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

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Abstract

Background: studies have raised concerns that medications with anticholinergic 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.

Subjects: we examined data collected from 21,636 men and women without cancer at the baseline who participated in a baseline survey 1993–97 in the European Prospective Investigation into Cancer (EPIC)-Norfolk. They were followed until 2009/11.

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 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 with people with no anticholinergic burden (ACB = 0), people with total ACB ≥3 from medications had hazards ratios 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.

Conclusion: 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 minimising ACB load where feasible.

Keywords: anticholinergic burden, mortality, cardiovascular diseases, epidemiology, older people
Introduction

The potential adverse effect of medications with anticholinergic (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 in 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. [6] did not find deterioration of cognition in people with a diagnosis of Alzheimer's dementia \( (n = 224) \), 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 (CVD) 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 by Fox et al. [6] (Supplementary data, Appendix 1 available in Age and Ageing online) to examine the relationships between total ACB at the study baseline and all-cause mortality and incidence of CVDs in a UK population-based study, European Prospective Investigation into Cancer (EPIC)-Norfolk.

Methods

Participants

Participants were men and women aged between 40 and 79 years from general practice age-sex registers at the study baseline during 1993–97 in the EPIC-Norfolk, UK. The detailed study protocol of EPIC-Norfolk has 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 1993–97. 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 Supplementary data, Appendix 2 available in Age and Ageing online (see also Supplementary data, Appendix 1 available in Age and Ageing online). 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 that collected information on participant’s educational status, occupational social class, physical activity, smoking status, alcohol consumption, prevalent illness and medications. Drugs associated with anticholinergic burden (Supplementary data, Appendix 1 available in Age and Ageing online) 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 anticholinergic score, and the total ACB was calculated using the formula: \{[the number of Class 1 anticholinergic drugs] + [the number of Class 2 anticholinergic drugs × 2] + [the number Class 3 anticholinergic drugs × 3]\}. Classification of drugs with ACB was Class 0 (none), Class 1 (mild) and also Classes 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, 110–179 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) (Supplementary data, Appendix 3 available in Age and Ageing online). We performed Cox-proportional hazards 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, socio-economic and cardiovascular risk factors.

We then performed stratified analyses to examine the relationships between total ACB and outcomes by age category (<65 years and ≥65 years), sex (male and female), social class (manual and non-manual), educational attainment (low and high) and physical activity level (low and high). To examine the impact of higher total ACB score by every 2-point 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 died and 7,328 had incident CVD. The flow diagram of participants and missing data table is shown in the Supplementary data, Appendix 4 and 5 available in Age and Ageing online.

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

Table 1. Sample characteristics of 21,636 men and women of the EPIC-Norfolk (1993/97–2009/11) according to the total ACB score

<table>
<thead>
<tr>
<th></th>
<th>ACB score 0 group (n = 17,317)</th>
<th>ACB score 1 group (n = 2,704)</th>
<th>ACB score 2–3 group (n = 1,324)</th>
<th>ACB score &gt;3 group (n = 291)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>57.9 (9.1)</td>
<td>62.9 (8.8)</td>
<td>62.2 (9.2)</td>
<td>63.1 (8.9)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Men</td>
<td>8,068 (47)</td>
<td>1,348 (50)</td>
<td>593 (45)</td>
<td>126 (43)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>9,249 (53)</td>
<td>1,356 (50)</td>
<td>731 (55)</td>
<td>165 (57)</td>
<td></td>
</tr>
<tr>
<td><strong>Social class</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Professional</td>
<td>1,268 (7)</td>
<td>164 (6)</td>
<td>68 (5)</td>
<td>19 (7)</td>
<td></td>
</tr>
<tr>
<td>Manager</td>
<td>6,475 (37)</td>
<td>927 (34)</td>
<td>446 (34)</td>
<td>80 (27)</td>
<td></td>
</tr>
<tr>
<td>Skilled non-manual</td>
<td>2,806 (16)</td>
<td>464 (17)</td>
<td>234 (18)</td>
<td>58 (20)</td>
<td></td>
</tr>
<tr>
<td>Skilled manual</td>
<td>3,978 (23)</td>
<td>637 (24)</td>
<td>321 (24)</td>
<td>78 (27)</td>
<td></td>
</tr>
<tr>
<td>Semi-skilled</td>
<td>2,239 (13)</td>
<td>403 (15)</td>
<td>193 (15)</td>
<td>43 (15)</td>
<td></td>
</tr>
<tr>
<td>Non-skilled</td>
<td>551 (3)</td>
<td>109 (4)</td>
<td>62 (5)</td>
<td>13 (4)</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Current smoker</td>
<td>2,038 (12)</td>
<td>256 (9)</td>
<td>155 (12)</td>
<td>51 (18)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>7,153 (41)</td>
<td>1,324 (49)</td>
<td>626 (47)</td>
<td>122 (42)</td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>8,126 (47)</td>
<td>1,124 (42)</td>
<td>543 (41)</td>
<td>118 (41)</td>
<td></td>
</tr>
<tr>
<td><strong>Alcohol use (units/week)</strong></td>
<td>7.5 (9.6)</td>
<td>6.8 (9.6)</td>
<td>6.0 (8.3)</td>
<td>5.2 (7.9)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No qualification</td>
<td>5,827 (34)</td>
<td>1,152 (43)</td>
<td>598 (45)</td>
<td>132 (45)</td>
<td></td>
</tr>
<tr>
<td>A-Level</td>
<td>1,886 (11)</td>
<td>255 (9)</td>
<td>111 (8)</td>
<td>25 (9)</td>
<td></td>
</tr>
<tr>
<td><strong>Higher degree</strong></td>
<td>7,202 (42)</td>
<td>1,039 (38)</td>
<td>504 (38)</td>
<td>108 (37)</td>
<td></td>
</tr>
<tr>
<td><strong>Physical activity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Inactive</td>
<td>4,608 (27)</td>
<td>1,037 (38)</td>
<td>552 (42)</td>
<td>142 (49)</td>
<td></td>
</tr>
<tr>
<td>Moderately inactive</td>
<td>5,017 (29)</td>
<td>760 (28)</td>
<td>361 (27)</td>
<td>86 (30)</td>
<td></td>
</tr>
<tr>
<td>Moderately active</td>
<td>4,417 (24)</td>
<td>520 (19)</td>
<td>234 (18)</td>
<td>40 (14)</td>
<td></td>
</tr>
<tr>
<td>Active</td>
<td>3,505 (20)</td>
<td>387 (14)</td>
<td>177 (13)</td>
<td>23 (8)</td>
<td></td>
</tr>
<tr>
<td><strong>Cholesterol (mmol/l)</strong></td>
<td>6.1 (1.1)</td>
<td>6.3 (1.2)</td>
<td>6.3 (1.2)</td>
<td>6.4 (1.1)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Systolic BP (mmHg)</strong></td>
<td>134 (18)</td>
<td>140 (19)</td>
<td>137 (19)</td>
<td>138 (19)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>26.1 (3.7)</td>
<td>27.0 (4.2)</td>
<td>26.9 (4.1)</td>
<td>27.2 (4.4)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td>1,425 (8)</td>
<td>346 (13)</td>
<td>184 (14)</td>
<td>40 (14)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>896 (5)</td>
<td>630 (23)</td>
<td>204 (15)</td>
<td>58 (20)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Aspirin use</strong></td>
<td>2,234 (7)</td>
<td>479 (18)</td>
<td>268 (20)</td>
<td>65 (22)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>New CVD events</strong></td>
<td>4,939 (29)</td>
<td>1,459 (54)</td>
<td>751 (57)</td>
<td>179 (62)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td><strong>Deaths</strong></td>
<td>2,833 (16)</td>
<td>887 (33)</td>
<td>498 (38)</td>
<td>124 (43)</td>
<td>&lt;0.0001*</td>
</tr>
</tbody>
</table>

Values presented are mean (sd) for continuous and number (%) for categorical data.

BP, blood pressure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CVD, cardiovascular diseases.

*Overall P value. Total ACB calculated as a score which is the sum of the [number of Class 1 anticholinergic drugs, the number of Class 2 anticholinergic drugs × 2 and the number of Class 3 anticholinergic drugs × 3]. Classification of drugs with ACB Classes 1, 2 and 3 based on criteria of Anticholinergic Cognitive Burden Scale (From Boustani et al. [5]).
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 with non-users (ACB ≥ 2 groups versus 0) had a significantly higher level of systolic BP. Higher rates of events for mortality and CVD 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 hazard ratios (HRs) remained highly significant. Exclusion of people with prevalent conditions and exclusion of events occurring within the first 2 years of follow-up did not alter the results.

Supplementary data, Appendix 6 available in *Age and Ageing* online show the adjusted HRs for mortality and incident CVD outcomes with various combinations of ACB online. In general, similar trends in HRs were observed as those without exclusion of prevalent illnesses.

Supplementary data, Appendix 8A available in *Age and Ageing* online show the adjusted HRs for selected models as in the Table 2 for both mortality and incident CVD outcome by every 2-point increase in ACB score. The crude event rates and data are shown in the Supplementary data, Appendix 9 available in *Age and Ageing* online. 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. Supplementary data, Appendix 8B available in *Age and Ageing* online show the risk of mortality and incident CVD outcomes with various combinations of ACB classes. This suggested an ACB class effect with combined

### 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

<table>
<thead>
<tr>
<th>Models</th>
<th>Mortality (Events/Total N = 4,342/21,636)</th>
<th>CVD incidence (Events/Total N = 7,328/21,636)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACB score 0 group</td>
<td>ACB score 1 group</td>
</tr>
<tr>
<td>A</td>
<td>1.00</td>
<td>1.42 (1.32–1.54)</td>
</tr>
<tr>
<td>B</td>
<td>1.00</td>
<td>1.39 (1.29–1.50)</td>
</tr>
<tr>
<td>C</td>
<td>1.00</td>
<td>1.28 (1.18–1.39)</td>
</tr>
<tr>
<td>D*</td>
<td>1.00</td>
<td>1.34 (1.24–1.48)</td>
</tr>
<tr>
<td>E*</td>
<td>1.00</td>
<td>1.25 (1.16–1.36)</td>
</tr>
<tr>
<td>F</td>
<td>1.00</td>
<td>1.27 (1.18–1.38)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Models</th>
<th>CVD score 0 group</th>
<th>CVD score 1 group</th>
<th>CVD score 2–3 group</th>
<th>CVD score &gt;3 group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.00</td>
<td>1.77 (1.66–1.87)</td>
<td>2.18 (2.02–2.36)</td>
<td>2.48 (2.14–2.88)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>B</td>
<td>1.00</td>
<td>1.65 (1.57–1.75)</td>
<td>2.09 (1.93–2.26)</td>
<td>2.40 (2.06–2.78)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>C</td>
<td>1.00</td>
<td>1.51 (1.42–1.61)</td>
<td>1.86 (1.72–2.02)</td>
<td>2.17 (1.87–2.52)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>D*</td>
<td>1.00</td>
<td>1.70 (1.58–1.83)</td>
<td>1.82 (1.64–2.02)</td>
<td>2.26 (1.84–2.77)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>E*</td>
<td>1.00</td>
<td>1.50 (1.41–1.60)</td>
<td>1.85 (1.71–2.01)</td>
<td>2.05 (1.73–2.40)</td>
<td>&lt;0.00001</td>
</tr>
<tr>
<td>F</td>
<td>1.00</td>
<td>1.48 (1.39–1.57)</td>
<td>1.81 (1.68–1.96)</td>
<td>2.10 (1.80–2.44)</td>
<td>&lt;0.00001</td>
</tr>
</tbody>
</table>

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 2 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 CVD events analysis.

*Model E = n/N = 4,141/21,435 for mortality analysis, n/N = 7,208/21,435 for CVD events analysis.
use of higher class ACB drugs associated with a worse outcome. The crude event rates and data are shown in the Supplementary data, Appendix 10 available in Age and Ageing online.

The propensity score matched analyses of the three matched cohorts showed similar increase in risk of death and CVD with ACB score ≥1 groups compared with ACB score 0 group (Supplementary data, Appendix 11 and 12 available in Age and Ageing online).

Discussion

We found that people with baseline higher total ACB from medications were at increased risk of mortality and cardiovascular events compared with those with no or lower total ACB in middle-aged and older UK general population. There appeared to be a linear dose–response relationship, as well as additive effect of combination of drugs with different ACB. While participants with higher ACB 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 hospitalised patients with hip fracture [12, 13], and elderly patients with CVD [4]. There are only a few studies that have been conducted among the community-dwelling older adults [4, 7, 14]. In general, the results of these studies are inconsistent. Cohorts of hospitalised particip-

ants with hip fractures [12, 13] and community-dwelling and institutionalised 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, 15] 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 [14]. It has been suggested the inhibition of parasymptomatic control of the heart may be associated with increased haemodynamic 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 reduce recall bias. The sample size was large enough to capture a sufficient number of participants with high ACB as well as allow us to test the differences in risk between individuals with higher and lower degrees of ACB. 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 (1993–97) 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, ~2,600 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 co-variates such as cholesterol, blood pressure, etc. The blood sample taken was non-fasting sample and therefore less standardised 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 that 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 CVD 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 randomised 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-aged and older 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 ACB may improve health outcomes.

**Key points**

- People with higher total ACB from medications had increased risk of mortality and cardiovascular events.
- There was a linear dose–response relationship, and an additive effect of combination of drugs with ACB.
- Future research should examine the relationship between ACB and adverse outcomes and possibly minimise the ACB load.
- It would be prudent to minimise the ACB load where feasible.

**Authors’ contributions**

K.T.K. and N.J.W. are the Principal Investigators of EPIC-Norfolk cohort. P.K.M. and C.F. conceptualised and designed the study. R.N.L. was responsible for data management and C.S.K. analysed the data. P.K.M. and C.S.K. drafted the manuscript. All authors contributed to the study design and writing of the paper. P.K.M. is the guarantor.

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**Conflicts of interest**

None declared.

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**Supplementary data**

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

**References**

15. Boudreau DM, Yu O, Gray SL, Raebel MA, Johnson J, Larson EB. Concomitant use of cholinesterase inhibitors and...

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Functional status and co-morbidities are associated with in-hospital mortality among older patients with acute decompensated heart failure: a multicentre prospective cohort study

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Abstract

Background: among patients admitted for acute decompensated heart failure (ADHF), half are aged 75 years or over. The high prevalence of co-morbidities and functional impairments in this age group may affect patient outcomes.

Objective: to assess the association between co-morbidities, functional status and in-hospital mortality in patients with ADHF aged ≥75 years.

Design: a prospective, multicentre cohort study.

Setting: five French hospitals.

Subjects: five hundred and fifty-five patients aged ≥75 years admitted to the emergency department with ADHF.

Methods: baseline clinical data and co-morbidities were recorded at admission. Functional status and cognition were assessed using the Katz index and Mini-Mental Status Examination score, respectively. The primary outcome was in-hospital mortality.

Results: we found high prevalences of co-morbidities and functional impairments including hypertension (74.0%), atrial fibrillation (40.2%), prior acute coronary syndrome (32.3%) and diabetes (18.2%). The average creatinine clearance was 56.3 ml/min/1.73 m² (interquartile range, 39.2–77.0). In-hospital mortality was 67/555 (12.1%; 95% confidence interval, 9.4–14.8). In