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► **To cite this version:**

Archana Singh-Manoux, Aline Dugravot, Joel Ankri, Hermann Nabi, Claudine Berr, et al.. Subjective cognitive complaints and mortality: does the type of complaint matter?. *Journal of Psychiatric Research*, Elsevier, 2013, 48 (1), pp.73-8. 10.1016/j.jpsychires.2013.10.005 . inserm-01152603

HAL Id: inserm-01152603

<https://www.hal.inserm.fr/inserm-01152603>

Submitted on 18 May 2015

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Subjective cognitive complaints and mortality: does the type of complaint matter?

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Word count: text: 3117; abstract: 204.

Number of figures: 0, tables: 3, and supplemental information: 0

Key words: subjective cognitive complaints, depression, mortality, dementia, mild cognitive impairment, memory

Abstract

Middle-aged subjects report subjective cognitive complaints (SCCs) but whether these are meaningfully related to health remains unknown. We examined the association between SCCs, both amnesic and non-amnesic, and mortality in a middle-aged population after taking into account the role of depression. 15510 participants (26.2% women), mean age 57.9 years in 2002, from the French GAZEL study provided data on 3 measures of SCCs: memory complaints, cognitive symptoms (forgetfulness, difficulties in recalling memories, retaining new information, mental calculation, in language, and orientation) and whether they sought medical advice for SCCs. All-cause mortality was assessed between 2002 and 2012. Over the follow-up 56.3% participants reported memory problems, 62.6% cognitive complaints, 22.3% sought medical advice and 651 died. All SCCs were strongly associated (odds ratio 2.08 to 6.35) with depression which was itself associated with greater mortality (HR=1.77, 95% CI: 1.50, 2.09). In analyses adjusted for age, sex, education, marital status and depression difficulty in mental calculation (HR=1.30, 95% CI: 1.08, 1.60) and seeking medical advice for cognitive symptoms (HR=1.41, 95% CI: 1.18, 1.68) were significantly associated with mortality, while memory complaints did not carry increased risk (HR=0.93, 95% CI: 0.79, 1.09). All SCCs were strongly associated with depression but not all carried excess risk of mortality.

Introduction

Subjective cognitive complaints (SCCs) have been widely investigated in recent years, the underlying hypothesis being that they are informative of the cognitive status of individuals and anticipate their future cognitive trajectory. They are seen by some to be an essential component of the diagnostic entity 'mild cognitive impairment' (MCI)(Petersen 2004;Portet et al. 2006;Winblad et al. 2004), an intermediate stage between normal ageing and dementia. However, the evidence for the association between SCCs and performance on neuropsychological tests is far from consistent. Early studies, mostly small scale and in clinical settings, did not find an association between SCCs and performance on cognitive tests.(Jonker et al. 2000;Reid and MacLulich 2006) Subsequent community-based studies showed some predictive value of SCCs for cognitive decline and dementia.(Jonker, Geerlings, & Schmand 2000;Reid & MacLulich 2006;Reisberg et al. 2008) However, their usefulness as criteria for MCI has been questioned because of their high prevalence and their strong association with psychological factors (Slavin et al. 2010), most importantly depression.(Bolla et al. 1991;de Groot et al. 2001;Mol et al. 2006;O'Connor et al. 1990;Schmand et al. 1997)

There is consistent evidence that SCCs increase with age.(Jonker, Geerlings, & Schmand 2000;Mitchell 2008;Reid & MacLulich 2006) Several recent papers have also demonstrated neuro-radiological correlates of SCC,(Reisberg, Prichep, Mosconi, John, Glodzik-Sobanska, Boksay, Monteiro, Torossian, Vedvyas, Ashraf, Jamil, & de Leon 2008;Stewart et al. 2008;Stewart et al. 2011;van Norden et al. 2008) with one interpretation of these findings being that SCCs represent a more realistic appraisal of brain function than measured cognition.(Stewart, Dufouil, Godin, Ritchie, Maillard, Delcroix, Crivello, Mazoyer, & Tzourio 2008;Stewart, Godin, Crivello, Maillard, Mazoyer, Tzourio, & Dufouil 2011) There is emerging evidence of associations with mortality (Ayalon 2008) and health care expenditure.(Waldorff et al. 2009) However, much research has

focused on memory complaints,(Mol, van Boxtel, Willems, & Jolles 2006;Pearman and Storandt 2004;Schmand, Jonker, Geerlings, & Lindeboom 1997) often including only a single question on perceived forgetfulness.(Clarnette et al. 2001;Mol, van Boxtel, Willems, & Jolles 2006;Paradise et al. 2011;Reid & MacLulich 2006;St and Montgomery 2002) Furthermore, even though SCCs are not confined to old age, much of the evidence comes from elderly subjects and it remains unclear if SCCs are associated with health outcomes in non-elderly populations. We examined the association between SCCs, including amnesic and non-amnesic complaints, and subsequent mortality in a middle aged cohort. Another major objective, given the strong associations between SCCs and depression,(Bolla, Lindgren, Bonaccorsy, & Bleecker 1991;de Groot, de Leeuw, Oudkerk, Hofman, Jolles, & Breteler 2001;Mol, van Boxtel, Willems, & Jolles 2006;O'Connor, Pollitt, Roth, Brook, & Reiss 1990;Schmand, Jonker, Geerlings, & Lindeboom 1997) was to assess the role of depression in this association.

Materials & Methods

Data are drawn from the GAZEL cohort, established in 1989 on employees of the French national gas and electricity company called EDF-GDF.(Goldberg et al. 2007) At baseline, 20625 employees (27% women) aged 35-50 consented to participate. The study design consists of an annual questionnaire on health, lifestyle, occupational factors and life events. The study is linked to national registers for mortality follow-up. Informed consent was obtained from all participants and the study received ethical approval from the French national ethics committee (*Commission nationale de l'informatique et des libertés* (CNIL)).

The SCC battery was included in the annual questionnaire used in the study, starting in 2002, and was composed of three parts, with response to all items being “yes” or “no”. The first part comprised a single-item assessment of memory complaint. The second part was a checklist of 6

symptoms: forgetfulness in daily activities (shopping, use of electrical appliances, etc.), difficulty recalling memories, difficulty in retaining simple new information, difficulty in mental calculation (compared to previously), language difficulties (finding words, names of objects) and difficulties of orientation in the city, the street, etc. The symptoms in the checklist were analyzed individually and summed into a score to assess whether greater numbers of symptoms were associated with higher risk of mortality. The score was categorized as 0, 1-3 and 4-6 symptoms to take possible non-linearity in associations into account. The final part of the battery was a single-item question where participants were asked whether they had consulted a physician about their symptoms.

Mortality data on all participants were obtained annually from EDF–GDF as it pays out retirement benefits. In the analysis we included deaths between 1 January 2003 and 31st December 2012.

Covariates

Besides age, sex, and marital status (married/cohabiting vs. other) we also included education, categorized as low (primary school or less, school leaving age approximately 11 years), intermediate (professional qualifications), and secondary school degree (the *baccalauréat* taken at around 18 years of age) and university degree.

Depressive symptoms were measured using the Center for Epidemiologic Studies Depression (CES-D) scale in 2002, 2005 and 2008. The CES-D, a widely used and validated instrument, is a 20-item self-report questionnaire designed to measure depressive symptoms in community studies.

Participants are asked to score the frequency of occurrence of 20 symptoms during the previous week on a four point scale (0 = "less than one day", 1 = "1-2 days", 2 = "3-4 days" and 3 = "5-7 days"). These items are summed to yield a total score between 0 and 60 with participants scoring ≥ 16 defined as having CES-D depressive symptoms.(Radloff L 1997)

Statistical analysis

Depression was assessed three times over the follow-up in the years 2002, 2005 and 2008. In order to ensure that concurrent measures of depression and SCCs could be considered in the analysis we created 3 time-windows: 2002-2004, 2005-2007, 2008-2012. Data on SCCs were available yearly but were analyzed using the same time-windows as depression. Once participants reported an SCC in a time window, they were considered to be 'exposed', i.e., to have the complaint in that time window and subsequent time windows (the end of the follow-up) or death.

We first used logistic regression to examine the association between SCCs (in any of the three time windows) and depression (in any of the time windows) in analysis adjusted for age, sex, education and marital status. We then used Cox proportional regression analysis with age as the time scale to estimate the Hazard Ratios (HR) and their 95% confidence intervals (CI) for the association between SCC and mortality. There were no sex differences in the association between complaints and mortality, p for interaction ranged from 0.11 to 0.98, leading us to combine men and women in the analysis. The first model included adjustment for sex and year of birth (Model 1).

Subsequently, marital status, education and depression were added to Model 1 one by one and then simultaneously. We also examined the p values in the final models associated with the 8 distinct components of the SCC battery (memory problems, 6 symptoms, and consulting a physician) after correction for multiple testing using the Holm method.(Aickin and Gensler 1996). Note that SCCs and all covariates were analyzed as time-dependent variables, with the three time windows described above. In sensitivity analyses, we replaced the dichotomous CES-D variable with the continuous measure to better capture lower levels of depression in the models.

The proportional hazard assumptions for Cox regression models, tested using Schoenfeld residuals, were found not to be violated. Statistical tests were 2-sided, a P -value of less than 0.05

was considered statistically significant. The analysis was performed using the statistical software STATA 10, StataCorp LP, Texas, USA.

Results

The GAZEL cohort comprised 20,625 persons at study inception in 1989. Our analyses on 15,510 persons (26.2% women) are based on measures introduced to the study in 2002 when the mean age (standard deviation) of participants was 57.9 (3.5); 651 died over the 10 year follow-up. Table 1 shows that women were more likely to report complaints: 65.5% women compared to 53.1% men reported memory problems and 25.5% women reported seeking medical advice about their cognitive symptoms compared to 21.1% men.

Table 2 further describes the sample as a function of SCCs. Those with cognitive complaints were somewhat older, the difference being small albeit statistically significant due to the large sample size, and more of them were not married or cohabiting. The prevalence of depression in those with SCCs was approximately double that in those without complaints, for example over the total follow-up 49.3% of those with memory complaints reported depression compared to 25.2% in those without memory complaints.

The association between SCCs and depression ($\text{CES-D} \geq 16$) in analyses adjusted for covariates is shown in Table 3. Among those with SCCs, the odds ratio for depression were between 2.11; 95% Confidence Interval (CI): 1.97, 2.27 (for complaint of “difficulty recalling memories”) and 6.44 times higher for those with over four cognitive complaints (95% CI: 5.78, 7.19). The associations with total symptom score and depression were somewhat stronger (1-3 symptoms OR= 2.64, 95% CI: 2.44, 2.85); 4-6 symptoms OR=7.46, 95% CI: 6.57, 8.47) when both measures were drawn from

the same time window. Depression (CES-D \geq 16) was associated with greater mortality (HR=1.77, 95% CI: 1.50, 2.09) in analysis adjusted for age, sex, education and marital status.

Table 4 presents the association of SCCs with mortality. In analyses adjusted for age and sex (Model 1), the hazard ratio for mortality was higher in those who reported difficulty retaining simple new information (HR=1.31, 95% CI: 1.11, 1.54), difficulty in mental calculation (HR=1.52, 95% CI: 1.25, 1.84), difficulties of orientation (HR=1.45, 95% CI: 1.09, 1.91), and consulting their physician (HR=1.63, 95% CI: 1.35, 1.98). Adjustment for marital status and education did not much change these associations. However, adjustment for depression attenuated the statistically significant associations between SCC and mortality between 28% and 48%. In fully adjusted models only difficulty in mental calculation and seeking medical advice about cognitive complaints remaining significantly associated with higher risk of mortality, the p-value adjusted for multiple testing for these two SCCs were 0.04 and 0.002 respectively. Memory complaints and high symptoms score were not associated with increased risk of mortality. Sensitivity analysis using the continuous rather than a binary measure of CES-D depression also showed difficulty in mental calculation (HR=1.23, 95% CI: 1.01, 1.51) and consulting a physician about cognitive complaints (HR=1.34, 95% CI: 1.12, 1.61) to be associated with higher mortality risk.

Discussion

We examined a range of subjective cognitive complaints for their association with depression and mortality. Our results show high prevalence of SCCs, particularly memory complaints, in this middle-aged population. All SCCs, both amnesic and non-amnesic, were very strongly associated with CESD-depression. However, only difficulty in mental calculation and seeking medical advice in relation to cognitive symptoms predicted mortality independently of depression. Memory

complaints, assessed in various ways in our study, were not associated with mortality. These results suggest that not all types of cognitive complaints carry risk for mortality. Our data also show no effect of complaint load, in terms of the number of SCCs on mortality risk although number of complaints had a dose-response association with CESD-depression.

Memory complaints were more frequently endorsed in our study than non-memory complaints, as has been reported previously.(Slavin, Brodaty, Kochan, Crawford, Trollor, Draper, & Sachdev 2010) Over 50% of participants reported memory complaints over the follow-up. Memory worries may be part of normal ageing even though they do not carry mortality risk. Besides memory, the other complaints that did not have an association with mortality were language and orientation difficulties. However, complaints regarding difficulty in mental calculation and seeking medical advice about complaints was associated with mortality even after adjustment for depression. Acalculia has been shown to be a hallmark of dementia, evident in early phases of the disease.(Martin et al. 2003;Remy et al. 2004) Mental calculation is a complex task and it is possible that it is good at discriminating those with neurocognitive problems atypical for their age. These findings warrant further attention and replication; if confirmed, our findings suggest that difficulties in calculation may be useful in identifying vulnerable older adults and that complaints leading persons to seek medical advice should not be disregarded.

One previous paper examined the association of mortality with different SCCs: memory problems, confusion, and difficulties recognizing familiar people.(Ayalon 2008) Only the latter was associated with mortality but the study differs from ours in that it was based on elderly participants and depression was not taken into account in the analyses. A previous study of older women found greater number of symptoms experienced to be associated with worse cognitive performance.(Amariglio et al. 2011) Our results do not show any effect of symptom load on

mortality but show a strong effect on CESD-depression. The examination of the association between SCCs and mortality is motivated by examination of similar effects using measure cognitive function. There is considerable evidence to show that poor neuropsychological performance is associated with greater risk of mortality in the elderly.(Dewey and Saz 2001;Neale et al. 2001) There is also evidence of this association in middle-aged populations.(Portin et al. 2001;Sabia et al. 2010) Our results showing difficulty in mental calculation in midlife to predict mortality extends this line of research and suggest that it is more likely to reflect true underlying cognitive dysfunction than other SCCs.

The importance of depression to subjective cognitive or memory complaints has been highlighted by many studies.(de Groot, de Leeuw, Oudkerk, Hofman, Jolles, & Breteler 2001;Jonker, Geerlings, & Schmand 2000;Mol, van Boxtel, Willems, & Jolles 2006;Reid & MacLulich 2006;Reisberg, Prichep, Mosconi, John, Glodzik-Sobanska, Boksay, Monteiro, Torossian, Vedvyas, Ashraf, Jamil, & de Leon 2008;Schmand, Jonker, Geerlings, & Lindeboom 1997) Despite the close association of SCC and depression, some studies have shown SCC to predict dementia independently of depression.(Schmand, Jonker, Geerlings, & Lindeboom 1997;St & Montgomery 2002) Cross-sectional data show that memory complaints correlate better with depression(O'Connor, Pollitt, Roth, Brook, & Reiss 1990) than with objective memory.(Bolla, Lindgren, Bonaccorsy, & Bleecker 1991) In our study a wider range of cognitive complaints were predictive of mortality in analyses that did not take depression into account. However, adjustment for depression over the course of the follow-up attenuated most associations, for some cognitive complaints there was no longer an association with mortality. Given the association of depression with both SCCs and mortality, it appears to be an important confounder of the association of SSC with mortality.

There is currently a great deal of research on cognitive ageing that focusses on MCI with a view to identifying factors that predict progression to dementia and those that increase the likelihood of non-progression. The success of this type of research hinges on better identification of individuals with MCI. Some investigators see cognitive complaint, as being essential to the diagnosis of MCI (Petersen 2004;Portet, Ousset, Visser, Frisoni, Nobili, Scheltens, Vellas, & Touchon 2006;Winblad, Palmer, Kivipelto, Jelic, Fratiglioni, Wahlund, Nordberg, Backman, Albert, Almkvist, Arai, Basun, Blennow, de, DeCarli, Erkinjuntti, Giacobini, Graff, Hardy, Jack, Jorm, Ritchie, van, Visser, & Petersen 2004) but this view has been challenged by others.(Hanyu et al. 2007;Mitchell 2008;Purser et al. 2006) Our results suggest that SCCs are problematic for two reasons. One, their high prevalence, 53.1% men and 65.5% women aged 58 years reported memory complaints. Two, all SCCs were strongly associated with depressive symptoms in our analysis. Taken together these results suggest that inclusion of memory complaint as a criterion for MCI is unlikely to be useful. The extent to which specific aspects, such as difficulty in mental calculation or consulting a physician about cognitive complaints are useful for MCI remain to be investigated.

The main strength of our study is the assessment of a range of cognitive complaints. Much of the research on SCCs has focused on memory complaints,(Mol, van Boxtel, Willems, & Jolles 2006;Pearman & Storandt 2004;Schmand, Jonker, Geerlings, & Lindeboom 1997) often including only a single question on perceived forgetfulness.(Clarnette, Almeida, Forstl, Paton, & Martins 2001;Mol, van Boxtel, Willems, & Jolles 2006;Paradise, Glozier, Naismith, Davenport, & Hickie 2011;Reid & MacLulich 2006;St & Montgomery 2002) The exception is of course studies on the effects of cardiac surgery and disease on objective and subjective cognitive functioning, see (Gunstad et al. 2006;Haley et al. 2009), that also include non-memory complaints. It is possible that the attention to memory complaints derives from research assessing whether they have special significance for mild cognitive impairment or dementia outcomes. Assessment of a wider

range of cognitive complaints, both amnesic and non-amnesic aspects, would provide a better characterization of the risk associated with cognitive complaints.(Haley, Hoth, Gunstad, Paul, Jefferson, Tate, Ono, Jerskey, Poppas, Sweet, & Cohen 2009)

The evidence of links of SCCs with brain structure is mostly based on studies that include a range of cognitive complaints.(de Groot, de Leeuw, Oudkerk, Hofman, Jolles, & Breteler 2001;Perrotin et al. 2012;Stewart, Dufouil, Godin, Ritchie, Maillard, Delcroix, Crivello, Mazoyer, & Tzourio 2008;van Norden, Fick, de Laat, van Uden, van Oudheusden, Tendolkar, Zwiers, & de Leeuw 2008) Our results clearly show the importance of examining both amnesic and non-amnesic components of cognitive complaints. The key limitation of our study is the lack of data to examine the mechanisms that link subjective cognitive complaint to death. Given that the age range at the end of the follow-up was 58 to 73 years, dementia deaths are unlikely to explain our findings. There is a two year lag in France between deaths and access to data on the underlying causes of deaths. Of the 651 deaths included in our analysis, causes of death were available for 478 deaths; 62.6% of these were cancer deaths, 14.9% cardiovascular deaths and 22.6% deaths from other causes. There was no difference in results as a function of these broad causes of death (results not shown). A further limitation, linked to the absence of a validated measure, is the use of an in-house SCC questionnaire, similar to the one used in the Nurses Health Study.(Amariglio, Townsend, Grodstein, Sperling, & Rentz 2011)

The value of SCC for assessing health status of older status remains debated as they may well be an early marker of cognitive decline, or simply a part of normal ageing. They are certainly strongly related to poor mental health. There have been many studies in the past ten years that have examined the association of SCC with concurrent or future cognitive status. However, there is little research on large studies that would allow risk profiling. Much previous research is also based on

small, selected samples.(Schmand, Jonker, Geerlings, & Lindeboom 1997) Our analyses using data on middle aged individuals from a large occupational cohort, not initially set up to study ageing or subjective cognitive complaints, show the importance of some complaints, particularly difficulties in mental calculation, for mortality. They also show memory complaints not to be associated with mortality. Finally, seeking medical advice was also associated with greater risk of mortality. If confirmed, these findings suggest that seeking medical advice for SCCs or reporting difficulties in calculation should be taken seriously and may help identify vulnerable persons who may benefit from further interventions.

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Table 1. Prevalence of subjective Cognitive Complaints in the GAZEL study.*

Subjective Cognitive complaint	Men N=11448	Women N=4062	p
Have you experienced memory problems?	53.1%	65.5%	<0.001
Have you experienced the following symptoms regularly?			
<i>forgetfulness in daily activities (shopping, use electrical appliances, etc.)</i>	26.2%	26.6%	0.69
<i>difficulty recalling memories</i>	32.5%	38.7%	<0.001
<i>difficulty in retaining simple new information</i>	32.2%	39.1%	<0.001
<i>difficulty in mental calculation (compared to previously)</i>	15.7%	23.5%	<0.001
<i>language difficulties (finding words, names of objects)</i>	34.4%	45.3%	<0.001
<i>difficulties of orientation in the city, the street</i>	5.8%	13.3%	<0.001
Total symptom score			
0 (none)	40.0%	30.3%	
1-3 (low)	47.0%	49.9%	<0.001
4-6 (high)	13.1%	19.8%	
Have you talked to your doctor about these symptoms?	21.1%	25.5%	<0.001

*The percentage represents any report of the complaint over the study period, 2003-2012.

Table 2. Sample characteristics as a function of SCCs.±

	Memory complaint		Total symptom score			Talked to doctor		Overall
	No	Yes	0	1-3	4.6	No	Yes	
N	6773	8737	5807	7402	2301	12058	3452	15510
Age, mean (SD)‡	57.8 (3.3)	58.0 (3.6)*	57.8 (3.3)	58.0 (3.6)	58.0 (3.7)*	57.8 (3.4)	58.3 (3.6)*	57.9 (3.5)
Education	72.2%	72.4%	72.2%	71.6%	74.5%*	71.8%	73.8%*	
≤Primary school	20.4%	21.2%	20.8%	20.2%	23.3%*	20.4%	22.4%*	20.9%
Professional qualifications	51.8%	51.2%	51.5%	51.5%	51.2%	51.4%	51.4%	51.4%
Secondary school degree	7.3%	7.5%	7.3%	7.6%	7.2%	7.5%	7.4%	7.4%
University	20.5%	20.1%	20.5%	20.8%	18.3%*	20.7%	18.8%*	20.3%
Not married/cohabiting	15.9%	19.2%*	16.2%	17.8%	21.5%*	16.9%	20.7%*	17.7%
CES-D ≥16±	25.2%	49.3%*	22.9%	42.6%	66.3%*	33.6%	56.8%*	38.8%

*p<0.05

±Any report over the study period 2002-2012 of the complaint / CESD scores ≥16.

‡Age at baseline, 2002.

Table 3. The association between subjective cognitive complaints and CES-D depression.±

Subjective Cognitive complaints	Adjusted for age & sex	Adjusted for age, sex, marital status, & education
	OR (95% CI)	OR (95% CI)
Have you experienced memory problems?	2.75 (2.56, 2.95)	2.78 (2.59, 2.98)
Have you experienced the following <u>symptoms</u> ?		
<i>forgetfulness in daily activities</i>	2.46 (2.29, 2.66)	2.48 (2.30, 2.68)
<i>difficulty recalling memories</i>	2.08 (1.94, 2.23)	2.11 (1.97, 2.27)
<i>difficulty in retaining simple new information</i>	2.97 (2.76, 3.19)	3.00 (2.79, 3.22)
<i>difficulty in mental calculation</i>	2.95 (2.70, 3.22)	2.95 (2.70, 3.22)
<i>language difficulties</i>	2.56 (2.39, 2.75)	2.60 (2.42, 2.79)
<i>difficulties of orientation</i>	2.99 (2.63, 3.39)	2.97 (2.61, 3.38)
<u>Total symptom score</u>		
	0	1
	2.45 (2.27, 2.65)	2.50 (2.31, 2.70)
	1-3	
	6.35 (5.69, 7.08)	6.45 (5.78, 7.19)
	4-6	
Have you talked to your doctor about these symptoms?	2.63 (2.43, 2.85)	2.63 (2.42, 2.85)

±Any report over the study period 2002-2012 of the complaint / CESD scores ≥16.

OR: Odds ratio; CI: Confidence Interval

Table 4. The association between subjective Cognitive complaints and mortality.*

Subjective Cognitive complaints	Model 1	Model 1	Model 1	Model 1	Model 1
	HR (95% CI)	+ marital status HR (95% CI)	+ education HR (95% CI)	+ depression HR (95% CI)	+ all HR (95% CI)
Have you experienced memory problems?	1.04 (0.89, 1.22)	1.04 (0.89, 1.21)	1.04 (0.89, 1.22)	0.92 (0.78, 1.08)	0.93 (0.79, 1.09)
Have you experienced the following <u>symptoms</u> ?					
<i>forgetfulness in daily activities</i>	1.10 (0.92, 1.32)	1.09 (0.91, 1.31)	1.11 (0.93, 1.32)	0.98 (0.82, 1.18)	0.99 (0.82, 1.18)
<i>difficulty recalling memories</i>	1.15 (0.98, 1.36)	1.15 (0.98, 1.36)	1.16 (0.98, 1.36)	1.06 (0.90, 1.26)	1.08 (0.91, 1.27)
<i>difficulty in retaining simple new information</i>	1.31 (1.11, 1.54)	1.31 (1.11, 1.54)	1.30 (1.10, 1.53)	1.16 (0.98, 1.37)	1.16 (0.98, 1.37)
<i>difficulty in mental calculation</i>	1.52 (1.25, 1.84)	1.50 (1.24, 1.82)	1.50 (1.24, 1.82)	1.33 (1.10, 1.63)	1.32 (1.08, 1.60)
<i>language difficulties</i>	0.93 (0.79, 1.10)	0.93 (0.79, 1.10)	0.94 (0.79, 1.11)	0.82 (0.69, 0.98)	0.83 (0.70, 0.99)
<i>difficulties of orientation</i>	1.45 (1.09, 1.91)	1.42 (1.08, 1.88)	1.43 (1.08, 1.89)	1.26 (0.95, 1.66)	1.24 (0.93, 1.65)
<u>Total symptom score</u>					
0	1	1	1	1	1
1-3	1.07 (0.90, 1.27)	1.07 (0.90, 1.27)	1.07 (0.90, 1.27)	0.98 (0.82, 1.16)	0.99 (0.83, 1.17)
4-6	1.08 (0.84, 1.41)	1.07 (0.83, 1.39)	1.08 (0.83, 1.40)	0.86 (0.66, 1.13)	0.87 (0.66, 1.14)
Have you talked to your doctor about these symptoms?	1.58 (1.32, 1.89)	1.56 (1.31, 1.86)	1.58 (1.32, 1.88)	1.42 (1.18, 1.70)	1.41 (1.18, 1.68)

Model 1: adjusted for age and sex.

*Deaths included ranged from 613 to 651 in the analyses, depending on non-response in relation to SCCs.