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Transient neurological symptoms in the older population: report of a prospective cohort study—the Medical Research Council Cognitive Function and Ageing Study (CFAS)

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ABSTRACT

Objective: Transient ischaemic attack (TIA) is a recognised risk factor for stroke in the older population requiring timely assessment and treatment by a specialist. The need for such TIA services is driven by the epidemiology of transient neurological symptoms, which may not be caused by TIA. We report prevalence and incidence of transient neurological symptoms in a large UK cohort study of older people.

Design: Longitudinal cohort study

Setting: The Medical Research Council Cognitive Function and Aging Study (CFAS) is a population representative study based on six centres across England and Wales.

Participants: Random samples of people in their 65th year were obtained from Family Health Service Authority lists. The participation rate was 80% (n=13 004). Interview at baseline included questions about stroke and three transient neurological symptoms, repeated in a subsample after 2 years. Patients were flagged for mortality.

Main outcome measures: Prevalence and 2-year incidence of transient neurological symptoms.

Results: In 11 903 participants without a history of stroke, 271 (2.3%) reported transient problems with speech, 872 (7.6%) with sight and 596 (5.1%) weakness in a limb with 1456 (12.7%) reporting at least one symptom. Of those reinterviewed (n=6748), 675 (9.8%) reported at least one symptom over 2 years.

Conclusions: Lifetime prevalence and incidence of transient neurological symptoms in people aged 65 years and over is high and is substantially greater than the incidence of TIA in hospital-based and population-based studies. These high rates of transient neurological symptoms in the community in the older population should be considered when planning TIA services.

ARTICLE SUMMARY

Article focus

- Prompt initiation of secondary prevention following transient ischaemic attack (TIA) is associated with up to 80% reduction in risk of subsequent stroke.
- Many people presenting to specialist TIA clinics with transient neurological symptoms do not have TIA.
- The prevalence and incidence of transient neurological symptoms (as opposed to TIA) in older age groups is unknown.

Key messages

- In a large multicentred community-based study representative of the older population in the UK, we found a high prevalence and incidence of transient neurological symptoms, significantly greater than that of TIAs in hospital-based and population-based studies.
- These high rates of transient neurological symptoms in the community in the older population should be considered when planning TIA services.

Strengths and limitations of this study

- Previous studies of incidence and prevalence of transient neurological symptoms have mostly been conducted in populations not representative of older age groups where TIA is most common and few have been undertaken in UK populations.
- The incidence of transient neurological symptoms in the study was determined in people without severe cognitive impairment, and may be an underestimation, since cognitive impairment can be a manifestation of vascular disease. The wording of questions to identify transient neurological symptoms may have picked up some people who had symptoms lasting more than 24 h.

INTRODUCTION

Transient ischaemic attack (TIA) is an established and powerful risk factor for stroke. Eight per cent of patients who have TIA suffer from stroke within 7 days, many within 48 h.[1 2] Immediate specialist assessment and treatment is associated with substantial reductions in this early risk of stroke,[3] and is recommended for people with suspected TIA.[4]

As awareness grows of the urgency of early management of TIA among both primary care practitioners and the general public,[5] more patients with symptoms suggestive of TIA are likely to present to primary and secondary care services. Need for specialist services will be driven by incidence of symptoms that might represent TIA (ie, transient neurological symptoms) rather than the epidemiology of TIA per se. Currently about 48 000 probable or definite TIAs (transient neurological symptoms lasting less than 24 h of likely vascular aetiology) and 43 000 minor strokes (stroke events causing minimal or no neurological deficits) are managed as outpatients every year in England, but it is not clear to what extent this might be the tip of the iceberg.[6] Data are available worldwide on the prevalence and incidence of TIA.[7–11] The epidemiology in the community of transient neurological symptoms (ie, neurological symptoms of sudden onset of which TIA is a subset) is however less well defined. Previous studies of incidence and prevalence of transient neurological symptoms have mostly been conducted in populations not representative of older age groups where TIA is most common.[7 11–16] Very few have been undertaken in UK populations. While incidence of transient neurological symptoms will drive the need for specialist TIA services, prevalence of transient neurological symptoms in the community is also important. TIA is associated with a long-term increase in risk of stroke,[17 18] so there may be value in diagnosing 'old' events that have not presented to medical services in order to target secondary prevention. Hence, the importance of determining both the incidence and prevalence of transient neurological symptoms in the community.

This study reports prevalence and incidence of three common transient neurological symptoms (limb weakness, loss of speech and disturbance of vision) in a population-based multicentred cohort study in the UK (England and Wales) in those aged 65 years and over, the Medical Research Council Cognitive Function and Ageing Study (CFAS).[19]

METHODS

The Medical Research Council CFAS is a population-representative study of individuals aged 65 years and over. The study began in 1991 and was designed to determine the incidence of dementia in the older population. It has six centres across England and Wales chosen to represent the national variation of urban–rural mix, socioeconomic deprivation and rates of chronic disease.[19] Five of these with identical study designs (Oxford, Nottingham, Cambridgeshire, Gwynedd and Newcastle) are used in the present investigation. The sixth centre (Liverpool) used a different design and is therefore excluded. Random samples of people in their 65th year and above were obtained from Family Health Service Authority lists (agency responsible for maintaining registers of general practice populations at that time). The sample was stratified by age (65–74, 75 years and over) and equal numbers were randomly selected from these groups with the aim of recruiting 2500 to each centre. All study centres obtained ethical approval from local research committees (REC Ref: 05/MRE05/37). Full details of methodology are available elsewhere.[19]

Eligible participants (or their proxies where appropriate) provided informed consent. Trained interviewers undertook baseline interviews in the participants' homes, including sociodemographic characteristics, cognitive function and disease history, including previous stroke, coronary heart disease and diabetes (full details at http://www.cfas.ac.uk). On the basis of baseline screening, the study sample was divided into two groups at baseline: people without cognitive impairment and a group consisting of those with cognitive impairment plus a stratified subsample of those without cognitive impairment. The first group underwent no further assessment at baseline and was 'rescreened' after 2 years. The second group underwent a further detailed cognitive assessment at baseline, but was not followed up for transient neurological symptoms. The estimates of prevalence of transient neurological symptoms are calculated for all people at baseline, while the incidence estimates use only the first group. All participants were flagged with the National Health Service (NHS) Central Register. Deaths and underlying causes of death attributed to stroke (International Classification of Diseases (ICD) codes 430–438) were notified to the study.

Prevalence of transient neurological symptoms

At baseline all participants were asked "Have you ever experienced sudden problems with:

1. speech, which got better after a day?
2. weakness in the arms or legs, which got better after a day?
3. sight, which got better after a day?"

Social class was determined using the Registrar General's Occupational Classification. Cognitive status was determined using the Mini-Mental State Examination (MMSE)[20] and the Automated Geriatric Examination for Computer Assisted Taxonomy (AGECAT).[21]

Incidence of transient neurological symptoms

All those in the 'rescreen' arm were asked at 2-year follow-up if they had experienced each transient neurological symptom in the past 2 years.

ANALYSIS

All analyses were carried out using STATA V.11. Inverse probability weights were used throughout to ensure that

the sample was representative of the target population. Weights were estimated with logistic regression using presence in each phase of the study as an outcome and taking into account oversampling of over-75s at baseline. Weights for incidence calculations adjust for attrition based on baseline characteristics and stratified selection into the assessment arm as appropriate. Baseline prevalence of each transient neurological symptom was calculated for age-specific strata and as a weighted percentage to provide a population estimate of prevalence for people aged 65 years and over. Associations with gender, age, social class (manual (IIIb, IV and V) and non-manual (I, II and IIIa)) and cardiovascular comorbidity were explored using logistic regression models adjusting for all other factors and cognitive function based on MMSE by score (less than 18, 18–21, 22–25 and 26–30).

Two-year incidence of transient neurological symptoms was estimated using weighted percentages of those reporting any of the symptoms during follow-up. Weights were adjusted for refusals, dropouts and for non-reassessment of people with cognitive impairment. Calculation of attrition weights for incident transient neurological symptoms excluded those who died between baseline and follow-up. These estimates are therefore applicable to the population over 65 years without severe cognitive impairment or stroke at baseline surviving at least 2 years.

RESULTS

The participation rate in the CFAS was 80% (13 004/16 258). For the prevalence analysis, participants who had a stroke at baseline (963, 7.4%) or for whom baseline information about stroke was missing (138, 1.1%) were excluded, leaving 11 903 participants. In total, 2283 of the original participants were not allocated to the 'rescreen' arm at 2 years; 754 died, 1973 declined to participate and 145 were lost to follow-up, leaving 6748 (76% response rate of potential participants) for the incidence analysis.

Table 1 shows the demographic features of participants in the CFAS, studied in this analysis at baseline. Forty per cent of participants were men and 60% were women. 12.3% of all participants reported at least one transient neurological symptom; 2.3% reported transient loss of speech, 5.1% transient weakness and 7.6% transient loss of sight.

Table 2 shows prevalence data with weighted percentages and ORs (adjusted for age, sex, social class, cognition and cardiovascular morbidities) of reported transient neurological symptoms at baseline by demographic factors and comorbidities. In total, 12.8% of men and 12% of women reported at least one of the three transient neurological symptoms of loss of speech, loss of sight or weakness. There was no significant association of gender with reporting at least one transient neurological symptom, but significantly lower odds of reporting a transient neurological symptom in the over 85 age group. The odds of reporting any transient neurological symptom were higher in those in manual compared to non-manual social classes. The presence of cardiovascular morbidities of angina and heart attack were also significantly associated with the odds of having at least one of the transient neurological symptoms.

Table 1 Demographics of participants in the Cognitive Function and Aging Study (CFAS) by sex, age, social class and comorbidity (data are counted in percentages)

	All (n=11903)		Males (n=4689)		Females (n=7214)	
	N	Per cent*	N	Per cent*	N	Per cent*
Age (years)						
65–74	5980	58.8	2635	64.5	3345	55.0
75–84	4624	32.1	1716	29.6	2908	33.8
85+	1299	9.1	338	5.9	961	11.2
Social class						
I	558	4.8	225	4.8	333	4.8
II	2988	26.1	1213	26.3	1775	25.9
IIIa	1337	11.6	456	9.9	881	12.8
IIIb	4295	37.7	1865	40.8	2430	35.5
IV	1727	14.9	650	13.9	1077	15.7
V	561	4.9	196	4.3	365	5.3
Comorbidity						
Angina	1923	16.3	878	15.3	1045	11.1
Diabetes	672	5.5	310	6.4	362	4.9
Heart attack	1139	9.5	632	13.6	507	6.8

*Weighted percentages.

There was no difference between genders with regard to reporting individual transient neurological symptoms of loss of speech, loss of sight or weakness. However, there was a significantly lower odds of reporting transient visual loss in those aged over 85 years, and an increased odds of reporting transient symptoms of weakness and loss of sight in manual compared to non-manual social classes. The presence of cardiovascular comorbidities of angina and heart attack were associated with higher odds of all three symptoms.

Table 3 shows 2-year incidence of transient neurological symptoms in respondents attending the 'rescreen'. A total of 9.8% of participants reported at least one transient neurological symptom over the past 2 years, with the highest incidence of reported transient neurological symptoms being due to loss of sight followed by weakness, with loss of speech being the least frequently reported transient neurological symptom. The incidence of each of the transient neurological symptoms was highest in the 75–84 age group and lowest in the over 85 age group.

DISCUSSION

Our findings suggest that transient neurological symptoms are common in the older population in England

Table 2 Distribution and adjusted odds of transient neurological symptoms in those aged 65 years or over in the Cognitive Function and Aging Study (CFAS) by sex, social class and comorbidity (data are counted in percentages)

	Loss of speech			Weakness			Loss of sight			At least one symptom		
	N	Per cent*	OR† (95% CI)	N	Per cent*	OR† (95% CI)	N	Per cent*	OR† (95% CI)	N	Per cent*	OR† (95% CI)
Gender												
Male	119	2.5	1.0	257	5.5	1.0	347	7.6	1.0	598	12.8	1.0
Female	152	2.2	0.9 (0.7 to 1.2)	339	4.8	0.9 (0.7 to 1.0)	525	7.6	1.0 (0.9 to 1.2)	858	12.0	1.0 (0.9 to 1.1)
Age (years)												
65–74	137	2.3	1.0	302	5.1	1.0	480	8.1	1.0	768	12.9	1.0
75–84	104	2.3	0.7 (0.7 to 1.2)	229	5.0	0.9 (0.7 to 1.1)	327	7.2	0.9 (0.7 to 1.1)	553	12.0	0.9 (0.8 to 1.0)
85+	30	2.5	0.8 (0.5 to 1.3)	65	5.4	0.9 (0.6 to 1.2)	65	5.4	0.6 (0.5 to 0.8)	134	10.4	0.7 (0.6 to 0.9)
Social class‡												
Non-manual	96	5.8	1.0	63	11.0	1.0	295	17.9	1.0	497	10.2	1.0
Manual	164	7.2	1.1 (0.9 to 1.5)	390	17.8	1.4 (1.2 to 1.7)	556	25.7	1.4 (1.2 to 1.6)	920	14.1	1.4 (1.2 to 1.6)
Comorbidity												
Angina (n=1538)	64	4.3	1.5 (1.0 to 2.2)	176	11.7	2.5 (2.0 to 3.2)	160	10.6	1.3 (1.0 to 1.6)	312	20.7	1.7 (1.4 to 1.9)
Diabetes (n=672)	28	4.0	1.4 (0.9 to 2.2)	40	6.1	1.0 (0.7 to 1.4)	66	10.1	1.3 (0.9 to 1.7)	102	15.2	1.1 (0.9 to 1.4)
Heart attack (n=1139)	52	4.7	1.8 (1.2 to 2.7)	131	10.5	1.4 (1.2 to 1.9)	119	11.5	1.4 (1.1 to 1.8)	233	12.4	1.4 (1.2 to 1.8)

*Weighted percentages.
†Adjusted for age, sex, social class, cognition and cardiovascular comorbidities.
‡Reference non-manual (I, II and IIIa) compared to manual social class (IIIb, IV and V).
156 participants had missing data on the speech questionnaire, 155 on the weakness and 154 on the sight question.

Table 3 Two-year incidence of transient neurological symptoms in the Cognitive Function and Aging Study (CFAS) in those without stroke at baseline at 2-year screening assessment, N at 2 years was 6748 (data are in N (%))

	Age (years)							
	All		65–74 (N=3657)		75–84 (N=2618)		85+ (N=473)	
Transient neurological symptoms	N	Per cent*	N	Per cent*	N	Per cent*	N	Per cent*
Loss of speech	149	2.1	55	1.5	84	3.3	10	2.0
Weakness	239	3.7	117	3.4	106	4.1	16	3.4
Loss of sight	410	6.3	214	6.3	170	6.6	26	4.5
At least one symptom	675	9.8	327	9.3	304	11.6	44	7.8

*Weighted percentage.
98 participants had missing data on the speech questionnaire, 97 on the weakness and 105 on the sight question.

and Wales, with at least 12% of people aged 65 years and over having experienced a transient neurological symptom of the arm or leg, speech or vision, which gets better after a day, and approximately 5% having experienced at least one such symptom over the course of a year. The commonest of these was transient symptoms of vision, followed by limb weakness. Those aged over 85 years reported lower rates of transient neurological symptoms, predominantly due to less frequent reporting of transient visual loss. Problems of memory and recall may have contributed to under-reporting, and higher mortality rates associated with neurological incidents to underestimation of rates of transient neurological symptoms in this age group. Chronic visual problems may have also potentially masked transient visual losses in the oldest-old population. Incidence of at least one transient neurological symptom in the CFAS population was approximately 2.6 times greater than that of confirmed TIA presenting to medical services in the Oxford Vascular (OxVASC) study in people aged over 85 years (approximately 15/1000/year), eight times greater in those aged 75–84 years (7/1000/year) and approximately 15 times greater in those aged 65–74 years (3/1000 population/year).[10]

The prevalence and incidence of transient neurological symptoms in the CFAS was somewhat higher than those found by questionnaires used in other studies internationally (mostly conducted in younger age groups), but comparable to those of Wilkinson *et al* in an over 60 age group in a US-based study.[7 12–14 16] Online supplementary table S4 shows the prevalence of sudden onset of neurological symptoms of weakness in a limb or of loss of speech or sight in previous population and community studies.[7 12–14 16] Questions used to elicit transient neurological symptoms in the CFAS are likely to have captured greater numbers of transient neurological events in the population compared with those seeking more specific vascular symptoms, or to the few studies defining more precisely the onset, offset and timing of the event.[7 12–14] While some respondents will have been describing true transient ischaemic events, it is likely that many did not have a true TIA. Validated measures to determine the presence of previous TIA are limited, and most studies of transient neurological symptoms in questionnaires overestimate true transient ischaemic attacks.[13 14 22] Wilkinson *et al*[14] suggest that around 10% of transient symptoms reported in a questionnaire are subsequently diagnosed as TIA after a neurologist's assessment. Self-reported transient neurological symptoms in other community-based studies have low positive predictive value, with higher values only in studies in outpatient populations (over 70%).[13 14 22–24] This suggests that the use of screening to identify possible past transient ischaemic attacks may generate unnecessary extra strain on primary care and secondary TIA services with limited benefit.

Patients presenting with transient neurological symptoms present considerable diagnostic dilemmas for primary care practitioners reflected in low rates of TIA diagnosis confirmation in patients referred to UK TIA clinics (over 50% being for non-TIA causes).[6 25 26] Many symptoms of TIA are non-specific and occur in non-vascular syndromes. Dizziness, ophthalmological problems, migraine, epilepsy, nerve entrapment or psychological states are the commonest non-TIA diagnoses.[25–29] Often, however, no diagnosis can be determined.[25 26] Scales such as the ABCD2[2] help determine the urgency of TIA referral, but do not distinguish TIA from non-TIA symptoms. Wilkinson *et al*[14] reported transient loss of speech and loss of sight to be more reliable than limb weakness for neurologist diagnosis of TIA, while Hart *et al*[7] found the strongest and most consistent relationship with subsequent stroke to be loss of power in an arm. Other studies suggest that the presence of certain symptoms such as headache, dizziness, loss of consciousness, memory loss, blurred vision, generalised weakness, pain in limbs and seizures make the diagnosis of TIA less likely.[14 29 30]

Study limitations

The incidence of transient neurological symptoms was determined in people without severe cognitive impairment, and may be an underestimate since cognitive impairment can be a manifestation of vascular disease.[31 32] Only three transient neurological symptoms were reported in this study. Some symptoms of TIA (eg, posterior circulation or pure sensory symptoms) were not sought. The wording of questions to identify transient

neurological symptoms may have picked up some people who had symptoms lasting more than 24 h. Such patients are nevertheless likely to draw on TIA services for further assessment. In addition, it was not possible to determine whether different transient neurological symptoms in a participant occurred simultaneously or separately in time. The problem of recall bias in these self-reports of transient symptoms needs to be considered. Questions were designed to be easily comprehensible to the older population. However, the need to consider multiple criteria when responding to a question, for example, 'sudden onset' and 'less than a day', may have led to difficulties in interpretation of the transient neurological symptoms questions for some participants. Finally, baseline and 2-year follow-up were carried out in the 1990s and changes in the rates of vascular events may have occurred since then. While the age-specific incidence of stroke appears to be declining, it is not clear that the same is true of TIA.[10 33 34] This study is more recent than many studies estimating rates of transient neurological symptoms in the population, many of which have been carried out during the 1970s or 1980s.[12–14]

CONCLUSION

In a large multicentred community-based study, highly representative of the older population in the UK and conducted in the age group where TIAs are most common, we found a high prevalence and incidence of transient neurological symptoms. The incidence of such symptoms in the community is significantly greater than that of TIAs. This highlights the need for adequate provision of TIA services and the potential importance of the development of valid diagnostic tools to assist the general practitioner and hospital doctor in better triage of people presenting with transient neurological symptoms.

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COHORT PROFILE

Cohort Profile: The Medical Research Council Cognitive Function and Ageing Study (CFAS)†

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Origin of the study

Global ageing is a recent phenomenon. Its potential impact on social and economic aspects of more affluent countries highlighted ageing as a sufficiently important issue towards which to direct resources. Discussion between the Department of Health, Medical Research Council, and experts from the scientific and medical communities resulted in the decision that brain changes, most particularly cognitive decline, dementia, and their relation to disability were key topics requiring investigation at the population level. This prompted a decision to invest in research into this area and a working group was convened, which included those with epidemiological and biostatistical expertise relevant to such investigation. Out of this working group a successful bid for the study now known as the MRC Cognitive Function and Ageing Study emerged.

Study design

The study is a six-centre multidisciplinary multiphased longitudinal design (see map, Figure 1). There are five identical sites and one with a different sampling and interview structure. This centre (Liverpool) was already funded at the time of the discussions noted above and thus started earlier than the other five centres.[1] The other five centres (Cambridgeshire, Gwynedd, Newcastle, Nottingham, and Oxford) were able to follow a standardized design and are referred to as the five identical sites. Their basic structure was a two-phase design with a screening interview followed by an assessment interview shortly afterwards, with a repeat at 2 years. The fieldwork began in 1991.[2] There are many additional features, which are more fully described on the website (see below).

The aims of the study

The aims of the study have evolved over its existence and cover a wide range including descriptive epidemiology, neuropathology, policy, molecular epidemiology, and ethics.

The main descriptive epidemiological aims include (i) the estimation of the prevalence and incidence of cognitive decline and dementia, and geographical variation in those rates; (ii) the determination of the natural history of dementia, in particular the rate of progression of cognitive decline including the distribution of the interval between the identification of cognitive impairment and death, and (iii) the identification of factors associated with differing rates of cognitive decline and with the risk of dementia.

The principal neuropathological aim was to determine the contribution of different underlying pathologies to the rates of dementia and the geographic variation in these rates and to the burden of disability. Additional aims included to: (i) determine the prevalence and severity of pathological lesions in the brain of an unselected cohort of older people with and without cognitive impairment; (ii) determine the frequency of specific pathological diagnoses in people with cognitive impairment, and (iii) correlate severity of specific pathologies with patterns of cognition, function, and behaviour in life independently of clinical and pathological diagnostic categories.

The core aim related to policy was the evaluation of the degree of disability associated with cognitive decline and impairment, and the service needs this disability generates. These needs were to be compared with the needs generated by physical impairment. The study also sought to form the basis for longer-term studies of trends over time and by birth cohort of the prevalence and incidence of cognitive decline. In addition to these aims the breadth of the data collected has allowed the study to incorporate the investigation of expectation of life in various states of health, depression, and depressive symptomatology in the older population.

The DNA resource has been incorporated in a later phase of the study. The main molecular epidemiological aim has been to support genetics studies that have sought genes associated with all dementia, Alzheimer's disease, mixed and vascular dementia, cognitive impairment and decline.

A later aim of the study was to explore the ethical and legal aspects of brain donation within a population-based sample given changing perception surrounding organ donation.

The study also aimed to act as a core resource and provide a framework to support specific sub-studies in lone or joint centres. The Resource Implication Study[3–9] utilized this framework to achieve the core policy aim (see above). Other

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Figure 1 Map of Great Britain showing CFAS centres

sub-studies include the study of Healthy Ageing[10–15] and the Network Study. This framework also extends to wider collaborations with CFAS centres contributing to European wide initiatives such as EURODEM[16] and EURODEP.[17]

What does it cover?

Because the main study is focused on cognition and dementia it has collected the necessary dimensions of physical and mental health to arrive at a study diagnosis of dementia. It now has four major themes: (i) dementia (covering all aspects including cognition), (ii) depression, (iii) disability and healthy life expectancy, and (iv) health policy and health. In addition it has particular strengths in that it is one of the very few truly population based programmes with a donation programme—individuals in the study have indicated whether they wish to contribute to brain research through the donation of their brain after death (declaration of intention to donate).

Who is in the sample?

The first aim of the study was to estimate age-specific rates of prevalence of cognitive impairment and dementia among those aged 65 and over. The population is thus all those aged 65 years and over on the index date for centre (1990, 1991), living within a specified geographical location. Background information on the demographics of the populations sampled was collected from the Office of Population Census and Surveys (OPCS), 1990–91 census now Office of National Statistics (ONS), to relate to regional and national data.

Family Health Service Authority (FHSA) lists were used as the sampling frame. The frame would be incomplete if eligible members of the population were not registered with a GP. However individuals in long-stay hospitals remain registered with their GP 2 years after institutionalization so sampling from FHSA lists ensured their inclusion. Each centre looked into the practices of long-stay hospitals in their area to confirm this. The FHSA list of individuals was used for sampling on a geographical basis. Each centre defined this area, and the study population was drawn from all those who were resident within it. Problems of inaccuracy, patients who died or moved away but were still on the FHSA list, were resolved by asking GP surgeries to check the lists. On this basis, a sample of sufficient size to yield 2500 interviews of individuals aged 65 years and over, stratified by age (equal numbers aged 65–74 and 75 plus) was chosen from the FHSA lists for each selected area (in Liverpool this was 5000 interviews stratified by sex and 5 year age band). The population is flagged at ONS for mortality and the database is updated continuously.

The follow-up has been determined by funding and the design of associated bolt-on studies. The main follow-up waves for the identical sites are captured in the audit trail shown in Figure 2, which shows the numbers for the main screen, assessment, 1 year follow-up and 2 year rescreen, new selection for assessment and further 1 year follow-up, 6 year follow-up of the assessed (with venepuncture), 8 year follow-up of those with intentions to donate, and 10 year follow-up of the total sample. In addition to this the main associated studies are the Resource Implication Study (4 centres—Cambridgeshire, Newcastle, Nottingham, Oxford), which followed those who provided care to the physically and cognitively frail at baseline, the ESRC funded Healthy Ageing Project, which interviewed in detail those who were not selected into the Resource Implication Study in Nottingham and Cambridgeshire, the Network Study conducted in Gwynedd and Liverpool to examine individuals' social networks, an embedded case–control study at 2 year incidence stage (Cambridgeshire), and the ongoing brain donation programme in all centres. This programme, in combination with the bloods taken at year 6 form the major components of the Biological Resource of the study.

Who is not in the sample?

Comprehensive analyses of those who were lost to follow-up have been conducted for all stages of the study. At baseline 19% of potential respondents refused, 6% had died, and 1% had moved out of the area. Similar percentages were found for all waves of the study. Individuals who had moved or refused had higher mortality than responders.[18] CFAS has used this attrition for a detailed investigation of attrition effects in both short and longer time intervals.[18,19]

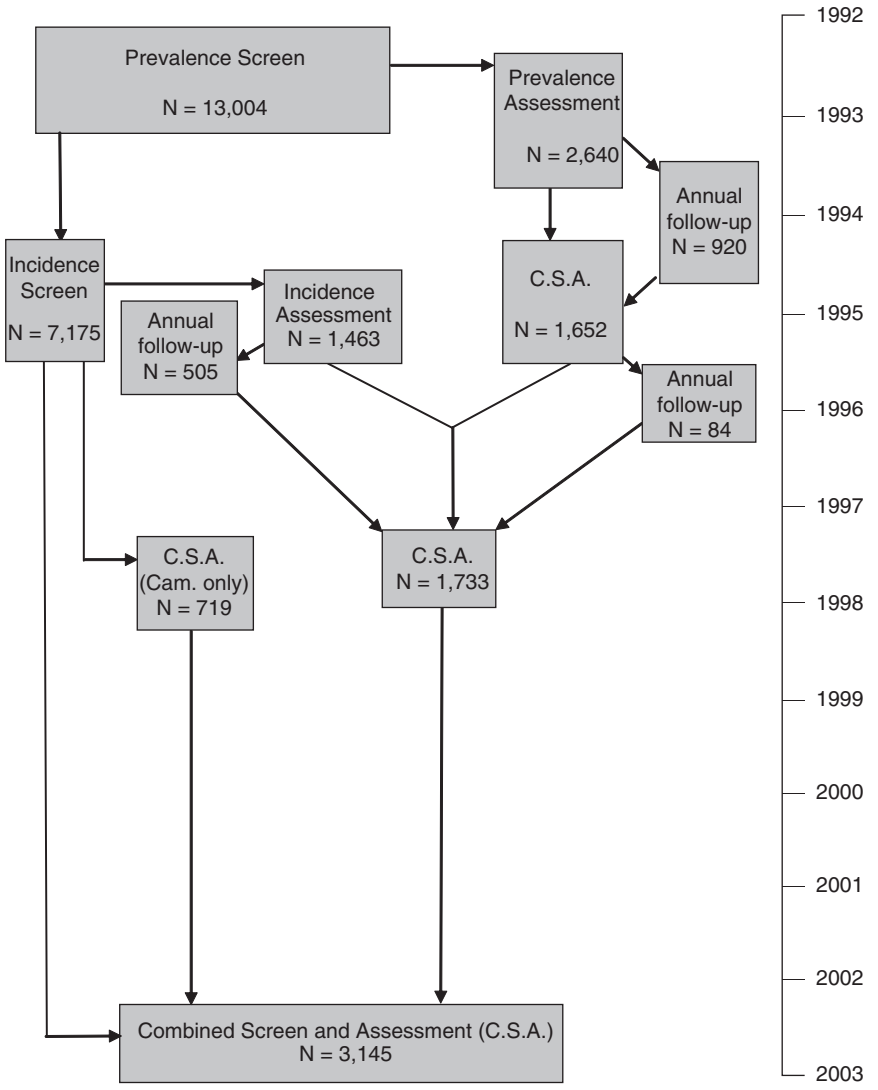

Figure 2 Time frame of CFAS interviews (identical centres)

How, when, and which interviews were conducted?

All interviews were conducted in the respondent's place of residence, using portable computers with customized software. If the interviewer felt that the respondent was frail and tiring, or becoming agitated, the short 'priority mode' set of questions could be invoked manually. Screening interviews were undertaken by lay interviewers, recruited for the purpose and trained by both the local and national coordinator. Reliability checks were made by both the local and the national coordinator. Proxy screening interviews were conducted where an interview was not possible with the named participant, owing to, for example, extreme confusion or frailty. If after four attempts to contact, an interview was not arranged, the approach was abandoned. The screening of the entire sample took 2 years to complete.

The assessment (designed to be conducted 1 month after the screening interview) and annual (designed to be conducted 1 year after the screening interview) interviews were also undertaken using customized portable computers. These interviews were carried out by interviewers from professions allied to medicine, who had not undertaken the screening interview, also recruited and trained for the purpose. Interviewers did not know the outcome of the first interview. The interviews lasted from 45 to 90 min, again with a 'priority mode' route. The annual interview consisted of a combined screen and assessment, where information on changes since last interview was recorded. At the assessment and biannual follow-up interview permission was sought to approach and interview a relative or carer to ask for an objective account of the respondent's health and abilities.

Six years after the initial screening interview, all respondents in the assessed groups were interviewed using the combined screen and assessment interview and at the end of that interview signed permission was requested to take a sample of blood or saliva. Permission was also sought to access GP and hospital notes. At 8 years only those who had indicated an

intention to donate brain tissue were re-interviewed with the combined screen and assessment interview.

At 10 years all survivors from the responding group of the complete study were recontacted for interview and if they agreed were interviewed using the combined screen and assessment interview.

What is collected at different interviews?

The screening interview contains questions on residence, marital status, education and occupation, living circumstances, contact with friends and family, health and social care contact, self-reported physical health, instrumental activities of daily living and activities of daily living, cognitive measures (Mini Mental State Examination with augmentation), and medication.

The assessment interview is mainly the Geriatric Mental State Examination (GMS) adapted for CFAS.[20] This is a structured psychiatric interview, which collects sufficient information for algorithmic 'diagnosis' in the major psychiatric disorders of old age (dementia, depression, anxiety, and psychosis). This has been validated against clinical diagnosis and the instrument has been widely used in Europe and now forms part of the 10/66 international instrument. This interview has been augmented with questions from the CAMDEX (Cambridge Examination for Mental Disorders in the Elderly) including CAMCOG,[21] the longer neuropsychological assessment. The relative or carer interview is mainly the History and Aetiological Schedule, the informant interview that accompanies the GMS.

The combined screen and assessment interview merges the two interviews but compresses some aspects of data collection. Complete versions of all the interviews including the interview questions and responses are available on the website.

The neuropathological assessment follows the standardized protocol of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[22], with the exception that the neuropathologist is blind to the interview data. This covers in a semiquantitative form the main areas required for the assessment of neurodegenerative and cerebrovascular disorders. The forms are available on the website. The main genetic analyses have been on apoE and ACE.

Data collection in Liverpool was broadly similar to the other five sites except that the screening interview consisted of the GMS plus some of the screening interview questions listed above.

What has the study found?

The study has reported on prevalence and incidence of dementia, and lack of variation in these across the five identical sites.[23–25] It has provided profiles of cognition for MMSE, extended MMSE, and CAMCOG, weighted back to the population.[26,27] It has reported on risk for incident dementia including apoE and ACE.[28–30] It has examined the relationship of cognition to mortality.[18,31] It has reported on the mixed neuropathology found in the brains of the oldest old.[32] In addition, the study has reported on a variety of impairments to healthy life in old age and their population burden.[33–38] The Resource Implication Study has provided data for examination of carer burden and the costs of care for physically and cognitively frail.[3–9,39] The data have been used for projection forward, for these vulnerable groups and also for the costs of long-term care. Liverpool has published on the prevalence of dementia, depression, and neurosis, together with incidence of dementia and schizophrenia.[40–43]

What are the main strengths?

The study is multisite and multidisciplinary. The population is truly representative with high response rates at each stage over diverse sites. Where there is no heterogeneity across sites the study is sufficiently large to provide indicative values for national estimates. The broad scope of measures has allowed the study to contribute to ageing research across a wide range of topics. There are repeat measures on cognition and function, which allows examination of trajectories. There are only two other population-based studies with brain donation in Europe.[44,45] The study weighted the sample towards the over 75 age group at baseline, which has provided more robust data for the oldest old.

What are the main weaknesses?

It would be desirable to have higher response and lower drop out between waves, but analysis can adjust for loss between interviews. Blood taking and clinical assessment (including imaging) at baseline was not possible because of funding constraints, but venepuncture was included at year 6. The risk measures are self-report, using the available validated measures of the era.

Can I get hold of data?

The study actively encourages collaboration, and there are established mechanisms for approaching us via the themes mentioned above (see What does it cover?). Information is available on the website and also through contact with theme leads.

Where can I find out more?

The study website, www.cfas.ac.uk, configures information under themes, documentation, publications, and data. There is also a list of study contacts.

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