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Featured Article

Anxiety is associated with increased risk of dementia in older Swedish twins

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Abstract

Introduction: We asked whether anxiety is associated with prospective risk of dementia, and the extent to which genetic influences mediate this association.
Methods: Nondemented twins (n = 1082) from the Swedish Adoption Twin Study of Aging completed an assessment of anxiety symptoms in 1984 and were followed for 28 years.
Results: Baseline anxiety score, independent of depressive symptoms, was significantly associated with incident dementia over follow-up (hazard ratio [HR] = 1.04; 95% confidence interval [CI] = 1.01–1.06). There was 48% increased risk of becoming demented for those who had experienced high anxiety at any time compared with those who had not. In co-twin analyses, the association between anxiety symptoms and dementia was greater for dizygotic (HR = 1.11; 95% CI = 1.02–1.20) compared with monozygotic twins (HR = 1.06; 95% CI = 0.95–1.20), indicating genetic mediation.
Discussion: Anxiety symptoms were associated with increased risk of dementia. Genetic factors common to dementia and anxiety partially mediated this association.

Keywords: Anxiety; Dementia; Genetics; Twins; Depression

1. Introduction

The rapid growth of the older adult population continues to make urgent the identification of potentially modifiable risk and protective factors for dementia. Moreover, discovering early and modifiable risk factors is essential to identifying potential targets for treatment and prevention of dementia [1]. Psychiatric symptoms and disorders often co-occur with dementia and may be potentially modifiable. Anxiety disorders and symptoms are the most prevalent psychiatric disorders and symptoms in the elderly [2]. They are associated with negative health outcomes such as increased health care costs [3], decreased quality of life, and increased disability [4]. Anxiety in later life is associated with worse cognitive functioning and frequently co-occurs with dementia [5]. Some studies have found links between anxiety disorders, posttraumatic stress disorder (one type of anxiety disorder), anxiety symptoms, benzodiazepine use (a routine pharmacologic treatment for anxiety), and increased risk of incident dementia [5–12].

Prior research examining anxiety as a risk factor for dementia, however, has produced mixed findings [6–10,13,14]. There is a considerable amount of research documenting depression as a risk factor for dementia [15]. It is also unclear

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whether anxiety, independent of depression, is associated with risk of dementia [10]. Mixed findings have also been observed with respect to the relationship between anxiety and cognitive decline [5,16,17].

If anxiety is a risk factor for dementia, little is known about what factors are mediating this association. Past research examining neuroticism (a dimension of personality most associated with anxiety [18]) has posited that genetic factors common to both neuroticism and dementia may be explaining this association [19], but this question has not been investigated with respect anxiety and dementia.

The purpose of this study was to examine whether symptoms of anxiety were associated with an increased risk of developing dementia over a follow-up period of 28 years in a representative sample of Swedish twins. Second, we examined the association between symptoms of anxiety and trajectories of cognitive performance. Finally, using co-twin analyses, we sought to determine if the association between anxiety and dementia in part reflected genetic factors in common to both phenotypes.

2. Methods

2.1. Data and study participants

Data from the Swedish Adoption Twin Study of Aging (SATSA) were examined for this study. SATSA contains a representative sample of Swedish twins drawn from the population-based Swedish Twin Registry [20]. SATSA consists of two components: questionnaire assessments (Qs) and in-person testing (IPT). In 1984, participants completed the first questionnaire assessment (Q1), which will be referred to as the baseline for this study. Subsequent questionnaires were completed approximately every 3 years. Beginning in 1986, a subsample of twins aged $\geq$50 years (n = 645) participated in the first IPT assessment including measures of cognition. Participants completed IPTs approximately every 3 years. Follow-up for dementia continued through 2012. The sampling procedure and methods of the SATSA study have been previously published [20]. SATSA was approved by the Ethics Committee at Karolinska Institutet. All participants provided informed consent for participation.

There were 1736 participants who completed the baseline questionnaire containing the measurement of anxiety. Of those participants, 1541 completed the anxiety questionnaire (88.7% response rate). Participants were excluded if they had a dementia diagnosis before the baseline assessment, if they had missing data on other study variables, or if they were <60 years at their last follow-up assessment, resulting in a final sample of 1082 participants.

2.2. Assessment of anxiety

State anxiety symptom severity was measured at baseline through Q4 using the state anxiety subscale of the State-Trait Personality Inventory (STPI) [21]. The STPI is a 10-item scale in which participants are asked how they feel "right now." Items are answered on a 5-point likert type scale (1 = fits me exactly to 5 = does not fit me at all) with higher scores representing greater state anxiety. The STPI contains a subset of items from the state anxiety subscale of the State Trait Anxiety Inventory (STAI). The STAI is reliable and valid with older adults [22].

2.3. Assessment of depression

Depressive symptoms were measured at baseline using the Older American Resources and Services (OARS) depression subscale [23]. This subscale is a 5-item measure in which participants reported dichotomously (no = 0; yes = 1) if they were experiencing each symptom. The OARS has been found to be a reliable and valid measurement for community-dwelling older adults [24]. The OARS was administered at Q1–Q3. The Center for Epidemiologic Studies Depression scale (CES-D) was available Q2–Q4 but not at baseline.

2.4. Diagnosis of dementia

Participants were screened for dementia throughout the study. Participants were identified for dementia work-up if they scored lower than a 24 on the mini-mental state examination (MMSE), declined three or more points from prior MMSE, exhibited poor performance on cognitive testing at an IPT, had a history of dementia documented in medical records, and/or a study nurse or family member offered that the participant had dementia or cognitive problems [25]. Additionally, participants who failed to respond to either a Q or an IPT assessment were contacted and asked to complete a brief telephone cognitive screening interview [26]. When participants were unable to respond, a proxy telephone interview was used.

Participants identified as possible dementia cases through any of these methods were invited to complete a clinical assessment including a medical examination, laboratory tests, and neuropsychological testing. The determination of dementia diagnosis was made by a consensus panel including the assessment team who were blind to twin status [25]. For these participants, diagnostic criteria from the then current Diagnostic and Statistical Manual of Mental Disorders [27] (DSM-III or DSM-IV) were used to diagnose dementia.

Finally, to supplement in-person clinical diagnostic assessments, all twins, including those who refused IPT or telephone screening, were followed until death or December 31, 2012, using the National Patient Registry and National Cause of Death Registry (CDR). The National Patient Registry contains information on hospital visits with diagnosis, admission, and discharge dates. The Cause of Death Registry has information on the underlying and contributing causes of death. Diagnoses in both registries used the then current International Classification of Diseases (ICD) edition [28–30]. Utilization of National Patient Registry