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1 **Anticholinergic burden and risk of stroke and death in people with different types of**  
2 **dementia**

3

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24



26 **Abstract**

27 **Background**

28 Anticholinergic burden is associated with poorer cognitive and functional outcomes in people  
29 with dementia. However, the impact of anticholinergics on significant adverse outcomes such as  
30 stroke has not been studied previously.

31

32 **Objective**

33 To investigate the association between total anticholinergic cognitive burden (ACB) and risk of  
34 stroke and death in people with different dementia subtypes.

35

36 **Methods**

37 This was a cohort study of 39107 people with dementia and no prior history of stroke registered  
38 in the Swedish Dementia Registry (SveDem) from 2008 – 2014. Data were extracted from the  
39 Swedish Prescribed Drug Register, the Swedish National Patient Register and the Swedish Total  
40 Population Register. Competing risk regression models were used to compute hazard ratios (HRs)  
41 and 95% confidence intervals (CIs) for the association between time-varying ACB score and risk  
42 of stroke and all-cause mortality.

43

44 **Results**

45 During a mean follow-up period of 2.31 (standard deviation 1.66) years, 11224 (28.7%)  
46 individuals had a stroke or died. Compared with non-users of anticholinergic medications, ACB  
47 score of 1 (HR 1.09, 95%CI 1.04 – 1.14) and ACB score of  $\geq 2$  (HR 1.20, 95%CI 1.14 – 1.26)  
48 increased the risk of developing the composite outcome of stroke and death. When stratifying by

49 dementia disorder, the association remained significant in Alzheimer's disease, mixed dementia  
50 and vascular dementia.

51

## 52 **Conclusions**

53 The use of anticholinergic medicines may be associated with an increased risk of stroke and death  
54 in people with dementia. A dose-response relationship was observed. Careful consideration  
55 should be made when prescribing medications with anticholinergic properties to people with  
56 dementia.

57

## 58 **Key words**

59 Anticholinergics, stroke, dementia, Alzheimer disease, vascular dementia, cohort studies,  
60 registries

61 **Introduction**

62 Medications with anticholinergic properties are commonly used in older people for a range of  
63 therapeutic indications. Anticholinergic burden, the cumulative effect of taking multiple  
64 medicines with anticholinergic properties, has been found to be associated with significant  
65 adverse effects on cognitive and physical function in older people; however, there is limited  
66 evidence for mortality and cerebrovascular outcomes.[1-5] A meta-analysis concluded that every  
67 unit increase in the anticholinergic cognitive burden (ACB) scale was associated with a doubling  
68 in odds of all-cause mortality (odds ratio [OR] 2.06, 95% confidence interval [CI] 1.82 –  
69 2.33).[3] A study in the general older population reported a significant dose-response association  
70 between total ACB score and mortality and cardiovascular outcomes, including stroke.[6]

71  
72 People with dementia have been shown to be high users of medications with anticholinergic  
73 properties.[7] Whilst the negative effects of anticholinergic medications on cognition and  
74 dementia progression have been studied extensively,[8] few studies have explored the impact of  
75 anticholinergics on other important adverse outcomes including stroke and mortality in  
76 individuals with dementia. There is some evidence to suggest that there is an increased risk of  
77 mortality with the use of anticholinergic medications in people with dementia; however, findings  
78 are inconsistent.[9-11] Additionally, these studies are limited by small sample sizes, short  
79 durations of follow-up and failure to differentiate between different subtypes of dementia which  
80 may be important regarding underlying mechanisms of the disease. To date, the association  
81 between anticholinergic burden and stroke risk in people with dementia has not been  
82 investigated. This is of importance as people with dementia are at a two-fold greater risk of stroke  
83 compared to those without dementia.[12]

84

85 The aim of this study was to investigate the association between anticholinergic burden with  
86 stroke and death in people with dementia, and whether this association varied by type of  
87 dementia disorder.

88

## 89 **Methods**

### 90 ***Study population***

91 This was a cohort study based on individuals registered at the time of the dementia diagnosis in  
92 the Swedish Dementia Registry (SveDem, [www.svedem.se](http://www.svedem.se)) from 2008 to 2014. The Swedish  
93 Dementia Registry (SveDem) is a national quality registry for monitoring the diagnosis, treatment  
94 and care of people with dementia in Sweden.[13] It covers 100% of memory clinics and 75% of  
95 primary care units in Sweden. It included a total of 48766 individuals with newly diagnosed  
96 dementia from 2008 to 2014. To be eligible for inclusion in this study, participants needed to  
97 have no prior history of stroke and complete baseline data. After excluding those with previous  
98 stroke (n=6191, 12.7%) and missing data (n=3468, 7.1%), a total of 39107 people were included  
99 in the analyses.

100

### 101 ***Data sources***

102 Information on dispensed drugs was extracted from the Swedish Prescribed Drug Register. All  
103 prescriptions dispensed by Swedish pharmacies are captured in this register together with unique  
104 patient identifiers. The National Board of Health and Welfare maintains this register and  
105 coverage is >99%.[14] All drugs are classified according to the Anatomical Therapeutic  
106 Chemical (ATC) code. To be considered a user of a medication, participants had to have at least 3  
107 prescriptions or 20 unit doses dispensed in the previous year.

108 Information on medical diagnoses at baseline and during follow-up were extracted from the  
109 Swedish National Patient Register. This register contains prospectively collected data from all  
110 inpatient and specialized outpatient visits in Sweden and is maintained by the Swedish National  
111 Board of Health and Welfare. The coverage of inpatient discharges is >99%.[15] The medical  
112 diagnoses of all individuals are classified according to the International Classification of  
113 Diseases, Tenth Revision, (ICD-10). Information on all-cause mortality were extracted from the  
114 Swedish Total Population Register. This register is maintained by Statistics Sweden and covers  
115 100% of all deaths in Sweden.[16]

116

### 117 *Anticholinergic exposure measure*

118 Anticholinergic exposure was defined using the Anticholinergic Cognitive Burden scale  
119 (ACB).[17, 18] The ACB scale assigns a score of zero for medications with no known  
120 anticholinergic activity, one for medication with possible anticholinergic properties, two for  
121 medications with definite clinical anticholinergic properties, and three for medications with  
122 definite anticholinergic properties that may cause delirium (Supplementary Table 1). The ACB  
123 scale is the most frequently validated tool for assessing the effect of anticholinergic medications  
124 on adverse outcomes.[4] A total ACB score was calculated for each patient annually by adding  
125 the individual scores of different medications in a patient's prescribed regimen. Annual total  
126 ACB score was analyzed as a time-varying variable i.e. the most recent score prior to outcome or  
127 study end was used in the analysis. Scores were further categorized into 0, 1 or  $\geq 2$ .

128

### 129 *Outcomes*

130 The primary outcome was the composite of first stroke (any) and all-cause mortality. Secondary  
131 outcomes were death, any stroke and ischemic stroke. Stroke was defined as first occurrence of

132 ICD-10 codes I61, I63 or I64. Ischemic stroke was defined as first occurrence of ICD-10 code  
133 I63.

134

### 135 *Confounders*

136 Demographic data at baseline were obtained from SveDem and included age, sex, Mini-mental  
137 state examination (MMSE),[19] living situation (institutionalized, living alone or living at home  
138 with a co-resident), home care use and dementia disorder.[13] Dementia diagnoses were made  
139 according to ICD-10 criteria[20] and coded as Alzheimer's disease (AD), vascular dementia,  
140 mixed dementia, dementia with Lewy bodies, frontotemporal dementia, Parkinson's disease  
141 dementia (PDD), unspecified dementia and other dementia types. Charlson comorbidity index  
142 was used as a measure of the number and severity of comorbid conditions at baseline.[21]  
143 Antidementia drugs at baseline were defined as ATC code N06D.

144

### 145 *Statistical analysis*

146 Analysis of variance and chi square statistics were used to compare participant baseline  
147 characteristics according to ACB score. Baseline was defined as the date of dementia diagnosis.  
148 Time-dependent Cox proportional hazards models were used to estimate hazard ratios (HRs) and  
149 95% confidence intervals (CI) for the association between time-varying annual total ACB score  
150 and the primary outcome and all-cause death. Adjusted subdistribution HRs (sHRs) and 95% CIs  
151 were calculated for the occurrence of any incident stroke and ischemic stroke, adjusting for  
152 mortality as a competing risk. All multivariable models were adjusted for age, sex, Charlson  
153 Comorbidity Index, living situation, home care, dementia disorder, MMSE and use of  
154 antidementia drugs at baseline. Survival time was defined as the time from date of dementia  
155 diagnosis (index date) to date of first stroke, death or 31 December 2014, whichever came first.

156 Subgroup analyses according to dementia disorder subtype was performed. To explore whether  
157 the association between anticholinergic burden and stroke and death was due to long-term effects,  
158 we also performed a sensitivity analysis using baseline total ACB score as the exposure i.e. total  
159 ACB score calculated based on medication use in the year preceding dementia diagnosis.

160

## 161 **Ethical considerations**

162 All patients in SveDem were informed about their participation in the registry and had the right to decline  
163 participation or withdraw consent. This study was approved by the regional human ethics committee  
164 in Stockholm (approval number 2015/743-31/4). Data were coded and anonymized before  
165 statistical analyses.

166

## 167 **Results**

### 168 **Study population and characteristics**

169 The study cohort consisted of 39107 people with a mean age of 79.9 (standard deviation [SD],  
170 7.90) years with the majority being female (60.7%). At baseline, 24573 (62.8%) participants had  
171 an ACB score of 0, 8239 (21.1%) a score of 1 and 6295 (16.1%) a score of  $\geq 2$ . The mean ACB  
172 score at baseline was 0.67 (range: 0 to 12) and the mean time-varying ACB score was 0.73  
173 (range: 0 to 12). The most commonly used drugs contributing to ACB score  $\geq 1$  were metoprolol  
174 (C07AB02) (39.6%), furosemide (C03AC01) (25.0%), and warfarin (B01AA03) (13.4%).

175 Participants with higher ACB scores were more likely to be older, institutionalized, receive home  
176 care, have a greater number of comorbidities, take a higher number of drugs and be less likely to  
177 use antidementia drugs. Whilst they were less likely to have AD, those with higher ACB scores  
178 were more likely to be diagnosed with other dementia subtypes including mixed dementia,  
179 vascular dementia and PDD. Detailed demographic information is reported in Table 1.

180

181 **Risk of death and stroke in the dementia cohort**

182 During the follow-up period (mean [SD] 2.31 [1.66] years), 11224 (28.7%) individuals had a  
183 stroke or died. Crude incidence rates for the primary outcome of the composite of stroke and  
184 death were higher in those with higher ACB score (111, 130 and 155/1000 person-years, for ACB  
185 scores 0, 1 and  $\geq 2$ , respectively) (Table 2). The individual crude incidence rates for death, stroke  
186 and ischemic stroke similarly increased with increasing ACB scores.

187

188 After adjusting for potential confounders, time-varying ACB score was associated with an  
189 increased risk of developing the primary outcome (HR 1.05, 95%CI 1.03 – 1.06) (Table 3). When  
190 categorizing time-varying ACB score, ACB score of 1 (HR 1.09, 95%CI 1.04 – 1.14) and ACB  
191 score of  $\geq 2$  (HR 1.20, 95%CI 1.14 – 1.26) were associated with the primary outcome, indicating  
192 a dose-response relationship. Similar findings were found for the outcome of death with  
193 continuous ACB score (HR 1.04, 95%CI 1.02 – 1.06), and categorized ACB score of 1 (HR 1.09,  
194 95%CI 1.04 – 1.14) and ACB score of  $\geq 2$  (HR 1.18, 95%CI 1.12 – 1.24) associated with an  
195 increased risk of death. A significant association was found between ACB score and any stroke  
196 (sHR 1.11, 95%CI 1.07 – 1.15) and ischemic stroke (sHR 1.06, 95%CI 1.02 – 1.11); however,  
197 this remained significant only for higher ACB score ( $\geq 2$ ) (any stroke: sHR 1.13, 95%CI 1.00 –  
198 1.27; ischemic stroke: sHR 1.15, 95%CI 1.00 – 1.31). Sensitivity analyses using baseline ACB  
199 score produced similar results (Supplementary Table 2).

200

201 Table 4 reports the hazard ratios for the association between time-varying ACB scores and the  
202 primary outcome, stratified by dementia disorder. Time-varying ACB score was associated with  
203 the primary outcome for patients with AD (HR 1.08, 95%CI 1.05 – 1.12), mixed dementia (HR

204 1.05, 95%CI 1.01 – 1.09), vascular dementia (HR 1.04, 95%CI 1.01 – 1.08) and unspecified  
205 dementia (HR 1.06, 95%CI 1.02 – 1.09). When categorizing ACB score, ACB score of  $\geq 2$   
206 remained significantly associated with the primary outcome for these dementia disorders.  
207 Compared with an ACB score of 0, an ACB score of 1 was found to be associated with a reduced  
208 risk of developing the primary outcome in patients with Parkinsons disease dementia (HR 0.53,  
209 95%CI 0.34 – 0.83). Sensitivity analyses found no significant association between baseline ACB  
210 score and the primary outcome after stratifying by dementia disorder, except for people with AD  
211 or unspecified dementia with ACB score of  $\geq 2$  (Supplementary Table 3).

212

## 213 **Discussion**

214 Our study found that higher total anticholinergic burden was associated with an increased risk of  
215 all-cause mortality and stroke in people with dementia, compared with those with lower or no  
216 anticholinergic burden. This association remained significant in those with AD, mixed dementia  
217 and vascular dementia after stratifying by dementia disorder.

218

219 Previous studies of anticholinergic burden and mortality in people with dementia have shown  
220 mixed findings. A recent study by Cross et al. reported that time-dependent ACB scores were  
221 associated with mortality (adjusted HR 1.18, 95% CI 1.02 – 1.32) in older people with cognitive  
222 impairment attending Australian memory clinics. Another study by Gnjidic et al. reported that  
223 baseline anticholinergic burden, measured using the Drug Burden Index (DBI), was associated  
224 with one-year mortality (adjusted HR 1.21, 95%CI 1.09 – 1.33) in people with AD in Finland.  
225 Conversely, other studies have found no association between the use of medications with  
226 anticholinergic properties and mortality in people with dementia.[11, 22]

227

228 To date, there has been limited research into the association between anticholinergic burden and  
229 stroke risk in people with dementia. However, there is evidence to suggest a possible association  
230 between anticholinergics and cardiovascular and cerebrovascular outcomes in the general older  
231 population.[23] Higher ACB scores have been found to be associated with both mortality and  
232 cardiovascular disease incidence, including stroke.[6, 24] Additionally, higher ACB scores in  
233 older patients with cardiovascular disease has been shown to increase risk of hospitalization and  
234 mortality.[25, 26]

235  
236 There are a few potential mechanisms which may explain why anticholinergic medications may  
237 increase mortality and incidence of stroke. It has been suggested that anticholinergic medications  
238 have pro-arrhythmic and pro-ischaemic properties.[27, 28] Anticholinergics may have an effect  
239 on cardiovascular homeostasis, producing tachycardia and orthostatic hypotension, both of which  
240 may be associated with an increased risk for ischemic stroke. Additionally, given the cholinergic  
241 system has a role in regulating immune response, another potential mechanism may be through  
242 immunomodulation. Anticholinergics may inhibit immune system processes leading to  
243 inflammatory responses and an increased risk of stroke and mortality in people with dementia with  
244 underlying risk factors.[29]

245  
246 To our knowledge, no previous studies have investigated the impact of anticholinergic  
247 medications across different dementia subtypes. Our study found that the regular use of definite  
248 anticholinergics (ACB score of  $\geq 2$ ) was associated with increased risk of stroke and death in  
249 those dementia subtypes with a probable underlying vascular component (AD, mixed dementia  
250 and vascular dementia). This may indicate these patients are inherently at risk of stroke and early  
251 mortality and that the use of anticholinergic medications may compound this. Alternatively,

252 several cardiovascular medications, such as diuretics, antihypertensives and antithrombotics,  
253 have anticholinergic properties, and these drugs were the main contributors to ACB score in our  
254 study population. It is thus possible that the use of these medications is reflective of underlying  
255 vascular problems that can increase risk of stroke and death in this population.

256  
257 The use of anticholinergics in people with dementia is questionable, given their negative impact  
258 on cognition.[5] The use of anticholinergics in conjunction with antidementia drugs, such as  
259 acetylcholinesterase inhibitors, appears counterintuitive given the conflicting mechanisms of  
260 actions of the two drug classes.[30] Acetylcholinesterase inhibitors have been shown to be  
261 associated with a reduced risk of stroke and mortality in people with Alzheimer's disease and  
262 dementia.[31, 32] The use of anticholinergic medications may thus oppose these protective  
263 effects. Although participants in our study were less likely to be using an acetylcholinesterase  
264 inhibitor if they had a higher ACB score, 40% of those with an ACB score of  $\geq 2$  were still  
265 concurrently prescribed an acetylcholinesterase inhibitor.

266  
267 Our study observed a linear dose-response relationship between anticholinergic burden and risk  
268 of mortality and stroke. In particular, we observed that the use of regular medications with  
269 definite anticholinergic properties (ACB score of  $\geq 2$ ) were associated with a 20% increase in the  
270 risk of stroke or death in people with dementia. This would be the equivalent of an individual  
271 taking a minimum of two ACB score 1 drugs e.g. metoprolol and venlafaxine together, or a single  
272 ACB score 2 or 3 drug e.g. carbamazepine or oxybutynin. Given that several common  
273 medications used in older people contain anticholinergic properties, these findings highlight the  
274 care that should be made when considering the addition of a new medication in people with  
275 dementia. In particular, medications with anticholinergic properties should be carefully assessed

276 for their risk versus benefit. Where possible, alternative medications with lower or no  
277 anticholinergic properties should be used instead. Additionally, medications used in people with  
278 dementia should be regularly reviewed to reduce anticholinergic burden where possible.[33]

279  
280 This study has several strengths and limitations. Strengths lie in the large, nationally  
281 representative cohort of individuals with dementia. Additionally, a wider range of dementia  
282 disorder subtypes were included compared with other studies, and we were able to make  
283 comparisons across different disorders. The ascertainment of medical diagnoses and medications  
284 employed the use of national registers that were complete and allowed for follow-up of  
285 individuals, thus eliminating any potential attrition or recall bias. Our medication exposure was  
286 time-dependent, taking into account the change in prescribing patterns that occur after dementia  
287 diagnosis and thus more accurately reflective of medication use at the time of event. We also  
288 supplemented this analysis using baseline medication exposure, to investigate long-term effects  
289 of anticholinergic burden. Although we know that medications were dispensed and collected  
290 from pharmacies, we did not explore the impact of medication adherence. Additionally, we did  
291 not consider non-prescription medications such as those obtained over-the-counter, nor  
292 medications used infrequently, thus we may have underestimated the effects. We cannot exclude  
293 the possibility of bias due to unmeasured confounding, in particular confounding by indication.  
294 Although we adjusted for a range of important covariates, it was not possible to control for all  
295 factors that may influence a physician's decision to prescribe anticholinergic medications.

296

## 297 **Conclusion**

298 Our study found that total anticholinergic burden was associated with an increased risk of all-  
299 cause mortality and incident stroke in people with dementia. A dose-response relationship was

300 observed. This association remained significant in those with AD, mixed dementia and vascular  
301 dementia after stratifying by dementia disorder. Careful consideration should be made when  
302 prescribing medications with anticholinergic properties to people with dementia.

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316

317 **Conflict of Interest**

318 The authors have no conflict of interest to report

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**Table 1. Baseline characteristics according to ACB score**

	<b>Total</b> <i>N</i> = 39107	<b>0</b> <i>N</i> = 24573	<b>1</b> <i>N</i> = 8239	<b>≥2</b> <i>N</i> = 6295	<b>p-value</b>
<b>Female, n (%)</b>	23735 (60.7)	15013 (61.1)	4955 (60.1)	3767 (59.8)	0.098
<b>MMSE, mean (SD)</b>	20.43 (6.03)	20.47 (6.01)	20.41 (5.98)	20.29 (6.16)	0.08
<b>Age, mean (SD)</b>	79.92 (7.90)	79.38 (8.14)	80.73 (7.35)	80.95 (7.45)	<0.001
<b>Residency, n (%)</b>					
<b>At home with coresident</b>	16617 (42.5)	10694 (43.5)	3350 (40.7)	2573 (40.9)	<0.001
<b>At home alone</b>	18976 (48.5)	11821 (48.1)	4129 (50.1)	3026 (48.1)	
<b>Institutionalized</b>	3514 (9.0)	2058 (8.4)	760 (9.2)	696 (11.1)	
<b>Home care, n (%)</b>	12076 (30.9)	7233 (29.4)	2593 (31.5)	2250 (35.7)	<0.001
<b>Dementia disorder, n (%)</b>					
<b>AD</b>	13269 (33.9)	9279 (37.8)	2462 (29.9)	1528 (24.3)	<0.001
<b>Mixed dementia</b>	7235 (20.7)	4262 (17.3)	1667 (20.2)	1306 (20.7)	
<b>Vascular dementia</b>	5967 (15.3)	3196 (13.0)	1474 (17.9)	1297 (20.6)	
<b>Dementia with Lewy bodies</b>	879 (2.2)	577 (2.3)	156 (1.9)	146 (2.3)	
<b>Frontotemporal dementia</b>	639 (1.6)	454 (1.8)	112 (1.4)	73 (1.2)	
<b>Parkinson's disease dementia</b>	601 (1.5)	351 (1.4)	90 (1.1)	160 (2.5)	
<b>Unspecified</b>	9531 (24.4)	5816 (23.7)	2089 (25.4)	1626 (25.8)	
<b>Other</b>	986 (2.5)	638 (2.6)	189 (2.3)	159 (2.5)	
<b>Charlson Comorbidity Index, mean (SD)</b>	2.12 (1.63)	1.88 (1.45)	2.34 (1.70)	2.75 (1.96)	<0.001
<b>Acute myocardial infarction</b>	3948 (10.1)	1436 (5.8)	1241 (15.1)	1271 (20.2)	<0.001
<b>Ischemic heart disease</b>	7389 (18.9)	2758 (11.2)	2308 (28.0)	2323 (36.9)	<0.001
<b>Atrial fibrillation</b>	5800 (14.8)	1949 (7.9)	1671 (20.3)	2180 (34.6)	<0.001
<b>Heart failure</b>	3962 (10.1)	1289 (5.2)	1076 (13.1)	1597 (25.4)	<0.001
<b>Diabetes</b>	4957 (12.7)	2369 (9.6)	1327 (16.1)	1261 (20.0)	<0.001
<b>Total number of drugs, mean, (SD)</b>	6.53 (5.03)	4.61 (3.85)	8.52 (4.46)	11.41 (5.48)	<0.001
<b>Use of any antedementia drugs, n (%)</b>	19072 (48.8)	12672 (51.6)	3776 (45.8)	2624 (41.7)	<0.001

MMSE: Mini-mental state examination, AD: Alzheimer's disease

**Table 2. Event rates for composite outcome, death, stroke and ischemic stroke by baseline ACB score**

	<b>Total</b> <i>N</i> = 39107	<b>0</b> <i>N</i> = 24573	<b>1</b> <i>N</i> = 8239	<b>≥2</b> <i>N</i> = 6295	<b>p-value</b>
<b>Composite outcome<sup>a</sup>, n (%)</b>	11224 (28.7)	6607 (26.9)	2466 (29.9)	2151 (34.2)	<0.001
<b>PY follow up</b>	92646.40	59757.56	19015.07	13873.77	
<b>Composite outcome/1000 PY</b>	121.1	110.6	129.7	155.0	
<b>Deaths, n (%)</b>	10357 (26.5)	6091 (24.8)	2294 (27.8)	1972 (31.3)	<0.001
<b>PY follow up</b>	94908.81	61087.21	19478.26	14343.34	
<b>Deaths/1000 PY</b>	109	100.0	117.8	137.5	
<b>Strokes, n (%)</b>	1904 (4.9)	1071 (4.4)	419 (5.1)	414 (6.6)	<0.001
<b>PY follow up</b>	92646.40	59757.56	19015.07	13873.77	
<b>Strokes/ 1000 PY</b>	20.6	17.9	22.0	29.8	
<b>Ischemic strokes, n(%)</b>	1461 (3.7)	804 (3.3)	335 (4.1)	322 (5.1)	<0.001
<b>PY follow up</b>	93118.28	60045.94	19105.77	13966.57	
<b>Ischemic strokes/1000 PY</b>	15.7	13.4	17.5	23.1	

PY: person-years

a. Composite of death or any stroke

**Table 3. Hazard ratios for the association between time-varying ACB score and stroke and death in people with dementia (N=39,107)**

	Composite stroke and death	Death	Stroke	Ischemic stroke
<b>HRs (95% CI)<sup>a</sup></b>				
<b>Continuous</b>	1.05 (1.03 – 1.06) <sup>***</sup>	1.04 (1.02 – 1.06) <sup>***</sup>	1.11 (1.07 – 1.15) <sup>***</sup>	1.06 (1.02 – 1.11) <sup>**</sup>
<b>Categorical</b>				
<b>0 (n=22919)</b>	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>1 (n=9184)</b>	1.09 (1.04 – 1.14) <sup>**</sup>	1.09 (1.04 – 1.14) <sup>**</sup>	0.97 (0.86 – 1.08)	1.01 (0.89 – 1.15)
<b>≥2 (n=7004)</b>	1.20 (1.14 – 1.26) <sup>***</sup>	1.18 (1.12 – 1.24) <sup>***</sup>	1.13 (1.00 – 1.27) <sup>*</sup>	1.15 (1.00 – 1.31) <sup>*</sup>

a. Adjusted for age, sex, Charlson Comorbidity Index, institutionalisation, living alone, home care, Mini-Mental State Examination score and use of antidementia drugs at baseline

b. Subdistribution hazard ratio

\*p < 0.05

\*\*p < 0.01

\*\*\*p < 0.001

**Table 4. Association between time-varying ACB scores and composite of stroke and death by dementia disorder (N=39,107)**

	<b>AD</b>	<b>MixedD</b>	<b>VaD</b>	<b>DLB</b>	<b>FTD</b>	<b>PDD</b>	<b>Unspecified</b>	<b>Other</b>
	<b>N = 13269</b>	<b>N = 7235</b>	<b>N = 5967</b>	<b>N = 879</b>	<b>N = 639</b>	<b>N = 601</b>	<b>N = 9531</b>	<b>N = 986</b>
<b>HRs (95% CI)<sup>a</sup></b>								
<b>Continuous</b>	1.08 (1.05 – 1.12)***	1.05 (1.01 – 1.09)**	1.04 (1.01 – 1.08)*	0.94 (0.86 – 1.03)	0.95 (0.85 – 1.07)	0.94 (0.86 – 1.03)	1.06 (1.02 – 1.09)***	1.04 (0.95 – 1.14)
<b>Categorical</b>								
<b>0 (n=22919)</b>	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>1 (n=9184)</b>	1.12 (1.02 – 1.22)*	1.04 (0.95 – 1.15)	1.10 (0.98 – 1.22)	1.04 (0.79 – 1.37)	1.04 (0.71 – 1.53)	0.53 (0.34 – 0.83)**	1.18 (1.08 – 1.30)***	0.97 (0.71 – 1.33)
<b>≥2 (n=7004)</b>	1.27 (1.15 – 1.40)***	1.17 (1.06 – 1.30)**	1.20 (1.08 – 1.34)**	0.83 (0.62 – 1.10)	0.88 (0.57 – 1.37)	0.82 (0.60 – 1.13)	1.30 (1.18 – 1.43)***	1.06 (0.78 – 1.45)

AD, Alzheimer's disease; MixedD, mixed dementia; VaD, vascular dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; PDD, Parkinson's disease dementia; HR, hazard ratio; CI, confidence interval

- a. Adjusted for age, sex, Charlson Comorbidity Index, institutionalisation, living alone, home care, Mini-Mental State Examination score and use of antidementia drugs at baseline

b. Additionally adjusted for dementia disorder

\*p < 0.05

\*\*p < 0.01

\*\*\*p < 0.001

## SUPPLEMENTARY MATERIAL

**Supplementary Table 1. Anticholinergic Cognitive Burden scale drug scoring**

<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>
Alimemazine	Amantadine	Amitriptyline
Alverine	Belladonna	Amoxapine
Alprazolam	Carbamazepine	Atropine
Aripiprazole	Cyclobenzaprine	Benztropine
Atenolol	Cyproheptadine	Brompheniramine
Bupropion	Loxapine	Carbinoxamine
Captopril	Meperidine	Chlorpheniramine
Chlorthalidone	Methotrimeprazine	Chlorpromazine
Cimetidine	Molindone	Clemastine
Clidinium	Nefopam	Clomipramine
Clorazepate	Oxcarbazepine	Clozapine
Codeine	Pimozide	Darifenacin
Colchicine		Desipramine
Desloratadine		Dicyclomine
Diazepam		Dimenhydrinate
Digoxin		Diphenhydramine
Dipyridamole		Doxepin
Disopyramide		Fesoterodine

<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>
Fentanyl		Flavoxate
Furosemide		Hydroxyzine
Fluvoxamine		Hyoscyamine
Haloperidol		Imipramine
Hydralazine		Meclizine
Hydrocortisone		Methocarbamol
Iloperidone		Nortriptyline
Isosorbide		Olanzapine
Levocetirizine		Orphenadrine
Loperamide		Oxybutynin
Loratadine		Paroxetine
Metoprolol		Perphenazine
Morphine		Promethazine
Nifedipine		Proprantheline
Paliperidone		Propeverine
Prednisone		Quetiapine
Quinidine		Scopolamine
Ranitidine		Solifenacin
Risperidone		Thioridazine
Theophylline		Tolterodine

<b>Score 1</b>	<b>Score 2</b>	<b>Score 3</b>
Trazodone		Trifluoperazine
Triamterene		Trihexyphenidyl
Venlafaxine		Trimipramine
Warfarin		Trospium

Adapted from: Aging Brain Care. Anticholinergic Cognitive Burden Scale—2012 Update.

Available: [www.agingbraincare.org/uploads/products/ACB\\_scale\\_-\\_legal\\_size.pdf](http://www.agingbraincare.org/uploads/products/ACB_scale_-_legal_size.pdf).

(Accessed February 7 2018)

**Supplementary Table 2. Hazard ratios for the association between baseline ACB score and stroke and death in people with dementia**

	<b>Composite stroke and death</b>	<b>Death</b>	<b>Stroke</b>	<b>Ischemic stroke</b>
<b>HRs<sup>a</sup></b>				
<b>Continuous</b>	1.02 (1.01 – 1.04)**	1.01 (1.00 – 1.03)	1.08 (1.05 – 1.12)***	1.09 (1.05 – 1.13)***
<b>Categorical</b>				
<b>0</b>	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
<b>1</b>	1.03 (0.99 – 1.08)	1.04 (0.99 – 1.09)	1.09 (0.97 – 1.22)	1.14 (1.00 – 1.30)*
<b>≥2</b>	1.11 (1.11 – 1.16)***	1.08 (1.02 – 1.13)**	1.36 (1.21 – 1.53)***	1.37 (1.20 – 1.56)***

c. Adjusted for age, sex, Charlson Comorbidity Index, institutionalisation, living alone, home care, Mini-Mental State Examination score and use of antidementia drugs at baseline

d. Subdistribution hazard ratio

\*p < 0.05

\*\*p < 0.01

\*\*\*p < 0.001

**Supplementary Table 3. Association between baseline ACB scores and composite of stroke and death by dementia disorder**

	<b>AD</b>	<b>MixedD</b>	<b>VaD</b>	<b>DLB</b>	<b>FTD</b>	<b>PDD</b>	<b>Unspecified</b>	<b>Other</b>
	<b>N = 13269</b>	<b>N = 7235</b>	<b>N = 5967</b>	<b>N = 879</b>	<b>N = 639</b>	<b>N = 601</b>	<b>N = 9531</b>	<b>N = 986</b>
<b>HRs<sup>a</sup></b>								
<b>Continuous</b>	1.03 (0.99 – 1.06)	1.02 (0.98 – 1.05)	1.02 (0.99 – 1.06)	0.95 (0.87 – 1.04)	1.04 (0.93 – 1.17)	1.03 (0.95 – 1.11)	1.03 (1.00 – 1.06)	1.10 (1.00 – 1.21)*
<b>Categorical</b>								
<b>0</b>	1.00 (Reference)	1.00 (Reference)						
<b>1</b>	1.09 (1.00 – 1.19)	0.92 (0.78 – 1.02)	1.08 (0.97 – 1.21)	1.11 (0.84 – 1.46)	1.19 (0.80 – 1.78)	0.80 (0.53 – 1.20)	1.05 (0.95 – 1.15)	0.97 (0.71 – 1.34)
<b>≥2</b>	1.11 (1.00 – 1.23)*	1.08 (0.97 – 1.20)	1.06 (0.95 – 1.19)	0.83 (0.62 – 1.11)	1.44 (0.92 – 2.26)	1.02 (0.75 – 1.39)	1.21 (1.09 – 1.33)***	1.17 (0.84 – 1.63)

AD, Alzheimer's disease; MixedD, mixed dementia; VaD, vascular dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; PDD, Parkinson's disease dementia; HR, hazard ratio; CI, confidence interval

- c. Adjusted for age, sex, Charlson Comorbidity Index, institutionalisation, living alone, home care, Mini-Mental State Examination score and use of antidementia drugs at baseline
- d. Additionally adjusted for dementia disorder

\*p < 0.05

\*\*p < 0.01

\*\*\*p < 0.001