

Correlates of frailty in Alzheimer's disease and mild cognitive impairment[†]

SIR—The global prevalence of dementia is rising with Alzheimer's disease (AD) accounting for 50–60% of all cases and mild cognitive impairment (MCI) its precursor [1, 2]. Although the clinical hallmark of AD is progressive loss of memory and cognition, several studies have also shown changes in mobility and body composition suggesting frailty [3, 4]. Frailty represents age-related reduction in physiological reserve and resistance to stressors that can be delineated from comorbidity [5, 6]. It infers increased risk of health decline, disability and mortality regardless of concurrent illnesses. Intervention in the early stages may lead to reversal of frailty and prevent some of its adverse outcomes [6]. Individual components of frailty; impaired grip strength, slowed gait and low body mass index (BMI), have been shown to predict development of dementia and are associated with incident MCI [7–10]. The frailty syndrome within cognitively impaired patients may represent an important area for intervention that has yet been adequately investigated. A diagnosis of AD or MCI can mean considerable heterogeneity in terms of age, comorbidity, course of illness, cognitive impairment, functional limitations and abnormalities of behaviour. This study enables a consideration of the relation, if any, between frailty and these domains of clinical heterogeneity in a group of patients with AD and MCI.

Methods

Participants were recruited through the cross-sectional Enhancing Care in Alzheimer's Disease (ECAD) study at the memory clinic of St James's University Hospital, a Trinity College affiliated hospital in Dublin, Ireland [11]. Inclusion criteria were community-dwelling persons of age >55 years with a diagnosis of probable AD or amnesic MCI. Patients were excluded if they had a significant independent cause of disability (e.g. Parkinson's disease or dense hemiplegia). Ethics approval was obtained. Probable AD was diagnosed according to the NINCDS-ADRDA criteria and MCI according to international consensus criteria [12, 13]. Diagnoses were reviewed and Mini-Mental State Examination (MMSE) conducted at the time of recruitment [14]. Sociodemographic and medical details to include all known comorbid illnesses were collected as part of a structured questionnaire. Patient function was assessed with the Disability Assessment for Dementia scale (DAD) and neuropsychiatric symptoms with the Neuropsychiatric Inventory (NPI) [15, 16]. Severity of illness was assessed using the Washington University Clinical Dementia Rating scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score [17].

[†]This work has been presented at the 6th Congress of the European Union Geriatric Medicine Society 2010 for which the President's Medal for best poster presentation was awarded.

Frailty

Frailty was measured using the Biological Syndrome Model [5, 18]. Shrinking was defined as a BMI of ≤ 18.5 kg/m². Exhaustion was defined by two questions from the Center for Epidemiologic Studies Depression scale (CES-D), 'I felt that everything I did was an effort', 'I could not get going' [19]. One of four responses were chosen, depicting frequency of occurrence in last week, giving a score of 0–3. Subjects answering '2' or '3' to either question were categorized as frail. Slowness was measured by usual pace walking speed and weakness by grip strength using cut points from the Cardiovascular Health Study [20]. Low activity was defined by kilocalories expended per week, <383 kcs for men and <270 kcs for women, based on responses to the Minnesota leisure time activity questionnaire [21]. Primary caregivers of the cognitively impaired participant confirmed all self-report criteria. Frailty score represented an ordinal variable of six categories ranging from 0 indicating completely robust with no frailty criteria present to five representing complete frailty. Participants with 0–1 criterion present could be determined as non-frail, those with two frailty criteria to be intermediately frail and those with three or more criteria to be fully frail [22].

Statistical analysis

The collected data were analysed using the SPSS 16.0 statistical package program. Frailty was included in all analysis as an ordinal variable with six categories from 0 to 5. Bivariate analysis using the Spearman correlation coefficient was performed to assess the strength of association between frailty and our explanatory factors which represented markers of clinical heterogeneity in our sample, to include; age, number of comorbid illnesses, cognitive impairment, a measure of global illness severity, functional limitations and neuropsychiatric symptoms. A proportional odds ratio model was then constructed to evaluate the relationship between frailty and the explanatory factors. Variables that on bivariate analyses were associated with frailty were entered into the model determined by the strength of their association. We set the critical value for significance in all analysis at $P < 0.05$. Test of parallel lines was completed to test the proportional odds assumption and the validity of our logistic regression model.

Results

A total of 115 patients were assessed, 44 men and 71 women. Ninety-five participants had a diagnosis of AD and 20 a diagnosis of MCI. Mean age was 74 years and mean MMSE was 20. Using the definitions of robust, intermediately frail and frail as described in the methodology, 51.3% of patients were classified as robust or not-frail, while 48.7% were at an intermediate or complete stage of frailty (29.6% intermediately frail, 19.1% fully frail). The only significant difference in frail criteria between groups

was in the category of weight loss which occurred more frequently in the AD group (Fisher's exact test, $P = 0.04$). Given the pathology was a binary variable (patients either had MCI or AD) it was tested as an additional predictor variable for frailty using a proportional odds ratio model. Frailty was not significantly different in either group (OR = 2.15, CI 0.88, 5.23, $P = 0.092$). Therefore, it was deemed both groups could be pooled for the analysis.

There was no significant correlation between frailty and gender in our sample (Spearman's rho, $P = 0.353$). Table 1 shows the explanatory variables that were significantly associated with frailty on bivariate analysis. Deteriorating functional ability, increasing neuropsychiatric symptoms, a higher number of medical comorbidities, increasing illness severity, declining cognitive scores and advancing age all correlated with escalating frailty. Having identified these significant associations we conducted ordinal logistic regression. A proportional odds model was constructed to include the variables described in Table 1 to determine the key correlates of frailty in our cognitively impaired older cohort. (Table 2) Increasing number of medical comorbidities and advancing age were retained as the factors positively associated with escalating frailty. For each additional comorbid illness, the expected odds of increasing frailty were 1.69 greater. (CI 1.24, 2.31, $P = 0.001$) With each advancing year, the odds of increasing frailty were 1.07 times greater. (CI 1.02, 1.12, $P = 0.007$). Test of parallel lines was completed to verify the proportional odds assumption in our logistic regression model. No difference was identified in the coefficients between models and so the validity of our model was confirmed. ($P = 0.999$)

Discussion

We present preliminary data that suggest frailty is a distinct entity measurable in AD and MCI that correlates with age and increasing comorbid illness rather than markers of

Table 2. Proportional odds model depicting key correlates of frailty

Variable	Estimate	Std. Error	Sig.	OR	95% Confidence interval	
					Lower	Upper
No. of comorbidities	0.526	0.159	0.001**	1.69	1.24	2.31
Age	0.063	0.023	0.007**	1.07	1.02	1.12
DAD score ^a	0.013	0.028	0.648	1.01	0.96	1.07
NPI score ^b	0.010	0.009	0.233	1.01	0.99	1.03
CDR-SOB ^c	0.049	0.122	0.690	1.05	0.83	1.33
MMSE ^d	0.041	0.061	0.503	0.96	0.85	1.08

^aPatient function was assessed with the Disability Assessment for Dementia scale.

^bNeuropsychiatric symptoms were measured with the Neuropsychiatric Inventory (NPI).

^cSeverity of illness was assessed using the Washington University Clinical Dementia Rating scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score.

^dCognition was measured using the Mini-Mental State Examination.

**Correlation is significant at the 0.01 level (two-tailed).

cognitive decline and illness severity. An association between frailty and ageing has already been shown in older cohorts [23]. Our findings suggest that in the cognitively impaired it continues to be an important correlation, other factors notwithstanding. Increasing burden of comorbid illness inferring a higher likelihood of frailty is also consistent with the current theory, where the cumulative effect of multiple age and disease-related impairments leads to a degradation of physiological systems. Frailty emerges from this vulnerable health state and may contribute to further decline in functional performance and an increased risk of poorer outcomes [24, 25] Optimized management of comorbid illness in dementia patients and adoption of stringent preventative health strategies in those at the stage of MCI may play a role in minimizing the health impact of frailty in this group.

The longitudinal association between frailty, incident MCI and AD has previously been reported in community-dwelling older persons [10, 26]. Further work, however, has shown the risk of developing dementia is five-fold in those with cognitive impairment irrespective of their frailty status [27]. This suggests frailty is not necessarily a predictor of dementia but may represent a separate pathophysiological process, independent of cognitive decline. Our results support this hypothesis. Markers of cognitive decline and illness severity did not retain significance with advancing frailty in our analysis. Other groups evaluating frailty beyond the biological syndrome model have included cognitive impairment as an inherent criterion for frailty. Our findings, however, show a high proportion of robust and intermediately frail participants within our cognitively impaired group. Not all cognitively impaired persons are frail. The importance of this lies in the modifiable nature of frailty and its potential role as a novel target for intervention. We hypothesize that the coincidence of cognitive

Table 1. Correlates of frailty on bivariate analysis

Variable	Spearman's Rho correlation coefficient	Significance
DAD score ^a	0.427	$P < 0.001^{**}$
NPI score ^b	0.333	$P = 0.001^{**}$
No. of comorbidities	0.285	$P = 0.002^{**}$
CDR-SOB ^c	0.270	$P = 0.004^{**}$
MMSE ^d	-0.223	$P = 0.019^{*}$
Age	0.199	$P = 0.045^{*}$

^aPatient function was assessed with the Disability Assessment for Dementia scale.

^bNeuropsychiatric symptoms were measured with the Neuropsychiatric Inventory (NPI).

^cSeverity of illness was assessed using the Washington University Clinical Dementia Rating scale (CDR) a global assessment instrument that yields a detailed quantitative general index in the form of a sum of boxes (SOB) score.

^dCognition was measured using the Mini-Mental State Examination.

*Correlation is significant at the 0.05 level (two-tailed).

**Correlation is significant at the 0.01 level (two-tailed).

impairment and frailty may accelerate the trajectory of decline in dementia. Preventive or treatment interventions focused on frailty independent of cognitive impairment could be effective at reducing poorer outcomes at a number of points on the pathway from MCI to end-stage dementia.

Limitations of our work include its cross-sectional nature. The validity of our results and hypotheses need to be evaluated in a longitudinal context. Further limitation is our combination of both AD and MCI participants, MCI may never in fact transition to AD. However, our interest lies in the investigation of frailty in those with established cognitive decline and our analysis identified the odds of frailty did not significantly differ between either group. This contributed to our rationale of combining both groups for evaluation. We also acknowledge our results may not be generalizable to a larger population. Findings from our population of patients with MCI and mostly mild to moderate AD may not be readily extrapolated to patients with more severe cognitive impairment. Similarly those persons who present to memory clinics may have more functional impairments or be frailer than other persons with MCI or AD. Another critical issue involves the assessment of dementia patients and the validity of the self-report measures used. To address this, we cross-checked any self-report measures with primary caregivers to ensure the accuracy of our data prior to the analysis.

Key points

- Detection of frailty at an early point is possible in dementia patients at various stages including pre-dementia states.
- Emerging frailty is closely associated with age and increasing comorbidity in cognitively impaired patients.
- Frailty may be a target for intervention to address adverse consequences of the combined effect of frailty and cognitive decline.

Conflicts of interest

None declared.

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Alcohol use of older adults: drinking alcohol for medicinal purposes

SIR—Of Finnish adults aged 65–84 years, 54% of females and 77% of males had consumed alcohol in the preceding year in 2007 [1–3]. Older adults are sensitive to the effects of alcohol as a consequence of the physiological changes associated with ageing, a high prevalence of diseases and the concomitant use of multiple drugs. Older adults also experience higher blood alcohol concentrations for a given amount of alcohol than younger adults due to changes in body mass [4].

Research on older people's use of alcohol has focused mainly on problem-drinking and consequent health problems [5, 6]. However, there is also public awareness about

the possible health promoting effects of moderate alcohol consumption demonstrated in epidemiological studies [7–13]. Alcohol has been used throughout history for medicinal purposes; since antiquity, wine has been believed to stimulate appetite and digestion [14].

Very few studies are available on how older people perceive the health effects of alcohol, and how they use alcohol for medicinal purposes [15]. The aim of this study was to investigate the medicinal use of alcohol by individuals aged 65 years and older. We investigated (i) the prevalence of alcohol consumption as self-medication, (ii) associated factors and (iii) the reasons for which alcohol is used to self-medicate.

Methods

In May 2007, a postal questionnaire was sent to computer-generated random sample of 2,100 older persons (≥65 years) from the Espoo Population Register, and re-sent after 3 months to non-respondents. Espoo is a city with 240,000 inhabitants (10% >64 years olds). The number of the potential respondents was 1973 when those in permanent institutional care ($n=92$), deceased ($n=16$), with native language other than Finnish/Swedish ($n=31$) or with unknown address ($n=14$) were excluded. Altogether 1,395 individuals returned the questionnaire (response rate 71.6%). The local ethics committee approved the study protocol.

A structured questionnaire was piloted prior to the postal survey on 17 elderly individuals to ensure that the questions were easy to understand. The question items concerning demographics and health-related variables were retrieved from our previous epidemiological studies [16–18]. The questionnaire consisted of demographic and health-related variables. In addition, respondents were asked to list any medical diagnoses received from their doctors. Some categorisations were made for health-related factors and current use of medications. Charlson comorbidity index was constructed from medical diagnoses. It is a weighted index taking into account the number and severity of comorbid conditions [19]. To analyse the number of regularly prescribed drugs, participants were inquired to list their prescribed drugs.

Alcohol consumption was charted with several questions developed from the clinical guidelines for alcohol use in older adults [20] and the AUDIT (alcohol use disorders identification test) [21]. Quantity and frequency were ascertained by asking: 'How often do you have a drink containing alcohol, including beer, cider, wine, or liquor; spirits?', and 'On a typical day when you drink, how many drinks do you have?' (1 drink = can or bottle (330 ml) of beer, 12 cl of wine, 4 cl of liquor; spirits (one shot-glass), or 8 cl of sherry or madeira or aperitif. Alcohol-related problems were inquired: (i) 'Have you forgotten to take your medication when you have used alcohol (never/sometimes/often)?'; (ii) 'Has any of your relatives or friends been