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Age-associated cognitive decline in healthy old people

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Abstract

Background: disease often confounds the identification of risk factors for age-associated cognitive decline in elderly subjects. If the cognitive effects of ageing are to be distinguished from those of disease, healthy people need to be studied.
Methods: we examined the effects of incident disease and drug prescription on cognitive change in a sample of initially healthy old people in a longitudinal study and related these to age, education, social class and blood pressure. We screened general practice case notes of 10 000 patients aged 70 years and over resident in Edinburgh to identify potentially healthy subjects. We visited 1467 potential subjects at home and enquired directly about health problems and medications, administered the Mini-Mental State Examination (MMSE) and National Adult Reading Test and recorded educational attainment, occupation and blood pressure.
Results: 603 subjects (237 male, 366 female), mean age 75.7 years (range 70–88 years), reported no health problems and were taking no regular medications. Four years after the initial visit we determined the outcome of all 603 subjects and retested available survivors. Psychometric tests were then administered to the 429 (71.1%) available survivors after a median period of 4.2 years (69 subjects were dead, 15 were too unwell, 12 had moved away and 78 either refused or failed to reply). Forty-two subjects had significant sensory impairment or interrupted testing, 195 remained in good health, 29 reported or had documented disease but were on no regular medication and 163 were on regular medication for diseases diagnosed during the follow-up period. MMSE score declined by 0.3 points in the healthy group ($P < 0.048$). However, once a single outlier whose MMSE score fell from 29 to 22 was excluded, the mean decline for the remainder was non-significant at 0.2 points ($P = 0.079$). There was no significant difference in cognitive decline between those who had and those who had not started medication ($P = 0.59$).
Conclusions: the study fails to support the hypothesis that cognitive decline can be attributed to age alone in healthy old people. If such a decline exists, we consider that it is unlikely to account for loss of more than 0.1 MMSE point per year.

Keywords: *age-associated cognitive decline, healthy old people*

Introduction

Central to any understanding of the cognitive decline associated with old age is the question as to whether all such cognitive decline is disease-related or whether it can occur as part of so-called 'normal' ageing. Among other difficulties in answering this question are the observation that pathological changes may not correlate well with the degree of intellectual impairment [1] and the ascertainment of 'health' in elderly people [2]. One approach is to label 'abnormal' cognitive decline pathological even in the absence of a definable biological substrate, using younger subjects to provide a 'normal' reference range [3]. Unfortunately, this approach is often confounded by inter-cohort comparison. A further problem is that the concept of decline implies a 'premorbid' level which may not only be hard to quantify but also, if quantifiable, leaves a difference over time in performance as the outcome measure. Such a measure is generally less reliable than a single score [4].

Although poor test-retest reliability reduces the clinical significance of small cognitive declines for individuals [5], the mean scores for populations will remain stable over time if no true decline occurs. Hence, the impact of disease on cognitive function may be inferred by comparing the performance of subjects who have disease with that of suitable controls.

However, when subjects with disease have already suffered from that condition for some time before baseline cognitive testing, the selection of suitable controls is problematic as it is impossible to match both current cognitive function and premorbid cognitive function (Figure 1). Since both these cognitive parameters are hypothesized to affect the rate of cognitive decline [6], an appropriate control group can only be selected with incident cases. Failure to control for premorbid cognitive function may lead to undetected confounding, since many diseases are associated with socio-economic deprivation [7] and the associated lower educational attainment.

These considerations are of even greater importance if cognitive decline attributable to disease or medication is non-linear over time. For example, the onset of a particular disease may result in a large fall in cognitive function at this time, but have no effect on cognitive function thereafter. Longitudinal measures of subjects with disease pre-dating baseline measurement will conclude incorrectly that the particular disease does not alter cognitive function. We therefore sought to relate age-associated cognitive decline to incident disease, i.e. disease newly-diagnosed after baseline measures of cognitive function had been made in healthy people.

Previously, we addressed these issues in a cross-sectional study of cognitive function in community-resident healthy old people [6, 8] and inferred the effect of premorbid IQ, as estimated by the National Adult Reading Test (NART) [9], on age-associated cognitive decline as measured by the Mini-Mental State Examination (MMSE) [10]. We now present the cognitive effects of incident disease and newly initiated medication on decline in MMSE score over time in this initially healthy sample and relate these to age, sex, estimated premorbid IQ, educational attainment and social class.

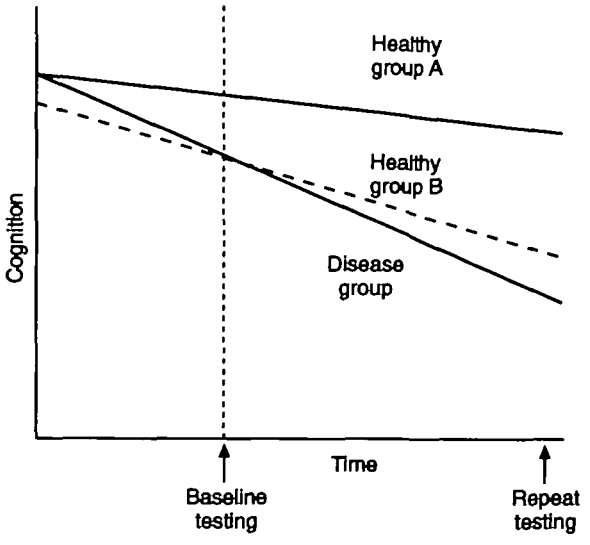

Figure 1. Model of cognitive decline in subjects with disease compared with healthy controls matched by premorbid cognitive function (group A) or current cognitive function (group B).

Subjects and methods

Subjects aged 70 years and over were identified from age-sex registers of 67 general practitioners in Edinburgh [6]. Trained research assistants screened case notes to exclude patients with significant disease [6]. Details of the remaining potential subjects were then scrutinized by the patient's own doctor to verify that, as far as they were aware, these patients were in good health. Of the patients asked to participate in the study, 1467 agreed and were visited at home by a research nurse who enquired directly about health problems and medication. Six hundred and three subjects (237 male, 366 female), mean age 75.7 years (range 70-88 years), reported no health problems and were taking no regular medications.

Each subject was asked to state their number of years of full-time education, and their main occupation was classified by the Standard Occupational Classification (SOC). Both the NART and the MMSE were administered. Blood pressure was measured at the end of the interview, a few minutes after completion of the cognitive tests when the subject had been sitting at rest for approximately 25-30 min, using a standard sphygmomanometer and recording diastolic pressure at the fifth Korotkov sound.

Follow-up was planned after 4 years, following consideration of change in MMSE score per year inferred from the cross-sectional data [8] and the expected attrition rate. Case notes of the 603 subjects were searched for at the original general practices. When these could not be located, the subject's records were traced at the local primary care division where the outcome was (i) transfer to another local general practitioner, (ii) transfer to a general practitioner outside the study area or (iii) death. If a subject had died in Scotland, their death certificate was located at centrally held records for Scotland at Register House, Edinburgh.

Subjects who were still living in Edinburgh were invited to participate in retesting. Those who agreed were again visited by a research nurse at home and the MMSE and NART readministered. Blood pressure was measured as before and direct enquiry made about health and medications. All available case notes of subjects were scrutinized by a research nurse (S.I. or S.C.) and reviewed by a physician (J.M.S.). Subjects were categorized as having newly diagnosed disease if either they reported it or it was documented in their case notes. Disease was categorized as: none; cardiovascular; cerebrovascular; hypertension; other vascular (mainly peripheral arterial disease of the legs);

neoplasia; diabetes; thyroid disease; dementia; and other. Subjects could be categorized as having more than one disease.

Data were collated on computer and analysed by SPSS 4.0 statistics package (SPSS Inc. Cary, NC, USA). Data for age, MMSE score and NART-predicted IQ met criteria for homogeneity of variance and repeated-measures analysis of variance was employed.

Results

Psychometric tests were administered to 429 of the 603 original subjects (71.1%) after a median period of 4.2 years (range 3.23–5.23 years, inter-quartile range 4.12–4.29 years). Tests were thought to be inadequate, due to poor vision, hearing impairment, interrupted testing etc., for 42 of these subjects. Baseline characteristics of the retested group are compared with those of subjects not retested in Table 1.

One hundred and ninety-five (69 male, 126 female) of the 387 adequately retested subjects reported no health problems, were on no regular medication and had no significant illness documented in their case notes. Twenty-nine (20 male, nine female) reported or had documented disease but were on no regular medication and 163 (63 male, 100 female) were on regular medication. The conditions which occurred in the adequately retested group during the follow-up period were: cardiovascular disease (38; 10%); cerebrovascular disease (7; 2%); hypertension (39; 10%); other vascular disease (4; 1%); neoplasia (9; 2%); diabetes (3; 1%); thyroid disease (7; 2%); dementia (5; 1%); other disease (76; 20%). Thirteen subjects (3%) were on medication for which they were unaware of the indication and where this was not clearly specified in the case notes.

Subjects who had started medication were significantly older and had higher initial systolic blood pressures than those remaining untreated (Table 2). Logistic regression analysis revealed the only significant predictors of starting treatment in this sample to be higher systolic blood pressure (odds ratio 1.03, 95% confidence interval 1.02–1.04 per mmHg) and SOC (χ^2 improvement = 24.6, $P < 0.01$ on nine degrees of freedom). No consistent pattern of risk emerged across major SOC groups. Repeated-measures analysis of variance found that medication use had no significant effect on MMSE score over time (untreated subjects' mean MMSE score fell from 28.4 to 28.0, treated subjects' from 28.3 to 27.9; F-value = 0.30, $P = 0.59$), although there was a significant fall in MMSE over the follow-up period (F-value = 17.85, $P < 0.001$). Drug usage remained non-significant in a model with systolic blood pressure as covariate ($F = 0.25$, $P = 0.62$), although systolic pressure itself had a significant effect ($F = 5.20$, $P = 0.023$).

Repeated-measures analysis of variance of MMSE scores was significant by disease type when subjects who became demented were included, but the 27 subjects with multiple and 13 subjects with unknown pathology were excluded ($n = 347$, $F = 14.54$, $P < 0.001$). MMSE scores by disease group are shown in Table 3. Mean MMSE score fell significantly from 28.5 to 28.2 ($P = 0.048$) in the 195 untreated, healthy subjects. There was a marginal difference in initial MMSE scores between disease groups ($F = 1.92$, $P = 0.048$), with no single group scoring significantly better or worse than any other, and a highly significant difference in follow-up MMSE scores ($F = 18.46$, $P < 0.0001$), due largely to the much lower scores of subjects designated as demented (by Scheffe's test).

Grouping subjects into those with no incident disease, those with dementia and those with other incident disease again revealed a significant effect of category over time ($F = 68.0$, $P < 0.0005$). Once subjects with dementia only ($n = 4$) were excluded, disease had no effect on MMSE score over time

Table 1. Baseline characteristics by group

Outcome	*n* (male, female)	Mean value (SD)		
		Age (years)	NART-IQ	MMSE
Retested				
Adequately	387 (152, 235)	75.1 (3.9)[a]	115.8 (7.5)	28.3 (1.4)[b]
Inadequately	42 (11, 31)	76.7 (4.4)	112.0 (8.1)	27.2 (2.0)
Refused	46 (13, 33)	76.3 (4.6)	112.2 (8.7)	27.1 (2.2)[b]
No reply	19 (4, 15)	75.0 (4.0)	112.4 (8.5)	27.6 (2.1)
Moved out of area	12 (3, 9)	75.5 (3.3)	114.5 (9.5)	28.9 (1.2)
Untraceable	13 (5, 8)	75.0 (3.9)	118.8 (6.4)	28.2 (1.6)
Dead	69 (40, 29)	78.3 (4.6)[a]	114.1 (7.4)	27.5 (2.1)
Too unwell	15 (9, 6)	77.3 (5.1)	115.4 (8.1)	27.3 (2.6)

[a] Scheffe's test $F = 6.16$, $P < 0.00005$.
[b] Scheffe's test $F = 3.22$, $P = 0.0024$.
NART-IQ, National Adult Reading Test-predicted IQ; MMSE, Mini-Mental State Examination.

Table 2. Means and standard deviations of age, National Adult Reading Test-predicted IQ (NART-IQ), Mini-Mental State Examination (MMSE) score and blood pressure for 163 treated and 224 untreated subjects after 4 years of follow-up

Variable	Mean value (SD) Treated	Untreated	*F*-value between groups	Significance
Age (years)	79.8 (4.2)	79.0 (3.8)	4.28	0.04
NART-IQ	112.8 (8.9)	114.4 (8.4)	3.29	0.07
MMSE score	27.8 (2.2)	28.0 (2.3)	0.93	0.33
Blood pressure (mmHg)				
Systolic	162 (21)	158 (21)	4.33	0.04
Diastolic	87 (11)	86 (10)	0.15	0.70

regardless of whether subjects with multiple pathology (F = 0.50, P = 0.87) or subjects taking medication for unknown reasons (F = 0.49, P = 0.88) were included.

Discussion

A very small but significant age-associated cognitive decline was observed in our sample of initially healthy elderly people whom we were able to retest adequately. The initially healthy subjects represent a very select group from the approximate screened population of 10 000. They were chosen to minimize any discrepancy between current and 'premorbid' cognitive function: otherwise, distinguishing age-associated from disease-associated decline is problematic (Figure 1). For the even more highly selected 195 out of 603 subjects who remained untreated and apparently disease-free over 4 years, MMSE score fell marginally. The effect size was small and reached significance because of the large sample size.

In general, we detected no effect of medication use on MMSE score. Unsurprisingly, the small number of subjects who had been designated as demented by their general practitioners performed significantly worse than other subjects, but once these were excluded, the mix of disease incident in our sample had no impact on cognitive loss. However, although no specific disease type, except dementia, was associated with a significant cognitive decline, relatively small declines cannot be excluded due to type II statistical error, since there were few subjects per disease group.

Table 4 shows the power calculations for significance level 0.05 of detecting (α) and failing to detect (β, power = 95%) differences in MMSE scores compared with our healthy group (n = 195). Thus, we can conclude that the effect of newly diagnosed hypertension in old people is unlikely to produce more than a 0.9 MMSE point difference compared with their healthy counterparts, once adjusted for the effects of age and NART-predicted IQ. However, it is difficult to account for the effects of attrition when considering the impact of disease on cognition. Of our sample,

Table 3. Initial and 4 year follow-up, Mini-Mental State Examination (MMSE) scores by disease type in subjects with no or known single diseases (n = 347)

Disease type	n	Mean MMSE score (SD) Initial	4 year
None	195	28.5 (1.2)	28.2 (1.5)
Cardiovascular	30	28.3 (1.5)	27.5 (3.0)
Cerebrovascular	5	28.2 (1.7)	28.2 (1.5)
Hypertension	29	28.3 (1.3)	28.1 (1.8)
Other vascular	7	28.0 (0.8)	27.6 (1.3)
Neoplasia	7	28.4 (1.8)	27.7 (2.1)
Diabetes	2	29.5 (0.7)	30.0 (0.0)
Thyroid	6	26.8 (3.3)	26.3 (4.4)
Dementia	4	26.5 (3.3)	15.8 (4.8)
Other	62	28.3 (1.4)	28.0 (2.2)

Table 4. Power calculation of sample size required per Mini-Mental State Examination (MMSE) score difference compared with control group (n = 195)

MMSE score difference	Sample size required
0.4	190
0.5	122
0.6	71
0.7	48
0.8	35
0.9	27
1.0	21
1.1	17
1.2	14
1.3	12
1.4	11

11.4% died during the 4 year follow-up period and a further 2.5% were too unwell to be tested. Since a lower MMSE score is a recognized predictor of shortened survival [11], it remains unsafe to conclude that disease had no significant effect on cognitive function in our previously healthy sample.

Our sample size enables us to infer from the power calculations given in Table 4 that the group of subjects with incident disease, excluding those with dementia, were no more than 0.4 MMSE points worse than those with no disease and on no medication. However, when compared with a 0.3 MMSE point decline over 4 years for the healthy group, this apparently small potential deficit is of considerable importance—i.e. rate of cognitive decline in elderly people with disease may be more than twice that in healthy counterparts.

Previous investigators have excluded subjects with 'serious' disease from their studies [5, 12, 13], but more minor degrees of vascular disease are known to impair MMSE performance in cross-sectional studies [14]. We consider, therefore, that results from many previous studies of cognitive decline cannot be used to distinguish age-associated decline from the cognitive effects of disease. Furthermore, we found medication use to be associated with older age and systolic hypertension, both correlates of cognitive impairment, and we suggest that drug usage is included as a potential confounder in future studies of blood pressure and cognitive function in elderly people.

Before we can conclude that age-associated cognitive decline is a real phenomenon, the possibility that the decline in MMSE scores detected in our 'healthy' group is really attributable to undetected disease needs to be excluded. Such covert disease might explain the failure to find a difference between treated and untreated subjects. Our results suggest that the most influential disease process in this respect would be unrecognized dementia, most likely due to Alzheimer's disease.

Figure 2 shows the frequencies of differences in MMSE scores for the whole group. The right-hand tail represents those subjects diagnosed as demented (n = 5) and additional non-diagnosed outliers (n = 3) with declines more than three standard deviations from the mean. One of these outliers was included in the 195 apparently healthy old people and had a fall in MMSE score from 29 to 22 points. If this subject is excluded, mean MMSE scores in the remaining 194 subjects fell by only 0.2 points over the 4 years, which was no longer significant (P = 0.079). We consider that since this one subject is so influential, and their MMSE score falls below conventional cut-offs for dementia, their inclusion in the 'healthy' group is unsafe. Hence, we are unable to detect true age-associated cognitive impairment in 815 person-years of follow-up.

We therefore conclude from our power calculations

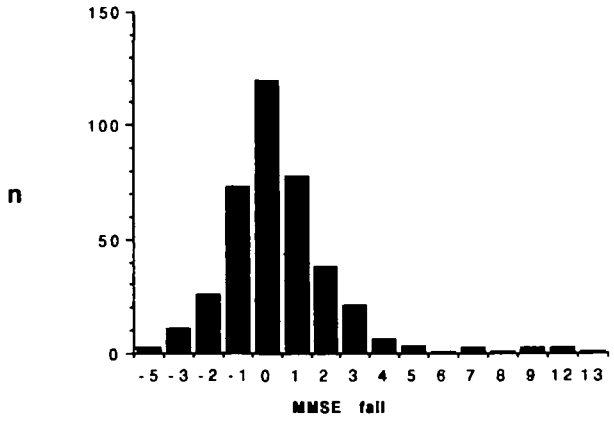

Figure 2. Number of subjects per fall in Mini-Mental State Examination (MMSE) score.

(Table 4) that, if age-associated cognitive impairment exists, it represents no more than 0.1 MMSE points loss per year for healthy people in their seventies and early eighties. The existence of cognitive decline attributable only to age has been questioned before [15]. Cognition is not a monolithic entity, but comprises many discrete functions. Nevertheless, information processing speed may be central to many cognitive domains [16] and a general cognitive factor is extractable from diverse psychometric tests [17]. The pattern of cognitive change in elderly people will probably consist of significant deficits in some areas and gains in others [3]. Thus, a general screening test like the MMSE may not be the most appropriate measure of age-associated cognitive decline, and further studies with tests more sensitive to changes in fluid intelligence are required before the concept of age-associated cognitive decline can be discarded. Furthermore, it is possible that a small practice effect persisted even after 4 years and this might mask a greater fall. However, this would have no effect on comparisons between healthy and unhealthy subjects.

We conclude that those who remain healthy into their seventies—as long as they do not die or become obviously demented—will find that over the next 4 years their MMSE score is likely to stay about the same. Most elderly people will suffer a minimal decline in cognitive function with age and this may be related to pervasive risk factors such as hypertension and cardiovascular disease. Our subjects with incident disease may not have been exposed to the adverse effects of these diseases for long enough to produce large cognitive deficits. However, over a long period these small declines may lead to a important diminution of cerebral reserve [18]. We hypothesize that it is in the effects of the interaction between age and disease on cognitive function that the importance of age-associated cognitive decline lies.

Key points

- Significant cognitive decline in elderly people cannot be attributed to age alone.
- If such a decline exists, it is unlikely to account for more than 0.1 MMSE point loss per year in initially healthy old people.

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