Chapter 3

Anxiety symptoms and cognitive performance in later life: results from the Longitudinal Aging Study Amsterdam

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Abstract

Objectives: *This study investigates whether and, if so, how anxiety symptoms are related to cognitive decline in elderly persons and whether anxiety symptoms precede cognitive decline.* ***Method:*** *Data were obtained from the Longitudinal Aging Study Amsterdam. Anxiety symptoms were measured with the Hospital Anxiety and Depression Scale. General cognitive functioning was measured with the Mini-Mental State Examination, episodic memory with the Auditory Verbal Learning Test, fluid intelligence with the Raven's Coloured Progressive Matrices and information processing speed with the coding task. Multilevel analyses were performed to investigate the relationship between anxiety symptoms and cognitive decline over nine years, taking into account confounding variables.* ***Results****: Although not consistent across all dimensions of cognitive functioning, a curvilinear effect of anxiety on cognitive performance was found. Furthermore, we found that previous measurement of anxiety symptoms were not predictive of cognitive decline at a later time-point.* ***Conclusion:*** *This study suggests that the effect of anxiety on cognition depends on the severity of the present anxiety symptoms with mild anxiety associated with better cognition, whereas more severe anxiety is associated with worse cognition. The effect of anxiety symptoms on cognitive functioning seems to be a temporary effect, anxiety is not predictive of cognitive decline.*

Introduction

Evidence for factors influencing cognitive decline is of great theoretical and clinical interest. Although there is good reason to suspect that anxiety is such a factor, prospective research investigating the effect of anxiety on cognitive decline in later life is scarce and inconclusive. Sinoff and Werner (2003) found anxiety to be associated with loss of memory function, and concluded anxiety could be an early predictor of cognitive decline. However, the nature of the relationship was not explored and the researchers were not able to establish whether anxiety symptoms cause memory problems or whether the memory problems caused the anxiety symptoms. Wetherell et al. (2002) found contradicting results, and concluded anxiety was not associated with cognitive decline.

With average prevalence rates of 22% for cognitive impairment and 10% for anxiety disorders, both are often found in the general population of older persons (Graham et al. 1997; Beekman et al. 1998; Unverzagt et al. 2001; Hanninen et al. 1996; Ritchie et al. 2001; Schroder et al. 1998). Therefore, in our aging society cognitive decline is an important issue and the treatment of anxiety is always in the patient's interest. However, if anxiety has an influence on cognition, anxiety symptoms could be a factor that should be taken into consideration in the treatment of cognitive decline.

Research studying the course of anxiety showed that 17.9% to 47% of subjects with anxiety suffered from chronic anxiety (De Beurs et al. 2000). Because such a large number of elderly people suffer from chronic anxiety, it is important to investigate the effect of prolonged anxiety symptoms on cognitive performance (Schuurmans et al. 2005). Chronic anxiety might contribute to cognitive decline for anxiety may cause motivational problems or attention deficits (Eysenck 1992). Furthermore, although not based on research among subjects with anxiety, Sapolsky provides an explanatory theoretical model for a possible association between prolonged anxiety symptoms and cognitive performance. Sapolsky's glucocorticoid cascade hypothesis assumes that prolonged high levels of glucocorticoids, the adrenal steroids secreted during stress, can lead to neurotoxicity in the brain and in particular in the hippocampus (Sapolsky 2000), which plays a critical role in memory function, especially in the consolidation of short-term memory into long-term explicit memory (Baddeley 1995). People with anxiety suffer from long-term stress, and are suspected of having prolonged elevated levels of stress hormones in the brain (Kirschbaum et al. 1996), which according to Sapolsky's theory can lead to poorer cognitive performance, especially on memory tasks. Previous cross-sectional research based on the Longitudinal Aging Study Amsterdam (Bierman et al. 2005), found a curvilinear relationship between anxiety and cognitive

performance. This finding suggests that a certain amount of arousal helps to perform optimally on cognitive tasks, whereas severe arousal can narrow one's attention, and therefore worsens cognitive performance (Mendl 1999; Yerkes & Dodson 1908).
The aim of the present study was to obtain more insight into the association between anxiety and cognitive decline in a longitudinal design with a nine-year follow-up. The following research questions were addressed. Firstly: what is the nature of the association between anxiety and cognitive functioning in a longitudinal design? The second question is: are there indications that anxiety precedes cognitive decline and thus contributes to cognitive decline?

Methods

Sample

To investigate the association between anxiety symptoms and cognitive performance in older persons we used data from the Longitudinal Aging Study Amsterdam (LASA; (Deeg et al. 2002)). LASA is a longitudinal study of the predictors and consequences of changes in well-being and autonomy in older persons, which started in 1992.

Ten months prior to LASA the respondents had participated in another study: NESTOR-Living arrangements and Social Network (NESTOR-LSN (Knipscheer et al. 2004)). The sampling procedures of the LASA are described in detail elsewhere (Deeg et al.2002) (Knipscheer et al. 2004), and will only be briefly summarised here. Random samples of older (55-85) inhabitants were drawn from the population registers of 11 municipalities in three regions of the Netherlands. The sample was stratified according to age and gender; the number of males and females in each category were weighted, using projected survival rates (Central Bureau of Statistics 1993), to ensure large enough numbers in all cells five years into the study. The response rate for the NESTOR-LSN interview was 62.3%. Non-response was associated with age, gender and urbanicity. The older elderly people, females and people living in more urbanized areas were less likely to respond. For the LASA study, all 3,805 NESTOR-LSN respondents were approached, 3,107 (81.7%) of whom participated. Non-response was related to age but not to gender. Details of this non-response have been described elsewhere (Deeg et al.2002). As expected, the older old were more often too ill or too cognitively impaired to participate.

For the present study, information on anxiety symptoms was obtained from the first four LASA measurements (1992, 1995, 1998, 2001). Additional testing of cognitive functioning was performed in subjects who were 62 years of age or older at baseline, because

cognitive decline is more common in these subjects (n = 2,615). Information on anxiety symptoms and cognitive performance of 2,351 respondents was obtained in the first LASA measurement, 2,288 respondents in the second measurement, and 1,870 respondents in the third measurement and 1,469 respondents in the fourth measurement. Drop-out was related to age, gender and level of education. Respondents with more anxiety symptoms, and lower scores on some of the cognitive performance tests, had higher drop-out rates. This selective drop-out did not restrict the range on the anxiety scale (0-21 on all measurements) and the cognitive performance scales. All interviews were conducted in the homes of respondents, by specifically trained and intensively supervised interviewers. Informed consent was obtained from each respondent, according to the prevailing legal requirements. The study was approved by the Medical Ethical Committee of the VU Medical Centre.

Measures

We selected cognitive performance tests which cover important aspects of daily cognitive functioning.

General cognitive functioning was measured by means of the Mini-Mental State Examination (MMSE (Folstein et al. 1975)) a frequently used screening instrument for global cognitive functioning. The scale consists of 23 items, and the scores range from 0 to 30, higher scores indicating better cognitive functioning.

Fluid intelligence, defined as the ability to deal with new information, was measured by means of two sub-sets of 12 items (A & B) from Raven's Coloured Progressive Matrices (RCPM) (Raven 1995). Each item consists of a drawing (matrix) of a pattern, from which a section is missing. On the bottom of the page there are six patterns, one of which fits the missing section. The respondent has to choose which of the six alternatives fits best. The items increase in difficulty, and so do the two sections. The 24 items result in a total score ranging from 0-24, with higher scores indicating better cognitive performance.

Information-processing speed was measured by means of an adjusted version of the coding task (Savage 1984). In this task, two rows of characters are shown; each character in the upper row belongs to a character in the lower row. The test section also contains two rows; one of which contains characters and the other is empty. The respondent has to complete as many character combinations as possible by naming the corresponding character in three cycles of one minute. The result of the last cycle was included in the present analysis with scores ranging from 2 to 53.

Episodic memory was measured with a modified Dutch version of the Auditory Verbal

Learning Test (AVLT: (Deelman et al. 1980;Rey 1964)). This test consists of 15 words, which have to be learned during five trials, in the present study the number of trials was reduced to three because of the limited amount of time available for the interview. After every trial the respondent is asked to recall as many words as possible. After a distraction period of 20 minutes, the respondent is again asked to name the words that were learned. The total number of words the respondent has learned during the three trials is the *learning score*, which ranges from 0-45. The number of words reproduced after 20 minutes is the *delayed recall score*, ranging from 0-15. The percentage of reproduced words in the delayed recall condition, divided by the total number of words reproduced in the learning condition, is called the *retention score*. Higher scores on all three variables indicate better memory functioning. *Anxiety symptoms* were measured with the Hospital Anxiety and Depression Scale-Anxiety sub-scale (HADS-A (Zigmund & Snaith 1993)), a measurement used to measure state anxiety and is commonly used to measure anxiety symptoms in population based samples. The anxiety sub-scale consists of 7 items and is self-rated by the respondents. Each answer is rated on a 4-point scale, ranging from 0 'rarely or never' to 3 'mostly or always'. Higher scores indicate more anxiety symptoms. Scores ranging from 0 to 7 (the commonly used cut-off score (Zigmund & Snaith 1993)) were considered to be in the normal range, scores from 8 to 10 indicated mild anxiety symptoms, and scores of 11 or higher indicated moderate/severe anxiety symptoms (Snaith 2003; Bierman et al. 2005).

Confounders

Possible confounders that may be associated with both cognition and anxiety include socio-demographics, level of education, physical health, depressive symptoms, alcohol consumption and use of benzodiazepines.

The *socio-demographic variables* included were the variables age, gender and level of education. The *level of education* was classified into three categories: low level of education (elementary not concluded, elementary education, lower vocational education), medium level of education (general intermediate education, intermediate vocational education, general secondary education), and high level of education (higher vocational education, college education and university education) categorised .

Physical health was assessed according to the number of chronic diseases, by asking respondents if they had any of the following: chronic non-specific lung disease, cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, arthritis, malignant neoplasms, or any other chronic diseases. The total number of diseases ranged from 0 to 8. The accuracy of

self-reports concerning these diseases, compared to general practitioner information, has been shown to be adequate and independent of cognitive impairment and anxiety (Kriegsman et al. 1996).

Depressive symptoms were measured by means of the Centre for Epidemiologic Studies Depression Scale (CES-D; (Radloff 1997;Beekman et al. 1997)). The CES-D is a self-report scale and was developed to measure depressive symptoms in the community.

It consists of 20 items. Each answer is rated on a 4-point scale ranging from 0 'rarely or never' to 3 'mostly or always'. Higher scores indicate more depression symptoms.

Alcohol consumption was assessed with a questionnaire developed by the Dutch Central Office of Statistics (Central Bureau of Statistics 1989) and classified, according to Garretsen's Indication of Present Alcohol Use (Garretsen 1983), into five categories: 1) non-drinker and 2) light, 3) moderate, 4) severe, and 5) excessive drinker) of present alcohol use.

Finally, the *use of benzodiazepines* was taken into account as a possible confounder. The use of prescribed drugs was assessed by asking the respondents to name any medications they had taken in the two weeks prior to the examination. This information was compared with the information on the drug containers, provided by the respondents. Drug use was classified into categories according to the Anatomic Therapeutic Chemical (ATC) classification. In the present study we assessed the number of prescribed drugs. A separate variable was computed for psychotropic drugs, indicating the use of hypnotic drugs or anxiolytic drugs (coded as 'yes' or 'no').

Analyses

We conducted multilevel analyses to investigate the effect of anxiety on cognitive decline. Firstly, we investigated a possible linear relationship. In a multilevel model, the correlations between the outcomes stemming from the same respondent were taken into account by the introduction of so-called random (participant-specific) effects. All analyses reported below included a random intercept and a random slope for the variable of 'time', coding for the measurement occasion (T0 = 1, T1 = 2, T2 = 3, T3 = 4). Anxiety symptoms and confounders were included as fixed effects. We hereafter investigated a possible presence of a curvilinear association by adding the quadratic term of anxiety as an additional covariate.

To determine the effect size, F^2 was calculated (Cohen 1988). According to Cohen (Cohen 1988), an effect size F^2 of 0.02 can be considered as small, an effect size F^2 of 0.15 as medium, and an effect size F^2 of .35 as large. To investigate whether anxiety symptoms precede cognitive decline we constructed a model with the previous measurement of anxiety

as a fixed effect, correcting for confounding variables and present anxiety symptoms. Determined by the number of measurements available for each respondent for the different cognitive performance tests, each model used a different segment of the overall sample. Effects for which the (two-sided) *p* values were lower than 0.05 were regarded as statistically significant. Statistical analyses were performed with SPSS version 12.0.1 and MLwiN version 2.02.

Results

Table 1 shows the distribution of the characteristics of the respondents in the four LASA measurements. At baseline 2,351 older persons were included, with a mean age of almost 69.5 years of age, of which 53.5% were female. The mean score, at the baseline measurement, on the anxiety scale was 2.53 with a standard deviation of 3.3 points, which can be considered as mild anxiety symptoms.

Table 1 Characteristics of the study sample on the four measurements

Measurement	T0	T1	T2	T3
	2351	2288	1870	1469
Age, years	69.49 (8.6)	72.21 (8.5)	74.04 (8.1)	75.67 (7.6)
Gender, N male (%)	1097 (46.7)	1072 (46.9)	841 (45.0)	643 (43.8)
Level of education, N (%)				
- low	1435 (61.0)	1390 (60.8)	1116 (59.7)	858 (58.4)
- medium	625 (26.6)	609 (26.6)	526 (28.1)	419 (28.5)
- high	288 (12.3)	286 (12.5)	227 (12.1)	191 (13.0)
Alcohol consumption, N (%)				
- none	428 (20.4)	384 (25.6)	286 (20.8)	265 (20.4)
- light	1110 (53.0)	746 (49.7)	761 (55.4)	680 (52.4)
- moderate	465 (22.2)	282 (18.8)	281 (20.5)	308 (23.7)
- severe	76 (3.6)	63 (4.2)	35 (2.5)	34 (2.6)
- excessive	16 (0.8)	25 (1.7)	11 (0.8)	11 (0.8)
Number of chronic diseases	1.33 (1.2)	1.68 (1.3)	1.93 (1.4)	1.99 (1.3)
CES-D	7.55 (7.5)	7.96 (7.8)	8.63 (7.6)	9.20 (7.5)
Benzodiazpine use, N (%)	261 (12.4)	206 (10.0)	229 (13.4)	164 (12.1)
HADS-A	2.53 (3.3)	2.70 (3.3)	2.83 (3.3)	3.16 (3.2)
MMSE	27.31 (2.4)	26.78 (3.3)	26.84 (3.3)	26.81 (3.4)
RCPM	18.27 (4.0)	17.89 (4.1)	17.71 (4.1)	17.94 (3.9)

Coding task	26.59 (7.3)	24.27 (7.7)	24.52 (7.5)	25.39 (7.5)
AVLT				
- Learning	19.28 (6.0)	18.92 (6.3)	18.42 (6.6)	20.29 (6.6)
- Delayed Recall	5.34 (2.7)	5.58 (3.0)	5.34 (3.0)	6.13 (3.1)
- Retention	63.38 (24.3)	66.65 (26.8)	63.77 (26.9)	68.56 (25.4)

Note: Values are mean (standard deviation), unless otherwise indicated.

HADS-A = Hospital Anxiety and Depression Scale- Anxiety sub-scale, CES-D = Centre for Epidemiologic Studies Depression Scale, MMSE = Mini Mental State Examination, RCPM = Raven's Coloured Progressive Matrices, AVLT = Auditory Verbal Learning Test

The first aim of the present study was to investigate the nature of the association between anxiety and cognitive functioning in a longitudinal design. The first research question was addressed by testing for a linear relationship by entering anxiety in the multilevel model, together with the variable for measurement occasion.

A significant effect was found for the RCPM (B = -0.05) and the Coding test (B =-0.06), indicating that more anxiety symptoms are associated with more cognitive decline over time on these two cognition tests. However, adjusting for depressive symptoms resulted in a reversal of the effect: anxiety now had a positive effect on cognitive decline for all cognitive performance tests but the RCPM (results not shown). After adjusting for all confounding variables, a significant positive effect was found for the MMSE only (B = 0.05) (Table 2). To determine the clinical relevance of our findings, effect sizes were calculated for all associations. All the effect sizes we found were small ($F^2 < 0.02$).

Table 2 Multilevel analysis of the effect of anxiety symptoms on cognitive performance

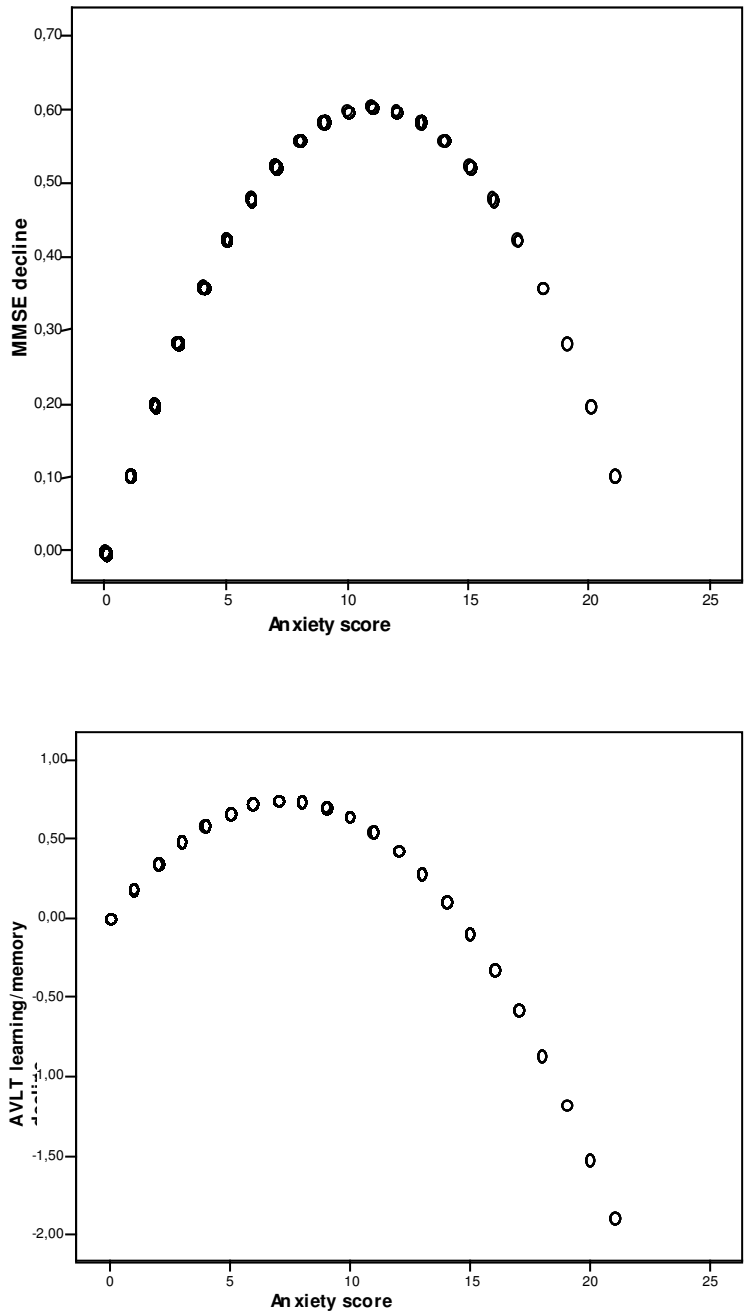
	B0	B	SE	P	B0*	B*	SD*	P*	F^2
	INTERCEPT				INTERCEPT				
MMSE	27.78	-.00	.01	.91	30.56	.05	.01	<. 01	. 02
RCPM	18.75	-.05	.01	<. 01	27.02	-.01	.02	. 51	<-. 01
Coding task	27.60	-.06	.02	<. 01	44.08	.01	.03	.70	<. 01
AVLT									
- Learning	19.64	-.01	.02	. 74	31.52	.05	.03	. 10	<. 01
- Delayed recall	5.45	.00	.01	. 72	10.93	.03	.01	. 35	<-. 01
- Retention	63.96	.10	.11	. 34	104.78	.18	.14	. 21	<. 01

Note: MMSE = Mini Mental State Examination, RCPM = Raven's Coloured Progressive Matrices, AVLT = Auditory Verbal Learning Test

*Adjusted for confounders (age, gender, level of education, alcohol consumption, benzodiazepine use, number of chronic diseases and depression symptoms).

We included a quadratic term for anxiety as an additional covariate of the multilevel models to test a possible curvilinear relationship between anxiety and cognition. A significant negative quadratic effect was found for the MMSE (B = -0.10) and the AVLT learning and memory (B = -0.02). These results indicate that there is a curvilinear association between anxiety symptoms and cognitive decline. The curvilinear association found for these two tests is displayed in Figure 1 for the observed range in anxiety scores. With regard to the MMSE, figure 1 shows mild anxiety symptoms are associated with an improvement on the MMSE until an optimal point, above which the beneficial influence decreases. The point at which anxiety symptoms are no longer beneficial is between 8 and 11 points on the anxiety scale. The scores on the AVLT learning condition show mild anxiety symptoms are associated with an improvement in performance on the AVLT learning. However, this positive effect of anxiety symptoms decreases with the increase of symptoms. Respondents scoring 15 points or more on the anxiety scale perform worse on the AVLT learning and memory longitudinally than respondents who do not suffer from any anxiety symptoms. For the other cognitive performance tests we also found a curvilinear trend, but these associations did not reach the level of significance (results not shown).

Figure 1
The predicted anxiety scores for the cognitive performance tests



The second question was whether there are indications that anxiety contributes to cognitive decline. Therefore we included the previous measurement of anxiety symptoms in the multivariate multilevel model. No significant effect was found for any of the cognitive tests (MMSE: p = .505, RCPM: p = .420, Coding test: p = .253, AVLT learning and memory: p = .688, AVLT recall: p = .113 and AVLT retention: p = .119). This implies that the level of anxiety symptoms on the previous measurement is not associated with cognitive decline three years later.

Discussion

The aim of the present study was to investigate whether anxiety symptoms are related to cognitive decline in elderly persons. A secondary goal was to investigate whether the relationship, if present, is such that anxiety precedes changes in cognitive performance, supporting the hypothesis of a causal effect of anxiety on cognitive decline. These research questions were addressed in a large community-based prospective study taking confounding variables into account. As far as we know, this is the first study to investigate the association between anxiety symptoms and cognitive decline longitudinally.

We found that the effect of anxiety symptoms on cognitive performance seems to depend on the severity of the present anxiety symptoms with mild anxiety associated with better cognitive performance, whereas more severe anxiety is associated with worse cognitive performance. All effect sizes were small, which suggests that the findings are marginally clinically relevant.

The findings indicate more evidence that suggest that the Yerks and Dodson (Mendl 1999; Yerkes & Dodson 1908) law applies to anxiety symptoms. This law implies that there is an inverted U-shaped relationship between arousal and cognitive performance. A certain amount of arousal helps us to perform optimally on cognitive tasks, whereas severe arousal can narrow our attention, and worsens cognitive performance. This is in line with the findings of earlier cross-sectional research based on the Longitudinal Aging Study Amsterdam (Bierman et al. 2005). However, these findings contradict the results of the research carried out by Wetherell and colleagues (Wetherell et al. 2002), who found no support for a curvilinear relationship between trait anxiety and cognitive performance. These contradicting results might be due to the difference between the construct of neuroticisme, used in the study by Wetherell as an indication for trait anxiety, and the anxiety symptoms measured with the HADS-A in the present study. Although these constructs are related, they are not identical.

Furthermore, we have investigated whether anxiety symptoms precede cognitive decline. Our main conclusion is that previous measurement of anxiety symptoms were not predictive of cognitive decline at a later time-point, and thus no evidence was found for the hypothesis that anxiety has lasting effects on cognitive decline. Our findings indicates that the effect of anxiety on cognitive functioning is a state effect, which does not point at Sapolsky's hypothesis, in which he postulates that prolonged levels of stress hormones irreversibly impairs cognitive performance (Sapolsky 2000). However, it may well be that the self-reports of anxiety did not correlate with the glucocorticoid release, and could therefore not have tapped the stress response.

Adjusting for depressive symptoms lead to a reversal of the effect of the initial negative effect anxiety had on cognitive performance. Depressive symptoms seem to suppress the positive effect mild anxiety symptoms have on cognitive performance (Bierman et al. 2005).

In most cognitive performance tests the breaking point at which cognitive performance declines in relation to anxiety symptoms, lies around a score of 8 points. This happens to be the cut-off point of the HADS-A anxiety scale (Snaith 2003), above which respondents suffer from clinically relevant anxiety symptoms. Our findings suggest that respondents scoring above this cut-off do not only suffer from a psychological disorder, but they also perform worse on cognitive performance tests than respondents who suffer from less anxiety symptoms. These respondents, scoring high on the HADS-A, and their cognitive performance are of the highest clinical relevance.

The findings have to be placed in the context of the strengths and limitations of this study. The strengths of the present study are that it is longitudinal, with nine years of follow-up, and that it is community-based, including large numbers of elderly people, providing data on relevant confounders and testing in four domains of cognition.

However there are also limitations. Firstly, selective non-response of the most frail is an inevitable problem in community-based research among the elderly. This might have led to an under-estimation of the effect of anxiety on cognition, because the subjects with the most severe anxiety symptoms and severe cognitive decline frequently drop out of such studies. Secondly, our data on anxiety are based on self-reports and no objective clinical assessments or diagnoses of anxiety disorders were made. Thirdly, the respondents were tested over an interval period of three years, during which the level of anxiety symptoms might have fluctuated. This might have resulted in a distortion in the effect of anxiety symptoms found in the previous measurement.

In conclusion, our results indicate that the effect of anxiety symptoms on cognitive decline, measured in a community-based sample, depends on the severity of the anxiety symptoms; mild anxiety is associated with better cognition, whereas more severe anxiety is associated with cognitive decline in elderly persons. Up to the generally accepted cut-off score on the anxiety symptoms scale, anxiety seems to be beneficial for cognition. However, these effects seem to be temporary, as previous measurement of anxiety symptoms were not predictive of cognitive decline at a later time-point.

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