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Total anticholinergic burden and risk of mortality and cardiovascular disease over 10 years in 21,636 middle and older aged men and women of EPIC-Norfolk prospective population study

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Abstract

Background—Studies have raised concerns that medications with anti-cholinergic property have potential adverse effects on health outcomes.

Objectives—The objective of this study is to examine the prospective relationships between total anticholinergic burden (ACB) from medications and mortality, and cardiovascular disease (CVD) in a general population.

Design—Observational study.

Setting—Community cohort.

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Contributors

KTK and NJW are the Principal Investigators of EPIC-Norfolk cohort. PKM and CF conceptualized and designed the study. RNL was responsible for data management and CSK analyzed the data. PKM and CSK drafted the manuscript. All authors contributed to the study design and writing of the paper. PKM is the guarantor.

Disclosures

The authors have no conflicts of interest to declare.

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Subjects—We examined data collected from 21,636 men and women without cancer at the baseline who participated in a baseline survey 1993-1997 in the European Prospective Investigation into Cancer (EPIC)-Norfolk. They were followed until 2009/2011.

Methods—We performed Cox-proportional hazards models to determine the associations between total ACB and the subsequent risk of all-cause mortality and incident CVD during the follow up.

Results—There were a total of 4,342 people who died and 7,328 had an incident CVD during the study follow up (total person years= 322,321 years for mortality and 244,119 years for CVD event). Compared to people with no anticholinergic burden (ACB=0), people with total ACB ≥3 from medications had HRs of 1·83(1·53,2·20) and 2·17(1·87,2·52) for mortality and CVD incidence outcomes, respectively, after adjusting for potential confounders. Repeating the analyses after excluding people with prevalent illnesses, and events occurring within the first 2 years of follow up, only slightly attenuated the results.

Conclusions—There appear to be a class effect as well as dose-response relationship between the ACB and both outcomes. Future research should focus on understanding the relationship between ACB and mortality, and cardiovascular disease and possibly minimizing ACB load where feasible.

Keywords

Anticholinergic burden; Mortality; Cardiovascular diseases; Epidemiology

Introduction

The potential adverse effect of medications with anti-cholinergic (antimuscarinic) property is of particular interest in ageing populations as older people are commonly exposed to these medications [1]. Previous research however was conducted in long-term care facilities [2,3], or older people with a specific medical conditions [4].

Recent studies have classified drugs with different degree of anticholinergic cognitive burden as class 1 (score value 1), 2 (score value 2) and 3 (score value 3) drugs based on their central effect [5]. Using the same scale, Fox et al did not find deterioration of cognition in people with a diagnosis of Alzheimer's Dementia (n=224) [6], but in a larger sample of general older population (n=12,250) participating in the Medical Research Council Cognitive Function and Ageing Study (MRC-CFAS) they showed increased cumulative risk of cognitive impairment and mortality [7].

There is also evidence to suggest the relationship between anticholinergic medication use and cardiovascular disease risk [8]. However, whether the use of anticholinergic medications in a general population is associated with increased risk of mortality and incidence of CVD has not been examined previously.

In this study we used anticholinergic burden (ACB) assessed as described in Fox et al [6] (Appendix 1 in the supplementary data on the journal website (http://www.ageing.oxfordjournals.org/) to examine the relationships between total ACB at the

study baseline and all cause mortality and incidence of cardiovascular diseases in a UK population based study, European Prospective Investigation into Cancer (EPIC)-Norfolk.

Methods

Participants

Participants were men and women aged between 40-79 years from general practice age-sex registers at the study baseline during 1993-1997 in the EPIC-Norfolk, UK. The detailed study protocol of EPIC-Norfolk have been described previously [9]. Briefly, all eligible community dwelling adults from 35 participating general practices were invited to participate. A total of 25,639 participants (99·6% White British) attended a baseline health examination during 1993-1997. They provided written consent to participate in the study and the Norwich Local Research Ethics Committee approved the study.

Measurements

Details of data collection and measurement methods were described in Appendix 2 (please see Appendix 1 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/). Trained nurses measured weight, height, body mass index (BMI) and blood pressure and non-fasting venous blood samples. At the baseline participants completed a detailed health and lifestyle questionnaire which collected information on participant's educational status, occupational social class, physical activity, smoking status, alcohol consumption, prevalent illness and medications. Drugs associated with anti-cholinergic burden (Appendix 1, http://www.ageing.oxfordjournals.org/) were identified by searching the database for exact and similar entries for both generic and brand name drugs. Each medication was assigned to the corresponding anti-cholinergic score and the total anticholinergic burden (ACB) was calculated using the formula: {[number of class 1 anti-cholinergic drugs] + [the number of class 2 anti-cholinergic drugs x 2] + [the number class 3 anti-cholinergic drugs x 3]}. Classification of drugs with ACB was class 0 (none), class 1 (mild), 2 and 3 (severe) [5].

Case ascertainment

All participants were identified for death at the Office of National Statistics. Participants were also linked to NHS hospital information system and ENCORE (East Norfolk COmmission Record) for admission episodes. Mortality and incident CVD were identified from the death certificates (Office of National Statistics) or hospital discharge code ICD 9, 401 – 448 or ICD 10, I10 - I79 for CVD incidence. The follow up methods of EPIC-Norfolk had been previously validated using incident stroke cases [10].

The follow up time started at baseline for this study (date of study enrolment) and ended at end of March 2009 for CVD events and end of December 2011 for mortality outcome.

Statistical analysis

Statistical analyses were performed using STATA version 10.0 (Texas, USA) (please see Appendix 3 in the supplementary data on the journal website http://www.ageing.oxfordjournals.org/ for details). We performed Cox-proportional hazards

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models to determine the associations between ACB score groups (ACB score 1 group, ACB score 2-3 group and ACB score >3 group) and the subsequent risk of all-cause mortality and incident CVD using the ACB score 0 group as the reference group. Multivariable adjustments were made to examine how far the associations might be explained by other known lifestyle, socioeconomic and cardiovascular risk factors.

We then performed stratified analyses to examine the relationships between total ACB and outcomes by age category (<65 yrs and ≥65 yrs), sex (male and female), social class (manual and. non-manual), educational attainment (low and. high), physical activity level (low and high). To examine the impact of higher total ACB score by every 2 points increase, we constructed Cox regression models using models A, B, C and D described above. Effect of ACB class was further examined by creating eight groups of ACB use (none, class 1 drug alone, class 2 drug alone, class 3 drug alone, class 1+2, class 1+3, class 1+2+3, and class 2+3 users).

As a sensitivity analysis, propensity score matching with nearest neighbour matching was used to control for potentially confounding factors.

Results

Of 25,639 EPIC-Norfolk participants who attended the first health examination, 21,636 (10,135 men and 11,501 women) were eligible to be included in the study, after excluding participants with any missing values and those with prevalent cancer at the baseline. The mean follow ups were 14·9 years (total person years = 322,321 years) for all-cause mortality and 11·3 years (total person years = 244,119 years) for incident CVD. During the follow up there were a total of 4,342 participants who died and 7,328 had incident CVD. The flow diagram of participants and missing data table is shown in the Appendix 4 and 5 in the supplementary data on the journal website (http://www.ageing.oxfordjournals.org/).

Table 1 shows the sample characteristics and the crude rates of outcome events according to the ACB score groups. Significant differences were observed with increasing ACB score group for all variables aside from age. The participants with the higher ACB score groups (2-3 or >3) at study baseline were more likely to be older and to be women. People in the higher ACB score groups were less active, more likely to be on aspirin, or have had a diagnosis of COPD and asthma, myocardial infarction, stroke and diabetes. There were a substantially higher proportion of people who smoked (defined as current smoker) in the highest ACB group. With large sample size, although the significant overall trends were observed between the ACB score groups, there were few material differences between occupational social class, educational attainment, level of physical activity, total cholesterol level, and BMI. People who used medications with anticholinergic activity compared to non-users (ACB ≥1 groups vs. 0), had a significantly higher level of systolic BP. Higher rates of events for mortality and cardiovascular disease were observed with higher ACB score group. The overall crude mortality rates were 10·8%, 23·4%, 27·8% and 33·7% for ACB score 0, 1, 2-3 and >3 groups respectively. The respective crude overall cardiovascular events were 14·0%, 33·3%, 40·1% and 49·3% over the entire duration of follow up.

Table 2 presents the Cox-proportional Hazards Ratios and corresponding 95% confidence intervals (95%CI) for the risk of death and incidence of CVD during the respective study follow up periods by ACB score group. Consistent results were observed with higher ACB score groups being associated with a worse outcome for both mortality and CVD incidence. For both outcomes, higher levels of adjustments were associated with attenuation in risk but the HRs remained highly significant. Exclusion of people with prevalent conditions, and exclusion of events occurring within the first two years of follow up did not alter the results.

Appendix 6 shows the adjusted HRs for mortality and incident CVD outcomes in stratified analyses. In all analyses higher ACB score group was associated with a significantly increased risk of both mortality and incident CVD. The subgroup analyses demonstrated that participants with higher ACB score and age less than 65 years lacked overlap between 95% confidence intervals but there was considerable overlap between the 95% confidence intervals for each strata of gender, social class, education level and physical activity given the same total ACB. The adjusted HRs for mortality and incident CVD outcomes after excluding people with prevalent chronic co-morbidities (asthma, COPD, diabetes, stroke and MI) by ACB score groups is shown in the Appendix 7 (http://www.ageing.oxfordjournals.org/). In general similar trends in HRs were observed as those without exclusion of prevalent illnesses.

Appendix 8 A shows the adjusted HRs for selected models as in the table 2 for both mortality and incident CVD outcome by every 2 points increase in ACB score. The crude event rates and data are shown in the Appendix 9 (http://www.ageing.oxfordjournals.org/). In fully adjusted model (model C), every 2 point increase in ACB was associated with an increase in 29% relative risk of death and an increase in 40% relative risk of incident CVD during follow-up. Appendix 8 B shows the risk of mortality and incident CVD outcomes with various combinations of ACB classes. This suggested an ACB class effect with combined use of higher class ACB drugs associated with a worse outcome. The crude event rates and data are shown in the Appendix 10 (http://www.ageing.oxfordjournals.org/).

The propensity score matched analyses of the 3 matched cohorts showed similar increased of risk of death and CVD with ACB score ≥1 groups compared to ACB score 0 group. (Appendix 11, Appendix 12).

Discussion

We found that people with baseline higher total ACB from medications were at increased risk of mortality and cardiovascular events compared to those with no or lower total ACB in a UK general population of middle and older age. There appeared to be a linear dose response relationship, as well as additive effect of combination of drugs with different anticholinergic burden. While participants with higher anticholinergic burden were older and more likely to have prior cardiovascular co-morbidities, similar results are seen even after adjustment for these variables and other potential confounders as well as repeating the analyses after excluding those with major prevalent illnesses.

The existing literature on anticholinergic drugs and mortality shows inconsistent results but they have been conducted on high-risk populations such as participants from elderly residential or long term care facilities [2,3], geriatric wards and nursing homes [11], among the elderly hospitalized patients with hip fracture [12,13], and elderly patients with cardiovascular disease [4]. There are only a few studies which have been conducted among the community dwelling older adults [4,7,15]. In general, the results of these studies are inconsistent. Cohorts of hospitalized participants with hip fractures [12, 13] and community dwelling and institutionalized participants [7] showed that a higher anticholinergic activity was associated with increased mortality. However other studies of long term or residential care facility participants [2,3], older community dwellers [4, 14] and geriatric wards or nursing homes [11] failed to demonstrate this relationship.

A few potential mechanisms may explain why anticholinergic medications may increase mortality and incidence of CVD. A recent report suggests that anticholinergic medications are pro-arrhythmic and pro-ischaemic [15]. It has been suggested the inhibition of parasympathetic control of the heart may be associated with increased hemodynamic lability, cardiac ischaemia, and cardiac dysrhythmias in response to cardiac ischaemia [16]. In addition, studies have found that certain anticholinergic drugs such as imipramine and clozapine decrease heart rate variability [17] and this may contribute to adverse cardiovascular events. Another plausible mechanism is via immuno-modulation as the cholinergic system plays an important role in regulating immune response. Nicotinic receptor activation causes autonomic and vagal systems to inhibit adaptive and innate immune response [18], and it is possible that inhibition of these systems may lead to an inflammatory response and subsequent increased risk of mortality and CVD in people who already possess risk factors.

Our study has several strengths. The data were prospectively collected which reduces recall bias. The sample size was large enough to capture a sufficient number of participants with high anticholinergic burden as well as allow us to test the differences in risk between individuals with higher and lower degrees of anticholinergic burden. Our sample population had wide age spectrum, social and demographic variation and we were able to take into account co-morbidities, other lifestyle factors.

Our study has limitations. Due to the requirement to attend a health examination, the response rate at the study baseline (1993-1997) was modest at ~ 40% in EPIC-Norfolk introducing a healthy responder effect from the outset. Nevertheless, baseline characteristics of the study population are similar to other UK population samples except with a slightly lower prevalence of smokers [9]. Moreover, this should not affect the associations observed within the study participants; if anything, truncation of the distribution is likely to reduce power for any associations. In addition, ~2600 participants were excluded due to missing data and this could potentially introduce bias to the regression coefficients. The current analysis was not part of the pre-registered analysis plan of the EPIC-Norfolk study and this may have implications on generalisability of the findings as the analysis to some extent is contingent on the data. There were only single measurements of covariates such as cholesterol, blood pressure etc. The blood sample taken was non-fasting sample and therefore less standardized for some of the parameters (e.g. cholesterol level). Nevertheless,

random measurement error is likely only to attenuate any associations observed. Ascertainment of drug exposure was based on a baseline self-report. We do not know whether participants continued to take their medication over the follow up period as we were unable to measure the pattern and the duration of drug usage over time and this could have led to misclassification. Although we were able to calculate total ACB, we were not able to identify particular drugs which are potentially linked to adverse outcomes. The validity of the models of analysis is unknown but the results appear to be robust to different parameterisations of ACB.

A major limitation in assessing the association between medications and health outcomes is the difficulty in evaluating the possible effect of confounding and reverse causality. Nevertheless, the associations remained after adjustment for known risk factors for cardiovascular disease and mortality and even after excluding individuals with known prevalent illnesses and those with events in the first few years who may have had preclinical conditions. Though we cannot exclude residual confounding, the limited data from randomized controlled trials of anticholinergics are also consistent with a causal relationship [8,19].

In summary, our study indicates a potential negative impact of medications with anticholinergic properties on mortality and CVD incidence in middle and older age population. This has implications in clinical practice as anticholinergic drugs are commonly prescribed, especially among the older people with long term conditions. While the relationships were prospective, it remains unclear whether there was a causal relationship. Nonetheless, the potential benefits of drug use must be weighed against adverse effects so it is recommended that patients should undergo regular medication review and discontinuation of unnecessary anticholinergic drugs should be considered. Future studies should explore whether systematic attempts to reduce the anticholinergic burden may improve health outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Chew ML, Mulsant BH, Pollock BG, et al. Anticholinergic activity of 107 medications commonly used by older adults. J Am Geriatr Soc. 2008; 56:1333–1341. [PubMed: 18510583]
2. Kumpula E-K, Bell JS, Soini H, Pitkala KH. Anticholinergic drug use and mortality among residents of long-term care facilities: a prospective cohort study. J Clin Pharmacol. 2011; 51:256. [PubMed: 20489026]
3. Wilson NM, Hilmer SN, March LM, et al. Associations between drug burden index and mortality in older people in residential aged care facilities. Drugs Aging. 2012; 29:157–65. [PubMed: 22276959]

4. Uusvaara J, Pitkala KH, Kautiainen H, Tilvis RS, Strandberg TE. Association of anticholinergic drugs with hospitalization and mortality among older cardiovascular patients. Drugs Aging. 2011; 28:131–138. [PubMed: 21275438]
5. Boustani M, Campbell N, Munger S, Maidment ID, Fox C. The Impact of Anticholinergics on the Aging Brain: A Review and Practical Application. Aging Health. 2008; 4:311–20.
6. Fox C, Livingston G, Maidment ID, et al. The impact of anticholinergic burden in Alzheimer's dementia-the LASER-AD study. Age Ageing. 2011; 40:730–5. [PubMed: 21926432]
7. Fox C, Richardson K, Maidment I, et al. on behalf of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Anticholinergic Medication Use and Cognitive Impairment in the Older Population: The Medical Research Council Cognitive Function and Ageing Study. J Am Geriatr Soc. 2011; 59:1477–83. [PubMed: 21707557]
8. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA. 2008; 300:1439–1450. [PubMed: 18812535]
9. Day N, Oakes S, Luben R, et al. EPIC-Norfolk: study design and characteristics of the cohort. European Prospective Investigation of Cancer. Br J Cancer. 1999; 80:95–103. [PubMed: 10466767]
10. Sinha S, Myint PK, Luben RN, Khaw KT. Accuracy of death certification and hospital record linkage for identification of incident stroke. BMC Med Res Methodol. 2008; 8:74. [PubMed: 19000303]
11. Luukkanen MJ, Uusvaara J, Laurila JV, et al. Anticholinergic drugs and their effects on delirium and mortality in the elderly. Dement Geriatr Cogn Disord Extra. 2011; 1:43–50.
12. Mangoni A, van Munster BC, Woodman RJ, de Rooij SE. Measures of anticholinergic drug exposure, serum anticholinergic activity, and all-cause post discharge mortality in older hospitalized patients with hip fractures. Am J Geriatr Psychiatry. 2013; 21:785–93. [PubMed: 23567395]
13. Panula J, Puustinen J, Jaatinen P, Vahlberg T, Aarnio P, Kivela SL. Effects of potent anticholinergics, sedatives and antipsychotics on postoperative mortality in elderly patients with hip fracture: a retrospective, population-based study. Drug Aging. 2009; 26:963–971.
14. Boudreau DM, Yu O, Gray SL, Raebel MA, Johnson J, Larson EB. Concomitant use of cholinesterase inhibitors and anticholinergics: prevalence and outcomes. JAGS. 2011; 59:2069–2076.
15. Singh S, Loke YK, Enright P, Furberg CD. Pro-arrhythmic and pro-ischaemic effects of inhaled anticholinergic medications. Thorax. 2013; 68:114–116. [PubMed: 22764216]
16. Parlow JL, van Vlymen JM, Odell MJ. The Duration of Impairment of Autonomic Control After Anticholinergic Drug Administration in Humans. Anesth Analg. 1997; 84:155–9. [PubMed: 8989017]
17. O'Brien P, Oyebode F. Psychotropic medication and the heart. APT. 2003; 9:414–423.
18. Razani-Boroujerdi S, Behl M, Hahn FF, Pena-Philippides JC, Hutt J, Sopori ML. Role of muscarinic receptors in the regulation of immune and inflammatory responses. J Neuroimmunol. 2008; 194:83–88. [PubMed: 18190972]
19. Daumit GL, Goff DC, Meyer JM, et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. Schizophr Res. 2008; 105:175–87. [PubMed: 18775645]

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Key points

1. People with higher total anticholinergic burden (ACB) from medications had increased risk of mortality and cardiovascular events.
2. There was a linear dose response relationship, and an additive effect of combination of drugs with ACB.
3. Future research should examine the relationship between ACB and adverse outcomes and possibly minimize the ACB load.
4. It would be prudent to minimize the ACB load where feasible.

Table 1

Sample characteristics of 21,636 men and women of the EPIC-Norfolk (1993/1997-2009/2011) according to the total anticholinergic burden (ACB) score

	ACB score 0 group (n=17,317)	ACB score 1 group (n=2,704)	ACB score 2-3 group (n=1,324)	ACB score >3 group (n=291)	P
Age (years)	57.9 (9.1)	62.9 (8.8)	62.2 (9.2)	63.1 (8.9)	0.07
Sex					0.003
Men	8,068 (47)	1,348 (50)	593 (45)	126 (43)	
Women	9,249 (53)	1,356 (50)	731 (55)	165 (57)	
Social class					<0.0001 *
Professional	1,268 (7)	164 (6)	68 (5)	19 (7)	
Manager	6,475 (37)	927 (34)	446 (34)	80 (27)	
Skilled non-manual	2,806 (16)	464 (17)	234 (18)	58 (20)	
Skilled manual	3,978 (23)	637 (24)	321 (24)	78 (27)	
Semi-skilled	2,239 (13)	403 (15)	193 (15)	43 (15)	
Non-skilled	551 (3)	109 (4)	62 (5)	13 (4)	
Smoking					<0.0001 *
Current-smoker	2,038 (12)	256 (9)	155 (12)	51 (18)	
Ex-smoker	7,153 (41)	1,324 (49)	626 (47)	122 (42)	
Never smoker	8,126 (47)	1,124 (42)	543 (41)	118 (41)	
Alcohol use (units/week)	7.5 (9.6)	6.8 (9.6)	6.0 (8.3)	5.2 (7.9)	<0.0001
Education level					<0.0001 *
No qualification	5,827 (34)	1,152 (43)	598 (45)	132 (45)	
0-Level	1,886 (11)	255 (9)	111 (8)	25 (9)	
A-Level	7,202 (42)	1039 (38)	504 (38)	108 (37)	
Higher degree	2,402 (14)	258 (10)	113 (9)	26 (9)	
Physical activity					<0.0001 *
Inactive	4,608 (27)	1,037 (38)	552 (42)	142 (49)	
Moderately inactive	5,017 (29)	760 (28)	361 (27)	86 (30)	
Moderately active	4,187 (24)	520 (19)	234 (18)	40 (14)	
Active	3,505 (20)	387 (14)	177 (13)	23 (8)	
Cholesterol (mmol/L)	6.1 (1.1)	6.3 (1.2)	6.3 (1.2)	6.4 (1.1)	<0.0001
Systolic BP (mmHg)	134 (18)	140 (19)	137 (19)	138 (19)	0.001
BMI (kg/m^2)	26.1 (3.7)	27.0 (4.2)	26.9 (4.1)	27.2 (4.4)	<0.0001
COPD	1,425 (8)	346 (13)	184 (14)	40 (14)	<0.0001
Asthma	896 (5)	630 (23)	204 (15)	58 (20)	<0.0001

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	ACB score 0 group (n=17,317)	ACB score 1 group (n=2,704)	ACB score 2-3 group (n=1,324)	ACB score >3 group (n=291)	P
Previous MI	253 (1)	222 (8)	153 (12)	31 (11)	<0.0001
Previous stroke	131 (1)	78 (3)	52 (4)	13 (4)	<0.0001
Diabetes	286 (2)	102 (4)	59 (4)	17 (6)	<0.0001
Aspirin use	1,234 (7)	479 (18)	268 (20)	65 (22)	<0.0001
New CVD events	4,939 (29)	1,459 (54)	751 (57)	179 (62)	<0.0001
Deaths	2,833 (16)	887 (33)	498 (38)	124 (43)	<0.0001

Values presented are mean (sd) for continuous and number (%) for categorical data. *overall P value. BP=blood pressure, BMI = body mass index, COPD= chronic obstructive pulmonary disease; MI=myocardial infarction, CVD= cardiovascular diseases. Total anticholinergic burden (ACB) calculated as a score which is the sum of the [number of class 1 anticholinergic drugs, the number of class 2 anticholinergic drugs x2 and the number class 3 anticholinergic drugs x3]. Classification of drugs with ACB class 1, 2 and 3 based on criteria of Anticholinergic Cognitive Burden Scale *(Boustani MA, et al 2008;4:311–320).*

Table 2

Risk of mortality and incident cardiovascular event according to total anticholinergic burden score (0, 1, 2-3 or >3) during follow up (1993-2011) in EPIC-Norfolk

Models	Mortality (Events (n)/Total N=4,342/21,636)				
	ACB score 0 group	**ACB score 1 group**	**ACB score 2-3 group**	**ACB score >3 group**	**p-value**
A	1.00	1.42 (1.32-1.54)	1.90 (1.73-2.10)	2.20 (1.84-2.64)	<0.00001
B	1.00	1.39 (1.29-1.50)	1.85 (1.68-2.04)	2.07 (1.73-2.48)	<0.00001
C	1.00	1.28 (1.18-1.39)	1.65 (1.49-1.82)	1.83 (1.53-2.20)	<0.00001
D*	1.00	1.34 (1.22-1.48)	1.58 (1.38-1.80)	2.08 (1.63-2.66)	<0.00001
E#	1.00	1.25 (1.16-1.36)	1.63 (1.47-1.81)	1.68 (1.38-2.04)	<0.00001
F	1.00	1.27(1.18-1.38)	1.63(1.48-1.81)	1.82(1.51-2.18)	<0.00001
Models	Cardiovascular disease incidence (Events (n)/Total N=7,328/21,636)				
	ACB score 0 group	ACB score 1 group	ACB score 2-3 group	ACB score >3 group	p-value
A	1.00	1.77 (1.66-1.87)	2.18 (2.02-2.36)	2.48 (2.14-2.88)	<0.00001
B	1.00	1.65 (1.57-1.75)	2.09 (1.93-2.26)	2.40 (2.06-2.78)	<0.00001
C	1.00	1.51 (1.42-1.61)	1.86 (1.72-2.02)	2.17 (1.87-2.52)	<0.00001
D*	1.00	1.70 (1.58-1.83)	1.82 (1.64-2.02)	2.26 (1.84-2.77)	<0.00001
E#	1.00	1.50 (1.41-1.60)	1.85 (1.71-2.01)	2.05 (1.75-2.40)	<0.00001
F	1.00	1.48 (1.39-1.57)	1.81(1.68-1.96)	2.10(1.80-2.44)	<0.00001

ACB = Anticholinergic burden score.
Model A: adjusted for age and sex.
Model B: Model A plus smoking, alcohol consumption, physical activity level, education level, occupational social class, systolic blood pressure, cholesterol level and body mass index.
Model C: Model B plus prevalent conditions asthma, COPD, diabetes, stroke and myocardial infarction.
Model D: as in Model B excluding people with prevalent asthma, COPD, diabetes, stroke and myocardial infarction.
Model E: as in Model C excluding all events occurring within first two years of follow up.
Model F: Model C plus aspirin use.

*Model D=n/N=3,029/17,242 for mortality analysis, n/N=5,270/17,242 for CV events analysis

#Model E= n/N=4,141/21,435 for mortality analysis, n/N=7,208/21,435 for CV events analysis.