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Baseline anticholinergic burden from medications predicts poorer baseline and long-term health-related quality of life in 16,675 men and women of EPIC-Norfolk prospective population-based cohort study

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Abstract:	Background: Previous studies investigating the association between anticholinergic burden (ACB) and health-related quality of life (HRQoL) showed conflicting results and focused on older adults or specific patient groups only. Methods: Participants from the European Prospective Investigation of Cancer Norfolk. study were divided into three groups according to their ACB from medications at baseline, representing ACB scores of 0, 1 and ≥2. Outcomes of interest were the physical and mental component summary scores (PCS and MCS) of the Short Form-36, collected at 18 months from the baseline and again after a mean 13 years of follow-up. Linear regression and logistic regression for cross-sectional and longitudinal associations between ACB and HRQoL were constructed adjusting for potential confounders. Results. A total of 16,675 participants, mean age 58.9±9.1 years (55.6% female) and 7133 participants, mean age at follow-up 69.1±8.7 years (56.8% female), were included in the cross-sectional and longitudinal analysis, respectively. In cross-sectional analysis higher anticholinergic burden was associated with higher odds of being in the

	lowest quartile of PCS (ACB=1: OR 1.85[1.64, 2.09] and ACB>2: 2.19[1.85, 2.58] and MCS (ACB=1:1.47[1.30, 1.66] and ACB>2:1.68[1.42, 1.98]). In longitudinal analysis higher anticholinergic burden was similarly associated with higher odds of being in the lowest quartile of PCS (ACB=1: 1.56[1.24, 1.95] and ACB>2: 1.48[1.07, 2.03]) compared to ACB 0 group. The association with MCS scores did not reach statistical significance. Conclusion The use of anticholinergic medications is associated with both short and long-term poorer physical function but association with mental functioning appears more short-term.

Baseline anticholinergic burden from medications predicts poorer baseline and long-term health-related quality of life in 16,675 men and women of EPIC-Norfolk prospective population-based cohort study

Running head: Anticholinergic burden and functional health in EPIC-Norfolk

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ABSTRACT

Background: Previous studies investigating the association between anticholinergic burden (ACB) and health-related quality of life (HRQoL) showed conflicting results and focused on older adults or specific patient groups only.

Methods: Participants from the European Prospective Investigation of Cancer Norfolk. study were divided into three groups according to their ACB from medications at baseline, representing ACB scores of 0, 1 and ≥2. Outcomes of interest were the physical and mental component summary scores (PCS and MCS) of the Short Form-36, collected at 18 months from the baseline and again after a mean 13 years of follow-up. Linear regression and logistic regression for cross-sectional and longitudinal associations between ACB and HRQoL were constructed adjusting for potential confounders.

Results. A total of 16,675 participants, mean age 58.9±9.1 years (55.6% female) and 7133 participants, mean age at follow-up 69.1±8.7 years (56.8% female), were included in the cross-sectional and longitudinal analysis, respectively. In cross-sectional analysis higher anticholinergic burden was associated with higher odds of being in the lowest quartile of PCS (ACB=1: OR 1.85[1.64, 2.09] and ACB≥2: 2.19[1.85, 2.58] and MCS (ACB=1:1.47[1.30, 1.66] and ACB≥2:1.68[1.42, 1.98]). In longitudinal analysis higher anticholinergic burden was similarly associated with higher odds of being in the lowest quartile of PCS (ACB=1: 1.56[1.24, 1.95] and ACB≥2: 1.48[1.07, 2.03]) compared to ACB 0 group. The association with MCS scores did not reach statistical significance.

Conclusion The use of anticholinergic medications is associated with both short and long-term poorer physical function but association with mental functioning appears more short-term.

Key words: Anticholinergic burden, antimuscarinic, health-related quality of life, physical functional health, mental functional health

Key messages

- Previous studies on anticholinergic burden (ACB) and health-related quality of life (HRQoL) have yielded conflicting results and been limited by small sample size.
- In the cross-sectional analysis of 16,675 participants, anticholinergic burden was independently associated with poorer physical and mental HRQoL.
- In the longitudinal analysis with 7133 participants we demonstrated that baseline anticholinergic burden predicted poorer physical HRQoL at 13 years follow-up.

INTRODUCTION

Polypharmacy is a common and growing phenomenon, especially in older people. Medications with anticholinergic properties are of special interest in this area, with up to 50% of the older population prescribed at least one such medicine (1). Anticholinergics have long been associated with potential adverse effects that can be caused by their cumulative burden. A systematic review by *Fox et al.* including 46 studies linked anticholinergics to decline in cognitive as well as physical function, with limited evidence associating them with mortality outcomes (2). Anticholinergics have also been associated with dry mouth, constipation and blurred vision (3), with recent studies linking them to risk of falls (4) as well as stroke (5). However, few studies have investigated the impact of anticholinergic burden on patients' health-related quality of life and they are limited by small sample sizes as well as they only focused on patients with specific conditions (e.g. dementia) or specific populations (older adults only) (6-9).

Health-related quality of life (HRQoL) is an important health concept that measures the effects of health conditions on an individual's subjective sense of physical and mental well-being (10). HRQoL questionnaires such as Short-Form 36 (SF-36) represents an individual's point of view on medical outcomes, something that is increasingly more valued (11). More generally, HRQoL based on self-reported physical and mental functional health using SF-36 is viewed as a valid measure of health (12) and has also been reported as a predictor of both short-term and long-term adverse health outcomes (13).

Previous studies on HRQoL and anticholinergic burden (ACB) have yielded conflicting results (6-9). One study reported no difference in the mean Short Form-8 score between patients with different ACB (9), another showed that a greater ACB was associated with lower physical HRQoL with no effect on mental HRQoL in people with dementia (7), while a recent longitudinal study demonstrated that an increase in ACB was associated with a statistically significant decrease in patient's physical HRQoL and a statistically significant increase in mental HRQoL (6).

Further studies with general populations over longer follow up using larger cohorts are needed to establish the link between ACB and HRQoL. This also has potential to validate HRQoL as an outcome measure in clinical trials assessing the clinical and cost effectiveness of ACB reduction strategies. This is particularly relevant as SF-36 can be converted to SF-6D, which is an utility index (14). Additionally, HRQoL is a highly rated outcome measure relevant for clinical practice, so understanding relationships between ACB and HRQoL may help clinicians judge the risks and benefits of starting or stopping anticholinergic medications for a range of conditions. In this study, therefore, we aimed to examine the relationship between total anticholinergic burden (ACB) from medications at study baseline and participants' self-reported physical and mental functional health from the SF-36 summary scores at 18 months from baseline and at 13-year follow up in a UK population-based study, the European Prospective Investigation of Cancer (EPIC)-Norfolk study. This study is representative of the British general population, with the exception of a lower proportion of current smokers (15).

METHODS

Participants

The participants were men and women between the ages of 39 and 79 years at baseline (1993-97), who took part in the EPIC-Norfolk study. The study protocol of EPIC-Norfolk has been previously described in detail (15). Briefly, participants were invited to participate from general practice age-sex registers in Norfolk, UK. In total, 25,639 participants (99.6% White British) attended a baseline health examination during 1993-97. The participants attended a health check after 13 years between 2004 and 2011, which included a total of 8623 participants. Participants who did not return for follow-up were more likely to have been smokers, older, heavier, of lower socioeconomic status and have higher blood pressure at baseline (16). Norwich Ethics Committee approved the study and all patients provided written informed consent.

Measurements

Participants completed a health and lifestyle questionnaire at study baseline, which provided information on educational status, physical activity, smoking status, alcohol consumption, prevalent illness and medication. Physiological and biological parameters such as weight, height, blood pressure and non-fasting venous blood samples were collected by trained nurses during the clinic visit.

Drugs associated with anticholinergic burden were identified by searching the database for exact and similar entries for both generic and brand name drugs. Each medication was assigned a corresponding anticholinergic burden (ACB) score. Classification of drugs with ACB was class 0 (none), class 1 (probable), classes 2 and 3 (definite) based on the criteria of Anticholinergic Cognitive Burden Scale from Boustani et al (17). The total anticholinergic burden was measured using the Anticholinergic Cognitive Burden scale with the formula of:

((number of class 1 anticholinergics) + (number of class 2 anticholinergics x 2) + (number of class 3 anticholinergics x 3)). The distribution of ACB scores was skewed with most participants expressing an ACB of 0 (86 %). Therefore, participants were divided into three groups according to their ACB score at baseline (ACB=0, ACB=1 and ACB ≥2)

Outcome measures

The primary functional outcomes were the physical and mental component summary scores (PCS and MCS) of the Short form 36 (SF-36) collected at 18 months after study baseline and at 13 year follow up. The SF-36 assesses HRQoL in eight different areas: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and general mental health (11). Subcategory scores range from 0 to 100, with higher scores indicating better health status. These subcategories can be summarised to two summary scores- Physical Component summary (PCS) score and Mental Health Component summary (MCS) score. These summary scores have been standardised using norm based methods (18). In a general U.S. population both PCS and MCS have a mean of 50 and standard deviation of 10 (18). These summary scores provide more coherent information in comparison to individual subcategory scores (19).

Exclusion criteria

Participants with incomplete baseline data were excluded from all analyses. For the main longitudinal analyses, participants were excluded if they did not return an SF-36 form at 13-year follow-up.

Statistical Analysis

The statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Baseline sample characteristics are presented for the whole sample and by ACB groups. Differences between ACB groups were assessed using the chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables. Linear regression was performed to determine the association of baseline ACB score and PCS and MCS scores at 18 months from baseline and 13 year follow up using ACB group 0 as reference category. Due to short term follow up between baseline clinic assessment and first SF-36 measurement we performed cross sectional analysis. Logistic regression models were constructed for both time points; both PCS and MCS were dichotomised using 25th centile values to provide estimates (odds) of being in the bottom quartile of the population health as representative of the individual having impaired physical or mental functional HRQoL (20). Separate models were constructed for both PCS and MCS as dependent variables with and without adjusting for covariates at study baseline.

We constructed four models by incremental adjustment of clusters of co-variates. Model A was unadjusted, Model B was adjusted for age and sex, Model C was additionally controlled for sociodemographic and lifestyle factors including age, sex, social class, smoking status, alcohol use, educational level, physical activity, BP and BMI. Finally, in Model D we adjusted for variables in Model C as well as prevalent stroke, cancer, diabetes, asthma, arthritis, liver disease, depression and other psychiatric illness, all of which could potentially confound both predictor and outcome. For longitudinal analyses an additional Model E similar to Model D was constructed with confounders that may have changed during the follow up collected at 3HC (smoking status, alcohol use, physical activity, BP, comorbidities, BMI) in order to address the participant's current health status at 3HC. A two-sided P-value <0.05 was considered statistically significant.

RESULTS

From the 25,639 participants who attended the first health check for EPIC-Norfolk, 8964 were excluded due to missing data (missing data table in supplementary data) on the variables included in this analysis leaving 16,675 participants. SF-36 scores were recorded for 19,535 participants (64.2% of total EPIC-Norfolk sample). Not all participants who attended the baseline health check completed the SF-36 form and vice versa. Therefore, from the baseline health check attendees, the SF-36 physical health summary score (PCS) and mental health summary score (MCS) were the variables with most missing data (8480 participants had missing data for both PCS and MCS scores).

Cross-sectional analysis

Table 1 depicts sample characteristics at baseline by ACB groups. The mean age (SD) was 58.9 years (9.1) and 55.6% of the participants were female. The mean (SD) PCS and MCS scores of the participants were 47.6 (10.1) and 52.3 (9.4), respectively. There were significant differences between ACB groups for almost all variables analysed. People in the higher ACB groups were older and of lower social class and educational level and had lower level of physical activity. In terms of comorbidities, high ACB was associated with higher blood pressure, and had higher prevalence of depression, arthritis and cancer. Significantly lower mean PCS and MCS scores were also observed in the higher ACB groups.

Table 1 here

In the fully adjusted linear regression models (see **Supplementary Table 1**), the associations between higher ACB scores and lower PCS and MCS scores remained (all $p<0.001$).

Table 2 demonstrates the results of binary logistic regression depicting the OR (95% CI) of a participant belonging to the bottom 25% of PCS and MCS scores at study baseline.

Participants in higher ACB groups had higher odds of belonging to the bottom quartile of both HRQoL summary scores. The differences were slightly attenuated after adjustment for potential confounders but remained significant. In the fully adjusted regression model ACB=1 was associated with an OR of 1.85 (95% CI 1.64, 2.09) (p<0.001) and ACB ≥ 2 an OR of 2.19 (95% CI 1.85, 2.58) (p<0.001) for being in the bottom PCS quartile compared to the ACB= 0 group. The corresponding ORs (95%CI) for being in the bottom quartile of the MCS were 1.47 (1.30, 1.66) (p<0.001) and 1.68 (1.42, 1.98) (p<0.001), respectively.

Table 2 here

Longitudinal analysis

Table 3 shows the characteristics of 7133 participants (56.8% female, mean (SD) age 69.1 (8.7) years) who attended follow-up health check and completed another SF-36. The mean PCS score at follow up was slightly lower than baseline 47.1 (10.6) and mean MCS score was higher 54.3 (8.0). People in the higher ACB groups were older and had lower educational attainment, had higher blood pressure, were less physically active and more likely to have a baseline diagnosis of depression, arthritis and myocardial infarction. People in higher ACB groups had lower HRQoL scores for both summary scores.

Table 3 here

In the fully adjusted longitudinal linear regression models (available in supplementary data), the baseline ACB =1 group had lower PCS (β -3.0 (95%CI -3.9 - -2.0, p<0.001) and MCS scores (β -0.6 (95%CI -1.3, 0.2, p=0.10) relative to those with ACB of zero. Baseline ACB ≥ 2 was also associated with lower PCS (β -2.5 (95%CI -3.8 - -1.2, p<0.001) and MCS scores (β 1.5, 95%CI -2.6 - -0.4, p=0.007). In the subgroup analysis adjusting for confounders at follow-up, the results were broadly similar (**Supplementary Table 2).**

Table 4 shows that participants with higher ACB scores at baseline had higher odds of being in the bottom quartile of both summary scores. In the fully adjusted model, ACB=1 was associated with an OR of 1.56 (95% CI 1.24, 1.95) (p<0.001) and ACB ≥ 2 an OR of 1.48 (95% CI 1.07, 2.03) (p=0.017) for being in the bottom PCS quartile compared to the ACB= 0 group. For MCS the adjustment for prevalent illnesses attenuated the results considerably. However an OR 1.27 (95% CI 1.01, 1.60) (p=0.042) was observed in the fully adjusted model for ACB=1 compared no ACB at baseline. Additional analysis adjusting for confounders measured at follow-up attenuated the results of ACB ≥ 2 group for both summary scores, but the ACB=1 group had an OR of 1.51 (95% CI 1.16, 1.97) (p=0.003) and 1.50 (95% CI 1.15, 1.95) (p=0.002) for PCS and MCS respectively.

Table 4 here

DISCUSSION

Our results demonstrate that participants with higher baseline anticholinergic burden (ACB) from medications had both lower PCS and MCS compared to those with no anticholinergic burden. The association remained after 13 years of follow up. The participant in the ACB 1 and ACB ≥ 2 groups were older, of lower occupational social class and had lower level of educational attainment, had higher blood pressure and were less physically active and more likely to have a baseline diagnosis of conditions such as depression, arthritis or cancer. However, even after adjusting for these potential confounders, the differences remained statistically significant. Baseline ACB =1 was associated with a decrease of 3.0 units [β(95%CI)] [-3.0 (-3.9, -2.0)] in the participant's follow-up PCS scores compared to no ACB at baseline, while baseline ACB ≥ 2 showed a decrease of 2.5 units [-2.5(-3.8,-1.2)] in the PCS scores and decrease of 1.5 units [-1.5 (-2.6, -0.4)] in the MCS at follow-up.

Clinically important differences for individual SF-36 subcategories were determined to be in the range of 5.0–12.5 for asthma, chronic lung disease or heart disease by an expert panel (21). However, clinically minimally significant differences have not been defined for PCS and MCS scales due to computation and conceptual difficulties associated with these estimates (21). We therefore also examined the participant's odds of having poor HRQoL (obtaining a score belonging to the bottom 25th percentile of PCS and MCS scores) in relation to anticholinergic exposure from medications. In the longitudinal analysis, compared to no ACB at baseline, those with remaining ACB categories had significantly higher odds ratios of 1.56 (1.24, 1.95) 1.48 (1.07, 2.03) for being in the bottom quartiles of PCS at 3HC for ACB = 1 and ACB ≥2, respectively. After adjustment for baseline illnesses the only association between ACB and being in bottom quartiles of MCS was observed in the ACB=1 group (OR=1.27 (1.01, 1.60)). In the additional analysis adjusting for confounders at follow-up, the ACB ≥ 2 group had a very small number of participants left (n=154), resulting in loss of power.

The 95% CIs of the ACB =1 and ACB ≥ 2 groups overlap in results of most of the regression models, something that has been previously reported in a study on the effects of ACB on stroke (5). This may be a reflection of the sample size or perhaps indicate that the effects on HRQoL are driven by any level of exposure to anticholinergics, rather than the magnitude of the exposure.

To our knowledge, amongst the studies which examined the association between ACB and HRQoL, this is the first study to include analysis of odds of participant's scoring lower PCS and MCS scores in relation to exposure to anticholinergic medications. The novelty of this

study also lies in the UK based general population and a larger sample size. Previous studies have shown varying results perhaps related to smaller sample sizes. A study of US community dwelling veterans reported no difference in the physical HRQoL (measured with SF-8) between participants (N=532) who were taking anticholinergic medications compared to those who were not (9). However, the use of anticholinergic medications measured with the ADS scale was linked to reduction in the physical HRQoL measured with the Australian World Health Organization Quality of Life questionnaire (WHOQOL-BREF) in a cohort study consisting of community dwelling elderly with and without dementia (N=1044) (8). A retrospective cohort study with 112 patients with dementia linked ACB measured with the ADS scale to 7.48 unit reduction in the PCS score of SF-12, without an effect on the MCS (7). In the most recent cohort study with community dwelling older adults (N=1793) an increase of 1 in the ACB was associated with a β value of -0.50 (95% CI -0.68, -0.31) in the PCS and a β value of 0.19 (95% CI 0.01, 0.37) in the MCS of the SF-36 during three year follow up period (6). Our results support these findings.

However, the longitudinal analysis showed β value of-1.5 in MCS scores in ACB ≥ 2 group in linear models indicating decrease in MCS scores, in contrast to a previously reported slight increase in MCS with higher ACB. The previous study, however, consisted of a smaller Canadian cohort of older patients (N=1793) (6). Our results are intuitively more logical, and suggest the previous finding in older adults may be potentially attributable to selection bias, with older adults prescribed and able to tolerate anticholinergic drugs having higher MCS. In the fully adjusted model, the longitudinal association between higher ACB and lower MCS did not reach statistical significance, possibly due to a lower sample size and the effects of adjusting for depression and other psychiatric illnesses such as dementia, which could arguably be partly attributable to anticholinergic burden.

Of note, previous studies on ACB and HRQoL have found a prevalence of anticholinergic drug use at 15% in a US study (7), 42% in another in Australia (8) and 33% in a Canadian population (6). In this study in a relatively unselected British cohort, anticholinergic drug use prevalence was 14% at the study baseline. These differences may be explained by the population settings, as one study consisted of only people with dementia while the others focused on older people.

Our study has several strengths. We used a large population-based cohort, which improves the generalizability of our results. This also allowed us to capture a sufficient number of individuals with high ACB and assess the differences in odds between participants with different degrees of ACB. We were able to control for variety of sociodemographic and lifestyle factors as well as comorbidities. We also used a well-validated ACB score against several health outcomes such as stroke, cardiovascular events, risk of falls and cognitive impairment (4,5,22,23).

We also note some limitations. As a volunteer study with long-term follow up, a degree of healthy volunteer bias is possible. However, the baseline characteristics of the EPIC-Norfolk participants are similar to other UK representative population samples (15). Potential confounders were measured at baseline, and it is possible that these may vary during the follow-up period. To address this for the longitudinal analyses, we constructed a regression model adjusting for participant's current health status at follow-up. Although we were able to calculate the total ACB, we were not able to identify particular drugs nor dosages linked to adverse outcomes. As ACB was calculated at baseline we do not know whether the participants continued taking the same medication regimen during the follow up period. The

assumption would be that individuals classified according to baseline ACB exposure would more or less maintain the same exposure during follow up or, if anything, ACB use would increase in all groups as the participants of an ageing cohort will accrue more disease burden and more polypharmacy. However, the measurement error in ascertainment of ACB exposure through individuals stopping or starting ACBs during the follow up time would be likely only to attenuate the observed relationships rather than produce spurious relationships. A general limitation in this field is the use of at least 12 different scales for evaluating exposure to anticholinergic medications (3), which makes generalization and comparison of results difficult.

Implications

The multiple guidelines available on management of polypharmacy recommend medications review and optimisation in collaboration with patients and multidisciplinary teams (24, 25). Although medications with anticholinergic properties play a key role in the management of certain diseases, minimizing anticholinergic burden should be considered when safer agents are available (24, 25). Being attentive to patient's HRQoL and ACB should be important during clinical medication review and deprescribing medications with ACB prioritized when relevant HRQoL assessed with SF-36 could be used as an outcome measure in clinical trials assessing the clinical and cost effectiveness of ACB reduction strategies.

Conclusion

Use of anticholinergic medications predicted poorer HRQoL in the EPIC-Norfolk general population, both at baseline and after a mean 13 years of follow-up. The association remained true after adjusting for multiple potential confounders, though maintained statistical

significance in all models only for physical health domains. In the absence of long-term clinical trials examining the impact of reducing ACB, our results add to the growing evidence that offer incentive to clinicians and the public to use medications with anticholinergic properties with caution. Future studies should explore whether reducing the ACB has an effect on improving health outcomes, including HRQoL.

Conflict of Interest Statement: None of the authors have conflict of interest to declare.

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Contributors

PKM conceived the study. KRY performed literature review, data analysis. KRY and SRN drafted the manuscript. RNL performed data linkage. KTK and NJW are PIs of the EPIC-Norfolk Cohort. All co-authors made significant contribution to the data interpretation and critical appraisal. All contributed in writing of the paper. PKM is the guarantor.

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Tables:

Table 1. Baseline sample characteristics of the 16,675 participants of EPIC-Norfolk according to ACB score groups

	All **N=16 675**	**ACB score 0** **N=14 414**	**ACB score 1** **N=1503**	**ACB score ≥ 2** **=758**	**P**
Mean age in years (SD)	58.9 (9.1)	58.2 (9.0)	63.6 (8.4)	62.7 (8.8)	<0.001
Sex (%)					
Men	7406 (44.4)	6313 (43.8)	753 (50.1)	340 (44.9)	<0.001
women	9269 (55.6)	8101 (56.2)	750 (49.9)	418 (55.1)	
Social class (%)					<0.001
Professional	1261 (7.6)	1118 (7.8)	99 (6.6)	44 (5.8)	
Manager	6399 (38.4)	5593(38.8)	563 (37.5)	243 (32.1)	
Skilled non-manual	2832 (17.0)	2431 (16.9)	261 (17.4)	140 (18.5)	
Skilled manual	3579 (21.5)	3054 (21.2)	333 (22.2)	192 (25.3)	
Semi-skilled	2081 (12.5)	1781 (12.4)	199 (13.2)	101 (13.3)	
unskilled	523 (3.1)	437 (3.0)	48 (3.2)	38 (5.0)	
Smoking (%)					<0.001
Current smoker	1692 (10.1)	1477 (10.2)	118 (7.9)	97 (12.8)	
Ex-smoker	6953 (41.7)	5855 (40.6)	757 (50.4)	341 (45.0)	

Never smoker	8030 (48.2)	7082 (49.1)	628 (41.8)	320 (42.2)	
Alcohol use (units/week) (SD)	7.2 (9.3)	7.3 (9.4)	6.7 (9.1)	5.7 (7.7)	<0.001
Education level (%)					<0.001
No qualifications	5550 (33.3)	4622 (32.1)	609 (40.5)	319 (42.1)	
0 level	1808 (10.8)	1592 (11.0)	139 (9.2)	77 (10.2)	
A level	6967 (41.8)	6076 (42.2)	607 (40.4)	284 (37.5)	
Higher degree	2350 (14.1)	2124 (14.7)	148 (9.8)	78 (10.3)	
Physical activity (%)					<0.001
Inactive	4608 (27.6)	3709 (25.7)	573 (38.1)	326 (43.0)	
Moderately inactive	4927 (29.5)	4271 (29.6)	450 (29.9)	206 (27.2)	
Moderately active	3958 (23.7)	3542 (24.6)	292 (19.4)	124 (16.4)	
active	3182 (19.1)	2892 (20.1)	188 (12.5)	102 (13.5)	
Systolic BP (mmHG) (SD)	135.0 (18.0)	134.0 (18.0)	141.0 (18.0)	138.0 (19.0)	<0.001
BMI (SD)	26.2 (3.9)	26.1 (3.8)	27.1 (4.0)	27.1 (4.4)	<0.001
MI (%)	477 (2.9)	223 (1.5)	161 (10.7)	93 (12.3)	<0.001
Stroke (%)	205 (1.2)	115 (0.8)	50 (3.3)	40 (5.3)	<0.001
Cancer (%)	916 (5.5)	754 (5.2)	104 (6.9)	58 (7.7)	0.001
Diabetes (%)	354 (2.1)	246 (1.7)	74 (4.9)	34 (4.5)	<0.001

Asthma (%)	1370 (8.2)	1167 (8.1)	132 (8.8)	71 (9.4)	0.33
Arthritis (%)	3911 (23.5)	3195 (22.2)	477 (31.7)	239 (31.5)	<0.001
Liver disease (%)	392 (2.4)	329 (2.3)	43 (2.9)	20 (2.6)	0.32
Depression (%)	2361 (14.2)	1887 (13.1)	199 (13.2)	275 (36.3)	<0.001
Other psychiatric illness (%)	494 (3.0)	362 (2.5)	44 (2.9)	88 (11.6)	<0.001
Mean PCS score (SD)	47.6 (10.1)	48.4 (9.5)	42.6 (11.3)	41.0 (12.2)	<0.001
Mean MCS score (SD)	52.3 (9.4)	52.5 (9.1)	51.9 (10.0)	49.1 (11.9)	<0.001

Values presented are mean (SD) for continuous and number (%) for categorical data. Total anticholinergic burden (ACB) was calculated with the formula of ((number of class 1 anticholinergics) + (number of class 2 anticholinergics x 2) + (number of class 3 anticholinergics x 3)). Classification of drugs with ACB was class 0 (none), class 1 (mild), classes 2 and 3 (severe) based on the Anticholinergic Cognitive Burden Scale. BP=blood pressure. BMI= body mass index. MI= myocardial infarction. PCS score= physical component summary score. MCS=mental component summary score.

Table 2. Binary logistic regression modelling of the odds ratios of participants belonging to the 25th centile of PCS (PCS<42.5) and MCS scores (MCS < 48.4) at baseline by ACB groups with ACB=0 as reference category.

	ACB=0	**ACB=1**			**ACB ≥ 2**		
	OR	OR	95% C.I	p	OR	95% C.I	p
PCS							
Model A	1.00 (ref)	2.65	(2.38, 2.96)	<0.001	3.43	(2.96, 3.97)	<0.001
Model B	1.00 (ref)	2.10	(1.87, 2.35)	<0.001	2.86	(2.46, 3.33)	<0.001
Model C	1.00 (ref)	1.94	(1.72, 2.17)	<0.001	2.49	(2.13, 2.90)	<0.001
Model D	1.00 (ref)	1.85	(1.64, 2.09)	<0.001	2.19	(1.85, 2.58)	<0.001
MCS							
Model A	1.00 (ref)	1.33	(1.18, 1.49)	<0.001	2.16	(1.86, 2.51)	<0.001
Model B	1.00 (ref)	1.58	(1.40, 1.78)	<0.001	2.49	(2.14, 2.90)	<0.001
Model C	1.00 (ref)	1.54	(1.36, 1.74)	<0.001	2.34	(2.00, 2.73)	<0.001
Model D	1.00 (ref)	1.47	(1.30, 1.66)	<0.001	1.68	(1.42, 1.98)	<0.001

OR= odds ratio; C.I= confidence interval
Model A: unadjusted model
Model B: adjusted for age and sex
Model C: as model B, additionally adjusted for social class, smoking status, alcohol use, educational level, physical activity, BP and BMI
Model D: as model C additionally adjusted for prevalent stroke, cancer, diabetes, asthma, arthritis, liver disease, depression and other psychiatric illness.

Table 3. Baseline sample characteristics of the 7 133 participants present at 13 year follow up by ACB groups.

	All **N=7 133**	**ACB 0** **N=6476**	**ACB 1** **N=454**	**ACB 2** **N=203**	**P value**
Mean age in years (SD)	55.8 (8.0)	55.8 (8.0)	60.1 (8.0)	57.8 (7.5)	<0.001
Sex (%)					0.001
Men	3081 (43.2)	2769 (42.8)	232 (51.1)	80 (39.4)	
women	4052 (56.8)	3707 (57.2)	222 (48.9)	123 (60.6)	
Social class (%)					0.20
Professional	640 (9.0)	588 (9.1)	38 (8.4)	14 (6.9)	
Manager	2936 (41.2)	2672 (41.3)	187 (41.2)	77 (37.9)	
Skilled non-manual	1195 (16.8)	1087 (16.8)	76 (16.7)	32 (15.8)	
Skilled manual	1445 (20.3)	1306 (20.2)	96 (21.1)	43 (21.2)	
Semi-skilled	761 (10.7)	686 (10.6)	49 (10.8)	26 (12.8)	
unskilled	156 (2.2)	137 (2.1)	8 (1.8)	11 (5.4)	
Smoking (%)					0.001
Current smoker	595 (8.3)	542 (8.4)	27 (5.9)	26 (12.8)	

Ex-smoker	2754 (38.6)	2467 (38.1)	210 (46.3)	77 (37.9)	
Never smoker	3784 (53.0)	3467 (53.5)	217 (47.8)	100 (49.3)	
Alcohol use (units/week) (SD)	7.3 (8.9)	7.4 (9.0)	7.2 (8.6)	6.2 (7.7)	0.20
Education level (%)					0.01
No qualifications	1841 (25.8)	1639 (25.3)	132 (29.1)	70 (34.5)	
0 level	855 (12.0)	781 (12.1)	48 (10.6)	26 (12.8)	
A level	3196 (44.8)	2906 (44.9)	207 (45.6)	83 (40.9)	
Higher degree	1241 (17.4)	1150 (17.8)	67 (14.8)	24 (11.8)	
Physical activity (%)					<0.001
Inactive	1536 (21.5)	1346 (20.8)	131 (28.9)	59 (29.1)	
Moderately inactive	2159 (30.3)	1958 (30.2)	144 (31.7)	57 (28.1)	
Moderately active	1798 (25.2)	1647 (25.4)	108 (23.8)	43 (21.2)	
active	1640 (23.0)	1525 (23.5)	71 (15.6)	44 (21.7)	
Systolic BP (mmHg) (SD)	132.2 (17.1)	131.2 (17.0)	138.6 (16.7)	134.8 (18.5)	<0.001
BMI (SD)	25.8 (3.7)	25.7 (3.7)	27.0 (3.8)	26.7 (4.0)	<0.001
MI (%)	102 (1.4)	51 (0.8)	38 (8.4)	13 (6.4)	<0.001
Stroke (%)	52 (0.7)	36 (0.6)	11 (2.4)	5 (2.5)	<0.001
Cancer (%)	360 (4.6)	287 (4.4)	28 (6.2)	15 (7.4)	0.04
Diabetes (%)	78 (1.1)	59 (0.9)	15 (3.3)	4 (2.0)	<0.001

Asthma (%)	564 (7.9)	508 (7.8)	41 (9.0)	15 (7.4)	0.60
Arthritis (%)	1406 (19.7)	1217 (18.8)	132 (29.1)	57 (28.1)	<0.001
Liver disease (%)	170 (2.4)	150 (2.3)	18 (4.0)	2 (1.0)	0.04
Depression (%)	1008 (14.1)	852 (13.2)	61 (13.4)	95 (46.8)	<0.001
Other psychiatric illness (%)	187 (2.6)	143 (2.2)	13 (2.9)	31 (15.3)	<0.001
Mean PCS score at follow up(SD)	47.1 (10.6)	47.7 (10.2)	41.4 (12.5)	42.2 (12.3)	<0.001
Mean MCS score at follow up (SD)	54.3 (8.0)	54.4 (7.8)	54.2 (8.5)	51.0 (10.7)	<0.001
Mean ACB score at follow up	0.4 (0.9)	0.3 (0.8)	0.8 (1.2)	1.4 (1.7)	<0.001

Values presented are mean (SD) for continuous and number (%) for categorical data. Total anticholinergic burden (ACB) was calculated with the formula of ((number of class 1 anticholinergics) + (number of class 2 anticholinergics x 2) + (number of class 3 anticholinergics x 3)). Classification of drugs with ACB was class 0 (none), class 1 (mild), classes 2 and 3 (severe) based on the Anticholinergic Cognitive Burden Scale. BP=blood pressure. BMI= body mass index. MI= myocardial infarction. PCS score= physical component summary score. MCS=mental component summary score.

Table 4. Binary logistic regression models of the odds ratios of participants belonging to the 25th percentile of PCS scores (PCS<41.5) and MCS scores (MCS <51.3) at 13 year follow up by ACB groups with ACB=0 as reference category.

	ACB=0	**ACB=1**			**ACB ≥ 2**		
	OR	OR	95% C.I	p	OR	95% C.I	p
PCS							
Model A	1.00 (ref)	2.64	(2.17, 3.20)	<0.001	2.44	(1.84, 3.24)	<0.001
Model B	1.00 (ref)	2.07	(1.68, 2.54)	<0.001	2.45	(1.67, 3.03)	<0.001
Model C	1.00 (ref)	1.86	(1.51, 2.30)	<0.001	1.97	(1.46, 2.67)	<0.001
Model D	1.00 (ref)	1.56	(1.24, 1.95)	<0.001	1.48	(1.07, 2.03)	0.017
Model E	1.00 (ref)	1.51	(1.16, 1.97)	0.003	1.45	(1.00, 2.13)	0.054
MCS							
Model A	1.00 (ref)	1.25	(1.01, 1.54)	0.038	1.77	(1.32, 2.37)	<0.001
Model B	1.00 (ref)	1.35	(1.09, 1.67)	0.006	1.81	(1.35, 2.43)	<0.001
Model C	1.00 (ref)	1.34	(1.08, 1.66)	0.008	1.73	(1.29, 2.33)	<0.001
Model D	1.00 (ref)	1.27	(1.01, 1.60)	0.042	1.12	(0.81, 1.54)	0.49
Model E	1.00 (ref)	1.50	(1.15, 1.95)	0.002	1.12	(0.78, 1.61)	0.55

OR= odds ratio; C.I= confidence interval
Model A: unadjusted model
Model B: adjusted for age and sex
Model C: as model B, additionally adjusted for social class, smoking status, alcohol use, educational level, physical activity, BP and BMI
Model D: as model C additionally adjusted for prevalent stroke, cancer, diabetes, asthma, arthritis, liver disease, depression and other psychiatric illness.
Model E: subgroup analysis of participants with follow-up covariate data (n=5685) as model D, however confounders (smoking status, alcohol use, physical activity, BP, comorbidities, BMI) measured at follow-up.