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Research paper

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 35–66 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-α 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.

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 (Li et al., 2016; Mandelli et al., 2015) and other stressful life-events (Friis et al., 2002; Kendler et al., 1999, 2004a, 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

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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 tumor necrosis factor-α (TNF-α) (Lamers et al., 2013), whereas non-melancholic depression has been found to be associated with increased levels of Interleukin-1β (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 hsCRP 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 35–75 year-old residents of the city of Lausanne (Switzerland) from 2003 to 2006 according to the civil register. Sixty-seven percent of the 35–66 year-old participants who underwent the physical exam (n = 5535) also accepted the psychiatric evaluation (Fig. 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, 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.