Maintaining function and well-being in later life: a longitudinal cohort study
CFAS-WALES

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Protocol

Background

This study will address key questions from a biopsychosocial perspective regarding later life and ageing in the 21st century that cannot be addressed from other data sources. It will establish and follow longitudinally a new cohort of older people (N=5000) across diverse geographical areas in Wales. Contemporary information is required for the projection of future needs recognising diversity and inequality. A greater understanding is required of health status and risk factors in the total older population, including those in institutions, of healthy active life expectancy, changing social support networks and demands for formal services. New knowledge is needed about the complex interplay between the individual and their physical, social and environmental contexts and the effects on function and well-being; the influence of variations between different social groups and generational and geographical cohorts needs to be taken into account. By evaluating function at individual, community and societal levels this study will provide data that will advance scientific understanding and inform policy and planning for the ageing population in an era where by 2025 one in five of the population in the UK will be over 65 and 5.5% over the age of 80 (UN, 2006). By building on the design and infrastructure of the renowned MRC-funded Cognitive Function and Ageing Study collaborative (MRC-CFAS) it will strengthen UK estimates and provide valuable data for between-country comparisons. CFAS with its robust and well-tested methods is the only UK-study that can provide the base from which to examine these issues rigorously. This proposed study will be of major international significance, in providing reliable data on function and well-being in later life from a biopsychosocial perspective.

The context

Cognitive ageing is widely acknowledged as a major consequence of the ageing of the population. Over the last 40 years, the most prominent conceptualisation of this phenomenon has been as reflecting several distinct disease processes, the dementias, which can occur in younger people but are much more common with increasing age. The prevalence of dementia increases with age, doubling with every five year increase across the age range from 1.3% (65-69) to 32.5% (95+) (Dementia UK, 2007). Mapping these prevalence rates onto demographic population projections leads to the dramatic and well-publicised prediction that the total number of people who would meet diagnostic criteria for dementia in the UK will increase by 38% over the next 15 years and 154% over the next 45 years (Dementia UK, 2007). The proven relationship of dementia with increased service use, needs for community and residential care and impact on family care-givers means that these projected increases in numbers are expected to lead to unprecedented increases in costs to the public purse and to families (Dementia UK, 2007).

The challenges are considerable for national and local policy makers and service providers. Accurate data are crucial for planning and future predictions. However, it is not enough simply to have indications of the number of people with dementia. Future planning also requires an understanding of the impact of chronic disease on function, the biopsychosocial risk factors and modifiers of impaired cognition and function, variations between different social groups and geographical cohorts, the changing nature of informal care and social support, the organisation of formal health, social and long-term care services and the impact of increasing diversity in the older population due to generational group differences (DoH, 2004).Our approach will generate new knowledge on the multi-layered complexities of ageing, which cannot be understood from a single perspective. Our research uses a critical human ecology framework to understand older people in the environments in which they live, and to evaluate older people's interactions with these

environments (Keating & Phillips, 2008). People do not exist in isolation but interact with, and are influenced by, their physical, social and environmental contexts (Bubolz & Sontag ,1993; Bronfenbrenner, 1994).

Wales provides the ideal setting within which to conduct this study, offering additional diversity across a number of key areas relevant to our research questions. Although there have been rapid improvements in mortality rates in the UK, in Wales, 50% people between the ages of 60 and 85, and 80% of over 85s have a limiting long-term illness, higher than the levels in England (Welsh Assembly Government, 2008a). Gains in life expectancy have occurred at different rates for different population groups. Wide variations exist by age, gender, social class and area of residence. Analysis of the 2001 census data shows a stepwise increase in mortality, poor health and limiting long term illness with increased deprivation of neighbourhood. Wales has some of the largest gaps in health expectancies between the most and the least deprived areas. This long-established and well-documented pattern of ill-health is consistent with the occupational history of heavy industry and mining in poor socio-economic conditions (WAG, 1998). These regional variations in health inequalities need to be considered in the design of longitudinal studies.

The population of Wales is older than the rest of the UK; nearly 1 in 4 people (23.6%) are over the age of 60, compared with England (21%), Scotland (21.7%), and Northern Ireland (18.8%). The proportion of people who are over the age of 80 in Wales (4.9 per cent) is slightly higher than the UK (4.5 per cent) or the EU average (4.3 per cent), and is at least one percentage point higher than 16 of the 27 EU countries (Welsh Assembly Government, 2008a). Population migration also has an impact on the age profiles of communities, with more of the population in rural Wales being beyond retirement age compared to those living elsewhere in the country (Welsh Assembly Government, 2008b), with the distribution of migrants' origins varying considerably between areas in Wales. These variations in population change need to be taken into account, e.g. in understanding the support networks of older people. In-migration may also impact on another unique feature of Welsh culture: language. 18% of those aged 65-74 and 21% of those aged 75+ in Wales are bilingual, with considerable regional diversity in these proportions (Welsh Language Board, 2001).

The community is important as the location for the formation and continuation of associations and relationships with others (Gustafson, 2001) as well as the formation of cultural convention, norms, values and beliefs .On the regional level, the construction of norms for example for supportive relationships or behaviour in the face of disease may impact on older people's lives. Social integration may be linked to the strong native culture of a community which may be exemplified either in a rural setting or a close knit industrial community (Burholt, 2006). The cultural representation of dementia has a stigmatising effect on everyday interactions both for the person with dementia (Corner et al., 2007), and their carer or partner (Goffman, 1968). However currently we do not know whether the norms or expectations for supportive relationships, social interaction or engagement in social activity for someone with dementia differ by location. These distinct countrywide characteristics present a unique setting within which to pose our research questions and to explore the dynamics of ageing from a multi-disciplinary perspective.

Cognitive impairment in later life

Whilst many of those experiencing cognitive changes attribute them to the effects of ageing (Clare et al., 2006), the biomedical research community has sought to make a clear distinction between a dementia, reflecting one or more specific disease processes, and 'normal ageing'. Alzheimer's *disease* is thought to be the most common of these processes, and the almost synonymous use of this term and dementia adds to this disease model. It is evident that a significant number of people in their 40's and 50's develop a dementia, so these are not conditions which only occur in late life. They are viewed as diseases, which have their own distinct pattern of brain changes, which can potentially be treated, even cured, and possibly prevented. However, it is increasingly clear from those epidemiological studies which are able to go on to study the brains of participants at post mortem that dementia in those aged 75+ is less straight-forward than the simple

disease paradigm suggests. Brayne (2007) points out that in such epidemiological studies, overlap between normal and pathological ageing is usual. In general, a dementia develops gradually and insidiously – the point at which it is diagnosed is, in life, a matter of clinical judgement: diagnostic criteria usually require memory plus another area of cognition to be impaired before the criterion of 'globality' is satisfied. Even at post-mortem, there are issues regarding how many plaques and tangles are needed for a diagnosis of Alzheimer's or how much vascular damage is needed for a vascular dementia to be identified. The MRC CFAS Neuropathology study (MRC CFAS 2001) investigated dementia and neuropathology in 209 individuals from the MRC Cognitive Function and Ageing Study. Two main findings emerged; firstly, the pathologies of several forms of dementia were often present; thus the characteristic Alzheimer changes might co-occur with widespread vascular changes. Secondly, there was considerable overlap in the pathologies found in the people with dementia and those without. Evidently, some older people show dementia during life, with no obvious brain pathology at post-mortem, whilst others have significant pathology, but have been apparently unimpaired during life. In older people, the link between clinical picture and pathology appears less certain than has conventionally been claimed. Snowdon (2003) draws a similar conclusion from the longitudinal Nun Study in the USA.

Clearly other factors also need to be considered, and the work of Kitwood (1997), who drew attention to the variety of factors, including physical health and social environment, interacting with neuropathological changes to produce the dementia picture in life gains credibility from such findings. Kitwood described 'excess disability', where the person might appear more impaired than their degree of neuropathological impairment might determine. This might arise from health problems (or medication) or withdrawal from an unstimulating or aversive social environment. Depression and anxiety might also play a part in 'excess disability', and studies have suggested that symptoms of anxiety and depression are common in people with dementia, with prevalence rates as high as 30 or 40% (Ballard et al., 1996a, b).

If normal ageing and dementia are seen as two opposite ends of a continuum, almost inevitably an area of uncertainty between them has been labelled and become the subject of much debate. The term most often used currently is mild cognitive impairment (MCI) (Tuokko & Zarit, 2003), characterised by subjective complaints of cognitive change, and objective impairment of cognitive impairment, not sufficient to affect function in daily life. Typically, memory alone is impaired, but other sub-types of MCI have been described (Tuokko & McDowell, 2006). Much of the interest in MCI stems from an interest in whether it represents a prodromal form of Alzheimer's disease or another dementia. If it did so, the welcome possibility of perhaps intervening and delaying the onset of the dementia might become a reality. There is wide variation between studies, depending on the exact population studied and the criteria and tests used, but annual rates of conversion of between 10 and 20% are typical within the clinic setting (Tuokko & McDowell, 2006). Within the population setting, the MRC Cognitive Function and Ageing Study has shown that different definitions are associated with very different population prevalences (Stephan et al, 2007; Matthews et al, 2007) with low conversion over two years (Matthews et al, 2008) and many individuals are excluded (Stephan et al, 2008). These figures do show an increased risk of dementia in MCI over the general population. However, it is important not to infer that because all prodromal Alzheimer's might be expected to look like MCI, that all people with MCI will develop a dementia. A significant proportion will show improvement in cognitive function, or remain stable, or be showing difficulties related to other factors, such as physical health problems highlighted previously (Matthews et al, 2008).

In summary, significant cognitive impairments are common in older people, especially those aged 80 and over. The presence of memory impairment does not necessarily indicate that a dementia is developing, and the presentation of dementia is not simply a matter of underlying neuropathological impairment. Other factors, including health, mood and social environment influence the extent to which the person is impaired. Our proposed research will be able to further the understanding of the dynamic interplay between such biopsychosocial factors and the expression of dementia.

Justification for research questions

Are current cohorts different from those on whom the current planning models are based?

The authoritative Dementia UK report, cited above, draws heavily on the original CFAS study, carried out in 6 centres, in England and Wales, around 15 years ago. There have been major changes over these years in the context of older people in society and in the lifestyles, life experiences and life expectancy enjoyed by older people. Simply put, older people in 2010 are likely to differ in many ways from their counterparts in 1995. There is virtually no data available on these forms of cohort differences based on rigorous population samples anywhere in the world, despite a general acceptance that such effects exist. CFAS remains the only large, multi-centred population-based study in the UK that has reached sufficient maturity, which focuses on cognition and other important factors.

Research question

1) Have the prevalence and incidence rates of cognitive impairment changed? This study will add additional comparative data for a rural area in relation to the study being undertaken in 3 areas of England (CFAS II).

In the first wave of CFAS, the North Wales site was the focus for in-depth examination of the social networks of older people, how they changed over time and their relationship with cognitive impairment (Wenger, 1994; 1996). Therefore there is a unique opportunity to use the first CFAS cohort in Wales as the baseline for differences in the next generation of the older population, not only for the young-old (aged 65-84) but also in the oldest old (85+), who may be very different to the generation before them. Cultural factors may have an impact on network content, and Wenger (1986) concluded that that the study of short-term change and stability in support networks raised important questions about the nature of support networks, their durability, form and content in the context of social change. Since Wenger's early work, there have been increases in family breakdown and reconstitution as well as significant changes in society. Thus, using the cross-sectional data from phase 1 (1993) and T1 for the proposed study (2009) we propose to examine changes in social support networks between cohorts.

Research question

2) What is the nature of any changes in social networks since the original CFAS cohort?

Resilience and cognitive impairment

Resilience is the ability to recover from or adjust to misfortune or change. Although exposed to substantial stressors and risks, people can still function positively, recover from set-backs and maintain well-being in the face of adversity and challenge. Cognitive impairment and dementia present significant challenges to well-being, yet it is reported that people with Alzheimer's disease consistently rate their quality of life highly (e.g. James et al., 2005) and equivalent to self-ratings by older people without dementia (e.g. Scocco et al., 2006). This disparity has also been found in non-clinical populations; although ageing is considered a threat to well-being, older people have been found to rate their health as good despite the presence of ill-health (Windle, in press). This disparity has been termed the 'well-being paradox' (Staudinger, 2000).

There are theoretical perspectives that help explain this paradox and highlight the role of regulatory mechanisms that are central to the individual. Aspects of the individual's personality influence the way a person might react to life changes, challenges and adversity (Diener, 1984). The model of selective optimisation with compensation (Baltes, 1993), describes regulatory processes which individuals use to deal with ageing and the age-associated tendency for increased losses and fewer gains. Consequently the moderating influence of the resilient self may compensate for change or adversity and maintain acceptable levels of well-being. Thus, resilience could be an important psychological resource influencing how older people respond to, manage and cope with the changes that lead to cognitive impairment, and influence the extent to which these changes become overwhelming.

Resilience can be examined from many levels of analysis, from the molecular to the global and as both a process and an outcome (Masten, 2007). Drawing similarities with the well-being paradox, as an outcome it has been conceptualised as a positive response to a stressful life event, such as illness or bereavement (Hardy, Concato & Gill, 2004) or as having few symptoms of post-traumatic stress after terrorist attack (Bonnano et al., 2006). However, the conceptualisation of resilience as the response to a stressful event such as this does not enable a deeper understanding of the internal personality characteristics that characterise psychological resilience that are drawn upon in such situations, and the interplay between these internal factors and those external to the individual. Recent work with a large non-clinical population sample of older people has developed a measure of psychological resilience (Windle, Markland & Woods, 2008) and further work has demonstrated how this measure of psychological resilience mediates the negative influence of chronic illness on subjective well-being in older age (Windle, in press). Consideration of this work indicates that psychological resources such as resilience can be a valuable mechanism for maintaining well-being and may constitute an important route to understanding differential resistance to, and recovery from daily stress such as ill-health, cognitive impairment and dementia in later life. In the proposed study we will examine whether resilience is able to ameliorate declines in cognitive function on well-being.

The study will also examine the associations of resilience, addressing the question 'why are some people more resilient than others?' As ageing proceeds, individuals will accumulate the impact from other areas of life such as health, lifestyles, living situation and material resources, which in turn are influenced by societal opportunities and barriers. . In many instances these factors will determine the point in life when individuals might be at risk for reductions to resilience, or which factors might be implicated in a more favourable outcome. We will determine how the characteristics of the resilient differ from the non-resilient in terms of demography, health, nutritional status, activity, functional ability, social support, language, receipt of care, health behaviour and social capital, and what role, if any, cognitive function has in the relationship. Importantly, we will examine change over time, enabling an understanding of the relative importance of the influences on resilience.

We will use qualitative methods to study the development of psychological resilience and how it affects the interpretation of cognitive impairment, examining how new vulnerabilities or strengths emerge over the life course. It will suggest which experiences might specifically inform the development of a resilient response when faced with challenges and perceived adversity, or which experiences might have a negative impact on resilience in later life. Of particular interest are significant experiences in the earlier part of life. Research on resilient children indicates that when tracked into young adulthood, between 50% and 70% of those in earlier 'high risk' circumstances had developed into highly successful individuals. In some instances this work shows examples of earlier life experiences that might have contributed to success later (Benard, 1997). Conversely protective factors may not always exist as a result of pleasurable happenings, or be regarded as a pleasant and desirable trait (Rutter, 1985). Taking a life course perspective, qualitative exploration will address life histories; the meaning and impact of life experiences, the extent to which these experiences may have enabled a positive adaptation to ill-health in later life, or which experiences may be a barrier to adaptation, and how these experiences may shape the development of resilience.

Research questions

3) How do the characteristics of the resilient differ from the non-resilient?
4) What is the influence of cognitive impairment on the relationship of resilience and well-being?
5) Does resilience at the initial assessment predict later adaptation regardless of the presence of cognitive impairment?
6) Do earlier life experiences impact on the development of resilience?

Protective effects of lifestyle factors

If the onset of dementia could be delayed by five years the number of people affected could be approximately halved, so that the number of people over 65 with dementia in 2031 would then

be similar to the 2007 figure (Alzheimer's Scotland, 2007). Given that estimates of the total cost of dementia amount to £17.03 billion per year (Dementia UK, 2007), realising this scenario presents significant reductions in costs, both financial and personal. Factors that may moderate the onset of dementia clearly deserve further investigation.

Lifestyle factors, such as cognitive stimulation and physical exercise have been suggested to be protective, by increasing brain reserve, along with the effects of education (Stern et al., 2003). Brain reserve may offer some protection against the emergence of impairment and disability in response to neuropathology, with cognitive plasticity compensating for neural dysfunction (Valenzuela & Sachdev, 2006), with some individuals functioning within the normal cognitive range despite the presence of dementia associated brain pathology. Valenzuela & Sachdev (2006) combined data from 22 studies (29,279 individuals) that had examined education, occupation, pre-morbid IQ and mentally stimulating leisure activities. They report that individuals classified as high reserve had a 46% lower risk for incident dementia after a median follow up interval of 7.1 years.

A number of studies have evaluated the role of cognitive activity in protecting against the onset of dementia. For example, Wilson et al. (2002a,b) report a longitudinal cohort study with an average follow-up of 4.5 years. At their initial interview they rated how often they participated in a range of cognitive activities, such as reading a newspaper or books, playing card games, crosswords and other puzzles, watching TV and visiting museums, as well as participation in physical activities (such as walking for exercise). Controlling for age, gender and education, the risk of developing Alzheimer's was reduced by 33% for each point increase in cognitive activity score at baseline. In contrast, number of hours of physical activity per week was not related to the risk of developing Alzheimer's disease. The apparent superiority of cognitive activity to physical exercise needs to be examined carefully. Laurin et al. (2001), analysing data from the Canadian Study on Health and Aging, report that regular exercise was associated with lower risks of dementia, for women. In Verghese's (2003) study, one form of physical exercise (dancing) was associated with lower risk of dementia, and the interaction between physical and cognitive activities must be acknowledged.

It is well-established that people with higher levels of education are less likely to be diagnosed with a dementia. This has been attributed to educated people having either greater brain reserve (more neurones and connections can be lost before function is impaired) and / or greater cognitive reserve (able to use cognitive strategies to make more effective use of remaining brain systems). However, from their analyses of data on the incidence of dementia from the Canadian Study on Health and Aging, a study of over 10000 older people, Tuokko et al. (2003) conclude that the lower incidence of dementia for high functioning people primarily results from an ascertainment bias. The interaction of education and cognitive activity needs further study.

Depression is, of course, also linked to reduced activity levels, and will also be an important factor to take into account. Wilson et al. (2002c) report that the greater the number of depressive symptoms at baseline, the greater the risk of developing Alzheimer's disease (with the risk increasing by 19% per depressive symptom). Wilson et al. conclude that their findings do not simply reflect a depressive reaction to cognitive impairment.

The relationship between cognitive activity and subsequent cognitive decline or dementia, appears consistent with the often quoted 'Use it or lose it' hypothesis, with the exhortation to use the brain, engaging in activities with significant cognitive demands, to maintain brain function (Hultsch et al., 1999). However, Salthouse et al. (2002) argue that 'it may be premature to reach a definitive conclusion about the validity of the use it or lose it perspective'. In a study involving 204 adults aged between 20 and 91 years of age, reported cognitive activity did not moderate age-related cognitive decline. The study was cross-sectional and the participants scored well above average on tests of cognitive ability, and perhaps cannot be generalised readily to those at immediate risk of developing a dementia. However, it does indicate the complexity of this area, and reinforces the need for prospective studies in at-risk populations.

Bilingualism reflects a particular form of cognitive activity characterised by practice in the ability to use one language while inhibiting the other, potentially competing, language.

Developmentally this is thought to provide advantages in cognitive control that may extend throughout the lifespan, while monolinguals may show advantages over bilinguals in other domains such as vocabulary knowledge (Bialystok et al, 2004). One recent Canadian study has suggested that being bilingual may delay the onset of dementia by as much as four years (Bialystok et al, 2007), based on a retrospective analysis of memory clinic records, controlling for gender, education and occupational status. It was concluded that while bilinguals and monolinguals had comparable MMSE scores at the time of their initial clinic visit, bilinguals were on average four years older, suggesting a significant delay in onset in the bilingual group that could equate to a 47% reduction in prevalence. If this is a reliable finding, then it could potentially be of great importance. Of course, these preliminary results from a retrospective clinic study cannot be regarded as definitive, and recently another retrospective Canadian study has failed to replicate this finding (Chertkow et al, 2008). However, a number of confounding factors may have influenced the results of both studies. For example, the bilinguals studied by Bialystok et al (2007) had come to Canada from a range of other countries, while the monolinguals were more likely to be indigenous. In the present study, sampling in Wales where the older population contains a mixture of native bilingual Welsh/English speakers and monolingual English speakers will make it possible to examine the influence of bilingualism prospectively in a sample that is socially and culturally *relatively* homogenous and in which the bilinguals share the same native language. By following these individuals over time it will be possible to identify the extent to which the onset and development of cognitive impairment is influenced by language status. In our North Wales site two-thirds of older people are bilingual, whilst just over a third of those in our South Wales area are anticipated to speak Welsh (Welsh Language Board, 2001).

Research questions

7) How do education, activity levels, mood and language status predict levels of cognitive impairment? Is there evidence in this cohort to support the cognitive reserve hypothesis? Do mild levels of cognitive impairment (using different definitions from the CFAS work) relate to differences in high level activity, social and community participation?

8) Do bilingual Welsh-English speakers develop cognitive impairment at a later age than monolingual English speakers in Wales?

Social networks

The literature suggests that contrary to popular assumptions about the attrition of the networks of older people, a mechanism of equilibrium or homeostasis exists which maintains networks through a process of exchange and substitution of members into the support network from the large social network (Wenger, 1986). There is evidence of withdrawal of non-kin and consanguineously distant relatives (e.g. nieces, nephews) over time from the support networks of older people, but at the same time increasing commitments from consanguineously close kin (e.g. sons and daughters) (Wenger 1986). Factors that influence network change include increased frailty or improved health, increased cognitive impairment, and provision of care or relief of provision of care (Wenger, 1990). Although limited, there is some evidence that in the face of high dependency close younger kin may be critical (Wenger, 1986), and that some types of networks are more robust than others (Wenger, 1990). Although most networks in the community are stable over time, when networks do shift, they tend to be to more dependent network types (Wenger 1990). Different networks reflect different combinations of relationships, with potential members available as a result of family formation, migration history and personality traits (Wenger & Shahtahmasebi,1990). Research has found that there are normative expectations about support which relate to the category (e.g. spouse, children) and gender of network members (Wenger & Shahtahmasebi, 1990). Data about normative responsibilities and expectations of network members, and the circumstances under which expectations are exceeded are now over a decade old. Therefore, it is important to determine whether responsibilities have changed over time, and whether the current cohort of older people has different normative expectations for support in later life.

A majority of the early work on support network types was carried out in largely stable communities with a high standard of living (Wenger, 1986). Research on support networks and place have found that women maintain more robust networks in urban areas, whilst men are more integrated in rural areas (Wenger, 1996). We know that residential relocation patterns lead to different types of social networks in particular locations (e.g. wider community focussed networks are a feature of retirement areas) (Wenger & St Leger, 1992), but we need to explore further the impact that different types of place (e.g. disadvantaged area) may have on the distribution of support networks types. For example, traditional images of 'rural solidarity' or 'working class solidarity' may impact on the preferred family forms in certain locations.

The findings from research on dementia and support network over a decade ago suggested that in order to remain living in the community older people with dementia needed to receive support from a nearby relative. Indeed, twice the proportion of people with dementia lived with the younger generation than did those without dementia (Wenger, 1994), suggesting that the findings reflected the need for a family carer, and a tendency for older people with dementia to become increasingly isolated as they experienced reduced contact with people outside the household (Wenger, 1994). However, this work was not able to identify whether older people with dementia were able to stay in the community (rather than entering residential care) because of pre-existing networks which were slightly modified to provide personal care and surveillance, or whether pre-existing networks shifted to provide this type of care (Wenger, 1994).

In addition to this key line of enquiry, the brain reserve hypothesis raises other significant areas for further research. The brain reserve theory suggests despite significant neurological changes, support networks may protect against cognitive decline. Social networks have been reported to modify the association between Alzheimer's disease pathology and cognitive function. Even at more severe levels of disease pathology, cognitive function was higher for individuals with larger networks. The modifying effects were most pronounced for semantic memory and working memory (Bennett et al., 2006). A community based cohort study in Sweden found that individuals with an extensive social network (being married and living with someone; having children with daily to weekly satisfying contacts; having relatives/friends with daily to weekly satisfying contacts) had a significantly less risk of incidence dementia (19 per 1000 person years) compared to those with a moderate social network (49.5 per person years); a limited social network (69.4 per person years) and a poor social network (156.9 per 1000 person years). When all components were combined a limited or poor social network increased the risk of dementia by 60% (Fratiglioni et al., 2000). However, Fratiglioni et al., did not use a validated social network measure and did not take into account past participation or social life, making it difficult to distinguish long-standing patterns of social participation from changes brought about by the cognitive impairment. In the first instance our data would enable an accurate and powerful examination of the link between social networks and the development of cognitive impairment.

Research questions

9) By observing the changes in support networks using longitudinal quantitative data at baseline and two-year follow-up, we can examine the relationship of changes in cognitive impairment and social networks; specifically, are those with more extensive social networks at the initial assessment less likely to show increased cognitive impairment at the two-year follow-up assessment?

10) Does the stability/instability of networks over time differ between those with no impairments, physical impairments and cognitive impairments?

11) From in-depth qualitative interviews, the following will be addressed: Are there shared 'understandings' of social support by different groups in a given location? What are the expectations for care, activity and participation in the face of cognitive impairment, and how do these vary by area? Is there evidence to suggest that adaptations in network and changes in participation are based on place-embedded normative expectations?

Nutritional status

To examine the relationship between nutrition (vitamin B12), activity and cognitive impairment.

Vitamin B_{12} deficiency is common in older people (Baik & Russell, 1999). Prevalence estimates range from 10% to 46% depending on the definition used and socioeconomic status of the population studied (Bates et al., 2003; Clarke et al., 2004). The diagnosis of vitamin B_{12} deficiency is complicated by the poor specificity and sensitivity of measuring serum vitamin B_{12} concentrations. Raised serum and plasma methylmalonic acid (MMA) concentrations are a more specific indicator of functional vitamin B_{12} deficiency although concentrations may be increased with renal impairment (Bates et al., 2003). Plasma concentrations of total homocysteine (tHcy) are elevated in persons with biologically significant vitamin B_{12} deficiency, but are also elevated in folate deficiency (Baik & Russell, 1999). Plasma holo-transcobalamin (holoTC) concentrations have been shown to be a sensitive diagnostic indicator (Hvas & Nexo, 2005).

Metabolically significant deficiency of vitamin B_{12}, as revealed by elevated blood levels of MMA, has been strongly associated with impaired cognitive function (principally language comprehension and expression) independently of age and education (McCracken et al., 2006; McCaddon et al, 1998). An elevated blood concentration of tHcy is a risk factor for cognitive impairment and dementia McCaddon et al., 1998; Clarke et al., 1998; Seshadri et al., 2002; Budge et al., 2002). Longitudinal analysis has shown that older participants without dementia with low vitamin B_{12} and holoTC levels and higher plasma tHcy and MMA at baseline have a greater decrease in brain volume over 5 years of follow-up (Vogiatzoglou et al., 2008).Low vitamin B_{12} status is implicated in and may therefore be a modifiable cause of brain atrophy and impaired cognitive function in the older people (Vogiatzoglou et al., 2008).

What is not known is how an individual's social, psychological, physical and economic circumstances contribute to their nutrient, and particularly their B_{12}, blood profile. Diet, in older people, has been shown to be influenced by such diverse factors as childhood eating patterns, illness, poor dentition, social isolation, socio-economic position and cooking skills (Maynard et al 2005; Hughes et al, 2004; Kohler et al, 2008; Hoffman et al, 2008). Diet and therefore nutrition are mediated by many factors, principally the culture in which an individual lives and their lifestyle within that culture. The proposed study will characterise the interplay between biochemical and cultural and lifestyle factors and determine their relationship to overall cognitive function and to discrete cognitive domains as this may have implications for prevention.

Research questions

(11a) How do longitudinal changes in measures of vitamin B12 deficiency and folate status impact on changes in cognition and depression and on separate cognitive domains

(12) What are respondents' key health issues and health behaviours focusing on diet, food shopping and physical exercise and how do these relate to their biochemical measures?

Dataset review – why we need to collect new data

Only the CFAS methodology allows comparison between cohorts on variables of interest over a 15 year period. The CFAS-II dataset includes 3 centres in England, but it is insufficient alone as it does not include sufficient detail on psychosocial variables (with no measure of personality / self resources) and does not include a significant number of bilinguals.

Research Methods

Sampling: The two centres to be included in the study will consist of urban and rural areas within the counties of Gwynedd, Anglesey and Neath Port Talbot. The former is selected as it was a CFAS-I site; the latter as it adds greatly to the mix of social and cultural diversity, whilst still retaining a significant proportion of bilinguals. The sampling frame will be identical to that used in the original CFAS enumeration. A population based sample of 2,500 individuals from each site, born before 1944 will be drawn from general practice records, with 50% of the individuals being from each of the age groups 65-74 and 75 years and over. The ascertainment of the sample in each

centre will use over-sampling to cope with the anticipated 15% of individuals with incorrect registration and ineligibility and an expected 80% response rate to the initial approach. Individuals ascertained from the general practitioners will, after approval from the GP, receive a letter from the GP followed by personal approach by interviewers. Any individuals included in the previous CFAS cohort in Gwynedd will be available for the new cohort study as this is a complete re-enumeration of the population and the last follow up was completed in 2004. To exclude these individuals is not necessary as there are a very small number of people who are still part of the active follow-up of potential brain donors and the sampled lists will be examined for their names.

Interviewing: Interviewers will be recruited from the local area. They will undertake CRB checks and be given training, support and quality checks by Cambridge using the methods developed for CFAS to ensure standardisation. Qualitative interview training will be provided by the project team. Regular liaison and rating sessions with the Cambridge will ensure quality control and progress. Welsh-speaking interviewers will administer the interview and cognitive tests in Welsh for those preferring this option. Interviews and follow-up interviews will be undertaken over two two-year periods. The procedure for bilingual interviewing will be as used in the CFAS-I study. The complete interview will be translated into Welsh, back-translated and piloted with Welsh speakers from each area, and be delivered in a computerised version on a lap-top alongside the English version, in accordance with the interviewee's preference. The interviewer reads out the questions from the computer, whether in Welsh or English, so that data collection is standardised across interviews.

Data collection (quantitative): The participant interview is the combined screen and assessment developed for CFAS with selected additional questions. This provides the AGECAT study diagnostic algorithm for dementia, depression and anxiety within a single interview, drawing on respondent and observer ratings. In 20% an informant interview will also be conducted for the refinement of study diagnosis and to provide essential proxy information where respondents are unable to answer questions. The 20% for whom an informant interview is sought include all the clear and marginal dementia cases (10%) and a similar size sample of 'normals' for comparative purposes (10%). For the dementia cases, the information is used to check and refine diagnosis and to obtain risk factor information for those who are cognitively impaired. The similar sized control group provide an indication of the accuracy of informant information. Proxy information is seen as supplementing rather than replacing participant information, and will not be substituted for subjective self-report measures, such as well-being, resilience and loneliness. The CFAS experience is that 'proxy only' interviews are very rare.

The interview will be administered twice within the current 5 year study – at baseline and after an interval of two years. The interview is administered using assisted computer direct data entry and has the following sections:

- Demographic characteristics - marital status, education, social class, social economic group (Elias et al., 1993), residential status and intellectual activity (as developed for EPIC protocol).
- Lifestyle variables – smoking and alcohol history (enhanced baseline questions), brief measure of physical activity (EPIC protocol).
- Health status including self-perceived health, self-reported chronic diseases (including heart disease, angina, diabetes, stoke, Parkinson disease, epilepsy and meningitis), Rose (1962) angina questionnaire and medication history (Chen et al., 2001).
- Functional limitations, disability and extended activities of daily living (Bond & Carstairs, 1982; Townsend, 1979) and objective assessments of physical function (ELSA protocol as developed by Melzer).
- Cognitive function (MMSE (Folstein et al., 1975) and extended items (MRC, 1993), verbal fluency, executive function); depression, dementia and anxiety from the Geriatric Mental

State Automated Geriatric Examination Assisted Taxonomy (GMS AGECAT; Copeland et al., 1986); CAMCOG (Huppert et al., 1996).

- Social support & social networks (Wenger, 1989) including receipt of informal care, social capital (Babb, 2005), Lubben social network scale, care needs (Bond & Carstairs, 1982).
- Measures of hearing and visual impairment.
- Sputum specimen (Oregan) for DNA acquisition.
- Individuals will be asked for permission to flag for death notification and embarkations at the Office of National statistics and access to health and social care records.
- An informant interview (20% sample of all respondents weighted towards those with cognitive and functional impairment). The two interviews together consist of the GMS and History and Aetiology Schedule that is used by AGECAT and enables the DSM IV and ICD 10 classification of organic and mood disorders (WHO, 1993). Receipt of health services, social services, special housing and disability benefits – questions relevant to policy included based on retrospective questions on use of services to respondents and informants (adapted from CFAS RIS and PSSRU).
- Personality (resilience – Windle et al., 2008)
- Well-being (Satisfaction with Life Scale; Diener et al., 1985)
- Language history and preference
- Measures of activity level/ social/civic participation and loneliness (de Jong Gierveld & Kamphuis, 1985).

Biochemical and haematological measures

Individuals will be approached for permission to take blood. 15% of the sample will be approached with the intention that a 10% sample will be achieved (based on 70% positive response in CFAS I). The bloods will be analysed in the University of Liverpool for the following measures: haemoglobin, full blood count, B12, serum folate, red cell folate, ferritin, glycated haemoglobin, urea, creatinine, sodium, potassium, albumin, C-reactive protein, fibrinogen, homocysteine, methylmalonic acid and holotranscobalamin. Values of clinical indices outside the normal range will be reported, with the respondent's consent, to the respondent's general practitioner. As this is a longitudinal sample this will be conducted on the same cohort twice over the duration of the study. The first wave will involve blood collection from 250 individuals and the second wave assuming a response of 70% will involve blood collection from 175 individuals. In all a total of 425 blood collections.

Data collection (qualitative)

Qualitative data will be collected at two time points. The interviews will be digitally recorded. At time 1, purposive sampling will be undertaken. In order to inform the research questions we will draw on those with (N=30) and without (N=60) dementia and with some degree of cognitive impairment (n=30) with high levels of measures of B12 (n=15), and with low levels (n=15).The sample will include men and women from urban and rural areas. Researcher-led focused in-depth interviews will be conducted, structured around a topic guide. The 'aide memoirs' will be designed to provide data that will be relevant for resilience, activity, social networks, and norms for informal care provision for older people, and expectations about engagement in activities for older people with and without cognitive impairment. At time 1 part of the interviews will be structured around a discussion of social support to establish key network members, and what types of care they provide/receive. The development of the caring/receiving relationships over time will be elucidated. Building on the work of Wenger (1990) we will explore the normative expectations for emotional and functional/practical care from various categories of network members and explore the circumstances under which normative expectation may be exceeded. We will explore the meaning and impact of early life experiences, how these may enable positive adaptation to ill-health, or present as a barrier to adaptation and shape the development of resilience. The lifestyle and cultural themes that impinge on diet will be explored, such as appetite, finance, importance of

cooking, the role of shopping as greater than food acquisition, gardening and the empowerment of food production.

At time 2 an additional sample (N=25) will be drawn to explore changes/stability in networks, by purposively selecting people whose networks had changed. At time 2, interviews will explore whether key people in the network at T2 are the same as at T1. It will be established whether network members provide/receive the same types of care and if there have been changes, why these have occurred. The normative expectations for care will be examined again to see if there have been changes/adjustments in expectations over time. In particular, interviewees will look for examples of where normative expectations were met/not met. Changes in B12 status of participants at time 2 (N=25) will be investigated against changes in the previously mentioned lifestyle and cultural factors.

Data management: The administration of the study will be undertaken using the mechanisms which have been developed during the previous interview phases of CFAS. A record for all participants is generated which records their progress throughout the study. This system will be used to allocate individuals to USB disks in batches of participants, and upon completion of the batch the data is fed back into the system within the Department of Public Health in Cambridge, which records dates and outcomes and sets up the record for the next interview allocation. Selection of individuals for informant interviews is automatic during the interview process. Manual entry of refusals and deaths, with dates and cause is an ongoing process. Data fed back from the interviews are anonymised, separated and sent to the data manager within the MRC Biostatistics Unit in Cambridge.

For the qualitative data, the project manager will set up a data management system, consisting of instructions on converting raw data to computer files (in the form of a transcription protocol), organising data storage, data archiving steps and a data management checklist. The transcription protocol will ensure that standard conventions would be adopted throughout the transcription process, and that a standard presentation format would be used. Qualitative data will be professionally transcribed and analysed in NVivo by the research team. Personal identifiers will be substituted during transcription. Qualitative data will be securely stored and password protected. Upon completion of transcription data files will be erased. Data will be archived according to ESDS procedures.

Framework and methods for analysis

Many of our analytical methods have been tried and tested on the earlier cohort and within the existing infrastructure. Quantitative methods planned include multi-level modelling using inverse probability weighting and multiple imputation as a means to investigate missing data. For discrete outcomes, logistic regression will be used (either weighted or multiply imputed). Results would be available within months of completion of the fieldwork. A critically important feature in this study is the ability to repeat the methodology precisely including the application of the algorithmic diagnosis. Because of the introduction of the MCI concept it is unlikely that clinicians boundaries of normal, mild and established dementia will have remained stable over time. Only studies such as CFAS can hold such boundaries steady. Data collection at Time 1 uses a concurrent–triangulation strategy where findings from both the quantitative and qualitative phase will be used to cross-validate the findings from each phase. At time 2, we will use a sequential explanatory strategy, where priority is given to the quantitative data. The qualitative data will enrich the interpretation of the results of the quantitative study. Groups of partners within the project team will collaborate to analyse the data and produce outputs based on the research questions. The quantitative data would be analysed in relation to the research questions cross-sectionally; it will be compared to data from CFAS I to look at changes between cohorts over time. The two year interval will provide comparisons with incidence, cognitive and functional change, network, activity and resilience change.

Power considerations: The sample size of 2,500 respondents in each site has been calculated to allow the identification of the overall sex-specific prevalence rate of dementia to within 2%. The use of the two age strata ensure sufficient numbers in the oldest old (particularly in men) to investigate this age group in detail. Estimated rates of attrition from CFAS-I are 23% in the younger age-group and 25% in the older group; death rates are estimated at 5% and 15% respectively, leaving 75% of the younger group and 65% of the older group ready and willing to be followed up at 2 years i.e. a follow-up sample of 3500 people, of whom half would be expected to be bilingual. This sample size allows for comparisons between sub-groups; for example, assuming 7% of the population decline in cognition (as seen in CFAS-I) between baseline and two year follow-up the study is sufficiently large to detect a difference of risk of 10% in any covariate where the sample has more than 10% of the data exposed (at least 80% power and a p-value<0.05).

Qualitative analysis: Interpretative Phenomenological Analysis (IPA) and thematic content analysis will be used to interpret the information on networks, nutrition and resilience. Whilst the qualitative interview will cover all the relevant aspects, we envisage analysis for each research domain e.g. resilience, nutrition, social networks proceeding separately, with thematic analysis being most appropriate for much of this process.

The networks analysis will examine normative responsibilities and expectations in relation to network types. This would be compared with previous work (Wenger,1990) to identify changes in normative expectations between cohorts CFAS I and T1. The procedure would be repeated at T2 to examine changes between the two data collection periods. In addition, to relating normative responsibilities to relationship categories, different hypotheses regarding the configurations of 'understanding of social support' will be tested. For example, the data for particular locations (e.g. disadvantaged urban area, advantaged urban area; rural retirement area) would be grouped to look for common themes in expectations. The situations where expectations for care are exceeded will be examined to establish whether there is evidence of place-embedded normative expectations. The nutrition analysis will explore the lifestyle and cultural factors that may interact with B12 status. Interviews will explore the self –reported health behaviour focussing on the impact of cognitive function on shopping patterns, consumption of food and activity levels. The resilience analysis aims to understand the development of the phenomenon (resilience) and will focus on the uniqueness of the participants' thoughts and perceptions of the phenomenon. It will aim to understand the meaning of earlier life experiences from the individual's own perspective and how these might have lead to the ability to successfully adapt in the face of challenge or adversity. At time 2 the qualitative data will assist in the interpretation of the results of the quantitative study. Changes or stability in networks and changes in B12 levels will be identified through quantitative data analysis (see above) and compared to the qualitative data. The transcripts of interviews will be independently analysed by two researchers, and following discussion key themes that capture interviewees' experience of and reasons for stability/change between T1 and T2 will be decided upon. In addition, themes that arise from changes/stability in expectations for care will also be elucidated.

Expected outputs

The findings will be published in high quality peer reviewed journals and presented at international conferences. Research summaries and short articles will be prepared for local and national government, voluntary organisations, the practitioner press and other interested persons. All findings will be available on the CFAS website. The findings will be disseminated through the CRC-Cymru / UKCRN networks to contribute to policy and practice development throughout the UK. Two large seminars will be organised in the final year to which key policy makers and all organisations with an interest in ageing will be invited. The findings will add to the evidence-base regarding the prevention of cognitive decline and shape a broader understanding of the nature of cognitive impairment in later. The collaboration between this study and CFAS-II will add value to both studies, which will include 5 sites in total. It will add a psychosocial dimension to the

combined analyses, and enable the data from the current proposed study also to be used to address more specifically biomedical research questions with greater precision.