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Sex differences in the relationship between depressive symptoms and risk of amnesic mild cognitive impairment

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Abstract

BACKGROUND—The relationship between depressive symptoms and subsequent cognitive impairment in older adults is controversial. Sex differences and the differences in the method of categorizing depressive symptoms may contribute to the inconsistencies.

OBJECTIVE—To examine the effect of severity of baseline depressive symptoms on risk of incident amnesic mild cognitive impairment (aMCI) separately in men and women.

METHODS—Community-dwelling and cognitively healthy older adults (aged ≥70 years) from the Einstein Aging Study completed the 15-item Geriatric Depression Scale (GDS-15) at their baseline visit. Participants were categorized into “no or low symptoms” (GDS-15 score=0–2), “mild symptoms” (GDS-15 score=3–5) and “moderate/severe symptoms” (GDS-15 score>6) groups. Sex-stratified Cox proportional hazards models, adjusted for age, education, and antidepressant medication, estimated hazard ratios (HR) and 95% confidence intervals (CIs) for incident aMCI as a function of depressive symptoms group.

RESULTS—We followed 572 women (mean age=78) and 345 men (mean age=77) for 4.2 years on average (range=1.0–14.6 years). Ninety women and 64 men developed aMCI during follow-up. Cox models revealed that compared to no/low depressive symptoms, mild symptoms were associated with a two times greater risk of developing aMCI in men (HR=2.22, 95% CI=1.26–3.89) but not in women (HR=1.26; 95% CI=0.77–2.06). Conversely, moderate/severe depressive symptoms were associated with a two times greater risk of developing aMCI in women (HR=1.99, 95% CI=1.05–3.77) but not in men (HR=0.28, 95% CI=0.04–2.11) possibly due to low statistical power in this subgroup.

CONCLUSIONS—Results indicate that mild depressive symptoms in men and moderate/severe symptoms in women may represent a marker for future cognitive impairment.

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Keywords

amnesic mild cognitive impairment; sex differences; depressive symptoms; Geriatric Depression Scale

OBJECTIVE

Mild cognitive impairment (MCI) is the intermediate state between normal cognitive aging and dementia; 10–12% of individuals transition from MCI to dementia annually but not everyone transitions (1,2). Amnesic MCI (aMCI) is characterized by clinically-evident memory impairment, subjective memory complaints and an increased risk of progression to Alzheimer's-type dementia (1,2).

One approach to preventing aMCI and Alzheimer's-type dementia is to reduce risk by modifying remediable risk factors (lifestyle and psychosocial factors). Late-life depression may be a remediable risk factor for aMCI as it affects 25% of older adults (3), amenable to treatment (4), and associated with cognitive decline and MCI risk (5–17). However, some studies did not find a relationship between depressive symptoms and cognitive outcomes (18,19) and, in others, the relationship varied by sex (5,9,13–16). Some reported that the relationship between depressive symptoms and cognitive outcomes was male-specific or stronger in men (9,13,14), whereas, others reported a female-specific relationship (5,15,16).

Sex differences and differences in the method of ascertaining and defining depressive symptomology may contribute to heterogeneity among studies. Women have higher rates of depression (20,21) and more severe depressive symptoms than men (20), perhaps partly because men under-report symptoms (13). Additionally, most studies have used a single cut-point to dichotomize depressive symptoms and this cut-point varies across studies. Many studies applied a conservative cut-point that creates a depressive symptom group with moderate/severe symptoms only, otherwise referred to as “clinically-significant” (5,8,9,12–16). Others applied a less conservative cut-point that combines mild or subclinical symptoms and moderate/severe symptoms in the depressive symptom group (6,22).

We examined the effect of baseline depressive symptoms, assessed by the 15-item Geriatric Depression Scale (GDS-15), on risk of incident aMCI in a sample of community-dwelling, older adults with up to 15 years of follow-up and how this effect differs by sex. Because the optimal cut-point for predicting incident aMCI is unclear and because men and women differ in depressive symptom severity (20), we determined whether there is a depressive symptom dose effect in relation to aMCI risk in men and women. Using two cut-points similar to those previously employed, depressive symptoms were trichotomized into the categories of “no/low” (GDS-15 ≤ 2), “mild” (GDS-15 = 3–5) and “moderate/severe” symptoms (GDS-15 > 5). Thus, we examined sex differences in the risk of aMCI associated with mild and moderate/severe symptoms compared to no/low symptoms in older adults.

METHODS

Participants

Data is from the Einstein Aging Study (EAS), a longitudinal, community-based, cohort study of older adults (70 years) who were systematically recruited from Bronx, NY beginning in 1993. EAS study design and recruitment has been described (23). EAS inclusion criteria include being ambulatory, non-institutionalized, proficient in English and no sensory loss that interferes with study assessments. EAS participants undergo clinical, neuropsychological and psychosocial assessments. Participants with a dementia, aMCI or non-amnesic MCI (naMCI) at study enrollment were excluded from analyses. Informed consents were approved by the local institutional review board and obtained at clinic visits according to study protocol.

Procedure

MCI and Dementia Diagnosis—Participants' cognitive status was evaluated annually and clinical diagnoses were made at diagnostic case conferences attended by a study neurologist and neuropsychologist. An aMCI diagnosis required objective memory impairment on the Free Recall portion of the Free and Cued Selective Reminding Test (FCSRT-FR) (24) and/or the Logical Memory Subtest of the Wechsler Memory Scale-Revised (25) and subjective memory complaints with no functional impairment (2). Objective memory impairment was defined using a previously established cut-score of 24 on the FCSRT-FR (range:0–48) (24) and/or an age-adjusted score of 5 on the Logical Memory Test (range:0–50) (25). Subjective memory complaints were determined according to self or informant responses on the Consortium to Establish a Registry for Alzheimer's Disease (26) and the EAS Health Assessment questionnaire. A naMCI diagnosis was given if criteria for aMCI were not met, but there was impairment (1.5 standard deviations below the age-adjusted mean) in at least one non-memory cognitive domain and no functional impairment. Dementia diagnosis was assigned according to standardized criteria from the Diagnostic and Statistical Manual of Mental Disorders IV.

Depressive Symptoms—The Geriatric Depression Scale (GDS-15) is a 15-item, self-report measure of depressive symptoms (27). Participants responded “yes” or “no” to whether 15 mood disturbance symptoms associated with geriatric depression were experienced over the past week. GDS-15 scores ranged from 0–15 with higher scores indicating more symptoms. Participants were grouped according to similar GDS-15 cut-points previously employed (8,12,14,17): “no/low” symptoms (GDS-15=0–2), “mild” (also called minor or lower level) symptoms (GDS-15=3–5), and “moderate/severe” symptoms (GDS-15>5). The GDS-15 has demonstrated reliability and validity in a community-based elderly population (27). EAS participants' first and second annual GDS-15 scores correlated at $r=0.71$ ($N=1,086$, $p<0.001$).

Covariates—The presence or absence of cardiovascular diseases (CVD) including diabetes, hypertension, heart failure, angina, myocardial infarction, or strokes were used to calculate a cardiovascular comorbidity index (range:0–6). History of a clinical depression diagnosis and antidepressant medications were self-reported. Participants were categorized

as users versus non-users of antidepressants based on use of tricyclics, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and/or serotonin and norepinephrine reuptake inhibitor.

Statistical Analysis—Sociodemographic and clinical characteristics were compared between sex, aMCI and depressive symptom groups using ANOVAs for continuous variables and chi-square tests for categorical variables. Participants who were without aMCI at baseline, but developed aMCI during follow-up are referred to as incident aMCI cases. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CIs) for incident aMCI as a function of depressive symptoms groups. The main effect of the trichotomized depressive symptoms variable on incident aMCI was assessed and, if statistically significant ($p < 0.05$), individual category contrasts were conducted with the no/low symptoms group as the reference group (mild versus no/low symptoms and moderate/severe versus no/low symptoms). Nested Cox models were performed with follow-up time as the scale. Time of aMCI diagnosis was the visit date corresponding to the diagnostic consensus conference date. Models were sex-stratified in order to compare results between women and men. We also tested the interactive effects of depressive symptoms and sex on incident aMCI in the overall sample. Model one measured the unadjusted relationship between depressive symptom groups and incident aMCI. Model two adjusted for age and years of education. Model three additionally adjusted for any clinical factor that significantly differed between symptom and/or aMCI groups and demonstrated significance in the model ($p < 0.05$). To compare this more refined analysis to a more standard, dichotomous categorization, analyses were repeated using GDS-15 scores that were dichotomized at a cut-point distinguishing no/low symptoms from mild to severe symptoms (GDS-15 ≥ 3). As a supplemental analysis, we repeated analyses with incident naMCI as the outcome to determine whether findings generalize to cognitive deficits in non-memory domains (e.g. executive function and processing speed). Two-sided probability values < 0.05 were considered statistically significant. Analyses were performed using SPSS 20 (SPSS Inc., Chicago, Illinois).

RESULTS

Sample characteristics

We followed 572 women initially free of aMCI, naMCI and dementia for an average of 4.2 years (maximum=14.6 years). Ninety (16%) women were incident aMCI cases. At baseline, 384 (67%) women reported no/low depressive symptoms, and among them, 54 (14%) were incident aMCI cases. Mild symptoms were reported by 135 women (24%), and, among them, 24 (18%) were incident aMCI cases. Moderate/severe symptoms were reported by 53 women (9%) and, among them, 12 (23%) were incident aMCI cases. The female incident aMCI (N=90) cases contributed 335 person-years to the cohort, and the female aMCI-negative group (N=482) contributed 2,058 person-years. The female sample was predominantly White (63%) with an average of 78 years of age and 14 years of education (Table 1). Current antidepressant medication use was self-reported in 4%. A history of clinical depression was self-reported in 10%.

We followed 345 men initially free of aMCI, naMCI or dementia for an average of 4.2 years (maximum=14.2 years). The male sample differed from the female sample in that it had a higher proportion of Whites and a higher cardiovascular comorbidity index. Sixty-four (19%) men were incident aMCI cases. At baseline, 254 (74%) men reported no/low depressive symptoms, and among them, 44 (17%) were incident aMCI cases. Mild symptoms were reported by 64 men (18%), and, among them, 19 (30%) were incident aMCI cases. Moderate/severe symptoms were reported by 27 men (8%) and, among them, 1 (4%) was an incident aMCI case. The small number of men reporting moderate/severe symptoms rendered us statistically underpowered in analysis involving this group and warrants caution when interpreting results. The male incident aMCI cases (N=64) contributed 215 person-years to the cohort, and the male aMCI-negative group (N=205) contributed 1,259 person-years. The male sample was predominantly White (78%) with an average of 77 years of age and 14 years of education (Table 1). Current antidepressant medication use was self-reported in 3%. A history of clinical depression was self-reported in 8%.

Baseline characteristics by incident aMCI status and depressive symptoms group

Among women, incident aMCI cases were older and less educated compared to the aMCI-negative group (Table 1). Women in the mild or moderate/severe depressive symptoms groups were less educated, had a higher cardiovascular comorbidity index, and had higher rates of antidepressant medication use and self-reported history of clinical depression compared to the no/low symptoms group (Table 2).

Among men, incident aMCI cases were older, less educated, and had fewer years of follow-up compared to the aMCI-negative group (Table 1). Men in the mild or moderate/severe depressive symptoms group had fewer years of follow-up and a higher rate of antidepressant medication use compared to men in the no/low symptoms group. Men in the moderate/severe depressive symptoms group had a higher cardiovascular comorbidity score and a higher rate of self-reported history of clinical depression compared to men in the no/low and mild symptoms groups (Table 2).

Results of Cox proportional hazards model

Cox models in the total sample revealed a significant interactive effect of sex with the 3-category depressive symptom variable on incident aMCI, X^2 (df=2, N=917)=6.36, $p=0.04$ (Supplementary Table 1). When examining the interactive effects of sex with the individual category comparisons of depressive symptom groups, the sex by mild symptoms (vs. no/low symptoms) interaction (HR=1.81, 95% CI=0.86–3.78, X^2 (df=1, N=917)=2.48, $p=0.11$) and the sex by moderate/severe symptoms (vs. no/low symptoms) were not significant (HR=0.15, 95% CI=0.02–1.20, X^2 (df=1, N=917)=3.21, $p=0.07$). Because of the significant interaction between sex and the overall 3-category depressive symptom variable, we focused on the sex-stratified analyses (Table 3). In women, the main effect of depressive symptoms on aMCI risk in model one (unadjusted model) was significant. Compared to women with no/low depressive symptoms, women with mild symptoms were not at increased risk of aMCI in model one; however, women with moderate/severe symptoms were at a significant, two-fold increased risk of aMCI. Results did not change after adjustment for age and education in model two. Due to significant differences between depressive symptom and/or

aMCI groups in women or men, cardiovascular comorbidity index, antidepressant medication use, and history of clinical depression were adjusted for in model three; however, only antidepressant use was statistically significant among men, but not women. To be consistent among models, antidepressant use was retained as a covariate in model three in both women and men. Among women, results did not change after covarying for antidepressant use in model three.

In men, the main effect of depressive symptoms on aMCI risk in model one was also significant. Compared to no/low symptoms, mild symptoms were associated with a significantly increased risk of aMCI in model one. Moderate/severe depressive symptoms were not associated with aMCI risk in men; however, this test is statistically underpowered considering the low sample size in this group ($n=27$). In model two, adjusting for age and education did not change results in men. In model three, the adjustment of antidepressant use slightly attenuated the relationship between mild depressive symptoms and aMCI risk in men, although it remained significant. Notably, antidepressant use in men was associated with a greater than three-fold increased risk of aMCI, although this was based on a very small sub-group of 11 antidepressants users.

In secondary analyses that used the dichotomous categorization of GDS-15 scores, the sex by depressive symptoms interaction was not significant in the total sample (Table 4). In sex-stratified analyses, mild to severe symptoms significantly related to increased aMCI risk in women in unadjusted analyses; however, this relationship was attenuated and not significant after adjusting for covariates. Among men, mild to severe symptoms were associated with a 1.6 times increased risk of aMCI compared to no/low symptoms in model one, although this association just missed significance. Adjusting for covariates did not change results.

In supplemental analyses that modelled incident naMCI as the outcome, 99 women and 57 men developed naMCI. Unlike the aMCI analysis, the interaction of sex with the 3-category depressive symptom variable was not significant in the total sample, X^2 ($df=2, N=917$)=4.54, $p=0.10$. However, results were similar to the aMCI analysis in sex-stratified analyses. Compared to no/low depressive symptoms, mild symptoms were associated with a two times greater risk of incident naMCI in men ($HR=2.12$, 95%CI=1.16–3.88, $X^2[df=1, N=345]=5.94$, $p=0.01$) but not in women ($HR=1.44$; 95%CI=0.91–2.28, $X^2[df=1, N=572]=2.67$, $p=0.23$). Conversely, moderate/severe depressive symptoms were associated with a two times greater risk of developing naMCI in women ($HR=2.06$, 95%CI=1.12–3.79, $X^2[df=1, N=572]=5.40$, $p=0.01$) but not in men ($HR=0.29$, 95%CI=0.04–2.10, $X^2[df=1, N=572]=1.51$, $p=0.22$; Supplementary Table 3).

CONCLUSION

We assessed baseline depressive symptoms at 3 severity levels (none/low, mild, moderate/severe) as a predictor of incident aMCI. The depressive symptom by sex interaction was significant in the total sample, so we focused on the relationship between depressive symptoms and aMCI risk in sex-stratified analyses. Among men, mild symptoms were associated with a more than two-fold increased risk of aMCI compared to no/low symptoms. Moderate/severe symptoms in men were not associated with aMCI risk; however, this test

was statistically underpowered given that only 27 men reported moderate/severe symptoms. Conversely, among women, moderate/severe depressive symptoms, but not mild symptoms, were significantly associated with two-fold increased risk of aMCI although this relationship was not as robust as that seen among mild symptoms and aMCI risk in men. Results suggest that symptoms must meet a threshold of moderate/severe intensity to impact aMCI risk in women.

We examined incident aMCI because it best characterizes the prodromal stage of AD; however, we repeated analyses using naMCI as the outcome given that non-memory cognitive domains (e.g. processing speed and executive impairment) are most commonly associated with late-life depression (28) and other forms of dementia (29). We found similar results with naMCI as the outcome suggesting that the sex difference in how depressive symptoms relate to risk of cognitive impairment also applies to non-memory domains and a risk of dementia. Our results provide support for the notion that depressive symptoms, even mild symptoms in men, are a risk factor for general MCI in older adults, and extend findings by indicating important sex differences.

Some longitudinal, sex-stratified studies have reported a relationship between baseline depressive symptoms and cognitive outcomes that is male-specific or stronger in men (9,13,14), whereas others have reported a female-specific relationship (5,15,16). Our results suggest that there are complexities to the relationship between depressive symptoms and MCI that require consideration including sex differences and the categorization of symptoms. In a secondary analysis where we dichotomized depressive symptoms, mild to severe symptoms were not significantly associated with aMCI risk compared to no/low symptoms in men or women after adjusting for covariates. Thus, significant associations between depressive symptoms and aMCI risk that were observed when we trichotomized symptoms were not evident with a coarser, dichotomous categorization of symptoms. This inconsistency within our study suggests that inconsistencies across studies may be due to differences in the categorization of depressive symptoms and highlights the importance of examining symptoms at different severity levels in relation to cognitive outcomes.

Biological and/or psychosocial factors could explain the sex difference in results. There are sex differences in the endocrine and neurotransmitter systems implicated in the pathophysiology of depression (30); in the reactivity of the hypothalamic pituitary adrenal axis (30); and in the relationship between depressive symptoms and structural brain changes (31). For instance, subthreshold depression has been associated with smaller medial frontal lobe volume in older men but not women (31) suggesting that male brains may be susceptible to depression-associated brain changes at a lower depression severity level than women. Thus, an increased risk for MCI may manifest at lower symptom severity in men versus women.

From a psychosocial perspective, there may be a gender bias in reporting depressive symptoms, wherein societal expectations and gender roles make men reluctant to disclose discomfort (32). Men may be inclined to underreport symptoms of discomfort (e.g. anxiety, depression) because they are incongruent with the stereotypical male role, whereas the stereotypical female role is associated with greater expressiveness and less resilience (32).

Consistent with this theory, evidence suggests that men who report depressive symptoms are reacted to more adversely by peers than women who report depressive symptoms (33). A gender reporting bias in depressive symptoms was purported by Dal Forno et al. (13) who found that a history of clinically-significant depressive symptoms (CES-D score 16) was a significant risk factor for incident dementia in men but not in women in the Baltimore Longitudinal Study of Aging. The authors suggested that men are less inclined to report depressive symptoms, and, thus, symptoms reported by men are more extreme versus symptoms reported by women (13). Herein, “mild” symptoms may be more severe when reported by men versus women and, thus, more strongly associated with MCI risk.

The small number of men in the moderate/severe symptoms group rendered us statistically underpowered in analyses involving this group. Given that clinical depression rates are doubled in women versus men (21) and that older cohort studies typically have more women than men due to their longer lifespan (34), statistical power to assess relationships with depressive symptoms in men is generally reduced. A sex difference in statistical power may contribute to a sex difference in the relationship between depressive symptomology and cognitive impairment. For example, in the Sachdev et al. study (16) that found a female-specific relationship between history of depression and incident MCI, there were more women (n=425) than men (n=332), and the proportion of women reporting a history of depression (n=72) was double that of men (n=41). Conversely, the Dal Forno et al. (13) study that found a male-specific relationship between depressive symptoms and incident dementia had more men (n=781) than women (n=576) with a similar proportion of men (10.2%) and women (11.9%) reporting clinically-significant depressive symptoms. Our findings underscore the importance of considering sex differences in statistical power when examining depressive symptoms.

It is unclear whether depressive symptoms are a true causative factor for cognitive impairment or an early manifestation (a biological consequence of pre-MCI brain changes versus a psychological reaction to perceiving cognitive decline). Evidence supporting the role of depressive symptoms as a causative factor includes findings of higher levels of hippocampal atrophy (35), brain inflammation, hypercorticoolemia, apoptosis (36) and beta-amyloid deposition (37), the pathological hallmark of AD, in individuals with late-life depression compared to non-depressed adults. Another possibility is the reverse causality hypothesis; depressive symptoms were in response to self-perceived cognitive deterioration that was not severe enough to be classified as MCI. We are unable to distinguish between possibilities.

Study strengths include its prospective assessment of a well-characterized, population-based cohort that enabled us to relate depressive symptoms at baseline with incident MCI and adjust for other MCI risk factors. Our sex-stratified analysis and examination of depressive symptoms at different severity levels helps to address inconsistencies in the literature. Our study has limitations. The small number of men reporting moderate/severe depressive symptoms renders us statistically underpowered to interpret results in this group. The ability of the GDS-15 to detect symptoms of non-major depressive disorder may be limited (38), and relying on the GDS-15 as our sole assessment of depressive symptoms is a limitation particularly at baseline when consistency among depression screening tools is variable (39).

Ideally, we would have adjusted for apolipoprotein ε4 (APOE4) status considering evidence that APOE4 modifies the relationship between depression and MCI risk (14); however, because APOE4 data was missing in 225 women and 128 men, we were statistically underpowered to do so. Given evidence that late-onset depression is a stronger risk factor for MCI than early-onset, recurrent depression (40), we would have ideally accounted for prevalence rates of late-onset versus early-onset depression; however, although we have self-reported history of clinical depression, we don't know the timing or frequency of depressive episodes. Lastly, results cannot be generalized to dementia.

In conclusion, mild depressive symptoms were a significant risk factor for incident MCI in older men, whereas moderate/severe depressive symptoms were a significant risk factor for incident MCI in older women. Larger, longitudinal studies are needed to examine sex differences in the relationship between depressive symptoms at different severity levels and incident MCI and test the hypothesis of a gender reporting bias. If replicated, results indicate the importance of conducting sex-stratified analyses when examining depressive symptoms in relation to cognitive outcomes. Clinically, results suggest that clinical assessments for depressive symptoms should be sensitive enough to detect mild symptoms in men as they may represent a remediable risk factor for cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Baseline characteristics of the male and female samples by incident aMCI status. Values are mean (SD) unless otherwise noted.

Background Characteristics	<i>W, M</i>	Women			Men		
		All N=572	No Incident aMCI N=482	Incident aMCI N=90	All N=345	No Incident aMCI N=281	Incident aMCI N=64
Age at baseline	<i>W, M</i>	77.98 (6.0)	77.69 (5.2)	79.52 (6.0)	77.28 (5.1)	76.86 (5.0)	79.12 (5.1)
Education (years)	<i>W</i>	13.82 (3.3)	14.00 (3.4)	12.86 (2.9)	14.17 (3.6)	14.11 (3.5)	14.41 (3.6)
Caucasian, N (%)	<i>S</i>	365 (64)	304 (63)	61 (68)	268 (78)	219 (76)	49 (77)
Follow-up time, yrs	<i>M</i>	4.19 (3.2)	4.27 (3.3)	3.73 (2.9)	4.24 (3.2)	4.48 (3.3)	3.21 (2.8)
Time to aMCI onset, yrs (aMCI-positive participants only)		–	–	3.7	–	–	3.2
APOE4 carrier ^a , N (%)		81 (23)	61 (22)	20 (29)	45 (21)	35 (20)	10 (24)
Cardiovascular comorbidity index ^S		1.00 (0.9)	0.99 (0.9)	1.05 (0.9)	1.13 (1.0)	1.15 (1.1)	1.03 (0.99)
Antidepressant medication, N (%)	<i>M</i>	21 (4)	18 (4)	3 (3)	11 (3)	6 (2)	6 (9)
History of clinical depression, N (%)		56 (10)	47 (10)	9 (10)	29 (8)	22 (8)	7 (11)

Notes. The F-test in univariate analyses of variance was used to test mean differences in continuous variables between incident aMCI groups in women, F(1,570) and men, F(1,343) separately. Chi-square tests were used to test differences in frequencies between incident aMCI groups in women, χ^2 (df=1, N=572) and men χ^2 (df=1, N=345) separately. Abbreviations: aMCI = amnesic mild cognitive impairment. APOE4 = apolipoprotein ε4 allele.

^a APOE genotype was available for only 347 women and 217 men.

^S There is a significant difference between sexes at $p < 0.05$.

M Main effect of incident aMCI status is significant in men at $p < 0.05$.

W Main effect of incident aMCI status is significant in women at $p < 0.05$.

Table 2

Baseline characteristics of the male and female samples by depressive symptom group. Values are means (SD) unless otherwise noted.

Background Characteristics	Women (N=572)				Men (N=345)	
	No/Low Depressive Symptoms N=384	Mild Depressive Symptoms N=135	Moderate/Severe Depressive Symptoms N=53	No/Low Depressive Symptoms N=254	Mild Depressive Symptoms N=64	Moderate/Severe Depressive Symptoms N=27
Age at baseline	77.86 (5.4)	78.36 (5.5)	77.89 (5.1)	77.07 (5.1)	77.61 (5.2)	78.5 (5.4)
Education (years) ^W	14.14 (3.4)	13.10 (3.0)	13.34 (3.6)	14.21 (3.6)	13.86 (3.6)	14.48 (3.5)
Caucasian, N (%)	242 (63)	90 (67)	33 (62)	195 (77)	50 (78)	23 (85)
APOE4 carrier ^a , N (%)	60 (26)	15 (17)	6 (21)	38 (24)	5 (12)	2 (12)
Follow-up time, yrs ^M	4.38 (3.3)	3.90 (3.1)	3.47 (2.7)	4.57 (3.4)	3.16 (2.3)	3.68 (2.8)
Incident aMCI cases, N (%) ^M	54 (14)	24 (18)	12 (23)	44 (17)	19 (30)	1 (4)
Incident naMCI cases, N (%) ^M	58 (15)	28 (21)	13 (25)	39 (15)	17 (26)	1 (4)
Time to aMCI onset, yrs (aMCI-positive participants only)	4.0 (3.1)	3.5 (2.8)	3.0 (2.3)	3.6 (3.0)	2.3 (2.0)	1.3 (na) ^b
Cardiovascular comorbidity index ^{W, M}	0.88 (0.8)	1.18 (0.9)	1.38 (1.1)	1.06 (1.0)	1.17 (1.0)	1.70 (1.3)
Antidepressant medication, N (%) ^W	9 (2)	8 (6)	4 (8)	6 (2)	4 (6)	2 (7)
History of clinical depression, N (%) ^{W, M}	28 (7)	17 (13)	11 (21)	17 (7)	6 (9)	6 (22)

Notes. The F-test in univariate analyses of variance was used to test mean differences in continuous variables between depressive symptom groups in women, F(1,570) and men, F(1,343) separately. Chi-square tests were used to test differences in frequencies between depressive symptom groups in women, χ^2 (df=2, N=572) and men, χ^2 (df=2, N=345) separately. Abbreviations: aMCI = amnesic mild cognitive impairment. naMCI = non-amnesic mild cognitive impairment. GDS = Geriatric Depression Scale. APOE4 = apolipoprotein e4 allele.

^a APOE genotype was available for only 347 women and 217 men.

^b No standard deviation is available for mean time to aMCI onset in men reporting moderate/severe depressive symptoms because only one incident aMCI case in this group.

^M Main effect of depressive symptom group is significant in men at p<0.05.

^W Main effect of depressive symptom group is significant in women at p<0.05.

Table 3

Results of Cox proportional hazards models examining the effect of depressive symptoms (trichotomized groups) on risk of incident aMCI.

Parameter	Women			Men		
	Hazard Ratio (95% CI)	Standard Error	p-value	Hazard Ratio (95% CI)	Standard Error	p-value
<i>Model 1 – Unadjusted depressive symptoms</i>						
Overall depressive symptoms	–	–	0.05	–	–	0.04
Mild vs. no/low depressive symptoms	1.38 (0.85–2.25)	0.25	0.19	2.33 (1.33–4.08)	0.29	0.003
Moderate/severe vs. no/low depressive symptoms	2.10 (1.12–3.94)	0.32	0.02	0.27 (0.04–1.96)	1.01	0.20
<i>Model 2 – Adjust for demographics</i>						
Age	1.08 (1.04–1.12)	0.02	<0.001	1.09 (1.04–1.14)	0.02	<0.001
Education (years)	0.90 (0.85–0.96)	0.03	0.002	1.04 (0.97–1.11)	0.04	0.32
Overall depressive symptoms	–	–	0.10	–	–	0.004
Mild vs. no/low depressive symptoms	1.25 (0.77–2.05)	0.25	0.37	2.32 (1.32–4.08)	0.29	0.003
Moderate/severe vs. no/low depressive symptoms	1.97 (1.05–3.70)	0.32	0.03	0.28 (0.04–2.04)	1.01	0.21
<i>Model 3 – Adjust for significant covariates</i>						
Age	1.08 (1.04–1.12)	0.02	<0.001	1.10 (1.05–1.15)	0.02	<0.001
Education (years)	0.90 (0.85–0.96)	0.03	0.002	1.03 (0.96–1.11)	0.04	0.38
Antidepressant medication use	0.89 (0.28–2.87)	0.59	0.84	3.28 (1.27–8.49)	0.48	0.01
Overall depressive symptoms	–	–	0.10	–	–	0.007
Mild vs. no/low depressive symptoms	1.26 (0.77–2.06)	0.25	0.36	2.22 (1.26–3.89)	0.29	0.006
Moderate/severe vs. no/low depressive symptoms	1.99 (1.05–3.77)	0.33	0.03	0.29 (0.04–2.11)	1.01	0.22

Notes. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CIs) with 2 degree of freedom for the main effect of the overall depressive symptom variable and 1 degree of freedom for the individual contrasts of depressive symptom groups and covariates. The Wald Chi-square test was the test statistic used to determine significance level of parameters in the Cox models.

Table 4

Results of Cox proportional hazards models examining the effect of depressive symptoms using a dichotomous GDS-15 categorization (mild to severe symptoms versus no/low symptoms) on risk of incident aMCI.

Parameter	Women			Men		
	Hazard Ratio (95% CI)	Standard Error	p-value	Hazard Ratio (95% CI)	Standard Error	p-value
<i>Model 1 – Unadjusted depressive symptoms</i>						
Mild to severe depressive symptoms vs. no/low symptoms	1.56 (1.02–2.40)	0.22	0.04	1.65 (0.96–2.85)	0.28	0.07
<i>Model 2 – Adjust for demographics</i>						
Age	1.08 (1.0–1.12)	0.02	<0.001	1.09 (1.04–1.15)	0.02	<0.001
Education (years)	0.90 (0.85–0.96)	0.03	0.002	1.03 (0.96–1.11)	0.04	0.39
Mild to severe depressive symptoms vs. no/low symptoms	1.43 (0.93–2.20)	0.22	0.10	1.66 (0.96–2.88)	0.28	0.07
<i>Model 3 – Adjust for significant covariates</i>						
Age	1.08 (1.04–1.12)	0.02	<0.001	1.10 (1.05–1.16)	0.02	<0.001
Education (years)	0.90 (0.85–0.96)	0.03	0.002	1.03 (0.96–1.10)	0.04	0.46
Antidepressant medication	0.94 (0.29–3.02)	0.59	0.92	3.64 (1.42–9.35)	0.48	0.007
Mild to severe depressive symptoms vs. no/low symptoms	1.43 (0.93–2.21)	0.22	0.11	1.63 (0.94–2.82)	0.28	0.08

Notes. Cox proportional hazards models estimated hazard ratios (HR) and 95% confidence intervals (CIs) with 1 degree of freedom. The Wald Chi-square test was the test statistic used to determine significance level of parameters in the Cox models.