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Life long changes in cognitive ability are associated with prescribed medications in old age

John M. Starr[1]*, Brian McGurn[1,2], Martha Whiteman[2], Alison Pattie[2], Lawrence J. Whalley[3] and Ian J. Deary[2]

[1]*Geriatric Medicine Unit, University of Edinburgh, Edinburgh, UK*
[2]*Department of Psychology, University of Edinburgh, Edinburgh, UK*
[3]*Department of Mental Health, University of Aberdeen, Edinburgh, UK*

SUMMARY

Objectives To determine the association between prescribed medication and life long changes in cognitive ability.
Design Retrospective cohort study.
Setting Community residents of a largely urban region of South East Scotland.
Participants Four hundred and seventy-eight survivors of the 1932 Scottish Mental Health Survey ($n = 87\,498$) without dementia.
Measurements The Moray House Test (MHT) of intelligence administered at age 11 and age 80 years. Hospital Anxiety and Depression Scale (HADS) score, history of disease and current prescribed medications age 80 years.
Results After adjusting for sex, neuroactive drugs had a detrimental effect on life long cognitive change age ($F = 12.2$, $p = 0.001$, partial eta-squared $= 0.026$), statins a beneficial effect ($F = 5.78$, $p = 0.017$, partial eta-squared $= 0.013$) and polypharmacy a detrimental effect ($F = 6.46$, $p = 0.011$, partial eta-squared $= 0.014$). In the optimal model estimated marginal means revealed: a relative improvement for statin users, IQ age $11 = 93.2$ (95% CI 87.9–98.4) and age $80 = 100.6$ (95% CI 95.3–105.9); compared with non-users, IQ age $11 = 100.9$ (95% CI 99.4–102.3) and age $80 = 100.0$ (95% CI 98.6–101.5).
Conclusions Clinically, the degree to which drugs impair cognition in relatively fit, older people may not be apparent. However, in population terms, medication use, particularly polypharmacy, is important. Statins, used as currently indicated for cardiovascular disease, appear promising in ameliorating cognitive decline in older people. However, firm recommendation of their use should await the outcome of ongoing randomised clinical trials.

KEY WORDS — cognition; older people; drugs; 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors

INTRODUCTION

Drugs are a common cause of delirium in older people (Johnson *et al.*, 1990; Inouye *et al.*, 1993). Some drugs may induce dementia by acting on neurotransmitters or neurotrophic factors (Starr and Whalley, 1994a). The cerebral reserve hypothesis (Kay *et al.*, 1964) would allow drugs to produce minor neuropsychological decrements in the majority of people taking them, but these decrements only to be clinically apparent in those close to some critical threshold (Foy and Starr, 2000). Pre-morbid mental ability would be an important determinant of such cerebral reserve (Starr *et al.*, 1992). Alternatively, drugs may have little effect on mental abilities in the majority of older people and only lead to cognitive decline in a vulnerable group (Larson *et al.*, 1987), but not healthy individuals (Starr *et al.*, 1997). In a review of cognitive side effects of medications (Meador, 1998), Meador concluded that 'a great deal of individual variability in tolerance may be seen across patients', that polypharmacy was associated with increased risk, but that much was unknown about this problem.

*Correspondence to: Dr J. M. Starr, Geriatric Medicine Unit, University of Edinburgh, Royal Victoria Hospital, Craigleith Road, Edinburgh, EH4 2DN UK. E-mail: john.starr@ed.ac.uk

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In his review, Meador parsimoniously divided candidate drugs into neuroactive and 'medicinal', though this division is somewhat arbitary because 'medicinal' drugs may exert their effects on cognition via central mechanisms. Cardiovascular agents, mainly antihypertensives and statins, dominated the 'medicinal' category. Elevated blood pressure, itself, is associated with cognitive impairment (Starr, 1999) and antihypertensive therapy reduces the risk of dementia (Forette *et al.*, 1998). However, calcium channel antagonists and loop diuretics have been associated with lower cognitive test scores than β-blockers and thiazides (Heckbert *et al.*, 1997). Other antihypertensive classes, such as angiotensin-converting enzyme (ACE) inhibitors either have a neutral (Bulpitt and Fletcher, 1992) or potentially beneficial (Starr and Whalley, 1994b) effect on cognition. Determining whether antihypertensive agents contribute to cognitive decline to any major degree in a naturalistic setting would further inform clinicians about any potential risks in everyday practice.

Some drugs may have a beneficial rather than adverse effect on cognition in older people. Hypercholesterolaemia is linked to increased β-amyloid deposition in a transgenic mouse model of Alzheimer's disease (Refolo *et al.*, 2001), and to the later development of mild cognitive impairment (Kivipelto *et al.*, 2000) and Alzheimer's disease (Jarvik *et al.*, 2000) in humans. Lowering cholesterol with statins is associated with reduced dementia prevalence and improved cognition in some studies (Hajjar *et al.*, 2002; Yaffe *et al.*, 2002), but not others (Muldoon *et al.*, 2000; Gibellato *et al.*, 2001). Other agents thought to ameliorate cognitive decline are aspirin (Meyer *et al.*, 1989) and non-steroidal anti-inflammatory agents (NSAIDS) (Rozzini *et al.*, 1996).

Approximately half of the variance in IQ scores in old age is explained by childhood IQ (Deary *et al.*, 2000); sex and Apolipoprotein E explain a further small proportion of individual differences (Deary *et al.*, 2001). Thus, allowing for error variance, it is likely that around 40% of variance in IQ scores in old age is determined by 'extrinsic' factors. Both disease and medication use are commoner in older than younger adults and are possible 'extrinsic' factors. However, it is unclear to what extent disease and drugs contribute to this variance. Knowledge of IQ before disease onset is essential in untangling possible causal directions because lower childhood IQ is itself related to greater risk of disease and premature mortality (Whalley and Deary, 2001). Lower cognitive test scores in old people with disease may just reflect their life-long mental ability. Previously, we investigated the effects of medication on cognitive change in 603 people born in Edinburgh between 1906–1920 who were disease free and on no drug treatment at baseline (Starr *et al.*, 1997). We found no significant difference between those who had started medication and those who remained drug free on the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) after four years of follow-up. However, the MMSE has limited variance in healthy populations and we may therefore have missed subtle effects. Such relatively insensitive cognitive outcome measures have been used in other studies of the influence of 'extrinsic' factors on cognition (Ford *et al.*, 1996; Cattin *et al.*, 1997; Cacciatore *et al.*, 1998). We investigated the association of disease and medication use in a sample from a unique national population of older people with known childhood IQ's using the same sensitive, validated cognitive measure nearly seventy years later.

METHOD

The Scottish Mental Survey of 1932 (SMS1932) tested mental ability in people born in 1921 ($n = 87\,498$). The SMS1932's Moray House Test (MHT) was validated against the Stanford Binet test and includes verbal reasoning, numerical, spatial and other items (Scottish Council for Research in Education, 1933). From 1999–2001 we traced and retested 550 people from Edinburgh who were born in 1921 (the Lothian Birth Cohort 1921). The study was conducted with permission from the local research ethics committee. All participants gave written informed consent and were living independently. As previously described (Deary *et al.*, 2002), we excluded people with a history of dementia or with a MMSE (Folstein *et al.*, 1975) of less than 24. We traced their scores on the MHT from SMS1932; re-administered the MHT using the same instructions and time limit as the SMS1932. We also administered the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), and collected information on years of full-time education, social class, whether the participant lived alone and smoking habit.

We enquired about history of any disease and categorised these, using criteria previously established for related cohorts (Starr *et al.*, 1997, 2000a), into cardiac, cerebrovascular, non-cardiac and non-cerebrovascular vascular disease (e.g. peripheral arterial disease, abdominal aortic aneurysm etc), hypertension, diabetes, thyroid disorder, neoplasia and other disease. We categorised regular drugs taken according to *ad hoc* hypotheses suggested by Meador's review into

neuroactive (e.g. major and minor tranquilisers, antidepressants, antiepileptics etc), β-blockers, ACE inhibitors, statins, aspirin and NSAIDs, any cardiovascular medication and any other medication.

Following data checking, analyses were performed using SPSS 11.0 statistical software package. MHT scores were converted to IQ scores corrected for exact age in days as previously described (Deary *et al.*, 2000). General linear modelling was performed using a repeated measures design for IQ at age 11 and 80 years. Full factorial models were specified to adjust for potential interactions between independent variables. Effect sizes, as an estimate of the proportion of variance in the dependent variable explained by an independent variable, were expressed as partial eta-squared; the proportion of variance explained by the model equates to the sum of all the partial eta-squareds. Of note is that conversion of absolute MHT scores to IQ scores meant that the analyses addressed relative rather than absolute cognitive change. Also in these repeated measures models, the partial eta-squared relates to only that variance unexplained by 'stable' life-long mental ability.

RESULTS

Four hundred and seventy-eight participants had MHT scores at ages 11 and 80 years and were not demented. MHT-derived IQ was standardised at each age; mean absolute scores were higher age 80. Men ($n = 199$) had a mean IQ of 99.6 (SD 15.7) age 11 and 101.1 (SD 14.8) age 80. Women ($n = 279$) had a mean IQ of 100.5 (SD 14.2) age 11 and 98.7 (SD 14.9) age 80]. As previously reported, there was a significant effect of sex on change in IQ score between age 11 and 80 ($F = 8.39$, $p = 0.004$) (Deary *et al.*, 2001). The sample contained relatively few participants from social class 4 or 5 (social class 1 $n = 101$, social class 2 $n = 174$, social class 3 $n = 180$, social class 4 $n = 12$, social class 5 $n = 8$); no effect of social class on change in IQ score between age 11 and 80 was detected ($F = 0.85$, $p = 0.51$). IQ scores for specific disease categories are presented in Table 1. The only significant effect uncorrected for any covariates was a relative improvement for participants with non-cardiac and non-cerebrovascular vascular disease ($F = 4.18$, $p = 0.016$). This effect remained significant after adjusting for sex ($F = 3.53$, $p = 0.030$, partial eta-squared = 0.015). IQ scores for specific classes of drug are presented in Table 2. The only significant effect uncorrected for any covariates was a relative deterioration over time for participants taking neuroactive drugs ($F = 19.0$, $p < 0.001$). This effect remained significant after adjusting for sex ($F = 12.2$, $p = 0.001$, partial eta-squared = 0.026), and the effects of statins also became statistically significant after adjusting for sex ($F = 5.78$, $p = 0.017$, partial eta-squared = 0.013), with those on statins showing a relative improvement in IQ. The total number of drugs taken was also significant after adjusting

Table 1. Standardised IQ scores age 11 and 80 years in the Lothian 1932 Scottish Mental Survey cohort according to presence (definite [def] or uncertain [uncrtn]) or absence of disease

Disease category	N with disease	Mean IQ (SD) age 11 years		Mean IQ (SD) age 80 years	
		Disease	No disease	Disease	No disease
Cardiac	82 def, 63 uncrtn	99.1 (17.0) 98.3 (13.6)	100.7 (14.5)	98.7 (16.3) 98.7 (14.3)	100.0 (14.7)
Cerebrovascular	37 def, 3 uncrtn	100.0 (12.8) 103.8 (19.5)	100.1 (15.0)	97.3 (19.9) 106.8 (17.2)	99.9 (14.6)
Non-cardiac, non-cerebrovascular vascular*	38 def, 2 uncrtn	98.9 (13.3) 105.7 (7.3)	100.3 (15.0)	100.8 (14.3) 82.5 (12.5)	99.7 (15.0)
Hypertension	198 def, 4 uncrtn	100.0 (13.3) 102.4 (28.3)	100.3 (15.7)	100.0 (14.3) 93.9 (25.2)	99.6 (15.3)
Diabetes	22 def	102.1 (10.7)	100.1 (15.0)	97.2 (19.5)	99.8 (14.7)
Thyroid	62 def	100.7 (15.5)	100.1 (14.8)	100.3 (13.9)	99.6 (15.1)
Neoplasia	30 def, 14 uncrtn	103.5 (14.0) 96.2 (17.0)	100.1 (14.8)	99.2 (13.5) 95.5 (11.9)	99.9 (15.1)
Other disease	50 def	99.5 (14.7)	100.3 (15.0)	95.9 (17.4)	100.1 (14.6)

*Significant categories at $p < 0.05$.

Table 2. Standardised IQ scores age 11 and 80 years in the Lothian 1932 Scottish Mental Survey cohort according to medication use

Drug class	N on drug	Mean IQ (SD) age 11 years		Mean IQ (SD) age 80 years	
		Drug	No drug	Drug	No drug
Aspirin	145	100.8 (14.0)	100.2 (14.9)	100.4 (14.9)	99.7 (14.6)
NSAID	46	102.6 (13.5)	100.1 (14.7)	101.1 (13.0)	99.8 (14.9)
β-blocker	82	102.6 (14.0)	99.9 (14.7)	101.4 (14.3)	99.6 (14.8)
ACE inhibitor	75	99.2 (16.0)	100.6 (14.3)	97.8 (17.3)	100.3 (14.1)
Statin	37	96.8 (15.1)	100.7 (14.5)	99.8 (12.4)	99.9 (14.9)
Any cardiovascular agent	262	100.6 (14.2)	100.1 (15.1)	99.9 (15.1)	99.9 (14.2)
Any neuroactive agent*	32	104.6 (14.0)	100.1 (14.6)	95.2 (14.2)	100.2 (14.7)

*Significant categories at $p < 0.05$.

for sex ($F = 6.46$, $p = 0.011$, partial eta-squared = 0.014), with participants on more drugs showing a worsening of IQ at age 80 relative to age 11.

The effects of non-cardiac and non-cerebrovascular disease, neuroactive drugs, statins and the total number of drugs taken all remained significant after adjusting for years of full-time education, social class, living alone, smoking habit and HADS anxiety and depression scores. Entering the four significant variables into a repeated measures, general linear model including sex, a history of non-cardiac and non-cerebrovascular disease ($F = 1.87$, $p = 0.16$) and neuroactive drugs ($F = 1.21$, $p = 0.27$, partial eta-squared = 0.022) were no longer significant. The optimal model comprised sex ($F = 10.5$, $p = 0.001$), total number of drugs ($F = 13.0$, $p < 0.001$, partial eta-squared = 0.028) and statin use ($F = 13.0$, $p < 0.001$, partial eta-squared = 0.028). Estimated marginal means revealed: a relative improvement for men, IQ age 11 = 93.4 [95% Confidence Intervals (CI) 89.2–97.6] and age 80 = 100.1 (95% CI 95.9–104.4), compared with women, IQ age 11 = 100.6 (95% CI 97.5–103.8) and age 80 = 100.5 (95% CI 97.3–103.7); for statin users, IQ age 11 = 93.2 (95% CI 87.9–98.4) and age 80 = 100.6 (95% CI 95.3–105.9), compared with non-users, IQ age 11 = 100.9 (95% CI 99.4–102.3) and age 80 = 100.0 (95% CI 98.6–101.5). Greater number of drugs taken was associated with a relatively lower IQ score age 80 compared with age 11.

DISCUSSION

In this sample, medication use was associated with a small, but significant effect on IQ change from childhood to old age. A greater number of medications used was associated with a relative worsening of IQ, explaining about 2.2% of the variance in change over time, whilst statin use was associated with a relative improvement, explaining about 2.8% of variance. Other medication classes mostly had more subjects than that of statins and neuroactive drugs, suggesting that if they had an effect in this sample it is likely that it is fairly small. Relative improvement in cognition with statins is consistent with those studies that looked at their effects in older people over prolonged periods (Hajjar *et al.*, 2002; Yatte *et al.*, 2002) rather than younger adults over shorter periods (Muldoon *et al.*, 2000; Gibellato *et al.*, 2001). Moreover, this sample of people without dementia manifested relative improvement in cognition at the age of 80 years, a cut-off age for benefit of statins in preventing Alzheimer's disease in the Canadian Study of Health and Aging (Rockwood *et al.*, 2002). Others report statins reducing Alzheimer's disease risk (Jick *et al.*, 2000; Wolozin *et al.*, 2000): statins may ameliorate adverse changes within the brain associated with cholesterol metabolism that render it vulnerable to Alzheimer's disease (Naidu *et al.*, 2002). Statin users had lower childhood IQ's, as might be expected, but had caught up relatively by age 80.

Although non-cardiac and non-cerebrovascular vascular disease was associated with a significant effect on IQ change, this disappeared once other variables were adjusted for. No other disease category had a significant association, but numbers in some disease categories were smaller than in drug classes, thus sizeable effects may have been missed. Moreover, the spectrum of severity of disease is likely to be biased towards minor, stable illness since the participants were fit enough to attend for a fairly lengthy assessment. Presence or absence of disease is probably a very imprecise measure of health status in old age (Starr *et al.*, 2000a). The total number of drugs taken may be a better indicator of disease burden, and it is unclear whether it is the drugs themselves or the underlying disease for which they are prescribed that is causing the relative decline in IQ. Within this, however, some drugs, and in particular statins, may

exert a beneficial effect, perhaps ameliorating effects of disease.

Other studies also found that the effect size of many diseases on mental ability to be generally quite small. Hypertension accounts for only a small proportion of the variance in mental ability in old age (Starr, 1999) and differentially impairs fluid intelligence compared with memory (Deary *et al.*, 1998). By contrast, Type 2 Diabetes mellitus predominantly affects domains of memory (Strachan *et al.*, 1997), thus its effects are less likely to be seen with a general intelligence test such as the MHT. Stroke, for which both hypertension and diabetes are important risk factors, is associated with more marked impairment of fluid intelligence (Starr *et al.*, 2000b) but this sample is likely to be biased towards those with more minor disability after stroke and hence with less cognitive decline.

Although medications had only a small effect on change in IQ over the lifetime, sample bias may have underestimated this. Drugs may have had a greater impact on potential participants who were sicker, and thus on more medications, who would be less likely to attend for assessment. Our sample contained people who were cognitively normal or who had only minor degrees of cognitive impairment (Deary *et al.*, 2001) so family doctors are unlikely to have limited medication use in those who they thought might be more unreliable taking tablets because of reduced mental ability. Trials, such as that ongoing for pravastatin (Houx *et al.*, 2002) provide the best evidence of cognitive change associated with drugs, but these cannot easily take into account the effects of polypharmacy. It may be due to interactions between different classes of drug that cognitive side effects most commonly occur, and clinical trials are unlikely to be powered to detect such sub-group effects. Polypharmacy was specifically identified by Meador's review as an important risk factor for cognitive side effects in old age (Meador, 1998). Older neuroactive agents were also singled out by Meador, but the prescription of newer atypical psychotics and antidepressants in our sample may explain why their effects on cognition disappeared once other factors were controlled for. Heterogeneity of agents within other classes of drug (e.g. more and less cardio-selective β-blockers) may also have masked effects of older drugs on cognition.

We conclude that if non-demented, older people are fit enough to attend for relatively lengthy assessments, disease makes a minimal contribution to their mental ability test scores, but that despite this medication, in particular polypharmacy, does have a significant, though probably not clinically detectable, effect. In population terms, this small effect of medication use, particularly polypharmacy, is important. In terms of public health policy aimed at preventing cognitive decline in old age, it may be more important to target people on multiple medications and reduce these rather than focus on specific classes of drug. Statins, used as currently indicated for cardiovascular disease, appear promising in preventing cognitive decline in older people. However, firm recommendation of their use should await the outcome of ongoing randomised clinical trials.

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