ORIGINAL ARTICLE

Prospective associations of depression subtypes with cardio-metabolic risk factors in the general population

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The mechanisms and temporal sequence underlying the association between major depressive disorder (MDD) and cardio-metabolic diseases are still poorly understood. Recent research suggests subtyping depression to study the mechanisms underlying its association with biological correlates. Accordingly, our aims were to (1) assess the prospective associations of the atypical, melancholic and unspecified subtypes of MDD with changes of fasting glucose, high-density lipoprotein-cholesterol, triglycerides, systolic blood pressure and the incidence of the metabolic syndrome, (2) determine the potential mediating role of inflammatory marker or adipokine concentrations, eating behaviors and changes in waist circumference during follow-up. Data stemmed from CoLaus|PsyCoLaus, a prospective cohort study including 35–66-year-old randomly selected residents of an urban area. Among the Caucasian participants who underwent the physical and psychiatric baseline evaluations, 2813 (87% participation rate) also accepted the physical follow-up exam (mean follow-up duration = 5.5 years). Symptoms of mental disorders were elicited using a semi-structured interview. The atypical MDD subtype, and only this subtype, was prospectively associated with a higher incidence of the metabolic syndrome (OR = 2.49; 95% CI 1.30–4.77), a steeper increase of waist circumference (β = 2.41; 95% CI 1.19–3.63) and independently of this, with a steeper increase of the fasting glucose level (β = 131; 95% CI 38–225) during follow-up. These associations were not attributable to or mediated by inflammatory marker or adipokine concentrations, eating behaviors, comorbid psychiatric disorders or lifestyle factors. Accordingly, our results further support the subtyping of MDD and highlight the particular need for prevention and treatment of metabolic consequences in patients with atypical MDD.

INTRODUCTION

Although the association between depressive disorders and cardiovascular diseases (CVD)[1,2] is well established, the mechanisms underlying this association are poorly understood.[3,4] Besides lifestyle (smoking, reduced physical activity and unhealthy diet) and treatment factors (medication and non-adherence to treatment),[3,5,6] increased vulnerability to cardio-metabolic diseases could be one explanation for the approximately doubled risk of CVD among depressed subjects.[1] Indeed, clinical and epidemiological studies revealed significant associations between depression and obesity,[7] diabetes[8–10] and hypertension.[11] Two recent meta-analyses have also shown cross-sectional associations between depression and the metabolic syndrome, which encompasses obesity, diabetes, dyslipidemia and hypertension.[12,13] The results of the 11 prospective cohort studies included in one of these two meta-analyses[13] suggested a bidirectional association. However, the measured effect sizes varied largely across studies, which was most likely to be attributable to the heterogeneity of depression and large methodological variance across studies. Moreover, among the four studies that prospectively assessed the effect of depression on the incidence of the metabolic syndrome, only one,[14] which was restricted to 42–52-year-old women, relied on a direct diagnostic interview, whereas the others assessed depressive symptoms using rating scales. However, these scales do not generally allow for characterization into depression subtypes and do not take into account the frequent occurrence of comorbid mental disorders or past psychopathology.

Given the heterogeneity of depression in terms of symptom manifestations, course and response to pharmacological treatment,[15,16] subtyping depression is likely to be a more promising approach to elucidate the mechanisms underlying associations with cardio-metabolic risk factors than studying depression as a whole.[5] It has been hypothesized that depression subtypes are differently associated with biological mechanisms: the atypical subtype, mainly characterized by increased appetite and hypersomnia, could be more strongly related to the metabolic syndrome and inflammation upregulations and the melancholic subtype to dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis.[15,17–19] Cross-sectional research has already provided support for associations between atypical depression and obesity markers,[20–22] diabetes[21] or fasting glucose,[22] triglycerides[22,23] and the metabolic syndrome,[21,22,24] but prospective data which could provide clues to the direction of causality are still scarce. Following a community sample over more than 5 years, we could demonstrate a strong prospective association between major depressive disorder (MDD) with atypical features and a steeper increase in body-mass index, waist circumference and fat-mass.[25] Similarly, a clinical cohort study conducted in the Netherlands has recently documented the persistence of a higher body-mass

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index, a higher prevalence and a larger number of components of the metabolic syndrome over 6 years in patients with atypical depression as compared with controls.[26] However, no study so far has prospectively assessed associations between depression subtypes and the specific components of the metabolic syndrome other than waist circumference. Therefore, it remains elusive whether the association between atypical MDD and the metabolic syndrome is explained by waist circumference increase alone or whether additional independent cardio-metabolic dysregulations are also involved. Likewise, it has not yet been tested to which degree cardio-metabolic dysregulations related to atypical MDD are attributable to eating behaviors or the atypical depression symptom 'increased appetite'. Moreover, although several studies have documented associations between atypical depression and elevated inflammatory marker concentrations,[22,27,28] which may predispose to CVD and mortality,[3,29,30] no study has prospectively examined their function in the interplay between depression and cardio-metabolic dysregulations. Similarly, the role of leptin and adiponectin remains uncertain. The concentration of leptin, which is secreted by white adipose tissue and exerts a primary homeostatic function by suppressing nutritional intake and allowing energy expenditure,[31] has recently been found to be elevated in patients with atypical depression, most likely due to leptin resistance.[32]

Accordingly, using data from a population-based cohort, the aims of the present study were to (1) assess the prospective associations of the atypical, melancholic and unspecified subtypes of MDD with changes of the levels of fasting glucose, high-density lipoprotein (HDL)-cholesterol, triglycerides, systolic blood pressure (SBP) and the incidence of the metabolic syndrome, (2) determine the potential mediating role of baseline inflammatory marker (high-sensitivity C-reactive protein (hs-CRP), interleukin-1β (IL-1β), interleukin-6 and tumor necrosis factor-α) or adipokine (leptin and adiponectin) concentrations, eating behaviors and changes of waist circumference during follow-up. Based on our cross-sectional findings we expected prospective associations between atypical depression, glucose level increase and the incidence of the metabolic syndrome. Regarding inflammation markers, adipokines and eating behaviors, we hypothesized that they could play a role as mediators in the associations between atypical depression and metabolic outcomes given that previous studies have shown them to be associated with both atypical depression[22,27,28,32] and metabolic outcomes.[20–22] In this case the associations between atypical depression and metabolic characteristics would decrease after introducing these variables into our models.

MATERIALS AND METHODS

Participants
These data of the present paper stemmed from CoLaus|PsyCoLaus,[33,34] a prospective cohort study designed to study mental disorders and cardiovascular risk factors in the community and to determine their associations. The sample was randomly selected from the residents of the city of Lausanne (Switzerland) from 2003 to 2006 according to the civil register. Sixty-seven percent of the 35–66-year-old participants of the physical baseline exam ($n = 5535$) also accepted the psychiatric evaluation (Figure 1).[34] 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. Among the remaining 3560 subjects, 45 died during the follow-up (mean duration 5.5 years, s.d. 0.4 years) and 3056 accepted the physical follow-up evaluation (86.9% participation among survivors). Non-participants at follow-up were more likely than participants to be male, to have lower socio-economic status, to live alone, to be less physically active, and to be current smokers. We needed to perform separate analyses on Caucasians ($n = 2813$) and non-Caucasians ($n = 243$) because the baseline adipokine levels of the latter were not measured.

Assessments
Physical measures were taken in identical ways at the baseline and the follow-up visits. Detailed procedures are described elsewhere.[33] Waist circumference was measured over the unclothed abdomen at the narrowest point between the lowest rib and the iliac crest. Blood pressure was measured three times on the left arm after at least a 10-min rest in the seated position. The mean of the last two measures was used. Venous blood samples were drawn after an overnight fast to measure the levels of glucose, HDL cholesterol, low-density lipoprotein-cholesterol, triglycerides and insulin. Insulin resistance was estimated from measures of the glucose and insulin concentrations using the Homeostasis model assessment-insulin resistance index.[35] The metabolic syndrome was diagnosed according to the adjusted Adult Treatment Panel III criteria.[36] Hs-CRP was assessed using immunoassay and latex HS (IMMULITE 1000-High, Diagnostic Products, LA, CA, USA), with maximum intra- and interbatch coefficients of variation of 1.3% and 4.6%, respectively.[33] For cytokine and adipokine measurements, serum samples were stored at − 80 °C before assessment and sent on dry ice to the laboratory. Cytokine concentrations were measured using a multiplexed particle-based flow cytometric cytokine assay.[37] Lower detection limits for IL-1β, interleukin-6 and tumor necrosis factor-α were 0.2 pg ml^{-1}. For concentrations below the lower detection limit (37.5% for IL-1β, 8.2% for interleukin-6 and 0.7% for tumor necrosis factor-α) a value of 0.1 pg ml^{-1} was assigned. Good agreement between signal and cytokine was found within the assay range ($R^2 \geqslant 0.99$). Adiponectin was assessed by ELISA (R&D Systems, Minneapolis, MN, USA) with a maximum inter- and intra-assay coefficient of variability (CV) of 8.3%. Leptin was assessed by ELISA (American Laboratory Products, Windham, NY, USA) with a maximum inter- and intra-assay CV of 12.8% and 5.8%, respectively.

Information on socio-demographic characteristics, current medication, alcohol consumption, smoking and physical activity was collected through a standardized interview. Caucasian origin was defined as having both parents and grandparents born in a restricted list of countries (available from the authors). Socio-economic status was determined using the Hollingshead scale.[38] Subjects were considered to be physically active if they reported physical activity for at least 20 min twice a week. Daily energy and carbohydrate consumption at follow-up were assessed using a validated, self-administered and quantitative Food Frequency Questionnaire.[39,40]

Diagnostic information on mental disorders was collected at baseline and follow-up using the French version of the semi-structured diagnostic interview for genetic studies (DIGS).[41,42] The DIGS was completed with anxiety disorder sections of the schedule for affective disorders and schizophrenia – lifetime version.[43] Psychiatric lifetime diagnoses were assigned according to the Diagnostic and Statistical Manual of Mental Disorders (4th edn; DSM-IV; American Psychiatric Association, 1994).[44] 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. To avoid potential redundancy with the metabolic disorder component abdominal waist circumference, 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: (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. The DIGS also assesses lifetime binge eating and early physical or sexual abuse. For subjects who refused the DIGS interview at follow-up (11.5%), MDD status at follow-up was assessed using the Centre for Epidemiologic Studies Depression (CES-D) scale. A score of 19 or higher was considered to be an indicator of the presence of a major depressive episode.[45,46] Interviewers were master-level psychologists, who were trained over a 2-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.
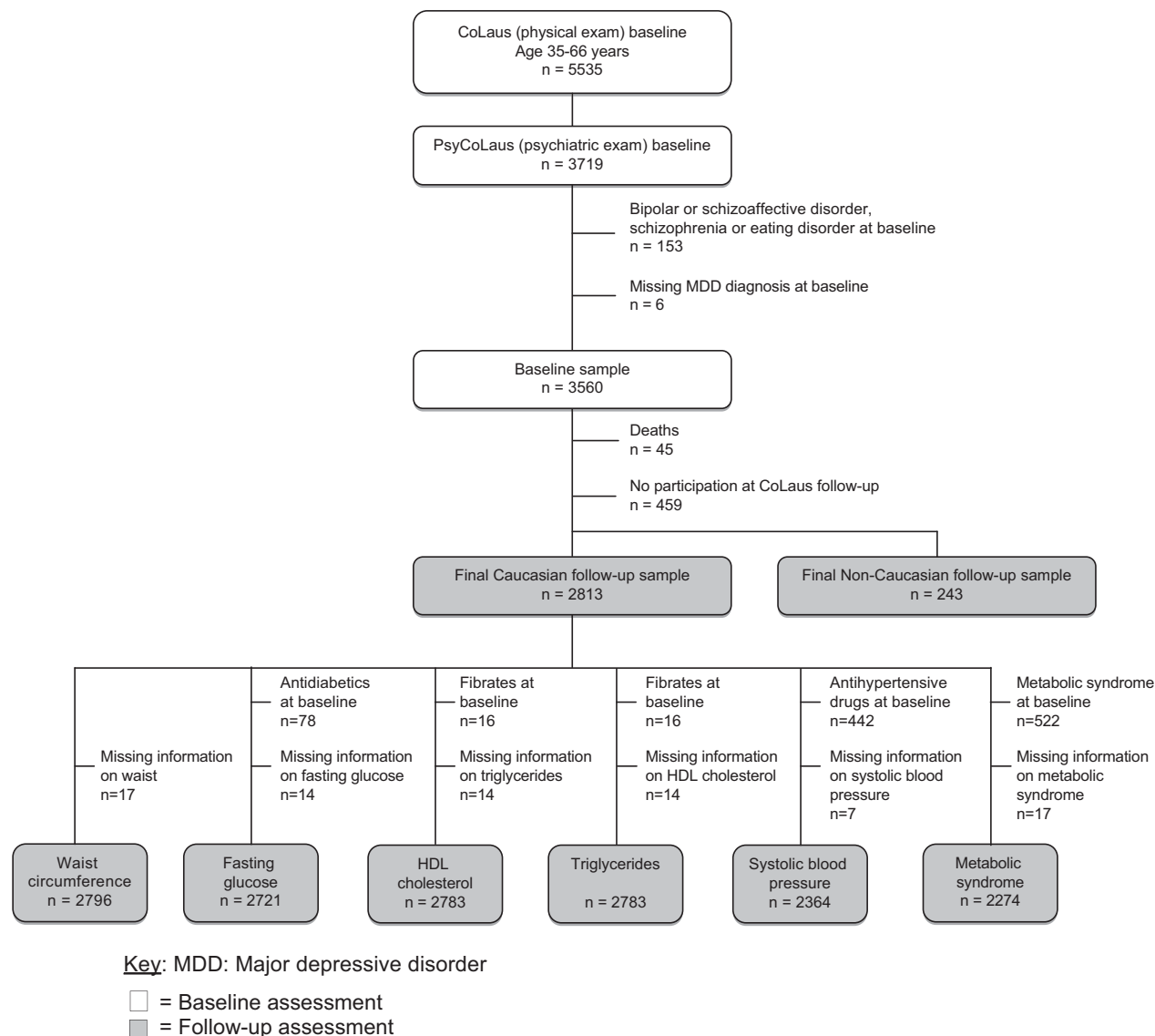
Figure 1. Flow chart of the study for the association between depressive subtypes at baseline and cardio-metabolic risk factors at follow-up. MDD, major depressive disorder; □, baseline assessment; ■, follow-up assessment.

Statistical analysis

Analyses were performed separately for Caucasians and non-Caucasians using the Statistical Analysis System (SAS, Cary, NC, USA), version 9.3, for Windows. The associations between lifetime MDD subtype status and changes in cardio-metabolic outcomes during follow-up (difference between follow-up and baseline levels for waist circumference, fasting glucose, HDL cholesterol, triglycerides and SBP) were assessed using robust[47] rather than multiple regression models, given that the residuals did not reveal a normal distribution. Subjects with medication for a specific cardio-metabolic condition at baseline (antidiabetic drugs, fibrates and antihypertensive drugs) were excluded from the respective analyses (Figure 1). Analyses with the incidence of the metabolic syndrome as the outcome variable were performed using logistic regression. To adjust for the effects of medication prescribed during the follow-up, values for treated subjects were assigned according to documented mean changes under medication.[48] For subjects treated with antidiabetic medication ($n = 63$) a value of 7.0 mmol l^{-1} was assigned when the glucose level was < 7.0 mmol l^{-1}; for those using fibrates ($n = 12$) 0.10 mmol l^{-1} was subtracted from HDL cholesterol and 0.67 mmol l^{-1} was added to triglycerides, and for those using antihypertensive drugs ($n = 251$) 10 mm Hg was added to the SBP. To test whether inflammatory marker

or adipokine concentrations at baseline and the change in waist circumference during follow-up were likely to be mediators of the associations between lifetime MDD subtype status and changes in cardio-metabolic outcomes, we used serially adjusted models. Model 1 was adjusted for potential confounding variables including socio-demographic characteristics (sex, age, socio-economic status and living alone), current versus remitted status, baseline level of the cardio-metabolic outcome variable, length of follow-up, occurrence of depressive episodes during follow-up, a lifetime history of comorbid anxiety disorders or drug dependence, health-related lifestyle factors (physical inactivity, alcohol consumption and smoking status), early physical or sexual abuse and treatment with antidepressants or possibly weight-increasing drugs (list extracted from micromedex[49] and the Swiss Compendium of Medications[50]). Model 2 was also adjusted for the effects of inflammatory markers and adipokines (only in Caucasians) and model 3 also accounted for the change of waist circumference during follow-up. Inflammatory marker and adipokine concentrations were log-transformed and standardized. In case of significant associations between the MDD subtypes and metabolic outcomes, additional analyses tested the influence on these associations of eating behaviors such as binge eating at baseline and follow-up as well as daily energy and carbohydrate consumption at follow-

up. Moreover, we assessed the associations between specific depression symptoms and the cardio-metabolic outcomes.

RESULTS

Baseline characteristics

Table 1 presents the characteristics of the Caucasian sample by depression status at baseline. A proportion of 6.4% of the participants met lifetime criteria for MDD with atypical features, 13.1% for MDD with melancholic features, and 24.3% for unspecified MDD (among them 15.3% with both atypical and melancholic features). All socio-demographic characteristics except for socio-economic status, length of follow-up, most of the behavioral factors, a lifetime history of anxiety disorders, early

physical or sexual abuse, current versus remitted depression status, occurrence of depressive episodes during follow-up, antidepressant and weight-gain inducing medication and cardio-metabolic risk factors were unequally distributed across diagnostic groups.

Regarding the distribution of potential mediating variables at baseline (Table 2), the IL-1β concentration was lower and the leptin concentration was higher in subjects with atypical MDD as compared with never depressed individuals. Moreover, subjects with MDD revealed binge eating more frequently at baseline and follow-up and those with melancholic MDD also had a higher daily carbohydrate consumption at follow-up than never depressed individuals. In addition, insulin resistance according to the homeostasis model assessment-insulin resistance index was elevated in subjects with atypical MDD at baseline.

Table 1. Characteristics of participants (among Caucasians, $n = 2813$)

	MDD status at baseline					
	Atypical (n = 179)	Melancholic (n = 369)	Unspecified (n = 685)	No MDD (n = 1580)	χ^2/F	P-value
Socio-demographic characteristics						
Age, mean (s.d.), y	49.1 (8.9)	49.5 (8.7)	49.4 (8.8)	50.5 (8.9)	$F_3 = 3.7$	0.011
Men (%)	27.9	31.7	37.2	57.0	$\chi^2_3 = 150.0$	< 0.001
Socio-economic status[a], mean (s.d.)	3.4 (1.1)	3.5 (1.2)	3.5 (1.2)	3.4 (1.2)	$F_3 = 1.6$	NS
Living alone (%)	29.6	29.3	29.2	19.8	$\chi^2_3 = 34.2$	< 0.001
Length of follow-up, mean (s.d.), y	5.5 (0.3)	5.5 (0.3)	5.5 (0.4)	5.6 (0.4)	$F_3 = 4.3$	0.005
Behavioral factors						
Physically inactive[b] (%)	43.6	39.0	41.8	40.9	$\chi^2_3 = 1.3$	NS
Smoking status (%)						
Current	27.9	29.5	32.9	24.9	$\chi^2_3 = 15.7$	0.001
Former	30.2	30.4	33.3	33.5	$\chi^2_3 = 2.0$	NS
Number of alcoholic drinks per week, mean (s.d.)	4.9 (5.3)	5.7 (7.8)	6.2 (7.9)	8.0 (10.0)	$F_3 = 13.3$	< 0.001
Comorbid disorders						
Substance dependence[c] (%)	0.6	3.0	3.2	2.2	$\chi^2_3 = 5.5$	NS
Anxiety disorders[d] (%)	25.7	27.9	23.4	12.4	$\chi^2_3 = 78.6$	< 0.001
Early trauma						
Early physical or sexual abuse (%)	5.0	2.7	1.6	0.6	$\chi^2_3 = 28.1$	< 0.001
Depression status at baseline and follow-up						
Current major depressive episode (%)	24.6	17.1	14.3	NA	$\chi^2_3 = 10.9$	0.004
Major depressive episode during follow-up (%)	13.0	15.6	13.9	6.2	$\chi^2_3 = 51.3$	< 0.001
Medication at baseline						
Antidiabetic drugs (%)	2.2	1.9	3.5	2.7	$\chi^2_3 = 2.6$	NS
Fibrates (%)	0.6	0.3	0.2	0.8	$\chi^2_3 = 4.5$	NS
Nicotinic acid (%)	0.0	0.0	0.0	0.0	NA	NA
Antihypertensive drugs (%)	19.0	14.9	15.8	15.5	$\chi^2_3 = 1.7$	NS
Antidepressant use (%)	21.2	20.3	12.1	2.6	$\chi^2_3 = 187.5$	< 0.001
Weight-gain-inducing drug use (%)	25.1	22.2	21.0	10.6	$\chi^2_3 = 69.5$	< 0.001
Cardio-metabolic risk factors at baseline						
Waist (cm), mean (s.d.)	88.7 (13.7)	85.3 (13.9)	85.9 (12.6)	89.0 (12.9)	$F_3 = 14.4$	< 0.001
Fasting glucose[e], mean (s.d.), mmol l^{-1}	5.3 (0.7)	5.4 (1.0)	5.4 (1.1)	5.5 (1.0)	$F_3 = 6.1$	< 0.001
HDL cholesterol[e], mean (s.d.), mmol l^{-1}	1.7 (0.5)	1.7 (0.4)	1.7 (0.4)	1.6 (0.4)	$F_3 = 5.4$	0.001
Triglycerides[e], mean (s.d.), mmol l^{-1}	1.4 (1.1)	1.3 (0.9)	1.3 (1.0)	1.4 (1.1)	$F_3 = 1.7$	NS
SBP[e], mean (s.d.), mm Hg	126.2 (18.3)	124.2 (16.3)	124.0 (16.8)	128.2 (17.9)	$F_3 = 12.0$	< 0.001
Metabolic syndrome[f] (%)	22.4	17.1	15.9	19.5	$\chi^2_3 = 6.4$	NS

Abbreviations: ANOVA, analysis of variance; HDL, high-density lipoprotein; MDD, major depressive disorder; NA, not applicable; NS, not significant; SBP, systolic blood pressure; s.d., standard deviation; SES, socio-economic status; y, year. χ^2/F: comparison with subjects with no MDD based on χ^2 tests (categorical variables) /ANOVA (continuous variables). [a]A value of 3 represents an SES of III (middle class) on the Hollingshead Scale. [b]Physically inactive < 20 min twice a week. [c]Lifetime dependence on cocaine, stimulant, sedative or hallucinogen. [d]Generalized anxiety disorder, social phobia, panic disorder or agoraphobia. [e]Prefixed values according to medication added (see the 'Materials and Methods section'). [f]Metabolic syndrome according to adjusted Adult Treatment Panel III criteria (see the 'Materials and Methods section').

Table 2. Potential mediators by depression status at baseline among Caucasians (n = 2813)

	MDD at baseline						No MDD
	Atypical		Melancholic		Unspecified		
	Median (IQR)	Test statistics[a] (95% CI)	Median (IQR)	Test statistics[a] (95% CI)	Median (IQR)	Test statistics[a]	Median
Inflammatory markers and adipokine concentrations at baseline							
IL-1β, pg ml⁻¹	0.31 (0.10, 1.66)	OR[b]=**0.72*** **(0.52, 0.99)**	0.43 (0.10, 1.98)	OR[b]=0.91 (0.72, 1.15)	0.42 (0.10, 2.00)	OR[b]=0.91 (0.76, 1.10)	0.43 (0.10, 1.94)
Interleukin-6, pg ml⁻¹	1.29 (0.56, 3.47)	β=0.05 (−0.20, 0.30)	1.22 (0.52, 2.81)	β=−0.08 (−0.26, 0.11)	1.19 (0.50, 3.21)	β=−0.10 (−0.25, 0.05)	1.35 (0.60, 3.39)
Tumor necrosis factor-α, pg ml⁻¹	2.96 (1.84, 4.93)	β=0.09 (−0.06, 0.23)	2.72 (1.62, 4.29)	β=−0.02 (−0.13, 0.08)	2.61 (1.58, 4.18)	β=−0.06 (−0.15, 0.02)	2.87 (1.86, 4.45)
hs-CRP, mg l⁻¹	1.20 (0.60, 2.60)	β=0.15 (−0.02, 0.31)	1.00 (0.50, 2.30)	β=−0.05 (−0.17, 0.07)	1.00 (0.50, 2.10)	β=−0.07 (−0.16, 0.03)	1.10 (0.50, 2.30)
Adiponectin, µg ml⁻¹	9.36 (5.69, 12.98)	β=−0.03 (−0.12, 0.07)	9.33 (5.42, 13.75)	β=−0.01 (−0.08, 0.06)	8.79 (5.61, 13.72)	β=0.02 (−0.04, 0.07)	7.82 (4.97, 11.84)
Leptin, ng ml⁻¹	11.78 (6.61, 21.44)	β=**0.16*** **(0.04, 0.28)**	10.86 (6.03, 18.22)	β=0.06 (−0.04, 0.15)	9.97 (5.18, 18.39)	β=0.01 (−0.06, 0.09)	8.30 (4.66, 15.16)
Eating behaviors	%		%		%		%
Binge eating at baseline	5.6	OR=**3.3*** **(1.5, 7.3)**	3.3	OR=2.0 (0.9, 4.2)	3.8	OR=**2.5*** **(1.3, 4.6)**	1.1
Binge eating at follow-up	3.4	OR=**8.9*** **(2.6, 30.4)**	2.4	OR=**6.6*** **(2.2, 20.3)**	1.6	OR=**4.4*** **(1.5, 12.8)**	0.3
	Mean (s.d.)		Mean (s.d.)		Mean (s.d.)		Mean (s.d.)
Energy consumption at follow-up, kcal per day	1708.7 (686.8)	β=−40.6 (−140.4, 59.3)	1799.0 (657.7)	β=64.7 (−8.6, 138.0)	1817.3 (727.7)	β=15.0 (−43.2, 73.2)	1869.9 (730.6)
Carbohydrate consumption at follow-up, kcal per day	784.7 (361.7)	β=−18.8 (−73.9, 36.3)	855.1 (363.2)	β=**48.4*** **(7.9, 88.6)**	848.1 (401.0)	β=16.1 (−16.1, 48.2)	851.8 (370.8)
Insulin resistance at baseline	Median (IQR)		Median (IQR)		Median (IQR)		Median (IQR)
HOMA-IR	1.75 (1.06, 2.62)	β=**0.13*** **(0.03, 0.23)**	1.56 (1.07, 2.40)	β=0.05 (−0.03, 0.12)	1.50 (1.01, 2.24)	β=0.00 (−0.06, 0.06)	1.57 (1.08, 2.45)

Abbreviations: CI, confidence interval; HOMA-IR, homeostasis model assessment-insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1β; IQR: interquartile range; LOD, lower detection limits; MDD, major depressive disorder; OR, odds ratio; s.d., standard deviation. *P < 0.05, **P < 0.01, ***P < 0.001. [a]Adjusted for age, sex, socio-economic status and living alone. [b]Logistic regression with Interleukin-1 beta concentration dichotomized at the median due to many (37.5%) values below the LOD. Bold values indicate statistical significance.

Among the 243 non-Caucasians (15% Asians, 27% Africans, 19% Arabs and 38% Latin Americans), the lifetime prevalence of MDD subtypes was almost identical to that of Caucasians (6.4% MDD with atypical features, 13.2% MDD with melancholic features and 28.9% unspecified MDD).

Waist circumference

Table 3 provides the changes of cardio-metabolic characteristics during the follow-up in function of the baseline depression status. The results of the robust regression model with adjustment for potential confounders (model 1) revealed that subjects with a lifetime history of both atypical and melancholic MDD at baseline had a steeper increase of waist circumference during follow-up than never depressed subjects. The size of these associations only marginally diminished after additional adjustments for inflammation marker or adipokine concentrations at baseline (model 2), although the hs-CRP and leptin concentrations were positively and the adiponectin concentration was negatively associated with increase in waist circumference. Additional analyses showed that eating behaviors did not account for the associations between increase of waist circumference and atypical (β = 2.28 after adjustment instead of 2.35) or melancholic MDD (β = 1.27 after adjustment instead of 1.36), although binge eating at follow-up was significantly associated with this metabolic outcome (β = 2.27, 95% C.I. 0.01–4.52, P = 0.049). Nevertheless, among the specific depression symptoms only the atypical depression symptom increased appetite during depressive episodes was a significant predictor of increase of waist circumference during the follow-up (β = 2.30, 95% C.I. 1.31–3.30, P < 0.001). To test whether the association between atypical MDD and increase in waist circumference was explained by increased appetite alone we ran an additional model testing this association with adjustment for the effect of this symptom. Despite a decrease of the effect size this model still revealed a significant association between atypical depression and increase in waist circumference (β = 1.41 instead of 2.35, 95% C.I. 0.07–2.75, P = 0.039), therefore supporting the contribution of other symptoms to this association. Among non-Caucasians there was no significant association between MDD subtypes and increase of waist circumference (β = 1.62, 95% C.I. −2.63–5.88 for atypical MDD, β = −1.55, 95% C.I. −5.38–2.28 for melancholic MDD, β = −2.83, 95% C.I. −6.29–0.64 for unspecified MDD according to model 2).

Fasting glucose

After the exclusion of subjects treated with antidiabetic drugs, those with atypical and melancholic MDD revealed a steeper increase of fasting glucose levels during follow-up than never depressed individuals (model 1). Additional adjustments for baseline inflammation markers and adipokines (model 2) as well as change of waist circumference during follow-up (model 3) led to a moderate decrease of the β-estimate for atypical MDD, although baseline hs-CRP and leptin concentrations were positively, and IL-1β and adiponectin concentrations negatively associated with increase in fasting glucose levels. In contrast, the effect of melancholic MDD on glucose increase no longer reached the level of statistical significance after adjustment for increase of waist circumference. An additional analysis showed that, after adding the effect of the baseline homeostatic model assessment-insulin resistance index to model 1, this indicator of insulin resistance was associated with glucose level increase (β = 40; 95% C.I. 18–61; P < 0.001) at follow-up and also slightly decreased the estimate for atypical MDD (reduction of β for atypical MDD from 149 to 145). In contrast, eating behaviors had no effect on the size of the association between atypical and melancholic MDD and glucose level increase (β = 149 and 89, respectively, after adjustment for eating behaviors). None of the five criteria for atypical

Table 3. Change of cardio-metabolic characteristics during follow-up by depression status at baseline among Caucasians

| | Change during follow-up | | | | | | | |
| | Crude change | | | Model 1 | | Model 2 | | Model 3 | |
	Mean (s.d.)	β[a]	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
Waist circumference, cm (n = 2796)									
Depression status									
Atypical	4.6 (7.9)	**1.58****	**(0.60, 2.56)**	**2.35****	**(1.11, 3.58)**	**2.41****	**(1.19, 3.63)**	–	–
Melancholic	4.7 (8.0)	0.64	(−0.08, 1.35)	**1.36***	**(0.28, 2.45)**	**1.43****	**(0.36, 2.51)**	–	–
Unspecified	3.7 (7.1)	0.04	(−0.53, 0.61)	0.65	(−0.35, 1.65)	0.76	(−0.23, 1.75)	–	–
No MDD (ref.)	3.2 (6.3)								
IL-1β (cont.)	–	0.03	(−0.21, 0.26)	–	–	−0.09	(−0.37, 0.18)	–	–
Interleukin-6 (cont.)	–	0.11	(−0.12, 0.34)	–	–	0.08	(−0.18, 0.35)	–	–
Tumor necrosis factor-α (cont.)	–	0.10	(−0.13, 0.34)	–	–	−0.02	(−0.28, 0.24)	–	–
hs-CRP (cont.)	–	**0.63****	**(0.37, 0.90)**	–	–	**0.44****	**(0.18, 0.71)**	–	–
Adiponectin (cont.)	–	**−0.38****	**(−0.64, −0.12)**	–	–	**−0.33***	**(−0.59, −0.07)**	–	–
Leptin (cont.)	–	**1.09****	**(0.77, 1.42)**	–	–	**1.07****	**(0.74, 1.39)**	–	–
Fasting glucose, μmol l^{-1} (n = 2721)									
Depression status									
Atypical	502 (685)	**106****	**(32, 180)**	**149****	**(55, 244)**	**143****	**(49, 237)**	**131****	**(38, 225)**
Melancholic	329 (775)	35	(−20, 89)	**90***	**(6, 174)**	**95***	**(12, 179)**	79	(−4, 162)
Unspecified	394 (630)	13	(−31, 56)	64	(−13, 141)	76	(−1, 153)	70	(−6, 147)
No MDD (ref.)	383 (747)								
IL-1β (cont.)	–	−14	(−32, 4)	–	–	**−24***	**(−45, −3)**	**−24***	**(−45, −3)**
Interleukin-6 (cont.)	–	16	(−2, 34)	–	–	19	(−1, 40)	20	(−1, 40)
Tumor necrosis factor-α (cont.)	–	4	(−13, 22)	–	–	0	(−20, 20)	0	(−20, 20)
hs-CRP (cont.)	–	**58****	**(40, 76)**	–	–	**41****	**(21, 61)**	**40****	**(20, 60)**
Adiponectin (cont.)	–	**−36****	**(−56, −16)**	–	–	**−29****	**(−49, −9)**	**−29****	**(−49, −10)**
Leptin (cont.)	–	**46****	**(25, 67)**	–	–	**27***	**(4, 49)**	**26***	**(4, 48)**
Change of waist circumference (cont.)	–	**56****	**(38, 74)**	–	–	–	–	**53****	**(35, 71)**
HDL cholesterol, μmol l^{-1} (n = 2783)									
Depression status									
Atypical	−29 (253)	−33	(−70, 5)	−38	(−86, 9)	−36	(−83, 11)	−27	(−74, 19)
Melancholic	−8 (285)	−18	(−46, 9)	−34	(−76, 8)	−34	(−76, 7)	−26	(−68, 15)
Unspecified	0 (277)	−14	(−36, 8)	−28	(−67, 10)	−30	(−68, 9)	−24	(−62, 14)
No MDD (ref.)	3 (274)								
IL-1β (cont.)	–	3	(−6, 12)	–	–	1	(−10, 11)	0	(−11, 11)
Interleukin-6 (cont.)	–	−2	(−11, 8)	–	–	−2	(−13, 8)	−1	(−11, 9)
Tumor necrosis factor-α (cont.)	–	2	(−7, 11)	–	–	4	(−6, 14)	4	(−6, 14)
hs-CRP (cont.)	–	**−11***	**(−20, −2)**	–	–	−4	(−14, 6)	−4	(−14, 6)
Adiponectin (cont.)	–	0	(−10, 11)	–	–	0	(−11, 10)	−1	(−11, 9)
Leptin (cont.)	–	**−27****	**(−38, −17)**	–	–	**−24****	**(−35, −13)**	**−24****	**(−35, −13)**
Change of waist circumference (cont.)	–	**−38****	**(−47, −29)**	–	–	–	–	**−39****	**(−48, −30)**
Triglycerides, μmol l^{-1} (n = 2783)									
Depression status									
Atypical	54 (1012)	13	(−52, 79)	−14	(−97, 70)	−11	(−94, 73)	−23	(−106, 59)
Melancholic	−16 (735)	16	(−32, 64)	−15	(−89, 58)	−14	(−88, 59)	−27	(−99, 46)
Unspecified	40 (888)	17	(−21, 55)	−15	(−84, 53)	−11	(−79, 57)	−12	(−79, 55)
No MDD (ref.)	16 (940)								
IL-1β (cont.)	–	2	(−14, 18)	–	–	9	(−10, 28)	9	(−10, 28)
Interleukin-6 (cont.)	–	−12	(−27, 4)	–	–	**−20***	**(−38, −2)**	**−21***	**(−39, −3)**
Tumor necrosis factor-α (cont.)	–	3	(−13, 18)	–	–	−1	(−18, 17)	−1	(−19, 17)
hs-CRP (cont.)	–	**23****	**(7, 40)**	–	–	12	(−6, 30)	11	(−6, 28)
Adiponectin (cont.)	–	**−54****	**(−71, −36)**	–	–	**−49****	**(−67, −32)**	**−48****	**(−65, −30)**
Leptin (cont.)	–	**35****	**(17, 54)**	–	–	**28****	**(8, 47)**	**26***	**(6, 45)**
Change of waist circumference (cont.)	–	**76****	**(60, 92)**	–	–	–	–	**75****	**(59, 91)**
SBP, mmHg (n = 2364)									
Depression status									
Atypical	−1.2 (15.2)	−1.05	(−3.01, 0.90)	−1.75	(−4.23, 0.73)	−1.80	(−4.28, 0.69)	−2.00	(−4.48, 0.48)
Melancholic	0.2 (11.6)	−0.60	(−2.01, 0.81)	−1.31	(−3.46, 0.84)	−1.32	(−3.47, 0.83)	−1.46	(−3.60, 0.69)
Unspecified	−0.3 (12.7)	**−1.53****	**(−2.65, −0.41)**	**−2.34***	**(−4.31, −0.37)**	**−2.29***	**(−4.26, −0.31)**	**−2.22***	**(−4.19, −0.26)**
No MDD (ref.)	1.0 (12.4)								
IL-1β (cont.)	–	−0.23	(−0.68, 0.23)	–	–	−0.35	(−0.91, 0.21)	−0.35	(−0.90, 0.21)
Interleukin-6 (cont.)	–	−0.13	(−0.58, 0.33)	–	–	−0.05	(−0.59, 0.49)	−0.04	(−0.58, 0.50)
Tumor necrosis factor-α (cont.)	–	−0.01	(−0.47, 0.44)	–	–	0.09	(−0.43, 0.61)	0.09	(−0.43, 0.60)
hs-CRP (cont.)	–	0.27	(−0.20, 0.74)	–	–	0.18	(−0.33, 0.68)	0.15	(−0.36, 0.65)
Adiponectin (cont.)	–	−0.45	(−0.95, 0.06)	–	–	−0.38	(−0.89, 0.13)	−0.37	(−0.88, 0.14)
Leptin (cont.)	–	0.27	(−0.28, 0.81)	–	–	0.12	(−0.46, 0.70)	0.10	(−0.48, 0.68)
Change of waist circumference (cont.)	–	**1.15****	**(0.68, 1.61)**	–	–	–	–	**1.17****	**(0.71, 1.64)**

Abbreviations: CI, confidence interval; cont., continuous variable; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1β; MDD, major depressive disorder; OR, odds ratio; ref., reference group; SBP, systolic blood pressure; s.d., standard deviation. Model 1 adjusted for socio-demographic characteristics, length of follow-up, behavioral factors, comorbid disorders, early trauma, depression status at baseline and follow-up, medication at baseline and cardio-metabolic risk factors at baseline. Model 2 = model 1 additionally adjusted for inflammatory marker and adipokine concentrations at baseline. Model 3 = model 2 additionally adjusted for change of waist circumference. *P < 0.05, **P < 0.01, ***P < 0.001. [a]Bivariate associations adjusted for age, sex and cardio-metabolic risk factors at baseline. Bold values indicate statistical significance.

depression features were significantly associated with this metabolic outcome.

Regarding non-Caucasians both atypical MDD ($\beta = 448$, 95% C.I. 125–771, $P = 0.007$ according to model 3) and unspecified MDD ($\beta = 382$, 95% C.I. 120–644, $P = 0.003$ according to model 3) were associated with glucose level increase regardless of the number of adjustments.

HDL cholesterol, triglycerides and SBP

Regarding HDL cholesterol, triglycerides and SBP, except for an association between unspecified MDD and decrease of SBP, depression status was not associated with changes of these cardio-metabolic outcomes during follow-up regardless of the number of adjustments. In contrast, higher concentrations of interleukin-6 at baseline predicted a decrease in triglyceride levels during follow-up. Similarly, higher baseline adiponectin concentrations were associated with a decrease in triglyceride levels during follow-up, whereas leptin concentrations were associated with a decrease in HDL cholesterol and an increase in triglyceride levels. Among non-Caucasians, the melancholic subtype was associated with HDL cholesterol increase during follow-up ($\beta = 188$, 95% C.I. 15–361, $P = 0.033$ according to model 3).

Metabolic syndrome

A total of 522 Caucasian subjects met diagnostic criteria for the metabolic syndrome at baseline and were excluded from analyses regarding the incidence of this syndrome. Among the remainders, 375 subjects (16.5%) developed the metabolic syndrome during the follow-up. Table 4 reveals that atypical MDD at baseline was significantly associated with the incidence of the metabolic syndrome after adjustment for potential confounders (model 1) and after adding inflammation marker or adipokine levels (model 2). In addition, increased IL-1β and adiponectin levels reduced the incidence of the metabolic syndrome. None of the five criteria for atypical depression features were significantly associated with the incidence of the metabolic syndrome. Among non-Caucasians, none of the MDD subtypes were significantly associated with the metabolic syndrome.

DISCUSSION

To the best of our knowledge, the present community study is the first to assess the prospective associations of MDD subtypes with changes of specific cardio-metabolic characteristics and the incidence of the metabolic syndrome and the influence of inflammation marker and adipokine levels as well as eating behaviors on these associations. The main findings were that (1) the atypical MDD subtype, and only this subtype, is a predictor for a steeper increase and higher fasting glucose level as well as the incidence of the metabolic syndrome across a 5.5-year follow-up period; (2) the steeper increase of glucose levels in subjects with atypical MDD is not attributable to the increase of waist circumference, eating behaviors, inflammatory marker or adipokine concentrations but it is likely to be partially mediated by insulin resistance.

The finding that only atypical MDD was prospectively associated with metabolic characteristics confirms results from previous cross-sectional research[21,22,24] and further advocates for the subtyping of the heterogeneous depression diagnosis. This association pattern was similar for Caucasian and non-Caucasian participants. Moreover, together with the recent findings of a Dutch cohort study over 6 years,[26] our results demonstrate that the association between atypical depression and metabolic outcomes is not simply attributable to the occurrence of atypical depressive symptoms in subjects already exhibiting metabolic diseases, but to a strong prospective association between the atypical MDD subtype and metabolic outcomes. Interestingly, the Dutch and our study converge in observing persistently higher body-mass index or waist circumference and a higher prevalence of the metabolic syndrome in patients with atypical depression as compared to unaffected subjects even after more than half of the group no longer had MDD in the Dutch study and after adjustment for the effect of the occurrence of new depressive episodes during follow-up in our study. Also the observed association between unspecified MDD and decrease of SBP is compatible with cross-sectional findings of this Dutch study.[22]

The present study provides additional insight into the complex relationship between atypical depression and metabolic outcomes by suggesting the existence of two independent pathways. First, atypical MDD and the atypical depression symptom increased appetite were associated with a steeper increase of waist circumference, which persisted after remission of the depressive

Table 4. Incidence of the metabolic syndrome at follow-up by depression status at baseline (among Caucasians, $N = 2274$)

	Incidence of the metabolic syndrome						
		Crude			Model 1		Model 2	
Characteristics at baseline	%	OR[a]	95% CI	OR	95% CI	OR	95% CI
Depression status							
Atypical	25.6	**2.38*** **	**(1.55, 3.65)**	**2.56** **	**(1.35, 4.87)**	**2.49** **	**(1.30, 4.77)**
Melancholic	13.1	0.94	(0.65, 1.37)	1.49	(0.81, 2.75)	1.45	(0.78, 2.69)
Unspecified	15.1	1.06	(0.80, 1.40)	1.44	(0.84, 2.47)	1.44	(0.83, 2.49)
No MDD (ref.)	16.9	1 (ref.)		1 (ref.)		1 (ref.)	
IL-1β (cont.)	–	0.92	(0.81, 1.03)	–	–	**0.84***	**(0.72, 0.99)**
Interleukin-6 (cont.)	–	1.07	(0.96, 1.20)	–	–	1.04	(0.89, 1.22)
Tumor necrosis factor-α (cont.)	–	1.10	(0.99, 1.24)	–	–	1.02	(0.87, 1.19)
hs-CRP (cont.)	–	**1.63*** **	**(1.44, 1.84)**	–	–	1.06	(0.91, 1.23)
Adiponectin (cont.)	–	**0.65*** **	**(0.57, 0.74)**	–	–	**0.82***	**(0.70, 0.95)**
Leptin (cont.)	–	**1.98*** **	**(1.71, 2.29)**	–	–	1.19	(0.99, 1.44)

Abbreviations: CI, confidence interval; cont., continuous variable; hs-CRP, high-sensitivity C-reactive protein; IL-1β, interleukin-1β; MDD, major depressive disorder; OR, odds ratio; ref., reference group. Model 1 adjusted for socio-demographic characteristics, length of follow-up, behavioral factors, comorbid disorders, early trauma, depression status at baseline and follow-up, medication at baseline and cardio-metabolic risk factors at baseline. Model 2 = model 1 additionally adjusted for inflammatory marker and adipokine concentrations at baseline. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. [a]Bivariate associations adjusted for age and sex. Bold values indicate statistical significance.

episode.[25] Second, the present results suggest that, independently of an increase in appetite or obesity, atypical depression is also associated with glucose level increase, which is likely to ultimately lead to diabetes. Regarding mechanisms that could link atypical depression and metabolic outcomes, it is possible that the increase of appetite related to the depressed episode temporarily persisted during the follow-up period and thereby contributed to the increase of waist circumference even after the offset of the depressive episode, although the increase of waist circumference in these subjects was not attributable to particularities in eating behaviors as assessed at the follow-up evaluation. However, although among the atypical depression symptoms only increased appetite significantly predicted increase of waist circumference, our data suggest that other symptoms also contribute to this metabolic outcome given that the association between atypical MDD and increase of waist circumference remained significant after adjustment for the effect of increased appetite. In contrast to increase of waist circumference, the symptom increased appetite was not associated with increase of glucose level during the follow-up or any other metabolic outcome. Our data also revealed that lifestyle factors including physical inactivity, smoking or alcohol consumption, early physical or sexual abuse, comorbid psychiatric conditions, antidepressants or other potentially weight-increasing medication hardly explain the associations between atypical MDD and waist circumference or glucose level increase. The same was true for baseline adipokines and inflammatory markers, although adipokines were predictive for changes in most metabolic outcomes and the hs-CRP was a significant predictor of glucose level increase. In contrast, insulin resistance, which was significantly associated with both atypical MDD at baseline and glucose level increase during the follow-up, is likely to be a modest mediator of the association between atypical MDD at baseline and subsequent glucose level increase, whereas eating behaviors were not mediators of this association in our data. The independence of glucose level increase from eating behaviors was further evidenced by the fact that this metabolic outcome was not associated with the atypical depression symptom increased appetite. Other mechanisms that could underlie the association between atypical MDD and metabolic outcomes are the functioning of the HPA axis, which however was not found to be altered in subjects with atypical depression in a previous study,[22] and shared genes. Regarding obesity, the FTO gene, which could be related to atypical depression[51] has been shown to selectively favor weight gain in depressed subjects.[52] Other genes may link atypical depression and glucose level changes despite previous negative evidence from twin and GWAS studies, which however relied on overall depression diagnoses.[53,54]

Our findings should be considered in the context of several limitations. First, 459 participants (13%) who did not participate at the follow-up visit had to be excluded from our analyses. However, although non-participation was associated with a less healthy lifestyle, differential bias is unlikely as non-participation did not differ across diagnostic groups. Second, the non-Caucasian sample was relatively small and information on baseline adipokine levels was missing. Third, data were based on an urban sample in Switzerland, which may partially explain the high prevalence of MDD. However, it is unlikely that the specific characteristics of this sample significantly affected the assessed prospective associations between MDD subtypes, inflammation marker or adipokine levels and metabolic characteristics. Fourth, our assessment of physical activity only partially reflected daily activity and energy expenditure. Fifth, we could not test the effects of cortisol because this variable was not assessed at baseline. Sixth, data on carbohydrate and caloric consumption were only available for the follow-up but not the baseline evaluation.

In conclusion, our results support differential biological profiles of MDD subtypes in both Caucasians and non-Caucasians by demonstrating a strong, prospective association restricted to the atypical subtype and glucose level increase, which in conjunction with the independent increase of waist circumference, may ultimately expose these subjects to elevated cardiovascular vulnerability and other diseases associated with metabolic dysregulations. This vulnerability is likely to be particularly high among subjects with atypical MDD and elevated levels of inflammation. Accordingly, the prevention and treatment of metabolic consequences in patients with atypical MDD deserve particular clinical attention. Further research including genotypic and HPA-axis data needs to determine to which degree these variables account for the steeper waist circumference and glucose increase among subjects with atypical MDD. In contrast, metabolic mechanisms hardly explain the potentially elevated cardiovascular risk among subjects with other subtypes of MDD. Hence, other biological pathways such as the HPA-axis need to be studied in these subjects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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1034

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