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ABSTRACT

OBJECTIVES: To examine in men and women the independent associations of anxiety and depression with incident cognitive impairment and to examine the association of cognitive impairment no dementia (CIND) and incident cognitive impairment with incident anxiety/depression.

DESIGN: Prospective cohort study.

SETTING: General community.

PARTICIPANTS: Population-based sample of 1942 individuals aged 65 to 96.

MEASUREMENTS: Two structured interviews separated by 12 months evaluated anxiety and mood symptoms/disorders according to DSM-IV criteria. Incident cognitive impairment was defined by no CIND at baseline, a follow-up Mini-Mental State Examination score of at least two points below baseline and below the 15th percentile according to normative data. The associations for incident cognitive impairment and incident anxiety or depression were assessed by logistic regressions adjusted for potential confounders.

RESULTS: Incident cognitive impairment was, independently of depression, associated with baseline anxiety disorders (odds ratio: 6.27, 95% CI: 1.39-28.29) in men and anxiety symptoms (2.14, 1.06-4.34) in women. Moreover, the results indicated that depression disorders (8.87, 2.13-36.96) in men and anxiety symptoms in women (4.31, 1.74-10.67) were particularly linked to incident amnestic cognitive impairment while anxiety disorders (12.01, 1.73-83.26) in men was especially associated with incident non-amnestic cognitive impairment. CIND at baseline or incident cognitive impairment were not associated with incident anxiety or depression.

CONCLUSION: Anxiety and depression appear to have different relations with incident cognitive impairment according to sex and the nature of cognitive impairment. Anxiety in older

adults should receive particular attention by clinicians since it can be shortly followed by incident cognitive impairment.

INTRODUCTION

Anxiety and depression are common psychiatric symptomatologies in the elderly population. In the community-dwelling elders, the prevalence rates are up to 15% for anxiety disorders and 52% for anxiety symptoms.[1] Regarding mood disorders (including major depressive disorder and minor depression) the prevalence rate is up to 35%.[2] Previous studies with cognitively intact elders indicated that depressive symptomatology often precedes cognitive decline[3-7] and this association may be more pronounced in men than in women.[3, 8-10] Recent studies also found that depressive symptomatology was related to incident cognitive impairment no dementia (CIND), but the relation was stronger for incident amnestic CIND (i.e. CIND that includes memory impairment).[5] Moreover, other results demonstrated that depressive symptoms occur along with cognitive decline in elders who develop Alzheimer's disease (AD), suggesting that depressive symptoms may be an early reaction to perceived cognitive decline rather than a "prodrome".[11]

There is evidence that anxiety, measured by dimensional scales or lists of symptoms, may precede cognitive decline in elders,[12-14] but there are controversial results.[15-17] Since anxiety and mood disorders have a high rate of comorbidity and given that scales assessing anxiety and depression are correlated,[18-21] it is essential to assess simultaneously both anxiety and depression in order to examine their independent associations with cognitive decline. At the moment very few community studies have assessed whether anxiety and depression are independently related to cognitive decline. Bierman *et al.* observed that a high anxiety level was not predictive of cognitive decline and only had a temporary effect on cognitive functioning.[16, 22] Palmer *et al.* showed that in elders with mild cognitive impairment (MCI), a group of symptoms labeled as "anxiety" (indecision, persistent worrying, anxiety, and social withdrawal), but not mood symptoms (dysphoria, suicidal ideation/thoughts of death, feelings of guilt, and appetite disturbance), were linked to incident AD. On the other hand, in elders with intact cognitive

functioning, mood, but not anxiety symptoms, were associated with incident AD.[13] Gallacher *et al.* observed that in cognitively intact older men, trait anxiety (i.e. relatively stable individual differences in anxiety-proneness) was related with incident CIND independently of depressive symptoms, but not with dementia.[14]

The main objective of the present study was to assess the independent relations of anxiety disorders and mood disorders with the incidence of cognitive impairment in community-dwelling older adults. Since clinically significant anxiety symptoms in elders are less likely to fully meet all DSM-IV criteria for anxiety disorders,[23-25] anxiety symptoms not meeting all DSM-IV criteria were also examined. The second objective was to examine whether CIND precedes the onset of anxiety and depression symptomatologies and whether incident cognitive impairment occurs along with incident anxiety/depression. Furthermore, since previous studies suggested that depression was more strongly associated with incident cognitive impairment in men and with amnestic incident cognitive impairment, sex differences were examined and the associations were assessed for amnestic and non-amnestic cognitive impairment.

METHODS

ESA Study

Data come from the *Enquête sur la santé des aînés* (ESA Study; in English, Study on Elders' Health), a population-based study on elders' mental health.[26] The aim of the ESA study was to assess the prevalence and incidence of many psychiatric disorders (mood disorders and anxiety disorders) in the province of Québec, Canada. In 2005-2006, a random sample (n = 2811) of community-dwelling French-speaking adults (95% of the Québec population speaks French)[27] aged 65 years or older and living in the province of Québec, Canada, were recruited. The sampling frame of the study used a random dialing method with a stratification of proportional

sample of households according to geographical areas (metropolitan, urban, and rural) and the 16 administrative regions of the Québec's province. A random sampling method was also used to select only one elder within the household. The response rate was 76.5% at the first interview.

Data were collected through in-home structured interviews conducted by trained research nurses who received 2 days of training by the principal investigator (M.P.) in the administration of the ESA computer-assisted questionnaire (ESA-Q). The ESA-Q comprises many questionnaires including an adapted version of the DSM-IV mood and anxiety disorders sections of the Diagnostic Interview Schedule and Composite International Diagnostic Interview, which have demonstrated satisfactory reliability and validity to establish psychiatric diagnoses.[28-30] Cognitive functioning was assessed with the Mini-Mental State Examination (MMSE).[31] To ensure the validity of the data in the ESA study, the complete interview was done only with participants who scored 22 or higher on the MMSE (26 participants had a MMSE score <22 at baseline). The follow-up interview occurred approximately 12 months after the baseline interview (mean: 12.5 SD: 1.4). Data from the ESA study were linked with medical records from the *Régie de l'assurance maladie du Québec* (RAMQ; Québec's public health insurance plan). All Québec residents are registered to the RAMQ coverage. The respondents were offered a $15 compensation for their participation. Written informed consent was obtained at the beginning of the interview from all participants. The research procedures were previously reviewed and authorized by the ethics committee of the *Institut universitaire de gériatrie de Sherbrooke*.

Study Sample

Figure 1 shows the flow chart of study enrollment and exclusion criteria. Among the 2785 participants who received the psychiatric interview at baseline, 47 died and 525 were not interviewed at follow-up. Medical records from the RAMQ were available for 2010 individuals and only these participants were included in the present study. The missing data from the RAMQ

records was due to refusal of consent to provide medical records, moving outside Québec, or having additional drug insurance. According to the medical records covering one year before the baseline to the follow-up interview, participants who received a diagnosis of dementia and/or were taking an approved pharmacological treatment for dementia (memantine, donepezil, galantamine, or rivastigmine) were excluded from the sample (n = 41). Moreover, nine participants were excluded because education level was unknown and eighteen others were excluded because their interview was incomplete. Thus, 1942 participants were included in the present study. For the second objective of the present study (analyses on the psychiatric interview at follow-up), data was available for 1930 participants since 12 participants did not receive the complete evaluation at follow-up because they had a follow-up MMSE score below 22.

Psychiatric variables

In both interviews, all psychiatric symptoms were identified for the 12-month period preceding the interview according to DSM-IV criteria.[32] Depression included major depressive episode and depressive disorder not otherwise specified. Subjects reporting that depressive symptoms began after the loss of a loved one were not considered as having depression. Anxiety disorders comprised specific phobia, social phobia, agoraphobia, panic disorder, and generalized anxiety disorder. Anxiety and depressive disorders were defined as syndromes meeting all DSM-IV criteria. Participants having at least one essential symptom of a DSM-IV anxiety or depressive disorder without meeting full criteria were considered as having symptoms. For example, minimal criteria for symptoms of panic disorder were “a discrete period of intense fear or discomfort, in which one (or more) symptom for panic attack developed abruptly” and minimal criteria for generalized anxiety disorder symptoms were “excessive anxiety and worry occurring more days than not for at least one month”. All minimal criteria for anxiety disorders symptoms (also called subclinical symptoms) were published elsewhere.[33] Minimal criteria for depression

symptoms were defined as two weeks of depressed mood or marked diminished interest/pleasure in daily activities. Moreover, symptoms were separated into two categories: clinically significant (*symptoms* +) and not clinically significant (*symptoms* -). Symptoms were considered clinically significant when one of the following criteria was met: 1) participants consulted or were thinking about consulting a health professional for their symptoms, 2) the symptoms produced major distress, or 3) caused impairment in any of the following areas of functioning: activities of daily living, social activities, and relationships with others. Finally, participants were considered having incident psychiatric symptoms/disorders only if they displayed no such symptom at baseline.

Cognitive impairment

The criterion used for CIND at baseline was similar to that of studies from the Kungsholmen Project group [34-35] and was defined as a MMSE score below the 15th percentile according to normative data for age, education and sex,[36] which is equivalent to a score below one standard deviation in a normal distribution. Incident cognitive impairment was defined as no CIND at baseline with a follow-up MMSE score below the 15th percentile according to norms for age, education and sex.[36] Since it was previously established that a reliable change in MMSE score for short intervals consisted in a loss of at least 2 points,[37] a loss of 2 MMSE points between baseline and follow-up was required in addition to a MMSE score below the 15th percentile to meet incident cognitive impairment criteria. Cognitive impairment was labeled as "general cognitive impairment" since the MMSE assesses general cognitive functioning. Moreover, based on previous findings,[5, 38] amnestic and non-amnestic subtypes of cognitive impairment were identified. The 3-word recall task of the MMSE was reported to be an adequate measure of episodic memory in epidemiologic studies.[39] Thus, cognitive impairment with a score of 0 or 1

out of 3 on the 3-word recall task of the MMSE was considered a cognitive impairment of the amnestic type.

Covariates

Potential confounders included age, education, sex, geographical living areas (urban/rural), psychotropic drug use, vascular conditions, chronic diseases, and brain disorders. Psychotropic drug use was assessed by the RAMQ medical records and drugs were coded according to the American Hospital Formulary Service.[40] Psychotropic drug use was defined as one prescription during the year between the baseline and the follow-up interview. The number of chronic diseases according to the International Classification of Diseases (ICD-10) was measured by asking participants at baseline if they had any of the following chronic health problems: arthritis or rheumatism, eye diseases, backache or spinal problems, digestive problems, thyroid disorders, other metabolic disorders, anemia, hypercholesterolemia, asthma or emphysema or chronic bronchial diseases, liver diseases, kidney or urinary problems, skin diseases, migraine or frequent headaches, schizophrenia and other forms of psychosis. A cardiovascular condition score was computed using the RAMQ medical records and by asking participants at baseline if they had high blood pressure, diabetes, and heart diseases. The score was the total of these three health problems. The presence of brain disorders was assessed by the RAMQ medical records covering the year between the baseline and the follow-up interview for the following disorders: cerebrovascular disease, brain trauma/tumor/infections, multiple sclerosis, Parkinson's disease, and epilepsy.

Statistical analysis

For the analyses on incident cognitive impairment, participants with cognitive impairment at baseline were discarded. Characteristics differences between participants with incident cognitive impairment and those with intact cognitive functioning were evaluated with *t*-tests and

chi-squares. The associations between incident cognitive impairment and anxiety/depression were first assessed by crude odds ratio (OR) with 95% confidence intervals (CI). Then, the independent associations were assessed by adjusted ORs computed by a logistic regression with incident cognitive impairment as the predicted variable, anxiety and depression at baseline as predictors, and was adjusted for age, education, sex, geographical living areas, MMSE score at baseline, psychotropic drug use, brain disorders, cardiovascular conditions score and chronic diseases. Anxiety was coded as disorders, *symptoms* +, *symptoms* -, or absent. The same coding was done for depression, but since very few cases of symptoms were identified, the categories *symptoms* + and *symptoms* - were merged. All other variables were categorized as described in the previous section.

The associations between incident anxiety or depression and cognitive impairment were assessed for both cognitive impairment at baseline (CIND) and incident cognitive impairment by crude and adjusted ORs. To allow a sufficient number of cases, disorders and symptoms categories were grouped. For the analysis on incident anxiety, participants with anxiety at baseline were discarded, cognitive impairment was used as predictor, and the OR was adjusted for depression at baseline. The equivalent was conducted for the analysis on incident depression. ORs were also adjusted for age, education, sex, geographical living areas, psychotropic drug use, brain disorders, vascular conditions score and chronic diseases. Finally, sex differences for all ORs were examined with Breslow-Day tests for homogeneity of odds ratios. Statistical assumptions were verified and analyses were performed using SPSS software (16.0) with the alpha level set at a two-tailed 5%.

RESULTS

At baseline, 174 participants met the criterion for CIND. At follow-up, 112 participants displayed incident cognitive impairment. Table 1 shows the characteristics of the participants with incident general cognitive impairment and participants with intact cognitive functioning. Compared to participants with intact cognitive functioning, participants with incident cognitive impairment were older, had a lower MMSE score at baseline and a higher number of chronic diseases. Moreover, the proportion of participants with incident cognitive impairment was lower in urban than in rural areas. Finally, the mean difference between MMSE scores at baseline and at follow-up was -3.5 for participants with incident cognitive impairment and 0.1 for participants with intact cognitive functioning; this difference was statistically significant.

A significant sex difference (p = .001) was observed for the association between incident cognitive impairment and anxiety disorders. Therefore, ORs for incident cognitive impairment were computed separately for men and women. Table 2 indicates, for men and women, the associations of baseline anxiety and depression with incident cognitive impairment. In women, anxiety *symptoms* - were significantly associated with general and amnestic incident cognitive impairment. In men, anxiety disorders at baseline were significantly linked with incident general and non-amnestic cognitive impairment while depressive disorders were significantly related to incident amnestic cognitive impairment. In both men and women, no case of depressive symptoms displayed incident cognitive impairment.

Table 3 shows the associations of CIND at baseline and incident cognitive impairment with incident anxiety or depression. No significant sex difference was observed in the ORs between incident anxiety or depression and cognitive impairment. CIND at baseline and incident cognitive impairment were not significantly related to incident depression or anxiety and these results were not influenced by the nature of the cognitive impairment (amnestic vs non-amnestic).

DISCUSSION

The present study aimed to examine in community-dwelling older men and women the independent associations of anxiety and depression assessed by DSM-IV criteria with the incidence of cognitive impairment. In women, anxiety symptoms not clinically significant were found to be associated with incident general cognitive impairment and the results suggested that this association was specific to incident amnestic cognitive impairment. In men, anxiety disorders and depressive disorders were both related to incident cognitive impairment. The results also suggested that anxiety disorders were especially linked to incident non-amnestic cognitive impairment while depressive disorders were specifically related to incident amnestic, but not non-amnestic, cognitive impairment. Moreover, the relations of cognitive impairment with incident anxiety and depression were investigated. CIND at baseline and incident cognitive impairment were not significantly linked to incident anxiety or depression. Together, these results suggest that anxiety, independently of depression, is associated with incident cognitive impairment and that the relations of anxiety and depression with incident cognitive impairment differ according to sex and the nature of the cognitive impairment.

Anxiety and cognitive decline

Previous results support a cross-sectional relationship in older adults between anxiety and cognitive impairment.[22, 33, 41-42] The present study indicated that anxiety, independently of depression, is often followed by cognitive decline within a year in older adults with intact cognitive functioning. Moreover, our results suggest that anxiety does not rise along with incident cognitive impairment or follow CIND. These findings agree with previous ones indicating that anxiety increases the risk of cognitive decline or AD.[12-14] Among these studies, Palmer *et al.* used a 3-year follow-up and showed that a group of symptoms labeled as “anxiety” (indecision,

persistent worrying, anxiety, and social withdrawal) increased the risk of AD in elders with MCI, but not in elders with intact cognitive functioning. It could be debated whether symptoms of indecision and social withdrawal are truly anxiety symptoms, nevertheless, Palmer *et al.* reported that persistent worrying alone had a fivefold increased risk of AD in elders with MCI compared to elders with MCI without persistent worrying.[13] Using a much longer follow-up (17 years), Gallacher *et al.* observed in a sample of older men that trait anxiety increased the risk of CIND.[14] Despite these results revealing links between anxiety and cognitive decline, other previous studies did not find any support for this hypothesis.[15-17] In fact, one study did not find that high anxiety level was linked to incident cognitive decline[16] and two others found that high anxiety level in elders with MCI or questionable dementia decreased the risk of converting to AD.[15, 17] Since all of these studies used diverse populations, follow-ups lengths, neuropsychological assessments, and anxiety assessments, it is difficult to draw a fair conclusion. Nevertheless, it is likely that the relation between anxiety and cognitive decline is modified by multiple factors and further studies are needed to develop a better comprehension of this relation.

Anxiety and depressive symptoms not meeting criteria for disorders

Many authors have pointed out that anxiety in older adults differs from that in younger adults and that clinically significant anxiety symptoms in elders are less likely to fully meet all DSM-IV criteria for anxiety disorders than in younger adults.[23-25] In addition, a study showed that elders with anxiety symptoms not meeting all DSM-III criteria for anxiety disorders did not differ in terms of disability, well-being, and medication use from elders with anxiety disorders.[43] In line with these results, a recent study suggested that older adults with anxiety symptoms not fully meeting DSM-IV criteria were similar in their health characteristics compared to older adults with anxiety symptoms fully meeting DSM-IV criteria.[44] Recent data also showed that symptoms of generalized anxiety disorders not meeting all DSM-IV criteria were associated to CIND.[45] In

the present study, we observed that anxiety symptoms that do not meet DSM-IV criteria and that are not clinically significant (i.e. not producing major distress or altering functioning), were associated with incident cognitive impairment in women. Moreover, contrasting with the results on anxiety, the results on depression revealed that symptoms that do not meet DSM-IV criteria were not common in our sample and they were even less common before incident cognitive impairment since no participant with depression symptoms displayed incident cognitive impairment. These findings strengthen the idea that anxiety symptoms not meeting DSM-IV criteria are not negligible in older adults and that these symptoms should receive a particular attention from clinicians.

Potential mechanisms

Many potential mechanisms could account for the association between anxiety/depression and incident cognitive impairment. First, depression is linked to higher glucocorticoid levels[46] and it was suggested that chronic exposure to glucocorticoid promotes neurons' death.[47] This explanation is known as the neurotoxicity hypothesis and has received extensive attention in the last decade (for a review on the topic see [48]). Previous studies also indicated that older adults with anxiety disorders display elevated cortisol level.[49-50] Thus, it is probable that the neurotoxicity hypothesis also applies to some anxiety disorders. Second, it is possible that anxiety and depression are consequences of an ongoing brain disease such as AD or a vascular pathology, altering normal brain functioning and leading to cognitive decline. A third explanation is that anxiety and depression may be risk factors for incident cognitive impairment only in the presence of other characteristics, for example a specific gene variant. [7] Fourth, as described earlier, anxiety and depression may be a reaction to early cognitive decline. While the present results showed that CIND and incident cognitive impairment were not linked to incident anxiety or depression, it is

possible that older adults with normal cognitive functioning, as measured by neuropsychological tests, perceive cognitive problems in their daily activities.

Sex differences

One of the main findings in the current study is that important differences between men and women were outlined. Depression was linked to incident cognitive impairment only in men. Anxiety was differently related to incident cognitive impairment according to sex since it was linked with disorders and symptoms, in men and in women respectively. Sex differences were reported in many previous studies on the relations of anxiety and depression with cognitive functioning or decline. In a recent cross-sectional study, we observed that generalized anxiety disorders symptoms were linked to CIND in older men, but not in older women.[45] Previous studies also observed that depression predicted the onset of dementia or cognitive decline in men, but not in women.[3, 8-10] Many hypotheses were proposed to account for these discrepancies. First, biological differences could be an explanation since estrogen might be a neuroprotective agent as it enhances cognitive functioning in animal models.[51-52] However, its protective effect on cognitive decline and dementia in humans is controversial.[53-54] Second. it was proposed that a vascular pathology accentuating cognitive decline may underlies depression in men.[9] However, other studies indicated that sex differences in the association between depression and cognitive decline was not explained by vascular factors.[3, 10] Third, another explanation resides in the different ways men and women tend to report their symptoms.[10] Compared to women, men are usually less willing to admit their symptoms.[55] This difference may result in an underestimation of psychiatric symptoms in men and an overestimation in women, leading to a higher number of false-positives in women and diluting the association in this group.[10] It is also possible that psychiatric symptoms preceding cognitive decline are reported in men as more severe symptoms than in women. This last hypothesis provides a parsimonious explanation to account for the

present results on anxiety. If anxiety has the same effect in men and in women, this hypothesis explains why the least severe symptoms of anxiety in women and the most severe anxiety symptoms in men were both linked to cognitive decline in the present study.

Strengths and limits of the study

There are several strengths and original contributions in the present study. First, it uses a large sample of community-dwelling older adults, randomly selected, and with a good response rate and thus, preventing potential selection biases. Second, the examination of sex differences and anxiety symptoms not fully meeting DSM-IV criteria revealed important patterns of results and these factors should be considered in future studies assessing the links between anxiety and cognitive functioning. Third, unlike previous studies on the relations of anxiety with cognitive decline or dementia which used brief dimensional scales or lists of symptoms,[12-17] the present study used DSM-IV criteria for anxiety disorders to assess anxiety symptoms. The DSM-IV criteria are standard and widely used. Therefore, they facilitate the comparison with future studies. This is an advantage over previous studies using uncommon anxiety assessments, which have major differences, and thus, renders the comparison between studies difficult. Finally, many potential socio-demographic and health-related confounders were taken into account in the statistical analyses of the present study.

The present study also has limitations. First, neuropsychological assessment was based on the MMSE, which is a screening instrument for general cognitive functioning. Therefore, this instrument does not adequately cover all cognitive functions (e.g. executive functioning) and different results could have been observed with an extensive neuropsychological battery. A more exhaustive neuropsychological evaluation is suitable for future studies on the relations between anxiety and incident cognitive impairment. Second, despite the fact that we used a large sample of older adults and that the examination of sex differences yielded interesting findings, the

separated analyses for men and women had the cost to reduce the number of cases with psychiatric symptoms. This was particularly notable in men because there were less male than female participants and the prevalence of psychiatric symptoms in men was lower than in women. Moreover, the analyses of the sex differences and the nature of the cognitive impairments were exploratory. Therefore, the present findings should be interpreted with caution and need to be replicated. Third, despite the fact that the extent of cognitive decline within 12 months in participants with incident cognitive impairment was relatively substantial (mean loss of 3.5 MMSE points), the present study had a single follow-up and it did not evaluated dementia. Hence, it is unknown whether participants with incident cognitive impairment remained stable, further declined or recovered afterwards. Future studies on anxiety and cognitive functioning with multiples follow-ups are suitable. Fourth, the data used in the present study did not allow to investigate the underlying mechanisms of the associations between anxiety/depression and incident cognitive impairment.

In summary, our results strengthened the idea that anxiety, independently of depression, is associated with incident cognitive impairment in older adults. The results also suggest that this relation is modified by sex as well as the nature of the cognitive impairment and that anxiety symptoms not meeting DSM-IV criteria should not be overlooked in older adults. Anxiety in older adults should receive particular attention by clinicians since it can be shortly followed by incident cognitive impairment. Anxiety could be a potential target for the prevention and early treatment of cognitive decline.

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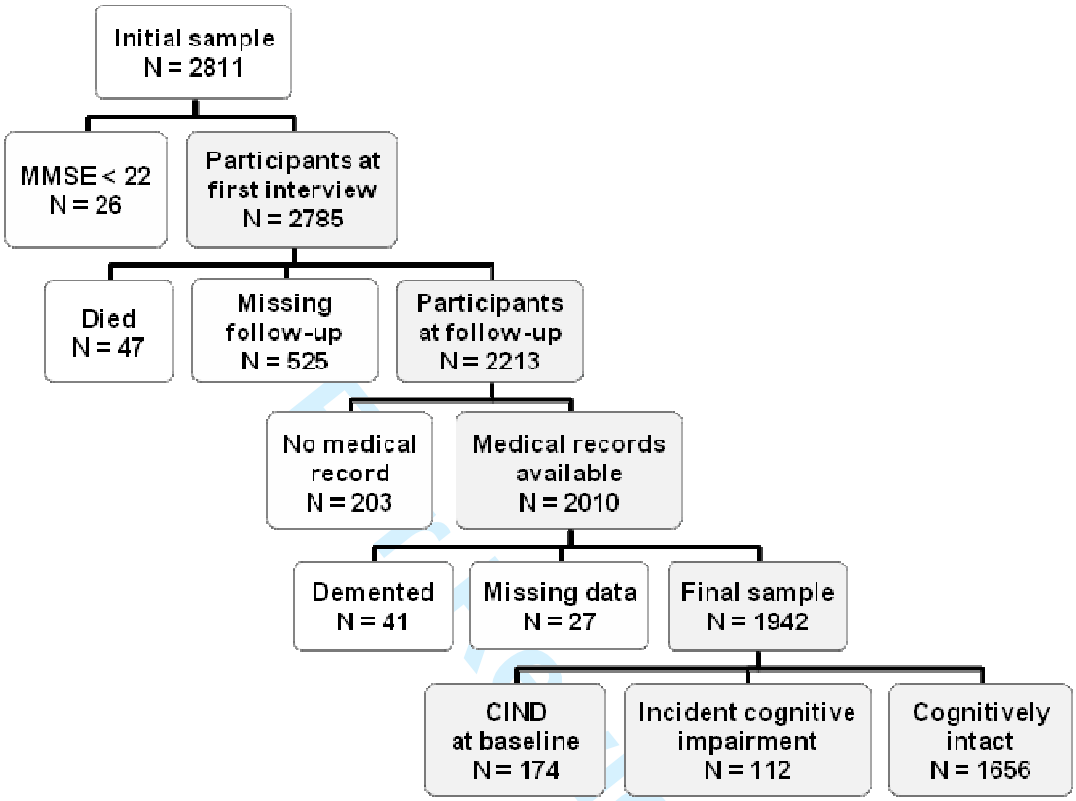

Figure 1. Flow chart of the study sample enrollment with white shapes representing exclusion criteria. CIND: cognitive impairment no dementia.

Table 1 Characteristics of participants with and without incident general cognitive impairment

Characteristic (N (%) or mean ±SD)	Incident general cognitive impairment (N = 112)	No cognitive impairment (N = 1656)	*p* [a]
Age	75.0 ±5.6	73.6 ±5.6	.010
Women	70 (62.5)	1161 (70.1)	.090
Education			
Primary or less	27 (24.1)	364 (21.9)	.725
Secondary	44 (39.3)	713 (43.1)	
Postsecondary	41 (36.6)	579 (35.0)	
Living in rural areas	49 (43.8)	540 (32.6)	.015
Psychotropic drug use	44 (39.3)	592 (35.7)	.450
Brain injury/disease	4 (3.6)	56 (3.4)	.915
Cardiovascular condition score	1.4 ±0.9	1.2 ±0.9	.133
Number of chronic diseases	2.6 ±1.9	2.2 ±1.7	.017
Baseline MMSE score	28.4 ±1.2	28.9 ±1.1	< .001
Δ MMSE score (baseline - follow-up)	-3.5 ±1.6	0.1 ±1.2	< .001

MMSE: Mini-mental state examination.
[a] Significance level from *t*-tests or chi-squares

Table 2. Association of anxiety and depression at baseline with incident cognitive impairment in older men and women (N = 1772)

	Incident cognitive impairment								
			General			Non-amnestic		Amnestic	
	Yes N (%)	No N (%)	Crude OR (95% CI)	Adjusted[a] OR (95% CI)	*p*	Adjusted[a] OR (95% CI)	*p*	Adjusted[a] OR (95% CI)	*p*
Women									
Anxiety									
DSM-IV	1 (1.4)	43 (3.7)	0.43 (0.06-3.20)	0.42 (0.06-3.18)	.403	0.62 (0.08-4.78)	.647	-	-
Symptoms +	8 (11.4)	92 (7.9)	1.61 (0.74-3.50)	1.49 (0.66-3.34)	.335	1.38 (0.51-3.77)	.525	1.69 (0.46-6.13)	.427
Symptoms -	11 (15.7)	99 (8.5)	2.06 (1.04-4.09)	2.14 (1.06-4.34)	.035	0.88 (0.26-2.97)	.838	4.31 (1.74-10.67)	.002
Depression									
DSM-IV	7 (10.0)	127 (10.9)	0.88 (0.40-1.97)	0.63 (0.27-1.48)	.292	0.62 (0.08-4.78)	.402	0.62 (0.17-2.27)	.473
Symptoms	0 (0.0)	24 (2.1)	-	-	-	-	-	-	-
Men									
Anxiety									
DSM-IV	4 (9.5)	6 (1.2)	8.48 (2.28-31.45)	6.27 (1.39-28.29)	.017	12.01 (1.73-83.26)	.012	4.78 (0.76-30.00)	.095
Symptoms +	3 (7.1)	22 (4.4)	1.73 (0.49-6.08)	1.83 (0.46-7.30)	.390	4.18 (0.79-22.13)	.093	0.68 (0.06-7.20)	.749
Symptoms -	0 (0.0)	22 (4.4)	-	-	-	-	-	-	-
Depression									
DSM-IV	5 (11.9)	25 (5.1)	2.50 (0.91-6.92)	3.29 (0.97-11.12)	.055	0.84 (0.07-9.64)	.887	8.87 (2.13-36.96)	.003
Symptoms	0 (0.0)	7 (1.4)	-	-	-	-	-	-	-

CI: confidence interval; OR: odds ratio; Symptoms +: anxiety symptoms clinically significant; Symptoms -: anxiety symptoms not clinically significant.
[a] ORs and 95% CI were estimated by a logistic regression with incident cognitive impairment as predictor adjusted for age, education, geographical areas, MMSE score at baseline, psychotropic drug use, brain injury/disease, cardiovascular conditions, and chronic diseases. *p* values were obtained by Wald *F* statistics with *df* = 1.

Table 3. Association of cognitive impairment with incident anxiety or depression in older adults (N = 1930)

Cognitive impairment	Incident anxiety					Incident depression				
	Yes N (%)	No N (%)	OR (95% CI)	Adjusted[a] OR (95% CI)	*p*	Yes N (%)	No N (%)	OR (95% CI)	Adjusted[a] OR (95% CI)	*p*
CIND at baseline										
General	14 (7.3)	112 (8.1)	0.90 (0.51-1.61)	0.88 (0.49-1.59)	.678	12 (12.4)	125 (7.8)	1.68 (0.89-3.15)	1.59 (0.83-3.02)	.159
Non-amnestic	10 (5.3)	49 (3.7)	1.47 (0.73-2.96)	1.38 (0.67-2.85)	.379	6 (6.6)	65 (4.2)	1.61 (0.68-3.83)	1.36 (0.56-3.28)	.499
Amnestic	4 (2.2)	63 (4.7)	0.46 (0.17-1.27)	0.47 (0.17-1.32)	.153	6 (6.6)	60 (3.9)	1.75 (0.73-4.16)	1.90 (0.79-4.62)	.154
Incident										
General	11 (6.2)	71 (5.6)	1.13 (0.58-2.17)	1.10 (0.56-2.18)	.775	7 (8.2)	90 (6.1)	1.39 (0.62-3.10)	1.22 (0.53-2.77)	.639
Non-amnestic	6 (3.5)	38 (3.1)	1.15 (0.48-2.76)	1.00 (0.40-2.47)	.996	4 (4.9)	48 (3.3)	1.49 (0.52-4.24)	1.38 (0.48-3.98)	.553
Amnestic	5 (2.9)	33 (2.7)	1.10 (0.42-2.86)	1.20 (0.44-3.22)	.725	3 (3.7)	42 (2.9)	1.28 (0.39-4.21)	1.06 (0.31-3.67)	.924

CI: confidence interval; CIND: cognitive impairment no dementia; OR: odds ratio

[a] ORs and 95% CI were estimated by a logistic regression with incident anxiety or depression as predictors adjusted for anxiety or depression at baseline accordingly, age, education, sex, geographical areas, psychotropic drug use, brain injury/disease, cardiovascular conditions, chronic diseases. *p* values were obtained by Wald *F* statistics with $df = 1$.