66 (6.45)	**0.12**	**(-0.66,0.91)**
Unspecified	0.57 (1.90)	-0.05	(-0.25,0.15)	4.26 (7.26)	**-0.81**	**(-1.70,0.09)**	2.09 (6.57)	-0.29	(-0.92,0.34)
None (ref.)	0.61 (1.77)	0 (ref.)		4.80 (6.75)	0 (ref.)		2.57 (6.80)	0 (ref.)	
MDE during follow-up									
Atypical	1.29 (2.08)	0.66**	(0.23,1.09)	7.03 (7.55)	2.31*	(0.37,4.24)	3.94 (4.58)	1.22	(-0.12,2.55)
Melancholic	0.16 (2.75)	**-0.58****	**(-0.96,-0.20)**	3.76 (8.56)	-1.05	(-2.76,0.66)	2.14 (6.71)	**-1.44***	**(-2.69,-0.18)**
Unspecified	0.92 (1.90)	0.07	(-0.20,0.33)	5.25 (6.59)	0.00	(-1.20,1.20)	2.52 (6.86)	-0.24	(-1.09,0.61)
None (ref.)	0.59 (1.90)	0 (ref.)		4.56 (7.35)	0 (ref.)		2.26 (6.67)	0 (ref.)	

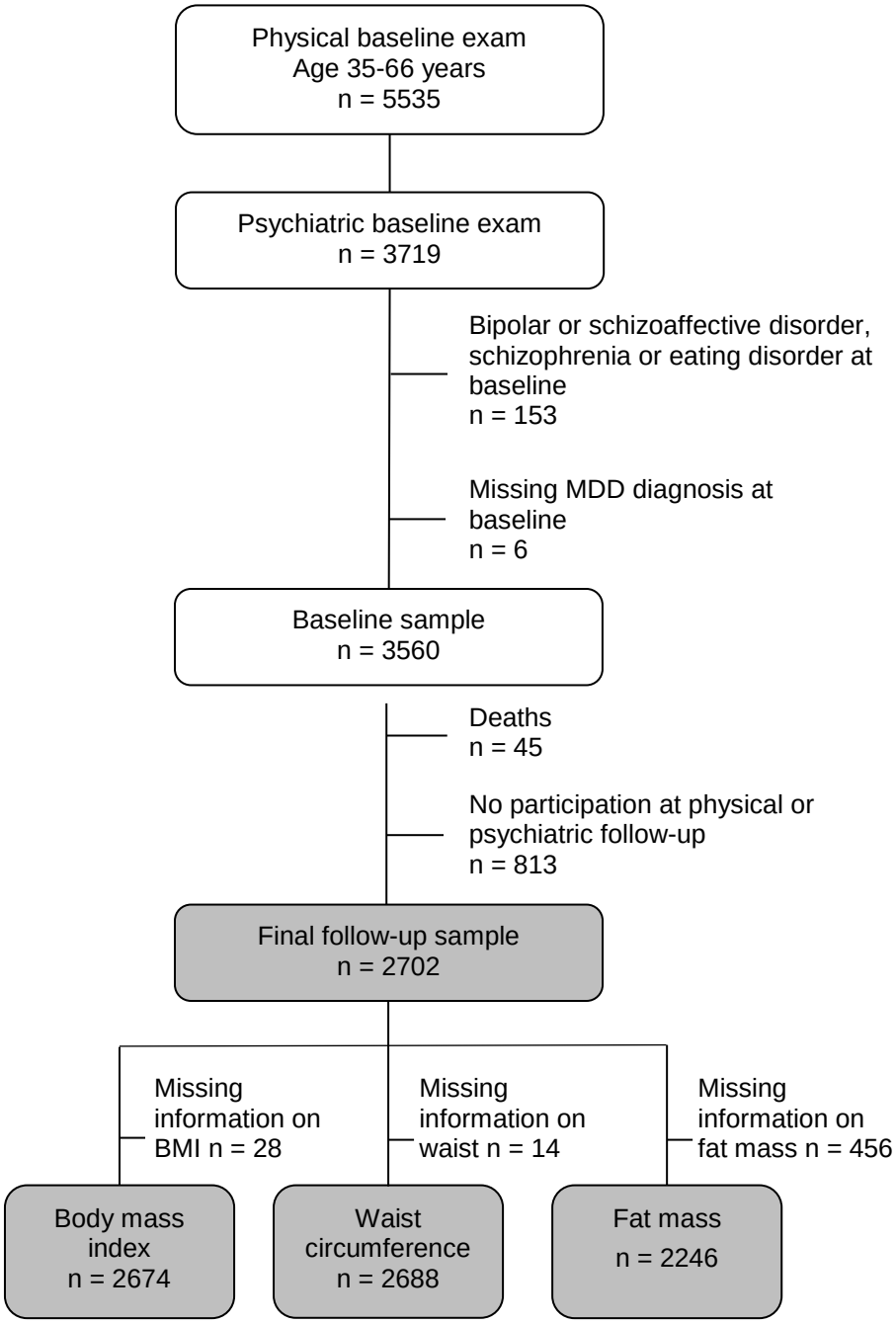
BMI: Body Mass Index; MDD: Major Depressive Disorder; MDE: Major Depressive Episode; 95CI: 95% confidence interval.

***p<0.001, **p<0.01, *p<0.05

[a] Robust regression models adjusted for age, ethnicity, length of follow-up, baseline and follow-up characteristics (living alone, physical activity, smoking habit, alcohol use, drug dependence, anxiety disorders, antidepressant use, weight-increasing drug use), remission status of depression at baseline and corresponding obesity marker at baseline.

Bold: β-estimates and 95% confidence intervals for the whole sample in case of absence of an interaction of the corresponding depression variable with sex and β-estimates and 95% confidence intervals for men and women separately in case of an interaction of the corresponding depression variable with sex

Figure 1: Flow chart of CoLaus|PsyCoLaus for the study of the association between MDD subtypes and obesity markers



Key: MDD: Major depressive disorder, BMI: Body mass index

□ = Baseline assessment
▒ = Follow-up assessment