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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

within 10 years, or more than 10 years before age at dementia onset in the case.

Finally, we categorized depression as late-life depression if first record of onset was at the age of 60 or later, or as midlife depression if first record of onset was before the age of 60. In both categorizations, cases and controls with first depression onset after the age at dementia onset in the case were considered non-depressed.

2.4. APOE genotype

APOE genotype was dichotomized into ε4 carriers and noncarriers, where carriers had genotypes 34 and 44. All other genotypes were considered noncarriers, including 24, which was considered neutral due to the protective effect of the ε2 allele. Information about *APOE* status was available for 1516 out of the 1519 unique individuals included in the study.

2.5. Covariates

Covariates included level of education, stroke before age at dementia onset in the case, and sources of depression data. Education was dichotomized into 0–7 years versus more than 7 years of education (information on education was missing for 7 individuals). Information about previous stroke was identified through the NPR (ICD-7 codes 331–332, ICD-8 and ICD-9 codes 431–434, and ICD-10 codes I61 and I63).

2.6. Statistical analyses

Three different analyses were performed. First, the effect of *APOE* ε4 on dementia and AD was investigated. Secondly, we investigated the effect of depression on dementia and AD, with both any history of depression as the exposure and with depression categorized relative to dementia onset and according to age of first record of depression. The association between depression and dementia was modeled with and without *APOE* status as a covariate. Lastly, we investigated the association between the different depression categories—timing and age of onset—and dementia after stratification on *APOE* status. The interaction between *APOE* and depression was evaluated by the use of an interaction term (*APOE* × depression) in the model. All analyses were adjusted for education and previous stroke. Analyses with depression included in the model also were adjusted for source of depression data. Sex and age were controlled for by design.

Conditional logistic regression was performed in SAS 9.3 (SAS Institute, Cary, NC) using the logistic procedure. Given the use of a nested case-control design, the regression coefficients were interpreted as log-incidence rate ratios (Rodrigues and Kirkwood, 1990). Because the use of twins across matched risk sets violates the assumption of independence between strata, we provide inference based on bootstrapped standard errors, where resampling with replacement was performed on the population of matched risk sets. The resulting *p*-values and confidence intervals (95% CIs) are conservatively corrected for potential correlation between risk sets but suffer from lack of convergence and are provided only as auxiliary evidence in the Supplement.

Additional sensitivity analyses are presented in the Supplementary Section with (1) each source of depression modeled separately as an exposure for dementia outcome; (2) each of the 4 studies modeled separately; (3) individuals with a previous stroke excluded; and (4) depression categorized based only on CES-D scores, medical records and diagnoses in the NPR, and further stratified on untreated or treated with antidepressant medication.

3. Results

3.1. Population characteristics

Of the 804 dementia cases, 469 had the differential diagnosis of AD. Among the 1519 unique individuals included in the study, 424 met the criteria for depression at some point. Of these, 332 were categorized as having had their first identified depression within 10 years of dementia development and 92 as having had depression more than 10 years before dementia. A total of 388 individuals were categorized as having had late-life depression, and 36 as having had midlife depression. A total of 520 individuals were carriers of the ε4 allele and 996 were noncarriers. Dementia and AD cases were significantly more likely to have low education, to have met criteria for depression, and to be carriers of the *APOE* ε4 allele (Table 1).

Mean age at dementia onset was 78 years. When stratified on *APOE* ε4 status, there was a significant difference in age at dementia onset between noncarriers and carriers of the risk-allele ($p < 0.0001$, mean age at onset 79 and 77, respectively). Mean age at depression onset was 74 years. Among dementia cases, mean age of onset was 78 years (range 58–90) for depression within 10 years of dementia onset, and 58 years (range 23–76) for depression more than 10 years previously. For the controls in the study, the corresponding numbers were 77 years (range 60–89) and 63 years (range 38–79), respectively.

3.2. Association between APOE and dementia

As expected, carriers of the *APOE* ε4 allele had significantly increased rate of dementia development (incidence rate ratio 1.96, 95% CI 1.64–2.35) as well as AD (incidence rate ratio 2.64, 95% CI

Table 1
Demographic characteristics of dementia cases and controls

	No dementia[a] (n = 715)	All dementia (n = 804)	Alzheimer disease (n = 469)
Age at baseline, mean (SD)	78.9 (6.6)	80.1 (6.6)[b]	81.0 (6.4)
Age at death, mean (SD)	88.2 (6.0)	85.8 (5.8)[b]	86.4 (5.8)[b]
Female sex, n (%)	424 (59.3)	515 (64.1)	333 (71)[b]
Low education, n (%)	441 (61.7)	569 (71.3)[b]	341 (73.5)[b]
Prior stroke, n (%)[c]	34 (4.8)	70 (8.7)[b]	12 (2.6)
Depression, n (%)[d]	131 (18.6)	293 (36.7)[b]	155 (33.3)[b]
APOE ε4 carriers, n (%)[e]	168 (23.5)	352 (44.0)[b]	224 (48.0)[b]

Number of exposed individuals (percent of number of individuals with covariate data) for binary variables, and mean age (standard deviation) for continuous variables.
Key: APOE, ε4; apolipoprotein, E ε4; SD, standard deviation.
[a] Unique individuals in the control group.
[b] Significant difference compared to the no dementia group, $p = 0.05$.
[c] For controls, stroke before onset of dementia of the matched case with the greatest age at dementia onset.
[d] Of 1503 individuals with available depression data. For controls, depression before the onset of dementia of the matched case with the greatest age at dementia onset.
[e] Of 1516 individuals with available *APOE* genotype. *APOE* ε4 carriers are defined as genotypes 34 and 44.

2.06–3.39) after we adjusted for education and previous stroke. These results did not change after bootstrapping (Supplementary Table S2).

3.3. Association between depression and dementia

A significant association was found between depression and both dementia and AD after we adjusted for education, previous stroke, and sources of depression data (Table 2, column 1). This association remained significant after including *APOE* as a covariate (Table 2, column 2).

The association with dementia and AD was much stronger for depression occurring within 10 years of dementia onset in the case compared with depression more than 10 years earlier (Table 2, column 1, rows 3–4 and 9–10). After we included *APOE* as a covariate, depression within 10 years of dementia remained a significant predictor of both dementia and AD; the effect of depression more than 10 years before the onset of dementia was nonsignificant for AD.

When depression was categorized according to age at first onset, both late-life and midlife depression was shown to be associated with dementia and AD (Table 2, column 1, rows 5–6 and 11–12). This effect remained significant after we included *APOE* status as a covariate.

After bootstrapping, the effect of depression within 10 years of dementia and late-life depression remained significant. However, the effect of depression more than 10 years before dementia onset and midlife depression were no longer significant (Supplementary Table S3, column 1).

3.4. Interaction between APOE and depression on outcome of dementia

There was a statistically significant interaction between overall depression and *APOE* on AD, but not dementia, although both carriers and noncarriers with depression showed an increased rate of dementia and AD compared with nondepressed individuals in the same genotype category (Table 2, column 3–4).

After we categorized depression into first onset occurring more or less than 10 years before the onset of dementia, the incidence rate of developing dementia and AD after a recent onset depression were significantly increased in both carriers and noncarriers of ε4 (Table 2, column 3–4 rows 3–4 and 9–10).

However, there was a statistically significant interaction between *APOE* and depression more than 10 years before the onset of dementia for both dementia and AD. Carriers of the ε4 allele with a depression more than 10 years before the onset of dementia had more than a 3 times greater incidence of dementia and more than 9 times greater incidence of AD, whereas the incidence for noncarriers of ε4 with a depression more than 10 years before dementia development was not increased (Table 2, column 3–4, rows 3–4 and 9–10).

When the analyses were repeated with depression stratified into onset before or after the age of 60, the general pattern was similar, but the differences between groups less pronounced (Table 2, column 3–4, rows 5–6 and 11–12). Neither depression late in life nor midlife was found to significantly interact with *APOE* genotype for dementia or AD.

Bootstrapping results showed the same pattern of significances for the interaction model, except for midlife depression and depression more than 10 years before the onset of AD, both of which displayed lack of convergence and extremely wide confidence intervals (Supplementary Table S3, columns 3–5).

Sensitivity analyses with each source of depression modeled separately lacked power but generally showed the same pattern as the main results (Supplementary Table S4). The exception was depression assessed by review of medical records, for which depression within 10 years of dementia and in late life also significantly interacted with *APOE*. Furthermore, the estimates for the effect of depression assessed by the CES-D scale on dementia were low for all groups. Sensitivity analyses modeling each of the 4 studies separately generally showed a similar pattern for the point estimates but suffered from low power with wide confidence intervals limiting the interpretation (Supplementary Table S5). The SATSA study showed generally lower estimates compared with the other studies.

Sensitivity analysis excluding stroke cases did not change the results or interpretations (Supplementary Table S6). Sensitivity analyses modeling treated and untreated depression separately showed a statistically significant interaction between *APOE* and untreated, but not treated depression (Supplementary Table S5).

Table 2
The association between depression and dementia/Alzheimer disease, and the interaction with APOE genotype

	Total sample n = 2404	Total sample	APOE × depression interaction model		
		Adjusted for *APOE* n = 2404	ε4 non-carriers[a] n = 1597	ε4 carriers[a] n = 801	*p*-value
Dementia					
No depression	1	1	1	1	
Any depression	**3.41 (2.72-4.27)**	**3.51 (2.78-4.41)**	**3.07 (2.34-4.02)**	**4.68 (3.16-6.93)**	0.07
Depression within 10 y of dementia	**4.46 (3.44-5.76)**	**4.67 (3.59-6.08)**	**4.40 (3.23-5.99)**	**5.25 (3.32-8.31)**	0.51
Depression >10 y before dementia	**1.58 (1.07-2.34)**	**1.55 (1.04-2.31)**	1.01 (0.60–1.70)	**3.39 (1.69-6.78)**	**0.01**
Late-life depression (≥60)	**3.56 (2.81-4.51)**	**3.67 (2.88-4.68)**	**3.26 (2.46-4.33)**	**4.79 (3.16-7.26)**	0.12
Midlife depression (<60)	**2.43 (1.35-4.35)**	**2.44 (1.34-4.44)**	1.74 (0.80–3.79)	**4.21 (1.53-11.58)**	0.17
Alzheimer disease					
No depression	1	1	1	1	
Any depression	**2.89 (2.09-4.00)**	**3.06 (2.18-4.30)**	**2.50 (1.69-3.70)**	**5.29 (2.75-10.18)**	**0.04**
Depression within 10 y of dementia	**3.45 (2.39-4.98)**	**3.76 (2.56-5.53)**	**3.57 (2.28-5.59)**	**4.49 (2.20-9.15)**	0.58
Depression >10 y before dementia	**1.75 (1.01-3.03)**	1.69 (0.95–3.01)	0.90 (0.43–1.89)	**9.60 (2.22-41.44)**	**0.01**
Late-life depression (≥60)	**2.93 (2.08-4.12)**	**3.09 (2.16-4.43)**	**2.57 (1.70-3.87)**	**5.08 (2.59-9.93)**	0.07
Midlife depression (<60)	**2.63 (1.13-6.09)**	**2.81 (1.17-6.76)**	2.03 (0.74–5.52)	9.49 (0.98–92.06)	0.22

Hazard ratios (95% confidence intervals) of dementia/Alzheimer disease in the presence of depression, for the total sample and stratified by *APOE* ε4 status.
The model is adjusted for education, previous stroke, and sources of depression data available.
Bold values indicate statistical significance.
Key: *APOE* ε4, apolipoprotein E ε4.
[a] *APOE* ε4 carriers are defined as genotypes 34 and 44, all other genotypes are considered noncarriers.

4. Discussion

Our results suggest that depression with onset close in time to dementia, and depression with first known onset late in life, increase the rate of dementia irrespective of *APOE* genotype, whereas depression that occurs more than 10 years before the onset of dementia is a risk factor only in carriers of *APOE* ε4. These findings offer further evidence regarding the temporal relationship between depression and dementia while also highlighting the complex nature of the association between the 2 diseases, especially the role of genetic risk.

Although the association between late-life depression and dementia has been rather consistent across studies, there have been discrepancies between studies of the association between early or midlife depression and dementia (Byers and Yaffe, 2011). We were able to provide further support to the relationship between late-life depression and dementia by showing this association to be robust and unaffected by *APOE* status. In these individuals, there remains the possibility that depression is a prodrome of the dementing disease. We also were able to suggest a resolution for the inconsistencies between studies of the association between early or midlife depression and dementia, by offering *APOE* status as an explanatory factor.

The results also highlight the differences between depression in late life and that in midlife. Compared with depression earlier in life, late-onset depression is known to present with a different symptomology as well as a different etiology. Late-onset depression is less likely to be associated with a family history of depression and more likely to include cognitive deficits, white matter intensities, and a vascular pathology (Fiske et al., 2009).

There are several mechanisms by which depression could increase the risk of dementia. Because depression increases the risk of vascular disease, it could thereby increase the vascular risk of dementia (Byers and Yaffe, 2011). Alternatively, depression could increase stress-induced increase of glucocorticoid levels, which can lead to decreased neurogenesis, reduction of neurotrophic factors, hippocampal atrophy, and possibly also to increased levels of Aβ formation (Byers and Yaffe, 2011; Jorm, 2001). Inflammatory changes have also been shown in depression and are known to play a central role in both dementia and vascular disease (Byers and Yaffe, 2011; Hansson and Libby, 2006).

Eriksson et al. (2010) demonstrated that, among those with nonstroke cardiovascular disease, only carriers of *APOE* ε4 are at increased risk of developing AD. Similarly, our results indicate that only carriers of the *APOE* ε4 allele have increased vulnerability to dementia after suffering from depression earlier in life. *APOE* is associated with dementia through several mechanisms, including neurotoxicity and impaired neural plasticity (Vance and Hayashi, 2010). The latter could lead to decreased ability of the brain to cope with the detrimental effects of depression, thereby magnifying other underlying mechanisms for *APOE* ε4 carriers.

The results presented here are based on a large cohort of twins with long follow-up time and enough information available to distinguish between depression with onset within or more than 10 years before dementia. The chief limitation is that ascertainment of depression comes from a variety of sources; the CES-D scale, medical records, antidepressant information, and diagnoses from the National Patient Registry. The latter only contains patients who receive a depression diagnosis while being admitted to a hospital, who are, naturally, more likely to have a severe depression. In general, geriatric depression has been shown to have a milder symptom load (Fiske et al., 2009), and for those with only NPR as a source of depression information, some cases of geriatric depression may hence have been missed. Antidepressant medication is used not only in depression but also for other psychiatric disorders, and this source of depression may therefore include some other psychiatric disorders (Thronson and Pagalilauan, 2014). Previous depression could not be assessed in prevalent dementia cases through the CES-D scale, which was available before the onset of dementia only for participants in the longitudinal studies, and for a small proportion of participants medical records were not reviewed. To deal with these issues, we matched on study origin and included source of depression data as a covariate. Furthermore, although sensitivity analyses where each source of depression information was modeled separately lacked power, all sources showed the same general patterns as the main analyses.

Estimation of the age at depression onset also may be biased. For cases identified through the NPR, the dates of hospitalization were used for age of onset. For cases identified by medical records, it was not possible to go back to early midlife for all individuals. For cases identified from CES-D scores, the age of depression onset was determined by the age at the interview when the CES-D was completed. Because of the rolling scheme of testing occasions, it is possible that depressive episodes occurring between testing occasions were missed. Furthermore, for individuals meeting the criterion for depression according to the CES-D scale at baseline but with no record of depression from other sources, age at onset may have been earlier than as assessed by age at interview. Information about depression before mid-life was only available from the NPR. The registry has a low sensitivity for depression, because not all depressed individuals are ever admitted to hospital. Furthermore, the registry did not have national coverage until 1987. In general, then, the earliest age of onset is therefore probably earlier than identified by our data, and early-onset depression is likely underascertained in this study. Additionally, individuals categorized as having had their first depression onset in late life, or within 10 years of dementia, may have had a previous episode of depression that would have been missed. However, misclassification of depression as late-life instead of midlife would drive the estimates toward the null-hypothesis for both the association between recent depression and dementia and for the interaction between APOE and depression more than ten years prior to dementia.

In conclusion, we provide new data in a large population-based sample about the interaction of depression and *APOE* as risk factors for dementia and AD. To the best of our knowledge, this is the first study to show APOE to affect the association between depression and dementia differently depending on the timing of depression onset in relation to dementia. Depression with onset close in time to dementia onset was strongly associated with disease and not affected by *APOE* genotype. However, the association between depression more distal to dementia onset and occurrence of dementia seems to be more complex, and was evident only in the presence of the *APOE* ε4 risk allele.

Disclosure statement

The authors have no actual or potential conflicts of interest.

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Dr. Pedersen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix A. Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2015.01.008.

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