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Apolipoprotein E ε4 genotype and the temporal relationship between depression and dementia

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ABSTRACT

To investigate how apolipoprotein E (*APOE*) affects the temporal relationship between depression and dementia, we conducted a nested case-control study with longitudinal depression and dementia evaluations from several population studies by using 804 dementia cases and 1600 matched controls, totaling 1519 unique individuals. Depression within 10 years of onset of dementia was strongly associated with dementia diagnosis regardless of APOE status (incidence rate ratio [IRR] 5.25, 95% confidence interval [95% CI] 3.32–8.31 for ε4 carriers, IRR 4.40, 95%CI 3.23–5.99 for noncarriers). However, we found a significant interaction between depression more than 10 years before the onset of dementia and APOE ($p = 0.01$), with depression more distal to dementia being a risk factor only in ε4 carriers (IRR 3.39, 95% CI 1.69–6.78 for carriers, IRR 1.01, 95% CI 0.60–1.70 for noncarriers). Thus, depression with onset close in time to dementia onset is associated with disease irrespective of *APOE* genotype, whereas depression more distal to dementia onset is a risk factor only in ε4-carriers. This is the first study to show the interaction between APOE and depression to be dependent on timing of depression onset.

1. Introduction

More than 24 million individuals are estimated to suffer from dementia worldwide, the most common form being Alzheimer disease (AD), and the number is expected to double every 20 years (Ferri et al., 2005). The strongest and most well-established genetic risk factor for AD is the apolipoprotein E (*APOE*) ε4 allele (Huang, 2010). Some of the other known risk factors are low education, hypertension, diabetes, and depression (Barnes and Yaffe, 2011). The focus of the present inquiry was the interaction between *APOE* and depression in relation to dementia and AD.

Depression has long been recognized as a risk factor for dementia (Jorm, 2001). However, the mechanism behind the association remains unclear, and there is an ongoing debate as to whether depression is a risk factor for dementia or rather a prodrome of the disease. A study from a sample of Swedish twins showed that depression with a first onset within 10 years of dementia was associated with disease, whereas depression with onset more than 10 years before dementia was not (Brommelhoff et al., 2009). Similarly, Li et al. (2011) found depression with a first onset after the age of 50 to be associated with dementia, whereas depression with onset earlier in life was not. Others have found both midlife and late-life, as well as recurrent depression, to be associated with dementia (Barnes et al., 2012), although the association was strongest for late-life and recurrent depression.

Considering this literature together, depression seems to increase the risk of dementia and to present most consistently during the prodromal stage, although the interpretation is far from clear. It has been suggested that *APOE* might play a role in this complex association. Four previous studies have analyzed the risk for dementia of having either only *APOE* ε4, only depression, or both risk factors (Irie et al., 2008; Kim et al., 2010; Meng and D'Arcy, 2012; Steffens et al., 1997). Two found a significant interaction between *APOE* and late-life depression in men. Only individuals with both risk factors were at increased risk of dementia (Irie et al., 2008; Kim et al., 2010). The other 2 studies did not find a significant interaction although the pattern of results was similar (Meng and D'Arcy, 2012; Steffens et al., 1997). Only 1 of the studies, using a sample of 142 twins, addressed the temporal relationship between depression and dementia, finding that *APOE* and late-onset depression were

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independent risk factors for AD and that the association between depression and dementia was stronger when depression onset was closer in time to dementia (Steffens et al., 1997).

In the present study, we investigate the association between depression and dementia and how this association is affected by the presence of *APOE* ε4, while considering differences between depression in the preclinical phase of dementia versus more distal to dementia onset, and depression with its onset in mid-versus late-life.

2. Methods

2.1. Study population

The Swedish Twin Registry (STR) was established in the late 1950s and now contains more than 194,000 twins born in Sweden between 1886 and 2000 (Magnusson et al., 2012). The participants in the present study include members from the STR who were ascertained similarly for dementia in 3 longitudinal and 1 cross-sectional study of aging: The Swedish Adoption/Twin Study of Aging (SATSA) (Finkel and Pedersen, 2004), Origins of Variance in the Oldest Old: Octogenarian Twins (OCTO-Twin) (McClearn et al., 1997), Aging in Women and Men (GENDER) (Gold et al., 2002), and The Study of Dementia in Swedish Twins (HARMONY) (Gatz et al., 2005). All studies have been described in detail previously.

To summarize, SATSA is an ongoing longitudinal study of twin pairs separated before the age of 11 matched with a sample of twins who were reared together. The study includes a face-to-face examination on a 3-year rolling schedule. Origins of Variance in the Oldest Old: Octogenarian Twins (OCTO-Twin) is a completed longitudinal study of 351 same-sex twin-pairs who were at least age 80 at baseline. All participated in at least 1 of 5 face-to-face examinations that occurred every 2 years. Aging in Women and Men (GENDER) is a completed longitudinal study of 249 unlike-sex twin pairs, consisting of 3 face-to-face examinations every 4 years Participants in any of these longitudinal studies who at any wave showed indications of cognitive dysfunction were referred for a complete dementia evaluation. HARMONY is a cross-sectional study that started with a telephone screening for cognitive dysfunction of all twins in the STR aged 65 or older. All individuals who screened positive for cognitive dysfunction, their co-twins, and a control sample, were invited to participate in a clinical phase with physical and cognitive examination. In total, 2884 individuals received a complete dementia work-up through 1 of the 4 studies.

In the current study, we used a nested case-control design. For each dementia case we randomly selected 2 controls originating from the same study, matched on year of birth within 2 years and sex. Matching was within study so that cases and controls would be comparable in any procedural differences across studies. Cases and controls were not allowed to be co-twins, and controls had to still be participating in the study and be cognitively intact at age of dementia diagnosis in the case. The sample for analyses included 804 dementia cases and 1600 matched controls. To obtain a representative sample of exposure status in the population and person-time at risk, we used incidence density sampling (Greenland and Thomas, 1982). Participants were hence allowed to serve as controls for more than 1 dementia case, and cases were allowed to serve as controls until onset of dementia; the final study sample contains 1519 unique individuals (the number of cases and unique individuals from each study can be found in Supplementary Table S1).

All participants provided informed consent, and this study was approved by both the Regional Ethics Board in Stockholm and the Institutional Review Board at the University of Southern California.

2.2. Assessment of dementia

Dementia ascertainment was performed similarly in all 4 studies (Gatz et al., 1997). In brief, a cognitive screening was performed using either the Mini-Mental State Examination (Folstein et al., 1975) or telephone screening with the TELE (Gatz et al., 2002) with individuals and informants. Cutoffs were set to maximize sensitivity. Every twin in the STR aged 65 or older was invited for screening on at least one occasion. Screening was followed by a clinical work-up of suspected cases and their co-twins, including cognitive testing, physical and neurological examinations, informant interviews, reviews of medical records, and laboratory tests. Final dementia diagnosis was set at multidisciplinary consensus conferences, according to DSM-III-R (American Psychiatric Association, 1987) or DSM-IV (American Psychiatric Association, 1987, 1994) criteria. Dementia was further differentially diagnosed into AD according to the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association criteria (McKhann et al., 1984). For prevalent dementia cases, age at onset was assessed by informant interviews and review of medical records.

2.3. Assessment of depression

Information about depression was available from 4 sources, namely from national registries, medical records, information about antidepressant medication, and the Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977).

Depression diagnoses were gathered from the National Patient Registry (NPR) through linking based on the national personal number assigned to all inhabitants of Sweden. The NPR contains information about all in-patient care at public hospitals in Sweden. Diseases are classified according to *International Classification of Diseases* (ICD) codes (Socialstyrelsen, 2000). ICD codes used to identify depression were ICD-7 code 314.99, ICD8 codes 296.00, 298.00, 300.40-41, 790.20, ICD-9 codes 296 C/D/W, 298A, 300E, 309 A/B, 311X, and ICD-10 codes F32, F33, F34.1, F41.2.

Medical records from both in-patient and out-patient care were collected and reviewed as part of each study. Use of antidepressant medication was also available, both self-reported and from medical records, and included as another criterion for depression.

The CES-D scale, a 20-item self-report scale developed for epidemiological studies of depressive symptoms in the general population (Radloff, 1977), was administered during every testing occasion in the longitudinal studies. A cut-off point of 20 was used to indicate depression in the present study (Himmelfarb and Murrell, 1983).

For all participants, any occurrence of depression before dementia onset in the case was recorded. Individuals with no depression information from medical records, the CES-D scale, nor antidepressant information were considered missing for depression ($n = 16$). For depression onset, age at the earliest record of onset was used.

The different studies contain slightly different depression information. CES-D scores were not available from prevalent dementia cases, including dementia cases identified by HARMONY. Depression from medical records was not available for all twins from SATSA. Because of the differences in depression information, we matched cases and controls on study of origin and included sources of depression information as a covariate. We also performed sensitivity analyses modeling each source of depression separately.

Depression was further categorized based on the temporal relation to dementia onset. For both cases and their controls, depression was categorized into first identified onset occurring