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WHEN THE HEART ACHES: ATYPICAL FEATURES IN DEPRESSION ARE A HALLMARK OF AN INCREASED CARDIO-METABOLIC RISK

Lasserre Aurélie

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WHEN THE HEART ACHES: ATYPICAL FEATURES IN DEPRESSION ARE A HALLMARK OF AN INCREASED CARDIO-METABOLIC RISK

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par

Aurélie LASSERRE

Médecin diplômée de la Confédération Helvétique

Jury

Prof. Brigitte Santos-Eggimann, présidente et répondante MD-PhD
Prof. Martin Preisig, directeur de thèse
Prof. Philippe Conus, expert
Prof. Femke Lamers, experte

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Directeur·trice de thèse	Monsieur Prof. Martin **Preisig**
Co-Directeur·trice de thèse	
Répondant·e	Madame Prof. Brigitte **Santos-Eggimann**
Expert·es	Monsieur Prof. Philippe **Conus**
	Madame Prof. Femke **Lamers**

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Madame Aurélie LASSERRE

Docteur en médecine de l'Université de Lausanne

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When the heart aches:
Atypical features in depression are a hallmark of an increased cardio-metabolic risk

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pour Le Doyen
de la Faculté de Biologie et de Médecine

B. Santos-Eggimann

Prof. Brigitte Santos-Eggimann

All the fruits of scientific work, in epidemiology or other disciplines,
are at best only tentative formulations of a description of nature,
even when the work itself is carried out without mistakes.

Kenneth J. Rothman, 2005

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Résumé

La dépression et les maladies cardiovasculaires représentent deux enjeux majeurs de santé publique en raison du grand nombre de personnes atteintes et de leur impact sur la qualité de vie. Ces troubles coexistent chez les mêmes individus plus souvent que ce que le hasard voudrait, pourtant les mécanismes qui sous-tendent cette association ne sont que peu compris. Compte tenu de l'hétérogénéité de la dépression, l'évaluation détaillée des symptômes, de la temporalité et des sous-types de la dépression semble être une piste vers une meilleure compréhension de ces mécanismes. Dans ce contexte, les objectifs de ce travail étaient (1) d'examiner l'effet des différents sous-types de dépression sur les facteurs de risque cardio-vasculaires métaboliques et (2) d'évaluer la mortalité associée à différentes caractéristiques de la dépression. Parmi les habitants de Lausanne âgés de 35 à 66 ans, un échantillon randomisé de 3719 personnes (étude PsyCoLaus) a accepté de se soumettre à des investigations physiques et psychiatriques étendues, cela à deux reprises à cinq ans d'intervalle. Des modèles linéaires généralisés ont permis d'analyser ces données. Les participants ayant présenté une dépression atypique au début de l'étude prenaient plus de poids, augmentaient plus leur tour de taille, et présentaient un taux plus élevé d'obésité et de syndrome métabolique à la fin du suivi que les participants sans dépression, indépendamment d'un grand nombre de facteurs confondants. Ce même groupe de participants a aussi présenté une plus grande augmentation de sa glycémie à jeûn, indépendamment de sa prise de poids. Enfin, les sujets qui présentaient une dépression lors de la première investigation étaient plus à risque de décéder durant les cinq années du suivi que les autres. Ces résultats soulignent la nécessité pour le chercheur comme pour le clinicien, d'évaluer en détail les divers aspects de la dépression, en particulier les caractéristiques atypiques, et de considérer leurs possibles conséquences métaboliques.

Summary

Depression and cardiovascular diseases represent two major issues of public health due to the large number of people affected and their heavy consequences on quality of life. They are known to coexist in the same individuals more frequently than what would be expected by chance, but the mechanisms underlying this association still need to be elucidated. Given the heterogeneity of depression, studying symptoms, courses or subtypes in detail rather than depression as a whole is likely to be a more promising approach to better understand these mechanisms. Accordingly, the aims the present work were to (1) assess the prospective associations between depression subtypes at baseline and the subsequent changes in metabolic cardio-vascular risk factors, and (2) determine the association of clinical and course characteristics of depressive disorders with all-cause mortality over a 5-year follow-up period. A randomly selected sample of 3719 persons aged 35 to 66 years from the population of Lausanne (PsyCoLaus) agreed to participate in thorough physical and psychiatric assessments at baseline and, five years later, at a follow-up visit. Generalized linear models were used. Participants with the atypical subtype of depression at baseline, compared to the never depressed, presented a higher increase of body mass index, waist, as well as a higher incidence of obesity and metabolic syndrome after five years, independently of a large range of known possible confounders. This same group had also a higher increase of fasting plasma glucose. Moreover, survival analyses showed that participants with a current episode of depression at baseline were at a higher risk of dying during the five following years than the never depressed. These results emphasize the need for assessing in detail the various characteristics of depression, in particular the atypical subtype, in research as well as in clinical settings and to consider their metabolic consequences.

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Introduction

Depression and cardiovascular diseases, two public health priorities

Worldwide, 350 million people have been affected by depression once in their lives, which causes great suffering and is accompanied by difficulties at work, at school and in the family and can lead to suicide at its worst. Moreover, treatment is typically provided many years after the disorder begins.[1] Such important consequences and the high prevalence of depression in the population make it a leading cause of disability worldwide.[2] Thereby, depression is a major contributor to the global burden of disease[3] (the collective disease burden produced by all diseases around the world). In Switzerland, about one person out of five suffers from depression during his or her life. The latter causes many work disabilities and is a frequent cause of early retirement. Thus depression is the mental disorder with the largest burden of disease in Switzerland[5] and one of the leading causes of disability-adjusted life years in Switzerland (blue arrow on Figure 1).

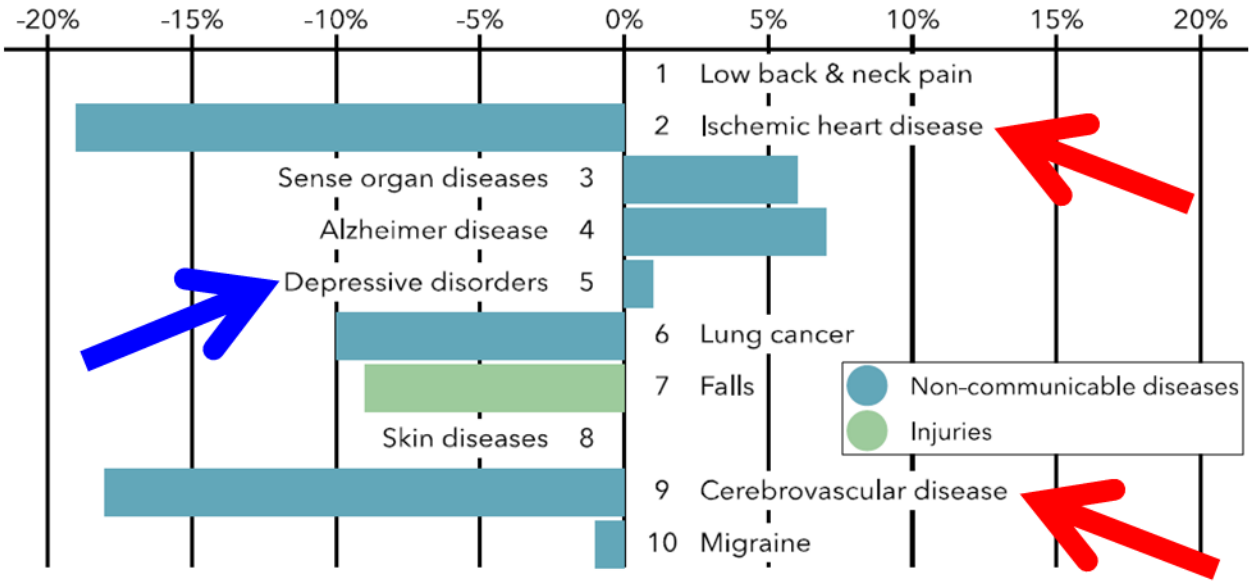

Figure 1. Leading causes of lost years of healthy life due to premature death or disability in 2015 in Switzerland and percent change, 2005-2015. Institute for Health Metrics and Evaluation (IHME). Seattle, WA: IHME, University of Washington, 2016. Available from http://www.healthdata.org/switzerland. (Accessed 06.02.2017)

Figure 1 also shows that ischemic heart disease and cerebrovascular disease (red arrows) have the second and ninth, respectively, most heavy burden of disease in Switzerland. Ischemic heart disease includes angina, myocardial infarction and sudden cardiac death, whereas cerebrovascular disease includes all types of stroke. Worldwide, ischemic heart disease and stroke are first and third, respectively, in terms of lost years of healthy life (disability-adjusted life years).[6] This group of diseases, called cardiovascular diseases (CVD), are very frequent and can be major debilitating diseases. A large proportion of CVD are caused by atherosclerotic disease. This is a complex pathological process in the blood vessels that develops over many years. In that process, deposits of fatty material and cholesterol are deposited inside the blood vessels and progressively narrow the lumen, making it hard for blood to flow through. Eventually, this deposit can rupture, triggering the formation of a blood clot and totally obstructing the vessel. If the blood clot develops in a coronary artery, it can cause a heart attack, if it develops in the brain, it can cause stroke. Factors that promote this process are known as cardiovascular risk factors (CVRF). Behavioral CVRF include tobacco use, physical inactivity, unhealthy diet (rich in salt, fat and calories) and harmful use of alcohol. Metabolic risk factors include high blood pressure (hypertension), high blood sugar (diabetes), dyslipidemia and overweight or obesity. Lipids profile include low density lipoprotein (LDL) cholesterol, often called "bad" cholesterol, high density lipoprotein (HDL) cholesterol, also called "good" cholesterol, and triglycerides. In general, a lower LDL cholesterol level is better for vascular health, whereas HDL cholesterol protects against vascular disease and high trigycerides increase the risk of atherosclerosis. Total blood cholesterol is a measure of LDL and HDL cholesterol.[7] Other risk factors include poverty, low educational status, age, sex and familial history.[7 8] A number of cohort studies in recent years have contributed to the growing body of evidence that depressive disorders and CVD coexist in an individual more frequently than what would be

expected by chance. However, the mechanisms underlying this association are far from being understood by current research.[9-13]

Some historical landmarks of the definition of depression

Despite the fact that depression is very frequent and has a major impact on general population health, this disorder is yet poorly understood. Depression, by its intimate nature, is a very heterogeneous disorder with a highly variable course, inconsistent response to treatment, and no established mechanism.[14] However, similar states to depression have always been described.

The secular history of depression evolved with that of humankind. In Ancient Greece, when four humors were thought to influence temperament and health, the black bile (*melaina chole* in Greek) was the essence of the melancholic temperament, depicted as cold, dry, sad and passive. Hippocrates, in the 4th century B.C., characterized melancholia as a disease due to an excess of this humor in his Aphorisms (section VI): "If a fright or despondency lasts for a long time, it is a melancholic affection". Avicenna developed this humoral theory further in the 9th century and the humors medical paradigm lasted for centuries.[15]

Figure 2. Acedia, engraving by Hieronymus Wierix (1553-1619)

During the same period, Evagrius of Pontus described various form of temptation met by the ascetic monks living a solitary life. He listed eight of them and described acedia as the most troublesome of all of evil thoughts. The demon of adecia threatened the monks until the Middle Age. Acedia was a torpor, an absence of caring, a lack of attention to daily tasks, a boredom and an overall dissatisfaction with life. Somatic signs were also described, such as sleepiness, weakness in the knees or fever.[16] It was then incorporated in the deadly sin of sloth.

In 1883, Robert Burton wrote a large medical textbook, The Anatomy of Melancholia, where he depicted, over 900 pages, the causes, symptoms and cures of "common" and "complex" melancholia. Various theories were included in this book regarding the possible origin of depression. During the 18th century, the humoral theory of melancholia was increasingly challenged. Heamodynamic theories emerged; a thickening of the blood, resulting in sluggish circulation within the brain was thought to explain depressive states. Melancholia was also used to describe a much broader spectrum of mental disorders, anxiety disorders, psychoses or

obsessive-compulsive disorder were encompassed in its definition.[17] More and more confusion was present around the concept of melancholia. In an attempt of clarification, new terms were created to indentify the 'emotional insanities': tristimania (Benjamin Rush, 1745-1815), lypemania (Esquirol, 1772-1840), circular madness (Jean-Pierre Farlet, 1795-1870).[15]

The clinico-anatomical view developed during the early 19th century and the term depression was introduced, derived from the latin *deprimere*. This suggested both a physiological and metaphorical lowering of emotional function.[18] Even though the equivalence between melancholia and depression was debated.[17] Emil Kraeplin (1856 – 1926) introduced a dichotomous view of mental disorders, where mood disorders were separated from "dementia praecox" (schizophrenia). In this model, he also distinguished depression, which represented one pole of his manic-depressive insanity from melancholia, which involved depression associated with fear, agitation, self-accusation and hypochondriacal symptoms.[19] He also brought the concept of endogenous and exogenous depression.

The introduction of electroshocks (1938) added a need to distinguish depressive states that would respond to this treatment or not. Two approaches competed; the first was the melancholia-electroshock model, whereby the electroshock was specific to a delimited pathology, the melancholia, supposed to be endogenous. The second model defended that electroshock would act similarly on all depressives pathologies, considered as a continuum.[15 20] In 1917, Freud published his essay *Mourning and Melancholia*, in which he used a psychological approach and explained melancholia as the reaction to a loss that would take place in the unconscious mind. The notion of neurosis was also introduced and depression became the result of an intra-psychic conflict. He describes self-critical and self-hating attitudes, which have characterized depressive states in the 20th century.[17]

In 1952, the American Psychiatric Association published the first edition of the *Diagnostic and statistical manual of mental disorders* (DSM), a classification system consistent with the concepts of that time. The depressive reaction was included within the psychoneurotic disorders.[21] It was also in the 50s that the first antidepressant drugs were discovered, a tricyclic agent called imipramine was widely used at that time. This brought a new approach to classify depression, based on psychopharmacological effects.[17] The recognition of endogenous depression lost its interest because response to treatment was not possible to predict according to clinical observations of depression.[15]

Shortly after the introduction of imipramine, another molecule was found and used as an antidepressant, a monoamine oxidase inhibitor (IMAO) called iproniazid. In 1959, in an attempt to organize depression around the psychopharmacological effect, West and Dally[22] defined a group of patients with specific symptoms of depression that would respond better to iproniazid than to other forms of treatment (tricyclic or electroconvulsive therapy). These supposedly better responders were described as having an atypical depression. West and Dally described depressions with "symptoms masked by phobic anxiety", "anxious and overreactive" and "fatigue" as a prominent complaint. Those patients did not present the "classical endogenous" symptoms of early morning awakening, self-reproach, and weight loss.[22] Thus, the term atypical depression was introduced and afterwards, often used in opposition to endogenous or melancholic depression.[23] With the introduction of a new class of antidepressant drug, the selective serotonin reuptake inhibitors, as first-line antidepressants for all types of depressions, the interest for the atypical subtype diminished as well.[24]

In the sixties, many approaches and concepts of mental disorders coexisted, to the point that the same term would describe many different states. The prevalence of mental disorders varied

considerably across the UK and the US; a high frequency of schizophrenia and a low frequency of affective disorders were observed among mental hospital admissions in New York compared to those in London. The US/UK Diagnostic Project could show that this was largely due to the diagnostic practice of the psychiatrists.[25] In order to unify the definition of mental disorders to better examine them across different communities, the third edition of the DSM was developed and published in 1980. Standardized diagnostic criteria were formulated; psychoanalytic (the concept of neurosis for example), physiologic or other etiological views were abandoned. The term Major depressive disorder (MDD) was introduced and defined as a cluster of symptoms (5 out a list of 9) during a period of time with impaired functioning.

However, even with the DSM definition, depression called MDD encompasses a wide variety of disorders, in terms of symptomatology, duration or severity. To refine the diagnosis of this very heterogeneous disorder, subtypes specifiers were also defined. The old idea of melancholia was introduced in the DSM-III as a specifier (melancholic features).[15] In the fourth version of the DSM, published in 1994, atypical depression subtype was formally recognized as an "episode specifier" as well.[23]

Mental health has a long history of marginalization and the enormous gap in resources across economic, social and scientific domains persists.[4] The recognition of mental health as an important contributor to global health emerged only in the 1990s, when a population health metric was introduced, the disability-adjusted life years, which encompassed both years of life lost and years living with disability, and thereby the measurement of the burden of disease became possible. It was only in 2001 that the World Health Organization (WHO) published its first Mental Health Atlas and in 2013 that the WHO's Comprehensive Mental health Action Plan was adopted by the World Health Assembly. We are thus confronted with a paradoxal situation,

whereby epidemiological studies describe the burden of depression as one entity, but whereby clinical practice and research shows that depression is a heterogeneous disorder, difficult to characterize.

Major depressive disorder, atypical and melancholic features, according to DSM-5

In the 5th version of the DSM, published in 2013, Major depressive disorder (MDD) is defined by a clinically significant distress or impairment in social, occupational or other important areas of functioning during at least 2 weeks, with the presence during this period of at least five symptoms including: depressed mood; loss of interest or pleasure (at least one of the latter two must be present); significant weight loss or gain; insomnia or hypersomnia; psychomotor agitation or retardation; fatigue or loss of energy; feelings of worthlessness or excessive guilt; diminished ability to think or concentrate; thoughts of death, suicidal ideation or suicide attempts.

Figure 3. Pablo Picasso, Woman with a Book, 1932 © Estate of Pablo Picasso, 2017, ProLitteris, Zurich

Atypical features are diagnosed when mood reactivity (mood brightening in response to events)

and two of the following four symptoms are present during the depressive episode: significant weight gain or increased appetite, hypersomnia, leaden paralysis of limbs and a long-standing pattern of interpersonal rejection sensitivity. Contrary to what the term atypical suggests, this subtype is frequent with a prevalence of 15 to 29% among depressives.[24] This subtype is known to be more frequent among women.[24]

Melancholic features are defined as the presence of loss of pleasure in all activities or lack of reactivity to usually pleasurable stimuli and three of the following symptoms: distinct quality of depressed mood, depression worse in the morning, early-morning awakening, marked psychomotor agitation or retardation, significant anorexia or weight loss and excessive guilt. The prevalence of this subtype varies across studies between 32 and 46%.[26 27] It is associated with a more severe form of depression in some studies,[26] but not all.[28]

Depression and cardiovascular diseases, a chicken-or-egg dilemma

The idea that life stressors can adversely impact the cardiovascular system is not new and is related with cultural beliefs about the role of the heart.[29] The high mortality associated with mental disorders has been studied for several decades,[30] in particular mortality associated with depression.[30-36] Indeed, a meta-analysis of community studies found a 1.8 times elevated risk of mortality in depressed compared to non-depressed subjects.[32] This is due to a various range of mortality causes,[37] but cardiovascular mortality among depressives is one of the best demonstrated.[10 38] During the last decades, a number of cohort studies have shown an association between depressive disorders and CVD.[9-13] However, the mechanisms and temporal sequence underlying this association remain largely unspecified.[10 13 39] Three possible hypotheses can be put forward (Figure 4):

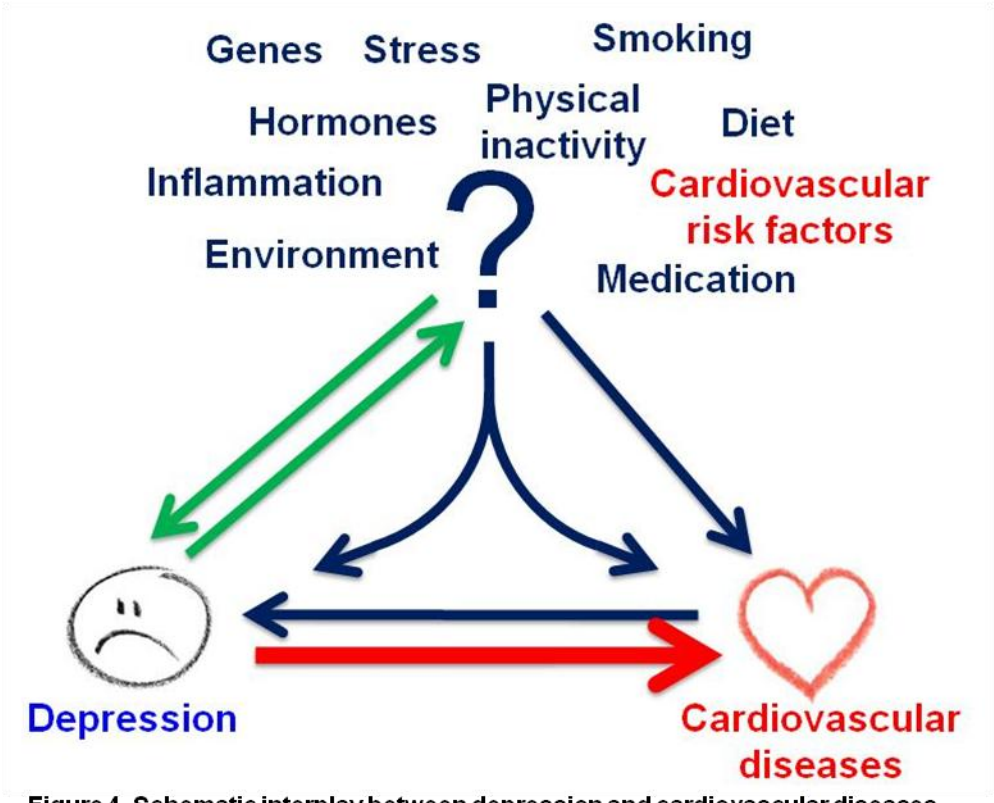

Figure 4. Schematic interplay between depression and cardiovascular diseases

- CVD increases the risk of developing depression. Indeed, the rate of depression is roughly threefold higher among patients with coronary artery disease than in the general population.[13 40]
- The reverse pathway is also presumed. Depression was shown to be a significant and independent risk factor for the development of cardiac disease, with a relative risk of 1.6 in depressed patients compared to the never depressed.[11 41] Many possible mediators of this causal pathway have been postulated, among them behavioral or metabolic CVRF or inflammation. A simple example is that depression is presumed to increase the risk of smoking,[42] which in turns increases the risk of developing CVD.
- Finally, CVD and depression might share a common etiological factor, such as genetic or environmental factors, meaning that no causal association would exist between depression and CVD. Among examples, environments conducive to physical inactivity[7 43] or childhood maltreatment[44 45] can be cited to be potential etiological factors of depression as well as CVD.

As depression and CVD both have multifactorial etiologies, it is probable that the three above pathways may be present at the same time. The above schema represents these three main hypotheses. Noteworthy, many more associations are possible in reality, because each of the possible confounding factors can interact with one another. Thus, the investigation of the whole picture goes far beyond the present work. Therefore, I will focus here on one direction of this potential causal association: how depression contributes to CVD onset in initially healthy individuals (red arrow on Figure 2).

Association or causation?

In the above diagram, the arrows represent causation (*is it depression which causes CVD or the reverse?*), however, we will further assess associations and not causations. This needs some further clarification. In everyday life, we observe that an action has a specific and immediately apparent effect and this is sufficient to consider this action as the *cause* of the effect. In scientific research, proof needs to be brought before affirming such an allegation. Many philosophers and scientists have worked on the process of scientific reasoning and the debate is still ongoing. A 18th-century philosopher, David Hume, even made the observation that proof was impossible in empirical science. Today, this observation has not been invalidated. In epidemiology, as in other disciplines, we use models which try to catch reality at its best, but which will always miss a part of it. This is particularly true when trying to demonstrate a causal association.[46] In the practice of epidemiology, a common definition of cause is needed to be adopted to further study the phenomena. In this purpose, Hill proposed a set of criteria in order to distinguish causal from noncausal associations: (1) strength, (2) consistency, (3) specificity, (4) temporality, (5) biological gradient, (6) plausibility, (7) coherence, (8) experimental evidence, and (9) analogy.[47] These criteria are only a help in the maze of the understanding of complicated associations. They must be applied with the goal of obtaining a quantified evaluation of the total error that afflicts the study, including errors induced by the study design, information acquisition and uncontrolled confounding and other sources of bias.[46] Statistical models assess whether an association is probable to exist or not, but they do not assess its causal nature. Causality can only be suspected after a careful assessment of all available information.

Potential mechanisms of the association between depression and cardiovascular diseases

Several mechanisms have been implicated in the association between depression and CVD. Inflammatory cytokines are associated with atherosclerotic plaque formation, progression and rupture, and are predictive of cardiovascular mortality and disease progression in healthy individuals.[13 48 49] Depression has also been associated with an inflammatory state, assessed by increased levels of cytokines, in some studies.[13 50] Moreover, the association between depression and cardiovascular mortality has been shown to be reduced by inflammatory markers in two studies, suggesting a small contribution to the effects of depression on cardiac events.[13] Thus, inflammation seems to play a role in the association between depression and CVD, but once again, the mechanism is not clear.

Abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis may also play a role in the connection between depression and CVD. Indeed, depression or chronic stress has been associated with hyperactivity of the HPA-axis,[51] and higher cortisol levels across various body fluids.[12 52] Again the role played by the HPA-axis dysregulation in the association between depression and CVD is still to be understood. Autonomic dysfunction, by an overstimulation of sympathetic nervous system and an increase of circulating catecholamines (adrenaline and noradrenaline) has also been suggested to be a possible link between depression and CVD.[53]

Behavioral factors, such as adherence to treatment, completion of rehabilitation programs or stress reduction might also be involved in the depression-CVD association.[13] Medication for depression may also present an adverse effect on cardiovascular health.[54] Many other mechanisms have been proposed in this highly complex association between depression and CVD. Among the frequently cited, endothelial dysfunction and prothrombic state can be mentioned.[13]

Finally, a pathway between depression and CVD would be that depression increases the chance of developing CVRF, which have a well known effect on CVD.[7] However, CVRF could also be a confounding factor in the association between depression and CVD (Figure 2, green arrows). Thus, assessing the association between depression and CVRF is of first importance in the understanding of the association between depression and CVD. Indeed, if the association between depression and CVD has been repeatedly shown, the association between depression and CVRF is still under discussion.[55]

Depression and cardiovascular risk factors

Cardiovascular risk factors can be divided into behavioral and metabolic. Among the behavioral CVRF, we find tobacco use, physical inactivity, unhealthy diet (rich in salt, fat and calories) and harmful use of alcohol. Metabolic risk factors include high blood pressure (hypertension), high blood glucose (diabetes), high cholesterol or triglycerides (dyslipidemia) and overweight or obesity.

The bidirectional link between depression and tobacco use has been repeatedly shown.[56] It seems that alcohol use disorders increase the risk of depression rather than the converse.[57] The association between physical activity and depression has been far less studied, but some studies reported a protective effect of physical activity on depression,[58 59 43] and a few others showed that depression could prevent from engaging in physical activity.[60 61] Less is known about the association between depression and diet. A recent study of 1003 Finnish men found that a healthy diet was associated with a lower rate of depression on cross-sectional and prospective analyses[62] and another study found an association between severity of depression and poorer diet quality among 161 women.[63]

Among the metabolic CVRF, the most studied is obesity. Indeed, a meta-analysis on 17 cross-sectional studies found a positive association between depression and obesity, more marked among women.[64] Similar results were found between depression and abdominal obesity.[65] Two meta-analyses on longitudinal studies found that obesity and overweight at baseline increased the risk of onset of depression, but results on baseline depression predicting overweight or obesity were more conflicting.[66 67] Depression was also shown to be prospectively associated with a higher risk of hypertension in a meta-analysis of nine studies, but the effects of other confounding factors could not be excluded.[68] Depressive symptoms have also been associated with a higher risk of diabetes in various studies, [69-71] but this association disappeared after taking possible confounding factors into account.[69] The reverse association has been observed too.[69 72] Finally, adverse lipoprotein patterns have been associated with depression in a meta-analysis, but the strength of the association diminished after adjustment for lifestyle variables.[73] However, another meta-analysis found lower total cholesterol levels in subjects with depressive symptoms versus controls.[74] In order to have a global picture of the above metabolic risk factors, the metabolic syndrome, a cluster of metabolic CVRF, is frequently used. The metabolic syndrome has several definitions, but more frequently, it is diagnosed when someone presents three out of five metabolic dysregulations at the same time, including elevated blood pressure, abdominal obesity, elevated plasma fasting glucose, increased plasma triglycerides and decreases in plasma HDL-cholesterol.[75] The metabolic syndrome is well known to predispose to CVD and diabetes.[76] [77] A longitudinal bidirectional association was found in a recent meta-analysis between depression and the metabolic syndrome.[78] In this meta-analysis, Pan et al. showed a prospective bidirectional association, nine cohort studies had examined the metabolic syndrome predicting depression and four studies the converse. A more recent study examined the bidirectional association of each of the components of the metabolic syndrome with depression, and found that

elevated depressive and anxiety symptoms were associated with poorer metabolic syndrome component outcomes, and most consistently with waist circumference and triglycerides, whereas there was no evidence that baseline metabolic syndrome components predicted psychopathology outcomes at follow-up.[79]

Similarly to the association between depression and CVD, the association between depression and CVRF could be explained by three different hypotheses. First, CVRF could increase the risk of developing depression.[69 78] Second, the reverse pathway could be presumed. Third, CVRF, and depression could share a common etiological factor, such as genetic or environmental factors. Moreover, the dysregulations hypothesized in the depression-CVD association (Figure 4), for example autonomic, HPA-axis, metabolic or immune-inflammatory dysregulation could also interfere in the association between depression and CVRF.[78 80]

The hypothesis of biologically different subtypes

Subtyping major depressive disorder has regained interest since differences in biological profiles have been observed.[50 80-84] It has been hypothesized that depression subtypes were differently associated with biological mechanisms: the atypical subtype could be more strongly related to metabolic dysregulation and inflammation up-regulations and the melancholic subtype to dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis.[81-83 85] Cross-sectional research has provided support for associations between atypical depression and obesity markers,[86-88] subjects with these features had a higher body mass index (BMI) than other depressives or never depressed subjects.[27 87 89 90] However, the cross-sectional design of three of these studies[27 87 89] impeded drawing conclusions regarding the direction of causality, whereas one prospective population-based study revealed a trend for a positive association between atypical depression and the average rate of weight gain over 20 years.[90] Moreover, the large majority of previous

studies assessing the association between depression and obesity are restricted to using BMI as an adiposity measure, although recent data suggest that waist circumference is more strongly associated with the risk of CVD than BMI[91] and that body fat percentage could be an independent risk factor for mortality.[92] The atypical subtype of MDD has also been shown to be associated with diabetes[87] or fasting glucose[88] and triglycerides[88 93] but no prospective data are available regarding this association. A cross-sectional association between metabolic syndrome and atypical depression has been shown in three studies, but none have shown a longitudinal association or specific association between atypical features and components of the metabolic syndrome.[87 88 94] Moreover, it has not yet been tested to which degree 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,[88 95 96] which may predispose to CVD and mortality,[13 48 49] 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,[97] has recently been found to be elevated in patients with atypical depression, most likely due to leptin resistance.[98] Adiponectin, an adipocyte-secreted protein with insulin-sensitizing, antidiabetic, anti-inflammatory and antiatherogenic properties,[99] has recently been shown to have a antidepressant-like effect and might also be implicated in the depression-CVD metabolic pathway.[100] Finally, atypical depression has been associated with higher levels of inflammatory markers in some recent studies,[88 95 96] but not after adjustment for socio-demographic characteristics, psychotropic medication and cardiovascular risk factors.[101]

Concerning the HPA-axis dysregulation, patients with melancholia seem to have an activated corticotrophin releasing hormone (CRH) system, whereas patients with atypical depression had a down-regulated hypothalamic-pituitary adrenal (HPA) axis and CRH deficiency.[85 86 88 102] These results need however to be taken with caution because atypical and melancholic depression were defined according to various definitions and compared with various control groups. Lamers and al. used a latent class analysis approach among chronically depressed participants,[88] Cizza and al. used DSM-IV definitions of subtypes of depression,[86] whereas Kaestner and al. compared melancholic versus non-melancholic.[85]

In a recent review,[80] Brenda Penninx summarized current knowledge about the clinical, biological and pathophysiological differences between the melancholic and atypical subtypes of depression (Figure 5). However, it must be pointed out that the articles on which this review was based, did not use the DSM definition of the subtypes, but the results of a latent class analysis performed on a clinical sample of depressives. In this definition, melancholic and atypical depression were the two most severe groups (among three) of depressives and were distinguished solely on the basis of neurovegetative symptoms (appetite, weight and sleep).

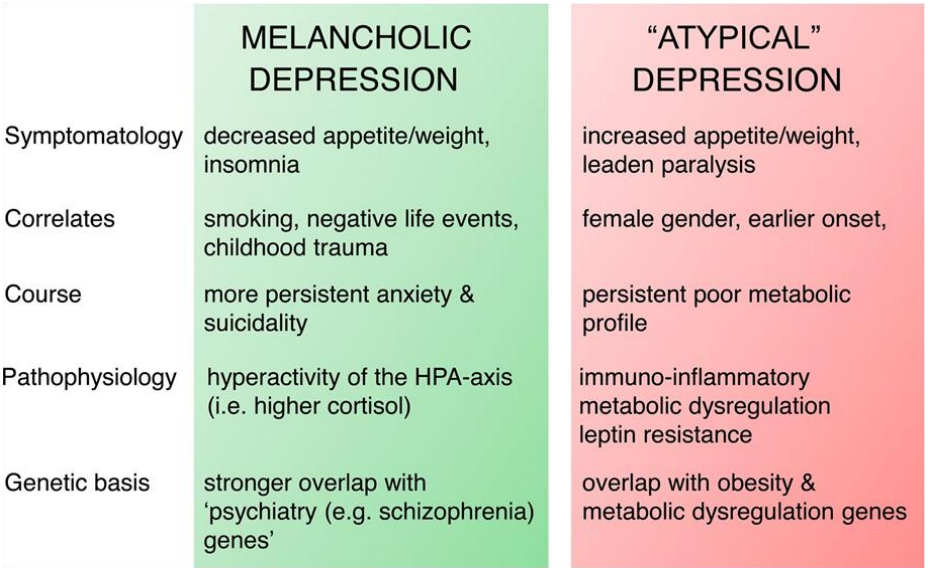

Figure 5. Summary of evidence for existence of depression subtypes with differential clinical and pathophysiological profile. Reprinted from Neuroscience and Biobehavioral Reviews, Volume 74, March 2017, Penninx BW, Depression and cardiovascular disease: Epidemiological evidence on their linking mechanisms, 277–286, ©2017, with permission from Elsevier.

Limitations of current research

In the literature about the associations between depression and CVRF, important variance across studies and contradictory findings, has been observed. [6267 68] This heterogeneity across studies could be due to different study designs, sample sizes, analysis strategies or participant characteristics. A frequently reported limitation of these studies is the inadequate adjustment for potential confounding. [59 69 78 103] For example, in their meta-analysis on longitudinal studies about the association between depression and obesity,[66] Luppino et al. were not able to adjust for potential covariates other than sex and age. None of the included studies reported on factors such as family history, hormonal status or use of medication. Another example is the meta-analysis about the association between depression and hypertension of Meng et al.,[68] where studies adjusted for psychological factors, exercise and smoking had a lower pooled relative risk than studies without adjustments for these confounders. Finally, in a large-scale study, Van Reedt et al. found that currently depressed subjects had significantly lower mean HDL cholesterol and higher triglyceride levels compared to subjects with a remitted depression and healthy controls. However, these differences disappeared after adjustment for smoking, alcohol use and BMI.[73]

Another important source of variance across studies is the diverse instruments of measure used.[33 67] Depression can be assessed with depressive symptom scales (e.g., Centers for Epidemiologic Studies Depression Scale (CESD) or Geriatric Depression Scale (GDS)), structured or semi-structured diagnostic interviews (e.g., Diagnostic Interview Schedule (DIS) or Structured Clinical Assessment for Neuropsychiatry (SCAN)), or psychiatric diagnoses. Most epidemiological studies use depression rating scales. Depression rating scales are only rough indicators of clinical depression,[104] which hardly allow characterization into depression subtypes and do not take the frequent occurrence of comorbid mental disorders or past psychopathology

into account. Indeed, depression is classically episodic and fluctuating in its course and the severity of symptoms at one time point is not the optimal way of capturing the longitudinal burden of illness. Thus capturing depression with more precision represents a challenge for modern psychiatric epidemiology.[105] In their meta-analysis, Pan et al. had found four studies which had examined depression predicting the metabolic syndrome. Among those four studies, only one used a direct diagnostic interview (429 women aged 42-52 years).[78] In their meta-analyses of the association between diabetes and depression, Golden and al. found studies using the CES-D, which was not designed to measure clinical depression[69] whereas Rotella et al. found only 3 studies using interviews among the 23 studies used.

Finally, current research on the association between the subtypes of depression and cardiovascular outcomes presents two major limitations. First, as developed above, the lack of longitudinal studies assessing prospective associations prevents drawing any conclusion about a potential causal association. Second, the lack of detailed assessment of the symptomatology of depressive disorders in a majority of studies makes the subtyping of depression difficult or impossible.[81] Moreover, the definition of the subtypes, particularly the atypical subtype, is still debated. A lot of research about subtypes of depression and biological profiles has been performed on a Dutch observational study, which used subtypes defined by a latent class analysis rather than the DSM.[27] Angst and colleagues, who used another observational study on the population of Zürich with three decades of follow-up duration also challenged the atypical subtype definition and proposed a non-hierarchical definition.[106] The melancholic subtype DSM definition is less challenged, even if it is still under discussion.[20]

Aims of the present work

Accordingly, the aims of the present work were to:

- assess the prospective associations between MDD subtypes at baseline and the subsequent changes in the metabolic CVRF, taking into account a wide range of potential confounding factors, such as socio-demographic characteristics, behavioral CVRF, psychiatric comorbidities, recurrence of depressive episodes, medication or early trauma, and examining putative mediating factors of these associations that are plasma inflammatory markers (Hs-CRP, interleukin-1β, interleukin-6, tumor necrosis factor-α) and adipose-derive hormones (leptin, adiponectin) levels or eating behaviors (Figure 6).

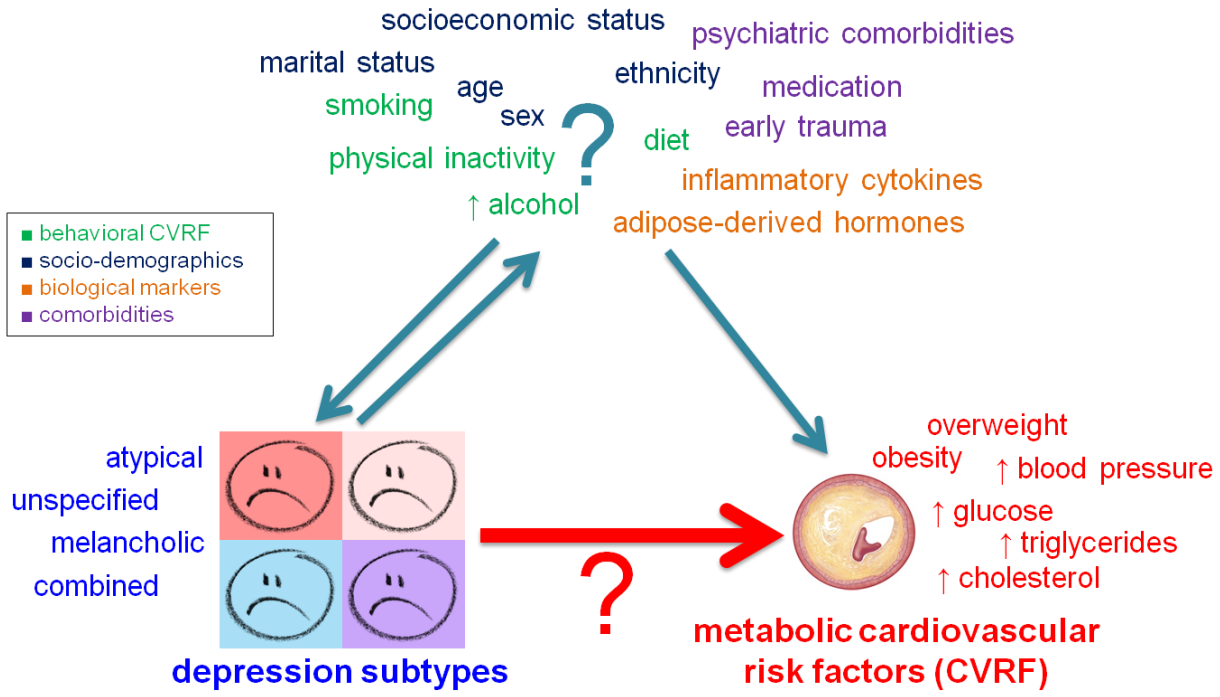

Figure 6. Illustration of the first aim. Prospective associations between the depression subtypes and the metabolic cardiovascular risk factors (CVRF), with hypothetical confounders or mediators

- determine the association of depressive disorders with incident cardiovascular events, mortality and all-cause mortality over a 5-year follow-up period, examining clinical (diagnostic severity level, atypical features) and course characteristics (recency, recurrence, time spent in episodes, age of onset) of depressive disorders and taking into account a large array of risk factors including socio-demographic, and behavioral and metabolic CVRF, comorbid anxiety disorders, antidepressant use as well as preexistent cardiovascular diseases (Figure 7).

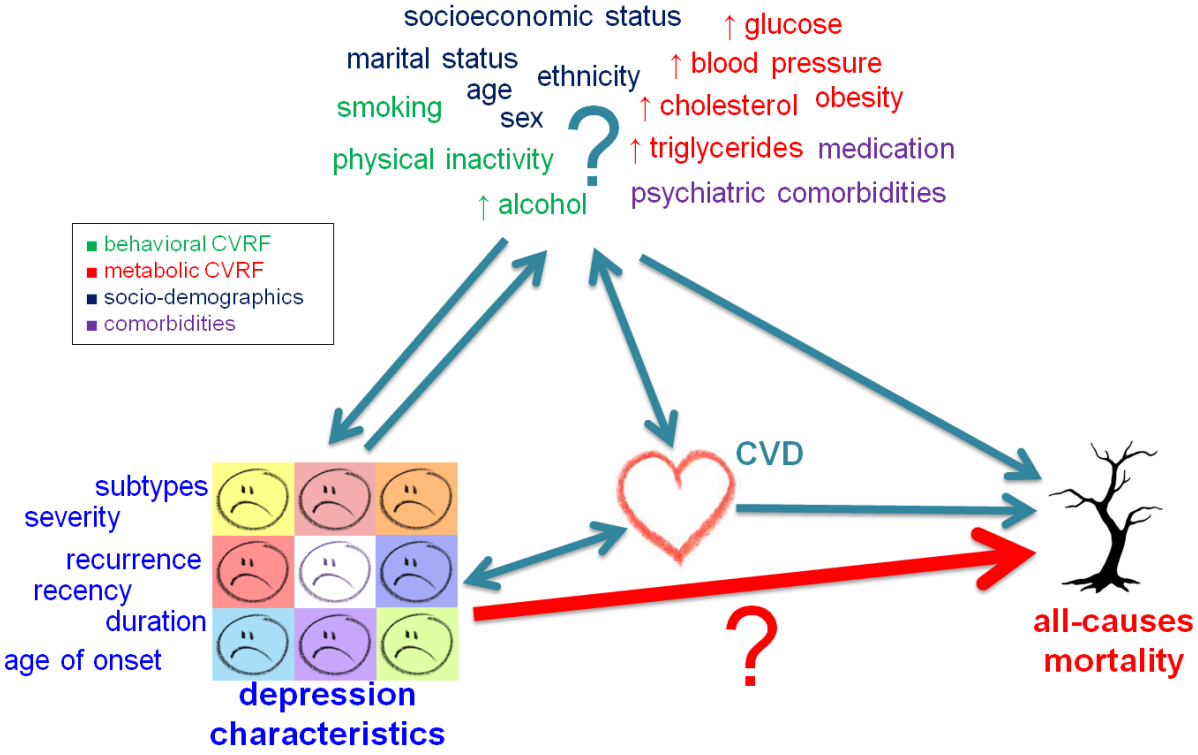

Figure 7. Illustration of the second aim. Prospective associations between the characteristics of depression and cardiovascular events and all-cause mortality, with hypothetical confounders and mediators

The PsyCoLaus study

The present work is based on data from PsyCoLaus,[107] a prospective population-based study designed to assess the prevalence of mental disorders, examine the validity of specific substhreshold mental disorders, assess associations between mental disorders and CVD and identify genetic variants and biomarkers associated with specific mental disorders in the general population of Lausanne. PsyCoLaus was originally a psychiatric sub-study of the CoLaus study,[108] designed to assess the prevalence and severity of CVRF, and explore their genetic determinants and biomarkers. The selection procedure of the PsyCoLaus sample is summarized in Figure 8.

The original sample of this study was selected from the inhabitants of Lausanne aged 35-75 years in 2003 (n=56'694). A simple, non-stratified random selection of 19'830 subjects, corresponding to 35% of the source population, was drawn and a letter to invite these individuals was sent. Subjects who didn't answer were sent a second invitation letter. If no answer was obtained, they were contacted by phone. Subjects were considered as non-participants if they refused to participate (n=6'189) and as non-responders if contact couldn't be made after two successive letters and three successive phone calls (n=4667). Individuals who no longer lived in Lausanne, who were dead or who didn't meet the age criterion were considered as non-eligible (n=853). Among the 8'121 subjects who agreed to participate, the first 6'734 were invited to attend the clinic and completed the examination. As the number of subjects who agreed to participate was higher than the number of subjects initially planned for the CoLaus study (6'000), 1'387 could not be included into the study although they were willing to participate. One subject withdrew after consent due to personal reasons. Recruitment began in June 2003 and ended in May 2006. The CoLaus study participants (n=6'733) were on average one year younger than the base

population, due to an under-representation of subjects aged over 65 years, while no differences were found for gender distribution. There was no gender or zip code distribution difference between the source population, the random sample and the CoLaus participants.

To select the PsyCoLaus sample, all 35 to 66-year old subjects of the CoLaus sample (n = 5,535) were invited by letters to participate in a psychiatric evaluation. Again, those who did not respond to the letter were contacted by phone. All subjects who were sufficiently fluent in French or English and agreed to participate were included (n=3719) and underwent a psychiatric assessment between 2004 and 2008.

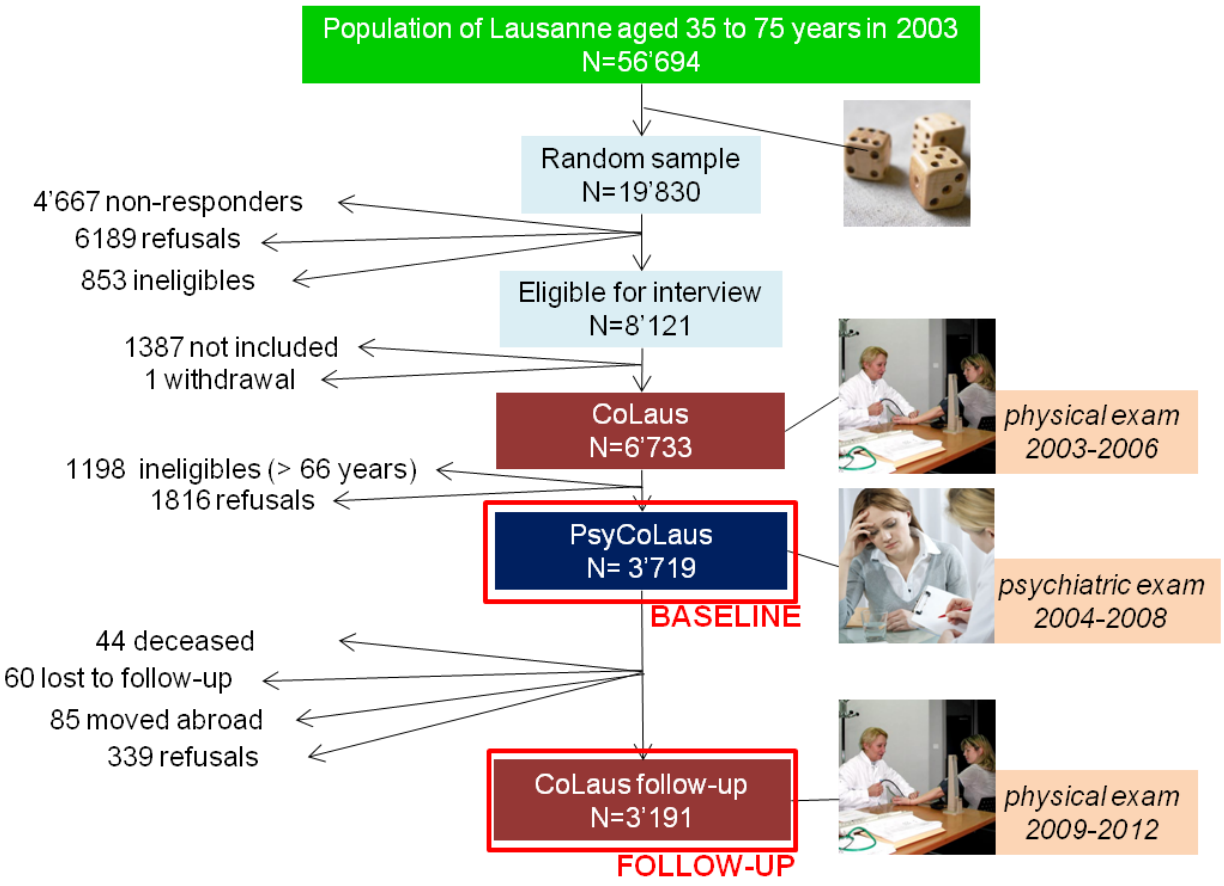

Figure 8. Flow-chart of the selection procedure of the PsyCoLaus sample

Five years after the baseline physical examination, a similar follow-up examination took place between 2009 and 2012. Out of the 3719 participants who had completed the baseline physical and psychiatric assessments, 3191 accepted to participate in the follow-up, 339 refused, 44 were deceased, 85 had moved abroad and 60 were lost to follow-up. A psychiatric follow-up was also organized between 2010 and 2013, but the data of the latter year were not available at the beginning of this work.

During the physical evaluations, data on socio-demographic and lifestyle (tobacco and alcohol use, physical activity) factors as well as on personal and family history of CVRF, CVD and the use of medication were collected by trained field collaborators using standardized questionnaires. The physical evaluation also included anthropometric measures (body weight, height, waist and hip circumferences), and the assessment of blood pressure and heart rate, described in detail elsewhere.[108] Venous blood samples were drawn from each participant after an overnight fast and a wide range of analyses were performed, including measures of plasma triglycerides, LDL-cholesterol, HDL-cholesterol, glucose, adiponectin, leptin, insulin and inflammation markers (hs-CRP, TNF-α, IL-6, IL-1β) levels. Genotyping was performed at baseline using the Affimetrix 500 K SNP chip.

The psychiatric baseline evaluation was performed by trained psychologists. Diagnostic information was collected using the French version of the semi-structured Diagnostic Interview for Genetic Studies (DIGS).[109] The DIGS was developed to obtain a more precise assessment of phenotypes through a wide spectrum of DSM-IV criteria, which mainly correspond to DSM-5 criteria as well. The DIGS depression section was completed with additional questions in order to elicit all the DSM-IV criteria of the atypical depression subtype. Moreover, the generalized anxiety disorder section of the Schedule for Affective Disorders and Schizophrenia - Lifetime

Version (SADS-L) was added and the brief phobia chapter of the DIGS was replaced by the corresponding more extensive chapters from the SADS-L. In addition, the original DIGS section on nicotine consumption was largely extended to elicit DSM-IV abuse and dependence criteria**.** Diagnoses were assigned according to the DSM-IV or DSM-5.

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

Results

The present work resulted in three articles as first author, published in peer-reviewed journals. The three articles are attached in the appendix section and their method and results are briefly presented below. For all three articles, the contribution of the doctoral student was an extended review of the literature, the analysis and interpretation of the data, the preparation of the manuscripts, the submission to the peer-reviewed journals and the preparation of the answers to the reviewers.

Depression with atypical features and increase in obesity, body-mass index, waist circumference and fat mass: prospective, population-based study (Appendix I)

Aims: determine whether the subtypes of major depressive disorder (melancholic, atypical, combined or unspecified) are predictive of adiposity, in terms of incidence of obesity and changes in body-mass index, waist circumference and fat mass.

Methods: After exclusion of participants with a diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia or eating disorders at baseline, 3054 subjects (mean age 50 years, 53% women) participated to the physical follow-up examination. Changes in body-mass index, waist circumference, fat mass during the follow-up period, in percentage of the baseline value, as well as incidence of obesity during the follow-up period among non-obese participants at baseline were assessed with robust and logistic regression models among the different current or remitted subtypes of MDD.

Results: The increase of BMI was higher among subjects with current or remitted atypical subtype of MDD at baseline than among never depressed. Moreover, subjects with current atypical MDD revealed a higher waist and fat-mass (only among men for the latter) and incidence of obesity during follow-up than subjects without MDD. These associations remained significant after adjustment for socio-demographic characteristics, comorbid anxiety or drug dependence, lifestyle characteristics (physical activity, alcohol consumption and smoking), medication use (antidepressants and drugs potentially inducing weight gain) at baseline and additional adjustment for the presence of a MDE during the follow-up.

Prospective associations of depression subtypes with cardio-metabolic risk factors in the general population (Appendix II)

Aims: 1) assess the prospective associations of the atypical, melancholic and unspecified subtypes of MDD with changes of fasting glucose, HDL-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.

Methods: After exclusion of the participants with a diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia or eating disorders at the psychiatric baseline exam, 2813 Caucasian (mean age 50 years, 53% women) participants also underwent the physical follow-up exam. The associations between lifetime MDD subtype status and changes in cardio-metabolic outcomes during follow-up were assessed using robust regression models. Analyses for the incidence of the metabolic syndrome as the outcome variable were performed using logistic regression.

Results: The atypical MDD subtype, and only this subtype, was prospectively associated with a higher incidence of the metabolic syndrome, a steeper increase of waist circumference and independently of this, with a steeper increase of the fasting glucose level 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.

Depression and cardiovascular events

No significant association was found between MDD or characteristics of MDD and CVD events. However, the estimated statistical power to detect these associations were too low (<90%) to detect a hazard ratio equal or higher to 1.5. Accordingly, these analyses were not included in the third article, as initially planned.

Clinical and course characteristics of depression and all-cause mortality: a prospective population-based study (Appendix III)

Aims: Determine the association between clinical and course characteristics of depressive disorders (DD) and incident all-cause mortality.

Methods: Vital status at follow-up was known for 3668 subjects (mean age 51 years, 53% women) who had underwent physical and psychiatric baseline evaluations (98.8% of the baseline sample). Clinical (diagnostic severity, atypical features) and course characteristics (recency, recurrence, duration, onset) of DD according to the DSM-5 were elicited using a semi-structured interview. Survival analysis were performed.

Results: Compared to participants who had never experienced depressive disorders, participants with current diagnose of DD were more than three times as likely to die of all-cause during the follow-up after adjustment for socio-demographic and lifestyle characteristics, comorbid anxiety disorders, antidepressant use, and cardiovascular risk factors and diseases. There was no evidence for associations between other depression characteristics and all-cause mortality.

Discussion

Main findings

In an attempt to better understand the association between depression and CVD, this work aimed to evaluate the potential effect of different depression subtypes and characteristics on cardiovascular risk factors, cardiovascular events and mortality. The main hypothesis was that the atypical subtype of depression would increase the risk of developing cardiovascular risk factors and, through that pathway, ultimately lead to a higher incidence of CVD and mortality compared to controls. I used data from a population-based cohort of over three thousand participants, the PsyCoLaus study, to test this hypothesis. The main result was that the atypical subtype of MDD, and only this subtype, was prospectively associated with a higher increase of adiposity, regardless of how it was measured, and independently of that, to a higher increase of plasma fasting glucose level, compared to controls. These associations were independent of age, sex, socio-economic or marital status, physical activity, eating behaviors, smoking, alcohol use, substance dependence, anxiety disorders, antidepressant or potential weight-inducing drugs and were not mediated by inflammatory markers or adipose-tissue hormones. The second part of the aim was to demonstrate if there was an increased risk of having cardiovascular events among particular groups of depressives. After a follow-up of 5.5 years, about one hundred participants had presented a cardiovascular event (mainly myocardial infarction or stroke). No association was found between depression or subgroups of depressive illness and the risk of developing an event. However, an analysis of the statistical power to detect this potential association revealed insufficient statistical power. In this respect, this negative result could not be considered or published. Despite this relatively low statistical power, we found that having a current depressive episode at baseline was associated with a higher risk of dying during a follow-up of 5.5 years,

compared to never having had a depressive disorder and even, to having had a remitted depressive episode. This result was independent of sex, age, socio-economic level, marital status, ethnicity, comorbid psychiatric disorders, smoking, alcohol use, inactivity, obesity, hypertension, dyslipidemia, diabetes, history of CVD and antidepressant use. Due to the low statistical power, the negative associations between other characteristics of depression, atypical features for example, and mortality should not be considered as definitive.

Interpretation

The results presented in the two first articles provide support to the hypothesis that the atypical subtype is prospectively associated with obesity and high fasting glucose, but not with dyslipidemia or high blood pressure. These results are consistent with previous findings that showed cross-sectional associations between this subtype of depression and obesity or diabetes.[87] [88] [94] The prospective association between the atypical subtype and an increase of BMI has been reproduced in a clinical study since the publication of this results.[110] In this study, the authors found an association between the atypical subtype of depression and the metabolic syndrome[110] but the finding of a prospective association between the atypical subtype and an increase of plasma fasting glucose has not been shown elsewhere. The assumption of a causal association is reinforced by these findings. Indeed, some of Hill's criteria have been fulfilled, noteworthy, the strength of the associations found, the consistency with other studies (at least concerning a cross-sectional association), and the specificity and the temporality of these associations could be demonstrated in this work. These associations were not mediated by inflammation or adipose-derived hormones. This is in line with previous studies that showed that atypical depression has been shown to not be associated with inflammation when taking confounders into account.[101] Inflammation might play a role in the association between depression and cardiovascular events,

in precipitating events, but this might be independent from CVRF.[39] The results did not confirm a previous finding of a cross-sectional association between atypical depression and LDL cholesterol.[73] Among non-Caucasians, we found that the melancholic subtype was associated with HDL-cholesterol increase during follow-up, which is conflicting with previous cross-sectional results of a Dutch study that found an association between melancholic features and a lower level of HDL cholesterol. The negative result for systolic blood pressure is in line with previous cross-sectional studies.[27 87] A meta-analysis on the prospective association between depression and hypertension found a significant association, but noted that only studies with the longer follow-ups reported a significant association and recommended a follow-up longer than 5 years. This study also showed that the lower the prevalence of depression was at baseline, the higher the risk of incidence of hypertension was.[68] As the prevalence of depression in the PsyCoLaus study was high compared to others and the follow-up was about 5 years, the negative result for blood pressure should be considered with caution.

The results presented in the third article of this work show that current depression is associated with an increase risk of dying in the following five years. Similar findings of associations between mortality and current or recent but not remitted depressive episodes have been observed in two previous community studies.[111 112] The observed excess mortality in currently depressed subjects in conjunction with a possibly diminished risk of dying in remitted subjects in this article and similarly in another study[112] could indicate an increased vulnerability of currently depressed subjects and potential resilience of those who survived the acute episode. The hypothesis that the effect of depression on mortality decreases after remission is also compatible with a meta-analysis that documented a lower relative risk of dying in studies with longer follow-up periods,[35] but not others.[31 32] Although it has not been possible to accurately determine disease-specific

mortality rates in subjects with current depression because of a limited number of subjects who died during the follow-up, the present results do not suggest that elevated mortality is attributable to one specific cause of death. This corroborates previous findings[37 113] and a meta-analysis that demonstrated comparable depression-related excess mortality in cancer, heart and kidney disease patients, suggesting the implication of generic rather than disorder-specific mechanisms.[36] Among the clinical manifestations and course features of depression, only the recency of episodes was predictive of mortality, which extends previous findings restricted to ischemic heart disease mortality.[112] It is remarkable that mortality did not differ between depressive subjects above and below the diagnostic threshold of MDD, which is consistent with a recent meta-analysis,[34] and further supports the clinical relevance of the newly defined DSM-5 category of *Other specified depressive disorders*. Regarding the atypical depression subtype, which has previously been found to be associated with metabolic diseases,[87 88 114] our data did not provide evidence for higher mortality in subjects exhibiting this depression subtype. Once again, these negative results need to be interpreted with results considering the small numbers of death examined in this paper.

Limitations

This work needs to be considered in the context of several limitations. First, the happily low rate of cardiovascular events and death of participants during the follow-up period also had its disadvantages. Indeed, the statistical power to assess the association between depression subtypes and characteristics and these events was low. Thus, the positive results can be interpreted but the negative results could simply be due to a lack of power and should, in this regard, be interpreted with caution. Second, as the potential confounding or mediating factors were all measured at the

same time point as the exposure, it is theoretically not possible to disentangle confounding from mediating factors in one model. The distinction between the two was made according to previous results in this cohort or other studies. Also, the statistical method can be discussed[115] and mediation analysis could have been proposed, such as inverse probability weighting using the Rubin model for example.[116] However, given the number of potential confounding and interactions, such models were not suited to the present data and including all possible confounding in the models was a safe choice. Third, the lifetime prevalence of MDD of about 40% in the PsyCoLaus sample was relatively high compared to other studies. This is partly due to the detection of milder forms of depression by the semi-structured interview.[117] For example, a recent report evaluated the lifetime prevalence of depression to be about 20% in the Swiss population.[5] In this same report, however, depression was described as a chronic disorder, while in the present data, about half of the participants who experienced depression, experienced it only once. This being said, it is unlikely that the associations between depression and cardiovascular outcomes would have been influenced by the high prevalence of depression, but the strength of the association might have been underestimated. Concerning mortality, it has been shown in a recent meta-analysis that even subthreshold depression has a similar effect on mortality to depression.[34] In that sense, assessing even mild forms of depression seems to be important in this area, even if it supposes a higher prevalence of depression in our study than what is currently expected. Fourth, dietary habits, physical activity and inactivity (in other words, energy intake and expenditure) have only been partially measured. These behavioral factors could represent important potential confounders. This might have attenuated the strength of the associations found. However, if this was the case, this implies that the subjects with the atypical subtypes have different dietary health-related behaviors than others, which would be an important finding in itself and needs further investigations. Fifth, cortisol salivary measures were not available at

baseline. As it has been postulated that cortisol dysregulation could be specific to the melancholic subtype of depression,[50] it would have been interesting to include this measure in the analysis. Sixth, data on inflammation markers, adipose-tissue hormones and medication were not available for non-Caucasian participants at baseline because of the original genetic aims of the study. This resulted in stratified analysis for the assessment of the association between atypical depression and the CVRF. However, this made it possible to reproduce the results of an association between atypical depression and subsequent increase of plasma fasting glucose between two different groups.

Future directions

Considering the present findings, many future developments of this research can be imagined. First, a second wave of physical and psychiatric assessments of the PsyCoLaus sample will lengthen the follow-up and give additional data. This will present many advantages and possibly help to deal with some of the above limitations. Having measures at three different time points will allow more refined analyses, to assess changes to the outcomes or to help differentiate confounding from mediating variables for example. With a longer follow-up and the aging of our sample, more cardiovascular events and deaths are expected. These outcomes will then be explored in more detail than what has been possible until now. Also, measures which were taken only in the first follow-up, in particular salivary cortisol measures, dietary questionnaires or detailed physical activity assessments, will be repeated and will allow for examination of their development over time. In particular, whether the specific metabolic consequences of the atypical subtype have an impact on future CVD, will be in important question to address.

Second, having postulated that depression subtypes had different biological profiles, it seems primordial to look further into these subtypes and examine specific symptoms separately. As

discussed above, no model to subtype depression into more homogeneous groups has reached a full consensus,[83 118 119] the current definition are still deeply debated, and it is highly probable that they do not represent natural types. Previous studies have shown that atypical and melancholic subtypes differentiate mainly in terms of neurovegetative symptoms[27 106] but others have found that mood reactivity was a significant indicator of treatment response to the monoamine oxidase inhibitors.[23] It is possible that each symptom plays a different role in the association between depression subtypes and biological outcome and this needs to be explored. Other approaches than subtyping depression could also be explored, for example assessing potential endophenotypes of depression.[120] Also, as the effect of atypical depression persists after the remission of the depressive episode, it would be interesting to examine if some of the symptoms persist or if these episodes are related to personality traits that would influence behavioral factors for example.

Third, common etiological factors between atypical depression and increased adiposity or plasma fasting glucose need to be explored. Indeed, a recent study has shown a genetic overlap between depression and diabetes.[121] Moreover, one of the two samples used in this analysis, the association was primarily attributed to genetic effects in females, but not in males. As the atypical subtype of depression is more prevalent among women, one could make the hypothesis that this gender difference could be explained by a difference of prevalence of the atypical depression could be made. Concerning obesity, the fat-mass and obesity-associated protein (FTO) gene has been shown to selectively favor weight gain in depressed subjects.[122] This gene could also be associated with the atypical depression subtype.[123] Environmental factors, such as urbanization or pollution might also represent important factors to consider.[7 124]

Fourth, as tobacco smoking, physical inactivity, unhealthy diet, harmful use of alcohol are shared causative risk factors of CVD, cancer, diabetes and respiratory diseases and that mental disorders

have also been shown to increase all-cause mortality,[125] it would seem sensible to investigate the cause of death in broader manner, and include the types of cancer in particular as well as other detailed causes of death.

Finally, clinical trials should examine whether the treatment of atypical depression improves the long-term risk of developing metabolic risk factors and ultimately cardiovascular diseases.

Conclusion

In conclusion, depressive disorders should be considered not only as a mental disorder but also as a risk for developing chronic physical diseases. In this respect, their global burden of disease is probably underestimated because it does not sufficiently take the impact of depression on physical heath[3 125] and mortality[125] into consideration. The present work, among others,[39 81 105 80] advocates for a careful assessment of depressive disorders, and a particular attention to their symptomatology and temporal development in research, public health policy, as well as in clinical settings. In research, this should help better understand this disorder with still many unanswered questions and its nesting within physical health. Depressive disorders are more and more recognized among public health actors,[4 5] but interventions to prevent depression[126] as well as its metabolic consequences[127] in the general population are urgently needed. In clinical settings, more awareness should be raised for the atypical subtype of depression and its metabolic consequences, which also calls for more intense collaboration between mental and physical health specialists.

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Appendices

Appendix I

Lasserre AM, Glaus J, Vandeleur CL, Marques-Vidal P, Vaucher J, Bastardot F, Waeber G, Vollenweider P, Preisig M. Depression with atypical features and increase in obesity, body-mass index, waist circumference and fat mass: prospective, population-based study. *JAMA Psychiatry*. 2014 Aug; 71(8):880-8.

Appendix II

Lasserre AM, Strippoli MF, Glaus J, Gholam-Rezaee M, Vandeleur CL, Castelao E, Marques-Vidal P, Waeber G, Vollenweider P, Preisig M. Prospective associations of depression subtypes with cardio-metabolic risk factors in the general population. *Molecular Psychiatry*. 2016 Oct 11, doi:10.1038/mp.2016.178 [ahead of print].

Appendix III

Lasserre AM, Marti-Soler H, Strippoli MP, Vaucher J, Glaus J, Vandeleur CL, Castelao E, Marques-Vidal P, Waeber G, Vollenweider P, Preisig M. Clinical and course characteristics of depression and all-cause mortality: a prospective population-based study. *J Affect Disord*. 2016 Jan 1;189:17-24.

Appendix I

Original Investigation

Depression With Atypical Features and Increase in Obesity, Body Mass Index, Waist Circumference, and Fat Mass
A Prospective, Population-Based Study

Aurélie M. Lasserre, MD; Jennifer Glaus, PhD; Caroline L. Vandeleur, PhD; Pedro Marques-Vidal, MD, PhD; Julien Vaucher, MD; François Bastardot, MD; Gérard Waeber, MD; Peter Vollenweider, MD; Martin Preisig, MD, MPH

IMPORTANCE Depression and obesity are 2 prevalent disorders that have been repeatedly shown to be associated. However, the mechanisms and temporal sequence underlying this association are poorly understood.

OBJECTIVE To determine whether the subtypes of major depressive disorder (MDD; melancholic, atypical, combined, or unspecified) are predictive of adiposity in terms of the incidence of obesity and changes in body mass index (calculated as weight in kilograms divided by height in meters squared), waist circumference, and fat mass.

DESIGN, SETTING, AND PARTICIPANTS This prospective population-based cohort study, CoLaus (Cohorte Lausannoise)/PsyCoLaus (Psychiatric arm of the CoLaus Study), with 5.5 years of follow-up included 3054 randomly selected residents (mean age, 49.7 years; 53.1% were women) of the city of Lausanne, Switzerland (according to the civil register), aged 35 to 66 years in 2003, who accepted the physical and psychiatric baseline and physical follow-up evaluations.

EXPOSURES Depression subtypes according to the *DSM-IV*. Diagnostic criteria at baseline and follow-up, as well as sociodemographic characteristics, lifestyle (alcohol and tobacco use and physical activity), and medication, were elicited using the semistructured Diagnostic Interview for Genetic Studies.

MAIN OUTCOMES AND MEASURES Changes in body mass index, waist circumference, and fat mass during the follow-up period, in percentage of the baseline value, and the incidence of obesity during the follow-up period among nonobese participants at baseline. Weight, height, waist circumference, and body fat (bioimpedance) were measured at baseline and follow-up by trained field interviewers.

RESULTS Only participants with the atypical subtype of MDD at baseline revealed a higher increase in adiposity during follow-up than participants without MDD. The associations between this MDD subtype and body mass index (β = 3.19; 95% CI, 1.50-4.88), incidence of obesity (odds ratio, 3.75; 95% CI, 1.24-11.35), waist circumference in both sexes (β = 2.44; 95% CI, 0.21-4.66), and fat mass in men (β = 16.36; 95% CI, 4.81-27.92) remained significant after adjustments for a wide range of possible cofounding.

CONCLUSIONS AND RELEVANCE The atypical subtype of MDD is a strong predictor of obesity. This emphasizes the need to identify individuals with this subtype of MDD in both clinical and research settings. Therapeutic measures to diminish the consequences of increased appetite during depressive episodes with atypical features are advocated.

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Author Affiliations: Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland (Lasserre, Glaus, Vandeleur, Preisig); Department of Mental Health and Psychiatry, Geneva University Hospital, Geneva, Switzerland (Glaus); Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland (Marques-Vidal); Department of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland (Vaucher, Bastardot, Waeber, Vollenweider).

Corresponding Author: Aurélie M. Lasserre, MD, Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, Site de Cery, 1008 Prilly, Switzerland (aurelie.lasserre@chuv.ch).

Major depressive disorder (MDD) is among the diseases with the greatest public health impact worldwide[1] and confers an approximately 50% elevated mortality of various causes.[2] Obesity represents another major burden for public health and is also associated with elevated mortality.[3] Moreover, both depression and obesity are associated with various chronic diseases such as diabetes mellitus, hypertension, dyslipidemia, cancer, and respiratory and osteoarticular diseases.[4-9] Obesity could also be one explanation for the approximately doubled risk for cardiovascular disease (CVD)[10] and cerebrovascular diseases and the excess mortality among depressed individuals.[2] Accordingly, gaining a better understanding of the mechanisms underlying the association between MDD and obesity is of high clinical and scientific relevance.

Although cross-sectional studies have consistently documented a strong association between obesity and depressive disorders or depressive symptoms,[11] the direction of this association and its underlying mechanisms are still poorly understood. Prospective studies have revealed contradictory findings regarding the sequence of onset of depression and obesity.[12,13] These inconsistent results could be due to the large heterogeneity of depression as well as to methodologic variance across studies including sample selection, the length of follow-up, and the assessment of depression and obesity. A major limitation of previous prospective studies, which also likely contributes to inconsistent findings, was the use of inaccurate measures. A recent review of population-based studies on the prospective association between obesity and depression could only identify 3 of 15 studies that included measured weight and height as well as direct diagnostic interviews to elicit standardized criteria for depression.[13] However, these 3 studies were restricted to adolescents and did not provide evidence showing an association between depression before the age of 15 years and obesity in young adulthood. The other studies used self-reported weight and height or assessed depressive symptoms using rating scales, which generally do not allow characterization into depression subtypes and do not take into account the frequent occurrence of comorbid mental disorders or past psychopathology.

Because of the large heterogeneity of depression in terms of symptom manifestations, course, and response to pharmacologic treatment,[14,15] studying subtypes of depression is likely to be a more promising approach than studying depression as a whole with respect to cardiovascular risk. Four studies that subdivided depression according to the presence or absence of atypical features, such as increased appetite and hypersomnia during depressive episodes, showed that participants with these features had a higher body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) than other individuals with depression or those who had never been depressed.[16-19] However, the cross-sectional design of 3 of these studies[16,17,19] impeded drawing conclusions regarding the direction of causality, whereas the population-based prospective Zurich Cohort Study revealed a trend for a positive association between atypical depression and the average rate of weight gain over 20 years.[18] Moreover, most of the previous studies assessing the association between depression and obesity were restricted to BMI as an adiposity measure, although recent data suggest that waist circumference is more strongly associated with the risk for CVD than BMI[20] and that body fat percentage could be an independent risk factor for mortality.[21]

Accordingly, the aims of the present study were to assess the prospective associations between MDD subtypes, including melancholic, atypical, combined, and unspecified, and the subsequent change of adiposity in terms of BMI, waist circumference, and fat mass, or the incidence of obesity, in a population-based prospective cohort using a standardized diagnostic interview and anthropometric measures.

Methods

Participants

The data of the present article stemmed from CoLaus (Cohorte Lausannoise)/PsyCoLaus (Psychiatric arm of the Cohorte Lausannoise),[22,23] cohort studies designed to prospectively study mental disorders and cardiovascular risk factors in the general population. The sample was randomly selected from the residents of the city of Lausanne, Switzerland, in 2003, according to the civil register. Sixty-seven percent of the 35- to 66-year-old participants (n = 5535) who underwent the physical examination between 2003 and 2006 also accepted the psychiatric evaluation, which resulted in a sample of 3719 individuals.[23] Participants with a diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, or eating disorders at the psychiatric baseline evaluation (n = 159) were excluded from the present analyses because these disorders are likely associated with changes in adiposity. Among the remaining individuals who had undergone the psychiatric baseline evaluation, 3054 also took part in the physical follow-up evaluation, whereas 42 individuals had died during the follow-up interval and 464 were not available for the physical examination, resulting in a participation rate of 87% among the survivors. The mean (SD) duration of the follow-up was 5.5 (0.4) years. Compared with those who participated at follow-up, nonparticipants were more likely to be men, have lower socioeconomic status, be smokers, have a higher alcohol consumption, be less physically active, meet criteria for obesity, and live alone at the baseline evaluation.

The institutional ethics committee of the University of Lausanne approved the CoLaus study (approvals 16/03 and 33/09) and subsequently the PsyCoLaus study (approvals 134/05 and 239/09). All participants signed a written informed consent after having received a detailed description of the goal and funding of the study.

Assessments

The physical measures were taken in identical ways at the baseline and follow-up visits. Participants had to have fasted for at least 8 hours and abstained from strenuous physical activity for 12 hours before the examination. Weight and height were measured in participants standing without shoes in light indoor clothes. Weight was measured in kilograms to the nearest 100 g and height was measured to the nearest 5 mm. Obe-

sity was defined as a BMI of greater than or equal to 30. Waist circumference was measured with a nonstretchable 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 was used for analyses. Fat mass was assessed by electrical bioelectrical bioimpedance[24] using the Bodystat 1500 analyzer.

In addition, information on sociodemographic characteristics, current medication, and health-related behaviors, including smoking, alcohol consumption, and physical activity, was collected through a standardized interview. White origin was defined as having both parents and grandparents born in a restricted list of countries (available from the authors). Socioeconomic status was assessed using the Hollingshead scale.[25] Alcohol consumption was considered to be low if participants drank between 1 and 13 units per week and high if they drank 14 or more units per week. Participants were considered physically active if they reported physical activity for at least 20 minutes twice a week.

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).[26,27] The DIGS was completed with anxiety disorder sections of the Schedule for Affective Disorders and Schizophrenia–Lifetime Version.[28] Psychiatric diagnoses were assigned according to the *DSM-IV*.[29] The criteria for atypical features according to the *DSM-IV* requires mood reactivity and at least 2 of the following 4 symptoms: (1) increased appetite or significant weight gain, (2) hypersomnia, (3) leaden paralysis, and (4) a long-standing pattern of interpersonal rejection sensitivity. Because weight change was an outcome variable, we only applied the appetite part of the criterion, which requires either increased appetite or weight gain. For the melancholic features specifier, the *DSM-IV* requires either a loss of energy or a lack of mood reactivity and 3 of the following 5 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. Major depressive disorder was subdivided according to the history of atypical or melancholic features into 4 subtypes: (1) MDD with atypical features only, (2) MDD with melancholic features only, (3) combined MDD with atypical and melancholic features simultaneously or during distinct episodes, and (4) unspecified MDD with neither atypical nor melancholic features. For individuals who refused the DIGS interview at follow-up (19%), MDD status at follow-up was assessed using the Center for Epidemiologic Studies Depression scale. A score of 19 or higher was considered an indicator of the presence of a major depressive episode (MDE).[30,31] Interviewers were required to be psychologists, who were trained over a 2-month period. Each interview and diagnostic assignment was reviewed by an experienced senior psychologist.

Statistical Analysis

Analyses were performed using the Statistical Analysis System version 9.2 for Windows (SAS). Associations between MDD status and continuous adiposity variables (BMI, waist circumference, and fat mass) were established at baseline using robust rather than multiple regression models because the residuals did not reveal a normal distribution. The association between MDD status and obesity was assessed using logistic regression. Similar serially adjusted models were used to determine the associations between depression status at baseline and changes of continuous variables (calculated in percentage of the baseline value) or the incidence of obesity during follow-up. The choice of the covariates in the models was determined by the findings of previous studies that suggested potential associations of these covariates with both MDD and adiposity variables. The first model (model 1) was adjusted for sociodemographic characteristics (sex, age, socioeconomic status, ethnicity, and living alone). The second model (model 2) was further adjusted for the effects of comorbid anxiety disorders or drug dependence, treatment with antidepressants or drugs possibly inducing weight gain (a list and the way in which it was extracted is provided in the eTable in the Supplement) and health-related behavioral characteristics (physical activity, alcohol consumption, and smoking status) at baseline. The third model (model 3) was also adjusted for the presence of an MDE during the follow-up to assure that a measured association was attributable to depression status at baseline and not to new episodes that occurred during the follow-up. When the association between MDD and the incidence of obesity was assessed, all models were also adjusted for baseline BMI. We found a significant interaction between sex and depression status to affect the body fat percentage (sex by current atypical MDD: $P = .04$ and $P = .006$ in models 1 and 2, respectively). Accordingly, data regarding this outcome were analyzed separately for women and men.

Results

Table 1 provides the sample description for all participants according to the MDD status. At baseline, 7.6% of the participants met criteria for current MDD and 36.7% reported at least 1 remitted MDE in the past. Among the participants with MDD, approximately 10% revealed atypical and melancholic episodes (combined), 14% had atypical episodes, 29% had melancholic episodes, and 48% had unspecified episodes. Among depressed participants taking antidepressant medication at baseline, approximately 75% reported taking selective serotonin or serotonin-norepinephrine reuptake inhibitors and less than 10% a tricyclic or tetracyclic drug.

The mean (SD) BMI of the whole sample at baseline was 25.3 (4.3) (mean [SD], 24.6 [4.7] in women and 26.2 [3.7] in men). **Table 2** presents the baseline BMI of the sample and the change of the BMI in percentage during the follow-up in function of the baseline depression status. Participants with current or remitted atypical MDD as well as those with the current combined MDD subtype revealed a higher BMI at baseline than individuals who had never been depressed. During the follow-up, the BMI of the whole sample increased by 2.6% (SD, 6.7%). After adjustment for sociodemographic characteristics (model 1), participants meeting the criteria for current atypical MDD and,

Table 1. Characteristics of Participants at Baseline

Characteristic	All Participants	MDD Status								
		Current				Remitted				
		Atypical	Melancholic	Combined	Unspecified	Atypical	Melancholic	Combined	Unspecified	No MDD
Total No.	3054	48	55	31	97	140	323	104	554	1702
Women, %	53.1	66.7	72.7	74.2	54.6	72.9	68.1	69.2	61.4	43.4
Age, mean (SD), y	49.7 (8.8)	50.1 (8.0)	49.1 (8.1)	50.2 (9.2)	48.2 (7.9)	48.0 (8.9)	49.3 (8.8)	49.3 (9.2)	49.0 (8.9)	50.2 (8.8)
SES, mean (SD)[a]	3.4 (1.3)	2.9 (1.3)	3.1 (1.3)	2.7 (1.2)	3.3 (1.3)	3.6 (1.2)	3.4 (1.3)	3.5 (1.3)	3.5 (1.2)	3.4 (1.3)
Nonwhite, %	8.0	6.3	9.1	9.7	14.4	7.9	8.4	8.7	7.9	7.5
Living alone, %	23.2	14.6	34.5	22.6	22.7	33.6	29.4	28.8	28.3	19.1
Anxiety disorders, %[b]	17.4	35.4	32.7	25.8	21.6	21.4	25.7	31.7	22.0	11.7
Smoking status, %										
Former	32.6	31.3	21.8	29.0	30.9	30.0	33.1	28.8	34.3	33.0
Current	27.3	22.9	41.8	29.0	30.9	28.6	27.2	35.6	31.8	24.6
Alcohol intake, %[c]										
Low	58.8	62.5	50.9	41.9	51.5	65.7	60.1	62.5	60.3	58.1
High	16.0	10.4	14.5	19.4	14.4	7.9	11.1	12.5	14.3	18.6
Substance dependence, %[d]	2.5	2.1	0.0	3.2	3.1	0.7	3.7	3.8	2.9	2.2
Physically active, %[e]	56.5	35.4	38.2	35.5	44.3	59.3	62.8	56.7	57.9	56.9
Antidepressant use, %	7.5	22.9	20.0	16.1	20.6	18.6	16.7	22.1	7.4	2.2
Weight gain–inducing drug use, %	14.4	31.3	12.7	25.8	21.6	20.7	21.4	30.8	16.6	9.8
Age at MDD onset, mean (SD), y	NA	33.6 (16.7)	35.9 (13.4)	32.3 (14.0)	35.2 (13.9)	32.7 (13.1)	31.3 (12.1)	29.4 (12.2)	33.7 (12.7)	NA
Time spent in episodes, mean (SD), wk	NA	398.2 (524.8)	252.5 (232.2)	364.2 (516.2)	352.0 (437.9)	136.2 (207.9)	155.1 (257.8)	191.3 (364.7)	121.1 (230.7)	NA
MDE during follow-up, %[f]	15.9	23.4	30.8	24.1	26.9	29.9	26.4	32.4	19.9	9.0

Abbreviations: MDD, major depressive disorder; MDE, major depressive episode; SES, socioeconomic status.

[a] Hollingshead Four-Factor Index of Social Status (5 is the highest status).

[b] Generalized anxiety disorder, social phobia, panic disorder, or agoraphobia.

[c] Number of drinks per week: low = 1-13 and high = 14 or more.

[d] Lifetime dependence on cocaine, heroin, stimulant, sedative, or hallucinogen.

[e] Physically active more than 20 minutes twice a week.

[f] Information on 2942 participants.

to a lesser degree, those who met criteria for remitted atypical episodes or remitted melancholic episodes at baseline had a higher BMI increase than participants who had never been depressed. These differences in BMI increase remained statistically significant after additional adjustment for comorbid anxiety or drug dependence, lifestyle characteristics (physical activity, alcohol consumption, and smoking) and medication use (antidepressants and drugs potentially inducing weight gain) at baseline (model 2) and additional adjustment for the presence of an MDE during the follow-up (model 3). In contrast to the participants with atypical MDD, those with remitted melancholic episodes did not reveal a higher BMI than those who had never been depressed at baseline (Table 2) or follow-up (mean [SD], 26.0 [4.5] and 25.7 [4.8], respectively; β = 0.17; 95% CI, −0.37 to 0.60).

During follow-up, the proportion of participants meeting criteria for obesity increased from 12.4% to 15.5%. At baseline, only participants with remitted atypical MDD revealed a significantly higher prevalence of obesity than those who had never been depressed (**Table 3**). Among participants who were not obese at baseline, current atypical MDD strongly increased the odds for being obese at the follow-up visit regardless of the number of variables for which the models were adjusted (Table 3). Similarly, remitted melancholic MDD predicted an increased risk for obesity after adjustment for potential confounders (models 2 and 3). However, the prevalence of obesity in participants with remitted melancholic MDD did not significantly differ from that of participants who had never been depressed at baseline (Table 3) or follow-up (mean [SD], 13.9% [1.9%] and 15.8% [0.9%], respectively; odds ratio [OR], 0.94; 95% CI, 0.66-1.33).

The mean (SD) waist circumference of the participants was 87.6 (13.0) cm. Participants with current or remitted atypical

Table 2. BMI at Baseline and BMI Change During Follow-up by Depression Status

Depression Status	BMI at Baseline (n = 3054)		BMI Change, % of the Baseline Value			
				β (95% CI)		
	Mean (SD)	β (95% CI)[a]	% (SD)	Model 1 (n = 3024)[b]	Model 2 (n = 3024)[c]	Model 3 (n = 2917)[d]
Current MDD						
Atypical	26.8 (4.1)	1.77 (0.71 to 2.82)[e]	4.3 (7.7)	2.86 (1.19 to 4.53)[f]	3.03 (1.35 to 4.71)[f]	3.19 (1.50 to 4.88)[f]
Melancholic	25.4 (5.2)	0.16 (−0.83 to 1.15)	3.6 (7.1)	0.51 (−1.05 to 2.07)	0.53 (−1.04 to 2.10)	0.91 (−0.70 to 2.52)
Combined	26.3 (4.2)	1.41 (0.11 to 2.72)[g]	2.0 (8.5)	1.18 (−0.87 to 3.22)	1.46 (−0.59 to 3.50)	2.07 (−0.03 to 4.18)
Unspecified	25.1 (4.5)	0.02 (−0.73 to 0.77)	2.5 (7.0)	0.28 (−0.90 to 1.46)	0.41 (−0.78 to 1.60)	0.43 (−0.78 to 1.63)
Remitted MDD						
Atypical	26.4 (5.2)	1.14 (0.50 to 1.78)[f]	3.2 (8.2)	1.12 (0.12 to 2.12)[g]	1.28 (0.28 to 2.29)[g]	1.18 (0.16 to 2.20)[g]
Melancholic	24.8 (4.8)	−0.31 (−0.75 to 0.13)	4.0 (7.7)	1.20 (0.50 to 1.89)[f]	1.36 (0.65 to 2.07)[f]	1.43 (0.71 to 2.16)[f]
Combined	25.1 (3.9)	0.13 (−0.60 to 0.86)	2.1 (6.5)	0.16 (−0.98 to 1.31)	0.34 (−0.82 to 1.50)	0.49 (−0.68 to 1.66)
Unspecified	24.8 (4.1)	−0.23 (−0.59 to 0.13)	2.6 (6.7)	0.14 (−0.42 to 0.70)	0.17 (−0.39 to 0.74)	0.23 (−0.34 to 0.80)
No MDD	25.5 (4.2)	0 [Reference]	2.2 (6.2)	0 [Reference]	0 [Reference]	0 [Reference]

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MDD, major depressive disorder.

[a] Robust regression adjusted for age and sex.

[b] Model 1: robust regression adjusted for age, sex, socioeconomic status, ethnicity, living alone, and length of follow-up.

[c] Model 2: model 1 and adjusted for physical activity, smoking habit, alcohol use, drug dependence, anxiety disorders, antidepressant use, and weight-increasing drug use.

[d] Model 3: model 2 and adjusted for the presence of major depressive episode during follow-up.

[e] $P < .01$.

[f] $P < .001$.

[g] $P < .05$.

Table 3. Obesity at Baseline and Incidence of Obesity During Follow-up by Depression Status at Baseline Incidence of Obesity During Follow-up According to Depression Status at Baseline

Depression Status	Obesity at Baseline (n = 3054)		Incidence of Obesity During Follow-up			
				OR (95% CI)		
	%	OR (95% CI)[a]	%	Model 1 (n = 2674)[b]	Model 2 (n = 2674)[c]	Model 3 (n = 2580)[d]
Current MDD						
Atypical	14.6	1.23 (0.54-2.79)	17.1	3.58 (1.25-10.25)[e]	3.66 (1.23-10.95)[e]	3.75 (1.24-11.35)[e]
Melancholic	16.4	1.49 (0.71-3.11)	8.7	2.53 (0.60-10.61)	2.80 (0.67-11.74)	3.20 (0.75-13.64)
Combined	19.4	1.73 (0.69-4.32)	4.0	0.63 (0.07-5.67)	0.80 (0.09-7.04)	0.78 (0.09-7.05)
Unspecified	13.4	1.16 (0.63-2.13)	1.2	0.19 (0.02-1.55)	0.18 (0.02-1.47)	0.18 (0.02-1.50)
Remitted MDD						
Atypical	20.0	1.98 (1.26-3.10)[f]	8.9	1.53 (0.65-3.58)	1.73 (0.72-4.15)	1.88 (0.77-4.55)
Melancholic	10.5	0.86 (0.58-1.27)	5.9	1.82 (0.94-3.55)	2.03 (1.03-4.02)[e]	2.11 (1.04-4.29)[e]
Combined	8.7	0.69 (0.34-1.39)	5.3	0.98 (0.32-3.07)	0.99 (0.32-3.07)	1.06 (0.34-3.32)
Unspecified	9.4	0.75 (0.54-1.04)	4.0	0.93 (0.51-1.67)	0.92 (0.50-1.67)	1.04 (0.57-1.92)
No MDD	13.0	1 [Reference]	5.1	1 [Reference]	1 [Reference]	1 [Reference]

Abbreviations: MDD, major depressive disorder; OR, odds ratio.

[a] Adjusted for age and sex.

[b] Model 1: logistic regression adjusted for age, sex, socioeconomic status, ethnicity, baseline body mass index, and length of follow-up.

[c] Model 2: model 1 and adjusted for physical activity, smoking habit, alcohol use, substance dependence, living alone, anxiety disorders, antidepressant use, and weight-increasing drug use.

[d] Model 3: model 2 and adjusted for presence of major depressive episode during follow-up.

[e] $P < .05$.

[f] $P < .01$.

MDD had a larger waist circumference than individuals who had never been depressed (**Table 4**). The waist circumference increased by 4.6% (8.3%) during the follow-up. Again, the presence of atypical MDD at baseline predicted elevated waist increase during the follow-up regardless of the number of variables for which we adjusted (Table 4).

The mean (SD) fat mass percentage was 33.0% (7.9%) in women and 22.7% (7.5%) in men at baseline. The fat mass was higher in women with current or remitted atypical MDD than in women who had never been depressed (**Table 5**). Similarly, men with remitted atypical MDD had an elevated fat mass at baseline. Depression status at baseline was only predictive of the increase of body fat percentage in men. Men presenting with a current atypical MDD at baseline revealed an elevated increase of body fat at follow-up.

Table 4. Waist Circumference at Baseline and Waist Circumference Change During Follow-up by Depression at Baseline

Depression Status	Waist at Baseline, cm (n = 3054)		Waist Change, % of the Baseline Value			
				β (95% CI)		
	Mean (SD)	β (95% CI)[a]	% (SD)	Model 1 (n = 2988)[b]	Model 2 (n = 2988)[c]	Model 3 (n = 2883)[d]
Current MDD						
Atypical	89.8 (11.8)	4.52 (1.53 to 7.51)[e]	6.8 (8.2)	2.31 (0.14 to 4.49)[f]	2.39 (0.20 to 4.58)[f]	2.44 (0.21 to 4.66)[f]
Melancholic	85.5 (14.6)	0.42 (−2.38 to 3.23)	5.4 (8.5)	0.55 (−1.46 to 2.57)	0.42 (−1.61 to 2.46)	0.51 (−1.59 to 2.61)
Combined	87.8 (10.6)	3.27 (−0.44 to 6.97)	4.2 (9.1)	−0.43 (−3.09 to 2.23)	−0.32 (−2.99 to 2.35)	0.12 (−2.64 to 2.89)
Unspecified	87.1 (13.0)	0.41 (−1.73 to 2.54)	5.5 (9.3)	1.09 (−0.45 to 2.63)	1.18 (−0.38 to 2.73)	1.04 (−0.55 to 2.64)
Remitted MDD						
Atypical	88.7 (14.5)	3.52 (1.71 to 5.33)[g]	5.5 (9.1)	0.9 (−0.42 to 2.21)	1.01 (−0.31 to 2.34)	0.86 (−0.49 to 2.21)
Melancholic	85.1 (13.9)	−0.64 (−1.89 to 0.61)	6.1 (9.9)	0.75 (−0.16 to 1.66)	0.81 (−0.12 to 1.74)	0.92 (−0.03 to 1.87)
Combined	85.6 (12.2)	0.65 (−1.42 to 2.72)	5.2 (9.2)	−0.34 (−1.83 to 1.15)	−0.31 (−1.82 to 1.20)	−0.14 (−1.67 to 1.40)
Unspecified	85.4 (12.2)	−0.74 (−1.75 to 0.27)	4.6 (8.3)	−0.03 (−0.77 to 0.70)	−0.09 (−0.83 to 0.65)	−0.12 (−0.88 to 0.64)
No MDD	88.8 (12.9)	0 [Reference]	4.0 (7.6)	0 [Reference]	0 [Reference]	0 [Reference]

Abbreviation: MDD, major depressive disorder.

[a] Robust regression adjusted for age.

[b] Model 1: robust regression adjusted for age, sex, socioeconomic status, ethnicity, living alone, and length of follow-up.

[c] Model 2: model 1 and adjusted for physical activity, smoking habit, alcohol use, drug dependence, anxiety disorders, antidepressant use, and weight-increasing drug use.

[d] Model 3: model 2 and adjusted for presence of major depressive episode during follow-up.

[e] $P < .01$.

[f] $P < .05$.

[g] $P < .001$.

Discussion

To our knowledge, the present study is the first to assess the prospective associations between subtypes of MDD and the subsequent changes in adiposity in the general population. The most salient findings were that (1) MDD with atypical features is prospectively associated over a 5.5-year period with a higher increase in adiposity in terms of BMI, incidence of obesity, and waist circumference in both sexes as well as fat mass in men. (2) The higher increase of adiposity in individuals with MDD with atypical features is not explained by potential confounders including sociodemographic and lifestyle characteristics, comorbid mental disorders, antidepressant medication, or other potentially weight-increasing medications. And (3) the elevated BMI increase in individuals with MDD with atypical features is not a temporary phenomenon but persists after the remission of the depressive episode and is not attributable to new episodes.

The results of the present study should be considered in the context of several limitations. First, the interval of approximately 1 year between the physical and the psychiatric baseline evaluations entailed the risk for 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 adiposity. Second, in 19% of participants who refused the diagnostic interview at the follow-up visit, the occurrence of a depressive episode during the follow-up period needed to be determined using a depression scale rather than a diagnostic interview. However, it is unlikely that this limitation introduced a differential bias because participation at the interview did not differ across diagnostic groups. Third, participants and nonparticipants at the physical follow-up differed with respect to sociodemographic and behavioral characteristics, suggesting that individuals with a less healthy lifestyle were less likely to participate. Nonetheless, because only 13% of the initial sample did not participate at the follow-up, it is unlikely that nonparticipation introduced a substantial bias. Fourth, the data of the present study were 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 adiposity. Fifth, our assessment of physical activity only partially reflected daily activity and energy expenditure.

The observed strong association between the atypical subtype of MDD and an increased BMI and waist circumference confirms findings from previous cross-sectional research[16,17,19] and is compatible with the results of a longitudinal study with multiple assessments between ages 20 and 40 years.[18] As the association between MDD and adiposity was almost exclusively restricted to MDD with atypical features in our study, it is not surprising that the ORs of developing obesity for individuals with this subtype (OR, 2.41) was much higher than that of the association between the overall diagnosis of depression and obesity according to a recent meta-analysis of longitudinal studies (OR, 1.59).[12] The discrepant results from previous studies, which did not assess specific MDD subtypes, could be attributable to variance in the proportion of the atypical subtype. This is probably also true for the inconsistent results of previous research regarding waist circumference. Indeed, previous cross-sectional studies, which did not subtype depression, yielded 2 positive[32,33] and 2 negative[34,35] find-

Table 5. Fat Mass at Baseline and Fat Mass Change During Follow-up by Depression Status at Baseline

	Body Fat Mass at Baseline, %		Fat Mass Change, % of the Baseline Value			
				β (95% CI)		
Depression Status	Mean (SD)	β (95% CI)[a]	% (SD)	Model 1[b]	Model 2[c]	Model 3[d]
Women, No.		1604		1324	1324	1281
Current MDD						
Atypical	36.8 (7.8)	3.58 (1.10 to 6.07)[e]	11.0 (17.3)	1.05 (−5.44 to 7.53)	0.52 (−6.03 to 7.06)	0.72 (−6.06 to 7.50)
Melancholic	33.6 (8.1)	1.30 (−0.94 to 3.53)	9.3 (23.1)	−3.91 (−9.49 to 1.67)	−3.49 (−9.15 to 2.17)	−2.84 (−8.76 to 3.08)
Combined	35.2 (7.8)	2.69 (−0.22 to 5.60)	11.9 (27.3)	4.26 (−3.19 to 11.71)	4.72 (−2.78 to 12.22)	4.46 (−3.35 to 12.28)
Unspecified	32.2 (7.0)	0.41 (−1.55 to 2.37)	7.3 (17.6)	−0.91 (−6.00 to 4.18)	0.14 (−5.01 to 5.29)	0.73 (−4.62 to 6.09)
Remitted MDD						
Atypical	34.9 (8.2)	2.45 (0.99 to 3.92)[e]	6.0 (20.1)	−0.96 (−4.58 to 2.65)	−0.63 (−4.27 to 3.02)	−0.45 (−4.18 to 3.28)
Melancholic	32.1 (7.9)	−0.31 (−1.38 to 0.76)	12.2 (26.2)	0.56 (−2.06 to 3.19)	0.87 (−1.80 to 3.54)	0.93 (−1.83 to 3.70)
Combined	33.5 (7.8)	1.12 (−0.58 to 2.82)	15.4 (72.6)	−0.68 (−4.93 to 3.57)	−0.6 (−4.94 to 3.73)	0.01 (−4.46 to 4.49)
Unspecified	32.5 (7.9)	−0.18 (−1.08 to 0.73)	12.6 (51.8)	−1.1 (−3.37 to 1.18)	−1.17 (−3.46 to 1.13)	−0.87 (−3.24 to 1.49)
No MDD	32.9 (7.9)	0 [Reference]	12.6 (41.6)	0 [Reference]	0 [Reference]	0 [Reference]
Men, No.		1423		1221	1221	1178
Current MDD						
Atypical	23.5 (6.0)	0.47 (−1.98 to 2.93)	30.7 (36.5)	15.87 (4.45 to 27.28)[e]	16.55 (5.06 to 28.04)[e]	16.36 (4.81 to 27.92)[e]
Melancholic	23.4 (6.3)	1.24 (−1.30 to 3.77)	18.2 (20.4)	5.85 (−4.64 to 16.33)	6.43 (−4.07 to 16.94)	8.06 (−2.99 to 19.11)
Combined	26.6 (7.0)	2.75 (−0.71 to 6.21)	2.7 (18.3)	−6.11 (−20.34 to 8.11)	−6.76 (−20.95 to 7.43)	−9.23 (−24.74 to 6.29)
Unspecified	22.9 (5.8)	0.33 (−1.17 to 1.83)	12.4 (19.8)	2.43 (−3.72 to 8.57)	3.36 (−2.82 to 9.55)	2.61 (−3.74 to 8.97)
Remitted MDD						
Atypical	23.6 (6.7)	1.66 (0.05 to 3.27)[f]	11.6 (22.2)	0.67 (−5.82 to 7.15)	2.02 (−4.64 to 8.69)	1.97 (−4.85 to 8.78)
Melancholic	22.3 (6.0)	−0.24 (−1.25 to 0.77)	16.6 (27.3)	3.15 (−1.07 to 7.38)	4.11 (−0.20 to 8.41)	3.28 (−1.21 to 7.76)
Combined	22.2 (4.6)	0.06 (−1.69 to 1.81)	8.5 (24.2)	−0.33 (−7.53 to 6.87)	0.40 (−6.90 to 7.70)	0.01 (−7.37 to 7.39)
Unspecified	21.9 (5.1)	−0.34 (−1.09 to 0.40)	12.4 (23.3)	0.84 (−2.27 to 3.95)	1.07 (−2.06 to 4.21)	0.90 (−2.32 to 4.13)
No MDD	22.8 (5.7)	0 [Reference]	10.5 (23.0)	0 [Reference]	0 [Reference]	0 [Reference]

Abbreviation: MDD, major depressive disorder.

[a] Robust regression adjusted for age.

[b] Model 1: robust regression adjusted for age, sex, socioeconomic status, ethnicity, living alone, and length of follow-up.

[c] Model 2: model 1 and adjusted for physical activity, smoking habit, alcohol use, drug dependence, anxiety disorders, antidepressant use, and weight-increasing drug use.

[d] Model 3: model 2 and adjusted for the presence of major depressive episode during follow-up.

[e] $P < .01$.

[f] $P < .05$.

ings. In addition, 1 prospective study based on a 5-year follow-up documented a positive association between current depression and visceral fat increase but not with waist circumference increase.[36] The finding of a stronger association of the atypical MDD subtype with adiposity in current than in remitted depressed participants in our study was attributable to the higher degree of severity of current disorders. Indeed, individuals who were depressed at baseline were more likely to experienced long-lasting or highly recurrent depressive episodes, which was reflected by the significantly longer time they had spent in episodes than participants with remitted depression.

Interestingly, participants with remitted melancholic depression, who typically have decreased appetite during depressive episodes, also gained more weight and had a higher incidence of obesity during the follow-up period than those who had never been depressed. However, these participants did not reveal a higher BMI or a higher prevalence of obesity at the follow-up than those who had never been depressed as their low baseline measures aligned themselves to those of individuals who had never been depressed across time. The weight gain of these participants likely reflected the compensation of the weight loss that occurred during the previous depressive episode.

Conclusions

The present study provides additional insight into the complex relationship between atypical depression and adiposity by demonstrating that the high comorbidity between this depression subtype and obesity is not simply attributable to the occurrence of atypical depressive symptoms in already obese individuals, but to a strong prospective association between the atypical MDD subtype and adiposity. Moreover, this finding strongly advocates the subtyping of the heterogeneous depression diagnosis in future research.[37] As suggested by previous research, specific depression subtypes are likely associated with different biological correlates and with differential pathways to cardiovascular risk.[37] Although it is plau-

sible that increased appetite during depressive episodes with atypical features can lead to temporary weight gain, our finding of persistently elevated BMI increase after a follow-up period of more than 5 years, even in individuals with remitted episodes, supports a potential obesity-related pathway from atypical depression to CVD and other chronic diseases related to obesity. Mechanisms that could link depression and obesity include adipokine, pro-inflammatory dysregulation, alterations in the hypothalamic-pituitary-adrenal axis,[38,39] weight-increasing effects of psychotropic medication, lifestyle factors (poor nutrition and physical inactivity[40]), and psychological factors such as emotional eating and beliefs about one's inability to maintain physical activity behaviors in depressed individuals.[41] Other research also suggests the potential involvement of genetic determinants, such as the *FTO* gene, which has been shown to selectively favor weight gain in depressed individuals.[42] This gene could also be associated with the atypical depression subtype.[43] Another study supports a specific association between the atypical depression subtype and elevated inflammatory markers, which are well known to be associated with obesity, whereas hypercortisolemia was linked to the melancholic subtype.[37] Our results do not support a significant role of medication or physical exercise in the prospective association between atypical depression and adiposity, whereas the role of the hypothalamic-pituitary-adrenal axis, adipokines, and inflammatory processes in this association still needs to be determined in longitudinal research.

For the clinician, the atypical subtype deserves particular attention because this subtype is a strong predictor of adiposity. Accordingly, the screening of atypical features and, in particular, increased appetite in individuals with depression is crucial. The prescription of appetite-stimulating medication should be avoided in these patients and dietary measures during depressive episodes with atypical features are advocated. Clinical studies need to determine to what degree the timely and appropriate treatment of depressive episodes with atypical features can prevent an increase of adiposity during and after such episodes and thereby reduce the long-term risk for CVD and other chronic diseases related to obesity.

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Study concept and design: Vollenweider, Preisig.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lasserre.
Critical revision of the manuscript for important intellectual content: Glaus, Vandeleur, Marques-Vidal, Vaucher, Bastardot, Waeber, Vollenweider, Preisig.
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Correction: This article was corrected online July 11, 2014, for errors in Table 3.

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CORRECTION

Typographical Error in Article: In the article titled "Neuroimaging Evidence for a Role of Neural Social Stress Processing in Ethnic Minority–Associated Environmental Risk" published in the June issue of *JAMA Psychiatry* (2014;71[6]:672-680. doi:10.1001/jamapsychiatry.2014.35), an error was made. Under the subhead titled Assessment of Stress Task–Related Psychological and Hormonal Variables in the Methods section, the first sentence appeared as "The separation of the doublet must have been 7 Hz. tress task–related psychometric assessments included a scale for subjective emotional responses to acute stress[45]…." It should read, "Stress task–related psychometric assessments included a scale for subjective emotional responses to acute stress[45]…." This article was corrected online.

Appendix II

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ORIGINAL ARTICLE

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

AM Lasserre[1], M-PF Strippoli[1], J Glaus[1,2], M Gholam-Rezaee[1], CL Vandeleur[1], E Castelao[1], P Marques-Vidal[3], G Waeber[3], P Vollenweider[3] and M Preisig[1]

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 ($\beta = 2.41$; 95% CI 1.19–3.63) and independently of this, with a steeper increase of the fasting glucose level ($\beta = 131$; 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.

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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

[1]Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, Prilly, Switzerland; [2]Genetic Epidemiology Research Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, USA and [3]Department of Internal Medicine, Lausanne University Hospital, Lausanne, Switzerland. Correspondence: Dr AM Lasserre, Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, University of Lausanne, Site de Cery, Lausanne, Prilly 1008, Switzerland.
E-mail: Aurelie.Lasserre@chuv.ch
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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.

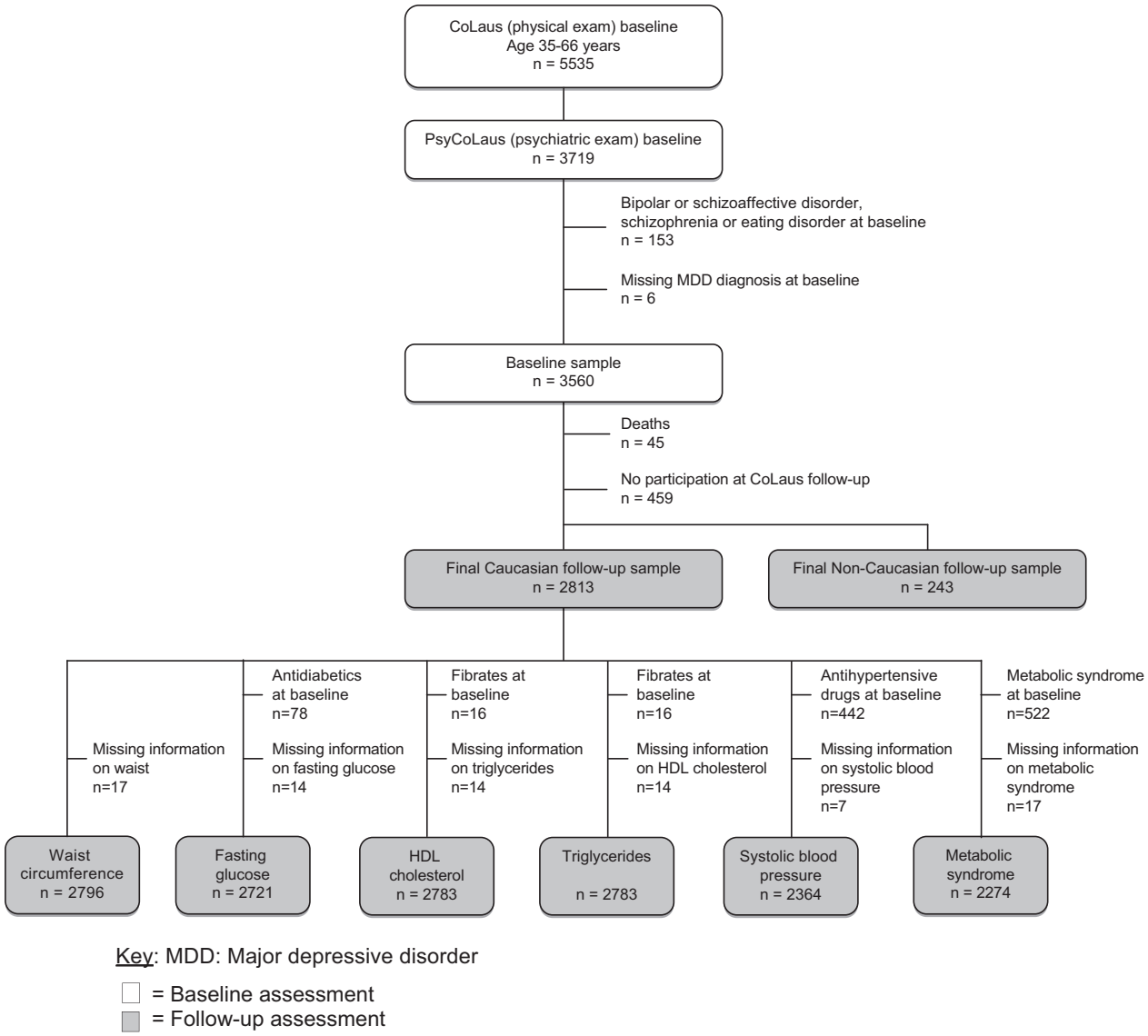

Figure 1. Flow chart of the study for the association between depressive subtypes at baseline and cardio-metabolic risk factors at follow-up. MDD, major depressive disorder; □, baseline assessment; ■, follow-up assessment.

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. X^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							
	Atypical		*Melancholic*		*Unspecified*		*No MDD*	
	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)	$\beta = 0.05$ (−0.20, 0.30)	1.22 (0.52, 2.81)	$\beta = -0.08$ (−0.26, 0.11)	1.19 (0.50, 3.21)	$\beta = -0.10$ (−0.25, 0.05)	1.35 (0.60, 3.39)	
Tumor necrosis factor-α, pg ml^{-1}	2.96 (1.84, 4.93)	$\beta = 0.09$ (−0.06, 0.23)	2.72 (1.62, 4.29)	$\beta = -0.02$ (−0.13, 0.08)	2.61 (1.58, 4.18)	$\beta = -0.06$ (−0.15, 0.02)	2.87 (1.86, 4.45)	
hs-CRP, mg l^{-1}	1.20 (0.60, 2.60)	$\beta = 0.15$ (−0.02, 0.31)	1.00 (0.50, 2.30)	$\beta = -0.05$ (−0.17, 0.07)	1.00 (0.50, 2.10)	$\beta = -0.07$ (−0.16, 0.03)	1.10 (0.50, 2.30)	
Adiponectin, μg ml^{-1}	9.36 (5.69, 12.98)	$\beta = -0.03$ (−0.12, 0.07)	9.33 (5.42, 13.75)	$\beta = -0.01$ (−0.08, 0.06)	8.79 (5.61, 13.72)	$\beta = 0.02$ (−0.04, 0.07)	7.82 (4.97, 11.84)	
Leptin, ng ml^{-1}	11.78 (6.61, 21.44)	**$\beta = 0.16$* (0.04, 0.28)**	10.86 (6.03, 18.22)	$\beta = 0.06$ (−0.04, 0.15)	9.97 (5.18, 18.39)	$\beta = 0.01$ (−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)	$\beta = -40.6$ (−140.4, 59.3)	1799.0 (657.7)	$\beta = 64.7$ (−8.6, 138.0)	1817.3 (727.7)	$\beta = 15.0$ (−43.2, 73.2)	1869.9 (730.6)	
Carbohydrate consumption at follow-up, kcal per day	784.7 (361.7)	$\beta = -18.8$ (−73.9, 36.3)	855.1 (363.2)	**$\beta = 48.4$* (7.9, 88.6)**	848.1 (401.0)	$\beta = 16.1$ (−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)	**$\beta = 0.13$* (0.03, 0.23)**	1.56 (1.07, 2.40)	$\beta = 0.05$ (−0.03, 0.12)	1.50 (1.01, 2.24)	$\beta = 0.00$ (−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 ($\beta = 2.28$ after adjustment instead of 2.35) or melancholic MDD ($\beta = 1.27$ after adjustment instead of 1.36), although binge eating at follow-up was significantly associated with this metabolic outcome ($\beta = 2.27$, 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 ($\beta = 2.30$, 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 ($\beta = 1.41$ 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 ($\beta = 1.62$, 95% C.I. −2.63–5.88 for atypical MDD, $\beta = -1.55$, 95% C.I. −5.38–2.28 for melancholic MDD, $\beta = -2.83$, 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 ($\beta = 40$; 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 ($\beta = 149$ 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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Appendix III

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Research report

Clinical and course characteristics of depression and all-cause mortality: A prospective population-based study

Aurélie M. Lasserre [a,*], Helena Marti-Soler [b], Marie-Pierre F. Strippoli [a], Julien Vaucher [c], Jennifer Glaus [a], Caroline L. Vandeleur [a], Enrique Castelao [a], Pedro Marques-Vidal [b], Gérard Waeber [c], Peter Vollenweider [c], Martin Preisig [a]

[a] Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, 1008 Prilly, Switzerland
[b] Institute of Social and Preventive Medicine (IUMSP), Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland
[c] Department of Internal Medicine, Lausanne University Hospital, 1011 Lausanne, Switzerland

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ABSTRACT

Background: Given the large heterogeneity of depressive disorders (DD), studying depression characteristics according to clinical manifestations and course is a more promising approach than studying depression as a whole. The purpose of this study was to determine the association between clinical and course characteristics of DD and incident all-cause mortality.

Methods: CoLaus|PsyCoLaus is a prospective cohort study (mean follow-up duration=5.2 years) including 35–66 year-old randomly selected residents of an urban area in Switzerland. A total of 3668 subjects (mean age 50.9 years, 53.0% women) underwent physical and psychiatric baseline evaluations and had a known vital status at follow-up (98.8% of the baseline sample). Clinical (diagnostic severity, atypical features) and course characteristics (recency, recurrence, duration, onset) of DD according to the DSM-5 were elicited using a semi-structured interview.

Results: Compared to participants who had never experienced DD, participants with current but not remitted DD were more than three times as likely to die (Hazard Ratio: 3.2, 95% CI: 1.1–10.0) after adjustment for socio-demographic and lifestyle characteristics, comorbid anxiety disorders, antidepressant use, and cardiovascular risk factors and diseases. There was no evidence for associations between other depression characteristics and all-cause mortality.

Limitations: The small proportion of deceased subjects impeded statistical analyses of cause-specific mortality.

Conclusions: A current but not remitted DD is a strong predictor of all-cause mortality, independently of cardiovascular or lifestyle factors, which suggests that the effect of depression on mortality diminishes after remission and further emphasizes the need to adequately treat current depressive episodes.

1. Introduction

The high mortality associated with mental disorders has been studied for several decades (Harris and Barraclough, 1998). An association between depression and mortality has also been observed in various studies (Cuijpers and Smit, 2002; Cuijpers et al., 2013, 2014; Harris and Barraclough, 1998; Schulz et al., 2002; Van den Akker et al., 2003; Wulsin et al., 1999). Indeed, a meta-analysis of community studies (Cuijpers and Smit, 2002) found a 1.8 times elevated mortality in depressed compared to non-depressed subjects. However, the results varied largely across studies, which was also reflected by a review of clinical and community studies (Wulsin et al., 1999) that documented 29 studies providing evidence for a positive association, 13 revealing no association and 15 providing a positive association only in subgroups.

The authors of previous reviews (Schulz et al., 2002; Wulsin et al., 1999) and meta-analyses (Cuijpers and Smit, 2002; Van den Akker et al., 2003) suggested that future research should measure covariates other than demographics, in particular lifestyle factors and physical comorbidity in order to better understand the possible mechanisms underlying the association between depression and mortality. Moreover, the review of Schulz et al. (2002) also showed that the type of instrument used to assess depression is an

* Correspondence to: Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, University of Lausanne, Site de Cery, 1008 Prilly, Switzerland. Fax: +41 21 314 84 69.
E-mail address: aurelie.lasserre@chuv.ch (A.M. Lasserre).

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important source of variance across studies. Compared with negative studies, those that revealed a positive association between depression and mortality relied more frequently on a formal interview procedure than on depression rating scales. Indeed, depression rating scales are only rough indicators of clinical depression (Roberts and Vernon, 1983), hardly allow characterization into depression subtypes and do not take into account the frequent occurrence of comorbid mental disorders or past psychopathology. Given the large heterogeneity of depression in terms of symptom manifestations, course and response to pharmacological treatment (Antonijevic, 2006; Ghaemi and Vohringer, 2011), studying characteristics of depression according to clinical manifestations and course is likely to be a more promising approach than studying depression as a whole and could also help to better understand the partially inconsistent results of previous research regarding the association between depression and all-cause mortality. However, up to this date the association between course characteristics, such as the age of onset (Ferentinos et al., 2015) or the time spent in episodes has hardly been studied, whereas a recent community study showed the recency of depression to be associated with mortality due to ischemic heart disease mortality (Surtees et al., 2008). Moreover, although the results of recent studies suggest that among the depression subtypes the atypical one was most strongly associated with cardiovascular risk factors (Glaus et al., 2013; Lamers et al., 2013; Lasserre et al., 2014), the association between this subtype and mortality has not yet been examined.

The present prospective population-based cohort study designed to determine the association between depressive disorders (DD) and incident all-cause mortality over a 5-year follow-up period attempted to overcome a series of limitations of previous research by (1) the use of a semi-structured diagnostic interview that also assessed clinical (diagnostic severity level, atypical features) and course characteristics (recency, recurrence, time spent in episodes, age of onset) of (DD) and (2) the assessment of a large array of other risk factors including socio-demographic and lifestyle (smoking, alcohol use and inactivity) characteristics, comorbid anxiety disorders, antidepressant use as well as preexistent cardiovascular diseases and cardio-metabolic risk factors (obesity, hypertension, dyslipidemia and diabetes mellitus). Accordingly, the established association between DD and all-cause mortality with adjustment restricted to demographic characteristics only of the present study should be comparable with findings of previous research that also relied on formal depression diagnoses. However, in contrast to previous research the present study also allowed us to test whether this association was independent of a series of other risk factors such as lifestyle characteristics, antidepressant use and physical conditions. Similarly, we could determine the influence of clinical and course characteristics of DD on the risk of dying.

2. Methods

2.1. Study design and participants

The present paper used data from CoLaus|PsyCoLaus, a prospective cohort study designed to assess the associations between mental disorders and cardiovascular diseases (CVD) or cardiovascular risk factors in the community. The sample was randomly selected from the residents of the city of Lausanne (Switzerland) in 2003 according to the civil register (Firmann et al., 2008). Sixty-seven percent of the 35–66 year-old subjects who underwent the physical exam (CoLaus; $n=5535$) between 2003 and 2006 also accepted the psychiatric evaluation (PsyCoLaus) (Preisig et al., 2009), which resulted in a sample of 3720 individuals who had both the somatic and psychiatric evaluation. The sex distribution of the PsyCoLaus sample did not differ significantly from that of the general population in the same age range (Preisig et al., 2009). Although the youngest 5-year band of the cohort was underrepresented and the oldest 5-year band overrepresented, participants of PsyCoLaus and individuals who refused to participate revealed comparable scores on the General Health Questionnaire (GHQ-12 (Goldberg, 1972), French translation (Bettschart and Bolognini, 1996)), completed during the somatic exam. Six subjects needed to be excluded from the present analyses because of incomplete information on depressive episodes.

All subjects who participated at baseline were invited to a first follow-up evaluation between April 1st, 2009 and July 31, 2012, which allowed us to assess the vital status of 3668 out of the 3714 subjects (98.8%) who had valid information on depressive episodes at the psychiatric baseline evaluation. The reminders (46 subjects) had all moved away from Switzerland. These subjects were more likely to be physically inactive (62.2% vs. 44.2%) and to have a history of CVD (8.7% vs. 2.5%). The median follow-up period of the cohort was 5.2 years (s.d.: 0.8 years) corresponding to 19,143 person-years.

2.2. Assessments

Diagnostic information on mental disorders was collected using the semi-structured Diagnostic Interview for Genetic Studies (DIGS), which was developed and extensively validated by the NIMH Molecular Genetics Initiative (Nurnberger et al., 1994). The French translation (Leboyer et al., 1995) also revealed excellent inter-rater reliability for major DSM-IV disorders (Berney et al., 2002; Preisig et al., 1999) and minor depression (Vandeleur et al., 2014), whereas the 6-week test-retest reliability was slightly lower (Berney et al., 2002; Preisig et al., 1999). The DIGS was completed with anxiety disorder sections of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L) (Endicott and Spitzer, 1978). Major Depressive Disorders (MDD) and Other Specified Depressive Disorders (OSDD) including short-duration depressive episodes (4–13 days) and depressive episodes with insufficient symptoms (depressed affect and at least one of the other eight symptoms of a major depressive episode) were diagnosed according to the DSM-5. According to the suggestions of Angst and colleagues (Angst et al., 2002) a depressive disorder was considered as atypical if one or more episodes met at least 3 out of the 5 criteria of the DSM specifier for atypical features (the specifier is identical for DSM-IV and DSM-5): (1) mood reactivity, (2) significant weight gain or increase in appetite, (3) hypersomnia, (4) leaden paralysis and (5) interpersonal rejection sensitivity). Given the ongoing controversy regarding the definition of atypical features (Parker et al., 2002; Thase, 2009), we have chosen the none-hierarchical approach recommended by Angst et al. (2002), which in contrast to DSM-IV and DSM-5, does not require the presence of mood-reactivity. A DD was considered as current if the criteria for a depressive episode were met at the time of the baseline interview and remitted if the lifetime criteria for DD were fulfilled but the criteria for a current depressive episode were not met at the baseline assessment. The time spent in episodes was assessed by adding up the duration of all depressive episodes that the participants had reported. Age of onset was the age of onset of the first recalled episode of the DD. The two latter variables were dichotomized at the median (one year and 33 years, respectively). A lifetime anxiety disorder was diagnosed if the participant fulfilled the criteria for generalized anxiety disorder, social phobia, panic disorder or agoraphobia. Interviewers were required to be master-level psychologists, who were trained over a two month-period. They received ongoing supervision throughout the study by an experienced senior psychologist.

Information on socio-demographic and lifestyle (current smoking, number of alcoholic drinks a week, physical activity) characteristics as well as medical history and current medication was elicited using structured interviews. Socio-economic status (SES) was determined according to the Hollingshead scale (Hollingshead, 1975). The physical evaluation included the measurements of body weight, height and blood pressure as well as the collection of venous blood samples. Subjects were considered as physically inactive if they did not report leisure time physical exercise for at least 20 min twice a week. A self-reported history of CVD included coronary heart diseases (myocardial infarction, angina pectoris, pacing and coronary revascularization), stroke or peripheral arterial disease. Dyslipidemia was defined as HDL-cholesterol <1 mmol/l or LDL-cholesterol ≥ 4.1 mmol/l or triglycerides ≥ 2.2 mmol/l or lipid-lowering treatment. Obesity was defined as a Body Mass Index (BMI) ≥ 30 kg/m^2. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or anti-hypertensive treatment. Diabetes was defined as fasting blood glucose ≥ 7 mmol/l or diabetes treatment.

The vital status of the participants was systematically ascertained at the first follow-up exam. All participants of the baseline investigation received letters explaining them the follow-up exam. In a second step they were contacted by phone in order to schedule the follow-up exam. If the letter was returned by the post office because the subject had moved away or if subjects could not be reached by phone, the civil register of the community in which the subjects was living at the time of the baseline exam was systematically perused to obtain information on address changes or the occurrence and date of death. In case of a move within Switzerland, the civil register could always provide us with the names of the communities subjects had moved to. If they could not be reached at their new address, we verified their vital status through the civil register of their new community. However, if subjects had moved outside of Switzerland the civil register could not provide us with information on the subjects' new address. This was the unique reason for missing information on the subjects' vital status ($n=46$).

If a relative or the civil register had informed us that a subject had died we established the cause of death using all available sources of information: (1) general practitioners; (2) any hospital in Switzerland where the death had occurred; (3) the pre-hospital emergency care unit of the City of Lausanne; (4) the forensic medicine department of the University Hospital of Lausanne; (5) the *Swiss Statistics of the Swiss Confederation* (governmental agency providing death statistics based on official death certificates). If medical records were available the causes of death was adjudicated by 2 internal medicine specialists. Owing to the lack of accuracy of official death certificates, (Ives et al., 2009), the latter were only used to assign the cause of death in the absence of medical records.

2.3. Statistical analysis

All analyses were performed using the Statistical Analysis System version 9.3 for Windows (SAS Institute, Inc., Cary, NC, USA). Univariate analyses were conducted using chi-square or Student's *t*-tests as appropriate. The association between DD or characteristics of DD and mortality was assessed using serially adjusted proportional hazard models. The association between the following depression characteristics and mortality were assessed: diagnostic severity level (MDD vs. OSDD vs. none), clinical subtype (atypical vs. non atypical depression vs. none), recency (current vs. remitted vs. none), recurrence (recurrent vs. single episode vs. none), time spent in episode (at least one year [median] vs. less than one year vs. none) and age of onset (before 33 years [median] vs. 33 years or later vs. none). These associations were first established in separate models for each characteristic (Model 1) with adjustment for demographic characteristics (age, sex, SES, living alone and ethnicity), anxiety disorders (generalized anxiety disorder, social phobia, panic disorder, agoraphobia), lifestyle factors (inactivity, smoking, alcohol consumption), cardio-metabolic conditions (obesity, hypertension, dyslipidemia, diabetes), a history of CVD and current antidepressant use. In a next step, the six characteristics of DD were allowed to compete in the same model. This model was first adjusted for socio-demographic characteristics (Model 2) and then also for anxiety disorders, lifestyle factors, cardio-metabolic conditions, a history of CVD and current antidepressant use (Model 3). The proportional hazards assumption was verified for all the characteristics of depression. Missing data (25 for physical activity, 10 for anxiety disorder status) were compensated with multiple imputations (Makov Chain Monte Carlo method (Schafer, 1997; White et al., 2011) and Rubin's multiple imputation strategy (Rubin, 1987; Sterne et al., 2009)).

2.4. Ethics approval

The Institutional Ethics' Committee of the University of Lausanne approved the CoLaus (approvals 16/03 and 33/09) and subsequently the PsyCoLaus study (approvals 134/05 and 239/09). All participants signed a written informed consent after having received a detailed description of the goal and funding of the study.

3. Results

3.1. Baseline characteristics of the sample

Subjects with a lifetime DD were more likely to be women and to be younger, to live alone, to have a lifetime history of anxiety disorders (generalized anxiety disorder, social phobia, panic disorder or agoraphobia), to be smokers, to drink less alcohol, to have less hypertension and dyslipidemia and to use more antidepressants than never depressed subjects (Table 1). About 80% of subjects with a DD met criteria for MDD and about a sixth fulfilled criteria for atypical features or exhibited a current depressive episode at the time of the psychiatric interview, more than a third of subjects with a DD experienced recurrent episodes and nearly half of them reported episodes lasting a year or more, or an onset before 33 years.

3.2. All-cause mortality associated with DD

During the follow-up, 56 subjects (1.6%; 2.3% of men, 1.0% of women) had died. Subjects with and without a lifetime history of a DD (1.3% vs. 1.8%, respectively; hazard ratio [HR]$=0.90$; 95% Confidence Intervals [C.I.] 0.52–1.57) did not differ after adjustment for socio-demographic variables, comorbid anxiety disorders, current antidepressant use as well as cardiovascular risk factors and diseases.

3.3. All-cause mortality associated with depression characteristics

The crude and adjusted associations between specific characteristics of DD and all-cause mortality in the whole sample are provided in Table 2. The table also shows the associations between potential confounders and all-cause mortality according to proportional hazard models. According to the crude associations in terms of unadjusted HRs subjects with remitted or recurrent DD and subjects with DD that started before the age of 33 years were at a lower risk of dying during the follow-up period. In a second

Table 1
Baseline characteristics of all participants and according to the presence of a lifetime depressive disorder (DD).

	All $N=3668$	With DD $N=1971$	No DD $N=1697$	X^2/t	p
Men (%)	47.0	36.1	59.5	200.4	*< 0.001*
Age, mean (s.d.)	50.9 (8.8)	50.4 (8.7)	51.5 (8.8)	3.8	*< 0.001*
SES, mean (s.d.)	3.4 (1.3)	3.4 (1.3)	3.4 (1.3)	−0.6	*n.s.*
Living alone (%)	33.1	39.3	26.0	72.6	*< 0.001*
Non-Caucasian (%)	8.2	8.9	7.3	3.0	*n.s.*
Anxiety disorders[a] (%)	17.9	22.7	12.4	65.1	*< 0.001*
Current smoking (%)	28.6	30.7	26.2	9.2	*< 0.01*
Alcohol units per week, mean (s.d.)	6.8 (9)	5.9 (8.0)	7.9 (10.0)	6.7	*< 0.001*
Inactivity[b] (%)	44.2	44.1	44.4	0.0	*n.s.*
Obesity (%)	13.4	12.4	14.4	3.2	*n.s.*
Hypertension (%)	29.9	27.3	32.8	13.3	*< 0.001*
Dyslipidemia (%)	32.4	30.6	34.5	6.3	*< 0.05*
Diabetes mellitus (%)	5.2	4.7	5.7	2.1	*n.s.*
History of CVD (%)	2.5	2.6	2.5	0.0	*n.s.*
Current antidepressant use (%)	8.3	12.6	3.3	104.2	*< 0.001*
Characteristics of DD:					
MDD (%)	n/a	81.7	n/a	n/a	n/a
Atypical features (%)	n/a	16.5	n/a	n/a	n/a
Current (%)	n/a	17.5	n/a	n/a	n/a
Recurrent (%)	n/a	35.4	n/a	n/a	n/a
Time in episodes ≥ 1 year (%)	n/a	46.5	n/a	n/a	n/a
Onset < 33 years (%)	n/a	49.0	n/a	n/a	n/a

SES: socio-economic status according to the Hollingshead Index (5 is highest level), CVD: cardiovascular disease, *MDD:* Major Depressive Disorder, X^2/t: Chi-square test (dichotomous variables)/*t*-test (continuous variables).

[a] Includes generalized anxiety disorder, social phobia, panic disorder and agoraphobia.

[b] Physical activity during 20 min less than twice a week.

step (Model 1) we run proportional hazard models separately for each of the 6 characteristics of DD with adjustment for demographic characteristics, anxiety disorders, lifestyle variables, cardio-metabolic diseases, a history of CVD and current antidepressant use (results not shown). Regardless of the number of variables models were adjusted for only current DD was significantly associated with mortality (HR for current DD according to the fully adjusted model=2.32, 95%CI 1.12–4.80), whereas the other characteristics of DD that were negatively associated with the risk of dying according to the crude HRs were not associated with mortality any longer (remitted DD: HR 0.62, 95%CI 0.33–1.19; recurrent DD: HR 0.42, 95%CI 0.14–1.24; age of onset before 33 years: HR 0.61, 95%CI 0.26–1.43). The fact that the unadjusted association between current DD and all-cause mortality did not meet significance criteria was due to confounding by sex and age; i.e. participants with a current DD were more likely to be women and younger, which were both negatively associated with mortality. In the next step all depression characteristics were simultaneously introduced in the same proportional hazard model adjusted for socio-demographic characteristics (Model 2) and subsequently also for anxiety disorders, lifestyle variables, cardio-metabolic diseases, a history of CVD current antidepressant use (Model 3). In order to avoid overspecification of the model, we could only enter the two levels of the depression characteristic recency (current vs. remitted), whereas for the other characteristics of DD the intermediate level needed to be dropped. According to these models, participants with current DD at baseline revealed significantly and more than three times elevated mortality (Table 2). Among the covariates a history of CVD was most strongly associated with mortality, followed by current smoking, living alone, male sex, inactivity and increasing age. Interestingly, the HR for a history of CVD was close to that of a current DD (3.50 vs. 3.23) and each of the two HRs lay within the 95% C.I. of the other HR.

As the HRs for subjects exhibiting a current depressive episode and that for subjects in remission at baseline differed significantly (the HR for subjects with current DD lay above the upper bound of the 95% C.I. of the HR for subjects with remitted DD and the HR for subjects with remitted DD lay below the lower bound of the 95% C. I. of the HR for subjects with current DD) regardless of the number of adjustments, we compared the two groups of subjects with DD regarding other characteristics (Table 3). These two groups did not differ in socio-demographic characteristics except for socio-economic status. However, the subjects with current DD were more likely to have a lifetime history of anxiety disorders, to be obese or inactive, to have antidepressant treatment, to meet criteria for a MDD rather than an OSDD, to exhibit an atypical depression subtype, to have a recurrent DD and to have spent more than one year in depression. Although these differences suggest higher severity of current depression, the HRs for current and remitted depression still significantly differed after an additional adjustment for lifetime social functioning (GAF score) as a supplementary indicator of disorder severity (HR=3.16, 95% 1.02–9.82 and HR=0.98, 95% 0.38–2.54, respectively). Regardless of the number of adjustments the HR for remitted depression always lay below the lower bound of the 95% C.I. of the HR for current depression.

3.4. Cause-specific mortality by depression status

Table 4, provides the results of the analyses regarding the associations between current/remitted depression status and specific causes of death. The HRs derived from proportional hazard models were adjusted for the other assessed depression characteristics, demographic and lifestyle variables, anxiety disorders, cardio-metabolic diseases and antidepressant use. Due to the small number of events, only the strong association between current DD and cardio-vascular death reached the level of statistical significance. However, given that the established HRs for the other causes of death lay all within the wide 95% C.I. of the HR for cardiovascular death, our results do not suggest that excess mortality related to current depression was attributable to one specific cause of death.

4. Discussion

The present study is, to our knowledge, the first to prospectively assess all-cause mortality associated with clinical and course-related features of depressive disorders in the community with adjustment for a comprehensive array of potential confounding covariates including socio-demographic and lifestyle characteristics, comorbid anxiety disorders, antidepressant use, a history of CVD as well as accurately measured cardiovascular risk factors. The most salient finding was that subjects with a current but not a remitted depressive disorder were more than three times as likely to die within a 5-year follow-up period than never depressed subjects. The magnitude of the risk of currently depressed subjects to die was nearly as high as that of subjects with a history of a CVD. Among all the clinical or course-related characteristics of depression, it was only the recency of depression that was associated with all-cause mortality.

Our results presented need to be viewed in the light of several limitations. First, the proportion of subjects who died was relatively small which impeded accurate analyses of cause-specific mortality. Second, for 46 subjects (1.2%) we could not determine the vital status at follow-up because all of them moved away from Switzerland. Considering the small proportion of subjects with missing vital status and given that there is hardly a reason to

Table 2
Associations between characteristics of depressive disorders and all-cause mortality ($N=3668$).

	Death	Crude HR		Model 2		Model 3	
	%	HR	95% C.I.	HR	95% C.I.	HR	95% C.I.
DD characteristics:							
Recency[a]*:*							
Current	3.2	1.90	(0.95;3.79)	3.90*	(1.28;11.91)	3.23*	(1.05;9.95)
Remitted	0.9	0.53*	(0.29;0.98)	1.06	(0.42;2.69)	0.95	(0.36;2.48)
Diagnostic severity[a]*:*							
MDD	1.2	0.72	(0.41;1.27)	0.66	(0.24;1.82)	0.68	(0.24;1.92)
OSDD	1.7	0.95	(0.39;2.27)				
Atypical features[a]*:*							
Yes	1.5	0.89	(0.35;2.3)	1.22	(0.45;3.34)	1.00	(0.36;2.82)
No	1.3	0.74	(0.42;1.29)				
Recurrence[a]*:*							
Recurrent	0.6	0.33*	(0.12;0.95)	0.36	(0.12;1.11)	0.38	(0.12;1.19)
Single episode	1.7	0.99	(0.57;1.72)				
Time spent in episode[a]*:*							
>1 year	1.5	0.90	(0.48;1.69)	1.23	(0.50;3.06)	1.47	(0.58;3.74)
≤ 1 year	1.1	0.65	(0.33;1.27)				
Age of onset[a]*:*							
<33 years	0.7	0.42*	(0.19;0.96)	0.76	(0.30;1.92)	0.79	(0.31;2.02)
≥ 33 years	1.9	1.09	(0.61;1.93)				
No DD (ref.)	1.8	1 (ref.)					
Men	2.2	2.39**	(1.36;4.18)	2.89***	(1.6;5.23)	2.17*	(1.14;4.13)
Women (ref.)	0.9	1 (ref.)					
Age (cont.)	–	1.07***	(1.04;1.11)	1.79***	(1.35;2.37)	1.66**	(1.22;2.26)
SES (cont.)	–	0.93	(0.76;1.14)	0.91	(0.69;1.19)	0.99	(0.74;1.31)
Living alone	2.4	2.14**	(1.27;3.62)	2.56***	(1.49;4.38)	2.52**	(1.45;4.38)
Not living alone (ref.)	1.1	1 (ref.)					
Non-Caucasian	0.7	0.70	(0.17;2.88)	0.80	(0.19;3.33)	0.75	(0.18;3.22)
Caucasian (ref.)	1.6	1 (ref.)					
Anxiety disorders[b]	1.1	0.63	(0.28;1.38)			0.73	(0.32;1.65)
No anxiety disorders[b] (ref.)	1.6	1 (ref.)					
Current smoking	2.9	2.82***	(1.67;4.76)			2.78	(1.59;4.84)
Not current smoking (ref.)	1.0	1 (ref.)					
Alcohol use (cont.)	–	1.02	(1.00;1.04)			0.91	(0.73;1.13)
Inactivity[c]	2.2	2.17**	(1.27;3.73)			1.91	(1.09;3.37)
No inactivity[c] (ref.)	1.0	1 (ref.)					
Obesity	2.5	1.71	(0.90;3.24)			0.89	(0.43;1.84)
No obesity (ref.)	1.4	1 (ref.)					
Hypertension	2.7	2.53***	(1.50;4.27)			1.31	(0.70;2.44)
No hypertension (ref.)	1.1	1 (ref.)					
Dyslipidemia	2.5	2.36**	(1.40;4.00)			1.42	(0.81;2.50)
No dyslipidemia (ref.)	1.1	1 (ref.)					
Diabetes mellitus	4.8	3.55***	(1.74;7.25)			1.29	(0.57;2.93)
No diabetes mellitus (ref.)	1.4	1 (ref.)					
History of CVD	8.6	6.39***	(3.02;13.51)			3.50**	(1.54;7.97)
No history of CVD (ref.)	1.3	1 (ref.)					
Current antidepressant use	1.0	0.62	(0.19;1.99)			0.45	(0.13;1.50)
No antidepressant (ref.)	1.6	1 (ref.)					

HR: hazard ratio, 95% C.I.: 95% confidence interval, *SES:* Socio-economic status according to the Hollingshead Index (5 is highest level), ref.: reference group, cont.: continuous variable, *CVD:* cardiovascular disease, *MDD:* Major Depressive Disorder, OSDD: Other Specified Depressive Disorders.

* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.
Model 2 and 3 are proportional hazard models.
[a] Reference group is no DD.
[b] Includes generalized anxiety disorder, social phobia, panic disorder and agoraphobia.
[c] Physical activity during 20 min less than twice a week.

assume that the association between DD and mortality differs between subjects who moved away from Switzerland and those who stayed in the country, it is unlikely that the loss of subjects due to missing vital status at follow-up had introduced a sizable bias. Third, we did not collect information on dietary patterns, help-seeking behaviors or non-adherence to treatment although these variables could have contributed to the association between depression and mortality (Cuijpers and Schoevers, 2004; Mykletun et al., 2007; Wulsin et al., 1999) and we did not assess other physical conditions than cardio-metabolic conditions. Fourth, our study was conducted in an urban area of Switzerland. However, although the particular features of the sample are likely to affect the prevalence estimate of depression, it is less likely that they significantly influenced the prospective association between depression characteristics and mortality. Fifth, the lifetime prevalence of DD is rather high compared to other population-based studies (Kessler et al., 2003). However, given that semi-structured diagnostic interviews conducted by trained interviewers entail higher prevalence estimates of depression than fully structured interviews conducted by lay interviewers according to previous research comparing the two types of diagnostic instruments, our high lifetime prevalence of DD is likely to be attributable to the use of a semi-structured interview (Eaton et al., 2000). Moreover, although the use of a potentially more valid semi-structured rather

Table 3
Baseline characteristics of participants with a depressive disorder (DD) according to current or remitted status ($N=1971$).

	Current DD $N=345$	Remitted DD $N=1626$	X^2/t	p
Men (%)	35.9	36.2	0.0	*n.s.*
Age, mean (s.d.)	50.4 (8.3)	50.4 (8.8)	0.0	*n.s.*
SES, mean (s.d.)	3.1 (1.3)	3.5 (1.3)	5.0	*< 0.001*
Living alone (%)	39.4	39.2	0.0	*n.s.*
Non-caucasian %	10.7	8.5	1.8	*n.s.*
Anxiety disorders[a] (%)	27.3	21.7	5.0	*< 0.05*
Current smoking (%)	31.9	30.4	0.3	*n.s.*
Alcohol units per week, mean (s.d.)	6.0 (9.0)	5.9 (7.7)	-0.2	*n.s.*
Inactivity[b] (%)	58.3	41.1	33.5	*< 0.001*
Obesity (%)	16.8	11.5	7.4	*< 0.01*
Hypertension (%)	30.4	26.6	2.1	*n.s.*
Dyslipidemia (%)	33.0	30.1	1.2	*n.s.*
Diabetes mellitus (%)	6.7	4.2	3.8	*n.s.*
History of CVD (%)	2.3	2.6	0.1	*n.s.*
Current antidepressant use (%)	20.0	11.1	20.6	*< 0.001*
Characteristics of DD:				
MDD (%)	91.0	79.8	24.1	*< 0.001*
Atypical features (%)	25.8	14.6	26.0	*< 0.001*
Recurrent (%)	46.1	33.1	21.0	*< 0.001*
Time in episodes ≥ 1 year (%)	76.5	40.1	151.8	*< 0.001*
Onset < 33 years (%)	44.9	49.8	2.7	*n.s.*

SES: socio-economic status according to the Hollingshead Index (5 is the highest position), CVD: cardiovascular disease, MDD: Major Depressive Disorder, X^2: Chi-square test (dichotomous variables)/*t*-test (continuous variables).

[a] Includes generalized anxiety disorder, social phobia, panic disorder and agoraphobia.

[b] Physical activity during 20 min less than twice a week.

than a fully structured diagnostic interview was likely to affect the prevalence estimate of DD, it is less likely that it significantly affected the assessed prospective associations between characteristics of DD and mortality.

Our finding of excess mortality in subjects with current depression is consistent with those of previous research (Cuijpers and Smit, 2002; Schulz et al., 2002; Van den Akker et al., 2003; Wulsin et al., 1999), as the bulk of these studies were generally restricted to current or recent depressive episodes. However, compared to previous research in the community, which generally relied on depression rating scales, the observed magnitude of the association between depression and mortality was higher. This is consistent with the review of Schulz et al. (2002), which showed that studies relying on diagnostic interviews more frequently found a positive association between depression and mortality.

Interestingly, in our study, subjects with remitted depressive episodes at the moment of the baseline evaluation revealed a significantly lower mortality than subjects with current depression. Their unadjusted risk to die was even significantly lower than that for never depressed subjects, although their hazard ratio failed to reach the level of statistical significance after multiple adjustments. Although compared to those who were in a current depressive episode at baseline the remitted depressives were more likely to experience a less severe DD according to several indicators of severity (SES, comorbid anxiety disorder, inactivity, antidepressant treatment, fulfillment of criteria for MDD, recurrency and time spent in most severe depressive episode), depression severity could hardly explain the differential mortality rates between the current and remitted depression groups given that our analyses adjusted for all these severity indicators. Similar findings of associations between mortality and current or recent but not remitted depressive episodes have been observed in two previous community studies, the ECA (Bruce et al., 1994), and the EPIC Norfolk study (Surtees et al., 2008). Moreover, in the latter study, mortality was significantly lower for episodes that remitted more than 12 months prior to the assessment than for current depressive episodes and was even slightly lower than that observed in never depressed subjects, although the latter association did not reach the level of statistical significance. Several hypotheses could explain the distinct effects of current and remitted depression on mortality: (1) measurement errors are more pronounced for remitted than for current depressive episodes (Surtees et al., 2008), (2) subclinical manifestations of a physical disease predispose to both current depression and the full blown disease that ultimately causes death (Surtees et al., 2008), (3) subjects exhibiting current depression are affected by a more severe disorder than those with remitted depression, and (4) the effect of depression on mortality decreases after remission. The first hypothesis appears unlikely given that measurement errors alone could hardly have attenuated the established hazard ratio for the association between remitted depression and mortality to less than 1 as observed in the present study, which was based on a semi-structured diagnostic interview. Indeed, the test-retest reliability for MDD assessed through such interviews has shown to be acceptably high even for intervals of up to 5 years (Prusoff et al., 1988). Regarding the second hypothesis, given that previous research has shown depression to be a risk factor for all major disease-related causes of death (Mykletun et al., 2007) it is unlikely that subclinical manifestations of these different diseases systematically preceded the depressive episodes observed at the time of the interview. The third hypothesis is hardly compatible with our findings given that the associations between the two types of depression and mortality did not change after adjustment for all typical severity characteristics. Our results rather support the fourth hypothesis, which is also compatible with a meta-analysis that documented a lower relative risk of dying in studies with longer follow-up periods (Van den Akker et al., 2003), but not others (Cuijpers and Smit, 2002; Wulsin et al., 1999). The observed excess mortality in currently depressed subjects in conjunction with a possibly diminished risk of dying in remitted subjects in our and similarly in the EPIC-Norfolk cohort study (Surtees et al., 2008) could

Table 4
Associations between current/remitted status of depressive disorders and cause specific mortality ($N=3668$).

Cause of death	Lifetime depressive disorder						No depressive disorder
	Current ($N=345$)			Remitted ($N=1626$)			($N=1697$)
	***N* (%)**	HR[a]	(95% C.I.)	***N* (%)**	HR[a]	(95% C.I.)	***N* (%)**
Cardiovascular	**2 (0.6)**	10.91*	(1.02;116.9)	**2 (0.1)**	0.92	(0.13;6.46)	**5 (0.3)**
Cancer	**5 (1.5)**	5.07	(0.96;26.80)	**5 (0.3)**	1.04	(0.28;3.92)	**13 (0.8)**
Suicide	**1 (0.3)**	7.33	(0.24;224.3)	**3 (0.2)**	4.73	(0.28;78.70)	**1 (0.1)**
Other	**3 (0.9)**	1.76	(0.20;15.82)	**5 (0.3)**	0.77	(0.14;4.20)	**11 (0.7)**

[a] Proportional hazard model adjusted for diagnostic severity, atypical features, recurrence, time spent in episodes, age of onset of depressive disorder, socio-demographics, anxiety disorders, lifestyle characteristics, cardio-metabolic risk factors and diseases and antidepressant use.

* $p < 0.05$.

indicate an increased vulnerability of currently depressed subjects and potential resilience of those who survived the acute episode.

Although we were not able to accurately determine disease-specific mortality rates in subjects with current depression because of a limited number of subjects who died during follow-up, our data do not suggest that the elevated mortality is attributable to one specific cause of death. This corroborates previous findings (Angst et al., 2012; Mykletun et al., 2007) and a meta-analysis that demonstrated comparable depression-related excess mortality in cancer, heart and kidney disease patients, suggesting the implication of generic rather than disorder-specific mechanisms (Cuijpers et al., 2014). Interestingly, in contrast to a Canadian community study, which however assessed 12-month rather than current major depressive episodes (MDE) (Patten et al., 2011), our data support current depression as an independent predictor of all-cause mortality as the magnitude of the association remained unchanged after multiple adjustments.

Among the clinical manifestations and course features of depression, only the recency of episodes was predictive for mortality, which extends previous findings restricted to ischemic heart disease mortality (Surtees et al., 2008). It is remarkable that mortality did not differ between depressive subjects above and below the diagnostic threshold of MDD, which is consistent with a recent meta-analysis (Cuijpers et al., 2013), and further supports the clinical relevance of the newly defined DSM-5 category of OSDD. Regarding the atypical depression subtype, which has previously been found to be associated with metabolic diseases (Glaus et al., 2013; Lamers et al., 2013; Lasserre et al., 2014), our data did not provide evidence for higher mortality in subjects exhibiting this depression subtype.

Regarding the assessed covariates, it was not surprising that a history of CVD, current smoking and lack of activity were associated with mortality. It was more remarkable but consistent with some previous evidence (Udell et al., 2012) that we also observed a significant association between living alone and mortality. In contrast and similar to the HUNT study (Mykletun et al., 2007) we did not find anxiety disorders to predict mortality. Moreover, antidepressant use was not associated with mortality, which contrasts with findings of Ryan et al. (2008), who reported an association between antidepressant use and mortality in men.

In conclusion, the present results support a significant association between current but not remitted depressive episodes and all-cause mortality. This association was similar in size to that of a history of CVD. Accordingly clinicians should consider current depression as a life-threatening condition. The fact that only current depression was associated with mortality underscores the need to take the time-point of the occurrence of depressive episodes into account in future studies and suggests that the effect of depression on mortality diminishes after remission. Future studies should carefully examine clinical depression, potential confounding or mediating variables and causes of death in order to gain additional insight into the mechanisms underlying the complex association between depression and mortality. These studies should include a more comprehensive range of both somatic conditions and behavioral factors and follow the participants over a longer period of time than the previous studies.

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