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Citation for published version:

Whalley, LJ, Sharma, S, Fox, HC, Murray, AD, Staff, RT, Duthie, AC, Deary, IJ & Starr, JM 2012, 'Anticholinergic Drugs in Late Life: Adverse Effects on Cognition but not on Progress to Dementia', *Journal of Alzheimer's Disease*, vol. 30, no. 2, pp. 253-261. <https://doi.org/10.3233/JAD-2012-110935>

Digital Object Identifier (DOI):

[10.3233/JAD-2012-110935](https://doi.org/10.3233/JAD-2012-110935)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Journal of Alzheimer's Disease

Publisher Rights Statement:

© Whalley, L. J., Sharma, S., Fox, H. C., Murray, A. D., Staff, R. T., Duthie, A. C., ... Starr, J. M. (2012). Anticholinergic Drugs in Late Life: Adverse Effects on Cognition but not on Progress to Dementia. *Journal of alzheimers disease*, 30(2), 253-261. 10.3233/JAD-2012-110935

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Anticholinergic Drugs in Late Life: Adverse Effects on Cognition but not on Progress to Dementia

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Accepted 1 February 2012

Abstract. Impaired cognitive function associated with use of anticholinergic drugs may be partly attributed to underlying physical illness and exposure to factors that increase the risk of some physical disorders such as low socioeconomic status (SES) and less education. To estimate the extent of cognitive impairment and risk of progress to dementia associated with anticholinergic drug use and to estimate confounding by gender, *APOE*, family history of dementia, lower SES, less education, and lower childhood mental ability, we recruited 281 volunteers at age 77–78 without overt dementia who had taken part in the Scottish Mental Survey of 1932. Clinical histories, use of medications, self reported frequency of emotional symptoms and standardized tests of cognitive function were obtained. With and without adjustment for age and childhood IQ, there were significant between-group differences in tests of non-verbal reasoning and spatial ability. During 10 year follow-up, progress to overt dementia was not associated with anticholinergic drugs use on recruitment but female gender and a history of dementia in parent or sibling were associated with dementia. We concluded that anticholinergic drug use in this narrow age range sample was linked to cognitive impairment but not to subsequent dementia.

Keywords: Aberdeen 1921 birth cohort, aging, anticholinergic, *APOE*, childhood intelligence, cognitive function, dementia, drug, family history

INTRODUCTION

Anticholinergic drugs are associated with adverse physical and cognitive effects in later life [1, 2]. These drugs are used to treat conditions as diverse as bladder over activity [3, 4] and depressive disorders [5]. Adverse effects of these drugs range from mild

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impairment of recent memory to severe acute confusional states [6, 7] and are mediated through brain nicotinic receptors [8]. Cognitively impaired old people with or without dementia in whom high affinity nicotinic receptors are already depleted [9–12] could, therefore, be more susceptible to further cognitive impairment when exposed to anticholinergic drugs [13, 14].

With increasing age, exposures to physical and psychiatric treatments increase. Although study samples, measures of cognition, and classification of anticholinergic drugs have differed between studies, the general view is that anticholinergic effects contribute to cognitive impairment in older people [15–19]. This conclusion, however, may not be secure for several reasons. First, there could be other sources of individual differences in cognitive aging not considered (e.g., apolipoprotein E genotype [20]). Second, when cognitive impairment is reported, it is generally uncertain if this is attributable to increasing age (with associated increased exposure to anticholinergic treatment), concomitant physical illness, or to the drugs themselves. Third, while the value of serum anticholinergic activity remains undecided [21–24], most studies rely upon self-report or prescribing records. Fourth, the choice of cognitive tests has sometimes been constrained so that when cognitive impairment attributable to anticholinergic drugs is reported, it was uncertain if all or only some cognitive domains are affected.

With one exception [19], published studies on anticholinergic drug use in the absence of severe mental disorder have examined subjects over the age of 65 years. We recognized that anticholinergic drugs are often used in later life when concerns about greater than expected cognitive aging arise. This line of reasoning prompted us to consider the possibility that lower performance on cognitive tests taken by older adults may reflect life-long lower cognitive performance, lower socioeconomic status (SES), less education, and gender differences and that these attributes could also plausibly be linked to greater morbidity of both physical and depressive disorders [25–27]; the same disorders that prompted introduction of medications in later life including anticholinergic drugs [28].

The first aim of the study was to identify associations between domains of cognitive functioning and exposure to anticholinergic drugs in a population-based sample in good general health. The second aim was to estimate the size of effect (if any) remaining after adjustment for confounding by childhood mental ability, education, SES, and gender. And, third, we aimed to

investigate a possible association between anticholinergic drug use and progress to dementia.

MATERIALS AND METHODS

Study design

We conducted a longitudinal observational study of a narrow age range sample living independently in the community and who were not known to be dementia sufferers by local health agencies. We conducted repeated clinical and neuropsychological assessments at intervals of about 15 months after recruitment at age 78 up to ages about 83 years in as many participants who remained available to study and who would agree to re-assessment (Fig. 1). Final dementia diagnoses were agreed by consensus between three authors (LW, RS, AM) who had available all study data and in subsets of the original sample relevant clinical records and the findings of brain MRI, CT or SPECT.

Samples

In 1932, the Scottish Council for Research in Education (SCRE) surveyed the mental ability (intelligence,

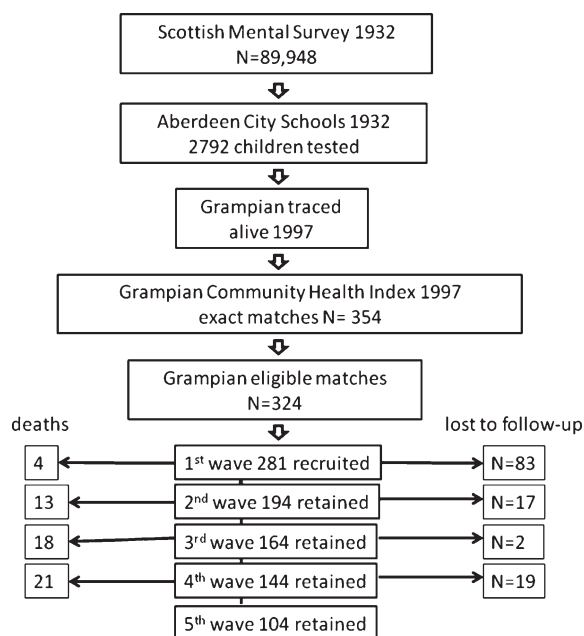


Fig. 1. Recruitment and retention of a sample of 281 volunteers all born in 1921 and who took part in the 1932 Scottish Mental Survey and who agreed in 1998–1999 to enter a prospective longitudinal study of brain aging and health. The study was designed to retain 200 volunteers in the 1st and 2nd wave of the study. Aberdeen City lies within the Grampian Region of Scotland where some of the eligible participants now live.

IQ) of the whole population of children born in 1921 [29]. More than 95% of eligible children were included. Permission to trace local survivors with archived intelligence test scores was given by SCRE to the University of Aberdeen in 1997 to allow exact matching by name and date of birth schoolchildren who had remained in the Aberdeen area and were listed on the local health register (more than 99% of the population are registered). With the approval of the Local Research Ethics Committee, we approached local family doctors, who wrote to their patients who had participated in the 1932 survey and were not known to be in treatment for a major illness, to have major sensory impairment, or to have recently been bereaved. We traced 354 individuals who had taken part in the 1932 survey and found 324 to be eligible. All were living independently in the local community and were then about 77 years old. In response to a postal invitation, 295 born in 1921 (88%) agreed to attend the University Clinical Research Unit to take part in a study of brain aging and health of whom 14 declined to take part after hearing more about the study (Fig. 1). On attending, written informed consent to the study procedures was obtained by a trained research nurse from 281 volunteers.

Measures

Participants knew they could withdraw from all or part of the study at anytime and some declined to complete all cognitive tests. Data were obtained at interview from all 281 participants about social background, education and occupational history, medical and obstetric history, and family history of dementia. A subsample of 98 individuals entered a longitudinal study of brain MRI changes and survival [30] and 47 others underwent brain CT ($n=4$), MRI ($n=9$), or SPECT ($n=34$) for investigation of suspected dementia from 1997 to 2010. Contact with participants was maintained to 2010 through repeat clinical assessments, home visits, cohort reunions and telephone enquiries. For the present study, selected items were taken from the complete research database to provide information about exposure to possible anticholinergic drugs. *APOE* $\epsilon 4$ status ($\epsilon 4$ present/absent) was determined in 225 participants using methods previously described in this sample [31].

Follow-up assessments

Participants were invited to return for re-assessment at intervals of about 15 months from age 77 to 83 years

(to a maximum of 5 assessments). At re-assessment, the study protocol was repeated and included the same questions about social circumstances, clinical history, history of dementia in a parent or sibling, exposure to drugs and repeat cognitive testing.

Dementia

Dementia diagnoses were based on ICD-10 criteria [32] using data from research assessments, mental testing, clinical records of contacts with treatment services, results of brain imaging examinations (SPECT, CT, or MRI), and telephone enquiries among family and managers of residential care facilities. Brain images were scrutinized by a specialist neuroradiologist (AM). At recruitment in 1998–2000, 24 volunteers were found to be cognitively impaired (Mini-Mental Status Examination (MMSE) <24) [33] and during follow-up to 2010, all 24 subsequently met criteria for Alzheimer's disease (13 cases) or vascular dementia with or without Alzheimer's disease (11 cases). Clinical dementia diagnoses were established by consensus between three authors (RS, AM, LW). During follow-up from 1998 to 2010, 46 volunteers who had scored >23 on the MMSE [33] on recruitment developed dementia. The cumulative total of 70 dementia cases from age 77–88 years among 281 volunteers recruited to the study comprised 24 possible (MMSE <24) but unrecognized cases on recruitment and 46 incident cases arising during follow up. Refusal to take part was significantly associated with lower Moray House test (MHT) scores ($p < 0.05$). SES was classified by usual occupation [34] and using the Carstairs-Morris deprivation index [35] which is an ecological measure of SES derived using small area geographical parameters obtained from the 1991 Census. This method of socioeconomic classification does not rely on a participant's or spouse's occupation and, therefore, has some advantages for women, over classification by husband's occupation.

Interview and cognitive measures

At interview with a trained research nurse, volunteers provided detailed medical histories, family history of dementia or stroke, accounts of numbers of current prescribed and non-prescribed medications, and completed tests of cognitive function supervised by one of us (HF). A standardized brief cognitive screening instrument, the MMSE [36], was used as a practical method for detecting significant cognitive pathology. Volunteers undertook five cognitive tests:

Raven's Standardized Progressive Matrices [37], a test of non-verbal reasoning; the Rey Auditory Verbal Learning Test [38], which measures memory and learning; and the Block Design subtest of the Wechsler Adult Intelligence Scale-Revised WAIS-R [39] measuring spatial ability. Emotional symptoms were recorded as self-reported scores on anxiety and depression subscales of the Hospital Anxiety and Depression Scale [40].

Anticholinergic drugs

We calculated an anticholinergic burden of each self-reported drug by reviewing relevant literature associating known anticholinergic drugs with their serum anticholinergic activity [17, 23]. Because there are large differences between and within European and North American clinical practices when prescribing anticholinergic drugs, exact comparisons between this and earlier studies are not possible. Each participant's interview accounts of current medications (obtained on recruitment and at re-assessments) were independently scrutinized by two of us (SS and LW) to classify the anticholinergic burden from 0 to 3 (0 = no drugs used, 1 = drugs used but with no likely effect, 2 = drugs used with low effect, 3 = drugs used with high effect). Duration of exposure to specific prescribed drugs was estimated by direct questions. Volunteers were classified as "regular" users of anticholinergics if one of these drugs had been taken most days over the past three months. Differences between scrutineers were reconciled at joint review. We identified 15 anticholinergic drugs common to this study and that reported by Ancelin et al. [17]; 12 other drugs were identified only in the Ancelin study and 35 other drugs were identified only in this study.

Statistical methods

With the exception of MMSE, data approximated to normal distribution and parametric statistics were used throughout. Associations between cognitive test scores and possible confounders were tested using Pearson's correlation coefficient. Using data obtained at recruitment, the effects of anticholinergic drugs were examined by general linear modeling (multivariate analysis of variance but excluding MMSE) with anticholinergic drug exposure, gender, as fixed effects, and socioeconomic status, number of prescribed drugs and childhood verbal mental ability as covariates. Repeated measures of cognitive performance were examined in a repeated measures mixed model using data provided

only by those participants who completed all five assessments. The prediction of progress to dementia by anticholinergic drug use was examined by binary logistic regression that included other possible risk factors for dementia. These included female gender, family history of dementia, *APOEε4* carrier status, childhood IQ, history of heart disease, or treated hypertension.

RESULTS

The sample is described in Fig. 1 and Table 1 where demographic characteristics are summarized for the complete sample ($n=281$) grouped by exposure to no prescribed drugs, prescribed drugs but none with anticholinergic effects and those exposed to anticholinergics sub-grouped as "mild/moderate" or "strong". We identified seven participants who were taking antidepressants and 20 who were taking a statin. These groups were too small for separate analysis and their distributions did not differ between subjects classified by exposure to anticholinergic drugs. We recognized that exposure to antidepressant drugs would be associated with a greater frequency of depressive symptoms and that these might impair performance on cognitive tests. Figure 2 shows the distribution of depressive symptoms and numbers of volunteers who met criteria for "caseness" for a depressive disorder. These distributions did not differ significantly between volunteers grouped by exposure to anticholinergic drugs. We examined the occurrence of exposure to prescribed and non-prescribed anti-inflammatory drugs, but this could not be quantified reliably largely because their use was very often limited to the winter months. There were significant differences between sub-groups classified by anticholinergic drug status in age at testing ($p=0.015$) and history of heart disease ($p=0.000$) or treated hypertension ($p=0.000$). Demographic variables (gender, occupational classification, deprivation index by area of residence, duration of education, childhood mental ability, smoking history, or MMSE score) did not differ between groups.

Among 281 subjects recruited to the study, complete sets of cognitive data were provided by 136 participants. These data comprised scores on Raven's Progressive Matrices, Auditory Verbal Learning, and Block Design Tests (Table 2). Univariate analysis of variance (Table 2) showed that Raven's Progressive Matrices, Block design, and MMSE scores were significantly lower in those exposed to "strong" anticholinergics. Auditory Verbal Learning Test scores did not distinguish between groups.

Table 1

Sample characteristics grouped by exposure to no drugs, prescribed drugs – not anticholinergic, mild-moderate or strong anticholinergic drugs. Values are means (standard deviation) or median (range). *Non-parametric test after combining mild/moderate and strong anticholinergic drugs.

**1 – most affluent, 6 – most deprived

	Not exposed to anticholinergic drugs		Exposed to anticholinergic drugs		Probability
	no drugs	prescribed drugs	mild-moderate	strong	
<i>n</i>	84	118	66	13	
Male/female	55/29	66/52	35/31	6/7	$\chi^2 = 3.53$, df = 3, $p = 0.317$
Age (years)	77.4 (1.0)	77.0 (0.7)	77.1 (0.6)	77.0 (0.6)	$F = 3.57$, df = 3, $p = 0.015$
Occupation					
<i>Prof/admin</i>	20	21	18	3	$\chi^2 = 5.18$, df = 4, $p = 0.270^*$
<i>Skilled manual</i>	41	65	27	6	
<i>Unskilled manual</i>	23	32	21	4	
Deprivation (1–6**)	2.9 (1.3)	3.3 (1.4)	3.3 (1.3)	2.7 (1.1)	$F = 3.70$, df = 3, $p = 0.111$
Education years <i>median (range)</i>	9.0 (7~17)	9.7 (8~16)	9.6 (8~18)	9.0 (9~16)	KW, df = 3, $p = 0.548$
IQ age 11 yrs	101.1 (14.4)	102.1 (14.6)	101.0 (13.6)	106.0 (10.3)	$F = 0.479$, df = 3, $p = 0.687$
Incident dementia	15	18	10	2	$\chi^2 = 0.424$, df = 3, $p = 0.81^*$
Family history dementia	10	25	13	3	$\chi^2 = 3.52$, df = 3, $p = 0.17^*$
History heart disease	6	33	35	7	$\chi^2 = 42.11$, df = 3, $p = 0.000$
History hypertension	3	58	17	6	$\chi^2 = 50.80$, df = 3, $p = 0.000$
Smoking history					
<i>Never smoked</i>	19	33	14	5	
<i>Ex-smoker</i>	34	52	37	5	$\chi^2 = 6.244$, df = 6, $p = 0.396$
<i>Current smoker</i>	5	16	4	2	
Alcohol (units/week)					
None	54	64	30	4	$\chi^2 = 6.820$, df = 6, $p = 0.338^*$
1–4	11	17	12	3	
5–14	14	23	15	5	
>14	5	14	9	1	

Multivariate analyses of cognitive test data with adjustment for age and childhood IQ showed differences between groups; Pillai's Trace = 0.140, $F = 2.02$, df 9,372, $p = 0.036$. These differences were located to the group using "strong" anticholinergics" in lower Raven's Progressive Matrices scores ($F = 3.70$, $p = 0.013$, $\eta^2 = 0.06$) and Block Design ($F = 3.53$, $p = 0.017$, $\eta^2 = 0.08$). Auditory Verbal Learning Test scores did not differ between groups ($F = 0.26$, $p = 0.852$, $\eta^2 = 0.006$).

Binary Logistic regression was used to examine prediction of progress to dementia. Two regression models were examined (Table 3). In Model 1 ($n = 257$), dementia prediction was tested in 257 subjects after exclusion of those who had scored <24 on the MMSE. In Model 2, dementia prediction was tested in 210 subjects after exclusion of those who had not agreed to blood sampling for APOE genotyping.

DISCUSSION

Our aims were to examine associations between exposure to anticholinergic drugs and cognitive performance with and without adjustment for likely confounders. Many studies [1, 2, 15–19] report

that anticholinergic medications produce cognitive impairments in the elderly. Without adjustment for covariables, in two non-clinical cohorts of independent, community dwelling volunteers, we found significantly lower cognitive scores in those using anticholinergic drugs. Specifically, scores on tests of verbal reasoning (Raven's Progressive Matrices) and spatial ability (Block Design) were significantly worse in participants who reported taking "relatively strong" anticholinergic. After adjustment for covariables (age on recruitment and childhood mental ability) in a multivariate analysis, the results of the univariate analysis were supported. In logistic regression analyses of prediction of progress to late onset dementia, inclusion of use of anticholinergic drugs as an additional predictor did not improve prediction beyond that provided by gender, age and a history of dementia in a parent or sibling.

The main strength of the study is that our subjects were non-clinical volunteers living independently in the community. Their cognitive functions were not compromised by intercurrent physical disorders sufficient to impair their ability to live independently in the community. Within the total study sample, there were small subgroups with long-term exposure to drugs (e.g., non-steroidal inflammatory agents) that

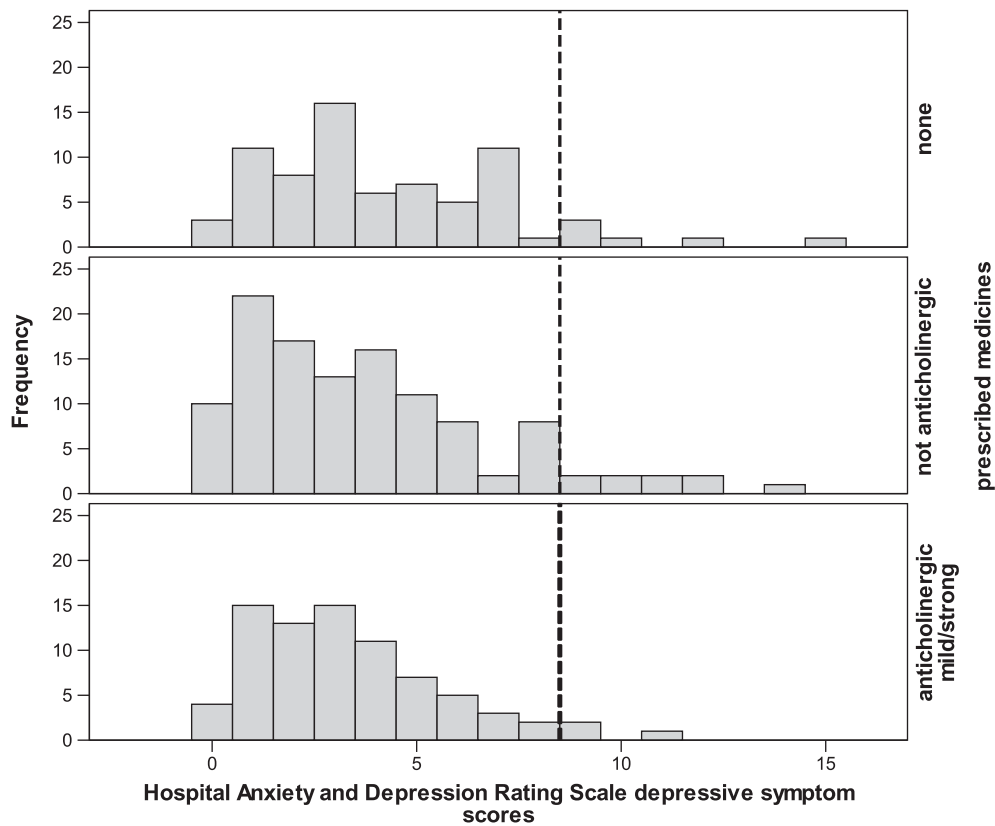


Fig. 2. Hospital Anxiety and Depression Scale (HADS) depressive symptom scores in 281 community residents without dementia classified by exposure to prescribed medicines (no medications, not anticholinergic and possible/definite anticholinergic drug). The broken vertical line is drawn at HADS = 8, a conventional cut-off for case recognition of depressive disorder [41].

Table 2
Cognitive test scores in 136 volunteers without dementia grouped by exposure to anticholinergic drugs. Values are means (standard deviation)

	Not exposed to anticholinergic		Exposed to anticholinergic		Probability df 3,129
	No drugs <i>n</i> = 39	Prescribed drugs <i>n</i> = 59	Mild-moderate <i>n</i> = 30	Strong <i>n</i> = 8	
Raven's progressive matrices	30.8 (9.4)	28.6 (8.3)	30.6 (8.5)	21.6 (7.1)	F = 2.89, <i>p</i> = 0.038
Block design	20.1 (6.9)	20.5 (7.2)	18.5 (7.3)	12.6 (5.8)	F = 3.22, <i>p</i> = 0.025
Auditory verbal learning test	47.6 (14.1)	48.6 (12.5)	48.8 (12.0)	44.5 (9.9)	F = 0.28, <i>p</i> = 0.838
Mini-mental state examination	28.6 (1.9)	28.1 (2.3)	28.2 (1.4)	26.8 (3.7)	Kruskal-Wallis, <i>p</i> = 0.021

may have modified their dementia risk. These groups were too small to merit separate analysis but in a larger study such subgroups may provide valuable insights into the modification of dementia risk by use of medications. Additional strengths were identification of other factors that could potentially explain some of the observed impairment of cognitive function. The main limitation of the study was that we did not exactly measure the anticholinergic load using serum assays and biological markers of anticholinergic effects were lacking. However, our review and classification of possible anticholinergic drugs is probably relevant to current

clinical practice in the United Kingdom. We based our review on studies which had determined anticholinergic activity directly from blood concentrations of anticholinergic drugs and their binding to cholinergic receptors. There are also international differences in the type of anticholinergic drugs prescribed. This point is emphasized when prescribed drugs are compared between this and the Ancelin study [17].

Our findings are relevant to therapeutic studies and epidemiological studies of cognitive aging and dementia incidence. From our data, it appears prudent to include self-reports of use of anticholinergic drugs as

Table 3

Binary logistic regression models of prediction of progression to dementia before age 88 in subjects without dementia at age 78 after exclusion of 24 subjects who scored <24 on MMSE at recruitment. Model 2 ($n=210$) includes *APOE*ε4 genotypic data that were unavailable for model 1 analysis ($n=257$). IQ – intelligence quotient at age 11; FHxDem – history of dementia in a parent or sibling; Heart Hx – personal history of treated heart disease; BP Hx – personal history of treated hypertension; Antichol – exposed to anticholinergic drugs (mild-moderate-strong); APOE – apolipoprotein E; CI confidence intervals: lower~upper

Predictor	Model 1 ($n=257$) Hosmer and Lemeshow $\chi^2 = 12.78$, df 8, $p=0.12$					Model 2 ($n=210$) Hosmer and Lemeshow $\chi^2 = 7.07$, df 8, $p=0.53$				
	β	S.E.	probability	exp β	95% CI. exp β	β	S.E.	probability	exp β	95% CI. exp β
Female gender	1.243	0.442	0.005	3.46	1.46~8.25	1.257	0.445	0.005	3.52	1.47~8.40
IQ age 11	0.006	0.015	0.67	1.01	0.98~1.04	0.01	0.015	0.619	1.00	0.98~1.04
Age	-0.959	0.43	0.026	0.38	0.17~0.89	-0.961	0.43	0.026	0.38	0.17~0.89
FHxDem	1.757	0.447	0.000	5.8	2.42~13.91	1.77	0.448	0.000	5.89	2.45~14.17
Education	-0.102	0.119	0.394	0.9	0.72~1.14	-0.1	0.119	0.381	0.9	0.71~1.14
Heart Hx	0.373	0.466	0.424	1.45	0.58~3.62	0.346	0.47	0.462	1.41	0.56~3.56
BP Hx	-0.219	0.451	0.627	0.8	0.33~1.95	-0.261	0.46	0.571	0.77	0.31~1.90
Antichol	-0.416	0.269	0.121	0.66	0.39~1.12	-0.396	0.272	0.146	0.67	0.40~1.15
<i>APOE</i> ε4	–	–	–	–	–	0.214	0.439	0.626	1.24	0.52~2.93

potential confounders in the study of individual differences in rates of cognitive aging. These data do not, however, suggest that anticholinergic drug use contributes to the risk of progression to dementia. In models 1 and 2, some established dementia risk factors were found to be associated with dementia (female gender and a history of dementia in a parent or sibling) while use of anticholinergics was not. The observation that increased age at recruitment is linked to reduced dementia risk is possibly an artifact of sampling.

Comparisons between these results and earlier reports suggest some similarities: we found spatial ability was significantly worse in anticholinergic drug users as did Ancelin et al. [17] in a larger study than reported here. However, it is striking that in our sample of relatively healthy volunteers we failed to obtain agreement for complete neuropsychological testing in almost 50% of those recruited whereas Ancelin et al. [17] achieved 100% compliance in a comparable sample also recruited from general practice and when using more demanding cognitive and psychophysiological tests. As in the present study, Ancelin et al. [17] did not find an association between anticholinergic drug use and progress to dementia. Comparisons between this and earlier studies show that we were unable to support associations between anticholinergic drug use and lower verbal memory scores [15] or deficits in attention [19] but lower scores on the MMSE found here are similar to reports elsewhere suggesting lower general cognitive ability is associated with anticholinergic drug use [42, 43]. In the largest study to date of this type, Campbell et al. [44] found that regular use of anticholinergics was associated with general cognitive impairment ascertained by either worse

performance on tests of general mental ability or progress to dementia.

We conclude that use of anticholinergic drugs is associated with lower scores on tests of cognitive ability and that consistent with other studies, this is supported by worse performance on tests of general ability and, spatial ability which may be selectively affected by anticholinergics. In our multivariate model, we found that anticholinergic drug use possibly accounted for 6–8% of the variability among old people in scores on non-verbal reasoning and spatial ability. Like others [17], we did not find a link between anticholinergic drug use and progress to dementia.

ACKNOWLEDGMENTS

The authors express their appreciation and admiration of the efforts made by the many volunteers from the local community who volunteered for these studies. The follow up in Aberdeen of local survivors of the Scottish Mental Surveys was supported by the Award (2001–2006) of a Professorial Clinical Research Fellowship to LW by the Wellcome Trust.

Authors' disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=1165>).

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