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Admixture analysis of age of onset in generalized anxiety disorder

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ABSTRACT

Age of onset is a marker of clinically relevant subtypes in various medical and psychiatric disorders. Past research has also reported that age of onset in generalized anxiety disorder (GAD) is clinically significant; but, in research to date, arbitrary cut-off ages have been used. In the present study, admixture analysis was used to determine the best fitting model for age of onset distribution in GAD. Data were derived from 459 adults with a diagnosis of GAD who took part in the Netherlands Study of Depression and Anxiety (NESDA). Associations between age of onset subtypes, identified by admixture analysis, and sociodemographic, clinical, and vulnerability factors were examined using univariate tests and multivariate logistic regression analyses. Two age of onset distributions were identified: an early-onset group (24 years of age and younger) and a late-onset group (greater than 24 years of age). Multivariate analysis revealed that early-onset GAD was associated with female gender (OR 2.1 (95%CI 1.4–3.2)), higher education (OR 1.1 (95%CI 1.0–1.2)), and higher neuroticism (OR 1.4 (95%CI 1.1–1.7)), while late-onset GAD was associated with physical illnesses (OR 1.3 (95%CI 1.1–1.7)). Study limitations include the possibility of recall bias given that age of onset was assessed retrospectively, and an inability to detect a possible very-late-onset GAD subtype. Collectively, the results of the study indicate that GAD is characterized by a bimodal age of onset distribution with an objectively determined early cut-off at 24 years of age. Early-onset GAD is associated with unique factors that may contribute to its aetiology; but, it does not constitute a more severe subtype compared to late-onset GAD. Future research should use 24 years of age as the cut-off for early-onset GAD to when examining the clinical relevance of age of onset for treatment efficacy and illness course.

1. Introduction

Age of onset is an important marker for aetiological and clinical variability in many medical disorders (Anderson, Chen, Brinton, & Devesa, 2007; Koedam et al., 2010). Growing evidence has demonstrated that it is important to consider age of onset in psychiatric conditions, with findings indicating that differences in age of onset are associated with varying levels of severity and treatment efficacy (Kessler et al., 2007). Specifically, recent studies have demonstrated that age of onset may be a marker that has clinical implications in obsessive compulsive disorder (Delorme et al., 2005) and panic disorder (Tibi et al., 2013), and can be used to discriminate a familial subtype in agoraphobia (Tibi et al., 2015). Likewise, previous studies on generalized anxiety disorder (GAD) have suggested that individuals with early-onset GAD can be distinguished from those with late-onset GAD on a number of demographic and clinical variables. In general, earlier age of onset in GAD has been associated with higher levels of education (Chou, 2009), higher rates of psychiatric comorbidity, greater symptom severity (Beck, Stanley, & Zebb, 1996; Chou, 2009; Goncalves & Byrne, 2012; Hoehn-Saric, Hazlett, & McLeod, 1993; Le Roux, Gatz, & Wetherell, 2005), and childhood adversity (Goncalves & Byrne, 2012). In contrast, later age of onset in GAD has been associated with more functional limitations due to physical problems (Chou, 2009; Le Roux et al., 2005).

To date, there is no consensus regarding the optimal cut-off age for early- versus late-onset GAD, with cut-off ages in past studies ranging from 20 years (Hoehn-Saric et al., 1993; Ramsawh, Weisberg, Dyck, Stout, & Keller, 2011) to 50 years (Le Roux et al., 2005). If age of onset can be used as a marker to identify homogeneous subtypes, determining of the optimal cut-off age is of critical importance for clinical care. Moreover, in order to facilitate research into the aetiology, course, and treatment efficacy for individuals with early- and late-onset GAD, cut-

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off age should be based on data-driven inferential statistics as opposed to an arbitrary determination.

Our study is the first to use admixture analysis, a data-driven technique, to assess whether age of onset is associated with phenotypically homogeneous subtypes in GAD. If age of onset is a marker of different phenotypes, early- and late-onset GAD should be the products of separate normal distributions. Using a data-driven technique allows the best cut-off age between early- and late-onset to be objectively determined. Accordingly, the first aim of our study was to examine whether a data-driven technique would identify clinically distinct subtypes of GAD based on age of onset. The second aim of this study was to determine whether these distinct subtypes differ with respect to sociodemographic, vulnerability, and clinical factors.

2. Material and methods

2.1. Study sample

The Netherlands Study of Depression and Anxiety (NESDA) is a multi-site, naturalistic cohort study of adults (18–65 years; Penninx et al., 2008). Participants were recruited from the general population, general practices, and mental health organizations, and provided written informed consent prior to participation. The study protocol was designed in accordance with the Declaration of Helsinki and approved by the Ethical Review Board of the VU University Medical Center. For the current study, we used only baseline data (n = 2981). At baseline, 464 respondents had a diagnosis of GAD for at least six months. Of these respondents, age of onset data were available for n = 459, which is the sample for the present study.

2.2. Psychopathology

The Composite International Diagnostic Interview (CIDI, version 2.1; WHO, 1998) was administered by trained staff to assess for GAD, age of onset of GAD, and comorbid disorders according to DSM-IV criteria. The CIDI is a reliable and valid instrument for assessing depression and anxiety diagnoses (Wittchen, 1994).

2.3. Characteristics

2.3.1. Socio demographic factors

Sociodemographic factors included age (in years), gender (male or female), and education (in years).

2.3.2. Clinical factors

Clinical factors assessed included severity and duration of GAD, psychiatric comorbidity, presence and number of suicide attempts, level of daily functioning, and alcohol use. Total scores of the 11-item Pennsylvania State Worry Questionnaire (PSWQ; Meyer, Miller, Metzger, & Borkovec, 1990), the 21-item Beck Anxiety Inventory (BAI; Beck et al., 1988), and the 16-item Inventory of Depressive Symptoms (QIDS; http://www.ids.qids.org; Rush, Gullion, Basco, Jarrett, & Trivedi, 1996) were used as measures of severity of worry, anxiety, and depressive symptoms. Duration (in months) of anxiety and depression in the five years prior to baseline was assessed using the Life Chart Interview (LCI; Lyketsos & Nestadt, 1994). The LCI was administered by a trained interviewer, who began by exploring the occurrence of life events during each year to refresh memory. Afterwards, the presence of depressive and anxiety symptoms was assessed for each month of the successive years. Comorbid disorders lasting for at least six months were all assessed with the CIDI. Comorbid anxiety disorders included panic disorder with and without agoraphobia, agoraphobia, and social phobia. Comorbid depressive disorders included major depressive disorder and dysthymia. Presence and number of suicide attempts was assessed by asking how many times, if ever, participants had seriously attempted to end their lives. Level of daily functioning was measured using total scores on the WHO Disability Assessment Schedule II (WHO-DAS II; Chwastiak & Von Korff, 2003). Finally, alcohol intake was categorized into low, moderate, and high based on the average number of drinks per week (for women: < 1, 1–14, and > 14; for men: < 1, 1–21, and > 21, respectively).

2.3.3. Vulnerability factors

Childhood trauma was assessed by asking participants whether they had experienced emotional neglect or psychological, physical, or sexual abuse prior to the age of 16 years. A cumulative childhood trauma index was used (see also Hovens et al., 2012). Life events were assessed using the Brugha-questionnaire, which examines exposure to 12 important negative life events, such as death or serious illness of family members, unemployment, and violent experiences (Brugha, Bebbington, Tennant, & Hurry, 1985). Anxiety and/or depression in first-degree family members was assessed using the family tree method (Fyer & Weissman, 1999). Physical conditions, including cardiovascular disease, diabetes, lung disease, osteoarthritis, cancer, gastrointestinal disease, liver disease, epilepsy, and thyroid disease, were included if the participant received medical treatment for the condition (see also Penninx et al., 2008). Anxiety sensitivity, the fear of anxiety-related sensations based on underlying cognitions that there may be harmful physical, social, or mental consequences, was assessed with the Anxiety Sensitivity Index (Peterson & Reiss, 1992). Cognitive vulnerability for depression was assessed using the Leiden Index of Depression Sensitivity-Revised (LEIDS-R), which assesses latent dysfunctional cognitions including hopelessness, acceptance, aggression, control/perfectionism, risk aversion, and rumination (Van der Does, 2002). Neuroticism and extraversion were assessed using the corresponding dimensions of the 60-item NEO personality questionnaire (Costa & McCrae, 1995).

2.4. Analytic strategy

Admixture analysis was used to identify the model that best fit the age of onset distribution in our sample. Admixture analysis uses maximum likelihood estimation to determine the probability of observing the sample data assuming K normally distributed populations of origin. To determine the most likely number of populations of origin (i.e., K), we estimated log likelihood and chi-square goodness of fit for one, two, and three populations of origin. In line with past research, we compared the log likelihoods for each of these models using forward stepwise estimation and maximum likelihood ratio tests (Aderka, Nickerson, & Hofmann, 2012; Anholt et al., 2014; Tibi et al., 2013; Tibi et al., 2015).

The first step of forward stepwise estimation with maximum likelihood ratio tests is to estimate the probability (i.e., log likelihood) of observing the sample data assuming a single normally distributed population of origin. The second step is to estimate the probability of observing the sample data assuming two normally distributed populations of origin. If the difference between the log likelihoods is non-significant according to the threshold value of a chi-square distribution with three degrees of freedom, the more parsimonious solution is to remain with the lower number of populations. If the difference between log likelihoods is significant and the log likelihood is higher for two populations, two populations are more likely to be at the origin of the data (Bellivier, Golmard, Henry, Leboyer, & Schürhoff, 2001; Bellivier et al., 2003; Delorme et al., 2005). If two populations are more likely than one, the procedure is repeated to examine the difference between two and three populations of origin.

In addition to forward stepwise estimation, we followed the recommendation of Kolenikov (2001) and used the largest chi-square goodness of fit probability to indicate the best-fitting model. The optimal cut-off for age of onset was derived from the models and used in subsequent analyses on distribution of characteristics (see below). All admixture analyses were performed using the script denormix (Kolenikov, 2001) and the statistics program Stata 10 (Stata Corpora-