

# Anxiety as a risk factor for cognitive decline

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# Anxiety as a Risk Factor for Cognitive Decline: A 12-Year Follow-Up Cohort Study

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**Objective:** *Anxiety might be a risk factor for cognitive decline, but previous studies had short follow-up or small sample sizes or studied general or single cognitive domain functioning. Methods:* Anxiety symptoms were assessed with the Symptom Checklist-90 in 918 participants of the Maastricht Aging Study aged 50 years or older. Anxiety was analyzed both dichotomously (highest versus lower quartiles as a group) and continuously. Neuropsychological tests measured executive function, memory, speed of information processing, and verbal fluency. Linear mixed models were conducted with anxiety symptoms as predictor and change in cognitive scores as outcome. Differences of associations by age and gender were studied with three-way interactions. **Results:** Higher anxiety symptoms were significantly associated with more decline in verbal memory in those aged 65 years and older (delayed recall:  $\chi^2 = 9.30$ ,  $df = 2$ ,  $p = 0.01$ ; immediate recall:  $\chi^2 = 11.81$ ,  $df = 2$ ,  $p = 0.003$ ). There were sex differences in executive function ( $\chi^2 = 6.63$ ,  $df = 2$ ,  $p = 0.036$ ), fluency ( $\chi^2 = 6.89$ ,  $df = 2$ ,  $p = 0.032$ ), and processing speed ( $\chi^2 = 8.83$ ,  $df = 2$ ,  $p = 0.012$ ), with lower performance in women over time. **Conclusion:** In participants without cognitive impairments at baseline, anxiety symptoms were associated with a decline in verbal memory in older adults and with poorer performance in nonamnestic domains in women. Adequate treatment of anxiety symptoms could have a beneficial influence on the risk of developing neurodegenerative diseases. Further research is needed to elucidate whether this association is causal. (Am J Geriatr Psychiatry 2019; 27:42–52)

**Key Words:** Anxiety, cognition, memory, executive function

## HIGHLIGHTS

- We investigated which cognitive domains are affected by anxiety in a twelve year follow-up cohort study.
- Anxiety symptoms were associated with a decline of verbal memory in older adults and with poorer performance in non-amnestic domains in women.
- Adequate treatment of anxiety symptoms could potentially beneficially influence the risk for developing neurodegenerative disease.

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## INTRODUCTION

Anxiety is a risk factor for cognitive impairment, and possibly for dementia,<sup>1</sup> but to date, research about the association between anxiety symptoms and specific cognitive functioning has been equivocal. In cross-sectional studies, larger effect sizes were found in memory problems compared with other cognitive domains.<sup>2</sup> A recent cross-sectional study in a large sample of younger and older adults (N = 82,360) showed a significant association between anxiety disorders and reduced executive function, but the authors did not find an effect of age on the association. A stronger association in the older age group is to be expected when neurodegeneration is assumed to be the underlying mechanism.<sup>3</sup> Indeed, our systematic review showed that anxiety might be associated with decline in executive function.<sup>1</sup> In contrast, the evidence from longitudinal studies for an association between anxiety and memory decline is scarce, with only one out of seven studies showing a significant decline in memory.<sup>1</sup>

Interpretation of previous studies in this field is difficult, as conflicting results are at least partly explained by methodological differences, such as variability in duration of follow-up, residual confounding, and different anxiety measures.<sup>1</sup> In our meta-analysis, we showed that the impact of anxiety on cognitive decline is strongest in the oldest adults (80 years or older), which seems to suggest that anxiety is a prodromal symptom of dementia.<sup>1</sup> As the asymptomatic and prodromal phase of Alzheimer disease may span 2 decades or more,<sup>4</sup> studies with a long follow-up duration are required for more definitive answers. To date, only one longitudinal study on individual cognitive domains had a follow-up of more than 10 years,<sup>5</sup> with the majority of studies having a follow-up of less than 5 years.<sup>1</sup> In addition, adjustment for relevant confounders is important, as different covariates have already been associated with the risk of cognitive decline, e.g., age and education.<sup>6,7</sup> Insufficient adjustment for confounders could lead to an overestimation of the effect of anxiety. Previous studies generally did not analyze potential heterogeneity by age or sex. Older adults have less cognitive reserve, which is associated with a higher risk of cognitive decline.<sup>8</sup> In women, the prevalence of Alzheimer disease is higher than in men, which

can be attributed to women living longer but also suggests that female gender may be another risk factor.<sup>9</sup> Finally, depression is often comorbid with anxiety and is also associated with a higher risk of cognitive decline;<sup>10</sup> however, few studies have accounted for this correlation. Anxiety disorders comorbid with major depression may further accelerate cognitive decline in older adults compared with those with major depression only.<sup>11</sup>

Prospective studies that assess multiple cognitive domains and include a longer follow-up duration and adequate control for confounding and comorbid depression are needed. Therefore, in this population study, we investigated the crude and adjusted associations—with 12 years of follow-up between anxiety and cognitive decline—with executive function (as the current literature suggests an association with anxiety) and, more exploratively, memory, speed of information processing, and fluency. Interactions of anxiety with age and gender were also investigated.

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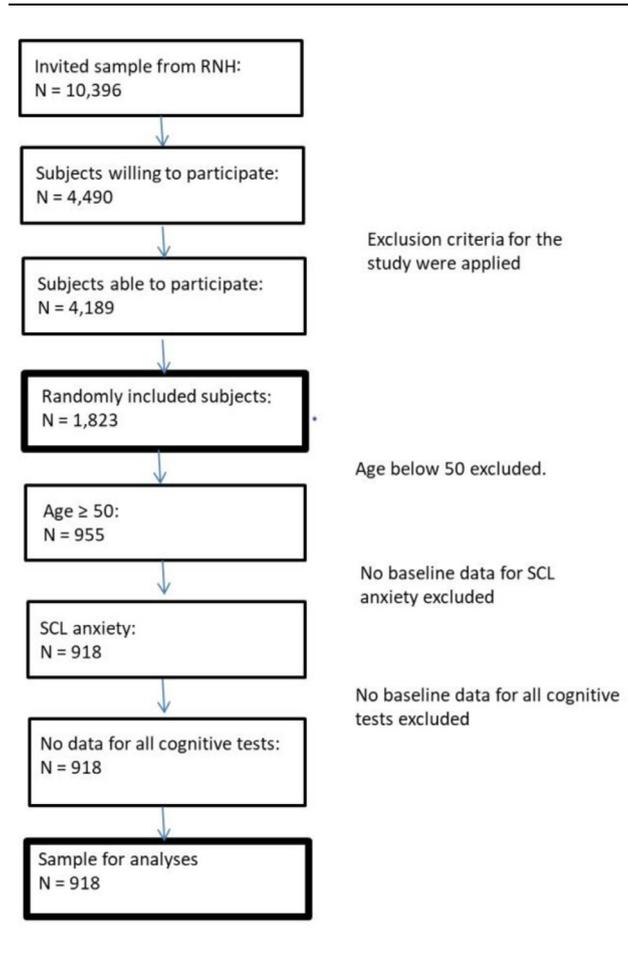
## METHODS

### Study Sample

The Maastricht Aging Study (MAAS), comprising 1,823 participants, investigated the determinants of cognitive aging.<sup>12</sup> Participants were recruited from the Registratienet Huisartspraktijken (RNH) (Registration Network Family Practices), a database managed by the Department of General Practice of Maastricht University.<sup>13</sup> A total of 10,396 participants were sampled from the RNH database. There were 4,490 participants willing to participate; others did not want to participate or did not respond to the invitation. After checking the exclusion criteria (see next paragraph), 4,189 participants were deemed suitable for participation. Of this group, 1,823 (43.5%) were randomly selected and stratified by age (12 age groups between 24 and 81 years), gender, and level of occupational activity (high/low) (Fig. 1). During a 12-year follow-up, adults aged 50 years and older were tested every 3 years.

Exclusion criteria defined in the RNH database were coma (active only), cerebrovascular pathology, any tumor of the nervous system, congenital

FIGURE 1. Flow diagram of selected participants.



malformations of the nervous system, multiple sclerosis, parkinsonism, epilepsy (all types), dementia, organic psychosis (other than dementia), schizophrenia, affective psychosis, and mental retardation. In addition, before participation in the test program, all participants were screened in a semistructured interview to update RNH exclusion criteria and to check for the following exclusion criteria not coded in the RNH database: history of transient ischemic attacks, brain surgery, hemodialysis for renal failure, electroconvulsive therapy, and regular use of psychotropic drugs. Finally, a score below 24 on the Mini-Mental State Exam led to exclusion from the study at baseline. Additional exclusion criteria for the current study were age below 50 years and no baseline data for the Symptom Checklist-90 (SCL-90). We included 918 participants in the present analysis.

## Baseline Measurements

### Anxiety

Anxiety was measured with the anxiety subscale of the SCL-90<sup>14</sup> and comprised 10 questions, with a 5-point Likert scale rating the degree of a specific anxiety symptom. The total score was calculated by adding up the individual scores per question (range: 10–50). Anxiety was used both dichotomously (high anxiety, yes/no, defined as being in the highest quartile) and continuously (anxiety symptom score).

### Depression

Depression was measured with the depression subscale of the SCL-90 and comprised 16 questions, using the same 5-point severity scale as that used for anxiety. The individual scores were added up to calculate the total score in a process that corresponded to the scoring of the anxiety subscale (range: 16–80). Depressive symptoms were used dichotomously (high depressive symptoms, yes/no, defined as being in the highest quartile) and continuously (depressive symptom score) as a covariate in the analysis of anxiety as primary predictor.

### Covariates

Age, sex, education level, and alcohol use were considered covariates based on their associations with both anxiety and cognitive decline. Education level was based on self-report data and defined in eight categories, ranging from primary education (one) to university degree (eight). For analysis, education level was recorded at three levels: low (levels 1–2), medium (levels 3–5), and high (levels 6–8) (included as dummy variables, with low education as reference). Alcohol use was measured by asking about both the amount of drinking days in a week and the number of drinks. Alcohol use was categorized as no use, social use, or excessive use. Excessive use was defined as 5 units or more per day or 4 days or more with 3 or more units of alcohol. Social use was defined as less than 5 units per day or less than 4 days with 3 or more units of alcohol. Social use was the dummy reference owing to the U-shaped relationship of alcohol and cognition. The use of psychotropic

medication was also self-reported by naming all used medication at baseline and every follow-up.

## Outcome

### *Primary outcome*

Executive function was the primary outcome variable using the Concept Shifting Test (CST) and the Stroop Color and Word Test (SCWT). The CST<sup>15</sup> measures cognitive flexibility and is a modification of the Trail Making Test.<sup>16</sup> It consists of three sheets (A, B, and C), each with 16 small circles. In these circles, the test items (numbers [A], letters [B], or both [C]) appear in a fixed random order. Participants are asked to cross out the items in the right order (alternating digits and numbers in the CST-C condition), the time to complete the tasks is recorded, and the shifting score is calculated by subtracting the average time needed to complete CST-A and CST-B from the time needed to complete CST-C.

The SCWT measures response inhibition. It involves three cards, each displaying multiple of stimuli: color names (card one), colored patches (card two), and color names printed using incongruously colored ink (card three).<sup>17,18</sup> Participants need to read the color names (card one), name the colored patches (card two), and name the incongruous color of the color names (card three). The SCWT score is calculated by subtracting the average time needed to complete cards one and two from the time needed to complete card three.

### *Secondary outcome*

Memory, speed of information processing, and fluency were considered secondary outcome measures. Memory was measured using the immediate and delayed recall subtests of the Verbal Learning Test (VLT), in which 15 nonrelated, monosyllabic words are successively presented.<sup>19,20</sup> For immediate recall, participants were asked to recall as many words as possible, and this procedure was subsequently repeated five times. The immediate recall score was calculated by summing the correctly named words over five trials. After 20 minutes, delayed recall was tested (one trial) and the amount of correctly named words scored.

Speed of information processing was tested with the Letter Digit Substitution Test (LDST).<sup>21</sup>

Participants were instructed to match—according to a key of letter/digit combinations included at the top of the sheet—as many digits to letters as possible within 90 seconds. Fluency was measured using a subtest of the Groningen Intelligence Test, asking the respondent to name as many animals as possible within 1 minute.<sup>22</sup>

## Statistical Analysis

Group differences between the two subgroups (high anxiety and low anxiety) were tested using independent *t*-tests (dimensional variables) and  $\chi^2$  tests (categorical variables). Linear mixed models were conducted for the longitudinal data, with the dichotomous variable of the high anxiety group and the dimensional score of anxiety symptoms at baseline and time as the independent variables and the outcome on the specific neuropsychological tests as the dependent variable. The analyses for high anxiety were adjusted for age, sex, education level, alcohol, and highest quartile on the depression subscale of the SCL-90 (yes/no). The same adjustments were made for the analysis of continuous anxiety symptoms as main predictor, except that the continuous depressive symptom scores was used instead of the binary depression variable (highest quartile yes/no). No adjustment for psychotropic drug use took place in the primary analysis since regular psychotropic drug use was already an exclusion criterion at baseline. The model included random effects for intercept and slope and an unstructured covariance structure, as this gave the best model fit, according to likelihood ratio testing. Differences in rate of change in cognition over time—as a function of baseline anxiety (dichotomous and continuous)—were tested by including the anxiety  $\times$  time (three levels: baseline and 6 and 12 years) interaction term in the model, using the Wald  $\chi^2$  test as a test of homogeneity of effects. In addition, three-way interaction terms tested the moderation effect of age and gender on the outcome of cognitive changes over time. If significant, stratified analyses were run for different age groups (<65 years and  $\geq$ 65 years) and for men and women separately. The same approach was used for the dichotomous depression variable as predictor. Analyses were conducted using SPSS Statistics 22.0 (International Business Machines Corporation, Armonk, NY) and Stata 15 (StataCorp, College Station, TX), with an alpha level of 0.05 in

**TABLE 1. Baseline Characteristics and Difference Between Participants With High and Low Anxiety Symptoms**

Characteristics <sup>a</sup>	High anxiety symptoms (N = 233)	Low anxiety symptoms (N = 685)	Statistics
<i>Sociodemographics/ confounders:</i>			
Age in years, mean (SD) range	65.0 (8.6) 50–82	64.2 (8.9) 50–82	$t = 1.28, df = 916, p = 0.202$
Female gender, n (%)	139 (59.7)	307 (44.8)	$\chi^2 = 14.7, df = 1, p < 0.01$
<i>Level of education, n (%)</i>			
Low	135 (57.9)	313 (45.7)	$\chi^2 = 10.4, df = 2, p = 0.005$
Medium	68 (29.2)	258 (37.7)	
High	30 (25.4)	114 (16.6)	
<i>Alcohol use, n (%)<sup>b</sup></i>			
• No use	69 (30.9)	116 (17.6)	$\chi^2 = 18.1, df = 2, p < 0.01$
• Social use	101 (45.3)	347 (52.6)	
• Excessive use	53 (23.8)	197 (29.8)	
<i>Psychopathology, mean (SD) range</i>			
SCL-90 anxiety	18 (5) 14–42	11 (1) 10–13	$t = -20.6, df = 238, p < 0.01$
SCL-90 depression	27 (9) 16–62	19 (3) 16–36	$t = -13.6, df = 250, p < 0.01$

Notes: SD: standard deviation.

<sup>a</sup>Missing data varied between variables: 35 missing for alcohol use, 8 missing for SCL-90 depression, and 0 missing for the other variables.

<sup>b</sup>Alcohol use: no use, 0 units per day; social use, less than 5 units per day or less than 4 days with 3 or more units; excessive use, 5 units or more per day or 4 days or more with 3 or more units.

two-tailed tests. For three-level interactions, stratified analyses were also done for  $p < 0.10$  given the low power of such tests.

To explore clinical significance by calculating a standardized effect size (Cohen's  $d$ ), we followed the recommendation by Feingold<sup>23,24</sup> and used the fixed effect of the group  $\times$  time interaction in the nominator and the standard deviation of the cognition score at baseline so that  $d = b_{\text{interaction}} / \text{standard deviation}_{\text{baseline\_raw}}$ . For anxiety symptoms, this was done for a 10-point change to get clinically meaningful results. An effect of 0.2 reflected a small effect, 0.5 a medium effect, and 0.8 a large effect.

## RESULTS

### Baseline Comparisons

At baseline, there were significant differences between participants with high anxiety symptoms and those with low anxiety symptoms, with the former being more often female and less educated. They also used less alcohol and had higher mean scores for depression (Table 1).

### High Versus Low Anxiety Symptoms

In the analyses testing the difference in rate of change among those with high versus low anxiety

symptoms (adjusted for age, gender, education, and alcohol), none of the primary or secondary cognitive outcomes revealed significant main effects. Analyses with adjustment for comorbid high depressive symptoms yielded similar results. Effect moderation by age group (<65 years versus  $\geq 65$  years) was not significant. There was, however, a significant difference between men and women regarding change in verbal fluency (overall  $\chi^2 = 8.10, df = 2, p = 0.017$ ). In analyses stratified by gender, men with high anxiety experienced a nonsignificant improvement over time ( $\chi^2 = 4.62, df = 2, p = 0.099$ ), whereas women with high anxiety experienced a nonsignificant decline ( $\chi^2 = 5.90, df = 2, p = 0.052$ ). This remained virtually unchanged after adjusting for comorbid high depressive symptoms.

### Severity of Anxiety Symptoms

Using continuous anxiety symptoms as predictor (adjusted for age, gender, education, and alcohol use) showed that rate of decline in VLT delayed recall was faster with increasing anxiety symptom levels in the total sample (Cohen's  $d$  after 6 years and 12 years: -0.19 and 0.02, respectively) (Table 2). The three-way interaction with age for VLT delayed recall warranted further inspection ( $\chi^2 = 5.17, df = 2, p = 0.076$ ). Age-stratified analyses showed that higher anxiety levels were associated with faster decline in the older age group only ( $\chi^2 = 9.30, df = 2, p = 0.010$ ; Cohen's  $d$  after

TABLE 2. Anxiety Symptoms at Baseline Related to Cognitive Decline Over 12 Years, Without Adjustment of Depressive Symptoms

Parameter	Time						Anxiety symptoms × time <sup>a</sup>
	Baseline		Change from baseline to 6-year FU		Change from baseline to 12-year FU		
	Difference	95% CI	Difference	95% CI	Difference	95% CI	
CST interference score	0.002	-0.003 to 0.006	0.003	-0.004 to 0.010	-0.001	-0.010 to 0.009	1.06
Stroop interference score	0.004	-0.002 to 0.011	-0.001	-0.008 to 0.006	0.000	-0.009 to 0.010	0.18
VLT immediate recall	-0.083	-0.220 to 0.055	-0.147	-0.299 to 0.004	-0.003	-0.180 to 0.173	4.41
VLT delayed recall	-0.021	-0.065 to 0.023	-0.056	-0.106 to -0.006	0.005	-0.055 to 0.065	6.60
LDST	-0.072	-0.203 to 0.059	-0.093	-0.211 to 0.025	-0.004	-0.158 to 0.150	3.19
Fluency	-0.046	-0.135 to 0.042	0.018	-0.073 to 0.110	0.114	0.005 to 0.223	4.56

Notes: All analyses adjusted for age, gender, education, and alcohol use. Scores for CST interference score and Stroop interference score were log-transformed. CI: confidence interval; FU: follow-up.

<sup>a</sup> Test of interaction between high anxiety (yes/no) and time (baseline, 6-year and 12-year follow-up) with 2 df.

6 and 12 years: -0.48 and -0.18, respectively) (Table 3). For VLT immediate recall, no overall effect was found, but the three-way interaction of anxiety symptoms × time × age group was significant ( $\chi^2 = 9.15$ ,  $df = 2$ ,  $p = 0.010$ ). Age-stratified analyses showed that increasing anxiety symptoms were associated with faster decline in the older age group only ( $\chi^2 = 11.81$ ,  $df = 2$ ,  $p = 0.003$ ; Cohen's  $d$  after 6 and 12 years: -0.53 and -0.28, respectively) (Table 3). Some notable gender differences were observed as well, with worse cognitive trajectories in women compared with men. For CST interference (interaction with gender:  $\chi^2 = 6.63$ ,  $df = 2$ ,  $p = 0.036$ ), stratified analyses suggested a nonsignificant improvement in men ( $\chi^2 = 3.08$ ,  $df = 2$ ,  $p = 0.215$ ) and a nonsignificant decline in women ( $\chi^2 = 5.93$ ,  $df = 2$ ,  $p = 0.052$ ) (Table 4). For LDST (interaction with gender:  $\chi^2 = 6.54$ ,  $df = 2$ ,  $p = 0.038$ ) and fluency interaction with gender ( $\chi^2 = 6.89$ ,  $df = 2$ ,  $p = 0.032$ ), stratified analyses showed that anxiety symptoms predicted faster decline on the LDST in women only ( $\chi^2 = 8.83$ ,  $df = 2$ ,  $p = 0.012$ ; Cohen's  $d$  after 6 and 12 years: -0.20 and -0.05, respectively), whereas fluency scores improved significantly in men with more severe baseline anxiety symptoms ( $\chi^2 = 8.75$ ,  $df = 2$ ,  $p = 0.013$ ; Cohen's  $d$  after 6 and 12 years: 0.28 and 0.49, respectively) but not in women ( $\chi^2 = 2.80$ ,  $df = 2$ ,  $p = 0.246$ ) (Table 4). All associations persisted after additional adjustment for depressive symptoms.

### High Versus Low Depressive Symptoms

In the total sample, high depressive symptoms were not significantly associated with rate of change in primary or secondary cognitive outcomes before or after adjustment for comorbid high anxiety symptoms. Significant effect moderation by age on CST interference ( $\chi^2 = 6.87$ ,  $df = 2$ ,  $p = 0.032$ ) and VLT delayed recall ( $\chi^2 = 7.78$ ,  $df = 2$ ,  $p = 0.020$ ) was observed. A faster decline in those with high versus low depressive symptoms was observed in older participants on both the CST ( $\chi^2 = 6.23$ ,  $df = 2$ ,  $p = 0.044$ ; Cohen's  $d$  after 6 and 12 years: 0.100 and -0.813, respectively) and VLT delayed recall ( $\chi^2 = 9.40$ ,  $df = 2$ ,  $p = 0.009$ ; Cohen's  $d$  after 6 and 12 years: -0.398 and -0.206, respectively). No interactions with gender were observed. All associations persisted after additional adjustment for high anxiety symptoms.

**TABLE 3. Anxiety Symptoms in Younger and Older Adults Related to Verbal Memory Over 12 Years, Without Adjustment for High Depressive Symptoms**

Parameter	Time								
	Baseline		Change from baseline to 6-year FU		Change from baseline to 12-year FU		Anxiety symptoms × time <sup>a</sup>		
	Difference	95% CI	Difference	95% CI	Difference	95% CI	$\chi^2$	p	
Younger adults	VLT immediate recall	-0.097	-0.263 to 0.068	-0.009	-0.182 to 0.165	0.053	-0.136 to 0.243	0.46	0.794
	VLT delayed recall	-0.041	-0.094 to 0.012	-0.020	-0.078 to 0.038	0.013	-0.051 to 0.077	1.14	0.566
Older adults	VLT immediate recall	0.092	-0.145 to 0.330	-0.503	-0.790 to -0.216	-0.269	-0.656 to 0.118	11.81	0.003
	VLT delayed recall	0.014	-0.060 to 0.088	-0.143	-0.235 to -0.051	-0.055	-0.235 to 0.075	9.30	0.010

*Notes:* All analyses adjusted for age, gender, education, and alcohol use. CI: confidence interval; FU: follow-up.  
<sup>a</sup>Test of interaction between anxiety symptoms and time (baseline, 6-year and 12-year follow-up) with 2 df.

**TABLE 4. Anxiety Symptoms in Men and Women Related to CST, Fluency, and LDST Over 12 Years, Without Adjustment for High Depressive Symptoms**

Parameter	Time								
	Baseline		Change from baseline to 6-year FU		Change from baseline to 12-year FU		Anxiety symptoms × time <sup>a</sup>		
	Difference	95% CI	Difference	95% CI	Difference	95% CI	$\chi^2$	p	
Males	CST	0.003	-0.005 to 0.011	-0.013	-0.027 to 0.002	-0.013	-0.033 to 0.008	3.08	0.215
	Fluency	-0.077	-0.237 to 0.084	0.164	-0.002 to 0.331	0.290	0.093 to 0.488	8.75	0.013
	LDST	-0.095	-0.330 to 0.140	0.123	-0.091 to 0.336	0.078	-0.185 to 0.341	1.26	0.531
Females	CST	0.001	-0.004 to 0.007	0.009	0.002 to 0.017	0.003	-0.005 to 0.012	5.93	0.052
	Fluency	-0.033	-0.138 to 0.072	-0.068	-0.178 to 0.041	0.033	-0.097 to 0.163	2.80	0.246
	LDST	-0.074	-0.232 to 0.083	-0.196	-0.336 to -0.055	-0.048	-0.240 to 0.145	8.83	0.012

*Notes:* All analyses adjusted for age, gender, education, and alcohol use. CI: confidence interval; FU: follow-up.  
<sup>a</sup>Test of interaction between anxiety symptoms and time (baseline, 6-year and 12-year follow-up) with 2 df.

## DISCUSSION

### Main Findings

In contrast to our hypothesis, higher anxiety symptoms did not predict a faster decline in executive function over time. Nonetheless, the impact of anxiety on the course of executive function over time differed significantly between both sexes, with increasing anxiety symptoms predicting a worse cognitive trajectory in women compared with men. A similar sex-specific effect was found for processing speed and verbal fluency. In contrast, faster decline in verbal memory (immediate and delayed recall) was associated with higher anxiety symptoms irrespective of sex but was more pronounced in the older age group. A faster decline in executive function and verbal memory (delayed recall) was also found in older adults with high depressive symptoms compared with older adults with low depressive symptoms.

### Anxiety and Cognition

We found no significant association between anxiety and executive function in the total population. There was, however, a significant difference between sexes, with women with increasing levels of anxiety showing a faster deterioration in executive function over time. Previous research showed conflicting results, with some studies reporting a significant deterioration in executive function over time<sup>25–29</sup> and others not.<sup>30,31</sup> Inconsistent findings in the literature may be explained by researchers' use of different components of executive function. In MAAS, we tested response inhibition and cognitive flexibility. However, a previous study that used a sample restricted to women with phobic anxiety tested only verbal fluency and working memory as measures of executive function and did not find any decline over time.<sup>31</sup> Furthermore, previous studies did not study potential sex differences in executive function.<sup>25–30</sup> However, our results suggest a specific effect on cognitive flexibility in women only. The stronger association in women might be because of a more severe<sup>32,33</sup> or more chronic anxiety phenotype.<sup>34</sup> Indeed, women in MAAS have a higher prevalence of anxiety symptoms ( $\chi^2 = 14.7$ ,  $df = 1$ ,  $p < 0.01$ ) and a higher severity of anxiety symptoms ( $t = -4.73$ ,  $df = 772$ ,  $p < 0.01$ ), though they do not differ significantly in chronicity of

anxiety symptoms compared with men ( $\chi^2 = 3.39$ ,  $df = 1$ ,  $p = 0.07$ ). Previous research has also shown an increased risk of coronary heart disease in women with anxiety symptoms.<sup>35</sup> Since the vascular disease burden could potentially mediate the association between anxiety and deterioration of executive function, this may explain these sex-specific findings as well. The higher prevalence and higher severity of anxiety symptoms in women in our sample might also explain the differences between the sexes in processing speed and fluency over time.<sup>32–34</sup> Processing speed and executive function are also often affected by cerebrovascular damage.<sup>36</sup> Further research on these sex differences, including the role of differences in vascular burden, is needed.

Older participants (>65 years) with increasing levels of anxiety symptoms had a significantly greater decline in immediate and delayed recall of verbal memory than older participants with less anxiety symptoms. This association was not found in the younger adults (50–65 years), suggesting that anxiety symptoms in late life can be a prodromal symptom of dementia. Deficits in verbal memory are considered a marker of Alzheimer disease, as memory deficits (especially involving delayed recall) are almost always present in the early phase.<sup>37</sup> Previous longitudinal studies on the impact of anxiety on memory decline were largely negative,<sup>25–27,30,31,38</sup> with only 1 study finding a significant association.<sup>39</sup> Whether late-life anxiety could be prodromal or causally related to neurodegeneration remains unclear. Anxiety and cognitive dysfunction could also be caused by an unknown third factor. A recent meta-analysis found suggestions for anxiety as a prodromal symptom of neurodegenerative diseases, as the associations were strongest in those 80 years and older. Anxiety could then be a consequence of diminished cognitive capacities that are only experienced on a subjective level. These people may benefit from a structuring of daily life. In our study, the older participants (65+ years) had a mean age of 72 years and therefore had a lower a priori chance of underlying neuropathology compared with the group (80 years and older) in the meta-analysis.<sup>1</sup> There are also different pathways that could explain the role of anxiety as a causal factor in the development of neurodegeneration.

According to the hypercortisolemia hypothesis,<sup>40</sup> prolonged exposure to anxiety-related stress will lead to chronic hypothalamic-pituitary-adrenal

dysregulation and therefore to higher levels of cortisol.<sup>1</sup> It has been suggested that cortisol-induced overstimulation of glucocorticoid receptors of glutamatergic neurons in the medial temporal lobe leads to hippocampal atrophy and cognitive dysfunction.<sup>1,41–43</sup> Other possible mechanisms are cardiovascular disease (as stated above),<sup>44</sup> low-grade inflammation,<sup>45,46</sup> brain-derived neurotrophic factor suppression,<sup>47</sup> and diminished cognitive reserves.<sup>8</sup>

In line with previous studies, high depressive symptoms were also associated with a decline in delayed recall of verbal memory, as well as executive function, in the older age group.<sup>48</sup> In our study, the impact of high depressive symptoms on verbal memory and executive function was higher than the impact of high anxiety levels. Results of research comparing the effect of anxiety and depression on cognitive decline in the same study sample are contradictory. Some previous studies also found smaller effect sizes (albeit nonsignificant) for anxiety—compared with depression—on cognitive decline,<sup>5,49</sup> whereas others found larger effect sizes.<sup>50,51</sup> To establish the clinical significance of our results, Cohen's *d* effect sizes were calculated. For anxiety symptoms, these effect sizes ranged from small to medium; for high depressive symptoms, they ranged from small to large.

### Strengths and Limitations

A particular strength of this study is the longitudinal design that used one of the longest follow-up periods compared to previous studies. A limitation of the study is that we included a healthy population from the community with low scores on the symptom dimensions of the SCL-90. Therefore, participants with more severe levels of anxiety were more likely to be excluded, limiting the generalizability of our findings to this group. The average score of 18 in the anxious group is relatively low for a psychiatric population and could have led to an underestimation of the association between anxiety and cognition. Another

limitation is the use of self-report measures for anxiety and depression, which may have led to exposure misclassification. Importantly, such misclassification is probably nondifferential, i.e., unlikely to be affected by someone's subsequent course of cognition. Further, no information was available in our data regarding age of onset of anxiety symptoms or history of anxiety disorder, which could have been relevant for differentiating between a prodromal symptom and a causal factor of neurodegenerative disease. Next, factor analysis showed a high correlation between anxiety and depression,<sup>52</sup> which makes it difficult to exclusively evaluate either anxiety symptoms or depressive symptoms. Correcting for the other affective domain as a confounder is conservative but can lead to overcorrection. As there is also overlap in the clinical presentation of depression and anxiety, this problem will likely persist with other measurements. A final limitation is the possibility that changes over time in the severity of anxiety symptoms have influenced our outcome.

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### CONCLUSION

In our study, anxiety symptoms predicted decline in executive function over time in women and decline in verbal memory in an older age group (65+ years). Further longitudinal research is needed to fully understand the heterogeneous relationship between anxiety and cognition, including potentially mediating mechanisms. Adequate treatment of anxiety symptoms could potentially have a beneficial influence on the risk of developing neurodegenerative disease.

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### References

1. Gulpers B, Ramakers I, Hamel R, et al: Anxiety as a predictor for cognitive decline and dementia: a review and meta-analysis. *Am J Geriatr Psychiatry* 2016;24(10):823–842
2. Beaudreau SA, O'Hara R: Late-life anxiety and cognitive impairment: a review. *Am J Geriatr Psychiatry* 2008;16(10):790–803
3. Gulpers B, Lugtenburg A, Zuidersma M, Verhey FRJ, Voshaar RCO. Anxiety disorders and figural fluency: a measure of executive function. *J Affect Disord* 2018;234:38–44.
4. Villemagne VL, Burnham S, Bourgeat P, et al: Amyloid  $\beta$  deposition, neurodegeneration, and cognitive decline in sporadic

- Alzheimer's disease: a prospective cohort study. *Lancet Neurol* 2013;12(4):357-367
5. Bunce D, Batterham PJ, Mackinnon AJ, et al: Depression, anxiety and cognition in community-dwelling adults aged 70 years and over. *J Psychiatr Res* 2012;46(12):1662-1666
  6. Anstey K, Christensen H: Education, activity, health, blood pressure and apolipoprotein E as predictors of cognitive change in old age: a review. *Gerontology* 2000;46(3):163-177
  7. Larson EB, Kukull WA, Katzman RL: Cognitive impairment: dementia and Alzheimer's disease. *Annu Rev Public Health* 1992; 13:431-449
  8. Stern Y: Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurol* 2012;11(11):1006-1012
  9. Mielke MM, Vemuri P, Rocca WA: Clinical epidemiology of Alzheimer's disease: assessing sex and gender differences. *Clin Epidemiol* 2014; 6:37-48
  10. Cooper C, Sommerlad A, Lyketsos CG, et al: Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. *Am J Psychiatry* 2015;172(4):323-334
  11. DeLuca AK, Lenze EJ, Mulsant BH, et al: Comorbid anxiety disorder in late life depression: association with memory decline over four years. *Int J Geriatr Psychiatry* 2005; 20:848-854
  12. Jolles J, Houx PJ, van Boxtel MPJ, et al: The Maastricht Aging Study: determinants of cognitive aging. (online). Available at: [breinweb.nl/maas/assets/maas\\_pb\\_intro.pdf](http://breinweb.nl/maas/assets/maas_pb_intro.pdf). Accessed October 22, 2018
  13. Metsemakers JF, Höppener P, Knottnerus JA, et al: Computerized health information in the Netherlands: a registration network of family practices. *Br J Gen Pract* 1992; 42:102-106
  14. Arrindell WA, Ettema JHM: SCL-90. Een Multidimensionale Psychopathologie Indicator (SCL-90. A Multidimensional Psychopathology Indicator). Lisse, Netherlands: Swets Test Publishers, 1986
  15. van der Elst W, van Boxtel MP, van Breukelen GJ, et al: The Concept Shifting Test: adult normative data. *Psychol Assess* 2006;18(4):424-432
  16. Vink M, Jolles J: A new version of the Trail-Making Test as an information processing task. *J Clin Neuropsychol* 1985; 7:162
  17. Houx PJ, Jolles J: Age-related decline of psychomotor speed: effects of age, brain health, sex, and education. *Percept Mot Skills* 1993; 76:195-211
  18. van der Elst W, van Boxtel MP, van Breukelen GJ, et al: The Stroop color-word test: influence of age, sex, and education; and normative data for a large sample across the adult age range. *Assessment* 2006;13(1):62-79
  19. Brand N, Jolles J: Learning and retrieval rate of words presented auditory and visually. *J Gen Psychol* 1985;112(2):201-210
  20. van der Elst W, van Boxtel MP, van Breukelen GJ, et al: Rey's verbal learning test: normative data for 1855 healthy participants aged 24-81 years and the influence of age, sex, education, and mode of presentation. *J Int Neuropsychol Soc* 2005;11(3):290-302
  21. van der Elst W, van Boxtel MP, van Breukelen GJ, et al: The Letter Digit Substitution Test: normative data for 1,858 healthy participants aged 24-81 from the Maastricht Aging Study (MAAS): influence of age, education, and sex. *J Clin Exp Neuropsychol* 2006;28(6):998-1009
  22. Luteijn F, van der Ploeg FAE: Handleiding Groninger Intelligentietest (GIT) (Manual Groningen Intelligence Test [GIT]). Lisse, Netherlands: Swets & Zeitlinger Publishers, 1983
  23. Feingold A: Effect sizes for growth-modeling analysis for controlled clinical trials in the same metric as for classical analysis. *Psychol Methods* 2009;14(1):43-53
  24. Feingold A: A regression framework for effect size assessments in longitudinal modeling of group differences. *Rev Gen Psychol* 2013;17(1):111-121
  25. de Bruijn RF, Direk N, Mirza SS, et al: Anxiety is not associated with the risk of dementia or cognitive decline: the Rotterdam Study. *Am J Geriatr Psychiatry* 2014;22(12):1382-1390
  26. Pietrzak RH, Scott JC, Neumeister A, et al: Anxiety symptoms, cerebral amyloid burden and memory decline in healthy older adults without dementia: 3-year prospective cohort study. *Br J Psychiatry* 2014; 204:400-401
  27. Brodaty H, Heffernan M, Draper B, et al: Neuropsychiatric symptoms in older people with and without cognitive impairment. *J Alzheimers Dis* 2012;31(2):411-420
  28. Kassem AM, Ganguli M, Yaffe K, et al: Anxiety symptoms and risk of cognitive decline in older community-dwelling men. *Int Psychogeriatr* 2017;29(7):1137-1145
  29. Pietrzak RH, Lim YY, Neumeister A, et al: Amyloid- $\beta$ , anxiety, and cognitive decline in preclinical Alzheimer disease: a multicenter, prospective cohort study. *JAMA Psychiatry* 2015;72(3):284-291
  30. Pietrzak RH, Maruff P, Woodward M, et al: Mild worry symptoms predict decline in learning and memory in healthy older adults: a 2-year prospective cohort study. *Am J Geriatr Psychiatry* 2012;20(3):266-275
  31. Okereke OI, Grodstein F: Phobic anxiety and cognitive performance over 4 years among community-dwelling older women in the Nurses' Health Study. *Am J Geriatr Psychiatry* 2013;21(11):1125-1134
  32. Kessler RC, Berglund P, Demler O, et al: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005;62(6):593-602
  33. Yonkers KA, Bruce SE, Dyck IR, et al: Chronicity, relapse, and illness—course of panic disorder, social phobia, and generalized anxiety disorder: findings in men and women from 8 years of follow-up. *Depress Anxiety* 2003;17(3):173-179
  34. de Beurs E, Beekman AT, Deeg DJ, et al: Predictors of change in anxiety symptoms of older persons: results from the Longitudinal Aging Study Amsterdam. *Psychol Med* 2000;30(3):515-527
  35. Nabi H, Hall M, Koskenvuo M, et al: Psychological and somatic symptoms of anxiety and risk of coronary heart disease: the health and social support prospective cohort study. *Biol Psychiatry* 2010;67(4):378-385
  36. Vasquez BP, Zakzanis KK: The neuropsychological profile of vascular cognitive impairment not demented: a meta-analysis. *J Neuropsychol* 2015;9(1):109-136
  37. Cummings JL: Alzheimer's disease. *N Engl J Med* 2004;351(1):56-67
  38. Bunce D, Batterham PJ, Mackinnon AJ, et al: Depression, anxiety and cognition in community-dwelling adults aged 70 years and over. *J Psychiatr Res* 2012;46(12):1662-1666
  39. Palmer K, Berger AK, Monastero R, et al: Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology* 2007;68(19):1596-1602
  40. Mantella RC, Butters MA, Amico JA, et al: Salivary cortisol is associated with diagnosis and severity of late-life generalized anxiety disorder. *Psychoneuroendocrinology* 2008;33(6):773-781
  41. Sapolsky RM: Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 2000;57(10):925-935
  42. Erickson K, Drevets W, Schulkin J: Glucocorticoid regulation of diverse cognitive functions in normal and pathological emotional states. *Neurosci Biobehav Rev* 2003;27(3):233-246

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43. Lupien SJ, Fiocco A, Wan N, et al: Stress hormones and human memory function across the lifespan. *Psychoneuroendocrinology* 2005;30(3):225-242
44. Lambiase MJ, Kubzansky LD, Thurston RC: Prospective study of anxiety and incident stroke. *Stroke* 2014;45(2):438-443
45. Furtado M, Katzman MA: Neuroinflammatory pathways in anxiety, posttraumatic stress, and obsessive compulsive disorders. *Psychiatry Res* 2015;229(1-2):37-48
46. Reichenberg A, Yirmiya R, Schulz A, et al: Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry* 2001;58(5):445-452
47. Teixeira AL, Barbosa IG, Diniz BS, et al: Circulating levels of brain-derived neurotrophic factor: correlation with mood, cognition and motor function. *Biomark Med* 2010;4(6):871-887
48. Riddle M, Potter GG, McQuoid DR, et al: Longitudinal cognitive outcomes of clinical phenotypes of late-life depression. *Am J Geriatr Psychiatry* 2017;25(10):1123-1134
49. Biringer E, Mykletun A, Dahl AA, et al: The association between depression, anxiety, and cognitive function in the elderly general population—the Hordaland Health Study. *Int J Geriatr Psychiatry* 2005;20(10):989-997
50. Burtona C, Campbell P, Jordan K, et al: The association of anxiety and depression with future dementia diagnosis: a case-control study in primary care. *Fam Pract* 2013;30(1):25-30
51. Potvin O, Forget H, Grenier S, et al: Anxiety, depression, and 1-year incident cognitive impairment in community-dwelling older adults. *J Am Geriatr Soc* 2011;59(8):1421-1428
52. Strauman TJ, Wetzler S: The factor structure of SCL-90 and MCMI scale scores: within-measure and interbattery analyses. *Multivariate Behav Res* 1992;27(1):1-20