Changes in Anticholinergic Cognitive Burden and Risk of Single and Recurrent Falls: Population-Based Cohort Study

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Background: Medications with high anticholinergic cognitive burden (ACB) are associated with increased fall risk in older adults. However, the potential alteration of risk with changes in ACB over time has yet to be established.

Objective: To estimate the association between the changes in ACB with single and recurrent falls.

Methods: Data from European Investigation of Cancer-Norfolk (EPIC-Norfolk) study participants, aged 40 years and above, who attended the first (1HC:1993-98), second (2HC:1998-2000) and third (3HC: 2004-2011) health checks were utilized. The main outcome was a single fall event or recurrent (≥ 2) falls occurring during the 12 months preceding the time point of the 3HC.

Results: Data from10717 participants with a median (IQR) age of 55.6 (13.1) years were included. 3445 (32.2%) participants had ACB of one or greater at baseline. Participants were classified into four groups: no (67.8%), late (21.1%), transient (6.8%) and continuous (4.3%). Late (OR 1.49, 95%CI 1.25 to 1.79), transient (1.66, 1.28-2.14) and continuous (1.67, 1.22-2.29) exposure were significantly associated with increased recurrent falls compared with no exposure. Mediation analysis revealed that gait speed contributed to 16.9% (CI: 9.4%-27.8%) of the increase in risk of recurrent falls associated with ACB.

Discussion: Anticholinergic medication use, in adults aged 40 years and above, was linked to recurrent falls at 14-year follow-up, regardless of whether introduction or

cessation occurred during the follow-up. Future research should determine effective strategies for minimising the long-term risk of falls when starting anticholinergic medications, which could include gait speed as a risk-detection and monitoring tool.

Keywords: anticholinergic, falls, gait speed, mediation, population-based.

Key Points

- Continued exposure to anticholinergic medications was associated with increased risk of recurrent falls after 11 to 18 years.
- Risk of recurrent falls is still increased even if anticholinergics are stopped or started later.
- Preventive strategies for recurrent falls with anticholinergics could include gait speed as a screening tool.

Introduction

Falls occur at least once annually in 19-30% of community-dwelling adults 65 years or older with at least 10% of older adults falling at least twice annually [1-3]. Participants visiting healthcare facilities regularly are presumed to have a higher risk of falling, given the prevalence of diseases and impairments in these individuals. Most falls result from a combination of intrinsic risk and extrinsic risks which include gait and balance disorders, cognitive impairment, hypotensive events, medications and environmental hazards [4].

Medication use, especially drugs with anticholinergic effects, is one of the most common risk factors for falls in older adults. Studies have suggested that nearly one in every three community-dwelling older adults takes medication with anticholinergic effects [5-7]. Adverse effects associated with medications with anticholinergic properties include mental confusion, constipation, urinary retention, dry mouth, and blurred vision [8]. While some drugs are prescribed for their anticholinergic effects, such as in the treatment of detrusor instability, most drugs often have anticholinergic activity as an unwanted adverse effect. While the above side effects are immediate, emerging evidence has identified an increased risk of long-term adverse events including cardiovascular events, dementia and mortality with exposure to anticholinergic medications [9,10].

Medications with anticholinergic properties increase the risk of fall occurrence. Exposure to anticholinergic drugs at baseline has been linked to increased risk of falls at three and five-year follow-up and falls hospitalization at 20-year follow-up [11,12]. Few research studies have, however, explored the relationship between changes in anticholinergic use and falls over time. Furthermore, the mechanisms underlying the relationship between anticholinergic exposure and long-term fall risk

remain unclear. The objective of this study was, therefore, to determine the relationship between changes in anticholinergic exposure over time with single and recurrent falls.

METHOD

Data Sources

This study utilized data from the European Prospective Investigation of Cancer Norfolk (EPIC-Norfolk) longitudinal cohort study.

Study Design and Sample Population

Retrospective analysis of data obtained from a population-based cohort study, the EPIC-Norfolk study, which recruited over 30,000 men and women aged 40-79 between 1993 and 1998 from 35 participating general practices in Norfolk. Further details on the EPIC-Norfolk study have been published elsewhere [13]. Participants who attended the first health check (1HC), second health check (2HC) and third health check (3HC) and completed the falls questionnaire were selected. Details on demographics, education level, lifestyle information, diagnoses and medication were recorded by general practitioners. We excluded participants with incomplete medication records at the three time points and incomplete fall data at 3HC.

Anticholinergic Exposure

The exposure of interest in this study was the measure of changes in anticholinergic burden over the three health checks. Firstly, exposure to medications with anticholinergic effects was determined with the Ageing Brain Care 2012 Anticholinergic Cognitive Burden (ACB) scale, with ACB considered present if the participant used at least one medication with an ACB score of one or greater[11,14]. The four groups which emerged were determined based on ACBs changes over the three health checks: 1. No exposure at all three health checks (No Exposure, NE), 2. No baseline exposure, but anticholinergic drug commenced at the second or/and third health check (Late Exposure, LE), 3. Exposed at baseline, but deprescribed at

second or/and third health check (Transient Exposure, TE) and 4. ACB present at all three health checks (Continuous Exposure, CE) (Table 1). See Appendix 1 in the Supplementary Data section for the full details of ACB group classification.

Table 1. Classification of Anticholinergic Cognitive Burden Score Groups

1HC	2HC	3HC	Group
ACB=0	ACB=0	ACB=0	NE
		ACB≥1	LE
	ACB≥1	ACB=0	LE
		ACB≥1	LE
ACB≥1	ACB=0	ACB=0	TE
		ACB≥1	TE
	ACB≥1	ACB=0	TE
		ACB≥1	CE

1HC: first health check, 2HC: second health check, 3HC: third health check. ACB: Anticholinergic Cognitive Burden. NE: No Exposure; LE: Late Exposure; TE: Transient Exposure; CE: Continuous Exposure.

Main Outcomes

The main outcome was fall occurrence detected at 3HC. This was determined through retrospective recall using the questions, 'Have you fallen in the past 12 months?'. If the participant provided a "yes" response to the above question, they were asked a follow-up question, "How many times have you fallen?". Falls responses were subsequently categorized into: non-fallers, single fall and recurrent falls (two or more falls in the past year).

Covariates

We considered potential confounders to be any factor suspected to be linked to falls occurrence. The physical function outcomes considered in this study comprised hand

grip strength (HGS) and gait speed (GS). Measurements were recorded by trained research staff using standard protocols [15]. Further details on methods of measurement have been published elsewhere [16]. Briefly, hand grip strength was measured using a hand strength dynamometer (Smedley's Dynamometer, Denmark). Walking speed was obtained from a flying start at the usual walking speed over four metres, obtained over a six-meter course, with the timing starting one meter after the beginning and stopping one meter before the end of the walk way.

Cognitive function was determined through the Paired Associated Learning (PAL) test and the short form Mini-Mental State Examination (SF-MMSE) [17-19]. The PAL tests episodic memory and new learning, which has been shown to be a sensitive tool for the determination of memory deficit in the early stages of dementia. The task consisted of eight stages and up to ten presentations after which the task was terminated. The variable of interest used here was the 'first trial memory score' (FTMS). The 11-item SF-MMSE was used to evaluate global cognitive function to improve acceptability and reduce the response burden of the standard MMSE.

Statistical Analysis

Descriptive statistics were calculated for baseline demographics and compared across the anticholinergic exposure groups. We presented means and standard deviations for normally distributed continuous variables and medians with interquartile ranges for non-normally distributed continuous variables, which were compared using analysis of variance and the independent sample median test respectively. We reported categorical variables using frequencies and percentages. Characteristics were compared between the groups using Chi-squared tests. Power

calculations were performed post-hoc using G*Power 3.1.9.6. A sample of 9000 participants will provide 98% power to detect an effect size of 0.05 which is an extremely small effect size, with an alpha value of 0.05 using chi-squared comparisons with three degrees of freedom. All statistical analyses were conducted using SPSS 29.0 (BMI™, USA).

Multi-nominal Logistic Regression

Multi-nominal logistic regression was utilized for multivariate analyses using fall occurrence as the dependent variable. Non-fallers were considered the reference group, hence parameter estimates were obtained for single fall and recurrent falls over the past year at 3HC compared to non-fallers. Variables were selected based on their potential confounding effects, informed by univariate comparisons of basic characteristics and clinical judgement. Seven models were developed with model 1 as the unadjusted model. Additional adjustments were then made for age and gender (model 2), with additional adjustments for cardiometabolic conditions, cancer, asthma/ bronchitis and education level conducted in model 3. Subsequent models were developed to determine the influence of physical and cognitive performance on the model after adjustment for potential confounders. Hence, in addition to the variables included in model 3, separate adjustments were made for GS (model 4), HGS (model 5), SF-MMSE (model 6) and PAL (model 7). These variables were adjusted for separately to avoid potential multicollinearity.

Mediation Analysis

We then performed a mediation analysis to determine whether the association between changes in ACBs with fall occurrence was a direct effect or an indirect effect influenced by cognitive (PAL and SF-MMSE) or physical function (Gait speed and hand grip strength). The mediation model was tested using the SPSS macro PROCESS.

Sensitivity Analysis

We investigated Pearson correlation analysis with ACB and others' definitions of anticholinergic exposure used as sensitivity analysis: Anticholinergic Risk Scale (ARS), Anticholinergic Drugs Scale (ADS) and Anticholinergic effect on cognition (AEC), Anticholinergic Impregnation Scale (AIS), Anticholinergic Load Scale (ALS).

Ethical approval and informed consent

This study was approved by the Norfolk Local Research Ethics Committee (05/Q0101/191) and East Norfolk and Waveney NHS Research Governance Committee (2005EC07L). Participants gave signed informed consent at both baseline and then subsequently at the 3HC to cover new measures that were not present in previous health examinations.

RESULTS

Baseline characteristics

Data from 10717 participants were included in the final analysis. The median age (IQR) of participants was 55.6 (13.1) years, and 6033 (56.3%) participants were women (Table 2). There were 459 (4.3%) participants in the CE group, 2263 (21.1%) participants in the LE group and 724 (6.8%) participants in the TE group. 7271 (67.8%) participants had no exposure to anticholinergics throughout the study period. Differences existed in age, education level, smoking status, cardiometabolic factors, asthma/bronchitis, cancer, dementia, GS, HGS, SF-MMSE, PAL and falls between ACB groups.

Table 2 Baseline characteristics of participants according to anticholinergic exposure over time

Characteristic	All participants (n=10717)	ACB Exposure				P-value
		NE (n=7271)	LE (n=2263)	TE (n=724)	CE (n=459)	
Age, Median (IQR)	55.6 (13.1)	54.0 (12.0)	59.0 (13.4)	57.8 (13.3)	61.9 (11.1)	**<0.001**
Gender (n, %)						
Male	4684 (43.7)	3216 (44.2)	976 (43.1)	288 (39.8)	204 (44.4)	0.124
Female	6033 (56.3)	4055 (55.8)	1287 (56.9)	436 (60.2)	255 (55.6)	
Education level (n, %)						
Low education level	4352 (40.6)	2805 (38.6)	1010 (44.6)	329 (45.4)	208 (45.3)	**<0.001**
A level and above	6362 (59.4)	4463 (61.4)	1253 (55.4)	395 (54.6)	251 (54.7)	
Smoking (n, %)						
Currently	988 (9.3)	641 (8.9)	240 (10.7)	77 (10.7)	30 (6.6)	**<0.001**
Former	4144 (38.9)	2725 (37.7)	920 (40.9)	286 (39.6)	213 (46.7)	
Never	5533 (51.9)	3869 (53.5)	1092 (48.5)	359 (49.7)	213 (46.7)	
Comorbidities (n, %)						
Cardiometabolic	357 (3.3)	123 (1.7)	105 (4.7)	56 (7.7)	70 (15.3)	**<0.001**
Asthma/bronchitis	1518 (14.2)	990 (13.6)	334 (14.8)	123 (17.0)	71 (15.5)	**<0.001**
Cancer	474 (4.4)	281 (3.9)	122 (5.4)	48 (6.6)	23 (5.0)	**<0.001**
Dementia	754 (7.0)	419 (5.8)	225 (9.9)	71 (9.8)	39 (8.5)	**<0.001**
Physical Function*(n, %)						
Gait speed	1.10 (0.25)	1.14 (0.24)	1.02 (0.26)	1.03 (0.27)	0.97 (0.24)	**<0.001**
Hand grip strength	31.01 (10.06)	31.77 (10.06)	29.48 (9.81)	28.84 (9.98)	28.57 (9.65)	**<0.001**
Cognitive Function*(n, %)						
SF-MMSE	13.29 (1.74)	13.40 (1.65)	13.05 (1.86)	12.91 (2.08)	12.95 (1.78)	**<0.001**
PAL	15.65 (4.25)	15.96 (4.11)	14.51 (4.46)	14.95 (4.65)	14.07 (4.34)	**<0.001**
Falls outcomes*(n, %)						
Falls	2933 (27.4)	1786 (24.6)	739 (32.7)	248 (34.3)	160 (34.9)	**<0.001**
Recurrent falls	1300 (12.1)	698 (9.6)	381 (16.8)	133 (18.4)	88 (19.2)	**<0.001**

SF-MMSE: Short Form Mini-Mental State Exam; PAL: Paired Associates Learning.

Cardiometabolic: Heart attack, stroke and diabetes.

Bold font indicates significance at p-value <0.05.

*Measurements obtained at third health check.

NE: No Exposure; LE: Late Exposure; TE: Transient Exposure; CE: Continuous Exposure.

Multinomial Logistical Regression

Table 3 shows the multinomial logistic regression analyses using fall outcomes as the dependent variable, and no falls as the reference category. Changes in ACB were included as an independent variable, with the NE group as the reference category. The unadjusted models (model 1) and two models adjusted for the potential confounders of age, gender (model 2), cardiometabolic conditions, cancer, asthma/bronchitis and education level for fall occurrence were first presented (model 3). The unadjusted model shows that both the risk of one fall in the preceding year as well as recurrent falls were increased regardless of whether the participant had LE, TE or CE compared to those with NE. Following adjustments for age and gender differences, the risk of a single fall was no longer increased for any of the three ACB groups compared to the NE group. However, after adjustments for all known potential confounders, anticholinergic exposure at any point of the study regardless of whether ACB was present at baseline or subsequent follow-up, was associated with recurrent falls.

Subsequently, models 4-7 explored the potential mediating effects of physical and cognitive function on the risk of falls associated with change in ACB. The separate addition of HGS, GS, SF-MMSE and PAL into the adjusted model 3 did not influence the significant relationship. However, reductions in the parameter estimates were observed with gait speed in particular, with a smaller reduction observed with handgrip strength. No changes in the parameter estimates were observed with cognitive function, with a slight decrease in the parameter estimates observed with SF-MMSE and a small increase in parameter estimates with PAL.

Table 3. Multinomial Logistical Regression

	VS. no falls, odds ratio (95% confidence interval)					
	Single fall (reference: NE)			Recurrent falls (references: NE)		
	LE (n=2263)	TE (n=724)	CE (n=459)	LE (n=2263)	TE (n=724)	CE (n=459)
Model 1	**1.184 (1.038-1.352)**	1.218 (0.984-1.508)	1.214 (0.931-1.583)	**1.965 (1.713-2.253)**	**2.196 (1.784-2.703)**	**2.313 (1.800-2.971)**
Model 2	1.079 (0.943-1.235)	1.111 (0.895-1.378)	1.059 (0.809-1.386)	**1.802 (1.567-2.073)**	**2.028 (1.645-2.501)**	**2.030 (1.574-2.617)**
Model 3	1.088 (0.950-1.246)	1.114 (0.897-1.384)	1.061 (0.808-1.393)	**1.785 (1.551-2.055)**	**1.975 (1.598-2.440)**	**1.951 (1.507-2.526)**
Model 4	1.091 (0.932-1.277)	1.121 (0.871-1.444)	1.140 (0.831-1.565)	**1.484 (1.254-1.785)**	**1.656 (1.279-2.143)**	**1.669 (1.217-2.289)**
Model 5	1.102 (0.942-1.290)	1.087 (0.842-1.403)	1.137 (0.827-1.563)	**1.643 (1.390-1.942)**	**1.844 (1.433-2.373)**	**1.768 (1.282-2.438)**
Model 6	1.094 (0.934-1.281)	1.114 (0.887-1.475)	1.084 (0.786-1.496)	**1.670 (1.413-1.974)**	**1.792 (1.386-2.318)**	**1.854 (1.353-2.539)**
Model 7	1.081 (0.913-1.281)	1.127 (0.861-1.475)	1.242 (0.889-1.735)	**1.620 (1.349-1.945)**	**1.700 (1.282-2.254)**	**2.035 (1.449-2.859)**

NE: No Exposure; LE: Late Exposure; TE: Transient Exposure; CE: Continuous Exposure.

Model 1: Unadjustment. Model 2: Age, gender; Model 3: Age, gender, cardiometabolic conditions, cancer, asthma/ bronchitis and education level.

Model 4: Model 3 and gait speed. Model 5: Model 3 and hand grip strength. Model 6: Model 3 and SF-MMSE. Model 7: Model 3 and PAL.

Cardiometabolic conditions: heart attack, stroke and diabetes.

Bold font indicates significance at p-value <0.05.

Mediation Analysis

The mediation effects of physical performance (GS and HGS) and cognitive function (SF-MMSE and PAL) in the relationship between changes in ACB and recurrent falls were then assessed. In the GS pathway, the results revealed a significant indirect effect of the impact of changes in ACB on recurrent falls (b= 0.0112 ($p<0.001$), 16.9% mediation effect) after adjustments for potential confounders. Furthermore, the direct effect of changes in ACB on recurrent falls in the presence of the mediator was also significant ($b = 0.0552$, $p < 0.001$). Hence, GS partially mediated the relationship between changes in ACB and recurrent falls. There was also a significant indirect effect on the impact of changes in ACB on the recurrent falls (b= 0.0038 ($p<0.001$), 5.8% mediation effect), HGS and (b= 0.0015 ($p<0.001$), 2.3% mediation effect) SF-MMSE pathways after adjustments for potential confounders. PAL did not display any mediation effect in the changes in ACB and recurrent falls. The mediation analyses summary is presented in Table 4.

Table 4. Summary the Mediating Effects of Physical and Cognitive Performance in Change Anticholinergic Use and Recurrence Falls

Relationship	Mediator	Model	Total Effect	Direct Effect	Indirect Effect	Confidence Interval		Mediation effects	Conclusion
						Lower Bound	Upper Bound		
ACB→GS→Falls	GS (N=8302)	Unadjusted	0.0797 (<0.001)	0.0596 (<0.001)	0.0202	0.0127	0.0302	25.3%	Partial Mediation
		Adjusted	0.0663 (<0.001)	0.0552 (<0.001)	0.0112	0.0062	0.0184	16.9%	Partial Mediation
ACB→HGS→Falls	HGS (N=8266)	Unadjusted	0.0784 (<0.001)	0.0673 (<0.001)	0.0110	0.0083	0.0141	14.0%	Partial Mediation
		Adjusted	0.0659 (<0.001)	0.0621 (<0.001)	0.0038	0.0021	0.0059	5.8%	Partial Mediation
ACB→SF-MMSE→Falls	SF-MMSE (N=8276)	Unadjusted	0.0767 (<0.001)	0.0737 (<0.001)	0.0030	0.0010	0.0053	3.9%	Partial Mediation
		Adjusted	0.0639 (<0.001)	0.0624 (<0.001)	0.0015	0.002	0.0031	2.3%	Partial Mediation
ACB→PAL→Falls	PAL (N=7270)	Unadjusted	0.0751 (<0.001)	0.0729 (<0.001)	0.0022	-0.0003	0.0048	N/A	No mediation Effect
		Adjusted	0.0636 (<0.001)	0.0629 (<0.001)	0.006	-0.0007	0.0021	N/A	No mediation Effect

GS: Gait speed; HGS: Hand grip strength; SF-MMSE: Short form Mini-Mental State Examination; PAL: Paired Associated Learning.

Adjusted variables: Age, gender, cardiometabolic conditions, cancer, asthma/ bronchitis and education level

Sensitivity Analysis

Pearson correlation analysis was conducted between ACB and ARS, ADS, AEC, ALS and AIS, separately. The results revealed a strong and statistically significant positive correlation between ACB and ARS γ (10717) = .673, $p < .001$. ACB and ADS γ (10717) = .843, $p < .001$. ACB and AEC γ (10717) = .647, $p < .001$. ACB and ALS γ (10717) = .584, $p < .001$. ACB and AIS γ (10717) = .766, $p < .001$ at baseline. We also conduction Pearson correlation analyses between these anticholinergic scales at 2HC and 3HC, showing strong and statistically significant correlations (Appendix 2).

DISCUSSION

Principal findings

We found that the presence of any anticholinergic exposure over the duration of the cohort study was significantly associated with recurrent falls at 14 years' follow-up. The risk of recurrent falls after an initial exposure persisted even when drugs with ACB were discontinued. Reduced gait speed had a partial mediating effect on the relationship between ACB change and recurrent falls.

Comparison with other studies

This study has demonstrated that individuals who had ACB drugs started or discontinued during the course of the study, as well as individuals who remained on ACB drugs throughout the study, had an increased risk of recurrent falls at follow-up compared to those with no ACB. A US study involving over 3000 participants found a non-significant association between anticholinergic exposure at any time point with recurrent falls cumulatively over seven years of follow-up [20]. As fall recurrence occurs less frequently than any fall occurrence, a larger sample size is necessary to determine the effect of anticholinergic exposure on recurrent falls. Within this study, with a far larger study population and longer follow-up, we had established that a persistent increase in the risk of recurrent falls over the year preceding the third health check at 11 to 17 years after the baseline measures even when medications with anticholinergic effects had been withdrawn.

Similarly, a Canadian study involving over 9000 participants found a statistically significant association between anticholinergic medication use and falls but this association was lost after correction for important confounding variables [21]. The

reasons for loss of significance may include the lack of tracking of changes in the use of anticholinergic drugs, and it is unclear whether the potential risks have changed when prescriptions have changed. This previous study had addressed the occurrence of falls rather than recurrent falls. Within the published literature, it is considered well established that serious, injurious falls tend to occur in those who suffer recurrent falls, while single falls are often isolated events which are not necessarily avoidable [22]. Hence within the World Falls Guidelines [23], which has introduced the new concept of fall severity, recurrent falls are considered severe falls.

The analytical strategies required to establish the impact of prescription changes on potential associated risks remain challenging. A Danish study used four different scales to identify anticholinergic burden and found that anticholinergic medication use was associated with an increased risk of major advanced cardiovascular effects (MACE). Subsequent monitoring of anticholinergic medications use found no association between reduction in anticholinergic load and risk of MACE after 180 days [24]. While the follow-up period of the previous prospective, observational study was limited, our study has now demonstrated that the risk of recurrent falls was not removed following a reduction in anticholinergic burden over a much longer follow-up period. Given the observational nature of both studies, however, there is a possibility that the medications with anticholinergic properties had been discontinued by the individuals' physicians when the risk of falls was perceived to be high.

Mechanistic understanding and implications for future research

Anticholinergic exposure contributes to factors such as balance impairment, reduced walking ability and physical performance ability, all of which are established risk factors for falls [25]. A cross-sectional study found that the use of anticholinergic medications was associated with reduced physical performance including reduced gait speed and poorer short physical performance battery scores [26]. Danijela et al provided similar evidence that medications with anticholinergic properties were associated with poorer physical performance and functional status in community-dwelling older Australian men [27]. The World Guidelines for Falls Prevention also recommend including gait speed as the risk stratification tool for determining the severity of falls, for individuals who have reported at least one fall in the preceding 12 months during opportunistic screening [23]. As our results suggest that simply deprescribing anticholinergics may not completely abolish the increased in falls risk related to their use, caution must be exercised with prescribing decisions within clinical practice. Future research could consider evaluating the value of gait speed as a risk stratification and monitoring tool for individuals who require the prescription of medications with anticholinergic properties. In addition, the potential role of rehabilitation interventions which may help preserve gait speed and reduce other adverse physical and cognitive effects should be explored. A recently published randomized controlled trial revealed the benefits of exergaming in a three arm study comparing exergame with cognitive training and education [28]. Technological innovations such as these which could reduce the need for therapist time may be the answer to improving patient care in this respect without overburdening current systems.

Strengths and limitations of this study

The strength of this study includes the tracking of anticholinergic medication use within a large number of participants over a long follow-up period. However, it is possible that attrition bias could have been introduced during the 10- to 15-year study period with only 10,717 out of the original 30,437 participants returning for the third health check [13]. Attending clinicians may also be more likely to stop or reduce anticholinergic medications in individuals at risk of falls which may confound the findings of increased risk of recurrent falls despite a reduction in ACB. Additionally, falls history and physical measurements had not been collected during the baseline health check. While the presence of falls at baseline are known to increase the subsequent risk of falls, with the substantial time intervals between each health check, however, the potential influence of a history of falls on the risk of fall occurrence at the subsequent health check would have reduced [29].

CONCLUSION

Anticholinergic exposure was associated with recurrent falls in adults, over a mean follow-up period of 14 years, regardless of whether anticholinergic medications were discontinued. Continued use of anticholinergic medications had a stronger association with discontinuation or initiation of anticholinergic drugs which suggests that deprescribing may still be considered. Future research to identify effective strategies to minimise long-term risk of falls during the initiation of medications with anticholinergic properties should be explored, and the potential role of gait speed as a risk-identification and monitoring tool could also be determined.

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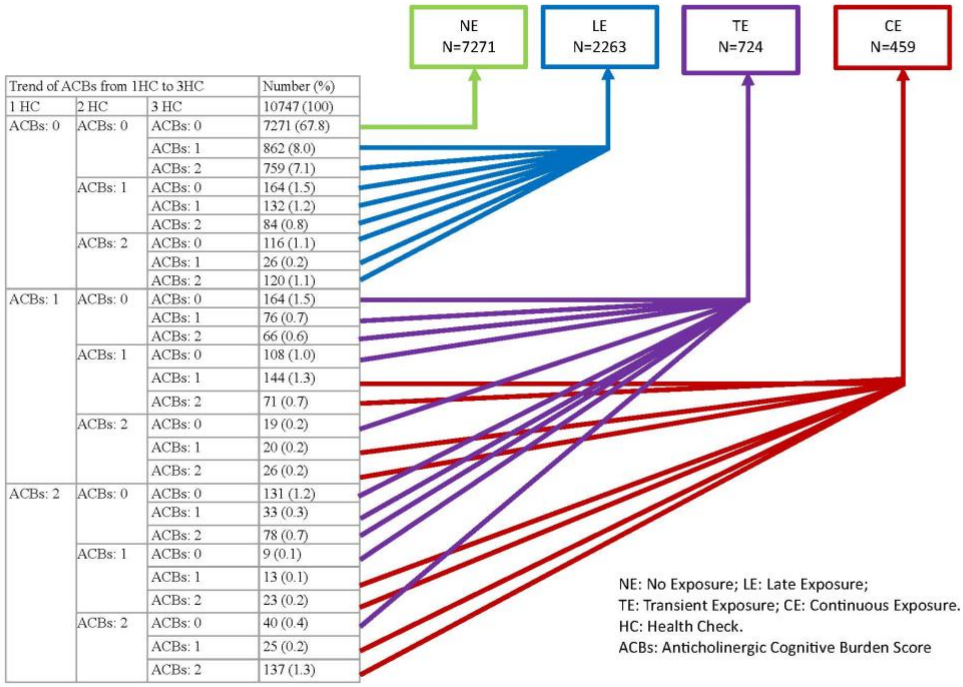
Appendix 1



Trend of ACBs from 1HC to 3HC			Number (%)
1 HC	2 HC	3 HC	10747 (100)
ACBs: 0	ACBs: 0	ACBs: 0	7271 (67.8)
		ACBs: 1	862 (8.0)
		ACBs: 2	759 (7.1)
	ACBs: 1	ACBs: 0	164 (1.5)
		ACBs: 1	132 (1.2)
		ACBs: 2	84 (0.8)
	ACBs: 2	ACBs: 0	116 (1.1)
		ACBs: 1	26 (0.2)
		ACBs: 2	120 (1.1)
ACBs: 1	ACBs: 0	ACBs: 0	164 (1.5)
		ACBs: 1	76 (0.7)
		ACBs: 2	66 (0.6)
	ACBs: 1	ACBs: 0	108 (1.0)
		ACBs: 1	144 (1.3)
		ACBs: 2	71 (0.7)
	ACBs: 2	ACBs: 0	19 (0.2)
		ACBs: 1	20 (0.2)
		ACBs: 2	26 (0.2)
ACBs: 2	ACBs: 0	ACBs: 0	131 (1.2)
		ACBs: 1	33 (0.3)
		ACBs: 2	78 (0.7)
	ACBs: 1	ACBs: 0	9 (0.1)
		ACBs: 1	13 (0.1)
		ACBs: 2	23 (0.2)
	ACBs: 2	ACBs: 0	40 (0.4)
		ACBs: 1	25 (0.2)
		ACBs: 2	137 (1.3)

Appendix 1. Classification of Anticholinergic Cognitive Burden Score Groups

Appendix 1 Legend.

This graph shows ACBs changes from 1HC to 2HC to 3HC. We identified 27 groups based on these changes and combined them into four categories: No Exposure Group (NE), Late Exposure Group (LE), Transient Exposure Group (TE), and Continuous Exposure Group (CE). The difference is the anticholinergic exposure at different times between LE and TE, that LE is no exposure at 1HC, so these group participants are prescribing anticholinergic medication after IHC, TE is exposure at 1HC, but they may be stopped taking anticholinergic for a while or stopped.

Appendix 2. Pearson correlation analysis between ACB and other anticholinergic tools.

Anticholinergic Tools	ACB					
	1HC		2HC		3HC	
	γ	Sig.	γ	Sig.	γ	Sig.
ARS	.673	<0.001	.639	<0.001	.654	<0.001
ADS	.843	<0.001	.819	<0.001	.825	<0.001
AEC	.647	<0.001	.657	<0.001	.659	<0.001
AIS	.766	<0.001	.780	<0.001	.766	<0.001
ALS	.584	<0.001	.585	<0.001	.622	<0.001

HC=health check, ACB=Anticholinergic Cognitive Burden, ARS=Anticholinergic Risk Scale, ADS=Anticholinergic Drugs Scale, AEC= Anticholinergic effect on cognition, AIS=Anticholinergic Impregnation Scale, ALS=Anticholinergic Load Scale.