

## **Aspirin Use, Depression and Cognitive Impairment in Later Life: The Health In Men Study**

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## **ABSTRACT**

Objectives: Cerebrovascular disease has been associated with the development of depression and cognitive impairment in later life. We designed this study to determine if the use of aspirin, a drug that inhibits platelet aggregation and reduces the risk of cardiovascular events, is associated with decreased prevalence of both depression and cognitive impairment.

Methods: We recruited a community sample of 5,273 men aged 69 to 87 years and assessed them for the presence of clinically significant depressive symptoms with the Geriatric Depression Scale 15 items (GDS-15  $\geq$  7) and of cognitive impairment with the Mini-Mental State Examination (MMSE  $\leq$  23). Exposure to aspirin was ascertained at the time of assessment as well as 5 years earlier.

Results: Overall, 5.9% of men displayed clinically significant symptoms of depression and 22.6% of cognitive impairment. In total, 40.5% of participants were using aspirin at the time of assessment and 36.4% had been using aspirin 5 years earlier. The odds of depression associated with past but not current use of aspirin were 1.41 (95%CI=1.00-1.99) compared with men who had not used aspirin (adjusted for age, education, country of birth, smoking, prevalent cardiovascular disease, arthritis and the Charlson index of medical comorbidity). Past or present exposure to aspirin showed no obvious association with cognitive impairment. Men who had used aspirin in the past but not at the time of assessment of depression or cognitive function had significantly more contacts with the health services during the preceding 5 years than men who had never used aspirin.

Conclusions: Aspirin use does not seem to be an effective strategy to decrease the prevalence of depression and cognitive impairment in later life, and its consumption is associated with a higher prevalence of depression and use of health services, possibly because of co-existing medical morbidity or complications arising from the use of the medication. Large randomised trials are needed to conclusively determine if aspirin can prevent depression and cognitive impairment in later life.

### **Key-words**

Depression, depressive disorder, vascular depression, cognitive impairment, dementia, cerebrovascular disease, vascular dementia, aspirin, acetyl salicylic acid, antiplatelet therapy, anticoagulation.

## INTRODUCTION

Evidence from randomised clinical trials has shown that treatment with low dosages of aspirin (with or without dipyridamole or clopidogrel) reduces the risk of recurrent strokes or other serious vascular events by about 13%.<sup>1,2</sup> These findings have obvious implications for the management of adults at risk of cardiovascular events and could also play a role in guiding the development of effective strategies to prevent cognitive impairment and depression in later life. This is potentially important because depression and dementia are leading causes of disability and mortality worldwide,<sup>3,4</sup> and there is growing evidence that cerebrovascular disease plays a central role in the clinical expression of these conditions<sup>5,6</sup>

Vascular dementia accounts for 15-20% of all cases of dementia in Western societies,<sup>7</sup> and the presence of cerebrovascular disease contributes to the development and progression of cognitive impairment even amongst older adults with typical Alzheimer's disease.<sup>5,8</sup> Similarly, cardiovascular risk factors and diseases have been associated with the late onset of depressive symptoms in observational, neuroimaging and neuropathological studies.<sup>9-12</sup> These results suggest that if cerebrovascular disease causes dementia and depression in later life, then the appropriate prophylactic management of cardiovascular risk factors and diseases should reduce their incidence and prevalence. Secondary analyses of data from randomised trials of statins and anti-hypertensive agents are generally consistent with this notion,<sup>13,14</sup> but it remains unclear whether these drugs can in fact prevent dementia and depression, particularly when their use is limited to later life.<sup>15</sup> The assumption, in this case, is that treatment should be started in mid-life to have a measurable protective effect in old age.<sup>16</sup>

Antiplatelet therapy reduces the recurrence of cardiovascular events and death days to weeks after its introduction,<sup>17,18</sup> which suggests that this class of drugs may be especially useful in decreasing the progression of cerebrovascular disease in older people at risk for both dementia and depression. Despite this potential, there is limited information on whether aspirin and other antiplatelet agents modulate the risk of cognitive impairment and depression. We designed the

present study to determine if exposure to aspirin treatment is associated with decreased prevalence of depression and cognitive impairment in a large community sample of older Australian men.

## **METHODS**

### Recruitment of participants

Our analyses are based on a community-derived sample of older men living in Perth, Western Australia, who collectively constitute the Health In Men Study (HIMS) cohort. Details regarding enrolment and assessment procedures have been described elsewhere.<sup>19</sup> Briefly, the present analyses involve 5,556 men aged 69 to 87 years who form part of a larger community-representative sample of older men living in Perth, Western Australia. Between 2001 and 2004 these men completed a 2-stage assessment that included the evaluation of mood by self-rating and a face-to-face ascertainment of cognitive function. Figure 1 shows the flow of information for men recruited into HIMS. In total, 5,273 participants completed the assessment of depression and 3,679 of cognitive function. Information on exposure to aspirin was collected at the HIMS assessment as well as 5 years before.

The Human Research Ethics Committee of the University of Western Australia approved the study protocol.

### FIGURE 1

### Outcomes of interest

Participants were asked to complete the 15-item Geriatric Depression Scale (GDS-15) and, *a priori*, those with a total score of 7 or more were considered to display clinically significant depressive symptoms at the time of assessment (primary outcome of interest). This relatively high cut-point was chosen to ensure high specificity for the diagnosis of depression in this sample.<sup>20</sup>

A subsample of 3,679 agreed to complete a face-to-face cognitive assessment with the Mini-Mental State Examination (MMSE), and we used a total score of 23 or lower as indicative of the presence of cognitive impairment.<sup>21</sup>

### Exposure to aspirin

During the 2001-2004 HIMS assessment we asked participants to record all medications they had been using on a regular basis (both prescribed and over the counter). We used the Anatomical Therapeutic Chemical (ATC) Classification System for Drug Coding, with the following codes indicating the oral use of acetylsalicylic acid (aspirin): B01AC06, M01BA03, N02BA01, N02BA51 and N02BA71 (World Health Organisation Collaborating Centre for Drug Statistics Methodology, Oslo, Norway, 2005). We then retrieved data on the use of aspirin that had been collected from these men between 1996 and 1998, when participants were asked: *'In the last month have you been taking aspirin tablets to prevent or treat heart disease?'* Possible answers to this question were 'yes' or 'no'. For the purposes of this study, participants were grouped according to their pattern of exposure to aspirin: negative for past and current assessments, positive for past and negative for current, negative for past and positive for current, and positive for both assessments.

### Procedures to assess other relevant exposures

Consenting men were asked to complete a self-report questionnaire that included items assessing demographic and clinical information. Age was calculated as the difference in years between the date of the assessment and the subject's date of birth. Country of birth was recorded as *'Australia'* or *'other'*. Education was rated according to the completion of high school. Participants were also asked to indicate whether they had ever smoked (yes/no) and if they were still smoking at the time of assessment (every day / not every day / never). Men who answered 'every day' or 'not every day' were classified as current smokers.

We investigated the presence of cardiovascular diseases or risk factors by asking men at the 1996-8 survey whether they *'have ever been told by a doctor that you have'* hypertension,

diabetes, high cholesterol, high lipids, angina, or had a heart attack or stroke (yes/no). Participants were also asked if they were taking tablets for the treatment of hypertension, diabetes and high lipids or cholesterol (yes/no). During the HIMS assessment in 2001-4, men were asked if *'in the last 5 years have ever been told for the first time by a doctor that you have'* hypertension, diabetes, angina, or had a heart attack or stroke (yes/no). In addition, we used the ATC codes C10 to determine which men were taking lipid-lowering agents. Participants who answered yes to any of the above questions or who were taking a lipid-lowering agent were classified as having a cardiovascular disease or a risk factor for cardiovascular disease. In addition, all men were asked whether a doctor had advised them that they had arthritis (yes/no).

We then obtained administrative medical information from the Western Australian Data Linkage System (WADLS)<sup>22,23</sup> during the 10 years prior to assessment at HIMS to calculate the Charlson index.<sup>24</sup> The index takes into account 17 common medical conditions that predict 1-year mortality: myocardial infarction, congestive heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes (including diabetes with end organ damage), hemiplegia, renal disease, leukemia, lymphoma, other tumours, metastatic tumours and AIDS. Charlson and colleagues used adjusted relative risks to assign integer weights to these conditions within a composite index score that ranges from 0 to 37. Coding algorithms to define comorbidities followed the procedures described by Quan et al.<sup>25</sup> and scores were calculated using Stagg's Charlson's index Stata 9.2 routine (StataCorp, College Station, Texas). We stratified scores to reflect the increasing severity of comorbidity associated with the index.<sup>26</sup>

### Analysis of the data

Data were managed and analyzed with the statistical package Stata release 10.0 (StataCorp, College Station, Texas). Participants were grouped according to whether they showed evidence of clinically significant depressive symptoms or cognitive impairment, and the odds ratios (OR plus 95% confidence intervals, 95% CIs) were calculated from 2 X 2 tables for measured

exposures: median age, country of birth, education, smoking, presence of cardiovascular diseases or risk factors, and the Charlson index. Exposures associated with a p-value of 0.2 or less were included in a multivariate logistic regression to calculate the adjusted strength of the association between measured exposures and depression or cognitive impairment (OR and 95%CI), as well as the relevant z-statistic and p-values.

### Power calculation

We calculated that with a sample size of 5,273 men, the study would have 80% power to declare as significant a reduction of 3% in the prevalence of depression associated with the use of aspirin (from about 7% to 4%), with two-sided alpha set at 5%. According to these estimates, for every 33 men treated with aspirin 1 less person would display clinically significant depressive symptoms. (The converse is also true: this study would be powered to declare as significant an increase of 3% in the prevalence of depression associated with the use of aspirin.) We used a similar approach to estimate the required relative reduction in the prevalence of cognitive impairment in a sample of 3,679 older men, of whom 25% used aspirin and 20% had cognitive impairment: the study would have 80% power to declare as significant a treatment effect associated with an absolute reduction (or increase) of 4% in the prevalence of cognitive impairment.

## **RESULTS**

The 5,273 men had a mean (SD) age of 75.5 (4.2) years. Table 1 summarises their demographic, lifestyle and clinical characteristics according to the presence of depression and cognitive impairment. The odds of depression increased with age and were higher for men who had not completed high school education, were born overseas, had ever smoked (past or current) or reported doctor diagnosed cardiovascular diseases or arthritis. Men who were using aspirin in 1996-8 had 34% greater odds of depression than men not using aspirin, but there was no obvious association between current aspirin use (2001-4) and depression.

Similarly, the odds of cognitive impairment were higher in the older age groups, as well as amongst men who did not complete high school education, had been born overseas or had smoked in the past. The current use of aspirin was associated with a 17% increase in the odds of cognitive impairment compared with non-users (Table 1).

#### TABLE 1

We then examined the interaction between exposure to aspirin in the past and at present and the presence of prevalent depression and cognitive impairment in our sample. Table 2 summarises the results of these analyses. Compared with men who were not using aspirin in both assessments, men who had been using aspirin in 1996-8 but not in 2001-4 had greater odds of displaying clinically significant symptoms of depression, even after the analyses were adjusted for the possible effect of confounding (OR= 1.41, 95%CI=1.00 to 1.99;  $z=1.98$ ,  $p=0.047$ ).

#### TABLE 2

Finally, we conducted a series of post hoc analyses to clarify if medical morbidity amongst past and current users of aspirin differed. We used WADLS to determine the number of medical contacts with secondary and tertiary health services between these assessments according to aspirin use. The average number of contacts was 2.6, 4.5, 3.2 and 3.8 for men in each of the following aspirin intake groups: [1] past (no) current (no), [2] past (yes) current (no), [3] past (no) current (yes), [4] past (yes) current (yes). Men in group 2 had more contacts with the health services than men in groups 1 (Mann-Whitney test  $z=8.54$ ,  $p<0.001$ ) and 3 (Mann-Whitney test  $z=2.52$ ,  $p=0.012$ ), but not 4 (Mann-Whitney test  $z=1.34$ ,  $p=0.181$ ). We also retrieved information from WADLS for medical contacts due to haemorrhagic strokes and gastrointestinal bleeding between the 1996-8 and 2001-4 assessments, but the numbers in the cells were too small for meaningful analysis (data not shown).

## DISCUSSION

Contrary to our expectations, the results of this study show that the use of aspirin is not associated with reduced odds of depression or cognitive impairment in older men. They also indicate that men who discontinued the use of aspirin between the two study assessments had greater odds of displaying clinically significant symptoms of depression than non-aspirin users. These men also had more frequent contact with the health services during that 5-year period, a finding that is consistent with the possibility that aspirin use was discontinued because of medical complications that occurred between assessments. But before drawing conclusions from these results, we should consider the merits and limitations of our study design.

This project was based on observational data (cross-sectional and retrospective cohort) and the use of aspirin was not random. Aspirin has a well established role in decreasing the risk of recurrent cardiovascular events,<sup>1</sup> which makes people at risk of recurrent cardiovascular events feature prominently among users of this medication. As cardiovascular diseases are associated with both prevalent and incident cases of depression,<sup>12</sup> the link between aspirin use and depression could potentially be due to confounding (i.e., cardiovascular disease leading to both depression and use of aspirin). We attempted to minimise this effect by adjusting our analyses for the presence of hypertension, diabetes, hyperlipidemia, smoking, angina, as well as history of heart attacks or strokes, and also took into account other potential confounding factors, such as age, education, presence of prevalent arthritis and significant medical comorbidity: the association between past use of aspirin and depression remained statistically significant after all these adjustments. We accept, however, that other unmeasured factors could have confounded the association between past exposure to aspirin and prevalent depression. For this reason, we conducted a series of post hoc analyses that revealed that men who had discontinued use of aspirin between assessments had more frequent contact with the health services than other men (we used the number of contacts with secondary and tertiary health services as a surrogate measure of medical complications). Therefore, there are two possible ways of explaining the association between past aspirin use and higher odds of depression. First, men who stopped using aspirin might have been frailer, which may have contributed to a larger

number hospital admissions, depression and discontinuation of treatment with aspirin to avoid further complications. In this case, the association between aspirin and depression would have been confounded by frailty. The second possibility is that aspirin use led to greater morbidity (for example, medical complications due to bleeding), which in turn could have contributed to increase both depression and the resulting discontinuation of treatment.

We also acknowledge that the assessment of depression in this study was not based on a structured clinical interview and, as a consequence, our data do not allow for direct inferences to be made about the association between exposure to aspirin and presence of a DSM-IV episode of major depression. However, the approach that we used has been previously shown to have good sensitivity and specificity for this diagnosis.<sup>20</sup> Another limitation of our survey is that it was limited to men and our results may not necessarily apply to women. Finally, our study did not collect information about the dose or duration of treatment with aspirin, and we are therefore unable to comment on how this might have influenced our results.<sup>27</sup>

Our data also indicate that the use of aspirin does not reduce the odds of cognitive impairment in later life, a finding that is consistent with the results of a recently published randomised trial of over 3,000 people aged 50 years or over treated with 100 mg of aspirin or placebo for 5 years.<sup>28</sup> In fact, a previous cohort study of 985 older adults who were followed up for 6 years found that the use of aspirin was associated with a higher risk of incident Alzheimer's disease (RR=1.8, 95%CI= 1.1 to 2.8) amongst participants who did not carry the  $\epsilon$ 4 allele of the apolipoprotein E gene, but not amongst  $\epsilon$ 4 carriers (RR=1.6, 95%CI= 0.9 to 3.0).<sup>29</sup> However, the results of studies looking at the association between use of aspirin and the development of cognitive impairment have been inconsistent, with early investigations suggesting that exposure to high dosages of aspirin may decrease the risk of Alzheimer's disease.<sup>30</sup>

Recently published data from the Rotterdam Scan Study showed that older adults who used aspirin were 2.7 (95%CI= 1.4 to 5.0) times as likely to show lobar microbleeds on magnetic

resonance imaging as non-users.<sup>31</sup> Likewise, the results of the AD2000 trial showed that daily treatment for 3 years with 75 mg of aspirin had no effect on the mood, cognition or functional capacity of patients with Alzheimer's disease, although medication use did increase the relative risk of serious bleeding (RR=4.4, 95%CI= 1.5 to 12.8).<sup>32</sup> These findings suggest that treatment with aspirin in later life may increase rather than decrease the risk of small cerebrovascular lesions, which in turn could contribute to increase the risk of both depression and cognitive impairment.

Large randomised trials are needed to conclusively determine if aspirin has a role to play in the prevention of depression and cognitive impairment in later life, although the results of our study indicate that the use of aspirin does not reduce the prevalence of either. In addition, our data suggest that the past use of aspirin is associated with a greater number of health events and may contribute to increase the risk of depression over time. At this point, it is unclear if other antiplatelet agents could potentially reduce the prevalence of depression and cognitive impairment, but similarities between those drugs and aspirin suggest that they are unlikely to be a viable and helpful alternative.

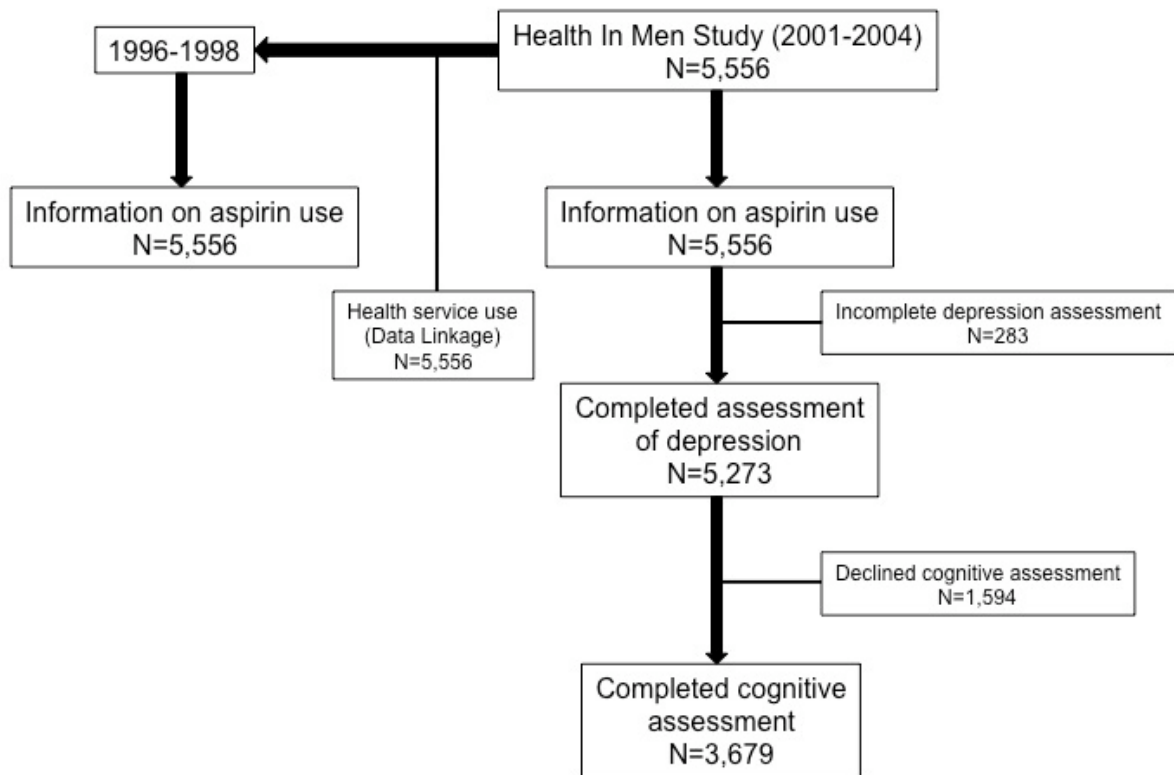
The vascular hypotheses of depression and cognitive impairment have not yet delivered measurable health gains to the population. We may need to consider alternative approaches<sup>33</sup> in the way we manage and attempt to prevent depression and cognitive impairment in later life.

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**Figure 1.** The diagram shows the flow of information available for men taking part in the Health In Men Study.

**Table 1.** Demographic, lifestyle and clinical characteristics of older men according to the presence of depression and cognitive impairment.

		No Depression N=4,964 n (%)	Depression N=309 n (%)	Odds Ratio (95%CI)	No Cognitive Impairment N=2,838 n (%)	Cognitive Impairment N=841 n (%)	Odds Ratio (95%CI)
Age group (years)	69-74	2,393 (48.2)	110 (35.6)	1 [Reference]	1,473 (51.9)	375 (45.0)	1 [Reference]
	75-79	1,664 (33.5)	121 (39.2)	<b>1.58 (1.21, 2.06)<sup>1</sup></b>	930 (32.8)	280 (33.3)	1.18 (0.99, 1.41)
	80-84	753 (15.2)	60 (19.4)	<b>1.73 (1.25, 2.40)<sup>2</sup></b>	372 (13.1)	148 (17.6)	<b>1.56 (1.25, 1.95)<sup>12</sup></b>
	85+	154 (3.1)	18 (5.8)	<b>2.54 (1.51, 4.30)<sup>3</sup></b>	63 (2.2)	38 (4.5)	<b>2.37 (1.56, 3.60)<sup>13</sup></b>
High school education (yes)		2,270 (45.7)	107 (34.6)	<b>0.63 (0.49, 0.80)<sup>4</sup></b>	1,518 (53.5)	300 (35.7)	<b>0.48 (0.41, 0.57)<sup>14</sup></b>
Australian migrant (yes)		1,985 (40.0)	145 (46.9)	<b>1.33 (1.05, 1.67)<sup>5</sup></b>	911 (32.1)	356 (42.3)	<b>1.55 (1.33, 1.82)<sup>15</sup></b>
Smoking	never	1,637 (33.0)	64 (20.8)	1 [Reference]	1,003 (35.4)	257 (30.6)	1 [Reference]
	past	3,063 (61.8)	216 (70.1)	<b>1.80 (1.36, 2.40)<sup>6</sup></b>	1,698 (59.9)	543 (64.6)	<b>1.25 (1.06, 1.48)<sup>16</sup></b>
	current	256 (5.2)	28 (9.1)	<b>2.80 (1.76, 4.45)<sup>7</sup></b>	135 (4.8)	41 (4.9)	1.19 (0.81, 1.73)
Cardiovascular disease (yes)		4,461 (89.9)	295 (95.5)	<b>2.38 (1.38, 4.09)<sup>8</sup></b>	2,453 (86.4)	746 (88.7)	1.23 (0.97, 1.57)
Arthritis (yes)		1,645 (33.1)	148 (47.9)	<b>1.85 (1.47, 2.34)<sup>9</sup></b>	932 (32.8)	294 (35.0)	1.10 (0.93, 1.29)
Charlson weighted index $\geq$ 3		686 (13.8)	96 (31.1)	<b>2.81 (2.18, 3.62)<sup>10</sup></b>	347 (12.2)	142 (16.9)	<b>1.46 (1.18, 1.80)<sup>17</sup></b>
Current aspirin use (yes)		2,013 (40.5)	124 (40.1)	0.98 (0.78, 1.24)	1,159 (40.8)	376 (44.7)	<b>1.17 (1.00, 1.37)<sup>18</sup></b>
Past aspirin use (yes)		1,787 (36.0)	133 (43.0)	<b>1.34 (1.06, 1.70)<sup>11</sup></b>	1,009 (35.5)	324 (38.5)	1.14 (0.97, 1.33)

The superscript numbers that follow the univariate odds ratio are associated with the following statistical values: <sup>1</sup>z=3.38, p=0.001; <sup>2</sup>z=3.32, p=0.001; <sup>3</sup>z=2.54, p<0.001; <sup>4</sup>z=3.78, p<0.001; <sup>5</sup>z=2.40, p=0.016; <sup>6</sup>z=4.05, p<0.001; <sup>7</sup>z=4.36, p<0.001; <sup>8</sup>z=3.12, p=0.002; <sup>9</sup>z=5.24, p>0.001; <sup>10</sup>z=7.97, p<0.001; <sup>11</sup>z=2.49, p=0.013; <sup>12</sup>z=3.95, p<0.001; <sup>13</sup>z=4.04, p<0.001; <sup>14</sup>z=8.96, p<0.001; <sup>15</sup>z=5.46, p<0.001; <sup>16</sup>z=2.59, p=0.010; <sup>17</sup>z=3.48, p=0.001; <sup>18</sup>z=2.00, p=0.046.

**Table 2.** Odds ratio of depression and cognitive impairment according to exposure to aspirin over a 5-year period.

Aspirin Use	No Depression N=4,964 n (%)	Depression N=309 n (%)	Odds Ratio (OR) (95%CI)	Adjusted OR* (95%CI)	No Cognitive Impairment N=2,838, n (%)	Cognitive Impairment N=841, n (%)	Odds Ratio (OR) (95%CI)	Adjusted OR* (95%CI)
Past (no) Current (no)	2,396 (48.3)	130 (42.1)	1 [Reference]	1 [Reference]	1,390 (49.0)	374 (44.5)	1 [Reference]	1 [Reference]
Past (yes) Current (no)	555 (11.2)	55 (17.8)	<b>1.83 (1.31, 2.54)<sup>1</sup></b>	<b>1.41 (1.00, 1.99)<sup>2</sup></b>	289 (10.2)	91 (10.8)	1.17 (0.90, 1.52)	1.10 (0.84, 1.45)
Past (no) Current (yes)	781 (15.7)	46 (14.9)	1.09 (0.77, 1.53)	0.96 (0.68, 1.37)	439 (15.5)	143 (17.0)	1.12 (0.97, 1.51)	1.16 (0.92, 1.46)
Past (yes) Current (yes)	1,232 (24.8)	78 (25.2)	1.17 (0.87, 1.56)	0.95 (0.70, 1.28)	720 (25.4)	233 (27.7)	1.20 (1.00, 1.45)	1.15 (0.95, 1.40)

The superscript numbers that follow the odds ratio are associated with the following statistical values: <sup>1</sup>z=3.59, p=0.001; <sup>2</sup>z=1.98, p=0.047.

\*Adjusted for age group, schooling, migrant status, smoking, cardiovascular disease, arthritis and a Charlson index weighted score  $\geq 3$ .