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# Partially distinct combinations of psychological, metabolic and inflammatory risk factors are prospectively associated with the onset of the subtypes of major depressive disorder in midlife

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**Abstract**

**BACKGROUND** Given the well known heterogeneity of Major Depressive Disorder (MDD), dividing this complex disorder into subtypes is likely to be a more promising approach to identify its determinants than to study it as a whole.

**METHODS** In a prospective population-based cohort study (CoLaus|PsyCoLaus) with 5.5 years of follow-up, 1524 participants without MDD at baseline, aged 35 to 66 years (mean age 51.4 years, 43.4% females), participated in the physical and psychiatric baseline and the psychiatric follow-up evaluations.

**RESULTS** The incidence of both atypical and melancholic MDD during the follow-up period were predicted by female sex, a lifetime history of minor depressive disorders and higher neuroticism scores. Higher baseline body mass index was associated with the onset of atypical MDD, whereas the absence of hypertension and younger age were associated with the development of melancholic MDD. Unspecified MDD was predicted by younger age, low concentrations of tumor necrosis factor alpha and elevated life-event impact scores.

**LIMITATIONS** The age range of our cohort restricts the identification of risk factors to MDD with onset in midlife and the recruitment in an urban area limits the generalizability of the findings.

**CONCLUSIONS** Our data suggest that MDD subtypes are predicted by partially distinct combinations of baseline characteristics suggesting that these subtypes not only differ in their clinical manifestations but also in factors that contribute to their development. Subjects with minor depressive episodes, especially in combination with particular personality features, deserve close clinical attention to prevent the subsequent onset of atypical and melancholic major depression.

**Keywords**

Major depressive subtypes

Risk factors

General population

Cardio-metabolic risk

Life-events

Personality

## 1. Introduction

Major Depressive Disorder (MDD) is a complex disorder with presumably a considerable number of underlying, interrelated etiologic pathways (Kendler et al., 2002). Previous studies have suggested a large series of risk factors to be associated with the onset of MDD, including a positive family history of MDD (Wilde et al., 2014), female sex (Essau et al., 2010; Kendler et al., 2004a; Mattisson et al., 2005; Palsson et al., 2001; Vinberg et al., 2013; Wang et al., 2010), younger age (Angst et al., 2009; Friis et al., 2002; Vinberg et al., 2013; Wang et al., 2010), lower socio-economic-status (SES) (Lorant et al., 2003), smoking (Luger et al., 2014), lack of physical activity (Mammen and Faulkner, 2013), childhood trauma (M. Li et al., 2016; Mandelli et al., 2015) and other stressful life-events (Friis et al., 2002; Kendler et al., 1999; Kendler et al., 2004a; Kendler et al., 2004b; Vinberg et al., 2013; Whisman and Bruce, 1999), personality features such as elevated neuroticism (Jeronimus et al., 2016), inadequate coping (Ormel et al., 2004), as well as pre-existing mental conditions including dysthymic disorder (Horwath et al., 1992; Murphy et al., 2002), minor depressive syndromes (Murphy et al., 2002), anxiety disorders (Beesdo et al., 2010) and substance use disorders (Brook et al., 2002; Bulloch et al., 2012). In addition, meta-analyses have suggested associations between MDD and the metabolic conditions of obesity (Luppino et al., 2010), type-II diabetes (Mezuk et al., 2008; Nouwen et al., 2010) and the metabolic syndrome (Pan et al., 2012), although the mechanisms underlying these associations are still poorly understood. Finally, several studies have found inflammation markers such as the high sensitive C-Reactive Protein (hsCRP) or Interleukin 6 (IL-6) to be predictive for the onset of MDD (Khandaker et al., 2014; Pasco et al., 2010; Wium-Andersen et al., 2014).

Given the heterogeneity of depression in terms of symptom manifestations, course and response to pharmacological treatment (Antonijevic, 2006; Ghaemi and Vohringer, 2011), the subtyping of depression is likely to be a promising approach to identify its determinants. Indeed,

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 up-regulation, whereas the melancholic subtype could be related to dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis (Antonijevic, 2006; Baune et al., 2012; Harald and Gordon, 2012; Kaestner et al., 2005; Penninx et al., 2013).

Cross-sectional research has already provided support for associations between atypical depression and obesity markers (Cizza et al., 2012; Glaus et al., 2013; Lamers et al., 2013), diabetes (Glaus et al., 2013) or fasting glucose (Lamers et al., 2013), triglycerides (Lamers et al., 2013; Vogelzangs et al., 2014) and the metabolic syndrome (Glaus et al., 2013; Lamers et al., 2013; Takeuchi et al., 2013), 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 MDD with atypical features and a steeper increase in body-mass index (BMI) (Lasserre et al., 2014), waist circumference (Lasserre et al., 2014), fat-mass (Lasserre et al., 2014) and fasting glucose levels (Lasserre et al., 2016). Similarly, a clinical cohort study conducted in the Netherlands has recently documented the persistence of a higher BMI, a higher prevalence and a larger number of components of the metabolic syndrome over six years in patients with atypical depression as compared to controls (Lamers et al., 2016). Although the findings of the few studies that assessed cross-sectional associations between depression subtypes and inflammatory markers were partially inconsistent, several clinical studies revealed differential associations of depression subtypes with inflammation markers. Chronic atypical depression was found to be associated with elevated levels of the CRP, IL-6 and TNF-α (Lamers, Vogelzangs, et al., 2012), whereas non-melancholic depression has been found to be associated with increased levels of IL-1β (Kaestner et al., 2005). In contrast, melancholic patients did not reveal increased levels of

inflammatory markers as compared to non-depressed individuals (Rothermundt et al., 2001). Similarly, a community based study (Hickman et al., 2013) and our own study (Glaus et al., 2014) found levels of CRP to be higher in subjects suffering from atypical depression compared to non-atypical and non depressive subjects. To our knowledge, no previous study has yet prospectively assessed the risk factors for the incidence of these depression subtypes in midlife. Accordingly, using data from a population-based cohort study relying on semi-structured diagnostic interviews as well as thorough physical and biochemical investigations, the aim of the present study was to simultaneously assess the associations of a comprehensive array of potential socio-demographic, lifestyle, environmental, psychological, inflammatory and cardio-metabolic risk factors with the incidence of the subtypes of MDD during a more than 5-year follow-up.

Given cross-sectional evidence from previous studies, we hypothesized that the cardio-metabolic risk factors BMI, diabetes and dyslipidemia as well as inflammation markers would potentially predict the incidence of atypical MDD but not the other MDD subtypes. In contrast, regarding other potential risk factors we could not formulate subtype-specific hypotheses given the paucity of studies that have assessed their associations with depression subtypes. Accordingly, based on the literature that assessed associations between these risk factors and MDD as a whole, we could only hypothesize that female sex, younger age, low socio-economic status, elevated neuroticism scores, pre-existing anxiety or substance use disorders, lack of physical activity, smoking and exposure to stressful life-events could predispose to the onset of MDD, regardless of the subtype.

## 2. Material and methods

### 2.1. Study design and sample

The data for this article stemmed from CoLaus/PsyCoLaus (Firmann et al., 2008; Preisig et al., 2009), a prospective cohort study designed to investigate mental disorders and cardiovascular risk factors in the community and to determine their associations. The sample was randomly selected from the 35 to 75 year-old residents of the city of Lausanne (Switzerland) from 2003 to 2006 according to the civil register. Sixty-seven percent of the 35 to 66 year-old participants who underwent the physical exam (n=5535) also accepted the psychiatric evaluation (**Figure 1**). Participants with a lifetime baseline diagnosis of MDD, bipolar disorder, schizoaffective disorders, schizophrenia and schizophreniform disorder were excluded from the present analyses. Among the remaining 1993 subjects 32 died during the follow-up (mean duration 5.5 years, s.d. 0.4 years) and 1524 accepted the psychiatric follow-up evaluation (77.7% participation among survivors). Non-participants at follow-up had a lower SES and were less likely to have relatives with MDD than participants.

### 2.2 Measures

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) (Nurnberger et al., 1994; 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). Psychiatric lifetime diagnoses were assigned according to the DSM-IV (American Psychiatric Association. Task Force on DSM-IV, 2000). Criteria for atypical depression 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. 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 or weight loss 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 into four subtypes according to the presence of atypical or melancholic features of the depressive episode that occurred during the follow-up: 1) MDD with atypical features only, 2) MDD with melancholic features only, 3) combined MDD with both atypical and melancholic features, and 4) unspecified MDD with neither atypical nor melancholic features. Lifetime diagnoses of depressive disorders below the threshold of MDD and dysthymic disorder were assigned according to the DSM-5 criteria for Other Specified Depressive Disorders (OSDD). The DIGS also collects information on socio-demographic characteristics (sex, age and SES). SES was defined according to the Hollingshead scale (Hollingshead, 1975).

Childhood stressful life events before the age of 18 years encompassing 1) accident or severe catastrophe, 2) violent crime, 3) active combat or war, 4) witnessing trauma to others, and 5) exposure to sexual trauma, including rape, sexual abuse and exhibitionism were assessed in the post-traumatic stress disorder section of the DIGS. Events during adulthood were elicited using the life-event interview of Amiel-Lebigre (Amiel-Lebigre et al., 1984), which includes 52 potentially stressful life-events that could occur from age 17 onwards. Participants were also asked to assess the impact of the event from 0 (no negative impact) to 100 (extreme negative impact) and the sum of all impacts of events up to the time of the baseline assessment was computed.

Family history information on MDD was collected using the Family History – Research Diagnostic Criteria (FH-RDC) (Andreasen et al., 1977). The validity of the French version of the FH-RDC has previously been established through the assessment of agreement between diagnoses relying on family history reports and direct interviews including MDD (Vandeleur et al., 2015).

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

Neuroticism (N) was assessed using the French Eysenck Personality Questionnaire (EPQ) (H. J. Eysenck and Eysenck, 1975). The originator of this instrument reported Cronbach's α coefficients of 0.78 to 0.87 for Neuroticism using three different French samples (H. J. Eysenck, Eysenck, S.B.G., Gauquelin, M., Gauquelin, F., Pascal C., Pascal, D., 1980)

Coping strategies were evaluated using the French version (Bodmer and Grob, 1996) of the coping section of the Euronet questionnaire (Grob et al., 1993), which includes the factors Emotion-focused coping, Help-seeking behaviors, and Problem-focused coping according to principal component analysis (Perrin et al., 2014). The standardized Cronbach's α coefficients for these dimensions were 0.65, 0.69 and 0.44, respectively (Perrin et al., 2014). As emotion-focused coping was highly correlated with neuroticism ($r=0.63$; $p<.0001$) we could not include it in our analyses.

Physical measures taken at baseline are described in detail elsewhere (Firmann et al., 2008). The assessment included weight, height and blood pressure as well as venous blood samples to determine body mass index (BMI) and the levels of glucose, HDL-cholesterol, LDL-cholesterol, triglycerides, Interleukin 1β (IL-1β), IL-6, Tumor Necrosis Factor – α (TNF-α) and hsCRP. Hs-CRP was assessed using immunoassay and latex HS (IMMULITE 1000-High, Diagnostic Products Corporation, LA, CA, USA), with maximum intra- and interbatch coefficients of variation of 1.3% and 4.6%, respectively (Firmann et al., 2008). 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 (Marques-Vidal et al., 2011). Lower detection limits (LOD) for interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) were 0.2 pg/ml.

For concentrations below the LOD (37.5% for IL-1β, 8.2% for IL-6, 0.7% for TNF-α), a value of 0.1 pg/ml was assigned. Good agreement between signal and cytokine was found within the assay range ($R^2 \geq 0.99$). Intra and inter-assay coefficients of variation were 15% and 16.7% for IL-1β, 16.9% and 16.1% for IL-6 and 12.5% and 13.5% for TNF-α, respectively. Repeated measurements were conducted in 80 subjects randomly drawn from the initial sample; Spearman rank correlations between duplicate measurements were 0.914, 0.961 and 0.891 for IL-1β, IL-6 and TNF-α (all $p<0.001$). A diagnosis of hypertension was assigned in the case of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or if drug treatment was prescribed for hypertension. Diabetes was diagnosed when fasting blood glucose ≥7 mmol/l was measured or when the subject was treated for diabetes. Diagnostic criteria for dyslipidemia were: HDL-cholesterol <1 mmol/l, or LDL-cholesterol ≥4.1 mmol/l, or triglycerides ≥2.2 mmol/l, or when treated with a lipid-lowering drug.

Information on smoking and physical activity was collected through a standardized interview. Nicotine consumption entailed a current daily consumption of at least 10 cigarettes for at least 2 months. Participants were considered to be physically inactive if they reported engaging in physical activity for less than 20 minutes twice a week.

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

### 2.3 Statistical Analysis

Analyses were performed using the Statistical Analysis System (SAS) version 9.3 for Windows. Multiple imputations were used for missing data. Using the Markov Chain Monte Carlo with noninformative Jeffreys prior (proc mi), 10000 complete datasets were created, analyzed

separately and then combined according to Rubin's multiple imputation strategy. Marginal comparisons between baseline characteristics and depression status at follow-up were performed using chi-square tests of independence and ANOVA wherever appropriate.

Multinomial logistic regression was then used to simultaneously assess the potential effect of these baseline characteristics on the incidence of MDD subtypes during the follow-up (proc logistic). Adult life-event impact scores as well as levels of cytokine and hsCRP concentrations were log-transformed. Continuous variables were standardized in order to obtain comparable sizes of odd's ratios for all exposure variables.

**3. Results**

During the follow-up 31 of the subjects (2.03%) developed MDD with atypical features, 43 MDD with melancholic features (2.82%), 20 MDD with both atypical and melancholic features (1.31%) and 98 MDD with unspecified features (6.43%). Given the limited number of subjects that developed combined MDD (n=20) and because none of them were exposed to childhood events or dysthymia, we could not include them into our multinomial logistic regression model.

Table 1 presents the description of the whole sample and the subgroups according to the MDD status at follow-up. Significant inter-group differences were found for sex, age, the presence of pre-existing OSDD, anxiety disorders and hypertension as well as for the adult life-event impact and neuroticism scores. There were more women among subjects who developed a first major depressive episode during follow-up, as compared to those who did not develop MDD, regardless of the depression subtype. Those who developed melancholic MDD were younger at baseline than those who developed either atypical or no MDD. Similarly, subjects who developed unspecified MDD were younger than those who did not develop MDD. Moreover, both subjects who developed atypical and those who developed melancholic MDD reported a

lifetime history of OSDD at baseline more frequently than those who did not develop MDD. Subjects who developed atypical or melancholic MDD reported lifetime anxiety disorders at baseline more frequently than those who developed either unspecified MDD or no MDD. Those with melancholic or unspecified MDD also reported hypertension less frequently at baseline than those who did not develop MDD. In addition, subjects with unspecified MDD revealed a higher baseline adult life-event impact score than those who did not develop MDD. Finally, subjects who developed MDD, regardless of the subtype, scored higher on neuroticism at baseline than those who did not develop MDD; those with melancholic MDD also scored higher on neuroticism than those with unspecified MDD.

Table 2 provides the results of the multinomial logistic regression analysis which simultaneously included all baseline variables into one model. Women as well as subjects with a lifetime history of OSDD, with a higher BMI and a higher neuroticism score at baseline were more likely to develop a first major depressive episode with atypical features during the follow-up. Female sex, a lifetime history of OSDD and a higher baseline neuroticism score also predicted the onset of melancholic MDD. In addition, younger age was associated with the development of melancholic MDD, whereas hypertension decreased the likelihood of the occurrence of this MDD subtype. Finally, being of younger age, having lower TNF-α concentrations and a higher life-event impact score at baseline predicted the onset of unspecified MDD during follow-up.

## 4. Discussion

To our knowledge, this is the first study to prospectively assess a wide array of potential predictors of the incidence of MDD subtypes in midlife. Our major finding is that the three MDD subtypes are predicted by partially distinct combinations of baseline characteristics suggesting that these subtypes not only differ in their clinical manifestations but also in factors that

contribute to their development. Although atypical and melancholic MDD share female sex, pre-existing OSDD and elevated scores on neuroticism at baseline as common risk factors, they revealed opposite associations with cardio-metabolic characteristics. Indeed, the incidence of atypical MDD was associated with elevated BMI, whereas the incidence of melancholic MDD was negatively associated with hypertension at baseline. In contrast to atypical and melancholic MDD, the incidence of unspecified MDD was essentially associated with a high life-event impact score at baseline and a low concentration of TNF-α.

In line with previous research (Piccinelli and Wilkinson, 2000) we found a strong association between female sex and MDD, but in contrast to studies that supported a particularly high predominance of women in atypical depression (Angst et al., 2007; Blanco et al., 2012), we did not observe significant sex differences across MDD subtypes. We also observed that younger age was predictive for the onset of both melancholic and unspecified MDD which is consistent with observations of higher prevalence of MDD in younger cohorts in the community (Kessler et al., 1994).

Unlike unspecified MDD, the onset of both atypical and melancholic MDD was associated with preexisting OSDD, which corroborates findings from previous prospective studies that showed subthreshold depressive episodes to be a risk factor for the subsequent development of MDD as a whole (Forsell, 2007; Horwath et al., 1992). In contrast to previous studies (Beesdo et al., 2010; Brook et al., 2002; Bulloch et al., 2012), neither anxiety nor substance use disorders were predictors of the onset of MDD subtypes in our study, which could be due to the higher age of our cohort at baseline. Moreover, the discrepant results with respect to the NESDA study, which revealed a significant cross-sectional association between anxiety disorders and the atypical or melancholic depression subtypes (Lamers et al., 2016), could be attributable to the higher degree of severity of depressed patients in the clinical NESDA study as compared to those in our population-based sample. In addition, depression subtype diagnoses were assigned

according to different procedures in the two studies. In the NESDA study the assignment relied on latent class analysis, whereas in our study DSM-IV specifier criteria were applied.

The observed prospective association between BMI at baseline and the onset of atypical MDD confirms previous cross-sectional findings of strong links between this MDD subtype and overweight or obesity (Cizza et al., 2012; Glaus et al., 2013; Kendler et al., 1996; Lamers et al., 2013; Y. Li et al., 2014; Sullivan et al., 2002). Moreover, in a previous article (Lasserre et al., 2014) we could show that this MDD subtype is a predictor of a steeper increase of obesity markers during the 5.5-year follow-up period, whereas the present finding also supports an inverse association. Such a bidirectional relationship is compatible with two meta-analyses for MDD as a whole (Luppino et al., 2010), and the results of a recent genetic study that revealed an association between polygenic risk scores of BMI and atypical depression (Milaneschi et al., 2015), suggesting shared genetic liability. In contrast, a study relying on Mendelian randomization analysis did not support a causal relationship between elevated BMI and the risk of MDD as a whole (Hung et al., 2014), which however could be due to the heterogeneity of MDD. Indeed, according to our data the magnitude of the association with BMI varies largely across MDD subtypes. Among the other cardio-metabolic factors, hypertension was associated with the incidence of melancholic MDD, but as a protective factor. This finding is in line with the results of Lamers et al. (Lamers et al., 2013), who also documented lower blood pressure among melancholic subjects compared to controls. It has been hypothesized that low blood pressure leads to depression through somatic symptoms and fatigue (Licht et al., 2009). Alternatively, altered levels of neuropeptides such as the neuropeptide Y could be involved in depression and suppress sympathetic activity resulting in decreased blood pressure (Licht et al., 2009). In contrast to the BMI, diabetes was not a predictor of atypical MDD in our study and the previously reported cross-sectional association between diabetes and this MDD subtype may rather be explained by an opposite causal link given our recent observation of a significant

longitudinal association between atypical MDD at baseline and a steeper increase of the fasting glucose level during the follow up (Lasserre et al., 2016).

Regarding inflammatory markers, we observed a significant association between a low baseline TNF-α concentration and the incidence of unspecified MDD, and a similar association with a trend towards statistical significance (OR=0.82, p=0.094) that emerged for lower CRP levels. These findings may suggest that higher inflammatory activity at baseline is rather protective, as it was associated with a lower risk of unspecified MDD. However, given the anti-inflammatory effects of cortisol (Sternberg, 2006) and catecholamines (Elenkov et al., 2005), the low inflammatory marker concentrations at baseline in subjects who developed unspecified MDD during the follow-up could also be attributable to activation of their HPA axis and sympathetic nervous system as a consequence of elevated life-event stress reported by these subjects at baseline. A cross-sectional association between higher cortisol and lower inflammation marker levels was previously demonstrated for instance by Lamers et al. (Lamers et al., 2013). Although both IL-6 and IL-1β were significantly associated with TNF-α baseline levels in our study, their baseline levels showed no significant associations with unspecified MDD at follow-up. This could be due to the lack of reliable plasma measures for IL-1β, as was recently discussed (Ridker, 2016), and anti-inflammatory properties of IL-6, which activates the HPA axis to secrete cortisol in the context of stress (Elenkov et al., 2005). Therefore, in the above scenario, an increase in IL-6 would have been more expected than a decrease. However, we acknowledge that the proposed complex neuroendocrine and immune interactions in the context of life-event stress at baseline predicting unspecified MDD at follow-up must remain speculative. Particularly so, as we had no baseline cortisol and catecholamine measures available to further test this hypothesis, including the temporal dynamics in these parameters.

Our analyses also revealed associations between high neuroticism scores at baseline and the onset of both atypical and melancholic MDD during the follow-up, which is consistent with the

findings of the NESDA study (Lamers et al., 2010; Lamers, Rhebergen, et al., 2012) as well as with a recent meta-analysis showing elevated neuroticism to predispose to MDD as a whole (Jeronimus et al., 2016). Moreover, a recent genetic study found the polygenic risk score of neuroticism, derived from GWAS meta-analysis, to significantly predict MDD indicating either a causal relationship between neuroticism and MDD or underlying shared liability (Smith et al., 2016). However, our finding regarding the predictive effect of neuroticism needs to be taken with caution given that some subjects may have been unable to recall remote depressive episodes, which could have resulted in both elevated neuroticism scores and an increased risk of new depressive episodes.

In contrast to several previous studies (M. Li et al., 2016; Mandelli et al., 2015) we did not find childhood events to predict any of the MDD subtypes, which could be due to the relatively old age of our cohort. Indeed, subjects with childhood trauma were likely to have already developed MDD before the age at study intake and were therefore excluded from the present analyses, whereas those who did not develop depression prior to baseline despite such trauma were likely to be resilient. The perceived impact of adult life-events was exclusively associated with the onset of unspecified MDD. Given that the subjects who developed this MDD subtype did not differ from those who developed atypical or melancholic MDD with respect to the adult life-event impact score at baseline, the onset of depressive episodes in these subjects could be attributable to both a higher level of perceived stress as well as reduced stress tolerance. The two mechanisms have been suggested as a risk factor for MDD as a whole (Hammen, 2005). Unlike the other MDD subtypes, the onset of unspecified MDD was not associated with pre-existing psychiatric disorders, cardio-metabolic conditions or elevated neuroticism scores.

The lack of association between the family history of depression and MDD subtypes in our study, which contrasts with meta-analytical findings (Wilde et al., 2014), could be attributable to the advanced age of our cohort. Indeed MDD with an onset after age 35 may be less determined

by genetic and factors related to the family of origin than depression that occurs earlier in life (Valkanova and Ebmeier, 2013). In addition, specific MDD subtypes may be better predicted by a family history of the same MDD subtype than by MDD as a whole. Unfortunately, our family history information did not allow for the subtyping of MDD in first-degree relatives.

The results of the present study should be considered in the context of several limitations. First, the age range of our cohort does not cover the main risk period for the onset of MDD. Indeed, surveys conducted in the community revealed that more than 50% of MDD start before the age of 32 years (Kessler et al., 2005). For this reason our findings may not be generalizable to subjects younger than 35 years of age. Second, given the mean age of our cohort it is possible that subjects did not recall remote episodes and hence risk factors for recurrence could have been confounded with risk factors for the incidence of MDD subtypes. Third, despite a large cohort, the number of subjects who developed a specific subtype of MDD was still rather low which diminished the statistical power to detect significant predictors of the onset of each MDD category and did not allow us to determine the risk factors for combined MDD given the low number of subjects who developed this outcome. Fourth, our analyses focused on the factors predicting the onset and type of the first depressive episode, which does not need to be followed by the same type of episode over time. As a subject can switch across MDD subtypes over lifetime, the factors predicting the first episode are not necessarily identical with those predicting the final MDD subtype diagnosis over lifetime. Moreover, our diagnostic instrument only assessed the full range of symptoms for one depressive episode during the follow-up, whereas 11.6% of subjects revealed more than one episode and could potentially be misclassified. Fifth, data were based on an urban sample in Switzerland which may not be representative of the general population. However, it is unlikely that the specific characteristics of this sample significantly affected the assessed prospective associations. Sixth, we could not test whether the HPA axis functioning is differentially associated with the melancholic and atypical MDD subtypes

(Harald and Gordon, 2012) as no cortisol measure of stress was available at baseline. Seventh, given that subjects with low SES or a family history of MDD at baseline were less likely to participate it is possible that we have underestimated the effect of these potential risk factors on the outcomes. This would have been the case if, among subjects exposed to one of these two potential risk factors, those who developed MDD subtypes were more likely to refuse participation than those who did not develop MDD subtypes.

In conclusion, the findings of this study have important clinical and scientific implications. Our data suggest that demographic and cardio-metabolic characteristics, inflammatory marker levels, life stressors and psychological factors differentially predict the incidence of MDD subtypes in midlife, which further highlights the need of subtyping the heterogeneous category of MDD. Moreover, they further suggest that minor depressive disorders, especially in combination with particular personality features, deserve close clinical attention in order to prevent the subsequent onset of the atypical and melancholic depression subtypes. In the last years, algorithms designed to predict the onset of MDD as a whole have led to the development of personalized prevention strategies based on the both the level and the profile of risk for an individual (King et al., 2008). Our finding of differential risk profiles for MDD subtypes could contribute to refining such personalized prevention strategies by shifting them from a general MDD prevention to a more specific prevention of MDD subtypes. However, our results derived from a midlife sample first need to be confirmed by longitudinal studies that ideally follow subjects from adolescence on and by genetic research based on Mendelian randomization, which could provide additional clues to the complex interplay between MDD subtypes and personality or metabolic traits.

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