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RESEARCH PAPER

Anticholinergic drug use and cognitive performances in middle age: findings from the CONSTANCES cohort

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2018-318190).

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Received 8 February 2018
Revised 11 June 2018
Accepted 9 July 2018
Published Online First 7 September 2018

To cite: Ziad A, Olekhnovitch R, Ruiz F, *et al*. *J Neurol Neurosurg Psychiatry* 2018;**89**:1107–1115.

ABSTRACT

Background Previous studies have shown associations between the use of anticholinergics (AC) and cognitive performance in the elderly, considering AC as a homogeneous set of drugs. The present study aims to assess the relationship between exposure to AC drugs and cognitive performance in middle-aged adults according to AC potency and drug class.

Methods Our cross-sectional study used baseline data of 34 267 participants aged 45–70 from the Consultants des centres d'examen de santé de la sécurité sociale (CONSTANCES) cohort. The cumulative exposure to AC was measured using national reimbursement databases over the 3-year period preceding assessment of cognitive performance. Eight classes of AC drugs were differentiated. Episodic verbal memory, language abilities and executive functions were evaluated by validated neuropsychological tests. Analyses were controlled on lifestyle and health status variables.

Results This study showed a negative association between overall cumulative AC exposure and cognitive performances after adjustment. The use of drugs with possible AC effect according to the Anticholinergic Cognitive Burden scale (ACB-1 score) was only associated with executive functions. Analyses of AC exposure across drug classes showed a negative association between the use of AC antipsychotics and all cognitive functions assessed. Heterogeneous associations were found for the use of AC anxiolytics, AC opioids and AC drugs targeting the gastrointestinal tract or metabolism. We did not find significant associations between the use of antihistamines, antidepressants, cardiovascular system or other AC medications and cognitive function.

Conclusion Association between AC drugs and cognitive performance was highly heterogeneous across drug classes; this heterogeneity will have to be considered by future studies.

INTRODUCTION

Anticholinergic (AC) drugs are extensively used to treat a broad range of medical conditions. A first group encompasses muscarinic receptor antagonists that block acetylcholine-mediated neurotransmission in the smooth muscle, heart, central and peripheral nervous systems.[1] This effect is expected to induce therapeutic benefits in various conditions such as Parkinson's disease, overactive bladder syndrome and chronic obstructive airway diseases. For a second group, the therapeutic effect relies on other pharmacological properties and the AC potency is therefore unwanted. Among others, this group includes certain diuretics, antihistamines and psychotropic drugs (eg, antidepressants). For both groups, side effects vary depending on whether the targeted muscarinic receptors are peripheral (dryness of the mouth, constipation, dysuria and mydriasis),[2] central (confusion, delirium, hallucinations, and memory impairments, especially in elderly patients) or both.[3 4]

The detrimental effects of AC drug use have been mainly studied in elders without dementia. In France, 7.5%–14% of them are prescribed AC drugs.[5 6] Several observational studies have documented an association between AC drug use and cognitive impairment in elderly patients,[7–10] sometimes with a dose–effect association.[11] However for neurodegenerative diseases such as Alzheimer's disease and other forms of dementia, the early symptoms develop gradually over the years as a result of progressive brain cell damage.[12] Therefore, to identify potential contributors, exposures must be measured several years before symptom onset, that is, in middle age.

Moreover, most of these studies either focused only on drugs with marked AC effects or pooled all AC drugs, regardless of the level of their AC potency and drug class. Consequently, their findings about specific AC effects are difficult to interpret, as the most widely prescribed ACs have a low AC potency,[13] and some drug classes (such as anxiolytics) can also exert non-AC-related effects on cognition.[14] Thus, studies of associations between AC drug use and cognitive impairment should specifically consider the level of AC potency and the drug class.

The main objective of this population-based study was first to test the hypothesis that AC exposure may dose-dependently affect cognitive performances as early as 45 years of age. Another objective was to test whether this association varied according to the AC potency of the considered drugs and according to their drug class.

MATERIALS AND METHODS

All participants gave written informed consent to participate in the present study.

Study design and population

This population-based study relied on individuals enrolled in the CONSTANCES cohort. CONSTANCES is a large (200 000 participants at the end of the recruitment planned early 2019),

population-based, prospective cohort composed of a randomly selected sample of adults living in France and aged 18–70 years at recruitment. The general design of CONSTANCES is detailed elsewhere.[15] Briefly, eligible individuals were invited by mail and completed a self-administered questionnaire on lifestyle, health status, medical history, socioprofessional status and lifetime employment history. Each participant attended a health screening centre for a comprehensive evaluation including a physical examination and laboratory tests. Participants aged 45–70 years underwent a battery of cognitive tests.[16] The CONSTANCES cohort is also linked to the electronic database of the French statutory health insurance administrative database.[17]

We included cohort participants enrolled between February 2012 and June 2016 who were 45 or over at recruitment, and used data collected through baseline questionnaires, medical examination and cognitive tests; information about drugs used during the previous 3 years was extracted from the insurance administrative database to calculate the cumulative exposure to AC drugs.

AC drug exposure measurement

For each drug delivered, the following information was collected from the insurance database: drug name according to the Anatomical Therapeutic Chemical (ATC) classification, date the drug was dispensed and amount dispensed (number of packages, number of tablets per package or total volume for liquids, tablet strength or concentration for liquids) and route of administration.[18] Total dose (in mg) dispensed at each prescription fill was computed by multiplying the number of tablets per package by tablet strength and by number of packages dispensed. Then, we calculated the standardised daily dose (SDD) for each prescription fill by dividing the total dose dispensed by the defined daily dose (DDD, a reference dose defined by international experts from the WHO as the average dose recommended for the main indication in an adult weighing 70 kg, for each ATC-5th level code and route of administration).[19] All medications prescribed by a physician (including medications-as-needed) were taken into account. Since DDDs are not available for eye-drops and topical steroids, these drugs were excluded from our analyses.

Finally, cumulative exposure was obtained as the total standardised daily dose (TSDD) for each participant by summing the SDDs for all ACs dispensed over the 3 years preceding the cognitive testing. Participants were divided into five groups based on their TSDD: non-user, 1–90 days, 91–365 days, 366–1095 days (ie, 3 years) and more than 1095 days.[11]

We used the Anticholinergic Cognitive Burden (ACB) scale to characterise AC potency.[20 21] A panel of healthcare experts assigned a score to each drug: ACB-1, possible AC effect on cognition based on in vitro results or affinity for muscarinic receptors but without relevant clinical evidence; and ACB-2 or ACB-3, clinically documented AC effect on cognition, with ACB-3 indicating greater ability to cross the blood–brain barrier and to induce confusion.[22] We assembled drugs with a clinically confirmed AC effect (ACB-2 and ACB-3) into a single category (ACB-2/3).

The potential role of the drug class on the association between cumulative AC exposure and cognitive performances was assessed by splitting AC drugs in several groups according to the third level of the ATC classification level. However, AC drugs targeting the gastrointestinal tract or metabolism and AC cardiovascular drugs were grouped according to the first level of the ATC classification to ensure sufficient group size.

Cognitive tests

Cognitive functions were evaluated under standard conditions by trained neuropsychologists using four well-recognised tests described in detail elsewhere.[23]

1. The Free and Cued Selective Reminding Test was chosen to assess episodic verbal memory. Sixteen items to be memorised are shown on index cards in groups of four.[24] The participant is asked to remember as many items as possible, first freely then in response to a cue (semantic category—that is, the item to remember 'grape' corresponds to the semantic category 'fruit') if free recall fails. Trials are carried out three times immediately after the learning phase then 20 min later. For this study, we considered both the immediate free recall score (sum of the number of items retrieved freely at the first three recall trials) and the delayed free recall score (number of items retrieved freely during the delayed trial).
2. Language abilities were assessed using verbal fluency tests.[25 26] We counted the number of items named by the participant in 1 min in the 'animals' category (semantic fluency task) and starting with the letter R (phonemic fluency task).
3. The Digit Symbol Substitution Test (DSST) of the Wechsler's Adult Intelligence Scale was used to assess psychomotor speed.[27] Nine-digit symbol pairs are followed by a list of digits. Under each digit, the participant must write the corresponding symbol, as fast as possible, in 120 s.
4. The two parts of the Trail Making Test evaluate attention and visuospatial perception (TMT-A) and shifting abilities (TMT-B); the task is to connect with a pencil as fast as possible and in ascending order a sequence of 25 circles.[28 29] In part A, the circles contain only digits, whereas circles in part B contain digits alternating with letters. For this study, we used the following: (number of correct moves/total time)×10.

Covariates

The main confounding factors related to cognitive functions were taken into consideration.[23] They were collected through a self-administered questionnaire and medical examination.

Sociodemographic variables were gender, age (in six 5-year groups) and education level (in six categories: no academic qualification, certificate of primary or secondary education, GCE (General Certificate of Education) or A level, up to 4 years of university education, 5 years of university education, and master's degree or higher).

The following lifestyle variables were used: living with versus without a partner, smoking status (never, past or current), alcohol consumption (none; moderate defined as three glasses or less per day for men, and two glasses or less per day for women; and excessive if above), physical activity (on a 7-point scale where 0 indicated none and 6 a high level of activity) and body mass index (in four categories: underweight, <18.5; normal, 18.5–25; overweight, 25–30; and obese, ≥30).

Finally, the following health variables were recorded: depression disorders assessed using the Center for Epidemiological Studies-Depression scale with scores of 16 or greater indicating a high risk of depression,[30] self-rated health (from 1, very good, to 8, very bad), diabetes, respiratory disease (asthma and/or chronic obstructive pulmonary disease), cardiovascular diseases (myocardial infarction, high blood pressure, stroke, angina, peripheral arterial occlusive disease of the lower limbs), musculoskeletal disorders, hypercholesterolaemia and cancer.

Statistical analyses

Categorical variables were described as percentages and continuous variables as means and SD. Cumulative exposure groups were compared using the χ^2 test for categorical variables and analysis of variance for continuous variables, with α set at 0.05. Sociodemographic variables such as age, gender and education level are known to be associated with cognitive performances. For comparisons of cognitive scores, we therefore computed the adjusted z-scores for age, gender and education level for each cognitive test, using multivariable linear regression according to the Barona method.[31 32]

Univariate linear regression models were built to assess the effect of cumulative AC exposure on cognitive performances. For each cognitive test, the z-score was the dependent variable and cumulative exposure was the independent variable. In addition, for each model, we adjusted on lifestyle variables first, then on both lifestyle and health status variables.

Effect size has been defined as small, medium or large, for beta values of 0.2, 0.5 or 0.8 since difference in adjusted z-score means can be interpreted as an adjusted Cohen's d.[33]

In secondary analyses, we developed multivariable linear regression models to evaluate associations between cumulative AC exposure and cognitive performances according to the level of AC potency, then according to the drug class (ATC classification level).

We performed several sensitivity analyses for overall exposure (1) according to age group (<65 vs 65+); (2) by excluding participants who had at least one delivery of antipsychotics; and (3) according to drug class but restricted to ACB-1 drugs.

Missing data (5.6% of the data) were handled using multiple imputations with chained equations (mice) package in the R project. The imputed data set was generated by performing 50 imputation cycles.

All analyses were done using R V.3.3.2 (https://cran.r-project.org/).

RESULTS

Between February 2012 and June 2016, 37 304 participants with a mean age of 57.8 years undertook the cognitive tests. Study population corresponded to participants with available data to compute cognitive z-scores (N=34 267 participants presenting all cognitive z-scores). Table 1 shows the main characteristics of participants. During the 3-year period preceding inclusion, AC drugs were dispensed at least once to 16 172 (47.2 %) participants. For nearly two-thirds of these AC drug users, cumulative exposure was less than 3 months. Elderly, women and individuals with low education levels were more likely to have a high cumulative AC exposure (table 1).

Table 2 shows the frequency of AC drugs dispensing across ACB scores and drug classes. Among AC drug users, 12 220 (76%) received at least one ACB-1 drug, 822 (5%) at least one ACB-2/3 drug, and 3130 (19%) at least one drug in both ACB categories. Exposure to two or more different AC drugs was recorded for 52.4% of AC drug users (table 2). The distribution of AC drug classes by AC potency is detailed in online supplementary e-table 1.

Table 3 shows the associations between cumulative AC exposure and cognitive test z-scores. In univariate analyses, being exposed to ACs was negatively associated with all cognitive test z-scores for most of the exposure levels. In all the studied tests, the effect size increased with the cumulative AC exposure (p trend <0.001). After adjustment for cofounders, this association remained highly significant—although smaller—for the executive function tests, that is, the DSST (β=−0.193 (p<0.001)) and the TMT (A: β=−0.167 (p<0.001); B: β=−0.163 (p<0.001)) within individuals highly exposed to AC drugs (>3 years). The association with verbal fluency was no longer significant after adjustment. A significant association persisted for the episodic memory tests with a small effect size (immediate free recall: β=−0.103 (p=0.018); delayed free recall: β=−0.125 (p=0.004)). In addition, after adjustment, significant associations with a gradient were observed for the 1–3 years and more than 3 years' exposure levels in DSST and TMT-A (p trend <0.001). The results of sensitivity analysis according to age group (<65 vs 65+) are displayed in online supplementary e-table 2.

Cumulative exposure to ACB-2/3 drugs was associated with episodic memory, that is, delayed free recall (β=−0.360 (p<0.001)) with a significant dose–effect (p trend <0.001), while cumulative exposure to ACB-1 drugs was associated with executive functions, that is, the DSST (β=−0.179 (p<0.001)) (table 4).

The association between cumulative exposure to AC drugs and cognitive scores was heterogeneous across AC drug classes (table 5). For executive functions, it was large among antipsychotics (DSST, β=−0.658 (p<0.001); TMT-A, β=−0.590 (p<0.001); TMT-B, β=−0.511 (p<0.001)), small and medium among drugs targeting the gastrointestinal tract or metabolism (DSST, β=−0.154 (p=0.17); TMT-A, β=−0.287 (p=0.01); TMT-B, β=−0.344 (p=0.002)), and small among anxiolytics (DSST, β=−0.197 (p=0.005); TMT-A, β=−0.176 (p=0.01); TMT-B, β=−0.170 (p=0.01)) (table 5). For episodic memory, it was medium among antipsychotics (immediate free recall, β=−0.433 (p<0.001); delayed free recall, β=−0.493 (p<0.001)) and small among opioids (immediate free recall, β=−0.161 (p=0.15); delayed free recall, β=−0.101 (p=0.37)) and anxiolytics (delayed free recall, β=−0.185 (p=0.01)). Only exposure to AC antipsychotic was associated with impaired verbal fluency (semantic fluency, β=−0.380 (p<0.001); phonemic fluency, β=−0.262 (p=0.009)). There was a significant dose–effect in all cognitive scores for exposure to AC antipsychotics (table 5): for example, the effect size in DSST in the group >1 year (β=−0.658 (p<0.001)) was almost twice that of the group <1 year (β=−0.347 (p<0.001)) (p trend <0.001). Of note, no significant association was found between exposure to AC antihistamines, AC antidepressants or AC drugs for the cardiovascular system and cognitive performance.

In the sensitivity analysis after excluding participants with antipsychotics deliveries, we noted that the effect size of association between overall cumulative AC exposure and cognitive performance—for the most exposed participants (>3 years)—is almost halved compared with the analysis, taking into account participants with antipsychotics deliveries (online supplementary e-table 3).

Sensitivity analysis performed on ACB-1 drugs (online supplementary e-table 4) shows very similar results with an important effect size of antipsychotics.

DISCUSSION

This cross-sectional study of 34 267 individuals aged 45–70 demonstrated a negative association between overall cumulative exposure to AC drugs and cognitive performance. This association was medium for executive functions (DSST, TMT-A and TMT-B) and less pronounced for episodic memory (immediate and delayed free recall). To our knowledge, the present study is the first reporting such an association in

Table 1 Characteristics of participants (n=34 267) by cumulative exposure to anticholinergic drugs

Variable	n	Cumulative exposure to anticholinergic drugs					P values
		None 18 095	<3 months 10 437	3–12 months 3385	1–3 years 1786	>3 years 564	
Socioeconomic variables							
Age (years)		57.8±7.1	57.4±7.2	57.7±7.1	59.1±7.1	59.2±7.0	<0.001
Male gender	16 157	50%	45%	42%	40%	45%	<0.001
Education level							
No academic degree	1046	3%	3%	4%	5%	8%	<0.001
Certificate of primary or secondary education	11 277	31%	35%	35%	39%	42%	
GCE or A level	5877	17%	17%	17%	17%	16%	
1–4 years of university	7455	22%	21%	23%	20%	18%	
5 years of university	2828	9%	8%	7%	7%	6%	
Master's degree or higher	5784	18%	16%	14%	13%	11%	
Lifestyle variables							
Living with a partner	26 047	78%	76%	74%	70%	65%	<0.001
Smoking status							
Never	14 511	46%	43%	42%	43%	37%	<0.001
Current	4437	13%	14%	14%	15%	21%	
Former	13 772	41%	43%	43%	43%	43%	
Alcohol consumption							
None	4266	13%	14%	16%	18%	23%	<0.001
Moderate	22 221	75%	73%	71%	68%	62%	
Excessive	3796	12%	13%	13%	15%	16%	
Physical activity score (0: none, 6: high activity level)		4.8±1.5	4.7±1.5	4.6±1.6	4.4±1.6	4.2±1.7	<0.001
Body mass index		25.4±4.2	25.6±4.3	26.2±4.7	26.9±5.0	28.1±5.5	<0.001
Health status variables							
Self-rated health status							
1 (very good)	2283	8%	6%	4%	2%	2%	<0.001
2	11 423	39%	35%	26%	20%	13%	
3	10 663	33%	33%	33%	31%	25%	
4	4424	11%	14%	19%	20%	23%	
5	2425	5%	8%	10%	17%	20%	
6	1191	3%	3%	5%	8%	13%	
7	188	0%	0%	1%	2%	3%	
8 (very bad)	39	0%	0%	0%	0%	1%	
Depressive symptoms*							
Yes	6826	17%	22%	31%	37%	48%	<0.001
Diabetes							
Yes	2104	9%	7%	9%	13%	18%	<0.001
Respiratory disease							
Yes	3117	7%	9%	16%	20%	22%	<0.001
Cardiovascular diseases							
Yes	7062	18%	19%	27%	37%	48%	<0.001
Musculoskeletal disorders							
Yes	4903	13%	15%	17%	22%	20%	<0.001
Hypercholesterolaemia							
Yes	7366	17%	23%	30%	37%	45%	<0.001
Cancer							
Yes	3017	8%	9%	10%	12%	12%	<0.001

Categorical variables are described as percentages and continuous variables as mean±SD.
*Defined as a score ≥16 on the Center for Epidemiological Studies-Depression scale.
GCE, General Certificate of Education.

middle-aged adults, consistent with what has been observed in older individuals, whether regarding impairments in executive functions,[34] episodic memory[35] and risk of dementia.[6 11] Another novel finding of our study is that association between exposure to AC drug and cognitive performance was highly heterogeneous across drug classes: the effect size was medium for antipsychotics and small for drugs targeting the gastrointestinal tract or metabolism, opioids and anxiolytics. More specifically, a substantial proportion of the initially reported association between overall cumulative exposure to AC drugs

Table 2 Features of anticholinergic drug dispensed in the study population (n=16 172)

Variable	n=16 172	Cumulative AC exposure			
		<3 months 10 437	3–12 months 3385	1–3 years 1786	>3 years 564
Number of different ACs dispensed					
1	7690 (47%)	62%	21%	22%	12%
2	4371 (27%)	26%	30%	28%	19%
3	2246 (14%)	9%	24%	21%	23%
4	1049 (7%)	2%	15%	14%	17%
≥5	816 (5%)	0%	10%	15%	29%
ACB score*					
1: possible AC effect	12 220 (76%)	84%	66%	57%	42%
2 or 3: moderate or severe AC effect	822 (5%)	6%	3%	5%	4%
Both	3130 (19%)	10%	31%	38%	54%
AC drug class* (ATC classification level)					
Antihistamines (R06A)	7882	43%	62%	56%	52%
Opioids (N02A)	4983	30%	33%	30%	33%
Alimentary tract and metabolism drugs (A)	4713	27%	34%	29%	34%
Anxiolytic drugs (N05B)	4016	20%	33%	34%	42%
Antidepressant drugs (N06A)	2051	4%	19%	37%	48%
Cardiovascular system drugs (C)	950	2%	7%	20%	31%
Antipsychotic drugs (N05A)	318	0%	2%	6%	18%
Other AC drugs	3493	15%	35%	29%	34%

*At least one dispensed AC drug.
AC, anticholinergic drug; ACB, Anticholinergic Cognitive Burden scale; ATC, Anatomical Therapeutic Chemical classification system.

and cognitive performance seems ascribable to individuals exposed to AC antipsychotics.

Strengths and limitations

To our knowledge, this is the first study assessing the association between exposure to AC drugs and cognitive performance within such a young population. Most of the previous studies on AC drugs and cognition included individuals aged 65 or over, whereas this study included individuals aged 45–70 (mean age: 57.8). In addition, this study combines high-quality data on both cognitive functions and exposure to AC drugs. A comprehensive set of well-established cognitive tests was administered by neuropsychologists who were specially trained and monitored, while precise quantification of the doses of AC drugs used and limited impact of recall bias were possible using claims national reimbursement databases. Also, the large sample size provided enough statistical power for considering each drug class separately contrary to most of the earlier observational studies which relied on analyses pooling all ACs regardless of drug class. In contrast, we studied the association between cumulative exposure to ACs and cognitive performance according to their level of AC potency and their drug class and highlighted an important heterogeneity of this association across ACB scores and drug classes. Besides, we used a more precise approach than a simple computation of the AC burden, which does not take into account either the drug dosage or the duration of exposure. Another strength of our study is the wide panel of variables collected on CONSTANCES participants, which allowed us to correct for many potential confounders associated with either cognitive performance or prescription of AC drugs. Finally, the dose–effect relationship provides an additional argument for discussing a causal association. In the literature, authors already used it and found a dose–effect association between AC drug use and cognitive performances.[11]

One of the limitations of our study is that AC exposure quantification was based on the amount of AC drugs dispensed and not on the amount actually taken by the participants. However, this bias may be limited for participants with regular prescriptions. Therefore, it is very unlikely to affect our findings. Another limitation is that we did not include AC drugs for which a DDD was not available, that is, ocular solutions and topical glucocorticoids. These drugs are mainly topical and accounted for only 3% of AC drugs dispensed to the study participants; consequently, their exclusion is unlikely to have a substantial effect on our results. Finally, non-refundable medicines were not taken into account due to the lack of available data in the reimbursement databases. Finally, because our study focuses on the side effects of treatments rather than efficacy, we have not corrected our results for multiple comparisons. This practice is consistent with the literature in observational epidemiology.[36] However, given this point, it is possible that some of our results may be falsely positive, especially when the effect size is small.

Comparison with other studies

Previous studies investigating the association between exposure to ACs and cognitive performance were conducted in patients aged 65 years and over.[7 8 10 37] However, focusing on elderly people may be associated with potential protopathic bias, notably with psychotropic drugs. Indeed, these drugs may be prescribed to treat the early symptoms of an underlying cognitive disease. Investigating this association within a younger population may reduce this protopathic bias.

Moreover, few studies made a distinction between drugs based on the level of AC potency.[9] We chose to use the ACB scale, which was extensively used in studies on cognitive ageing, over other valid scales to categorise AC drugs.[13 38 39] In two cohort studies,[21 40] cognitive impairment was significantly associated with cumulative exposure to ACB-2/3 ACs but not to ACB-1

Table 3 Relation between cumulative exposure to anticholinergic drugs over a 3-year period and z-scores on cognitive function tests (n=34 267)

		Episodic memory				Verbal fluency				Executive functions					
		Immediate free recall		Delayed free recall		Semantic fluency		Phonemic fluency		DSST		TMT-A		TMT-B	
Cumulative AC exposure		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)	
	n	Univariate model													
None	18 095	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
<3 months	10 437	−0.024 (0.012)		−0.025 (0.012)	*	−0.030 (0.012)	*	−0.010 (0.012)		−0.023 (0.012)		−0.019 (0.012)		−0.027 (0.012)	*
3–12 months	3385	−0.092 (0.019)	***	−0.081 (0.019)	***	−0.073 (0.019)	***	−0.045 (0.019)	*	−0.100 (0.019)	***	−0.040 (0.019)	*	−0.073 (0.019)	***
1–3 years	1786	−0.055 (0.025)	*	−0.076 (0.025)	**	−0.097 (0.025)	***	−0.055 (0.025)	*	−0.160 (0.025)	***	−0.112 (0.025)	***	−0.104 (0.025)	***
>3 years	564	−0.189 (0.043)	***	−0.207 (0.043)	***	−0.126 (0.043)	**	−0.151 (0.043)	***	−0.373 (0.043)	***	−0.239 (0.043)	***	−0.275 (0.043)	***
P trend			***		***		***		***		***		***		***
	n	Adjustment on lifestyle variables†													
None	18 095	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
<3 months	10 437	−0.022 (0.012)		−0.024 (0.012)	*	−0.029 (0.012)	*	−0.007 (0.012)		−0.017 (0.012)		−0.020 (0.012)		−0.027 (0.012)	*
3–12 months	3385	−0.085 (0.019)	***	−0.077 (0.019)	***	−0.066 (0.019)	***	−0.031 (0.019)		−0.083 (0.019)	***	−0.043 (0.019)	*	−0.071 (0.019)	***
1–3 years	1786	−0.043 (0.025)		−0.067 (0.025)	**	−0.083 (0.025)	***	−0.031 (0.025)		−0.131 (0.025)	***	−0.113 (0.025)	***	−0.095 (0.025)	***
>3 years	564	−0.166 (0.043)	**	−0.189 (0.043)	***	−0.102 (0.043)	*	−0.108 (0.043)	*	−0.311 (0.043)	***	−0.241 (0.043)	***	−0.257 (0.043)	***
	n	Adjustment on lifestyle† and health status variables‡													
None	18 095	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
<3 months	10 437	−0.014 (0.012)		−0.016 (0.012)		−0.022 (0.012)		0.000 (0.012)		−0.004 (0.012)		−0.013 (0.012)		−0.017 (0.012)	
3–12 months	3385	−0.060 (0.019)	**	−0.050 (0.019)	**	−0.039 (0.019)	*	−0.006 (0.019)		−0.035 (0.019)		−0.013 (0.019)		−0.032 (0.019)	
1–3 years	1786	−0.002 (0.025)		−0.022 (0.025)		−0.041 (0.025)		0.008 (0.025)		−0.050 (0.025)	*	−0.065 (0.025)	*	−0.032 (0.025)	
>3 years	564	−0.103 (0.044)	*	−0.125 (0.043)	**	−0.040 (0.043)		−0.054 (0.043)		−0.193 (0.043)	***	−0.167 (0.043)	***	−0.163 (0.043)	***
P trend			**		**		**				***		***		***

Each value is the adjusted cognitive z-score difference between two groups.
P value and p trend: *0.01–0.05, **0.001–0.01, ***<0.001.
P trend: we tested whether there was an ordered relationship between categories of cumulative exposure to AC and cognitive performance (dose–effect).
†Lifestyle variables: living with a partner, smoking status, alcohol consumption, physical activity and body mass index.
‡Health status variables: self-rated health status, depressive symptoms, diabetes, respiratory diseases, cardiovascular diseases, osteoarticular disease, hypercholesterolaemia and cancer.
AC, anticholinergic drug; DSST, Digit Symbol Substitution Test; ref, reference; TMT, A and B, Trail Making Test.

Table 4 Relation between cumulative exposure to anticholinergic drugs over a 3-year period and z-scores on cognitive function tests according to anticholinergic potency, adjusted on lifestyle and health status variables (n=34 267)

		Episodic memory				Verbal fluency				Executive functions					
		Immediate free recall		Delayed free recall		Semantic fluency		Phonemic fluency		DSST		TMT-A		TMT-B	
Cumulative AC exposure		Estimate (SE)		Estimated (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)	
		Adjustment on lifestyle† and health status variables‡													
	None	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
ACB-1§	<3 months	−0.016 (0.012)		−0.010 (0.012)		−0.020 (0.012)		−0.002 (0.012)		0.002 (0.012)		−0.016 (0.012)		−0.014 (0.012)	
	3–12 months	−0.048 (0.020)	*	−0.040 (0.020)		−0.030 (0.020)		−0.011 (0.020)		−0.032 (0.020)		−0.027 (0.020)		−0.037 (0.020)	
	1–3 years	0.041 (0.028)		−0.025 (0.028)		−0.030 (0.028)		0.037 (0.028)		−0.047 (0.028)		−0.092 (0.028)	**	−0.043 (0.028)	
	>3 years	−0.056 (0.052)		−0.040 (0.052)		−0.010 (0.052)		−0.107 (0.052)	*	−0.179 (0.052)	***	−0.194 (0.052)	***	−0.145 (0.052)	**
	P trend									**		***		**	
	None	Ref				Ref		Ref		Ref		Ref		Ref	
ACB-2/3§	<3 months	−0.028 (0.020)		−0.040 (0.020)		−0.010 (0.020)		−0.002 (0.020)		−0.013 (0.020)		0.047 (0.020)	*	0.002 (0.020)	
	3–12 months	−0.090 (0.042)	*	−0.110 (0.042)	*	−0.070 (0.042)		−0.026 (0.042)		−0.082 (0.041)	*	−0.025 (0.042)		−0.025 (0.042)	
	1–3 years	−0.141 (0.048)	**	−0.150 (0.048)	**	−0.050 (0.048)		−0.081 (0.048)		−0.060 (0.047)		−0.026 (0.048)		−0.045 (0.047)	
	>3 years	−0.159 (0.109)		−0.360 (0.109)	***	−0.090 (0.109)		0.138 (0.109)		−0.165 (0.108)		−0.034 (0.109)		−0.160 (0.108)	
	P trend	***		***						*					

Each value is the adjusted cognitive z-score difference between two groups.
P value and p trend: *0.01–0.05, **0.001–0.01, ***<0.001.
P trend: we tested whether there was an ordered relationship between categories of cumulative exposure to AC and cognitive performance (dose–effect).
†Lifestyle variables: living with a partner, smoking status, alcohol consumption, physical activity and body mass index.
‡Health status variables: self-rated health status, depressive symptoms, diabetes, respiratory diseases, cardiovascular diseases, osteoarticular disease, hypercholesterolaemia and cancer.
§Anticholinergic potency was assessed using the ACB scale, with scores of 2 and 3 (moderate to marked anticholinergic effect) collapsed into a single group (ACB-2/3).
AC, anticholinergic drug; ACB, Anticholinergic Cognitive Burden; DSST, Digit Symbol Substitution Test; ref, reference; TMT, A and B, Trail Making Test.

ACs, without precision concerning the AC exposure duration. In contrast, in our study, exposure to ACB-1 ACs was significantly associated with impaired cognitive performances, particularly those assessing executive functions. However, caution is advised, since the cognitive tests used in these two studies differed from those of our study. Nevertheless, the association between cognitive impairment and exposure to ACB-1 AC drugs would be of considerable clinical relevance, since these drugs are the most widely prescribed ACs. Indeed, among the study participants, 45% had been dispensed at least one ACB-1 AC during the 3 years preceding their inclusion into the cohort against 12% of those who had been dispensed at least one ACB-2/3.

To our knowledge, this study is the first that assessed the association between exposure to AC drugs and cognitive performance separately for each drug class. Pooling drug classes can increase statistical power but do not allow to study the association between a given drug class and cognitive performance.[41] For example, in our study, no significant association was found between exposure to ACs among antihistamines, antidepressants, cardiovascular drugs and cognitive performance. In contrast, the effect size of this association was medium among antipsychotics, small among anxiolytics and opioids (for episodic memory), and medium among drugs targeting the gastrointestinal tract or metabolism (for executive functions). Thus, the association between AC exposure and cognitive performances varied markedly across drug classes. These variations may ensue from differences in AC potency, non-AC effects specific to each drug, and/or indications for prescribing AC drugs. For instance, evidence exists about impaired cognitive function in antipsychotic users, but whether this finding was related to the drug class (ie, indication bias, schizophrenia is known to be associated with cognitive dysfunction) or to AC properties was not determined.[42] Similarly, opioids and anxiolytics were found associated with an increased risk of dementia and Alzheimer's disease, respectively, but the underlying mechanisms were also not elucidated.[14 43]

A major finding of our study is that the effect size of the association between cumulative exposure to ACs and cognitive performance was substantially smaller in the sensitivity analysis after excluding participants with filled prescription for antipsychotics. This finding suggests that AC antipsychotic drugs contributed for a large part in this association. However, whether this association is mainly due to the AC properties of these drugs, to properties shared by all antipsychotic drugs (including those without AC properties) or to an indication bias remains to be clarified. The same issue arises for anxiolytics, drugs targeting the gastrointestinal tract and opioids.

Cognitive impairments (in episodic memory and executive functions) demonstrated by the earlier cited studies can lead to a marked deterioration in life quality and a possible shift to social disability. Given the early results of this study, practitioners could not be encouraged to prescribe non-AC drugs at the expense of AC drugs since our analyses focused only on AC drugs. Future studies comparing drugs with and without AC effects within a given drug class may help distinguish between these potential explanations. Similarly, the eventual intervention of the drug–drug interaction will have to be studied in subsequent works.

Table 5 Associations linking cumulative exposure to anticholinergic drugs over a 3-year period and z-scores on cognitive function tests according to anticholinergic class†, adjusted on lifestyle‡ and health status§ variables (n=34 267)

			Episodic memory				Verbal fluency				Executive functions					
			Immediate free recall		Delayed free recall		Semantic fluency		Phonemic fluency		DSST		TMT-A		TMT-B	
Cumulative AC exposure			Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)		Estimate (SE)	
Antihistamines	None	26 385	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
	<1 year	7298	0.015 (0.014)		0.009 (0.014)		−0.007 (0.014)		0.010 (0.014)		0.015 (0.014)		0.024 (0.014)		0.027 (0.014)	*
	≥1 year	584	0.027 (0.042)		0.058 (0.042)		−0.020 (0.042)		−0.003 (0.042)		0.037 (0.042)		0.011 (0.042)		**0.049** (0.042)	
Opioids	None	29 284	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
	<1 year	4902	−0.040 (0.016)	*	−0.048 (0.016)	**	−0.004 (0.016)		−0.016 (0.016)		−0.013 (0.016)		−0.005 (0.016)		−0.018 (0.016)	
	≥1 year	81	−0.161 (0.112)		−0.101 (0.112)		0.094 (0.112)		0.182 (0.112)		0.014 (0.112)		0.094 (0.112)		0.085 (0.112)	
Alimentary tract and metabolism drugs	None	29 554	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
	<1 year	4635	0.014 (0.016)		0.011 (0.016)		0.006 (0.016)		−0.007 (0.016)		0.015 (0.016)		0.005 (0.016)		−0.019 (0.016)	
	≥1 year	78	0.099 (0.114)		−0.082 (0.114)		−0.024 (0.114)		−0.130 (0.114)		−0.154 (0.114)		−0.287 (0.114)	*	−0.344 (0.114)	**
Anxiolytic drugs	None	30 251	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
	<1 year	3812	−0.043 (0.018)	*	−0.044 (0.018)	*	−0.007 (0.018)		0.011 (0.018)		−0.005 (0.018)		0.008 (0.018)		−0.014 (0.018)	
	≥1 year	204	−0.060 (0.072)		−0.185 (0.072)	*	−0.060 (0.072)		−0.024 (0.072)		−0.197 (0.072)	**	−0.176 (0.072)	*	−0.170 (0.072)	*
Antidepressant drugs	None	32 216	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
	<1 year	1427	−0.022 (0.028)		−0.012 (0.028)		−0.030 (0.028)		−0.012 (0.028)		0.006 (0.028)		0.058 (0.028)	*	0.049 (0.028)	
	≥1 year	624	0.014 (0.042)		−0.034 (0.042)		0.039 (0.042)		−0.010 (0.042)		0.018 (0.042)		−0.014 (0.042)		−0.017 (0.042)	
Cardiovascular system drugs	None	33 317	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
	<1 year	537	−0.033 (0.044)		0.003 (0.044)		−0.002 (0.044)		0.006 (0.044)		−0.045 (0.044)		−0.087 (0.044)	*	−0.075 (0.044)	
	≥1 year	413	0.052 (0.050)		0.144 (0.050)	**	0.027 (0.050)		−0.001 (0.050)		−0.080 (0.050)		−0.085 (0.050)		−0.028 (0.050)	
Antipsychotics	None	33 949	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
	<1 year	217	−0.146 (0.069)	*	−0.177 (0.069)	*	−0.183 (0.069)	**	−0.049 (0.069)		−0.347 (0.069)	***	−0.148 (0.069)	*	−0.268 (0.069)	***
	≥1 year	101	−0.433 (0.101)	***	−0.493 (0.101)	***	−0.380 (0.101)	***	−0.262 (0.101)	**	−0.658 (0.101)	***	−0.590 (0.101)	***	−0.511 (0.101)	***
Other AC drugs	None	30 774	**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**		**Ref**	
	<1 year	3235	−0.015 (0.019)		−0.038 (0.019)	*	0.017 (0.019)		0.012 (0.019)		−0.022 (0.019)		−0.037 (0.019)	*	−0.001 (0.019)	
	≥1 year	258	−0.082 (0.063)		−0.057 (0.063)		−0.054 (0.063)		0.007 (0.063)		−0.086 (0.063)		−0.090 (0.063)		−0.054 (0.063)	

Values are given as the adjusted difference between two groups in terms of cognitive z-score.
P values: *0.01–0.05, **0.001–0.01, ***<0.001.
†Drug classes of anticholinergic agents were determined based on the ATC classification level.
‡Lifestyle variables: living with a partner, smoking status, alcohol consumption, physical activity and body mass index.
§Health status variables: self-rated health status, depressive symptoms, diabetes, respiratory diseases, cardiovascular diseases, osteoarticular disease, hypercholesterolaemia and cancer.
AC, anticholinergic drug; ATC, Anatomical Therapeutic Chemical classification system; DSST, Digit Symbol Substitution Test; ref, reference; TMT, A and B, Trail Making Test.

CONCLUSION

The impact of AC drugs on cognitive performance and dementia has been widely studied in elderly people. This study showed a negative association between overall cumulative AC exposure to AC drugs and cognitive performance in middle-aged adults, suggesting that this impact may be observed years before the onset of clinical symptoms. However, this association was highly heterogeneous across ACB scores and drug classes. Importantly, antipsychotic drugs contributed for a large part in this association. Future studies should investigate in more details the specific involvement of AC properties on cognitive performance within each drug class.

Acknowledgements The authors thank the National Health Insurance Fund ('Caisse nationale d'assurance maladie des travailleurs salaries', CNAMTS) and its health screening centres ('Centres d'examens de santé'), which are collecting a large part of the data, and ClinSearch, which is in charge of data quality control.

Contributors AZ, RO and TM comanaged the literature searches and undertook the statistical analysis. AZ wrote the first draft of the manuscript. RO and TM have made substantial modifications in the manuscript and have approved the final version of it. CB, FR and BB comanaged the literature searches, have made substantial modifications in the manuscript and have approved the final version of it. MZ and MG codesigned the cohort study CONSTANCES and wrote the protocol, have made substantial modifications in the manuscript, and have approved the final version of it. All authors read and approved the manuscript.

Funding The CONSTANCES Cohort Study is supported by the Caisse nationale d'assurance maladie des travailleurs salariés (CNAMTS). The CONSTANCES Cohort Study benefits from a grant from ANR (ANR-11-INBS-0002), and it is also partly funded by MSD, AstraZeneca and Lundbeck.

Competing interests None declared.

Patient consent Not required.

Ethics approval The study protocol was approved by the appropriate ethics committee. According to French regulations, the CONSTANCES Cohort project has been approved by the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, CNIL) and the INSERM institutional review board.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Karimi S, Dharia SP, Flora DS, *et al*. Anticholinergic burden: clinical implications for seniors and strategies for clinicians. *Consult Pharm* 2012;27:564–82.
2 Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry* 2001;62(Suppl 21):11–14.
3 Gerretsen P, Pollock BG. Drugs with anticholinergic properties: a current perspective on use and safety. *Expert Opin Drug Saf* 2011;10:751–65.
4 Voss B, Thienel R, Reske M, *et al*. Cholinergic blockade under working memory demands encountered by increased rehearsal strategies: evidence from fMRI in healthy subjects. *Eur Arch Psychiatry Clin Neurosci* 2012;262:329–39.
5 Ancelin ML, Artero S, Portet F, *et al*. Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study. *BMJ* 2006;332:455–9.
6 Carrière I, Fourrier-Reglat A, Dartigues JF, *et al*. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Arch Intern Med* 2009;169:1317–24.
7 Pasina L, Djade CD, Lucca U, *et al*. Association of anticholinergic burden with cognitive and functional status in a cohort of hospitalized elderly: comparison of the anticholinergic cognitive burden scale and anticholinergic risk scale: results from the REPOSI study. *Drugs Aging* 2013;30:103–12.
8 Kalisch Ellett LM, Pratt NL, Ramsay EN, *et al*. Multiple anticholinergic medication use and risk of hospital admission for confusion or dementia. *J Am Geriatr Soc* 2014;62:1916–22.
9 Montastruc F, Retailleau E, Rousseau V, *et al*. Atropinic burden of prescription forms in France: a study in community pharmacies in 2013. *Eur J Clin Pharmacol* 2014;70:1147–8.
10 Campbell NL, Perkins AJ, Bradt P, *et al*. Association of anticholinergic burden with cognitive impairment and health care utilization among a diverse ambulatory older adult population. *Pharmacotherapy* 2016;36:1123–31.
11 Gray SL, Anderson ML, Dublin S, *et al*. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* 2015;175:401–7.
12 de la Torre JC. Pathophysiology of neuronal energy crisis in Alzheimer's disease. *Neurodegener Dis* 2008;5:126–32.
13 Mebarki S, Trivalle C. Évaluation de la charge anticholinergique en gériatrie à l'aide de 3 échelles. *NPG Neurologie - Psychiatrie - Gériatrie* 2014;14:81–7.
14 Billioti de Gage S, Moride Y, Ducruet T, *et al*. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ* 2014;349:g5205.
15 Zins M, Goldberg M, CONSTANCES team. The French CONSTANCES population-based cohort: design, inclusion and follow-up. *Eur J Epidemiol* 2015;30:1317–28.
16 Ruiz F, Goldberg M, Lemonnier S, *et al*. High quality standards for a large-scale prospective population-based observational cohort: Constances. *BMC Public Health* 2016;16:877.
17 Bezin J, Duong M, Lassalle R, *et al*. The national healthcare system claims databases in France, SNIIRAM and EGB: Powerful tools for pharmacoepidemiology. *Pharmacoepidemiol Drug Saf* 2017;26:954–62.
18 WHOCC - ATC/DDD Index. https://www.whocc.no/atc_ddd_index/
19 Hanlon JT, Boudreau RM, Roumani YF, *et al*. Number and dosage of central nervous system medications on recurrent falls in community elders: the Health, Aging and Body Composition study. *J Gerontol A Biol Sci Med Sci* 2009;64:492–8.
20 Campbell N, Boustani M, Limbil T, *et al*. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging* 2009;4:225–33.
21 Campbell NL, Boustani MA, Lane KA, *et al*. Use of anticholinergics and the risk of cognitive impairment in an African American population. *Neurology* 2010;75:152–9.
22 Mebarki S, Trivalle C. Échelles d'évaluation de l'effet anticholinergique des médicaments. *NPG Neurologie - Psychiatrie - Gériatrie* 2012;12:131–8.
23 Mura T, Amieva H, Goldberg M, *et al*. Effect size for the main cognitive function determinants in a large cross-sectional study. *Eur J Neurol* 2016;23:1614–26.
24 Grober E, Buschke H, Crystal H, *et al*. Screening for dementia by memory testing. *Neurology* 1988;38:900–3.
25 Borkowski JG, Benton AL, Spreen O. Word fluency and brain damage. *Neuropsychologia* 1967;5:135–40.
26 Cardebat D, Doyon B, Puel M, *et al*. [Formal and semantic lexical evocation in normal subjects. Performance and dynamics of production as a function of sex, age and educational level]. *Acta Neurol Belg* 1990;90:207–17.
27 D W. Wechsler adult intelligence scale-revised. *Psychol Corp*.
28 Boll TJ, Reitan RM. Effect of age on performance of the Trail Making Test. *Percept Mot Skills* 1973;36:691–4.
29 Miner T, Ferraro FR. The role of speed of processing, inhibitory mechanisms, and presentation order in trail-making test performance. *Brain Cogn* 1998;38:246–53.
30 Morin AJ, Moullec G, Maïano C, *et al*. Psychometric properties of the Center for Epidemiologic Studies Depression Scale (CES-D) in French clinical and nonclinical adults. *Rev Epidemiol Sante Publique* 2011;59:327–40.
31 Barona A, Reynolds CR, Chastain R. A demographically based index of premorbid intelligence for the WAIS–R. *J Consult Clin Psychol* 1984;52:885–7.
32 Dion M, Potvin O, Belleville S, *et al*. Normative data for the Rappel libre/Rappel indicé à 16 items (16-item Free and Cued Recall) in the elderly Quebec-French population. *Clin Neuropsychol* 2015;28(Suppl 1):1–19.
33 Sawilowsky SS. New Effect Size Rules of Thumb. *J Mod Appl Stat Methods* 2009;8:597–9.
34 Sittironnarit G, Ames D, Bush AI, *et al*. Effects of anticholinergic drugs on cognitive function in older Australians: results from the AIBL study. *Dement Geriatr Cogn Disord* 2011;31:173–8.
35 Papenberg G, Bäckman L, Fratiglioni L, *et al*. Anticholinergic drug use is associated with episodic memory decline in older adults without dementia. *Neurobiol Aging* 2017;55:27–32.
36 Bender R, Lange S. Adjusting for multiple testing–when and how? *J Clin Epidemiol* 2001;54:343–9.
37 Bottiggi KA, Salazar JC, Yu L, *et al*. Long-term cognitive impact of anticholinergic medications in older adults. *Am J Geriatr Psychiatry* 2006;14:980–4.
38 Durán CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *Eur J Clin Pharmacol* 2013;69:1485–96.
39 Mayer T, Haefeli WE, Seidling HM. Different methods, different results–how do available methods link a patient's anticholinergic load with adverse outcomes? *Eur J Clin Pharmacol* 2015;71:1299–314.
40 Fox C, Richardson K, Maidment ID, *et al*. Anticholinergic medication use and cognitive impairment in the older population: the medical research council cognitive function and ageing study. *J Am Geriatr Soc* 2011;59:1477–83.
41 Cai X, Campbell N, Khan B, *et al*. Long-term anticholinergic use and the aging brain. *Alzheimers Dement* 2013;9:377–85.
42 Désaméricq G, Schurhoff F, Meary A, *et al*. Long-term neurocognitive effects of antipsychotics in schizophrenia: a network meta-analysis. *Eur J Clin Pharmacol* 2014;70:127–34.
43 Dublin S, Walker RL, Gray SL, *et al*. Prescription opioids and risk of dementia or cognitive decline: a prospective cohort study. *J Am Geriatr Soc* 2015;63:1519–26.