Title: Anxiety disorders, depressive episodes and cognitive impairment no dementia in community-dwelling older men and women

Running head: Anxiety and cognitive impairment

Keywords: anxiety, cognitive impairment, depression, elderly

Key points:

- In men, CIND was related to clinical/subclinical generalized anxiety disorder whether or not there was a comorbid depressive episode.
- In women, CIND was not associated with any clinical or subclinical anxiety disorders.
- The associations between anxiety disorders and poor global cognitive functioning follow different patterns according to sex, are not affected by the presence of depressive episodes and are restricted to generalized anxiety disorder.

Authors:
Olivier Potvin, Ph.D.; Carol Hudon, Ph.D.; Mélissa Dion, B.A.; Sébastien Grenier, Ph.D.; and Michel Préville, Ph.D.

Authors' affiliations:

Centre de recherche Hôpital Charles LeMoyne, Longueuil, Québec, Canada (Drs Potvin, Grenier, and Préville), Centre de recherche Université Laval Robert-Giffard, Québec, Québec, Canada (Drs Potvin and Hudon, and Ms Dion), Université de Sherbrooke, Sherbrooke, Québec, Canada (Drs Potvin, Grenier and Préville), Université Laval, Québec, Québec, Canada (Dr Hudon and Ms Dion)

Corresponding author:

Olivier Potvin
Centre de recherche Université Laval Robert-Giffard
2601 de la Canardière
Québec, QC,
Canada, G1J 2G3

Phone: 418 663-5000 ext. 6857
Fax: 418 663-5971
Email: Olivier.Potvin@crulrg.ulaval.ca

Acknowledgments:

This study was supported by research grants from the Canadian Institutes of Health Research (200403MOP) and the Fonds de recherche en santé du Québec (FRSQ; ref: 9854). Olivier Potvin is supported by a postdoctoral trainee award from the FRSQ and Alzheimer Society of Canada Partnership Program. Sébastien Grenier is supported by a postdoctoral trainee award from the FRSQ. Michel Préville is supported by a Senior Research Scientist Award from the FRSQ.

Total number of words: 3494

Total number of figures/tables: 5

SUMMARY

Background Anxiety symptoms are highly prevalent in elders with mild cognitive disorders, but little is known about the associations of specific anxiety disorders to mild cognitive disorders.

Objective To identify the clinical and subclinical anxiety disorders associated with cognitive impairment no dementia (CIND) and to determine whether these associations differ depending on sex and concomitant depressive episodes.

Method Participants constituted a random sample (N = 2414) of community-dwelling adults aged 65 to 96 years. The following clinical and subclinical DSM-IV anxiety disorders were identified with a semi-structured interview: specific phobia, social phobia, agoraphobia, panic disorder, obsessive-compulsive and generalized anxiety disorder (GAD). Major depressive episodes or minor depression (MDE/MD) were also determined based on the DSM-IV criteria. CIND cases were defined based on Mini-Mental State Examination cut-offs (15^{th} percentile) stratified for age, education and sex. Potentially confounding variables (age, education, MDE/MD, chronic diseases, and psychotropic drug use) were statistically controlled.

Results In men, after adjusting for confounding variables, CIND was associated with subclinical GAD (odds ratio: 4.93, 95% confidence interval: 1.84-13.23). Further analyses showed that in men, CIND was related to clinical/subclinical GAD whether MDE/MD was present (7.05, 1.88-26.43) or absent (9.33, 3.24-26.83). In women, CIND was not linked to any clinical or subclinical anxiety disorder.

Conclusions These results suggest that in community-dwelling elders, GAD is the main anxiety disorder associated with poor global cognitive functioning. Moreover, this association is modified by sex, but not by the presence of depressive episodes.

INTRODUCTION

It is well known that elders with mild cognitive disorders such as cognitive impairment no dementia (CIND) and mild cognitive impairment (MCI) are at high risk of developing dementia (Fisk *et al.*, 2003; Hsiung *et al.*, 2006; Palmer *et al.*, 2008; Palmer *et al.*, 2002; Tuokko *et al.*, 2003). The identification of modifiable risk factors of dementia for elders with mild cognitive disorders is now a primary issue as it is a necessary step to develop new interventions that could prevent or delay cognitive decline. Previous data indicated that anxiety symptoms are highly prevalent in elders with mild cognitive disorders (Forsell *et al.*, 2003; Lyketsos *et al.*, 2002) and suggested that neuropsychological profiles in elders with MCI may differ between those with low and high anxiety levels (Rozzini *et al.*, 2009). A longitudinal study showed that anxiety symptoms in elders with MCI could be an independent risk factor for dementia (Palmer *et al.*, 2007), but other results did not support this hypothesis (Devier *et al.*, 2009). Moreover, results from cross-sectional studies revealed inconsistencies on the relations between anxiety and cognitive functioning in elders. Some results demonstrated that high anxiety levels were negatively associated with cognitive performance (Bierman *et al.*, 2005; Wetherell *et al.*, 2002) while others suggested that co-morbid depressive symptoms account for this association (Biringer *et al.*, 2005). Another study showed that high anxiety level was related to poorer global cognitive functioning in non-depressed, but not in depressed, men whereas no link was observed between anxiety level and cognitive functioning in women (Paterniti *et al.*, 1999). Together, the results from cross-sectional studies indicated inconsistencies in the relations between anxiety symptoms and cognitive functioning and suggest that depressive symptoms and sex modify these relations.

The anxiety measures of all of the aforementioned studies consisted of brief dimensional anxiety scales. While this approach has the advantage to assess anxiety symptoms on a

continuum, it does not provide much information on the nature of the anxiety disorder and not much is known about the specific anxiety disorders related to cognitive impairment. One study indicated that a clinical sample of elders with generalized anxiety disorders (GAD) displayed poorer memory than a control group of elders without psychiatric disorders (Mantella *et al.*, 2007). We also observed, in a preliminary report, that anxiety disorders were significantly associated with CIND (Potvin *et al.*, 2009). However, their respective links with CIND are unknown and these results are limited for two reasons. First, manifestations of anxiety in older adults differ from that in younger adults and elders with significant anxiety symptoms are less likely to fully meet all DSM-IV criteria for anxiety disorders (Jeste *et al.*, 2005; Palmer *et al.*, 1997). It was demonstrated that elders with subclinical anxiety (i.e., anxiety symptoms not meeting all DSM criteria) do not differ in terms of disability, well-being, and medication use from elders with clinical anxiety disorders (i.e. anxiety symptoms that fully meet DSM criteria; de Beurs *et al.*, 1999). Thus, similarly to clinical anxiety, some subclinical anxiety disorders might be related to mild cognitive disorders. Second, anxiety disorders in elders often co-occur with depressive episodes (Beekman *et al.*, 2000; Kessler *et al.*, 2003) and the associations between high anxiety level and poor cognitive functioning might be modified by depressive symptoms (Paterniti *et al.*, 1999). Therefore, it is essential to examine whether the relations between anxiety disorders and CIND differ in presence and absence of comorbid depressive episodes.

The examination of anxiety disorders experienced by older men and women with CIND could provide a better comprehension of the psychiatric symptomatology that arises in these persons at high risk of dementia. It might also suggest which anxiety disorders in elders with mild cognitive disorders could particularly benefit from treatment. The first aim of the present study was to assess in older men and women the relations between CIND and clinical or subclinical

anxiety disorders. The second aim was to determine whether depressive episodes modify the relations between CIND and anxiety disorders. Thus, the associations between CIND and each clinical/subclinical anxiety disorder were assessed in the presence and in the absence of major depressive episodes/minor depression (MDE/MD).

METHOD

ESA study

Data from this cross-sectional study were collected through the *Étude sur la santé des aînés* (ESA study; in English, Study on elders' health), a population-based study conducted in 2005–2006 to estimate the prevalence rate of mood and anxiety disorders in the Province of Québec, Canada (Préville *et al.*, 2008). Participants constituted a sample (N = 2811) of community-dwelling adults aged 65 years or older and living in Québec. The sample was randomly recruited and stratified for geographical areas and administrative regions (for details see Préville *et al.*, 2008).

Data were collected through semi-structured in-home interviews conducted by trained research nurses. The respondents' mental health status according to DSM-IV criteria for anxiety and mood disorders (American Psychiatric Association, 2000) was measured using a computer-assisted questionnaire, the ESA-Q, developed by the research team. The ESA-Q comprises an adapted version of the 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 (Erdman *et al.*, 1992; Robins *et al.*, 1981; Wittchen *et al.*, 1991). Cognitive functioning was assessed with the Mini-Mental State Examination (MMSE; Folstein *et al.*, 1975). The interview was completed only with participants who scored 22 or higher on the MMSE (26 participants with a MMSE score <22 were excluded).

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) for a period covering one year before and after the interview. The RAMQ coverage is universal and all Québec residents are registered and entitled to medical services. Written 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. Medical records from the RAMQ were available for 2494 individuals and only these participants were included in the present study. The missing data from the RAMQ records relate to refusal of consent to provide medical records, moving outside Québec, or having additional drug insurance. Excluded participants with missing RAMQ data did not differ statistically from those included in the study in terms of mean MMSE score, prevalence of psychiatric diagnoses and of CIND (data not shown). In addition to the exclusion of participants with a MMSE score below 22, potential dementia cases were excluded using the RAMQ public medical records. Participants who received a diagnosis of dementia from a medical doctor and/or were taking an approved pharmacological treatment for dementia (memantine, donepezil, galantamine, or rivastigmine) during the year before or after the interview were excluded from the sample (n = 48). Nine participants were excluded because their education level was unknown and twenty-three others were excluded because they did not complete the interview on psychiatric symptoms. The final sample size comprised 2414 individuals.

Psychiatric disorders

Psychiatric disorders were identified for the 12-month period preceding the interview. The anxiety disorders investigated included specific phobia, social phobia, agoraphobia, panic

disorder, obsessive–compulsive disorders (OCD), and GAD. Clinical anxiety was defined as a syndrome meeting all DSM-IV criteria (American Psychiatric Association, 2000). Participants with at least one essential symptom of a DSM-IV anxiety disorder without fully meeting all criteria were considered as having subclinical anxiety. Minimal criteria for subclinical anxiety disorders are presented in Table 1. Exclusions criteria for clinical and subclinical anxiety disorders were identical (e.g. symptoms caused by a substance or a medical condition). The presence of MDE/MD was assessed based on the DSM-IV criteria and subjects reporting that depressive symptoms began after the loss of a loved one were not considered as having MDE/MD.

Definition of CIND

To identify individuals with CIND, quantitative criteria similar to that of studies from the Kungsholmen Project group was used (Palmer *et al.*, 2002). CIND cases were defined based on MMSE cut-offs stratified for age, education and sex. We adopted the criterion of a score below the 15^{th} percentile within each sex, age and education subgroup, which is equivalent to a score below one standard deviation in a normal distribution. Four categories of age (65-69, 70-74, 75-79, 80 and over) and three categories of education (primary or less, secondary, postsecondary) were used to allow sufficient numbers of participants in each group. Depending on the sex, age and education levels stratifications, the MMSE median varied between 27 and 30 while the criteria to be classified with CIND varied between scores below 25 and 28.

Potential confounders

Variables potentially associated with cognitive functioning and psychiatric symptoms were considered as potential confounders. These variables included age, education level, sex, psychotropic drug use, chronic diseases, and MDE/MD. Psychotropic drug use during the year before the interview was assessed by the RAMQ medical records and coded according to the

American Society of Health System Pharmacist (2001). The number of chronic diseases according to the International Classification of Diseases (ICD-10) was measured by asking participants if they had any of the following chronic health problems: high blood pressure, arthritis or rheumatism, heart diseases, eye diseases, backache or spinal problems, digestive problems, metabolic disorders, diabetes, anemia, hypercholesterolemia, asthma, emphysema, chronic bronchial diseases, liver diseases, kidney or urinary problems, skin diseases, schizophrenia and other forms of psychosis.

Statistical analysis

Data were weighted to ensure that the actual proportion of older adults in each region and in each geographical area was reflected in the analysis (for details see Préville *et al.*, 2008). All results refer to weighted data and frequencies are rounded to the nearest whole number.

Characteristic differences between men and women were evaluated with *t*-tests and chi-squares. Associations between anxiety disorders and CIND were first described by bivariate odds ratios (OR). Each anxiety disorder was coded as clinical, subclinical or absent. Then, adjusted ORs for age, education, the presence of MDE/MD, psychotropic drug use and the number of chronic diseases were assessed by logistic regression analyses. All covariables were coded as seen in Table 2. Associations between CIND and anxiety disorders with or without MDE/MD were assessed by adjusted ORs computed by logistic regressions. However, for these analyses, clinical and subclinical anxiety disorders were grouped and panic disorder and social phobia were not examined because their prevalence was too low (see Table 3). All statistical analyses were carried out separately for men and women and the alpha level was set at a two-tailed 5% divided by the number of regressions. Outliers and multicollinearity among predictors were verified and analyses were performed using SPSS software (version 16.0).

RESULTS

Table 2 shows the characteristics of the participants. Frequencies for education level and psychotropic drug user significantly differed between men and women. The most common education level was secondary for women and postsecondary for men. Mean age, number of chronic diseases and prevalence of MDE/MD and psychotropic drugs use were higher in women compared to men. The prevalence of clinical/subclinical anxiety disorders was of 19.3% and 31.5% of these cases had more than one disorder. The prevalence of psychotropic drugs use was higher ($p < 0.001$) in participants with clinical (43%) and subclinical anxiety (52%) disorders than in non-anxious participants (33%).

The procedure to identify CIND cases led to the identification of 83 men and 151 women with CIND. The mean MMSE scores were 25.4 (95% CI: 25.2-25.7) for women with CIND and 25.0 (24.7-25.2) for men with CIND. In those without CIND, the mean MMSE scores were 29.0 (28.9-29.1) for women and 28.7 (28.6-28.8) for men. When anxiety disorders were analyzed together, no significant association was observed between CIND and clinical (Men, OR: 2.69, CI: 0.88-8.18; Women, 1.24, 0.40-3.87) or subclinical (Men, 1.13, 0.57-2.22; Women, 1.06, 0.70-1.60) anxiety disorders and having more than one clinical/subclinical anxiety disorders was not significantly associated with CIND (Men, 0.65, 0.15-2.73; Women, 1.24, 0.69-2.25). These results remained the same when adjusted for potential confounders (results not shown). Table 3 indicates the prevalence of each clinical and subclinical anxiety disorder in participants with and without CIND. In men, CIND was significantly linked with subclinical GAD. Clinical GAD was also significantly associated with CIND, but not after adjusting for confounding variables. In

women, no significant association was found between CIND and any clinical or subclinical anxiety disorders.

The prevalence of MDE/MD was higher ($p < 0.001$) in participants with clinical (25%) and subclinical (19%) anxiety disorders compared to participants without anxiety (6%). Table 4 displays the associations between CIND and anxiety disorders with or without comorbid MDE/MD. In men, CIND was significantly associated with GAD in either the absence or the presence of MDE/MD. In women, CIND was not significantly linked with any of the anxiety disorders with or without MDE/MD.

DISCUSSION

The first aim of the present study was to assess the relations between CIND and subclinical/clinical anxiety disorders. The results revealed that in men, CIND was associated with subclinical GAD, but not with any other anxiety disorders. The second aim was to verify whether depressive episodes modify the relations between anxiety disorders and CIND. In men, CIND was linked to clinical/subclinical GAD whether or not there was comorbid MDE/MD. In women, CIND was not significantly associated with any clinical/subclinical anxiety disorder and MDE/MD did not modify these associations. Together, these results provide important precisions about the clinical/subclinical anxiety disorders experienced by elders with mild cognitive disorders.

Previous studies assessing the links between anxiety and cognitive functioning suggested sex differences and generated conflicting results about the influence of depressive symptoms on these associations (Biringer *et al.*, 2005; Paterniti *et al.*, 1999). Biringer *et al.* (2005) observed that high anxiety level was related to cognitive functioning only when it was occurring with

depressive symptoms whereas Paterniti *et al.* (1999) found that high anxiety level was associated with poor global cognitive functioning in non-depressed, but not in depressed, men. Similarly to Paterniti *et al.*, our results showed that the relations between anxiety disorders and poor cognitive functioning differ between men and women. However, unlike Paterniti *et al.*'s findings, the present study indicated that some anxiety symptoms were linked with poor global cognitive functioning in men when these symptoms occur with or without comorbid MDE/MD. Moreover, Paterniti *et al*. reported a link between high anxiety level and poor cognitive impairment in women prior to the adjustment for psychotropic drug use. In the present study, women were using psychotropic drugs in a higher proportion than men, but no significant OR was observed in women even before adjusting for potential confounders.

The present results suggest that GAD is the main type of anxiety disorder linked with CIND. These results differ from those with younger adults showing that social phobia, panic disorders, and OCD, but not specific phobia or GAD, were impaired in episodic memory and executive functioning (Airaksinen *et al.*, 2005). Our results are coherent with those in older adults showing that elders with GAD displayed memory deficits (Mantella *et al.*, 2007). Altogether, these results suggest that cognitive functioning in individuals with anxiety may differ between older and younger adults. Our results also suggest that subclinical GAD in elders should not be overlooked since it can co-occur with cognitive deficits and its prevalence is higher than that of clinical GAD. Moreover, while a significant portion of older men with GAD had CIND, many others did not. Factors associated with cognitive deficits in late-life GAD should be investigated. It is possible that age of onset of anxiety symptoms could modify the relations between CIND and anxiety disorders. A previous study showed that health characteristics of late-life GAD differ according to the age at onset of symptoms (Le Roux *et al.*, 2005). Le Roux et *al.* (2005) observed that elders with late onset GAD (50 years and over) had less GAD symptom severity, less

psychiatric comorbidity, less psychotropic drug use, but more limitations caused by physical problems compared to elders with early onset GAD. However, no difference was found in MMSE scores between late and early GAD onset. Studies using more elaborated cognitive assessment should investigate this hypothesis.

The present results showed that while CIND was link to GAD in men when clinical and subclinical syndromes were grouped, it was not significantly associated with clinical GAD alone. This is likely to be due to a lack a power since the prevalence of clinical GAD in men was relatively low (less than 1% in non-CIND). This is also likely to be the case for clinical specific phobia. Similarly to clinical GAD, clinical specific phobia in men had a high OR, but it was not significant and the prevalence of this anxiety disorder in men was small.

Since the present study is cross-sectional, it is unknown whether the anxiety disorders associated with CIND preceded, accompanied, or followed the onset of cognitive impairment. So far, the few studies that evaluated whether anxiety was a risk factor for cognitive decline used lists of symptoms or brief dimensional anxiety scales and their results did not provide a clear answer. These results suggested that anxiety symptoms are a risk factor for Alzheimer's disease in elders with MCI in population-based (Palmer *et al.*, 2007), but not in clinical (Devier *et al.*, 2009) samples. In elders with normal cognitive functioning, three studies using different approaches indicated conflicting results (Bierman *et al.*, 2008; Gallacher *et al.*, 2009; Sinoff and Werner, 2003). A study with a clinical sample showed that high level of anxiety predicted cognitive decline (Sinoff and Werner, 2003). Population-based studies indicated that in men, a high level of anxiety was associated with the development of CIND, but not dementia, (Gallacher *et al.*, 2009). Moreover, results from the Longitudinal Aging Study Amsterdam found that anxiety level was not predictive of cognitive performance on four assessments in a 9-year follow-up (Bierman *et al.*, 2008) and that the cross-sectional association between high level of anxiety

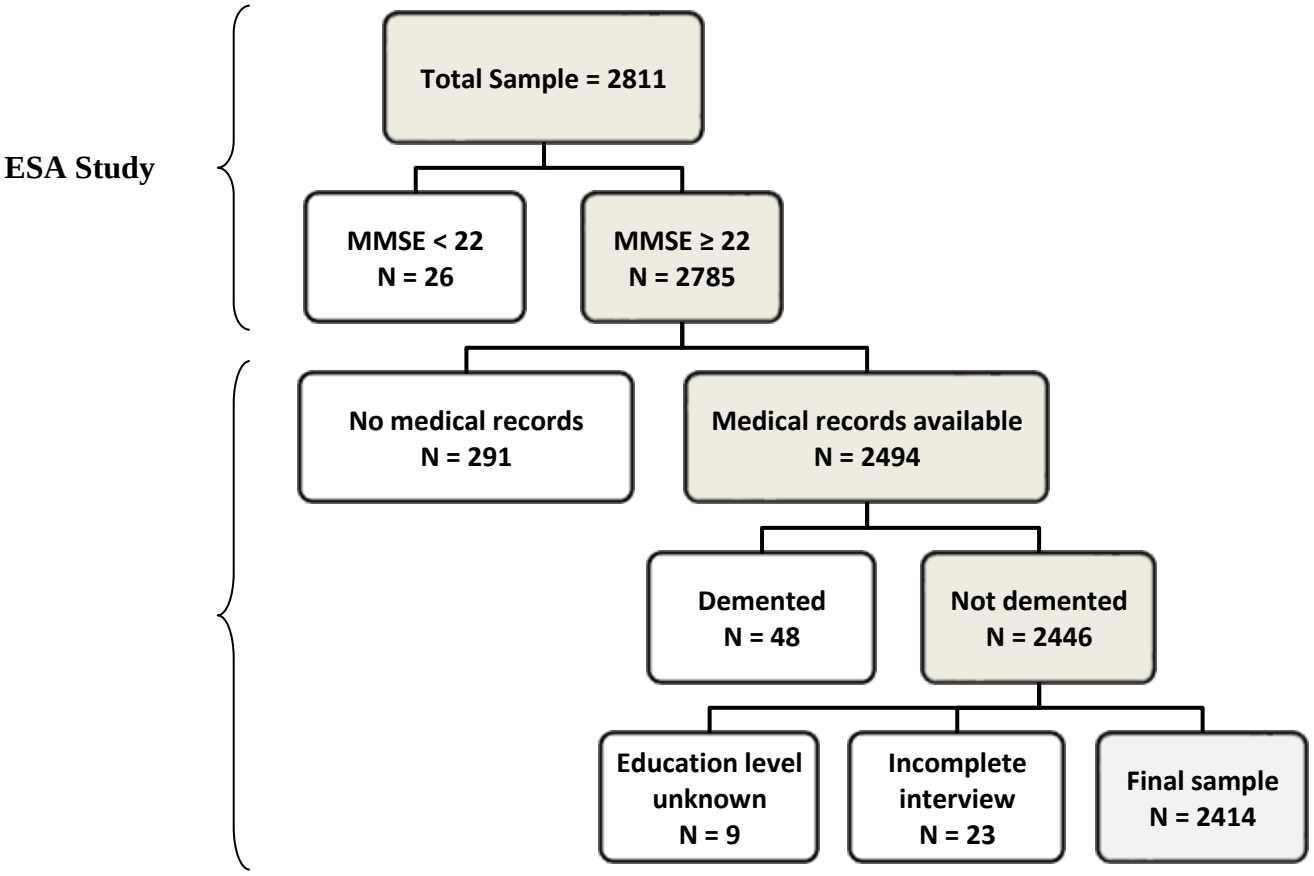
and poor cognitive functioning is temporary (Bierman *et al.*, 2005; Bierman *et al.*, 2008). Finally, most of these studies did not investigate whether anxiety had different outcomes for men/women. According to our results, future longitudinal studies could benefit from investigating the specific anxiety disorders associated with cognitive decline as well as the influence of sex in these relations.

This study has several strengths and original contributions. First, it used a large representative sample of community-dwelling elders randomly recruited. Second, unlike other population studies that used a dimensional measure of anxiety, the present study examined separately six anxiety disorders giving more precisions about the specific relation of each on cognitive difficulties. In addition, the fact that men and women were analyzed separately showed different patterns of results that should be considered for assessing the links between anxiety and cognition. Finally, many potential confounders were taken into account: chronic diseases, psychotropic drug use, MDE/MD, age, and education level. There are also some limitations to our study. First, despite two procedures to exclude potential dementia cases (MMSE score below 22 and dementia according to medical record), a few cases of dementia could remain in the sample. However, it is likely that most dementia cases were not in the study since these procedures excluded 2.6% of the initial sample while the prevalence of dementia in community-dwelling Canadians aged 65 years and over is estimated at 2.8% (Graham *et al.*, 1997). Second, the participants' cognitive functioning was measured using the MMSE, which is a screening instrument and, therefore, is somewhat limited in detecting mild cognitive difficulties. However, this limitation is minimized by the fact that we used a normative approach based on age, education and sex to identify CIND, which is superior to using an absolute cut-off. Despite this procedure, the prevalence of CIND appears conservative (9.7% of the study sample) since it was established that the age-standardized prevalence of CIND in community-dwelling Canadians

aged 65 years and over is 15.8% (Graham et al., 1997). Thus, the associations observed between CIND and anxiety disorders could have been underestimated. Third, since psychiatric symptoms were assessed for a 12-month period, it is possible that individuals with CIND, especially those with memory deficits, have underestimated their psychiatric symptoms. Therefore, the associations observed between CIND and subclinical anxiety could have been underestimated. Fourth, the cause of the anxiety symptoms remained unknown and since it is a cross-sectional the study, it was not possible to verify whether CIND occurred before or after the onset of anxiety symptoms. Thus, it is unknown whether anxiety was triggered by cognitive symptoms or was a prodrome of cognitive decline.

In summary, the present results clarify the associations between mild cognitive disorders and clinical/subclinical anxiety disorders. In men, CIND was found to be associated with clinical/subclinical GAD with or without MDE/MD. In women, CIND was not linked to any clinical or subclinical anxiety disorder. At last, these findings suggest that the associations between anxiety disorders and cognitive functioning follow different patterns according to sex, are not affected by the presence of depressive episodes and are restricted to GAD.

Figure 1. Flow Chart of the ESA Study and the Study Sample Enrollment



Notes. White and gray shapes represent exclusion and inclusion criteria, respectively.

Study Sample

Table 1. Minimal criteria for subclinical anxiety disorders

Disorders	Criteria
Panic	A discrete period of intense fear or discomfort, in which one (or more) symptom for panic attack developed abruptly.
Agoraphobia	Anxiety about being in places or situations from which escape might be difficult (or embarrassing) or in which help may not be available in the event of having an unexpected or situationally predisposed panic-like symptoms.
Social phobia	Fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. The individual fears that he or she will act in a way that will be humiliating or embarrassing.
Specific phobia	Fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation.
Generalized anxiety	Excessive anxiety and worry occurring more days than not for at least one month.
Obsessive-compulsive	Either 1) recurrent and persistent thoughts, impulses, or image that are experienced, at some time during the disturbance, as intrusive and inappropriate and that cause anxiety or distress, or 2) repetitive behaviors or mental acts that the person feels driven to perform in responses to an obsession, or according to rules that must be applied rigidly.

Table 2. Characteristics of participants

Characteristic (Mean ±SD or %)	Women (*n* = 1387)	Men (*n* = 1027)	*p*[a]
Age	74.4 ±6.3	72.8 ±5.5	< 0.001
Education level			
Primary or less	24.3	19.6	< 0.001
Secondary	47.0	34.4	
Postsecondary	28.7	46.0	
Psychotropic drugs users	42.7	27.3	< 0.001
Number of chronic diseases	3.5 ±2.1	3.0 ±2.0	< 0.001
Presence of depressive episodes	11.0	5.6	< 0.001

a. *p* value from *t*-tests or chi-squares.

Table 3. Clinical and subclinical anxiety disorders in elders with CIND (*n* = 2414)

Anxiety disorders	Non-CIND *n* (%)	CIND *n* (%)	OR (95% CI)	Adjusted[a] OR (95% CI)	*p*[b]
Women					
Panic					
Clinical	13 (1.0)	2 (1.5)	1.45 (0.35-6.05)	1.57 (0.37-6.59)	0.54
Subclinical	14 (1.1)	2 (1.6)	1.44 (0.36-5.79)	1.51 (0.37-6.11)	0.56
Agoraphobia					
Clinical	10 (0.8)	1 (0.6)	0.70 (0.08-5.97)	0.74 (0.09-6.45)	0.79
Subclinical	80 (6.5)	5 (3.0)	0.45 (0.17-1.16)	0.47 (0.18-1.22)	0.12
Specific phobia					
Clinical	16 (1.3)	2 (1.5)	1.20 (0.30-4.82)	1.27 (0.31-5.18)	0.74
Subclinical	149 (12.0)	22 (14.8)	1.28 (0.79-2.07)	1.33 (0.82-2.17)	0.25
Social phobia					
Clinical	2 (0.2)	1 (0.5)	2.62 (0.21-33.42)	2.47 (0.19-31.81)	0.49
Subclinical	22 (1.8)	4 (2.4)	1.36 (0.44-4.19)	1.48 (0.48-4.59)	0.50
Generalized anxiety					
Clinical	7 (0.6)	1 (0.5)	0.89 (0.08-9.47)	1.01 (0.09-11.02)	0.99
Subclinical	69 (5.6)	9 (5.9)	1.06 (0.52-2.17)	1.12 (0.53-2.38)	0.76
Obsessive-compulsive					
Clinical	9 (0.7)	1 (0.4)	0.56 (0.04-7.17)	0.62 (0.05-7.98)	0.71
Subclinical	33 (2.7)	5 (3.0)	1.13 (0.42-3.06)	1.16 (0.43-3.15)	0.77
Men					
Panic					
Clinical	3 (0.3)	1 (1.2)	3.65 (0.37-35.97)	2.89 (0.27-30.73)	0.38
Subclinical	3 (0.3)	0 (0.0)	-	-	-
Agoraphobia					
Clinical	1 (0.1)	0 (0.0)	-	-	-
Subclinical	51 (5.4)	1 (1.3)	0.23 (0.04-1.57)	0.23 (0.03-1.57)	0.13
Specific phobia					
Clinical	7 (0.8)	3 (3.2)	3.90 (0.94-16.14)	3.93 (0.88-17.50)	0.07
Subclinical	52 (5.6)	1 (0.7)	0.12 (0.01-1.58)	0.12 (0.01-1.65)	0.11
Social phobia					
Clinical	0 (0.0)	0 (0.0)	-	-	-
Subclinical	10 (1.1)	1 (1.2)	1.17 (0.15-8.94)	1.43 (0.18-11.40)	0.74
Generalized anxiety					
Clinical	2 (0.3)	2 (2.9)	12.40 (2.05-75.01)	8.33 (1.22-56.80)	0.03
Subclinical	17 (1.8)	7 (8.7)	5.50 (2.22-13.61)	4.93 (1.84-13.23)	0.002
Obsessive-compulsive					
Clinical	14 (1.5)	0 (0.0)	-	-	-
Subclinical	15 (1.6)	2 (1.9)	1.21 (0.23-6.29)	1.04 (0.19-5.60)	0.96

CI, confidence interval; CIND, cognitive impairment no dementia; Non-CIND, normal cognitive functioning, OR: odds ratio.

a. ORs were adjusted for age, education, psychotropic drug use, depressive episodes, and chronic diseases.

b. The critical *p* value after correction for the number of regressions is 0.008.

Table 4. Anxiety disorders with or without depressive episodes in elders with CIND (*n* = 2414)

Anxiety disorders[a]	Women				Men			
	Non-CIND *n* (%)	CIND *n* (%)	Adjusted[b] OR (95% CI)	*p*[c]	Non-CIND *n* (%)	CIND *n* (%)	Adjusted[b] OR (95% CI)	*p*[c]
Agoraphobia								
MDE/MD	16 (1.3)	2 (1.1)	0.84 (0.17-4.23)	0.83	4 (0.4)	0 (0.0)	-	-
No MDE/MD	74 (6.0)	4 (2.5)	0.41 (0.14-1.17)	0.10	48 (5.1)	1 (1.3)	0.29 (0.04-1.98)	0.21
Specific phobia								
MDE/MD	31 (2.5)	4 (2.9)	1.30 (0.46-3.67)	0.62	6 (0.7)	2 (2.1)	3.96 (0.68-23.14)	0.13
No MDE/MD	134 (10.8)	20 (13.4)	1.29 (0.77-2.14)	0.33	54 (5.7)	2 (1.8)	0.41 (0.08-2.13)	0.29
GAD								
MDE/MD	34 (2.7)	5 (3.4)	1.26 (0.48-3.31)	0.63	7 (0.8)	4 (4.3)	7.05 (1.88-26.43)	0.004
No MDE/MD	43 (3.5)	5 (3.0)	0.87 (0.32-2.32)	0.77	12 (1.2)	6 (7.2)	9.33 (3.24-26.83)	< 0.001
OCD								
MDE/MD	10 (0.8)	2 (1.4)	1.76 (0.38-8.10)	0.47	4 (0.4)	0 (0.0)	-	-
No MDE/MD	33 (2.6)	3 (2.1)	0.79 (0.24-2.56)	0.69	25 (2.6)	2 (1.9)	0.78 (0.15-4.02)	0.77

CI, confidence interval; CIND, cognitive impairment no dementia; Non-CIND, normal cognitive functioning; OR, odds ratio; GAD, generalized anxiety disorder; MD, minor depression ; MDE, major depressive episode; OCD, obsessive-compulsive disorder.
a. Anxiety disorders include clinical and subclinical disorders.
b. ORs were adjusted for age, education, psychotropic drug use, and chronic diseases.
c. The critical *p* value after correction for the number of regressions is 0.013.

REFERENCES

Airaksinen E, Larsson M and Forsell Y. 2005. Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. *J Psychiatr Res* **39**, 207-214.

American Psychiatric Association. 2000. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR)*. Washington DC: American Psychiatric Publishing, Inc.

American Society of Health System Pharmacist (2001). AHFS drug information.

Beekman AT, de Beurs E, van Balkom AJ *et al.* 2000. Anxiety and depression in later life: Co-occurrence and communality of risk factors. *Am J Psychiatry* **157**, 89-95.

Bierman EJ, Comijs HC, Jonker C and Beekman AT. 2005. Effects of anxiety versus depression on cognition in later life. *Am J Geriatr Psychiatry* **13**, 686-693.

Bierman EJ, Comijs HC, Rijmen F *et al.* 2008. Anxiety symptoms and cognitive performance in later life: results from the longitudinal aging study Amsterdam. *Aging Ment Health* **12**, 517-523.

Biringer E, Mykletun A, Dahl AA *et al.* 2005. The association between depression, anxiety, and cognitive function in the elderly general population--the Hordaland Health Study. *Int J Geriatr Psychiatry* **20**, 989-997.

de Beurs E, Beekman AT, van Balkom AJ *et al.* 1999. Consequences of anxiety in older persons: its effect on disability, well-being and use of health services. *Psychol Med* **29**, 583-593.

Devier DJ, Pelton GH, Tabert MH *et al.* 2009. The impact of anxiety on conversion from mild cognitive impairment to Alzheimer's disease. *Int J Geriatr Psychiatry*.

Erdman HP, Klein MH, Greist JH *et al.* 1992. A comparison of two computer-administered versions of the NIMH Diagnostic Interview Schedule. *J Psychiatr Res* **26**, 85-95.

Fisk JD, Merry HR and Rockwood K. 2003. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology* **61**, 1179-1184.

Folstein MF, Folstein SE and McHugh PR. 1975. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.

Forsell Y, Palmer K and Fratiglioni L. 2003. Psychiatric symptoms/syndromes in elderly persons with mild cognitive impairment. Data from a cross-sectional study. *Acta Neurol Scand Suppl* **179**, 25-28.

Gallacher J, Bayer A, Fish M *et al.* 2009. Does anxiety affect risk of dementia? Findings from the Caerphilly Prospective Study. *Psychosom Med* **71**, 659-666.

Graham JE, Rockwood K, Beattie BL *et al.* 1997. Prevalence and severity of cognitive impairment with and without dementia in an elderly population. *Lancet* **349**, 1793-1796.

Hsiung GY, Donald A, Grand J *et al.* 2006. Outcomes of cognitively impaired not demented at 2 years in the Canadian Cohort Study of Cognitive Impairment and Related Dementias. *Dement Geriatr Cogn Disord* **22**, 413-420.

Jeste DV, Blazer DG and First M. 2005. Aging-related diagnostic variations: need for diagnostic criteria appropriate for elderly psychiatric patients. *Biol Psychiatry* **58**, 265-271.

Kessler RC, Berglund P, Demler O *et al.* 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA* **289**, 3095-3105.

Le Roux H, Gatz M and Wetherell JL. 2005. Age at onset of generalized anxiety disorder in older adults. *Am J Geriatr Psychiatry* **13**, 23-30.

Lyketsos CG, Lopez O, Jones B *et al.* 2002. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA* **288**, 1475-1483.

Mantella RC, Butters MA, Dew MA *et al.* 2007. Cognitive impairment in late-life generalized anxiety disorder. *Am J Geriatr Psychiatry* **15**, 673-679.

Palmer BW, Jeste DV and Sheikh JI. 1997. Anxiety disorders in the elderly: DSM-IV and other barriers to diagnosis and treatment. *J Affect Disord* **46**, 183-190.

Palmer K, Backman L, Winblad B and Fratiglioni L. 2008. Mild cognitive impairment in the general population: occurrence and progression to Alzheimer disease. *Am J Geriatr Psychiatry* **16**, 603-611.

Palmer K, Berger AK, Monastero R *et al.* 2007. Predictors of progression from mild cognitive impairment to Alzheimer disease. *Neurology* **68**, 1596-1602.

Palmer K, Wang HX, Backman L *et al.* 2002. Differential evolution of cognitive impairment in nondemented older persons: results from the Kungsholmen Project. *Am J Psychiatry* **159**, 436-442.

Paterniti S, Dufouil C, Bisserbe JC and Alperovitch A. 1999. Anxiety, depression, psychotropic drug use and cognitive impairment. *Psychol Med* **29**, 421-428.

Potvin O, Hudon C, Forget H *et al.* (2009). Prevalence of psychiatric disorders with cognitive impairment no dementia (CIND) in a community-dwelling sample of elderly men and women. In *Int Psychogeriatr Association Congress*. Montréal, Canada.

Préville M, Boyer R, Grenier S *et al.* 2008. The epidemiology of psychiatric disorders in Quebec's older adult population. *Can J Psychiatry* **53**, 822-832.

Robins LN, Helzer JE, Croughan J and Ratcliff KS. 1981. National Institute of Mental Health Diagnostic Interview Schedule. Its history, characteristics, and validity. *Arch Gen Psychiatry* **38**, 381-389.

Rozzini L, Chilovi BV, Peli M *et al.* 2009. Anxiety symptoms in mild cognitive impairment. *Int J Geriatr Psychiatry* **24**, 300-305.

Sinoff G and Werner P. 2003. Anxiety disorder and accompanying subjective memory loss in the elderly as a predictor of future cognitive decline. *Int J Geriatr Psychiatry* **18**, 951-959.

Tuokko H, Frerichs R, Graham J *et al.* 2003. Five-year follow-up of cognitive impairment with no dementia. *Arch Neurol* **60**, 577-582.

Wetherell JL, Reynolds CA, Gatz M and Pedersen NL. 2002. Anxiety, cognitive performance, and cognitive decline in normal aging. *J Gerontol B Psychol Sci Soc Sci* **57**, P246-255.

Wittchen HU, Robins LN, Cottler LB *et al.* 1991. Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *Br J Psychiatry* **159**, 645-653, 658.