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Research paper

Precursors in adolescence of adult-onset bipolar disorder

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ABSTRACT

Background: Although the estimated contribution of genetic factors is high in bipolar disorder, environmental factors may also play a role. This Swedish register-based cohort study of men examined if physical and psychological characteristics in late adolescence, including factors previously linked with bipolar disorder (body mass index, asthma and allergy), are associated with subsequent bipolar disorder in adulthood. Unipolar depression and anxiety are analysed as additional outcomes to identify bipolar disorder-specific associations.

Methods: A total of 213,693 men born between 1952 and 1956, who participated in compulsory military conscription assessments in late adolescence were followed up to 2009, excluding men with *any* psychiatric diagnoses at baseline. Cox regression estimated risk of bipolar disorder, depression and anxiety in adulthood associated with body mass index, asthma, allergy, muscular strength stress resilience and cognitive function in adolescence.

Results: BMI, asthma and allergy were not associated with bipolar disorder. Higher grip strength, cognitive function and stress resilience were associated with a reduced risk of bipolar disorder and the other disease outcomes.

Limitations: The sample consisted only of men; even though the characteristics in adolescence pre-dated disease onset, they may have been the consequence of prodromal disease.

Conclusions: Associations with body mass index and asthma found by previous studies may be consequences of bipolar disorder or its treatment rather than risk factors. Inverse associations with all the outcome diagnoses for stress resilience, muscular strength and cognitive function may reflect general risks for these psychiatric disorders or intermediary factors.

1. Introduction

Bipolar disorder [BD] is a debilitating mental disorder affecting an estimated 0.7–0.8% of the population (Ferrari et al., 2011) and is characterised by alternating periods of depression and mania. The burden of disease includes impairments in cognitive function, a high rate of comorbidity and risk of suicide (Conus et al., 2014), with on average more than 40 days of difficulty working or carrying out day-to-day tasks per year (Alonso et al., 2011).

Although the estimated contribution of genetic factors is high in BD, ranging from 59% (Lichtenstein et al., 2009) to 93% (Kieseppä et al., 2004), other characteristics may also contribute to the risk (Seifuddin et al., 2012; Winham et al., 2014). However, due to its insidious and relatively early onset, many of the existing studies examined associations with disease progression, *after* onset of the disease. Examples of such factors include higher body mass index [BMI] (Bai et al., 2015; Goldstein et al., 2008; McElroy and Keck, 2012), asthma (Wu et al., 2016), allergic diseases and systemic inflammation (Anderson and Maes, 2015; Bai et al., 2015; Frey et al., 2013; Goldstein et al., 2009). Results of these studies therefore might suggest these diseases are risks for BD, but alternatively they could be consequences of its treatment or behavioural change following BD onset. Some studies focused on incident BD diagnoses, but the follow-up was of relatively limited duration (Lin et al., 2014) or the information on exposures, such as asthma and allergy, was limited to medical treatments (Chen et al., 2015, 2014).

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BD patients can exhibit tendencies to psychological maladaptation (Ak et al., 2012), and therefore psychosocial stress may influence risk of BD characteristics leading to frank onset and diagnosis. Although a body of research has investigated precursors of BD in relation to psychological and psychiatric characteristics (Faedda et al., 2015, 2014), to the best of our knowledge, the risk of BD associated with stress resilience has not yet been investigated comprehensively (Dienes et al., 2006; Goldstein et al., 2009; Post and Leverich, 2006). Therefore, we examined the associations of characteristics in adolescence, especially if BMI, asthma and allergy, are associated with subsequent risk of BD in adulthood using a population-based cohort of Swedish men (n = 213,693) with prospectively measured information. Measures in adolescence were from the compulsory military conscription assessment when most of the men were 18–19 years old. These measures included information on physical, cognitive and psychological functions and diseases and symptoms. To minimise the risk of reverse causation, cohort members with *any* psychiatric diagnoses in adolescence were excluded. To clarify if the associations with characteristics from adolescence are specific to BD, diagnoses of unipolar depression and anxiety were also used as outcomes.

2. Methods

The study population is men born from 1952 to 1956 in Sweden who underwent compulsory military conscription examinations between ages 17 and 20 years (n = 284,257). Fewer than 3% of men were exempted from the examination, mainly due to severe illness or disability (Otto, 1976). Further exclusions were for inconsistencies in vital status (n = 2848), emigration before conscription assessment (n = 440), conscription examination not between ages 17 and 22 years (n = 2833), and missing data for relevant variables (n = 29,883). This resulted in a sample of 248,253 (87%). Men with any mental health diagnosis by the time of the conscription assessment (Swedish International Classification of Diseases [ICD]-8 290–309) were excluded (n = 34,560), with a final sample of 213,693.

2.1. Psychiatric diagnosis

The *Patient Register* records inpatient (available from 1970 in our data) and outpatient (2001-) hospital diagnoses. Combining primary and secondary diagnosis, BD was identified using: ICD-8 296.10-30, 296.88; ICD-9 296A, 296C E, 296X; ICD-10 F30-31 (Power et al., 2013; Sellgren et al., 2011). ICD codes for depression were: Swedish ICD-8 296.00, 296.99, 298; ICD-9 296B, 296W, 298A, 300E F, 309A B, 311X; and ICD-10 F32, F33, F34, F38.1 and F48.8 (Hiyoshi et al., 2015; Power et al., 2013). Anxiety was: ICD-8 300.00, 300.30; ICD-9 300A, 300D; ICD-10 F41-42 (Hiyoshi et al., 2015).

2.2. Characteristics in adolescence

The *Conscription Register* provided information on physical and psychological information when most of the men were 18–19 years old (Otto, 1976). **BMI** (kg/m^2) was derived from body height and weight and classified into underweight (15 to < 18.5), normal weight (18.5 to < 25), overweight (25 to < 30) and obese (30 or higher). Values less than 15 were treated as invalid. Body mass index (BMI) is influenced not just by adipose tissue, but also muscle mass, so muscular strength may help with interpretation of associations with BMI. **Hand grip-strength** (Newton [N]) was used as a marker of muscular strength, and the strongest 20% (≥690 N) were compared with the rest. Using ICD-8 codes recorded at the medical examination, **asthma** (493) and **allergy** (691 and 507) were identified. **Erythrocyte sedimentation rate** (ESR) was assessed using the Westergren method (the distance that a column of anticoagulated blood falls per hour (Toss et al., 2013)) and was used as a marker of systemic inflammation. Erythrocyte volume fraction (EVF) was included together with ESR in the analysis for adjustment of ESR. **Cognitive function** was estimated by written examination of linguistic understanding, spatial recognition, general knowledge and ability to follow technical instructions, producing a standardised nine-point score, collapsed into three categories of high, moderate and low. The **stress resilience** measure was derived from a semi-structured interview with a psychologist and summarised as a standardised nine-point score based on ratings of psychological energy, emotional control and social maturity, which was grouped into three categories of high, moderate and low. **Body height** was used as a marker of development (Datta Gupta et al., 2013; Taki et al., 2012). Results of medical examinations were summarised as **a disease score**, which was recoded into five categories of: very significant problem, significant problem, fairly significant problem, no serious problem and no diagnosis (Perugi et al., 2015). **County of residence** in 1985 (with missing values replaced using the information in 1970) was grouped into six regions and used for adjustment.

2.3. Demographic and socioeconomic characteristics

Household crowding and parental socioeconomic index in childhood were obtained from the *1960 Census* and included as markers of childhood living environment. Occupation of head of household was grouped into six categories of **a socioeconomic index**; manual workers, agricultural workers, farm workers, office workers, business owners, and other. **Household crowding** was derived by dividing number of household members by number of habitable rooms and classified into three categories, less than or equal to 1, 1–2 and more than or equal to 2 persons per room. These variables were used to adjust for markers of childhood living conditions.

2.4. Statistical analysis

Using age as the underlying time scale, Cox regression estimated hazard ratios [HR] and 95% confidence intervals for the risk of BD, anxiety and depression using STATA V.14/SE. Each of the three outcome diseases was analysed separately. The independent measures were all modelled as a series of dummy variables. Follow-up started from immediately after the conscription assessment, and ended on the date of first diagnosis of BD (or anxiety or depression), death, emigration or 31 December 2009, whichever occurred first. The proportionality of association between independent variables and BD, anxiety and depression was confirmed by Kaplan-Meier survival plot and Schoenfeld residuals. Some variables showed violation of the proportional hazards assumption when tested by Schoenfeld residuals; the effect of violation was, however, minimal as assessed using survival curves. We therefore present the analyses assuming proportionality.

2.5. Ethical permission

This study was approved by the Uppsala Regional Ethics Committee (Dnr 2014/324).

3. Results

Table 1 shows the distribution of the measures in the entire study population and among those with BD, anxiety and depression diagnoses (excluding those with onset before the conscription assessment) to age 58 years. While grip strength, cognitive ability and stress resilience were associated with BD, anxiety and depression, BMI, asthma and height were associated with anxiety and depression, but not with BD.

There is no evidence of raised BD and depression risk for overweight or underweight compared with the normal range (Table 2). Raised risk was seen in underweight for anxiety but a reduced risk of anxiety was observed among those who were obese in adolescence. There is a statistically significant reduced risk of BD – also seen for the other outcome diagnoses – associated with higher grip-strength, and the