Non-valvular atrial fibrillation and cognitive decline: a longitudinal cohort study

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Abstract

Objectives: non-valvular atrial fibrillation (NVAF) is an established risk factor for thromboembolism and stroke. Small cross-sectional studies suggest associations between NVAF, silent cerebral infarction and decreased cognitive function. We compared change in cognitive function between patients with recent onset NVAF and controls 12 and 36 months after baseline assessment, and examined the impact of anti-thrombotic therapy.

Design: prospective longitudinal cohort study with follow-up at 12 and 36 months.

Setting: Sunderland and South Tyneside, North East of England.

Participants: community-dwelling men and women aged over 60 with recently identified NVAF or in sinus rhythm, matched for age, sex and general practice (N = 362, 174 NVAF, 188 sinus rhythm). Participants were stratified for use of anti-thrombotic therapy.

Measurements: assessment included stroke risk factors and a comprehensive battery of neuropsychological tests.

Results: at 3 years, 74 cases and 86 controls remained, giving an attrition rate for cases (59%) versus controls (52%); p = 0.15. Analysis of change in cognitive function between baseline and follow-up at 12 and 36 months revealed no clinically important differences between cases and controls, nor between subgroups on aspirin, warfarin or neither. Age and other confounders did not influence the results.

Conclusions: there was no association between overall cognitive decline and NVAF after 3 years’ follow-up, nor any apparent effect of anti-thrombotic therapy. This is consistent with our baseline results, but conflicts with previous studies. Cognitive decline is probably multifactorial and any influence of NVAF was not identified in this study.

Keywords: atrial fibrillation, cognition, dementia, elderly

Introduction

There is increasing evidence that risk factors for cerebrovascular disease such as hypertension and atherosclerosis are associated with greater risk of cognitive decline and dementia [1]. Non-valvular atrial fibrillation (NVAF) is an established risk factor for thromboembolism and stroke [2], and these risks are significantly reduced by anti-thrombotic therapy [3]. Previous cross-sectional studies report associations between NVAF, silent cerebral infarction and cognitive impairment [4–11], but there has been no relevant longitudinal work in this area except for one small, highly selective comparison of cognition before and after coronary artery bypass grafting [12]. Since NVAF is prevalent in older people [13], we wished to determine whether NVAF is a preventable cause for cognitive decline. The Cognition in Atrial Fibrillation Evaluation (CAFE) was a prospective, longitudinal, community-based cohort study, baseline findings from which demonstrated no difference in cognitive function between NVAF cases and controls [14]. This paper reports our follow-up results at 12 and 36 months, comparing detailed neuropsychological testing of NVAF patients and controls, and assessing the relationship of anti-thrombotic therapy with change in cognition.
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Methods
Details of recruitment of the original CAFE study cohort can be found in Appendix 1 in the supplementary data on the journal website (http://www.ageing.oxfordjournals.org.uk). Ethical approval was provided by the appropriate NHS local research ethics committees. Written, informed consent was obtained from all participants.

Participants underwent a home visit, comprising a validated battery of neuropsychological tests [16]; a health questionnaire including stroke risk factors and contraindications to anti-coagulation; a health status questionnaire (the SF-36 [17]); physical examination and an ECG to confirm atrial fibrillation (AF). Participants were revisited at 12 and 36 months, when the neuropsychological tests were repeated.

Neuropsychological tests
Details of the neuropsychological test battery can be found in Appendix 1 on the journal website (http://www.ageing.oxfordjournals.org.uk). It included measures of selective/divided/sustained attention, short and long-term verbal and non-verbal memory, information processing and pre-morbid intelligence: Rey Complex Figure [18], Mini-Mental State Examination (MMSE) [19, 20, 21, 22], logical memory and digit span subtests of the Wechsler Memory Scale (WMS) [23, 24, 25], Map Search and telephone task subtests of tests of everyday attention [26, 27], Paced Auditory Serial Addition Test (PASAT) [28, 29], and National Adult Reading Test (NART) [30, 31].

Statistical analysis
Data were analysed via SPSS Version 14.0. Between and within-group comparisons were performed via a general linear model incorporating repeated measures analysis of variance (ANOVA). Differences were normally distributed and where this was not the case, results were confirmed via non-parametric equivalent tests. Sidak corrections were applied where appropriate in order to adjust p-values for multiple comparisons [32]. Analysis was in two stages with the following factors: (a) AF status and (b) anti-thrombotic drug status.

The possible effects of age, educational attainment and stroke risk (for NVAF cases only) were tested before confirmation of the final model. Stroke risk was calculated using the Stroke Prevention in Atrial Fibrillation stratification scheme [33]. Literature searches informed the selection of other confounding variables, including duration of AF, coronary heart disease (CHD), diabetes, hypertension, cholesterol, health status (SF-36) and congestive heart failure (CHF). The SF-36 mental health component was used to assess mental health, having been validated for this purpose [34, 35].

Sample size and power
The residual sample of 160 participants (74 cases and 86 controls) who took part in all three stages of the study provided 99% power at the 5% level to detect within-group (longitudinal) differences of one point on the MMSE, and 85% power at the 5% level to detect an overall between-group difference (cases versus controls) of the same size. These calculations assume a standard deviation of two points on the MMSE. Although the power calculation was based on the MMSE, the sample size also provided 80% power for comparisons of clinically meaningful differences on all of the measures used. Furthermore, the sample sizes also provided 80% power to detect differences of two points (SD = 2.2) on the MMSE, based on anti-thrombotic drug use.

Results
Screening of 2866 sets of general practice (GP) notes identified 938 (33%) potential participants who were invited to interview (466 cases and 472 controls). Four hundred and twenty-three (47%) agreed and were visited at home. Sixty-one (14%) participants were found to be ineligible at baseline interview, leaving 362 included. The attrition rate at 12 months was 13.4% for controls and 17.7% for cases, and at 36 months was 52% for controls and 59% for cases. This left 305 participants at 12 months, and 160 at 36 months (See Figure 1).

Characteristics of the cohort
The characteristics of the CAFE study cohort have been reported previously [14], but in brief, there were 74 cases (43% male) and 86 controls (61% male) in the residual sample of 160, of whom 76 were females (47.5%). At baseline, the mean age was 75.6 years, mean duration of NVAF from diagnosis (cases) was 677 days (SD = 531.4 days) and mean duration of AF 598 days. Stroke risk for NVAF cases applying the SPAF model [33] was high in 49.4%, intermediate in 16.3% and low in 34.1%.

Response bias
We found no significant differences in documented co-morbidities (CHD, CHF, hypertension, diabetes, thyrotoxicosis, Parkinson’s disease, peripheral vascular disease and depression) between those who agreed to participate and those who declined. At baseline, female non-responders (median age 77 years) were significantly older than responders (median age 77 years, p = 0.001), and non-responders had significantly less CHD (29% of non-responders versus 37%, p = 0.009). Of the 305 participants followed up, 16 died, 24 refused and 18 were too ill at 12 months (34, 40 and 70 respectively at 36 months; Figure 1). Two participants were lost to follow-up due to development of dementia. There were no significant differences in attrition rates for NVAF cases and controls at 12 or 36 months. At 12 months, there were no significant differences between responders (those followed-up) and non-responders for age, gender, education or documented co-morbidities listed above, the only significant difference at 12 months being the physical function, role, physical and general health domains of
Is AF linked with cognitive decline?

Figure 1. Flowchart of attrition for CAFÉ study cohort.

Repeated measures analysis of variance

The effect of time and AF on cognitive decline at 12 months and 36 months, was tested using a general linear model (repeated measures analysis of variance). Before selecting the final model and to examine the effect of age, educational attainment, and stroke risk (for NVAF only), these three variables were entered into the model as covariates. Subsequent analyses indicated that none of these factors influenced the results of cognitive tests. Extensive additional analysis confirmed that the following confounding factors also had no effect on the relationship between NVAF and cognitive decline: duration of AF, CHD, diabetes, hypertension, cholesterol, SF-36.

Effect of atrial fibrillation

Baseline values for all cognitive function tests were not significantly different between cases and controls, as previously reported [14]. In order to test the effect of group (AF or control) on cognitive functioning, we introduced this variable as a between-subject factor. In 18 of the 19 tests there was no significant effect for group; indeed most of the mean scores were very similar (Table 2). However, there was a statistically significant decline for the AF group when compared to the control group on one element of the map search test, although this result is in isolation and is not supported by any other measures.

Analysis by anti-thrombotic therapy at 12 and 36 months

At 12 months, 46 cases (32%) were on aspirin, 73 (51%) were on warfarin, 24 (17%) were on neither, and one patient was receiving both. Forty-eight controls (30%) were on aspirin, one took both aspirin and warfarin and 112 (70%) were receiving neither. At 36 months, seventeen cases (23%) were on aspirin, 45 (61%) were receiving warfarin, and 12 (16%) took neither. Twenty-six controls (30%) were on aspirin, none were on warfarin, and 60 controls (70%) were not receiving anti-platelet therapy. When cases taking aspirin, warfarin and neither therapy were compared at each time point, there were no statistically significant differences between neuropsychological test scores of each sub-group. Sub-groups of controls on aspirin or no anti-thrombotic therapy similarly showed no significant differences in change in test scores. Overall, there were no significant differences in cognitive test results between any of the five sub-groups of cases and controls.

Analysis by stroke risk stratification at 12 and 36 months (AF cases)

Results for neuropsychological tests were compared for the sub-groups of AF cases at high, intermediate and
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Table 1. Changes in test scores over time for all participants (cases and controls; n = 160)

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline to 12 months (p-value)</th>
<th>Baseline to 36 months (p-value)</th>
<th>12 to 36 months (p-value)</th>
<th>Positive change</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.02 (1.0)</td>
<td>−1.3 (&lt;0.001)</td>
<td>−1.3 (&lt;0.001)</td>
<td>Yes</td>
</tr>
<tr>
<td>Logical memory immediate (raw)</td>
<td>1.2 (0.002)</td>
<td>2.7 (&lt;0.001)</td>
<td>1.5 (&lt;0.001)</td>
<td>Yes</td>
</tr>
<tr>
<td>Logical memory immediate (%)</td>
<td>4.3 (0.18)</td>
<td>15.6 (&lt;0.001)</td>
<td>11.3 (&lt;0.001)</td>
<td>Yes</td>
</tr>
<tr>
<td>Logical memory delayed (raw)</td>
<td>0.7 (0.15)</td>
<td>3.7 (&lt;0.001)</td>
<td>3.0 (&lt;0.001)</td>
<td>Yes</td>
</tr>
<tr>
<td>Logical memory delayed (%)</td>
<td>3.3 (0.70)</td>
<td>16.4 (&lt;0.001)</td>
<td>13.0 (&lt;0.001)</td>
<td>Yes</td>
</tr>
<tr>
<td>Rey figure copy</td>
<td>−0.9 (0.10)</td>
<td>0.4 (0.75)</td>
<td>1.3 (0.004)</td>
<td>Yes</td>
</tr>
<tr>
<td>Rey figure delayed</td>
<td>−0.2 (1.0)</td>
<td>−0.7 (0.23)</td>
<td>−0.5 (0.58)</td>
<td>Yes</td>
</tr>
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<td>−1.4 (0.26)</td>
<td>−2.0 (0.03)</td>
<td>Yes</td>
</tr>
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<td>0.7 (0.78)</td>
<td>−1.7 (0.05)</td>
<td>−2.4 (0.001)</td>
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</tr>
<tr>
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<td>−1.6 (0.16)</td>
<td>0.05 (1.0)</td>
<td>Yes</td>
</tr>
<tr>
<td>Map search 2 min right</td>
<td>0.6 (1.0)</td>
<td>0.9 (0.95)</td>
<td>0.2 (1.0)</td>
<td>Yes</td>
</tr>
<tr>
<td>Telephone task no. of targets</td>
<td>0.2 (0.9)</td>
<td>0.1 (1.0)</td>
<td>−0.1 (1.0)</td>
<td>Yes</td>
</tr>
<tr>
<td>Telephone task time taken</td>
<td>−5.5 (0.02)</td>
<td>3.8 (0.2)</td>
<td>9.3 (&lt;0.001)</td>
<td>No</td>
</tr>
<tr>
<td>Telephone task dual task decre</td>
<td>−0.1 (1.0)</td>
<td>−0.6 (0.22)</td>
<td>−0.5 (0.5)</td>
<td>No</td>
</tr>
<tr>
<td>NART no. of errors</td>
<td>1.3 (0.003)</td>
<td>−1.9 (&lt;0.001)</td>
<td>−3.1 (&lt;0.001)</td>
<td>No</td>
</tr>
<tr>
<td>NART predicted IQ</td>
<td>−1.8 (&lt;0.001)</td>
<td>2.4 (&lt;0.001)</td>
<td>4.2 (&lt;0.001)</td>
<td>Yes</td>
</tr>
<tr>
<td>Digit span</td>
<td>−0.6 (0.2)</td>
<td>−0.3 (0.6)</td>
<td>0.3 (0.66)</td>
<td>Yes</td>
</tr>
<tr>
<td>PASAT 4 s</td>
<td>−0.6 (1.0)</td>
<td>−10.1 (&lt;0.001)</td>
<td>−9.5 (&lt;0.001)</td>
<td>Yes</td>
</tr>
<tr>
<td>PASAT 2 s</td>
<td>−4.1 (&lt;0.001)</td>
<td>−10.0 (&lt;0.001)</td>
<td>−5.9 (&lt;0.001)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

low risk of stroke. Overall there was no consistent trend for differences in test scores between the three subgroups. Further details of this analysis can be found in Appendix 2 of the supplementary data on the journal website (http://www.ageing.oxfordjournals.org.uk).

Discussion

This is the largest longitudinal cohort study comparing cognitive function over time in older people with NVAF with those in sinus rhythm and adds considerably to previous, predominantly cross-sectional, data. Our results demonstrate no consistent or significant change in cognitive performance over the 36-month period for the total cohort, and no consistent or significant difference in cognitive performance between cases and controls, nor between patients treated with anti-thrombotic therapies. These findings support the null hypothesis that decline in cognitive function over time in people with NVAF is no different to that of controls.

The findings from this study conflict with previous cross-sectional studies. The cross-sectional element of the CAFE study showed no difference in baseline cognitive function in a community-based cohort of older people with NVAF when compared with matched controls in sinus rhythm [14]. However, most of the earlier studies used smaller sample sizes, apart from the Rotterdam study, which included 195 AF cases [9]. Furthermore, these studies did not include matched controls, employed less extensive cognitive testing, often recruited from highly selected populations and included patients with longer-standing AF [7–12]. No previous high quality longitudinal studies of this research question have been published, and no studies with comparable follow-up are known to the authors.

Limitations to this study included the neuropsychological tests employed. There is some evidence that vascular cognitive impairment is associated with deficits in executive function, attention and speed of information processing more than other domains [36]. Therefore, ideally, the CAFE neuropsychological test battery would have included more extensive evaluation of executive function. The CAFE battery contained several valid assessments of attention and speed of information processing, but it would have been useful to have more such measures, such as computerised tests, since change in speed of processing is also reported to be a relatively early feature in the natural history of cognitive decline [36]. However, the speed tests that were performed in CAFE did not show significantly greater change over time than tests of other domains.

Attrition rates were reasonable at 12 months and relatively high at 36 months (upto 59%). However, compared to other studies of older cohorts, with attrition rates up to 80%, these attrition rates are not excessive and not surprising, given the cohort involved [37]. Much of the attrition is inevitable and would be a feature of any cohort study in such a population. The study design and follow-up minimised attrition and is much less than other reported studies. In our analysis, we compared differences between those who did and did not complete follow-up assessments. There was no differential loss to follow up with regard to gender, CHD or other vascular risk factors at either 12 or 36 months. There were differences in age and educational level between the responders and non-responders at 36 months, but analysis confirmed that these findings did not influence the results of the cognitive tests. Similarly, differences in health status (SF-36) between those who did and did not undergo follow up assessments had no effect on the results. Loss to follow-up was no more likely in cases than in controls.
It has been postulated that NVAF predisposes to cognitive impairment as a result of occult cerebrovascular disease; previous work documents associations between NVAF and silent cerebral infarction [4–6]. Ideally this study would have included cranial magnetic resonance imaging (MRI) of all or some participants, looking for evidence of silent cerebral infarction or other possible underlying pathological mechanisms. Unfortunately, lack of resources made this impossible. It is of interest to note a recent cross-sectional analysis of Framingham study data demonstrating that individuals with a higher 10-year risk of stroke performed less well on neuropsychological testing. Although not specifically designed to look at NVAF, this study found that the prevalence of NVAF in 65 people with no prior history of stroke or dementia was associated with poorer performance on tests of abstract reasoning and visuo-spatial memory [39]. In the CAFE study cohort, however, stratification of NVAF cases using SPAF criteria failed to show an increased likelihood of cognitive decline in people at the highest risk of stroke. Evidence of the potential causative mechanism would have been most helpful had our study confirmed a difference in cognitive function in NVAF compared with sinus rhythm. Nevertheless, despite the lack of brain imaging, any potential confounding effects of CHD and other vascular risk factors were thoroughly explored in the analysis.

Although an inception cohort study would have been the most robust methodology with which to examine change in cognition over time, this was not feasible since NVAF is often asymptomatic and detected opportunistically [13, 38]. We therefore chose to include NVAF cases of fairly recent onset. It is possible that if we had included people with NVAF of known duration longer than 5 years, we may have found evidence of cognitive decline over time.

### Table 2. Mean test scores at baseline, 12 and 36 months

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline mean (SD)</th>
<th>12 months mean (SD)</th>
<th>36 months mean (SD)</th>
<th>p-value for overall difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AF Control AF Control</td>
<td>AF Control AF Control</td>
<td>AF Control AF Control</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>28.7 (1.5) 28.7 (1.6)</td>
<td>28.8 (1.8) 28.7 (1.6)</td>
<td>27.5 (2.0) 27.3 (2.2)</td>
<td>0.71</td>
</tr>
<tr>
<td>Logical memory immediate (raw)</td>
<td>15.3 (5.7) 16.1 (5.6)</td>
<td>16.6 (5.4) 17.2 (5.4)</td>
<td>18.6 (6.2) 18.3 (7.2)</td>
<td>0.70</td>
</tr>
<tr>
<td>Logical memory immediate (%)</td>
<td>27.7 (24.7) 29.5 (24.1)</td>
<td>31.4 (23.4) 34.3 (24.2)</td>
<td>45.4 (28.2) 42.9 (31.0)</td>
<td>0.83</td>
</tr>
<tr>
<td>Logical memory delayed (raw)</td>
<td>11.8 (6.4) 12.1 (5.8)</td>
<td>12.5 (5.7) 12.9 (6.2)</td>
<td>15.5 (7.4) 15.8 (8.2)</td>
<td>0.73</td>
</tr>
<tr>
<td>Logical memory delayed (%)</td>
<td>40.1 (24.3) 40.9 (22.2)</td>
<td>42.5 (20.1) 45.2 (22.2)</td>
<td>57.5 (26.6) 56.4 (27.1)</td>
<td>0.81</td>
</tr>
<tr>
<td>Rey figure copy</td>
<td>32.0 (4.2) 31.5 (5.6)</td>
<td>30.8 (4.9) 30.9 (5.5)</td>
<td>32.0 (6.0) 32.3 (5.1)</td>
<td>0.97</td>
</tr>
<tr>
<td>Rey figure delayed</td>
<td>12.6 (6.5) 13.9 (7.1)</td>
<td>13.4 (6.4) 12.9 (6.2)</td>
<td>12.8 (6.1) 12.4 (5.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Map search 1 min left</td>
<td>17.6 (8.1) 18.6 (9.7)</td>
<td>16.7 (10.2) 20.7 (9.3)</td>
<td>14.7 (9.1) 18.7 (8.7)</td>
<td>0.008 *</td>
</tr>
<tr>
<td>Map search 1 min right</td>
<td>5.3 (7.4) 5.9 (8.1)</td>
<td>6.7 (8.3) 5.9 (7.8)</td>
<td>4.3 (6.6) 3.6 (6.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Map search 2 min left</td>
<td>9.4 (7.3) 10.1 (8.5)</td>
<td>8.2 (6.8) 7.9 (6.8)</td>
<td>8.7 (7.7) 7.6 (6.5)</td>
<td>0.75</td>
</tr>
<tr>
<td>Map search 2 min right</td>
<td>10.1 (8.5) 10.6 (9.7)</td>
<td>10.3 (8.3) 11.7 (8.9)</td>
<td>9.7 (8.8) 12.8 (9.7)</td>
<td>0.12</td>
</tr>
<tr>
<td>Telephone task no of targets</td>
<td>17.5 (3.9) 17.7 (2.6)</td>
<td>17.7 (2.2) 17.8 (5.4)</td>
<td>17.8 (3.6) 17.7 (3.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>Telephone task time taken</td>
<td>91.0 (24.9) 85.1 (23.7)</td>
<td>84.5 (23.7) 84.5 (23.1)</td>
<td>92.9 (23.7) 90.7 (17.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>Telephone task dual task</td>
<td>2.2 (2.4) 2.4 (2.0)</td>
<td>2.4 (2.1) 2.3 (2.4)</td>
<td>2.0 (2.3) 1.6 (3.9)</td>
<td>0.92</td>
</tr>
<tr>
<td>NART no of errors</td>
<td>20.2 (9.3) 20.2 (9.9)</td>
<td>22.0 (9.6) 21.1 (10.5)</td>
<td>18.3 (8.0) 18.5 (9.8)</td>
<td>0.87</td>
</tr>
<tr>
<td>NART predicted IQ</td>
<td>106 (11.4) 105 (12.2)</td>
<td>103 (11.9) 104 (13.3)</td>
<td>108 (9.9) 108 (12.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>Digit span</td>
<td>14.0 (3.5) 14.2 (4.0)</td>
<td>13.4 (3.5) 13.7 (3.1)</td>
<td>13.9 (3.9) 13.7 (3.8)</td>
<td>0.93</td>
</tr>
<tr>
<td>PASAT 4 s</td>
<td>29.9 (17.8) 30.9 (18.3)</td>
<td>30.1 (19.0) 29.4 (21.0)</td>
<td>19.9 (22.5) 20.7 (23.3)</td>
<td>0.90</td>
</tr>
<tr>
<td>PASAT 2 s</td>
<td>11.4 (11.6) 14.0 (14.3)</td>
<td>7.0 (11.1) 10.2 (14.5)</td>
<td>2.5 (6.5) 2.9 (9.2)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

*Significant p<0.01.
Cognitive function did not appear to be affected by use of antithrombotic therapy. We followed up a cohort of older people for 3 years and found no evidence of increased cognitive decline in those with NVAF compared with controls in sinus rhythm. Cognitive function did not appear to be affected by use of anti-thrombotic therapy.

Key points
- Previous research suggests an association between NVAF and cognitive decline or dementia.
- We followed up a cohort of older people for 3 years and found no evidence of increased cognitive decline in those with NVAF compared with controls in sinus rhythm.
- Cognitive function did not appear to be affected by use of anti-thrombotic therapy.

Acknowledgements
We are very grateful to the patients who participated in this study, to the participant general practitioners and their staff and to Professor Ian Robertson (Department of Psychology, Trinity College, Dublin) for advice on the cognitive test battery. We wish to acknowledge the hard work provided by Angela Farrell and Alyson Hutchinson, the CAFE research nurses and Emma Hutchinson and Laura Stokoe, the project secretaries.

Conflict of interest
All authors of this manuscript confirm that there are no competing interests or financial disclosures to declare.

Author contributions
JO'C and RT devised the study. All authors contributed to the design of the study protocol. HP was responsible for recruitment of participants and data collection. Data analysis was undertaken by HP and AH. All authors were involved in interpretation of results, preparation of the manuscript and approval of the final version of the paper. JO'C will act as guarantor of the work.

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The funders of this study were not involved in any aspect of the design, conduct, analysis or reporting of the work.

Prior presentation
This paper was presented at the British Geriatrics Society Autumn Meeting, Harrogate, in October 2005, and is published in abstract form in 'Age and Ageing'.

References
The long list of references supporting this article has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website http://www.ageing.oxfordjournals.org as Appendix 3.

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