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Increase in anticholinergic burden from 1990 to 2015

ORIGINAL ARTICLE

Increase in anticholinergic burden from 1990 to 2015: Age-period-cohort analysis in UK biobank

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Background: The use of prescription drugs with anticholinergic properties has been associated with multiple negative health outcomes in older people. Moreover, recent evidence suggests that associated adverse effects may occur even decades after stopping anticholinergic use. Despite the implicated importance of examining longitudinal patterns of anticholinergic prescribing for different age groups, few such data are available.

Methods: We performed an age-period-cohort (APC) analysis to study trends in an aggregate measure of anticholinergic burden between the years 1990 and 2015, utilising data from >220 000 UK Biobank participants with linked prescription data from primary care.

Results: Anticholinergic burden in the sample increased up to 9-fold over 25 years and was observed for both period and age effects across most classes of drugs. The greatest increase was seen in the prescribing of antidepressants. Female sex, lower education and greater deprivation were associated with greater anticholinergic burden.

Conclusions: The increase in anticholinergic prescribing is mostly due to an increase in polypharmacy and is attributable to both ageing of participants and period-related changes in prescribing practices. Research is needed to clarify the implications of rising anticholinergic use for public health and to contextualise this rise in light of other relevant prescribing practices.

KEYWORDS
anticholinergic drugs, drug prescribing, general practice, polypharmacy

1 | INTRODUCTION

Medicines with anticholinergic properties – antagonists to muscarinic receptors in the nervous system – are found among various classes of drugs.[1] Several anticholinergic drugs are listed in the American Geriatrics Society Beers Criteria for Potentially Inappropriate Medication[2] and the STOPP/START criteria for potentially inappropriate prescribing.[3] Age is the strongest predictor of polypharmacy, with the odds of taking 10 or more medicines doubling in every decade of life.[4] Moreover, due to the age-associated decline in the ability to metabolise drugs, older people are more sensitive to the side effects

This is a secondary investigation of an existing cohort study and therefore did not have a Principal Investigator.

of drugs.[5] This is especially pertinent in the case of anticholinergic compounds, which are commonly prescribed and whose side effects are well documented.[1] Anticholinergic burden in older adults is associated with reduced physical and cognitive ability,[6,7] impaired ability to perform activities of daily living,[8] increased risks of falls,[9] dementia[10] and mortality.[11] The association with dementia has been observed even when the anticholinergic exposure occurred decades prior to diagnosis.[10]

Several tools to assess inappropriate prescribing have been developed in the last few decades.[12] Subsequently, inappropriate prescribing in older people declined from 45.5% to 40.8% between 2006/2007 and 2009/2010 in the United States,[13] and from 32.2% to 28.3% between 1996 and 2005 in the UK.[14] However, older adults remain exposed to anticholinergic drugs,[15] the prevalence of which has remained stable in the United States,[16] but has increased by 3% in the UK from 1995 to 2010[17] and by 12.5% in Finland from 2007 to 2017.[18] While some studies have found associations between anticholinergic use and demographic factors,[16,17,19] these variables are rarely examined in detail. Moreover, it is not known whether these potential group differences persist over time.

The study of temporal changes of prescribing practices with in-depth assessment of age-period-cohort (APC) effects necessitates longitudinal designs. Cross-sectional studies[15] or repeated cross-sectional studies[17,18] have explored the extent of anticholinergic use in European countries,[17,18] but the last year of sampling in the UK was in 2010.[17] Moreover, they either lack longitudinal data or rely on participants from a relatively limited geographic area and within a narrow age range. In this paper, we address those limitations by using a large national sample from UK Biobank to characterise longitudinal prescribing patterns of anticholinergic drugs in 1990-2015.

2 | METHODS

2.1 | Hypotheses

We based our hypotheses on previous cross-sectional studies in the UK that showed greater polypharmacy[4] and anticholinergic burden[17] in 2010 when compared to 1995, and increased polypharmacy in older individuals.[4] We hypothesised that anticholinergic burden increased as a function of both period and age. Additionally, we hypothesised that anticholinergic burden was higher in women and in less educated individuals, as had been reported before.[15,17]

2.2 | Sample

UK Biobank is a prospective study of >500 000 participants aged 37-73 years, recruited in 22 assessment centres throughout the UK in 2006-10.[20] To ensure a representative sample in the given age range, eligible participants for the study were identified through general practice registers and invited by post. The assessments consisted of

What is already known about this subject

- Anticholinergic burden has been associated with reduced physical and cognitive ability, and an increased risk of dementia and all-cause mortality. Extant epidemiological studies in Europe suggest an increase in anticholinergic prescribing over time, but focus on limited geographic areas, utilise cross-sectional designs or focused on individuals in older age, despite the potential importance of anticholinergic exposure throughout life.

What this study adds

- We performed an age-period-cohort analysis of changes in anticholinergic burden in >220 000 participants from UK Biobank, using GP electronically prescribed longitudinal data from 1990 to 2015. Anticholinergic burden in the UK has increased across several age groups and classes of prescription drugs. The increase was related to both ageing of the underlying sample as well as period-related changes in prescribing.

touch-screen questionnaires, computer-assisted interviews, measures of physical function and the collection of blood, saliva and urine. Primary care prescriptions were available for ~230 000 participants to May 2017 for Scotland, to September 2017 for Wales and to August 2017 for England. The data were provided to UK Biobank by region-specific data providers and include, among other information, the dates of prescriptions, names of drugs prescribed and drug codes. The latter include BNF codes provided by the British National Formulary, which provides prescribing guidance on medicines (https://www.bng.org/), Read v2- and CTV3-codes provided by the Terminology Reference Data Update Distribution (TRUD) service (https://isd.digital.nhs.uk/), and dmd + d codes provided by the National Health Service (NHS) (https://www.nhs.uk/). The drug code systems are used as dictionaries for medicines.

2.3 | Assignment of anticholinergic burden and drug class

Several resources allow for the identification of drugs with anticholinergic properties and provide a score of anticholinergic potency for each drug. These anticholinergic burden scales derive the lists of drugs from different sources, utilise different methods to assign the scores and validate the resulting tools in different populations and on different outcome measures. Previous studies have compared various existing anticholinergic scales and have generally reported poor overlap among them.[21-23] For the purposes of our study, we identified

multiple scales[24–33] from a systematic review[34]; apart from two[30,33] all had a four-point (0-3) scoring system of anticholinergic potency, where a lower score corresponds to lower anticholinergic potency (Supporting Information Table S1). We derived a meta-scale (Supporting Information Table S2) by calculating the mean anticholinergic burden across all nine original scales that had rated a drug. Thus, scales that scored a drug (even if that score was zero) were included in the computation for that drug, while scales that did not score the drug were not. All prescriptions of medicines with ophthalmic, otic, nasal or topical routes of administration were assigned an anticholinergic score of zero, as has been done before.[29,31,34,35]

For prescription entries that did not list any drugs (ie, for which the column indicating the name of the drug was blank), drug codes were used to supplement them. A series of steps was taken to exclude incomplete data or low number of individuals (Supporting Information Figures S1 and S2). Drugs were classified based on the Anatomical Therapeutic Chemical (ATC) Classification System (https://www.whocc.no), representing (1) the anatomical target, (2) the therapeutic subgroup, (3) the pharmacological subgroup, (4) the chemical subgroup and (5) the chemical substance. For example, metformin (5) affects the alimentary tract and metabolism (1), treats diabetes (2), lowers blood-glucose (3) and is a biguanide (4). Not all classes were equally represented in the sample. To allow for comparability of frequency of occurrence, we classified anticholinergic drugs into classes that do not all correspond to the same level in the ATC hierarchy (see number in parentheses): "drugs for acid disorders" (3), "analgesics" (2), "antidepressants" (3), "antithrombotic drugs" (2), "cardiovascular drugs" (1), "drugs for diabetes" (2), "gastrointestinal drugs" (2), "psycholeptics" (2), "respiratory drugs" (1) and "urological drugs" (3). A final class of "other drugs" was constructed that contained drugs that primarily due to their low prevalence individually contributed relatively little to the total anticholinergic burden. These included anticonvulsants, antibiotics, anti-Parkinsonian drugs, corticosteroids, immunosuppressants, anti-inflammatory drugs, muscle relaxants and anti-diarrhoeal drugs.

2.4 | Statistical approach

To enable longitudinal analyses, the original format of the data was transformed into two different formats that reflected for each participant the monthly and yearly anticholinergic burden, respectively. These period-based anticholinergic burden scores were calculated by summing the anticholinergic burden of all prescriptions in that period (Supporting Information Figure S3 and Text S1). When individual-level data are collected longitudinally, changes can be due to age, period or cohort effects.[36] Because the three effects are colinear (age = period cohort), they cannot all be included in a regression analysis, as holding two terms constant keeps the third term constant as well.[37] While there have been attempts to estimate the unique contributions among the three effects,[38,39] no solution has been widely adopted. Hidden assumptions can have a strong effect on the interpretation of the APC effect,[40] and in our analysis we make the following assumptions. First, age is probably positively associated with anticholinergic burden due to the positive association between polypharmacy and age.[4] Second, we assume that birth cohort does not play a role in the above association, ie, we are only interested in whether a potential longitudinal change in anticholinergic burden is due to the participants' age or due to changes in prescribing practices over time. For the analysis of APC effects, we ran three models, excluding one of the APC terms at a time (ie, its effect was assumed to be zero). Thus, anticholinergic burden was modelled as a function of either period and cohort (period-cohort model), age and cohort (age-cohort model) or age and period (age-period model). This three-model approach represents the same process – the change in anticholinergic burden in the sample – from three different perspectives and allows for an appraisal of possible drivers of the observed trend. For example, assuming that the effect of birth cohort is zero, positive effects for both period and cohort in the period-cohort model, and a positive effect of period, but a negative effect of age in the age-period model demonstrates that anticholinergic burden (a) increases with time across cohorts, (b) is higher in younger cohorts in a given period, (c) decreases with age and (d) is higher in recent periods across age groups. This would suggest that the anticholinergic burden increased with the time period but decreased with age. We additionally computed the above models by fitting separate intercepts and slopes: for the period-cohort and age-cohort models separate intercepts and slopes for each cohort, and for the age-period model separate intercepts and slopes for each period. For analyses of lifestyle and demographic factors, we fitted tobit linear models[41] to average monthly anticholinergic burden, adjusting for sex, education, physical activity, social deprivation, region, smoking, body mass index (BMI), frequency of alcohol consumption and age at assessment. Tobit models are models of censored regression, where the values that fall either above or below a certain value are censored. In our analysis, tobit models were censored from below at 0, effectively simulating zero inflation. For models with random effects, we used generalised linear mixed models (R package glmmTMB[42]); for all other models, we used Tobit regression (R package censReg). Due to the relative infrequency of anticholinergic drugs, anticholinergic burden was right-skewed and models were adjusted for zero inflation. The results are reported in unstandardised beta coefficients. The figures accompanying the analyses were generated based on the output of these analyses. Descriptive figures depicting longitudinal changes were based on generalised additive smoothing; whenever the latter is the case, it is explicitly indicated. Data cleaning and statistical analyses were performed in Python version 3.7.4 and R versions 3.4.1 and 3.6.3.

Several covariates were ascertained during or immediately prior to the participants' recruitment to UK Biobank. These included sex (male vs female [ref.]), education (graduate degree, no graduate degree [ref.]), alcohol consumption (1, daily or almost daily [ref.]; 2 three or four times a week; 3, once or twice a week; 4, one to three times a month vs 5, only on special occasions; 6, never), smoking status (current smoker, past smoker, never smoker [ref.]), BMI and physical activity (strenuous, moderate, mild [ref.])[43] and the Townsend Index of Socioeconomic Deprivation[44] (range −6.3-11.0). The latter is derived from different variables available from census data and

calculated to yield *z* scores. These are then summed and provide with an index ranging from −12 to 12, with higher values indicating greater deprivation. Region (Scotland, Wales, England [ref.]) was derived by combining data providers so that all prescriptions issued in England, Scotland and Wales were classified under the same category.

Each model was run in three iterations: basic models were unadjusted; basic-adjusted models included sex, data provider, education and socioeconomic deprivation. Data providers were specific to each prescription and available longitudinally. Sex, education and deprivation were assumed constant (ie, treated as time-invariant covariates) within individuals: over 90% of UK Biobank participants reported the same educational attainment at reassessment, within-person stability of deprivation has been reported previously.[45] Fully adjusted models were additionally controlled for smoking, alcohol consumption frequency, BMI, and physical activity. While these covariates were available only cross-sectionally, they are important in health and disease. Outlier observations – for anticholinergic burden and for polypharmacy, observations five or more interquartile ranges beyond the median (without accounting for zero-values), for BMI values lower than 15 and greater than 50 – were removed prior to analysis. This resulted in the removal of at most (depending on iteration) 347 297 data points (∼0.1% of the sample) for the data with monthly anticholinergic burden, 42 425 data points (1.3% of the sample) for the data with yearly anticholinergic burden and 13 836 data points (6.2% of the sample) for the individual lifestyle and demographic data.

A sensitivity analysis was conducted that was limited to the period from 2000 to 2015. This was done due to the relatively low level of ascertainment in the sample before that period (Supporting Information Figure S2).

2.5 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[46]

3 | RESULTS

The 220 867 participants were born between 1938 and 1969 (Supporting Information Figure S4). Individuals were being added to the database of prescriptions throughout the sampling period (1990-2015), but the demographic structure of the sample (Table 1) remained relatively stable over time. However, it is unclear how demographic variables changed within individuals over time.

3.1 | Anticholinergic prescribing

Of 248 drugs on the meta-scale, 201 (81.0%) were found in the sample and constituted 25.0% of all prescriptions. A total of 199 652 participants (90.4%) were prescribed at least one anticholinergic drug and 28 525 (13.2%) participants were prescribed anticholinergic drugs every year during the prescribing period. Among previously published scales, anticholinergic prescriptions constituted 2.5-23.1% of all prescriptions (Table 2) and anticholinergic burden according to each scale exhibited an increasing trend over time (Figure 1A). Depending on the scale used, anticholinergic burden increased

Variable	Level	Median (IQR) or n (%)	Missing
Sex	Female	121 286 (54.9)	0
	Male	99 581 (45.1)	
Education	Graduate degree	69 745 (32.0)	2816
	No graduate degree	148 306 (68.0)	
Deprivation		−2.2 (4.1)	319
Alcohol consumption	Daily or almost daily	43 269 (19.6)	559
	Three or four times a week	50 753 (23.0)	
	Once or twice a week	57 934 (26.3)	
	Once to three times a month	24 891 (11.3)	
	Only special occasions	25 274 (11.5)	
	Never	18 187 (8.3)	
Smoking	Current smoker	23 069 (10.5)	1144
	Previous smoker	75 955 (34.6)	
	Non-smoker	120 699 (54.9)	
Physical activity	Strenuous	21 618 (10.6)	16 225
	Moderate	129 874 (63.4)	
	Light	53 150 (26.0)	
BMI		26.9 (5.8)	1332

TABLE 1 Demographic characteristics of the sample at the time of recruitment to UK Biobank

between 3- and 9-fold from 1990 to 2015. Most anticholinergic prescriptions were for antidepressants, which accounted for 32.5% of the total anticholinergic burden (Table 3 and Figure 1B). The anticholinergic burden for each drug class increased with time (Figure 1C).

3.2 | Age-period-cohort analysis

In the basic period-cohort model, anticholinergic burden was positively associated with period and negatively associated with cohort. In the basic age-cohort model, anticholinergic burden was positively associated with age and with cohort. In the basic age-period model, anticholinergic burden was positively associated with age and with period. The same trends were observed in the basic-adjusted and fully adjusted models (Supporting Information Table S3). These results indicate that greater anticholinergic burden relates to both ageing and later period. That is, in a given period, older individuals experience a higher anticholinergic burden than younger individuals in the same period. Moreover, in recent periods, individuals will experience a higher anticholinergic burden than individuals of the same age did in the past. For example, the average yearly anticholinergic burden of a 50-year-old was 2.32 in 2000, 2.92 in 2007 and 3.67 in 2015, while the average yearly anticholinergic burden of a 60-year-old was 3.06 in 2000, 3.94 in 2007 and 5.12 in 2015. The trends persisted when the outcome was the number of prescribed anticholinergic drugs (Supporting Information Table S4). The proportion of drugs with different anticholinergic potencies remained stable over time (Supporting Information Figure S5). Thus, the increase in anticholinergic burden was likely due to a general increase in anticholinergic prescribing, rather than a relative increase in the prescribing of stronger anticholinergic drugs.

In the mixed-effects models, anticholinergic burden increased by 0.22 each year (SE = 0.0012, P < .001). In the period-cohort model, earlier-born cohorts exhibited steeper slopes than later-born cohorts (n = 32, correlation between slope and cohort r = −0.97, SE = 0.041, P < .001; Figure 2A). In the mixed-effects age-cohort model, earlier-born cohorts exhibited steeper slopes than later-born cohorts (n = 32, correlation between slope and cohort r = −0.97, SE = 0.048, P < .001). In the mixed-effects age-period model, later periods exhibited steeper slopes than earlier periods (n = 25, correlation between slope and period r = 0.95, SE = 0.064, P < .001).

When the change in anticholinergic burden was plotted for each drug class separately (Supporting Information Figure S6), the same pattern was observed for all drug classes except for drugs for acid disorders and cardiovascular drugs. For the former, an increase in anticholinergic burden over time was observed, but was similar across periods and cohorts, suggesting an effect of age, but without a prominent period effect. For cardiovascular drugs, we observed an increase in anticholinergic burden over time and a higher anticholinergic burden in earlier cohorts and later periods, suggesting a positive effect of age, but a negative period effect.

When the basic models were adjusted by the addition of the total number of prescribed drugs (Supporting Information Table S5), all effect sizes were greatly diminished, more so by the total number of prescribed drugs than by all other covariates combined. Furthermore, the effect of birth cohort was reversed in the period-cohort model and the effect of age was reversed in the age-period model. Thus, the period effect was retained, but the effect of age was reversed when adjusted for the number of prescribed drugs. These results possibly indicate that whereas overall anticholinergic burden has increased over time, and more so among older adults, anticholinergic drugs in the latter group comprise a relatively lower proportion of overall prescriptions when compared to younger individuals (Supporting Information Figure S7).

TABLE 2 Comparison of the number of drugs on each anticholinergic scale, the number of drugs on each scale that were prescribed in our sample, the percentages of all prescriptions in the sample that the drugs on the scales constituted and the increase in the mean yearly anticholinergic burden from 1990 to 2015

| Scale	n drugs on the list	n drugs in the sample (%)	% total prescriptions	1990-2015 increase (%)
Han et al[24,35]	67	53 (79.1)	10.5	531
Ancelin et al[25]	27	21 (77.8)	2.5	464
Carnahan et al[26]	145	108 (74.5)	9.7	318
Chew et al[27]	39	33 (84.6)	11.3	697
Cancelli et al[28]	17	15 (88.2)	3.9	699
Rudolph et al[29]	69	62 (90.0)	5.9	374
Ehrt et al[30]	29	23 (79.3)	7.4	902
Sittironnarit et al[31]	49	42 (85.7)	12.5	533
Boustani et al[32] (2012)	99	85 (85.9)	12.3	478
Durán et al[33]	180	141 (78.3)	20.7	442
Kiesel et al[34]	165	141 (85.5)	23.2	525
Meta-scale	248	201 (81.0)	25.0	432
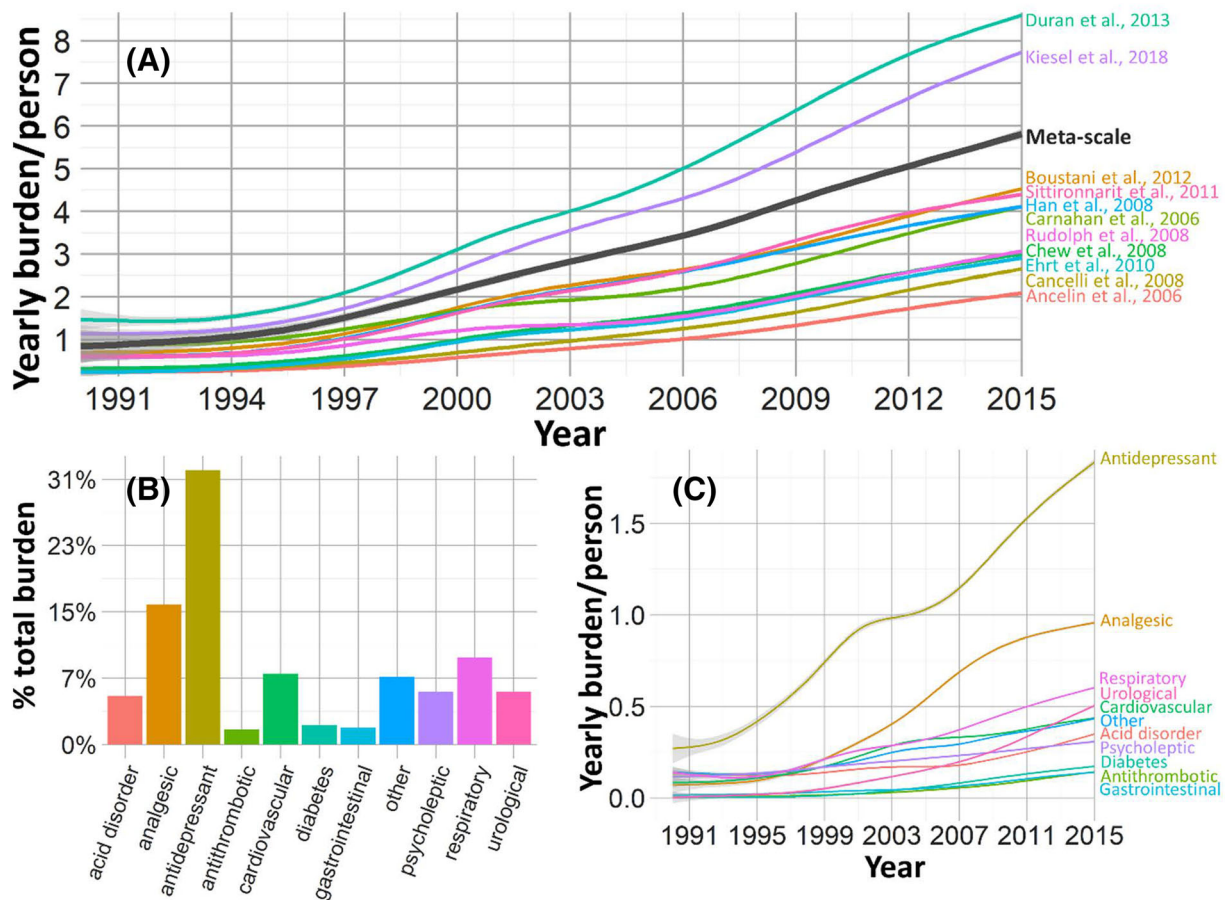
FIGURE 1 Anticholinergic burden over time based on different anticholinergic scales (A), percentage of anticholinergic burden in the sample due to each drug class (B) and the change in anticholinergic burden over time due to each drug class (C). The plots in (A) and (C) were generated using generalised additive smoothing

TABLE 3 Comparison of the number of anticholinergic drugs from different drug classes and their contributions to the total anticholinergic burden

| Drug class	n	%	Number of drugs in class	Mean anticholinergic burden per drug	% total anticholinergic burden
Acid disorders	1 464 542	10.3	5	0.50	5.8
Analgesics	1 426 703	10.1	12	1.48	16.5
Antidepressants	2 678 379	18.9	27	1.54	32.4
Antithrombotics	546 311	3.8	2	0.41	1.8
Cardiovascular	2 006 594	14.1	16	0.53	8.4
Diabetes	785 940	5.5	1	0.38	2.3
Gastrointestinal	220 269	1.6	9	1.18	2.0
Psycholeptic	690 894	4.9	35	1.16	6.3
Respiratory	1 499 455	10.6	33	0.88	10.3
Urological	330 314	2.3	8	2.41	6.2
Other	2 545 293	17.9	57	0.40	8.0
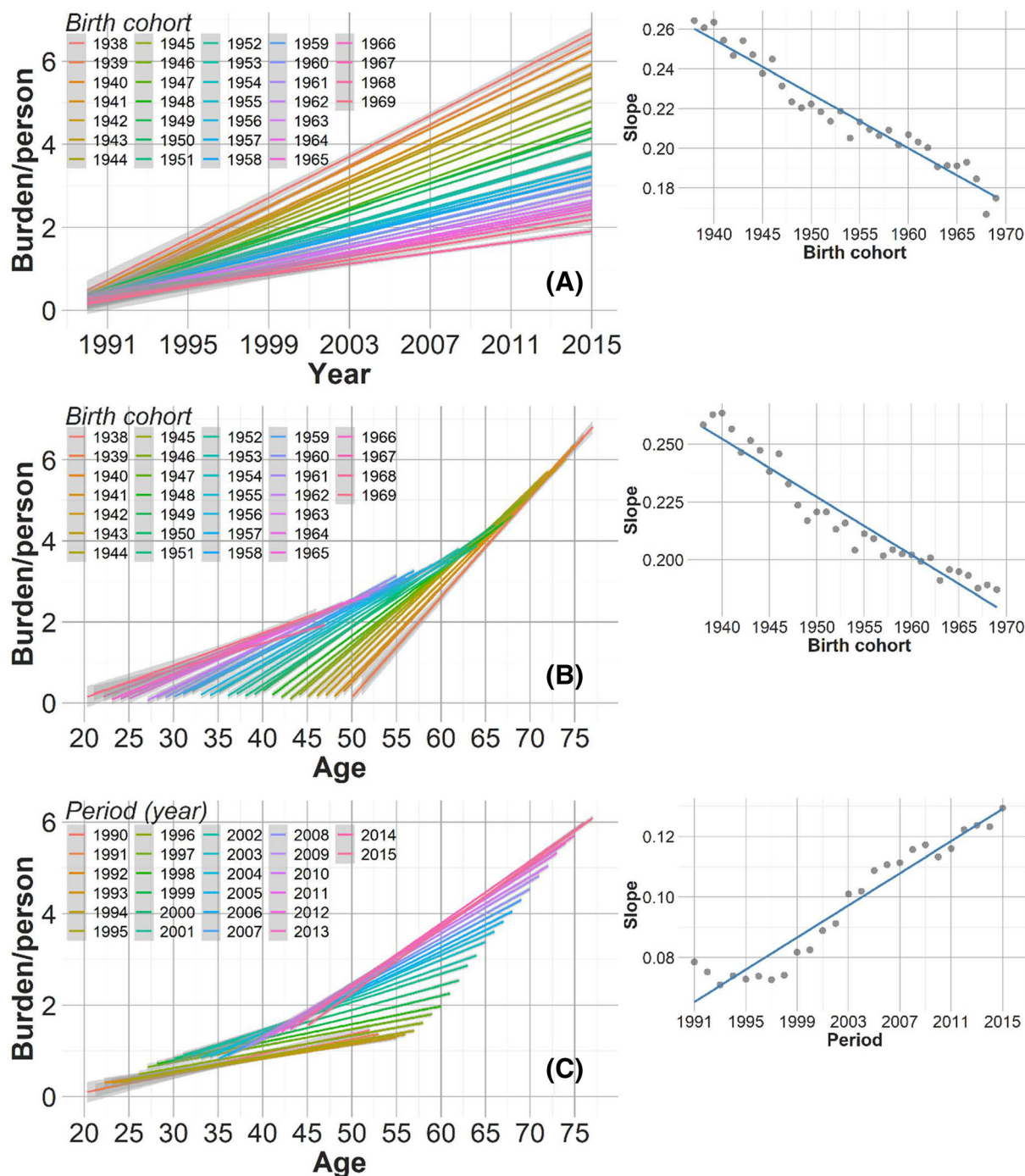
FIGURE 2 APC analysis with basic mixed models with random intercepts and slopes (left) and associations between slopes and different levels of predictors (right). (A) The period-cohort model with cohort as a random effect, (B) the age-cohort model with cohort as a random effect and (C) the age-period model with period as the random effect

3.3 | Anticholinergic burden and demographic factors

Higher anticholinergic burden was associated with female sex, lower educational attainment, greater deprivation, higher BMI, less frequent alcohol consumption and lower physical activity, and was greater in Scotland and Wales than in England (Table 4).

Examining each drug class separately, most effects remained (Supporting Information Table S6). However, anticholinergic burden due to antithrombotic drugs, cardiovascular drugs and drugs for diabetes was higher in males than in females. Moreover, regional differences in anticholinergic burden strongly depended on drug class. Deprivation was transformed into a binary categorical variable, with the median (~2.2) across all participants defining the groups. For

TABLE 4 Results of the model predicting monthly anticholinergic burden as a function of deprivation, smoking, BMI, sex, education, region, alcohol consumption, physical activity and age

Predictor	Level	Beta	SE	P
Deprivation		0.0058	2.6×10^{-4}	<.001
Smoking (*ref: non-smoker*)	Previous smoker	0.041	0.0016	<.001
	Current smoker	0.072	0.0027	<.001
BMI		0.010	1.7×10^{-4}	<.001
Sex	Male	−0.043	0.0015	<.001
Education	Graduate degree	−0.046	0.0016	<.001
Region (*ref: England*)	Scotland	0.047	0.0025	<.001
	Wales	0.029	0.0026	<.001
Alcohol consumption (*ref: daily or almost daily consumption*)	Three or four times a week	−0.004	0.0022	<.001
	Once or twice a week	0.014	0.0022	<.001
	Once to thrice a month	0.032	0.0028	<.001
	Special occasions only	0.066	0.0029	<.001
	Never	0.102	0.0033	<.001
Physical activity (*ref: mild or no physical activity*)	Moderate	−0.041	0.0018	<.001
	Strenuous	−0.072	0.0028	<.001

region, sex, education and deprivation, we then plotted anticholinergic burden as a function of period for different levels of predictor variables. Supporting Information Figure S8 illustrates the association between the above predictors and anticholinergic burden.

3.4 | Sensitivity analyses

When the observation period was restricted to prescriptions after 1999, the trends above were again observed for all models except for when polypharmacy was used as covariate (Supporting Information Tables S7-10, Text S2 and Figure S9). There, period was negatively associated with anticholinergic burden in the period cohort and in the age-period model. Age was negatively associated with anticholinergic burden in both the age cohort and the age-period model. Birth cohort was positively associated with anticholinergic burden in the period-cohort model, but negatively associated with anticholinergic burden in the age-cohort model. Thus, when accounting for polypharmacy, the sensitivity analysis supports an age-related decrease in anticholinergic burden, but does not support a period-related increase in anticholinergic burden.

4 | DISCUSSION

In a large longitudinal study of prescription drugs with anticholinergic properties, we showed that the anticholinergic burden in the UK is increasing, and older individuals continue to have the highest anticholinergic burden. Age-related increases in anticholinergic burden can be explained by polypharmacy in older adults. Indeed, when accounting for polypharmacy and period, anticholinergic burden decreases with

age, possibly demonstrating proportionate deprescribing of anticholinergic drugs in older age. We also find associations between higher anticholinergic burden and various demographic and lifestyle factors, including female sex, less education and greater socioeconomic deprivation.

4.1 | Anticholinergic burden over time

Anticholinergic burden increased in all APC models. Throughout time periods and across birth cohorts, ageing was associated with greater anticholinergic burden. Moreover, across age groups and birth cohorts, anticholinergic burden has increased in recent years. Finally, at a given age, later-born cohorts experienced a greater anticholinergic burden than earlier-born cohorts, while in a given period, later-born cohorts experienced a smaller anticholinergic burden than earlier-born cohorts.

Because of the collinearity of age, period and cohort (age = period cohort), they cannot all be included in a regression analysis, as holding two terms constant keeps the third term constant as well.[37] Some argue that the APC problem cannot be completely resolved[40] and that results from APC-based models should be based on well-founded and clearly communicated assumptions. In the present paper we assumed no cohort effects and predicted anticholinergic burden to increase with ageing. Based on current knowledge on polypharmacy and anticholinergic burden, the following conclusions can be drawn from our results. First, due to increased multimorbidity and polypharmacy in older individuals,[4] age contributed to the trend. When intercept and slope were modelled separately in mixed models with random effects, cohort was negatively associated with the slope, suggesting not only a greater anticholinergic burden, but also a more

rapid accumulation of burden in older individuals. Second, as previously reported,[4] individuals are now being prescribed more drugs than in the past. The increase in anticholinergic burden could be caused by a new generation of patients who either demand more or who are diagnosed with more maladies. Alternatively, the increase could be related to changes in prescribing practices due to societal changes or changes in medical training. Regardless of the underlying causes, people in the UK are being increasingly prescribed anticholinergic drugs.

The increases in anticholinergic burden could be related to an increase in general polypharmacy and not an increase in specifically anticholinergic prescribing. Indeed, when the models were adjusted for the number of prescriptions, the changes in anticholinergic burden were greatly diminished. Furthermore, earlier-born individuals exhibited a lower anticholinergic burden across periods and across age groups than those born later. Moreover, across age groups, anticholinergic burden was higher in later periods than in earlier periods. While correcting for polypharmacy had no effect on the trend of the age-cohort model, it changed the direction of birth cohort and age in the period-cohort model and the age-period model, respectively. Later-born individuals exhibited a higher anticholinergic burden, and this burden was positively associated with period, but negatively associated with age. The failure to exactly replicate these results when the period was restricted to 2000-2015 indicates that the relationship between polypharmacy and anticholinergic burden is complex and warrants more detailed study. While the results indicate that medical practitioners have been mitigating the increase in polypharmacy by deprescribing anticholinergic drugs in older people, this group nevertheless experienced the highest burden. Furthermore, older people experienced a greater anticholinergic burden in 2015 than at any point in the preceding 25 years.

4.2 | Demographic- and lifestyle factors

Anticholinergic use has been linked with some demographic and lifestyle factors.[16,17,19] In our study, female sex, lower education, higher socioeconomic deprivation, higher BMI, lower frequency of alcohol consumption, lower physical activity and being prescribed in Scotland or Wales (compared to England) were associated with a higher anticholinergic burden. Certain groups do require a greater number of medications but medical professionals may prescribe more to certain groups, independent of underlying medical conditions.

Interestingly, greater alcohol consumption was associated with decreased anticholinergic burden. Individuals who take many medications may reduce their alcohol consumption to reduce the risk of drug interactions or to reduce the impact of existing disease.

4.3 | Strengths and limitations

The present study used a very large, well-characterised sample and utilised primary care electronic prescription data over a wide period. However, we recognise several limitations. First, while visual inspection of anticholinergic burden across different scales did reveal a common upward trend, our newly computed meta-scale was not previously validated and estimates a higher anticholinergic burden than most other scales. Second, we did not include longitudinal data on over-the-counter drugs and dietary supplements. Considering the availability in the UK of over-the-counter anticholinergic medicines, especially histamines, the computed anticholinergic burden was likely an underestimate across all scales. Third, while our assumption that topical, ophthalmic, otic and nasal drugs do not have anticholinergic effects is common in the literature,[29,31,34,35] we are not aware of conclusive evidence to support it. Fourth, estimates of prevalence and statistical inferences are dependent on the underlying sample and UK Biobank is not representative of the UK population. On average, participants in the study are less likely to be obese, to smoke, have fewer health conditions and live in socioeconomically less deprived areas.[47] Thus, differences in anticholinergic burden and period-dependent disparities are possibly greater in real populations. Fifth, our analysis of the effects of demographic and lifestyle factors on anticholinergic burden assessed the correlation between the average value of a metric that changes with time (anticholinergic burden) and cross-sectional data (eg, BMI, smoking, alcohol consumption and physical activity), which was ascertained towards the end of the period in question when participants were of different ages. We also modelled deprivation and educational attainment as time-invariant covariates. Thus, our results cannot clarify the exact nature of potential temporal relationships. Finally, we did not have data on the oldest people, who represent the group most at risk of anticholinergic effects.

5 | CONCLUSION AND FUTURE DIRECTIONS

Prescribing drugs involves balancing their medicinal value with potential harms. Moreover, exhaustive longitudinal studies are required to fully determine all their effects. However, besides well-documented side effects,[48] exposure has been linked to an increased frequency of falls,[9] reduced physical, cognitive and functional ability,[6-8] and increased risks of dementia[10] and all-cause mortality.[11] Thus, anticholinergic drugs ought to be prescribed sparingly and the use of alternatives strongly considered. An understanding of temporal prescribing trends in a population may help to guide prescribing and stimulate further research. Our work represents an overview and future studies should describe prescribing trends and their relationship to age groups, and demographic and lifestyle characteristics in greater detail. There is also evidence of differences between drug classes in the association between anticholinergic burden and health outcomes.[10] Identifying distinct anticholinergic trends for individual drug classes for different groups could help to further improve prescribing guidelines. Additionally, future work should attempt to identify the causes for the increase in anticholinergic prescribing, and more precisely quantify the potential implications for important life outcomes, including brain and cognitive health, and dementia. Finally, decreases in potentially inappropriate prescribing have been reported even when

the same population experienced increases in polypharmacy and in anticholinergic use.[49] Thus, increases in anticholinergic burden should not be considered in isolation, but in the context of other prescribing practices.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

CONTRIBUTORS

J.M. designed the study, cleaned and analysed the data, interpreted the results, generated the figures and wrote the first draft of the manuscript. All authors assisted with the data analysis strategy, contributed to the editing of the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

All data are available via UK Biobank. The code used for cleaning and modelling the data is available on GitHub (https://github.com/JuM24/Anticholinergic-trends-UK-Biobank).

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