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Physical, Psychological, Demographic and Modifiable Risk Factors for Age Related Cognitive Impairment associated with possible Dementia and Frailty

A Doctorate Thesis

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ABSTRACT

The population of China is ageing. The percentage of people aged 65 years and over will rise from 5.5% in 1990, to a predicted 13.3% in 2025, and an estimated 23% of the population (or 114 million) by 2050 (Woo, 2002). Accompanying this aging population, dementia and frailty have a growing importance. Dementia is a progressive degenerative cognitive disorder which has a significant impact on the quality of life and the ability to live independently. Frailty is characterised by increased physical dependency and its symptoms are loss of physical ability due to muscle wasting, fatigue etc. (Fried, 2001). However there is little consensus on the association between dementia and frailty, in terms of how the criteria that are part of this two syndromes overlap, as both disorders are age-related and increase the risk for falls, further leading to loss of independence. For instance, it is unclear to which extent cognitive impairments contribute to frailty. This raises the need for more insight in these disorders, their early detection and prevention.

To meet the above needs, the thesis describes research into different frailty diagnostic criteria, as well as its association with dementia symptoms. We examined cognitive measures that can be used for assessment of Mild Cognitive Impairment (MCI) and dementia screening (the Hopkins Verbal Learning Test, HVLT) and compared its discriminant ability with the commonly used cognitive screening tool, the Mini-Mental State Examination (MMSE) in distinguishing Cognitive Impairment (including MCI and dementia) from No Cognitive Impairment (NCI, normal controls) in two community-dwelling elderly Chinese populations and in one institutionalised elderly population in Shanghai, China.

Subsequently we employed these two cognitive measures to investigate whether they were part of the frailty syndrome among elderly from the community-based studies. We investigated whether physical and cognitive symptoms clustered together to form frailty phenotypes. We employed

indicators that have been widely used to diagnose frailty, including physical measures (grip strength, Time-Up and Go test, 15 feet gait speed test and Berg balance test), and psychological measures (the HVLT and the MMSE) to predict cognitive impairment (CI). We found four distinct subtypes of elderly characterised by increasing care needs: 1. Persona 'elderly' as defined by age >78, year of education<6 years, grip strength <11.8 KG, and a MMSE total score <25; 2. Persona Physical frailty (fitness), defined by a total score on the Timed-Up and Go (TUG) test >12.7 seconds and15 feet gait speed >4.4 seconds; 3. Persona Cognitive impairment, defined by a MMSE total score <25, a HVLT Immediate Recall (IR) score <15, and a HVLT Delayed Recall (DR) <5; 4. Persona Physical frailty (balance,) defined by a Berg Balance test score of <53.

Additionally, we described demographics (age, gender, education) and other potential modifiers when detecting cognitive impairment and functional disability. We then built up a model for possible frailty phenotype using various indicators, Frailty here was defined as:

1. Low BMI as measured by this algorithm: BMI= Weight (kg)/Height $(m)^2$
2. Weakness (upper and lower body): grip strength in the lowest quintile, adjusted for gender; and TUG get up with assistance or unable to get up
3. Slowness (lower body): TUG score in the lowest quintile, adjusted for gender; and 15 feet gait speed in the lowest quintile, adjusted for gender;
4. Poor balance: Berg Balance test score in the lowest quintile, adjusted for gender;
5. Low physical activity: engaging in exercise less than once per week.

An individual with 4 or more present frailty components out of a total of 7 was considered to be 'frail', whereas equal or less than 3 characteristics were hypothesized to be 'pre-frail'. Those with no present frailty components were considered as robust.

Lastly, we examined whether demographic (age, gender, education and profession), and lifestyle (smoking/alcohol history, exercise frequency, and dietary habit) could be used to predict future cognitive impairment (as defined by a HVLT IR score of ≤19).

The results of our studies show that compared to the MMSE, the HVLT is superior in differentiating MCI and dementia from NCI, and is also less affected by demographic factors in detecting frailty.

Furthermore, in the current study, physical, psychological, demographic and other modifiable risk factors cluster together into different phenotypes of cognitive impairment and functional disability in these cohorts. A phenotype of frailty is built up using BMI, grip strength, TUG, 15 feet gait speed, balance and exercise frequency as indicators. The most common was the elderly phenotype followed by the cognitively impaired. A novel finding of the current study is that only 4.8% (8 out 168) of the whole sample fulfilled all three categories in the current study (cognitive impairment, functional disability and frailty).

Finally, advanced age, lower education (no or primary level), and being vegetarian were significant risk factors for cognitive impairment. Furthermore, whereas high consumption of green vegetables is a protector against cognitive impairment, high intake of tofu was negatively related to cognitive performance among community-dwelling elderly in China.

PUBLICATIONS AND PRESENTATIONS

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Journal of Alzheimer's Disease, 2014, 43 (2). In press.

Xu, X., Dong, Y., Hilal, S., Chong, E.J.Y., Kamran, M.I., Venketasubramanian, R., Chen, C.LH. (2014). The Utility of the Mini-Mental State Examination in Identifying Demented and non-Demented Patients in a Memory Clinic in Singapore. Submitted to International psychogeriatrics.

Ong, Y.T., Hilal, S., Cheung, C.Y., **Xu, X.,** Chen, C., Venketasubramanian, N., Wong, T.Y., Ikram, M.K. (2014). Cortical microinfarcts on 3T MRI: clinical correlates in memory-clinic patients. Accepted by Dementia and Geriatric Cognitive Disorders Extra in April 2014.

Van Veluw, S.J., Hilal, S., Kuijf, H.J., Ikram, M.K., **Xu, X.,** Tan, B.Y., Venketasubramanian, N., Biessels, G.Y., Chen, C. (2014). Cortical microinfarcts on 3T MRI: clinical correlates in memory-clinic patients. Submitted to to Alzheimer's & Dementia.

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Hogervorst, E., Clifford, A., Stock, J., **Xu, X.** and Bandelow, S. (2012). Exercise to Prevent Cognitive Decline and Alzheimer's disease: For Whom, When, What, and (most importantly) How Much? Journal of Alzhermer'd Disease & Parkinsonism, 2:3.

Xu, X., Dong, Y.H., Hilal, S., Venketasubramanian, N., Ikram, M.K., Chen, C. (2013). The validation of the NINDS-Neurocognitive Battery in Singapore. The 7th International Congress of the Asian Society Against Dementia. Oral presentation.

Xu, X., Hogervorst, E. (2012). HVLT and MMSE performance in A Chinese Population in Jakarta: Comparing Performance against That of Javanese and Sudanese Elderly. Alzheimer's Research UK 2012 conference. Poster Presentation.

Xu, X., Dai, J., Hogervorst, E., Xiao, S.F. (2012). Sensitivity of the Chinese version of Hopkins Verbal Learning Test and Mini-Mental State Examination to Dementia and Demographics. The 15th Asia-Pacific Regional Conference of Alzheimer's Disease.Oral presentation.

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ABBREVIATIONS

3MSE	Modified Mini-Mental State Examination
95% CI	95% Confidence Interval
AD	Alzheimer's Disease
ADL	Activities of Daily Living
aMCI	Amnestic Mild Cognitive Impairment
APA	American Psychiatric Association
AUC	Area Under Curve
BADL	Basic Activity of Daily Living
BDI	Beck Depression Inventory
BFI	British Frailty Index
BMI	Body Mass Index
CDR	Clinical Dementia Rating
CESD-R	Centres for Epidemiologic Studies Depression-Revised
CHS	Cardiovascular Health Study
CI	Cognitive Impairment
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPS	Cognitive Performance Scale
CVD	Cerebral Vascular Disease
CVLT	California Verbal Learning Test
TUG	Timed-Up and Go
DEXA	Dual Energy X-ray Absorptiometry
DI	Discrimination Index
DLB	Dementia with Lewy Bodies

DR	Delayed Recall
DSM	Diagnostic and Statistical Manual of Mental Disorders
EMG	Electromyography
FA	Factor Analysis
FFI	Fried's Frailty Index
FFQ	Food Frequency Questionnaire
FI	The Frailty Index
FI-CGA	The Frailty Index based on the Comprehensive Geriatric Assessment
FTD	Frontotemporal Dementia
GBD	Global Burden of Disease
GDS	Global Deterioration Scale
GPS	Global Positioning System
GUG	Get-Up and Go
HD	Huntington’s Disease
HR	Heart Rate
HVLT	Hopkins Verbal Learning Test
HVLT-R	Hopkins Verbal Learning Test- Revised
IADL	Instrumental Activities of Daily Living
IR	Immediate Recall
K-HVLT	Korean version of the Hopkins Verbal Learning Test
KMO	Kaiser-Meyer-Olkin
LLFDI	Late-Life Function and Disability Instrument
LR	Logistic Regression
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination

MRC	Medical Research Council
NCI	No Cognitive Impairment
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NS	Not Significant
OD	Odd Ratio
OPTIMA	The Oxford Project to Investigate Memory and Ageing
PCA	Principle Component Analysis
PD	Parkinson’s Disease
RA	Research Assistant
RCT	Randomised Controlled Trial
ROC	Receiver Operating Curves
SE	Sensitivity
SF-36	The Short Form (36) Health Survey
SOF	Study of Osteoporotic Fracture
SP	Specificity
SPPB	Short Physical Performance Battery
SRT	Story Recall Test
UK	United Kingdom
VCI	Vascular Cognitive Impairment
vMCI	Vascular Mild Cognitive Impairment
WHO	World Health Organization
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Inde

Author's contribution to the work discussed in this thesis

The author of this thesis was actively involved in many aspects of the projects which have been conducted in Shanghai, China. The author liaised with Professor Eef Hogervorst from Loughborough University and Professor Shifu Xiao from Shanghai Mental Health Centre regarding the concept and design of the whole PhD project. The author played a major role in compiling the questionnaire pack and in obtaining ethical approval from both the Shanghai Mental Health Centre and Loughborough University to carry out the work related to this thesis.

Subsequently, the author provided supervision to all the research assistants, and made sure all the necessary technical and material support was given throughout the whole data collection period. The author conducted all the necessary literature reviews and statistical analyses, including data cleaning and entry, choosing the appropriate statistical methods, running analysis, as well as presenting results to Professor Hogervorst and other investigators. The author also wrote all the manuscripts included in this thesis

1 CHAPTER 1 GENERAL INTRODUCTION

1.1 Introduction

The population of China is ageing. The percentage of people aged 65 years and over will rise from 5.5% in 1990, to a predicted 13.3% in 2025, and an estimated 23% of the population (or 114 million) by 2050 (Woo, 2002). The health and social consequences of an ageing population are well recognized by the Chinese government and much emphasis has been placed on the prevention of chronic age-related disease. Although China has an excellent infrastructure for carrying out surveys to monitor health and nutritional status, the estimation of the actual number of elderly afflicted with age-related morbidity such as frailty and dementia still poses a problem (Woo, 2002).

1.2 Dementia in China

As a progressive degenerative disorder that causes a decline in memory, intellect, personality, and communication skills (Bayles, 1987), dementia has a significant impact on the quality of life. Zhang (1990) reported a percentage of 4.6% of dementia in people over 65 years of age in Shanghai. Prince (2008) reported a similar prevalence of 5.6% of dementia cases in rural China using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria. Zhang (2005) also examined dementia subtypes in China, reporting a prevalence of 4.8% for Alzheimer's disease (AD, the most common form of dementia) and 1.1% for vascular dementia (VaD). These Chinese data are comparable with dementia figures of Western countries. Currently 5 million Chinese elderly are estimated to be afflicted with dementia. With an estimated 400 million Chinese people over 60 years of age in the next decades and an estimated 5 percent prevalence of dementia, this would result in 1 million new cases every year. With an older age being a risk factor for dementia and an ageing population worldwide, dementia will increase globally, especially thus in the Chinese community, with an expected increase over 300% in dementia cases in the next decades (Zhang, 2005).

1.2.1 Variance in cognitive performance increases with age

With an advanced age, there is an average decline in various areas of cognitive function, such as memory, intellect, language and information processing skills. However, while some elderly show successful aging, with no or minimal cognitive impairment, others may develop mild cognitive impairment (MCI) where there are cognitive problems but people can still function, or dementia, which exerts a negative impact on patients' daily life. There are various subtypes of dementia, such as VaD, frontal temporal dementia (FTD) and dementia with Lewy bodies (DLB), but AD is probably the most representative syndrome of pathological cognitive dysfunction (about 60% of all cases with dementia receive this diagnoses). AD patients develop short and long term memory impairment, and lose their sense of orientation in time/place/people, as well as other cognitive functions, such as planning, visuo-spatial functions and language ability. Behaviours, such as anxiety, depression and delusions are also seen in the moderate and advanced stages (Raj, 2008).

1.2.2 Costs of dementia

These cognitive dysfunctions eventually result in a total loss of a patient's ability to live independently. Moderate and advanced dementia patients are often bedridden, causing a series of potentially fatal complications, including Pressure Ulcers, Pulmonary Infection and Cardio-pulmonary Insufficiency. Cognitive dysfunction not only brings about misery to the patients themselves, but also places a heavy burden on their carer's shoulders, in both economic and social aspects. In 1993, WHO (World Health Organization), World Bank and Harvard University launched a combined study on the Global Burden of Disease (GBD). It forecasted a burden index caused by dementia based on disability adjusted life year of 0.7% and 1.3% in the years of 1990 and 2020, respectively, in China. Among all types of psychiatric disease, the burden index of dementia ranked No.5 in 1990 and 1998. However, the report predicted that the ranking of dementia will go up to No.3, exceeding Schizophrenia and Obsessions (Unipolar Depression and Bidirectional Emotional Disorder are listed on the 1st and the 2nd place).

1.3 Mild cognitive impairment

Bayles (1987) reported that many families have difficulty determining when they first noticed symptoms of dementia, due to misunderstandings between the individual suffering from dementia and family members' observations of memory and other cognitive problems as being part of normal ageing. This may be related to the period of time it takes for the conversion of normal cognitive impairment to progress to dementia. MCI is regarded as cognitive impairment worse than that in those who have a similar advanced age, but which causes no interference with activities of daily life, such as dementia does. It has been reported that individuals with MCI are at a higher risk of progressing to AD, at a rate of 10-12% per year (Petersen, 1999). However, this is a heterogeneous group with some reverting back to normal cognitive function.

There is a growing awareness of MCI, where most studies now focus on the discrimination between the normal ageing process and those MCI cases who would convert to dementia. The most common MCI diagnosis criteria were developed by Petersen et al. (Petersen, 2004). According to the different manifestations and progressions, it can be divided into Amnestic Mild Cognitive Impairment (aMCI), vMCI (Vascular Mild Cognitive Impairment), and cognitive MCI which includes other cognitive dysfunction than memory. The aMCI and vMCI are the most commonly seen types. In line with the characteristics of the impairment, MCI is categorized as having a dysfunction in a single domain (referring mainly to the aMCI, which has mainly memory problems) versus that with dysfunction in multiple cognitive domains.

1.4 Dementia and frailty screening

The clinical diagnosis of dementia is based on neuropsychological testing, medical history and examination to rule out systemic, psychiatric, neurological and other causes of cognitive impairment, and to identify the pattern of progression (McKhann, 1984; American Psychiatric Association (APA), 1994). However, most clinical screening tools originate from developed

countries and do not take into account some of the issues pertaining to many developing countries such as:

1) a general lack of resources (e.g. a lack of trained staff, time and financial constraints)
2) high rates of illiteracy and cultural/linguistic differences which can affect the validity of neuropsychological tests.

A community-based study reported that cognitive impairment, as well as low level of physical activity, was the main elements associated with frailty and disability affecting an individual's capacity to live independently (Avila-Funes, 2011). It is currently not entirely clear how dementia as a syndrome relates to frailty.

Frailty is characterised by increased physical dependency and its symptoms are loss of physical ability due to muscle wasting, fatigue etc. Some authors have included cognitive impairment as part of this syndrome (Fried, 2001). In the next chapter (chapter 2) we describe frailty and its different diagnostic criteria. It will become clear that there is little consensus on the criteria that together are part of this syndrome.

In chapter 3, we describe cognitive tests used to screen for dementia, which may be part of the frailty syndrome.

Subsequently we will describe the aims, hypotheses (chapter 4) and methods (chapter 5) used in this thesis to investigate dementia and frailty in China. In chapter 6 section 6.1, we describe results of a sample of community dwelling elderly in Shanghai (n=521) who had been diagnosed through clinical consensus as is the gold standard and who had been tested on our dementia screening tests (Hogervorst, 2011), previously found in Oxford (Hogervorst, 2002; De Jager, 2003, Schrijnemakers, 2008) and rural and urban Indonesia (Hogervorst, 2011) to have good validity for dementia and MCI. We also describe demographic modifiers for test performance. In chapter 6, section 6.2, we describe the sensitivity and specificity for the cognitive tests for dementia and MCI on another

sample of n=170 participants. In chapter 6, section 6.3 we describe a sample of older participants (n=50) who were institutionalised to further investigate validity of our cognitive tests for dementia. Here the focus was on differentiating between elderly suffering from psychiatric disorders and those with dementia.

In chapter 6, section 6.4 we describe factor analyses of the cognitive and physical ability tests to investigate whether some physical and cognitive symptoms clustered together to form functional disability in n=170 community dwelling participants.

In chapter 7, section 7.1 and 7.2, we describe the combination of 7 potential frailty characteristic together (BMI, grip strength, Timed-Up and Go (TUG)-get up, TUG-walk, 15 feet gait speed, Berg balance test, and physical activity), along with cognitive assessment (the HVLT and the MMSE) to predict cognitive impairment and functional disability. In section 7.3, we combined the most common assessments over all frailty criteria reported in the past literature to build up a phenotype of frailty. Subsequently we describe the prevalence of frailty in the current sample, and the extent to which frailty shows overlap in (physical) functional disability as well as cognitive impairment.

In chapter 8 we describe demographic risk factors for cognitive impairment in the cohort of n=521 community dwelling elderly using age, gender, education and profession as the essential characteristics to predict CI.

In chapter 9 we describe lifestyle risk and protective factors for cognitive impairment, especially the association between tofu intake and cognitive impairment (section 9.3). In chapter 10 we discuss the utility of the HVLT compared to the MMSE in detecting MCI and dementia, the prevalence of frailty world-wide, and the implications of the clusters of symptoms in elderly found for community based interventions, such as exercise and cognitive stimulation, which have previously been found to treat cognitive and possibly physical impairments (Clifford, 2009; Hogervorst, 2012). Finally we discuss the association between tofu intake and cognitive impairment.

1.5 References

American Psychiatric Association (APA, 1994). Diagnostic and Statistical Manual of Mental Disorders, American Psychiatric Publishing Inc.

Avila-Funes JA, Pina-Escudero SD, Aguilar-Navarro S, Gutierrez-Robledo LM, Ruiz-Arregui L, Amieva H. Cognitive impairment and low physical activity are the components of frailty more strongly associated with disability. J Nutr Health Aging 2011; 15(8):683-689.

Bayles, K.A., & Kaszniak, A.W. (1987). Communication and cognition in normal aging and dementia. Boston, MA: College-Hill Press.

Clifford A, Yesufu U.A, Edwards A, Bandelow S & Hogervorst E (2009).Maintaining cognitive health in elderly women: an invited review. Aging Health 2009; 5: 655–670.

De Jager, C.A., E. Hogervorst, M. Combrinck & M. M. Budge (2003). Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. Psychological Medicine, 33:1039-1050.

Fried LP, Tangen CM, Walston J et al (2001). Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci; 56A:M146–M156.

Hogervorst E, Combrinck M, Lapuerta P, Rue J, Swales K, Budge M (2002).The Hopkins Verbal Learning Test and screening for dementia.Dement Geriatric Cogn Disord,13(1):13-20.

Hogervorst, E., et al. (2011) Validation of Two Short Dementia Screening Tests in Indonesia: in Vascular Dementia: Risk Factors, Diagnosis and Treatment Editors:

McKhann, G., Drachman, D., Folstein, M., Katzman, R., Price, D., & Stadlan, E. M. (1984).Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology, 34(7), 939-944.

Petersen, R.C., Smith, G.E., Waring, S. C., Ivnik, R.J., Tangalos, E.G., & Kokem, E (1999). Mild cognitive impairment: Clinical characteristics and outcome. Archives of Neurology, 56(3): 303-308.

Petersen R.C. (2004). Mild cognitive impairment as a diagnostic entity. Journal of Internal Medicine, 256: 183-187.

Prince M. (2008). Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey, The Lancet (372): 464-474.Raj NK, Gladys EM, Raul A, et al. Alzheimer's disease and vascular dementia in developing countries: prevalence, management, and risk factors. Lancet Neurol, 2008, 7(9): 812-826.

Schrijnemaekers, A.M.C., Celeste A. de Jager; E. Hogervorst; M. M. Budge (2006). Cases with Mild Cognitive Impairment and Alzheimer's Disease Fail to Benefit from Repeated Exposure to Episodic Memory Tests as Compared with Controls. Journal of Clinical and Experimental Neuropsychology, 28(3):438 – 455.

Zhang, M.Y., Katzman, R., Salmon, D. et al. The prevalence of dementia and Alzheimer's disease in Shanghai, China: impact of age, gender, and education. Ann Neurol, 1990 (27):428–37.

Zhang, Z.X., Zahner, G.E., Román, G.C., Liu, J., Hong, Z., Qu, Q.M., Liu, X.H., Zhang, X.J., Zhou, B., Wu, C.B., Tang, M.N., Hong, X., Li, H. (2005).Dementia subtypes in China: prevalence in Beijing, Xian, Shanghai, and Chengdu. Arch Neurol.62 (3):447-53.

2 CHAPTER 2 PREDICTING AND DIAGNOSING FRAILTY AMONG COMMUNITY-DEWELLING ELDERLY PEOPLE USING PHYSICAL, PSYCHOLOGICAL AND OTHER INDICATORS: A SYSTEMATIC REVIEW

2.1 Introduction

An elusive and controversial concept, frailty is thought to be highly prevalent in old age, particularly in those with low education and those of low socioeconomic status (Fried, 2001). Prevention, by identifying modifiable risk factors for frailty and targeting these for modification, is important. For instance, Woo (2002) reported that with increasing urbanization in China in the past decades, levels of physical activity are reduced. There is also a rural-urban discrepancy in nutritional intake (e.g. 12–18% of energy is derived from fat in rural areas, versus 20–31% in urban areas) further exacerbating the risk for obesity and related morbidity (diabetes, heart disease, dementia etc.). Lack of appropriate nutrition (or the converse, resulting in obesity) and lack of activity leading to morbidity and poor health has been associated with frailty (Fried, 2001).

The diagnosis of frailty is mandatory for the early identification of a subset of elderly subjects at high risk, who can subsequently receive benefits from rehabilitation programs and thus reduce their risk for co-morbidity and disability. However, there is some variation in the definition of frailty and how to best assess this. The current thinking is that not only physical, but also psychological, cognitive and social factors contribute to this syndrome and these need to be taken into account in its definition and treatment (Fulop, 2010, Abate, 2007). This review investigates and compares different criteria for frailty, and their overlap to establish the best cost effective and easy to implement assessment.

According to Fried (1997; 2001), the phenotype of clinical frailty is characterized by a critical mass of 3 or more “core frail elements” which are: i) weight loss>10 lbs in past year, ii) weak grip strength (lowest quintile), iii) exhaustion (by self-report), and also iv) slow gait speed (lowest

quintile) and v) low physical activity (lowest quintile). Similarly, others (Ensrud, 2007) also identified the frailty phenotype as having the following components: i) unintentional weight loss, ii) self-reported fatigue and iii) diminished physical activity, which by these authors was measured using impaired grip strength and reduced gait speed. Campbell and Bucher (1997) measured frailty by using the following specific tests: i) grip strength, ii) chair stand, iii) sub-maximal treadmill performance, iv) 6 min walking test, v) the Static Balance Test, vi) Body Mass index (to assess weight loss), vii) arm muscle area (to assess sarcopenia, the muscle loss associated with frailty) and viii) the Mini Mental State Examination (MMSE, Folstein, 1977) for cognitive impairment (the psychological dimension).

These multiple assessments test the subject's appropriate interactions with the environment on the basis of their physiological and psychological limitations, and allow obtainment of an overall frailty score. This also allows for identification of different areas of potential disability associated with frailty which could perhaps be targeted by specific interventions. Abate (2007) suggested that both self-report and an objective evaluation of physical performance would be the best indicators of frailty in elderly subjects. Others also used fewer tests than described in the criteria above. For instance, Ravaglia (2008) only used a cut-off point of 24 on the Tinetti gait and balance performance test to obtain a "frailty score". However, their prognostic score was not adequately tested in a cohort of elderly, and also sensitivity and specificity of this test needs further investigation. Syddall (2003) examined grip strength as a single marker for frailty, suggesting that grip strength is a useful single marker of frailty for older people. Guyatt (1985) investigated participants' performance on a 6-minute walking test and concluded that it in itself is a useful and acceptable measure of functional exercise capacity and a suitable and meaningful predictor of frailty. Whether a single or a few assessments are useful in diagnoses of frailty is important, as this would reduce costs of screening.

In this systematic review we also aimed to assess the relationship of cognitive impairment, functional disability and frailty. According to some criteria, mental or cognitive impairment is a crucial factor for frailty and would need to be assessed using objective instruments. On the other hand, frailty may also be an early indicator for possible dementia. One study showed that at post-mortem AD brain pathology was associated with frailty in both people with and without dementia (Buchman, 2008). Risk for frailty was doubled in people with AD pathology independent of a history of other disease and level of physical activity. Another study of this group showed that those who were physically frail with no cognitive impairment at baseline had a higher risk of developing AD at follow-up. Frailty may thus be an early marker of AD pathology, occurring before memory loss. This could indicate common pathways (and treatments) for frailty and AD. For instance, accumulation of plaques and tangles found in the brain could affect areas associated with motor behaviours before other symptoms such as memory loss associated with other areas becomes apparent.

2.2 Methods

A systematic literature review was thus conducted aiming to assess the various frailty screening tools in search of the best combination of measurements to aid clinical practice of the frailty diagnosis.

2.2.1 Data sources

The electronic database of PubMed, Cochrane library and CINAHL were systematically scanned using the following search terms: outcome was defined as ‘physical’/’functional’/’cognitive’ and was combined with ‘disability’ or ‘frailty’. There was no restriction on years of publication. The references of the included studies were further searched for relevant articles. The last search was performed on 11 Jan, 2012. Both longitudinal cohort studies and randomized controlled trials were included. Cross-sectional studies (n=3) and studies using only special patient groups were excluded from the present review because they were considered to have less predictive validity for the

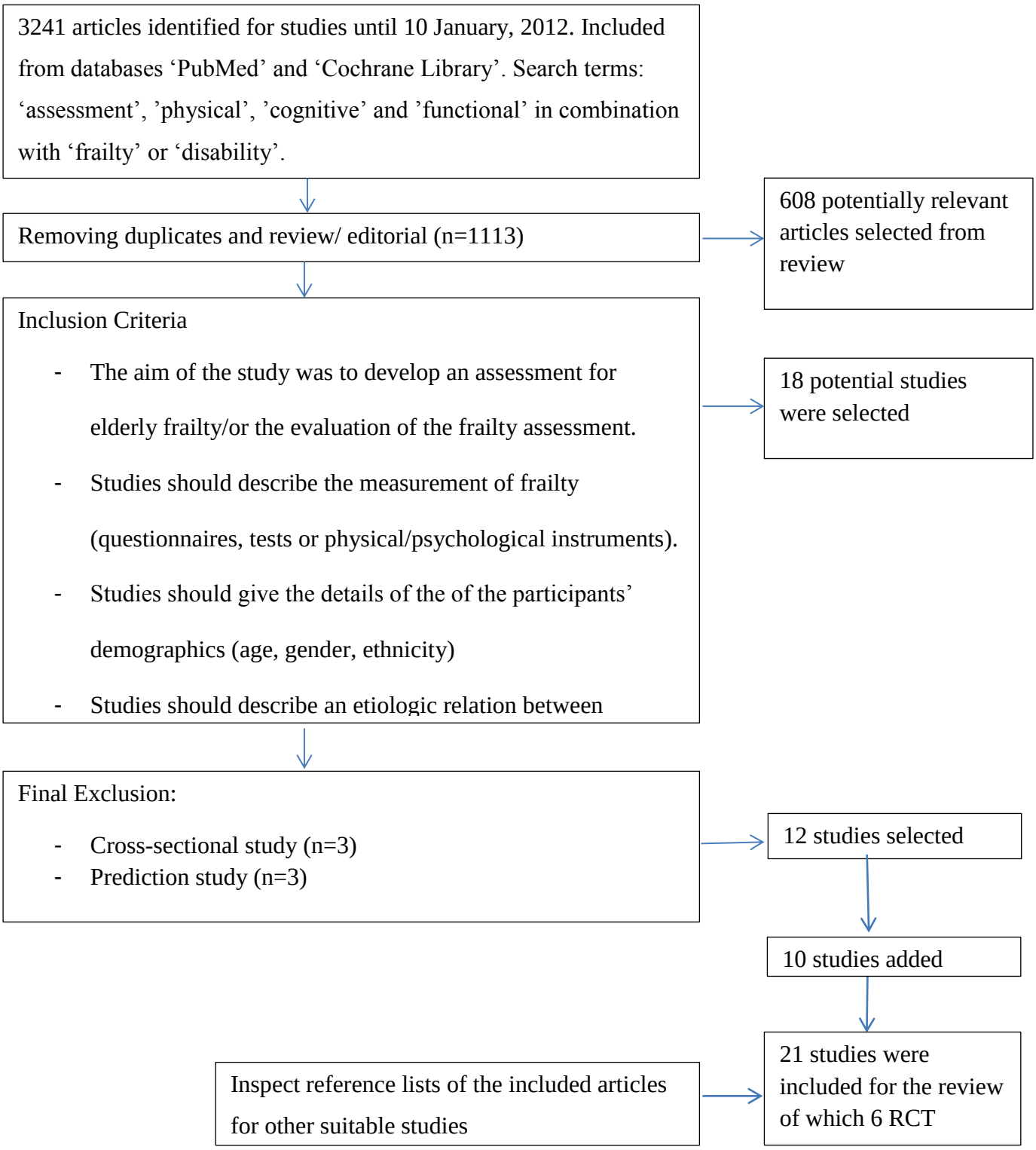
general elderly population and may have been confounded by other variables (i.e. co-occurring factors rather than causally related factors). Unpublished studies and book chapters (n=4) were also excluded as these usually have undergone a less rigorous peer review.

2.2.2 Selection process and quality assessment

Titles and abstracts of articles were identified through the search process for potentially relevant studies. Articles were eligible for inclusion if they met the following criteria: (i) written in English or Chinese; (ii) were a prospective longitudinal study or a randomised controlled study (RCT); (iii) focused on community-dwelling elderly aged 65 and over; (iv) having used activities of daily living (ADL) disability or Frailty according to certain operational criteria as the main outcome measure. Articles focused only on patients with certain diseases, such as diabetes, cancer or Parkinson's disease, were excluded from the review.

The quality of the included articles was assessed based on the guidelines of the Cochrane Library. Description of the study (e.g. age, gender, sample size), study design (outcome, measurement and the length of the follow-up), data collection, missing data/ drop out during the follow-up and data analysis were considered important as part of the scoring of study quality.

For each aspect one point was assigned to the study (see table 1: criteria + points). The total score was gained after calculating points over all aspects. The maximum score for longitudinal cohort studies was 22 and for RCTs were 23. A higher score indicates a higher quality of the methodology used.


3241 articles identified for studies until 10 January, 2012. Included from databases 'PubMed' and 'Cochrane Library'. Search terms: 'assessment', 'physical', 'cognitive' and 'functional' in combination with 'frailty' or 'disability'.
Removing duplicates and review/ editorial (n=1113)
608 potentially relevant articles selected from review
Inclusion Criteria
- The aim of the study was to develop an assessment for elderly frailty/or the evaluation of the frailty assessment.
- Studies should describe the measurement of frailty (questionnaires, tests or physical/psychological instruments).
- Studies should give the details of the of the participants' demographics (age, gender, ethnicity)
- Studies should describe an etiologic relation between
18 potential studies were selected
Final Exclusion:
- Cross-sectional study (n=3)
- Prediction study (n=3)
12 studies selected
10 studies added
Inspect reference lists of the included articles for other suitable studies
21 studies were included for the review of which 6 RCT

2.3 Results

The operationalization of the frailty indicators revealed in these 25 studies is shown in table 2. The characteristics and details of these studies are shown in table 3. All RCT (n=5) and longitudinal cohort (n=19) studies were included in the review. In the longitudinal studies the follow-up time ranged from 10 months to 9 years. All RCTs had a follow-up of at least one year, during which the participants were measured one to three times. Data extracted from the RCT are from the assessment, not the treatment.

The overall quality of the studies included in the review was modest to good. For cohort studies the quality ranged from 19 to 22, and for RCT from 20 to 23 (include in table 4 to discuss studies).

Studies that used physical indicators for the frailty diagnoses are shown in table 3. For this variable, RCT (n=6) and cohort (n=15) could be included.

Among included studies, frailty was measured using different criteria. The operational criteria of the studies were: SOF criteria (n=4), Fried's Frailty Index (FFI) (n=6), The Frailty Index (FI) (n=3), a combination of deficiencies in function (Functional Domains model), an index of health burden (Burden model), and biologic al syndromes (Biologic Syndrome model) (n=1) and others (n=6).

The outcome was mainly expressed as frailty (n=16), functional dependence/ limitations (n=2) and disability (n=6). See table 5 for an overview of these frailty criteria and their individual factors for assessment. This overview suggests that no consensus is derived on the best gold standard criteria to use in studies. However, the most common individual factors used are discussed in the following paragraph.

2.3.1 Characteristics of physical frailty indicators

The majority of the studies provided the height/weight/BMI figures of the participants (n=20). For the physical indicators of frailty, the next most commonly used marker was walking speed using the gait speed test (n=17).

Upper body strength and balance were also used as important measurements for frailty (n=13 and n=11, respectively). In comparison, only 5 studies measured lower body strength.

Self-assessed level of physical activity and exhaustion were reported in less than half of the studies (n=7 and n=8, respectively).

Besides these, other physiological measurements, such as bone mineral density (Ensrud, 2009), muscle activity measurements using Electromyography (EMG), heart rate (HR) recordings using HR monitoring, and walking distance using Global Positioning System (GPS, Theou, 2011) were also described in the included studies. Individual differences in assessments of these factors and their applicability (in terms of time and costs requiring instruments and trained staff) are described in the following paragraphs.

2.3.1.1 Weight loss

Gibson (2010) found that a lower Body Mass Index (BMI), which has been described as a physiologic precursor and etiologic factor in disability (Fried, 2001), was associated with functional limitations and suggested that it, should be a marker for advancing frailty. In most of the studies (n=17) body mass index was assessed as weight in kilograms divided by the square of the height in metres) which is relatively low cost to assess. There were no studies using Dual Energy X-ray Absorptiometry (DEXA) or other body scans, which are more costly and labour intense requiring specialist staff. However, this objective assessment is possibly preferable, as BMI is susceptible to bias due to muscle mass, is not reliable for people of short stature and needs to be adjusted for Asian populations (Esqueda, 2004).

Unintentional self-reported weight loss, defined as having 'lost 10 lbs in the past year' or '5% of body weight in the last 3-4 years', was reported in 8 studies (Freiheit, 2011, Gill,2006, Ensrud,2009,Gill, 2009, Kiely,2009, Strawbridge,1998, Ottenbacher,2005, Rothman,2008), as this is seen as a key indicator of frailty. However, self-report may not be a reliable reflection of actual

weight loss and only 11 studies used objective weight loss assessment. Unintentional weight loss or cachexia is also a symptom associated with multiple morbidities (cancer, depression, prolonged forced bed rest, etc.) which could lead to frailty (Fisher, 1990; murden, 1994; Bryant, 1995). Unexplained weight loss related to frailty might be associated with central nervous brain changes, such as those seen in dementia (McKhann, 1984 Gillette, 2000, 2007; Buchman, 2005; Tamura, 2007). However, others have shown that feeding (because people with dementia forget to eat) reverses weight loss in dementia (Berkhout, 1998; Smith, 2008).

Whether unexplained weight loss is an early factor in frailty and whether regulated feeding and exercise can reverse this and subsequent associated functional decline remains to be investigated.

2.3.1.2 Gait speed

The majority (n=17) of studies included gait speed as an individual physical indicator for frailty. The 6-metres walking test was the most common test to be used in these studies. All of these studies reported that those who have slower walking speed were at higher risk of frailty. Rothman (2008) reported that slow gait speed was the strongest predictor of chronic disability, increasing the risk three-fold (OR=2.97, 95% CI 2.32–3.80), and that this was the only significant predictor of injurious falls, doubling their risk over a 7.5-year follow-up (OR=2.19, 95% CI 1.33–3.60). This objective assessment is easy to perform, requiring little training for research assistants and few instruments (stopwatch, two chairs and measurement tape to establish 1 m distance between chairs).

2.3.1.3 Upper body strength

Handgrip strength was measured as the primary indicator for frailty in 13 studies using a handheld dynamometer. Those who fell into the lowest quintile of the grip strength group (according to gender and BMI-specific thresholds) were identified as being at risk of frailty. Grip strength was associated with risk of dementia before other symptoms became apparent (e.g. Baltimore

Longitudinal Study of Ageing BLSA, Verbrugge, 1996) and may thus be an early indicator of frailty and dementia.

2.3.1.4 Lower body strength

Although not included in the SOF (Study of Osteoporotic Fracture), The Frailty Index (FI) nor Fried's Frailty Index (FFI), several authors did include lower body strength as a part of the frailty syndrome (n=8) which showed good predictive value at follow-up for functional disability. Among these studies, participants were requested to do the chair standing up and sitting down test which was repeated 3 or 5 times (Guralnik, 1995; Gill, 2009; Kiely, 2009; Gill, 2009; Gibson, 2010). The total length of time needed for this chair stand test was recorded. Those who fell into the lowest quintile of the score were identified as being at risk of frailty.

Theou (2011) used a slightly different scoring method— counting the total movement finishing times within 30 seconds. Gill (2009) added hip abduction as a marker for lower body strength. The instrument in Strawbridge's study (1998) was not clearly described. From these data it could be concluded that lower body strength may need to be included in the criteria as it has low costs but its predictive validity needs to be further investigated.

2.3.1.5 Balance

12 studies provided information about the predictive value of balance using different types of measuring methods. One-leg standing balance was the most commonly used test (Guralnik, 1995; Shinkai, 2000; Kiely, 2009; Nemoto, 2011; Gill, 2009; Cigolle, 2009). Gibson (2009) adopted Postural Sway as a measurement of static balance and the 'timed up and go' test (TUG) as well as the 'step test' to measure mobility and dynamic balance, while Thoeu (2011a, b) used 8-foot up-and-go and an investigation of agility and standing balance. All of these studies reported the importance of balance in predicting frailty/disability. However, some used more complicated and costly assessments and a cost-benefit analyses needs to be made to establish the best (most predictive) and cost effective assessment for balance.

2.3.1.6 Exhaustion

Self-report exhaustion level was measured in 7 of the included studies to investigate its predictive value on frailty or disability as a criterion. By using one or two simple questions based on a depression scale, participants' energy level was determined (Fried, 2001; Ottenbacher, 2005; Ensrud, 2009; Cigolle, 2009).

However, Rothman (2008) concluded that exhaustion was not found to be independently associated with frailty, suggesting that only when it was used in a composite measurement of frailty did it show good predictive value in combination with other assessments. Only Freiheit' study (2011) reported the best individual predictive value of exhaustion on mortality (OR 1.61, 95% CI=1.20-2.15) in an assisted-living population.

2.3.1.7 Physical activity

In total 7 studies focused on the association between physical activity (PA) level and frailty/disability. Based on calculating kilocalories of physical activity expended per week using specific cut-off points, those who fell into the lowest quintile of PA were classified as at risk of frailty. Most of these studies (Jones, 2004; Gill, 2006; Ensrud, 2009; Cigolle, 2009) adopted physical activity as a part of the composite frailty predicting system and reported good predictive value of the assessing instrument. Additionally, the single predictive value of PA was reported by several authors. The risk of low physical activity for incident mortality (OR=1.60, 95% CI 1.19-2.16 for absolute and OR=1.50, 95% CI 1.11-2.03 for relative cut-points) in an assisted-living population was reported by Freiheit (2011). Similar results can be found in Rothman's study (OR=2.7, 95% CI 2.3-2.5) in predicting chronic disability. The OR of roughly 2.1 in short-term and 4.2 in long-term disability was shown in the graphs in Gill's study (2009). Peterson(2009) also concluded that individuals who exercise regularly were at lower risk of developing frailty in 5 years compared to sedentary individuals (adjusted OR = 1.45; 95% CI: 1.04 – 2.01). Again for self-

reported PA, bias can be introduced (i.e. self-report may be less reliable in those with early signs of dementia). Objective PA outcomes (using VO2max) are more complicated but have better validity.

2.3.1.8 Other physical indicators

Dizziness after doing the standing up test was surveyed in two studies as a symptom indicating poor physical function (Strawbridge, 1998; Cigolle, 2009). Nemoto (2011) adopted a 12-item Physical Function Test (PFT) to assess the physical indicators of frailty. Apart from gait speed, grip strength and balance, a number of other tests was involved, such as tandem walk/stance, functional reach, sit and reach, alternate step, moving beans with chopsticks, timed up-and go and hand working with peg board. They reported that except for the sit and reach test, the other tests all discriminated significantly across four different groups: no frailty, pre-frailty, frailty and dependent.

In Gill's study (2009), several physical assessments were applied in addition to the Short Physical Performance Battery (SPPB) which also showed strong associations with the 5 subtypes of disability. Manual dexterity, gross motor coordination, non-dominant upper body (shoulder flexion), lower body (hip abduction) strength and peak expiratory flow was investigated in the study. However, none of these was significantly related to disability.

Joint pain, stiffness and physical function measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was included in Gibson's study (2010) in addition to the physical assessments, although no strong association of any of these factors with frailty was found. The WOMAC (Bellamy, 1988) is a validated, 24- item, disease and joint-specific measure that evaluates knee pain, stiffness and physical function. The instrument has been designed as a self-report measure which contains three subscales: the physical function (difficulty) subscale comprises 17 items on a 0 to 100 horizontal scale; the pain subscale comprises five items based on a 0 to 100 VAS; and the stiffness subscale of the WOMAC Index comprises two items based on a 0 to 100.

In sum, none of these other factors really seems to add to the diagnoses of frailty over and above those that were earlier discussed.

2.3.2 Characteristics of Psychological Frailty Indicators

2.3.2.1 Cognitive symptoms

There were 15 studies which regarded cognitive ability as an indicator for frailty. To assess this, most of these studies (n=9) used the Mini-Mental State Examination (MMSE, Folstein 1975) or its modified version.

Furthermore, memory deficits were taken into consideration (n=3) as well as attentional dysfunction (n=2).Cognitive functional decline is regarded as a risk factor for adverse geriatric outcomes (Inouye, 2007). It is thus increasingly more common to involve cognitive status assessments in the clinical setting for geriatric syndrome evaluations. We previously discussed the association between dementia and frailty (see introduction). Indeed, Fried (2001) reported that lower cognitive performance (MMSE>18) was associated with frailty. Similarly, Rothman (2008) found that cognitive impairment (MMSE<24) was independently and strongly associated with chronic disability, long-term hospital stays and death, exceeding those from Fried's model of frailty criteria. In other studies, cognitive status measuring with MMSE also showed good predictive validity for frailty (adjusted OR=1.75, 95% CI 1.08-2.84) (Jones, 2004: cut-off MMSE=24) and disability (OR 0.89, 95% CI 0.85-0.94) (Feng, 2011: cut-off MMSE=21). The MMSE cut-off point of 16 was also one of the three independent predictors for mortality in Bilotta's research (2012) (OR 5.60, 95% CI 1.29-24.42), although it was not significantly related to frailty at baseline. They also showed that when combined (severe cognitive impairment (defined as MMSE<16) with gender (male) and presence of the frailty syndrome using the SOF criteria), the OR for one-year mortality was huge (16.31, 95% CI 1.28-208.14, p=0.03) after adjustment for age and co-morbidity. However as confidence intervals were also very large, caution needs to be taken and further research needs to confirm these findings.

Interestingly, Raji (2005) assessed the relationship between MMSE performance and grip strength and found that having poor cognition (MMSE score <21) was associated with a greater decline in muscle strength (estimate=-0.29, SE=0.07; P<.001) after adjustment for covariates and that it showed good predictive value for onset of activities of daily living (ADL) disability over a 7-year follow-up (OR 2.01, 95%CI 1.60-2.52). Notably, excluding those with an MMSE score less than 15, having a MMSE score between 15 and 21 was still significantly associated with greater risk of 7-year incident ADL disability (OR=1.75, 95% CI=1.37 to 2.23). The magnitude of the association decreased to 1.48 (95%CI= 1.15 to 1.91) when adjustment was made for handgrip strength and other potential confounds (age, sex and time in study).

Besides the MMSE, other cognitive assessments were also sometimes included in the studies. The Cognitive Performance Scale (CPS), for instance, was applied in Freiheit's study (2011) to measure the severity of cognitive impairment, although no strong relationship between this scale and frailty was reported. In addition, Kiely (2009) used not only the MMSE, but also the Hopkins Verbal Learning Test-Revised version (HVLT-R) in combination with other tests (Word Generation, Trails A, Trails B, Clock-in-a-Box) to assess cognitive function and showed its association with increasing frailty. Memory problems were also taken into account as a part of the psychological factors in Kamaruzzaman's study (2010). However, these were measured by self-reported together with diagnosis and thus have less validity. The HVLT was shown to be highly sensitive to dementia and other forms of cognitive impairment and is cross-culturally applicable (Hogervorst, 2011).

These findings highlight the extent to which adverse geriatric conditions are affected by cognitive status. Given the high prevalence of cognitive dysfunction among elderly people, it is reasonable to include cognitive impairment as a predicative factor for frailty in the future researches. Also the combination of the HVLT and MMSE are relatively easy to implement in large screening studies and are both sensitive to treatment effects (Hogervorst, 2011).

2.3.2.2 Depression

Nine studies investigated the association between depression and frailty/disability (Fried, 2001; Raji, 2005; Rothman, 2008; García-González, 2009; Kiely, 2009; Kamaruzzaman, 2010; Gibson, 2010; Bilotta, 2011; Freiheit, 2011). Among these, the most commonly used instrument was the Centre for Epidemiologic Studies Depression Scale (CES-D) scale with a cut-off of 16 to indicate the presence of depression. On the other hand, Kamaruzzaman (2010) assessed subjective feelings of depression/anxiety as a part of psychological problems together with memory problems. The CES-D was used in Kiely‘s study (2009) as a marker for reduced energy levels and they reported strong associations of the test scores with frailty. The Beck Depression Inventory (BDI) was administered in Gibson’s study (2010) and proved to be associated with functional ability (OR=-0.23, 95% CI=-0.34 to -0.12, $p<0.001$) and mobility disability (OR=-0.42, 95% CI=-0.60 to -0.24, $p<0.001$). Similar results can be found in the research papers by Fried (2001), García-González (2009), Freiheit (2011) and Bilotta (2012). Interestingly, high depressive levels were significantly related to weaker handgrip strength (Raji, 2005). However, depressive symptoms were not associated with any of the disability, long-term hospital stays and death in another study (Rothman, 2008). This suggests that the association between depression and frailty remains debatable.

2.3.2.3 Characteristics of the functional frailty indicator

People who suffer from ADL disability cannot live independently in the community. Although disability and frailty frequently coexist among elderly people, they are separate concepts. Frailty indicates vulnerability and risk of loss of physical and mental function. Disability demonstrates loss of function and dependency in activities of daily living, and is more likely to be a possibly result of frailty (Campbell, 1997). According to Topinková (2008), frailty was found to be strongly related to disability. Nevertheless, in some contexts, disability was included in the concept of frailty (Fried, 2004). Thus, finding a standardized definition for frailty and the place of disability in this context is challenging.

In this review, in order to provide as more specific materials as possible, we considered both 'frailty' and 'disability' as valid descriptions for outcomes. In this review, 14 studies involved functional assessment as a marker for frailty, amongst which 11 used ADL-relevant instruments for the assessment which proved to be significantly related to frailty according to the criteria they used (Fried, 2001; Jones, 2004; Kiely, 2009; Ensrud, 2009; Freiheit, 2011; Nemoto, 2011; Vest, 2011).

In Bilotta's study (2012), the Instrumental Activities of Daily Living (IADL, Lawton, 1969) and the Basic Activity of Daily Living (BADL, Katz, 1970) was used. Dependency as reported in the BADLs was also independently associated with frailty (OR=6.11, 95% CI 2.17-17.18, p=0.001), more specifically with dressing (OR=5.54, 95% CI 1.03-29.71, p=0.046). As a functional marker for disability, IADL was not as sensitive p=0.68). However, although Feng (2011) found that ADL performance differed between participants over 75 years of age from China and Singapore and showed a significant cultural difference, it did not independently contribute to disability.

Besides ADL-relevant instruments, other measures were taken along in other studies. Kamaruzzaman (2010) investigated participants' household chores, going up and downstairs, walking outside, washing and/or dressing and activity status levels as a part of their daily physical ability, although no clear result of these factors with frailty was reported. Gibson (2010) applied the Late-Life Function and Disability Instrument (LLFDI), one of the few disability instruments that provide a comprehensive assessment of all aspects of progressive disablement and disability, to assess self-reported physical functioning and disability. Their findings suggested that functional impairment was most significantly associated with objective physical measures (e.g. 6 minute walk and TUG test). Lower extremity function showed a strong predictive value for disability.

Physical functioning was measured using the Short Form (36) Health Survey (SF-36), a gold standard test for health to accompany the investigation of frailty in Nemoto's study (2011). It showed a strong relationship with the frailty diagnosis and could perhaps be used as an indicator of overall physical and mental health associated with frailty. ADL and IADL assessment is also useful

in establishing need to support in dementia and is crucial for its diagnoses as criteria stipulate that cognitive impairments should impact on activities of daily life (McKhann, 1984, APA, 1994).

2.3.3 Outcomes related to frailty

Falls was one of the major adverse outcomes of frailty among elderly, which could lead to a hospitalization and dependence. However, falls risk is also increased in dementia and risk for dementia increases with falls (Buchner, 1987; Van Dijk, 1993; Van Doorn, 2003). The relationship of this association is complicated (i.e. which symptom leads to which outcome). In 7 studies falls risk was assessed at both baseline and follow-up for its predictive validity for disability/frailty.

Applying different operational criteria, such as SOF (OR=2.2, 95% CI=1.2 to 4.0) and CHS (OR=1.9, 95% CI=1.2 to 3.1) (Kiely, 2009) risk for falls was doubled in those with frailty. Ensrud (2009) reported a three top four fold risk and found that frail men had a higher risk (OR=3.6) of recurrent falls than frail women (OR 3.0) over a 3-year period of follow-up. Fried (2001) measured incident falls among not frail, intermediate and frail groups and reported that risk for frailty was only increased by 29% after adjustment (OR=1.29, 95% CI=1.00 to 1.68, p=0.05) over a 3-year period and for the intermediate group only by 12% ($OR_{intermediate}$=1.12 (95%CI=1.00 to 1.26, p=0.05) over a 7-year period. In Rothman's study (2008), injurious falls leading to hospital admission showed strong connections with slow gait speed during a 7.5-year period of follow-up. Gibson (2010) investigated number of falls during the past 12 months as a risk for frailty and also as a determinant for disability, but reported no clear results. However, power of the study and duration of follow-up may have been insufficient to show associations. As falls are related to high cost outcomes (hospitalisation and dementia requiring support) interventions need to focus on risk and prevention for this in particular.

Frailty as a syndrome was associated with greater risk of hospitalization and mortality in older people (Fried, 2001). Thus vulnerability to hospitalization and mortality was taken into account in some of the studies included in the review (Raji, 2005; Gill, 2006; Kiely, 2009; Rothman, 2008;

Ensrud, 2009; Peterson, 2009; Gibson, 2010; Kamaruzzaman, 2010) and should be included in all screening studies investigating frailty as well as falls.

Gill (2006) provided the transition rates between the 3 frailty states and death for each of the 18-month follow-up intervals to determine the effect of the preceding frailty state. Their study reported an overall transition rate of 16.5% from pre-frail at 18 months to non-frail at 36 months. In addition, different transition rates of 31.8%, 14.8% and 0% from pre-frail, non-frail and frail at baseline to non-frail at 36 months were also revealed.

Hospital admission in the past four weeks was recorded by Rothman (2008) and Gibson (2010) and showed an association with frailty. Ensrud (2009) reported that mortality rates were higher with greater evidence of frailty identified using either the SOF or CHS index. Overnight hospitalization (OR=3.5, 95% CI=1.5 to 8.0); OR=4.4, 95% CI=2.4 to 8.2) according to SOF and FFI criteria respectively was also reported in Kiely's study (2009). Kamaruzzaman (2010) demonstrated that in the MRC (Medical Research Council) assessment study, frailty was proved to be a stronger predictor of mortality earlier on in the follow up period (between 0 to 2.5 years); The British Frailty Index (BFI) showed good predictive value of frailty on the risk of hospital admission (fully adjusted OR=1.5, 95% CI=1.4 to 1.6 vs. OR=1.3, 95% CI= 1.2 to 1.3) as well as institutionalization (fully adjusted OR=1.6, 95% CI= 1.4 to 1.8 vs. OR=1.3, 95% CI= 1.2 to 1.4) in the MRC cohort.

2.4 Discussion

In this systematic review, we summarized the results of various studies investigating the associations between physical, mental and health-related performance characteristics and frailty including dependency, limited function and disability.

This review provides evidence that not only can physical indicators predict frailty, but also can cognitive and demographical variables as well as personal habits be persuasive markers of frailty. Because there is no consensus on how to arrive at a clear definition of frailty, it was difficult to

create a standardised database searching strategy. Thus in this review, we not only focused on those criteria which were explicitly defined as ‘frailty’ by the researchers, but also chose those which investigated long-term adverse functional status, as assessed by ADL limitations, possibly resulted from frailty and measured using similar screening instruments.

Risk factors for frailty were the following. The majority of studies described a correlation between older age, lower education, and low scores on the IADL/ADL with frailty that would give rise to adverse outcomes, such as hospitalisation and mortality. Apart from that, low level memory and cognitive performance was found to have a long-term negative impact on frailty. The role of falls is important in both cognitive limitations and frailty.

Importantly, higher levels of physical activity were associated with a lower frequency of disability. Intervention studies also showed that exercises in balance, muscle strength and gait ware effective in reducing frailty, as assessed with TUG, 6 min walking speed, chair rise and grip strength tests(Hruda, 2003; Lord,2003; Seynnes, 2004).

Most of the included studies were conducted over a relatively long follow-up period. It would be useful to see to what extent those risk predictors, such as cognitive assessment scores and physical ability, did show an actual decline. A number of studies used quintiles as a discriminative standard between a robust group and frail group. However, most of these did not provide sufficient evidence that they established specific cut-off points for the measurements they took and that could be applied in the screening for frailty and in predicting its consequences.

In addition, some variables may have too low resolution because of little variance in the data distribution (yes/no presence of symptom) and it is important to establish their responsiveness to treatment effects to reverse frailty symptoms. Ideally screening tests would respond to treatments so that the costs of assessments would be kept low (screening can then be used as a baseline

assessment). A cost-effectiveness and accuracy/sensitivity assessment thus needs to be carried out on each assessment to establish the best frailty screening and treatment assessment battery.

A limitation of the review is that some relevant studies and unpublished studies may have not been retrieved in the searching stage. Besides, not many studies regarding frailty assessments in Asian countries were included. It would be interesting and meaningful to compare if there is a difference with respect to the risk markers for frailty between Eastern and Western countries. A suggestion for future research is how to apply an effective, convenient and well tolerated intervention programme using physical and/or cognitive training sessions on those who were defined as frail elderly. The consequences of economic cost reductions through successful interventions should also be taken into account. We therefore conducted a study to investigate whether the variables mentioned in this review clustered together in a large cohort in China to define a frailty syndrome.

In the next chapter, we will describe a more in depth review of cognitive tests for dementia which may also be predictive of frailty.

2.5 Reference

Al Snih S, Markides KS, Ottenbacher KJ, Raji MA (2004). Hand grip strength and incident ADL disability in elderly Mexican Americans over a seven-year period. Aging Clin Exp Res, 16:481-6.

Alyson Ross and Sue Thomas (2010).The Health Benefits of Yoga and Exercise: A Review of Comparison Studies. The Journal of Alternative and Complementary Medicine, 16(1): 3-12

APA, 1994.American Psychiatric Association, APA (1994). Diagnostic and statistical manual of mental disorders (4th Ed.). Washington, DC: Author.

Barry S. Oken, MD, Daniel Zajdel, Shirley Kishiyama, MA, Kristin Flegal, BS, Cathleen Dehen, Mitchell Haas, DC, MA, Dale F. Kraemer, PhD, Julie Lawrence, BS, and Joanne Leyva, BS, MHA (2006b).Randomized, controlled, sis-month trial of yoga in healthy seniors: effects on cognition and quality of life. Altern Ther Health Med, 12(1): 40–47.

Bellamy N, Buchanan WW, Goldsmith CH, *et al (*1988).Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol, 15:1833–40.

Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt L (1988). Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes following total hip or knee arthroplasty in osteoarthritis. J Orthop Rheumatol; 1:95–108.

Bellamy N (1998). WOMAC Osteoarthritis index – a user′s guide. London: London Health Sciences Centre.

Berkhout Aad M.M., Herman J. M. Cools and Hans C. Van Houwelingen (1998). The relationship between difficulties in feeding oneself and loss of weight in nursing-home patients with dementia. Age Ageing 27 (5): 637-641. doi: 10.1093/ageing/27.5.637

Bilotta Claudio, Luigi Bergamaschini, Paola Nicolini, Alessandra Casè, Gloria Pina, Silvia Veronica Rossi & Carlo Vergani (2011). Frailty syndrome diagnosed according to the Study of Osteoporotic Fractures criteria and mortality in older outpatients suffering from Alzheimer's disease: A one-year prospective cohort study. Aging & Mental Health, DOI:10.1080/13607863.2011.609534

Bryant Ryan C E, Eleazer P, Rhodes A, Guest K. Unintentional weight loss in long-term care: predictor of mortality in the elderly. South Med J. 1995; 88:721–4.

Buchman AS, Wilson RS, Bienias JL, Shah RC, Evans DA, Bennett DA (2005).Change in body mass index and risk of incident Alzheimer disease. Neurology, 65(6):892–897

Buchman Aron S., Julie A. Schneider, Sue Leurgans and David A. Bennett (2008). Physical frailty in older persons is associated with Alzheimer disease pathology. Neurology August 12, 71:499-504Buchner David M., Eric B. Larson (1987). Falls and Fractures in Patients With Alzheimer-Type Dementia. JAMA; 257(11):1492-1495

Cigolle Christine T, Mary Beth Ofstedal, z Zhiyi Tian, and Caroline S. Blaum (2009). Comparing Models of Frailty: The Health and Retirement Study. JAGS 57:830–839,

Colcombe SJ, Kramer AF (2003); Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol Sci, 14:125–30.

Carriere, I., Colvez, A., Favier, F., Jeandel, C., Blain, H. (2005). Hierarchical components of physical frailty predicted incidence of dependency in a cohort of elderly women. J. Clin. Epidemiol. 58, 1180–1187.

Campbell. M. Buchner (1997).Unstable disability and the fluctuations of frailty. Age and Ageing 26: 315-318

Cigolle, C.T., Ofstedal, M.B., Tian, Z., Blaum, C.S. (2009). Comparing models of frailty: the health and retirement study. J. Am. Geriatr. Soc. 57, 830–839.

Gealey, S.G (1997). Quantification of the term frail as applied to the elderly client. J. Am. Acad. Nurse Pract. 9, 505–510.

Dustman RE, Ruhling RO, Russell RM, et al. Aerobic exercise training and improved neuropsychological function of older individuals. Neurobiol Aging 1984; 5:35–42.

Ensrud KE, Ewing SK, Cawthon PM, Fink HA, Taylor BC, Cauley J, Dam TT, Marshall LM, Orwoll ES, Cummings SR (2009). A comparison of frailty indexes for the prediction of falls, disability, fractures, and mortality in older men. J Am Geriatr Soc, 57:492-8.

Esqueda A Lara-, C A Aguilar-Salinas, O Velazquez-Monroy, F J Gómez-Pérez, M Rosas-Peralta, R Mehta and R Tapia-Conyer(2004). The body mass index is a less-sensitive tool for detecting cases with obesity-associated co-morbidities in short stature subjects. International Journal of Obesity (2004) 28, 1443–1450. doi:10.1038/sj.ijo.0802705

Feng Lei, Tze-Pin Ng, Yanling He, Chunbo Li, Ee-Heok Kua, and Mingyuan Zhang (2011). Physical Health and Cognitive Function Independently Contributed to Functional Disability among Chinese Older Adults: Data from Two Asian Metropolises. Journal of Aging Research Volume, Article ID 96084

Fiatarone MA, O'Neill EF, Ryan ND, et al (1994). Exercise training and nutritional supplementation for physical frailty in very 25. Shimada H, Obuchi S, Furuna T, et al. New intervention for elderly people. N Engl J Med, Jun; 330 (25): 1769-75

Fischer J, Johnson MA. Low body weight and weight loss in the aged. J Am Diet Assoc. 1990; 90:1697–706.

Folstein MF, Folstein SE, McHugh PR (1975). ''Mini-mental state''. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res, 12:189–98.

Freiheit Elizabeth A, David B Hogan, Laurel A Strain, Heidi N Schmaltz, Scott B Patten1, Misha Eliasziw and Colleen J Maxwell (2011). Operationalizing frailty among older residents of assisted living facilities. BMC Geriatrics, 11:23

Fried Linda P, Luigi Ferrucci, Jonathan Darer, Jeff D. Williamson, and Gerard Anderson(2004). Untangling the Concepts of Disability, Frailty, and Comorbidity: Implications for Improved

Targeting and Care. J Gerontol A Biol Sci Med Sci, 59 (3): M255-M263. doi: 10.1093/gerona/59.3.M255

Fried LP, Tangen CM, Walston J et al (2001). Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci; 56A:M146–M156.

García-González José Juan, Carmen García-Peña, Francisco Franco-Marina and Luis Miguel Gutiérrez-Robledo (2009). A frailty index to predict the mortality risk in a population of senior Mexican adults. BMC Geriatrics, 9:47 doi: 10.1186/1471-2318-9-47

Gibson Kate, Lesley Day, Keith D Hill , Damien Jolley, Stuart Newstead, Flavia Cicuttini, Leonie Segal, Leon Flicker (2010). Screening for pre-clinical disability in different residential settings. BMC Geriatrics, 10:52

Gill T, Williams C, Tinetti M (1995). Assessing risk for the onset of functional dependence among older adults: the role of physical performance. J Am Geriatr Soc, 43: 603 – 609.

Gill T , Baker D , Gottschalk M , Peduzzi P , Allore H , Byers A (2002). A program to prevent functional decline in physically frail, elderly persons who live at home. New Engl J Med, 347:1068-1074.

Gill Thomas M., Evelyne A. Gahbauer, Heather G. Allore, Ling Han (2006).Transitions Between Frailty States Among Community-Living Older Persons. Arch Intern Med, 166:418-423

Gill TM, Murphy TE, Barry LC, Allore HG (2009). Risk factors for disability subtypes in older persons. J Am Geriatr Soc, 57:1850-5.

Gillette-Guyonnet S, Nourhashemi F, Andrieu S, de G, I, Ousset PJ, Riviere D, et al. (2000) Weight loss in Alzheimer disease. Am J Clin Nutr 71(2): 637S–642S

Gillette GS, Abellan VK, Alix E, Andrieu S, Belmin J, Berrut G, et al. (2007) IANA (International Academyon Nutrition and Aging) ExpertGroup: weight loss and Alzheimer's disease. J Nutr Health aging 11(1): 38–48

Guilley, E., Ghisletta, P., Armi, F., Berchtold, A., d'Epinay, C.L., Michel, J., Ribaupierre, A.D (2008). Dynamics of frailty and ADL dependence in a five-year longitudinal study of octegenarians. Res. Aging 30, 299–317.

Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB (1995). Lower extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med, 332:556-61.

Heyn P, Abreu BC, Ottenbacher KJ (2004).The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys MedRehab; 84:1694–704.

Hogervorst, E., et al. (2011) Validation of Two Short Dementia Screening Tests in Indonesia: in Vascular Dementia: Risk Factors, Diagnosis and Treatment Editors: Sarah R. Jacobsen. NY: Nova Science Publishers, Inc. ISBN: 978-1-61122-313-2.

Hruda KV, Hicks AL, McCartney N (2003).Training for muscle power in older adults: effects on functional abilities. Can J Appl Physiol Apr; 28 (2): 178-89

Inouye SK, Studenski S, Tinetti ME, et al (2007). Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc. May; 55(5):780–791.
Jones David M, Xiaowei Song and Kenneth Rockwood (2004).Operationalizing a Frailty Index from a Standardized Comprehensive Geriatric Assessment. JAGS 52:1929–1933

Kamaruzzaman Shahrul, George B Ploubidis, Astrid Fletcher, Shah Ebrahim (2010). A reliable measure of frailty for a community dwelling older population. Health and Quality of Life Outcomes, 8:1231

Karunananthan Sathya, Christina Wolfson, Howard Bergman, François Béland and David B Hogan (2009). A multidisciplinary systematic literature review on frailty: Overview of the methodology used by the Canadian Initiative on Frailty and Aging. BMC Medical Research Methodology 9:68. doi: 10.1186/1471-2288-9-68

Katz S, Downs TD, Cash HR, et al. Progress in development of the index of ADL. Gerontologist 1970; l: 20-30.Kramer AF, Hahn S, Cohen NJ, et al (1999). Aging, fitness, and neurocognitive function. Nature; 400:418–19.

Kiely Dan K., L. Adrienne Cupples and Lewis A. Lipsitz (2009). Validation and Comparison of 2 Frailty Indexes: The MOBILIZE Boston Study. J Am Geriatr Soc. September; 57(9): 1532–1539. doi:10.1111/j.1532-5415.2009.02394.x.

Lawton, M. Powell; Brody, Elaine M (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. The Gerontologist, Vol 9(3, Pt 1), 179-186. doi: 10.1093/geront/9.3_Part_1.179

Lord SR, Castell S, Corcoran J, et al (2003). The effect of group exercise on physical functioning and falls in frail older people living in retirement villages: a randomized, controlled trial. J Am Geriatr SocDec; 51 (12): 1685-92

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34(7):939–944

Mitnitski A, Nader F and Rockwood K (2011). A Multistate Model of Cognitive Dynamics in Relation to Frailty in Older Adults. Ann Epidemiol, 21:507–516.

Murden RA, Ainslie NK. Recent weight loss is related to short-term mortality in nursing homes. J Gen Intern Med. 1994; 9:648–50

Nemoto, M., et al. (2011). Assessment of vulnerable older adults' physical function according to the Japanese Long-Term Care Insurance (LTCI) system and Fried's criteria for frailty syndrome. Arch. Gerontol. Geriatr.doi:10.1016/ j.archger.2011.10.004

Oken BS, Kristin F, Daniel Z, Shirley S. Kishiyama, MA; Jesus L, Bridget B, Bourdette D (2006). Cognition and fatigue in multiple sclerosis: Potential effects of medications with central nervous system activity. Journal id Rehabilitation Research and Development, 43(1):83-90

Orjana Velikonja, Katarina Čurić, Ana Ožura, Saša Šega Jazbec (2010). Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis. Clinical Neurology and Neurosurgery, 112(7):597–601.

Puts, M.T., Lips, P., Deeg, D.J. (2005). Sex differences in the risk of frailty for mortality independent of disability and chronic diseases. J. Am. Geriatr. Soc. 53, 40–47.

Ravaglia, G., Forti, P., Lucicesare, A., Pisacane, N., Rietti, E., Patterson, C. (2008). Development of an easy prognostic score for frailty outcomes in the aged. Age Ageing 37, 161–166.

Ravi Prakash, Priyanka Rastogi, Indu Dubey, Priyadarshee Abhishek, Suprakash

Chaudhury & Brent J. Small (2011): Long-term concentrative meditation and cognitive performance among older adults, Aging, Neuropsychology, and Cognition, DOI:10.1080/13825585.2011.630932

Rothman MD, Leo-Summers L, Gill TM (2008). Prognostic significance of potential frailty criteria. J Am Geriatr Soc, 56:2211-116.

Seynnes O, Fiatarone Singh MA, Hue O, et al (2004). Physiological and functional responses to low-moderate versus high-intensity progressive resistance training in frail elders. J Gerontol A Biol Sci Med SciMay; 59 (5): 503-9

Shinkai S, Watanabe S, Kumagai S, Fujiwara Y, Amano H, Yoshida H, Ishizaki T, Yukawa H, Suzuki T, Shibata H (2000). Walking speed as a good predictor for the onset of functional dependence in a Japanese rural community population. Age Ageing, 29:441-6.

Smith Karen L., Carol E. Greenwood (2008).Weight Loss and Nutritional Considerations in Alzheimer Disease .Journal of Nutrition For the Elderly, 27, Iss.3-4.

Strawbridge, W.J., Shema, S.J., Balfour, J.L., Higby, H.R., Kaplan, G.A (1998). Antecedents of frailty over three decades in an older cohort. J. Gerontol. B: Psychol. Sci. Soc. Sci. 53, S9–16.

Studenski, S., Hayes, R.P., Leibowitz, R.Q., Bode, R., Lavery, L., Walston, J., Duncan, P., Perera, S., (2004).Clinical Global Impression of Change in Physical Frailty: development of a measure based on clinical judgment. J. Am. Geriatr. Soc. 52, 1560–1566.

Tamura BK, Masaki KH, Blanchette P (2007) Weight loss in patients with Alzheimer's disease. J Nutr Elder 26, (3–4):21–38

Topinková Eva (2008). Aging, Disability and Frailty. Ann Nutr Metab, 52 (Suppl. 1):6-11.

Van Dijk Pieter T. M., Oda G. R. M. Meulenberg, Herbert J. van de Sande and J. Dik F. Habbema(1993). Falls in Dementia Patients. The Gerontologist, 33 (2): 200-204.

Van Doorn, C., Gruber-Baldini, A. L., Zimmerman, S., Richard Hebel, J., Port, C. L., Baumgarten, M., Quinn, C. C., Taler, G., May, C., Magaziner, J. and for the Epidemiology of Dementia in Nursing Homes Research Group (2003), Dementia as a Risk Factor for Falls and Fall Injuries Among Nursing Home Residents. Journal of the American Geriatrics Society, 51: 1213–1218. doi: 10.1046/j.1532-5415.2003.51404.x

Verbrugge Lois M., Ann L. Gruber-Baldini, and James L. Fozard (1996). Age Differences and Age Changes in Activities: Baltimore Longitudinal Study of Aging. J Gerontol B Psychol Sci Soc Sci, 51B (1): S30-S41. doi: 10.1093/geronb/51B.1.S30

Table 1. List of quality control criteria

Criteria	Yes(1)	No(0)
1 Clear description on rationale of the study		
2 Clear description on objectives of the study		
3 Clear description on setting and timeframe of the study		
4 Clear description on independent variables of the study		
5 Clear description on dependent variables od the study		
6 Clear description on study population		
7 Clear description on eligibility criteria for participants		
8 Clear description on characteristics of the participants		
9 Clear description on methods of the study		
10 Clear description on the key-elements of the study design		
11 Include a 5-year-and-above period of follow-up		
12 Include physical measurements in the study		
13 Include cognitive measurements in the study		
14 Include disease, functional ability and others measurements in the study		
15 Include valid measurements for the predictors.		
16 Present potential types of bias in the report		
17 Use appropriate multivariate analysis techniques		
18 Include statistical methods controlling for confounding		
19 Include statistical methods examining between-group interactions		
20 Include discussion on key results of the study		
21 Express results in an Odds Ratio, Risk Ratio or Hazard Ratio with the corresponding 95% confidence interval		

22 Clear descriptions on the generalizability of the study results.

23 Clear description on Randomization design of the study

24 Clear description on intervention applied in the study include blinded comparisons of measurements in the study

25 Report the limitations of the study

Table 2. Operationalization of the Frailty Indicators

Factors/Risk markers	**Operationalization**
Demographic	Age, Gender, Education, Ethnicity
Physical Indicators	Height, Weight
	BMI
	Level of Physical Activity
	Muscle Strength
	Gait Speed
	Balance
	Exhaustion/fatigue
Cognitive Indicators	Memory impairment
	Cognitive Status
Functional Indicators	ADL
	IADL
Mood	Depression, Anxiety, Sadness
Risk factors	Co-morbidity
	Chronic Conditions
Potentially protective factors	Life Style (diet, smoking, exercise etc.)
	Social Support

Table 3. Studies including physical indicators for frailty

	Study	BMI	Gait Speed	Upper Body Strength	Lower Body Strength	Balance	Exhaustion	Physical Activity	Others
R	Jones, 2004					√		√	
	Kiely, 2009	√	√	√	√	√			√
C	Gibson, 2010	√	√		√	√			√
	Nemoto, 2011	√	√	√		√			√
T	Theou, 2011	√	√	√		√			√
	Theou, 2011	√	√	√		√			√
C	Guralnik, 1995		√		√	√			
	Strawbridge, 1998			√	√				dizziness
O	Fried, 2001	√	√	√			√		
	Shinkai. 2003		√	√		√			
H	Raji 2005	√		√					
	Ottenbacher,2005	√	√	√			√		
O	Gill, 2006	√	√					√	
	Gill, 2006	√	√				√	√	
R	Rothman, 2008	√	√				√	√	
	Cigolle, 2009	√	√	√		√	√		dizziness
T	Ensrud, 2009	√	√	√			√	√	√
	Gill, 2009	√	√	√	√	√		√	√
S	Peterson, 2009		√					√	
	Kamaruzzaman, 2010	√							
	Freiheit, 2011	√	√	√			√	√	

Table 4. Characteristics of Included Studies on Diagnosis of Frailty

Study	Jones, 2004	Kiely, 2009	Gibson, 2010	Nemoto, 2011	Theou, 2011	Theou, 2011	Bilotta,2011
Study Design	RCT	RCT (10-32 m)	RCT	RCT	RCT	RCT	Cohort (1 y)
Number Included	160	765	471	95	50	53	109
Mean Age (y)	82.1	78		76.4			82.8
Gender (% Female)	56.7	64		83.2	All	All	77
Operational Criteria/definition	FI-CGA	SOF and CHS criteria	Fried's screening tool	LTCI system	Frailty index	Frailty index	SOF criteria
Health Status	Frail	21% disabled	pre-clinically disabled	Vulnerable	nondisabled	nondisabled	AD
Ethnicity	Rural Nova Scotia	78% Caucasian, 15.8% African-American	Australian	Japanese	Greek	Greek	Italian
Outcome	Frailty	Frailty	Functional limitation and disability	Frailty	Frailty	Frailty	Frailty
Physical Assessment		x	x	x	x	x	x
Cognitive Assessment	MMSE	HVLT-R, MMSE, Verbal Fluency, The Trail making Test and Clock-in-a-Box Test					MMSE,CDR
Functional Assessment	GSS,Barthel Index, IADL, ADL, QOL	ADL, IADL	LLFDI	ADL, IADL, Barthel, SF-36			BADL,IADL
Mood Assessment		CESD-R	BDI				GDS, Cornell Scale
Risk Factors	Comorbidity, Nutrition, Social support, mood	recurrent falls, disability, hospitalization	Hospitalization, recurrent falls		Comorbidity, medication, recurrent falls	Comorbidity, medication, recurrent falls	Comorbidity (CIRS-m)
Covariates	Age, Gender, Self-rated health, Marital status, Living Status	Age, gender, race, education, income, chronically medical conditions	Age, Education, Marital status, Civil status, Chronic status and medication	Age, Gender	Age, education, social support, Civil status, fatigue, hospitalization, quality of life, mobility, nutrition, dependence		Age, Gender, Education, Civil status
Quality (0-25)	23	22	21	20	20	20	20

Freiheit, 2011	Gill, 2006	Ensrud, 2009	Fried, 2001			MITNITSKI, 2011	Peterson, 2009	Guranik, 1995	Shinkai. 2003
Cohort (1 y)	Cohort (54 m)	Cohort(3 y)	2 Cohorts (4 and 7 y)			Cohort (5 y)	Cohort (5 y)	Cohort (4 y)	Cohort (6 y)
928	557	3132	5317	305	44	6064	2401	1122	601
84.9	82.2	76.4		72.7	82.3	79.4	73.6		70.9
76.7	67.5	All Male	57.9	63.6	75	61.4	51		56.1
FFI	FFI	SOF and FFI	FFI			Frailty index	Gill's Frailty Model		ADL
Assisted Living	nondisabled		nondisabled	Independent	Dependent	nondisabled	ADL independent	nondisabled	nondisabled
Canadian	89.9%Caucasian	from US community	84.5% Caucasian,14.8% African-American			Canadian	White 59%, Black 41%		Japanese
Frailty	Frailty	Frailty	Frailty	Frailty	Frailty	Frailty	Frailty	ADL Disability	ADL Disability
x	x	x	x				x	x	x
CPS			MMSE			Modified MMSE			
ADL, Hierarchy Scale		IADL	ADL, IADL						
DRS			CES–D						
Comorbidity (Charlson Index & inter RAI- AL tool)	Mortality	recurrent falls, Disability, Fractures and Mortality	recurrent falls				disability, institutionalization and mortality		Functional dependence
Age, Gender	Age, Gender, Education, Civil Status,	Age,	Age, gender, race, Income, Living status, Self-Assessed Health, Medication, disease, hearing and visual impairment			Age, Gender, Education, Environmental exposures, Medical and family histories	age, sex, race, education, waist circumference, marital status, number of prevalent chronic conditions, smoking status, and alcohol consumption		age, gender, chronic condition
20	21	21	21			21	21	20	19

Study	Gill, 2009	Feng, 2011		Rothman, 2008	Vest, 2011	García-González,2009
Study Design	Cohort (9 y)			Cohort (8 y)	Cohort	Cohort (2 y)
Number Included	722	4639	2397	754	309	4082
Mean Age (y)	78.4	68.3	65.6	78.4	74.7	73
Gender (% Female)	65.2	54.1	62.4	64.6	53	52.5
Operational Criteria/definition						Fried, Mitnitski and Rockwood's model
Health Status	nondisabled			nondisabled	ICU Survivor	non-institutionalized
Ethnicity	90.4%Caucasian	Chinese in China	Chinese in Singapore	90.5 Caucasian	84% Caucasian	Mexican
Outcome	ADL Disability	ADL Disability	ADL Disability	ADL Disability	ADL Disability	
Physical Assessment	x			x	x	x
Cognitive Assessment		MMSE		MMSE	IQCODE	
Functional Assessment		ADL		ADL	ADL, QOL	ADL, IADL
Mood Assessment				CES-D		Depression using MHAS Questionnaire
Risk Factors	functional self-efficacy and social support, medical status and smoking, depressive symptoms			recurrent falls, disability, hospitalization	Comorbidity,	falls and fractures in the past 2 year, mortality
Covariates	age, sex, race, education, marital status, functional self-efficacy and social support, medical status and smoking	age, sex, environment, chronic diseases, self-rated health status, medical conditions social support		age, sex, race, education, number of chronic conditions, and the presence of the other potential frailty criteria,	age, sex, race, education	health problems before 10, self-assessed health, medical condition, nutrition, Body pain and difficulty with walking
Quality (0-25)	21	20		22	21	20

Study	Kamaruzzaman, 2010	Raji 2005
Study Design	Cohort (2-7.9 y)	Cohort (7 y)
Number Included	4286	2381
Mean Age (y)	60-79	72.1
Gender (% Female)	All Female	57
Operational Criteria/definition	BFI	
Health Status		non-disabled
Ethnicity	British	Mexican
Outcome	frailty	ADL Disability
Physical Assessment	x	x
Cognitive Assessment	memory problems report using BFI	MMSE
Functional Assessment	physical ability using BFI	ADL
Mood Assessment	Depression and Anxious using BFI	depressive symptomatology (CES-D)
Risk Factors	Physical Ability, cardiac disease or symptoms, respiratory disease or symptoms, comorbidity and visual impairment. morality	mortality
Covariates	self-report health, behavioural and lifestyle, including smoking habit, alcohol consumption, medical conditions and socio-economic position	demographic factors, medical conditions
Quality (0-25)	21	19

Table 5. Different Criteria of definition and assessment of frailty

		SOF	
Physical Vulnerability	*Body Composition*	direct measurement of weight	Weight Loss: >5% between the baseline and second examination
	Physical Activity		
	Strength	Chair Rise	Inability to rise from a chair five times without using the arms
	Mobility		
	Energy	Exhaustion	A question ‘‘Do you feel full of energy?’’
	others		
Cognitive Dysfunction	*Cognition*		
	Mood		
Social Isolation			
Functional limitation			
Others			
Definition			robust (0 components), pre- frail (previously referred to as “intermediate”) (1 component), and frail (2 or more components).

		CHS	
Physical Vulnerability	*Body Composition*	direct measurement of weight	Weight loss:5% or more between the baseline and second examination
	Physical Activity	Activity Scale(18 item)	score 270
	Strength	hand-held dynamometer	Grip strength ≤17 for BMI ≤23, ≤17.3 for BMI 23.1–26, ≤18 for BMI 26.1–29, or ≤21 for BMI >29 kg/m2
	Mobility	15 feet (4.75m) Walking Test	Time ≥ 7 for height ≤ 159 cm or Time ≥ 6 for height >159 cm
	Energy	Question for Exhaustion	Self-report of any of: i) felt that everything I did was an effort in the last week, or ii) could not get going in the last week
	others		
Cognitive Dysfunction	*Cognition*		
	Mood		
Social Isolation			
Functional limitation			
Others			
Definition			Robust (previously referred to as “not frail”) (0 components), pre-frail (previously referred to as “intermediate”) (1-2 components), and frail (3-5 components).

		WHAS		Fried
Physical Vulnerability	*Body Composition*	Weight Loss or BMI	i) Weight at age 60 – weight at exam ≥10% of age 60 weight or ii) BMI at exam < 18.5 kg/m2	direct measurement of weight
	Physical Activity	Activity Scale (6 items)	score 90	weighted score of kilocalories expended per week
	Strength	hand-held dynamometer	Grip strength ≤17 for BMI ≤23, ≤17.3 for BMI 23.1–26, ≤18 for BMI 26.1–29, or ≤21 for BMI >29 kg/m2	hand-held dynamometer
	Mobility	4-m Walking Test	Time ≥ 7 for height ≤ 159 cm or Time ≥ 6 for height >159 cm	15 Feet Walking Test
	Energy	Question for Exhaustion	Self-report of any of: i) felt that everything I did was an effort in the last week, or ii) could not get going in the last week	2 questions from CES–D scale
	others			
Cognitive Dysfunction	*Cognition*			
	Mood			
Social Isolation				
Functional limitation				
Others				
Definition			Robust (previously referred to as “not frail”) (0 components), pre-frail (previously referred to as “intermediate”) (1-2 components), and frail (3-5 components).	

	FI-CGA	
≥10 pounds in prior year or, at follow-up, of ≥5% of body weight in prior year	Vulnerable Elders Survey (VES 13) and Tinetti test	VES Scoring >3 identifies 4.2 times risk of functional decline/mortality over the next 2 years; Tinetti Testl Score Risk of Falls:≤18 High,19-23 Moderate,≥24 Low
the lowest quintile of physical activity for each gender		
the lowest quintile(by gender, body mass index)		
slowest quintile(by gender, height)		
Self-reported exhaustion		
	balance	the Lawton-Brody Physical Self-Maintenance Scale
	MMSE	
	Geriatric Depress Scale	>5 for suggestive depression; >10 for always depression
	Groningen Frailty Indicator	vision, hearing and speech problems
	IADL	lower score presents for vulnerability
	bowel and bladder function, nutrition and the number of comorbidities	Cumulative Illness Rating Scale (CIRS) or Charlson Comorbidity Index; Mini Nutrition Assessment
as three or more of these criteria to be to be considered.		

		Frailty Index (Rockwood,1999)	
Physical Vulnerability	*Body Composition*	geriatric status scale (GSS),	
	Physical Activity		
	Strength		
	Mobility		
	Energy		
	others		
Cognitive Dysfunction	*Cognition*	DSM-III-R criteria for Dementia and cognitive impairment with no dementia (CIND)	According to the classification of the Criteria
	Mood	Geriatric Depression Scale	Depressive Symptoms
Social Isolation			
Functional limitation		ADL	self-reported functional status
Others		bowel and bladder function	self-report
Definition			representing fitness to frailty: (0) Those who walk without help, perform basic activities of daily living (eating, dressing, bathing, bed transfers),are continent of bowel and bladder, and are not cognitively impaired; (1) bladder incontinence only; (2) one (two if incontinent) or more of needing assistance with mobility or activities of daily living, has CIND, or has bowel or bladder incontinence; and (3)two (three if incontinent) or more of totally dependent for transfers or one or more activities of daily life, incontinent of bowel and bladder, and diagnosis

		Gill's model		CSHA Clinical Frailty Scale (Rockwood, 2005)	
Physical Vulnerability	*Body Composition*				
	Physical Activity				
	Strength	Chair Rise	unable to rise from a chair once without arm support		
	Mobility	Rapid Gaits	<0.60m/s		
	Energy				
	others	360 degrees turn, and bending over			
Cognitive Dysfunction	*Cognition*			Modified Mini-Mental State Examination (3MS) and DSM-III-R criteria for dementia	3MS<77 for cognitive impairment; According to the classification of the DSM-III-R Criteria
	Mood				
Social Isolation					
Functional limitation				CSHA Function Scale	Higher score presents for higher risk for inability
Others				Cumulative Illness Rating Scale for comorbidity; 70-deficits CSHA Frailty Index; falls, delirium, and the presence and severity of current diseases	self-report and physical signs from clinical and neurologic exams
Definition			Anyone meeting either frailty criterion as moderately frail, and those meeting both criteria as severely frail.		CSHA rules-based definition of frailty,12 which categorizes subjects as 0 (having no cognitive or functional impairment), 1 (isolated urinary incontinence), 2 (dependent in 1 ADL or having a diagnosis of CIND) or 3 (dependent in at least 2 ADLs, having mobility impairment or having a diagnosis of dementia).

3 CHAPTER 3 THE HOPKINS VERBAL LEARNING TEST AS A SCREENING INSTRUMENT FOR MILD COGNITIVE IMPAIRMENT AND DEMENTIA

3.1 Introduction

With an advancing age, there is an average decline in various areas of cognitive function, such as episodic memory and speed of complex information processing (Hogervorst, 2008). Dementia is a separate progressive neurodegenerative disorder that causes a severe decline in memory and other cognitive abilities, which have a significant impact on the quality of life (Alzheimer's association, 2010, 2011). There is currently no effective treatment. Globally, the number of people afflicted with dementia has shown a steady growth over the last decades (Alzheimer's association, 2010, 2011). Mild cognitive impairment (MCI) is defined as cognitive decline worse than that of those who have a similar advanced age, but which causes no interference with activities of daily life, such as dementia does. The most commonly used MCI diagnostic criteria were developed by Petersen et al. and confer an increased risk for dementia (Petersen, 2004). It has been reported that 10-12% of individuals with MCI progress to dementia per year (Petersen, 1999). There is a growing awareness of MCI, where many studies now focus on the discrimination between those undergoing the normal cognitive aging process and those with MCI, who may convert to dementia. It may be that future interventions have a better chance of success in those who have not developed dementia yet, but are at risk for this. Good screening methods for MCI and early dementia are imperative. In this paper we review the Hopkins Verbal Learning Test (HVLT) and its ability to discriminate between people with mild dementia and MCI as compared to non-afflicted controls.

The HVLT (Brandt, 1991) is a word-learning test measuring episodic verbal memory. Version A consists of 12 words from 3 low frequency categories (human shelter, animals and precious stones), which are also late acquired words during development. These words are read out loud after which the participant recalls them in any order. 20 -30 minutes after obtaining the total immediate recall (reflecting learning ability, which is obtained by repeating the same word list 3 times and adding up

all correctly recalled words over the 3 trials), a delayed recall without cues or prompting is done. The HVLT should be particularly adept at identifying people with amnestic MCI (aMCI), where according to Petersen (1999) the primary distinction between control subjects and subjects with aMCI is in the area of verbal memory. To reduce slight learning effects in controls, six parallel versions exist, which have shown good inter-test reliability (Brandt, 1991). The HVLT has been shown to have good validity and reliability and is well tolerated by elderly people (Shapiro, 1999).

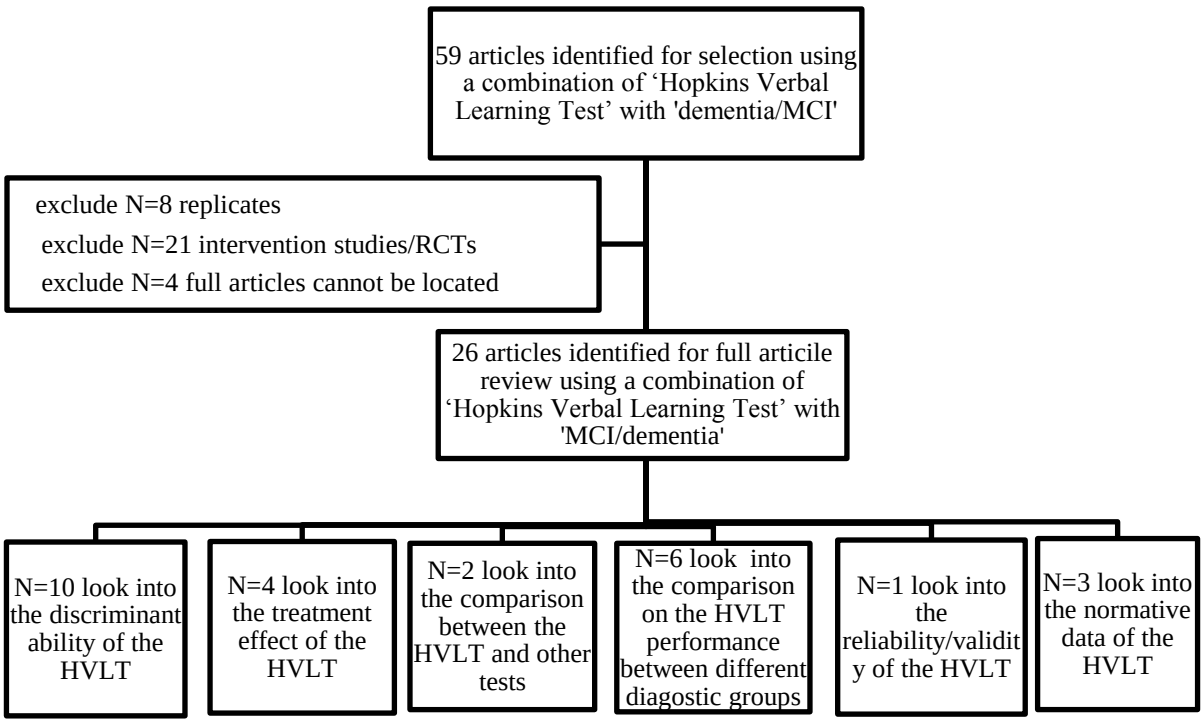
Here we review papers investigating the discriminative capacity of the HVLT to identify patients with MCI versus controls to establish whether similar cut-offs of the total immediate recall for screening were identified among different studies. We also included papers investigating participants with mild dementia, as the distinction between MCI and mild dementia is often not entirely clear.

3.2 Methods

3.2.1 Data sources

The PUBMED electronic database was systematically scanned using different combinations of search terms. There was no restriction on year of publication. The references of the included studies were searched for relevant articles (n=5). The last search was performed on the 8th of July, 2013. Using the term 'Hopkins Verbal Learning Test', 220 relevant publications were found. Using a combination of 'Hopkins Verbal Learning Test', 'dementia', 46 results were found. A combination of 'Hopkins Verbal Learning Test' and 'MCI', only rendered 13 relevant publications. After screening by reviewing abstracts, 26 articles were included for the full literature review. The schema below describes this process in more detail.

3.2.2 Selection process



3.3 Results

3.3.1 The utility of the HVLT as a screening test for MCI and dementia

We first investigated the most optimal cut-off scores when screening for MCI and mild dementia versus controls using the HVLT total immediate recall. According to a study by Hogervorst (2008) in an Oxfordshire (UK) based cohort of carefully matched cases and controls, 87% sensitivity and 98% specificity for mild to moderate dementia (versus controls) was obtained using a cut-off score of 14/15 of the HVLT total recall, whereas a cut-off score of 18/19 yielded better sensitivity (95%), but somewhat lower specificity (77%). Similarly, for mild dementia in Australia (Frank, 2000), the HVLT total immediate recall had a sensitivity of 96% and a specificity of 80% using the same cut-off score of 18/19. Significantly different HVLT total recall scores between age and education equated controls, patients with MCI, and with cerebrovascular disease (CVD, which included vascular cognitive impairment and vascular dementias) as well as Alzheimer's disease (AD, the

most common form of dementia) were also found in another Oxfordshire case-control study (on average: 26, 18, 17 and 10 words, respectively, were recalled per group) (De Jager, 2003). In addition, in this study when using a cut-off score of 21.5 for the total recall, 78% sensitivity and 80% specificity was reported at baseline between 51 healthy controls and 15 control participants who would develop MCI after a 2-3 year follow-up. A third Oxfordshire study (Schrijnemaekers, 2006) gave similar data on specificity and sensitivity for AD, MCI and controls as found in the previous Oxford based studies, and these were again maintained at follow-up. All those with dementia declined, controls all improved and half of MCI showed a decline in function, similar to the dementia cases (see table 7 for the studies described above). From these studies, which had al matched or equated for age, gender ratio and education, it may be suggested that a HVLT total immediate recall cut-off score of around 14/15 for dementia overall, and below 18/19 for mild dementia is best used for screening. Table 7 suggests that for MCI vs. controls, a cut-off score of 24/25 probably gives best sensitivity (with around 22 for Chinese populations). Between MCI and AD, the best cut-off score seems to be around 16/17 word recalled on the total immediate recall.

3.3.2 HVLT assessment at baseline as part of treatment trials for those with MCI

In this section we investigated the ability of the HVLT to detect treatment effects. The HVLT is regarded not only as a good test for the screening and detection of memory impairment, but also to assess treatment effects in participants with MCI. For instance, as individuals with MCI could benefit from learning strategies during word recall task, this could be further enhanced by pharmacological and-non pharmacological treatments (Riberiro, 2007). The HVLT was used successfully to assess effects of cognition enhancers in elderly both without dementia (Yasar, 2008) and with dementia, which included treatment using Chinese herbal medicine (Lu, 2001). HVLT has also been used to test cognitive improvement using other non-pharmacological techniques in elderly (Tracy, 2007). These results demonstrate the applicability of verbal memory tests, such as the HVLT, in determining effective treatments for normal cognitive ageing, as well as the mild decline in cognitive ability in MCI and the more severe decline in dementia. The HVLT could be used for

all these groups and thus for multiple purposes, such as both for baseline screening purposes, as well as subsequent treatment trials, which would be cost-effective.

3.3.3 Demographic factors and HVLT performance

In this section, we describe potential limitations in the use of fixed cut-off scores for the HVLT, if these performance scores are affected by demographic factors. In our matched case control studies (see above) analyses suggested this was not the case. However, many of the other studies investigating the HVLT (see table 7) had not matched or equated cases and controls for age, gender ratio, depression and education, which can all affect performance, and often MCI had not been included with controls (see Hogervorst (2008) for a discussion) For instance, in the first paper describing the HVLT (Brandt, 1991) cases and controls were not comparable in demographic factors and systematic differences between groups (in age, gender ratio, education etc.) could be responsible for the very large differences reported. This could also explain some of the differences in reported optimal cut-off scores (Frank, 2000; De Jager, 2003; Schrijnemaekers, 2006; Kuslansky, 2002; De Jager, 2009; Aretouli, 2010; Gonza´lez-Palau, 2013;).

Demographic factors could also potentially affect finding treatment effects, especially if both treatment and test scores are affected by these (e.g. gender affecting verbal memory performance differences, and hormones differentially affecting genders in verbal memory performance (Hogervorst, 2005)). Although, for instance, Kuslansky (2002) did not find any age, sex and education differences on single HVLT test performance in a multi-ethnic cohort, a number of other authors reported a significant influence of demographic factors on HVLT recall performance. In one study (De Jager, 2009), age was identified as the best predictor of the HVLT total immediate recall score, when age, years of further education, gender, activities of daily living (ADL) and subjective memory complaints (SMC) were entered as independent variables in regression analyses. However, in this study the MCI group was significantly older (81.95±5.4 VS 77.18±5.9, p=0.001) and had more SMCs (1.76±1.04 VS 1.32±1.00, p=0.032 based on a 0-4 range report) than the control group, so these results may have been susceptible to systematic confounds. Despite these

possible confounds, a cut-off score of 25.5 on the total immediate recall score of the HVLT (similar to the other better matched studies mentioned above) rendered 79% sensitivity and 95% specificity when discriminating between controls and those with MCI. Cherner (2007) examined a sample of middle-aged Spanish speakers with an average low educational level from the U.S.–Mexico border region on their HVLT-R performance and found that education ($p<0.001$), rather than age or gender (24.94± 4.47 for males and 25.44±4.29 for females), was significantly related to the HVLT-R total immediate recall score. Age in this study was only found to be related to the Recognition Discrimination Index of the HVLT-R, which we do not use, as it did not add to diagnostic discrimination (2002). Friedman (2002) reported significant, but moderate-sized effects of education in a community based African-American sample, as well as effects of age and gender ($p<0.01$) on the HVLT-R test performance. Another Australian study reported a significant impact of age and education, but not gender, on the HVLT-R total immediate recall (Hester, 2004). Gender differences were thus found in several (but not all) studies, as women are often reported to have better performance on tests involving verbal components, while men are thought to perform better on tests involving visuospatial skills (Trenerry, 1995; Herlitz, 1997; Proust-Lima, 2008). It becomes more difficult when cultural differences seem to further modify these demographic factors, such as gender. For instance, we found significant differences by gender when predicting HVLT total immediate recall performance in China (Xu, 2012, unpublished data), but no overall effects of gender on HVLT total immediate recall scores in Indonesia, although gender differences were also seen in some ethnic groups here, but in the opposite direction to those found in China (Hogervorst, 2011). Aging seemed to further modify the gender effect by culture (Hogervorst, 2011). However, in a meta-analysis, these age by gender differences could be largely explained by systematic differences in health status and prior education obtained between genders (Hogervorst, 2011). In table 4, we reported the immediate recall (IR) and delayed recall (DR) performance on the HVLT based on 3 reviewed multi-ethnic studies which provided normative data for the HVLT and which were stratified by age and education (Friedman, 2002; Hester, 2004; Benedict, 1998). From this

table it seems clear that less education decreases performance, and there may also be age and ethnic differences. However, as stated differences in health status (which can be affected by age) rather than these factors per se may affect performance and this was not controlled for.

The ethnic/cultural confounds are also not specific to the HVLT. Hogervorst (2011) and Schwartz (2004) reported disparities in memory recall of other word lists by ethnicity, even when controlling for age, sex and education. On the other hand, Tanaka (2005) failed to find better verbal learning on another (California) verbal learning test (CVLT) in a European American group when compared to that of Japanese Americans, who outperformed them. These differences were hypothesized to be related to an inherent systematic bias, with ethnic/cultural differences in educational quality and different cultural exposures to learning and vocabulary.

On the other hand, despite having slightly lower average HVLT total immediate recall scores, less educated Indonesian rural participants still had the same cut-off scores for dementia as the highly educated Oxfordshire cohorts (Hogervorst, 2011). This would argue against the need for educationally and ethnicity specific cut-off scores.

The Chinese version of the HVLT was administered to differentiate between aMCI, dementia (subsequently divided into AD and all types of dementia) and controls (Shi, 2012). There was a wide range of performance on the HVLT total immediate recall between groups (with on average 23.8 words recalled for controls, 18.0 for aMCI, 6.1 for AD, and 6.4 for all types of dementia, $p<0.001$). However, after applying an age split (50-64 vs 65-80 age group), a more optimal cut-off of 18.5 was obtained with 96% sensitivity and 92% specificity, when distinguishing AD from controls in the younger group (50-64), whereas a cut-off of 14.5 was found to be more accurate for the older group (65-80) with a sensitivity of 95% and specificity of 93%. This was similar to the results from the Oxfordshire and Indonesian data which participants were within this age-range. On the other hand, in those with early onset AD (before age 65 years) also assessed in Leicester (UK), an optimal cut-off score of 19 was found with 100% sensitivity and specificity (Clifford, in press), also similar to the findings from China as mentioned above (Shi, 2012). Our data from older

Chinese institutionalized elderly with an average age of 80 years also suggested that a lower cut-off of 10/11 words on the HVLT total immediate recall should be used for dementia, particularly when comparing elderly with psychiatric disorders to those with dementia (Xu, 2012, unpublished data). These data taken together would suggest that regardless of culture and education, when adequate back-translation and adjustment has been done, age-related cut-offs (<65 and >80 years of age) may still yield better specificity and sensitivity for dementia screening.

Importantly, an older age, the female gender and low education are all risk factors for dementia, so many case control cohorts (unless matching was done) will have these systematic biases. These systematic differences are difficult to control for in analyses, as they are inherent to being a case and not a control. In addition, systematic differences in exposure to a particular vocabulary perhaps or coping skills which can aid learning skills are difficult to control for, even when education is controlled for (Hogervorst, 2011) For these reasons we always translated and back-translated and if items were not recognized, adapted the list conform local knowledge (e.g. but these items would still be within the category of semi-precious stones, animals or human shelter). As stated, when case-control cohorts have been carefully matched for education, gender and age, these demographic variables, however, do not contribute to differences in HVLT total immediate recall performance associated with dementia and the cut-off scores (Hogervorst, 2002). In addition, as mentioned above, even when cases and controls are not matched for age, gender or education, our Indonesian and Chinese data (when compared to UK data) suggested that cut-off scores for MCI and mild dementia may be remarkably similar across cultures, except in patients with early onset AD (<age 65 years) or the institutionalized oldest old (>80).

3.3.4 Different language versions of the HVLT in detecting cognitive impairment

The HVLT has been widely translated and used in different countries, but there are only a limited numbers of studies which validated the HVLT in different language (e.g. using English, Spanish, Chinese, Indonesian and Korean) versions (Hogervorst, 2011; Tanaka, 2005; Honza'lez-Palau, 2013; Beak, 2011; Kang, 2003). This has not always led to controls obtaining similar scores on the total

immediate recall, as would be expected (see an earlier discussion also on Indian and Indonesian controls scoring lower on the Mini Mental State Examination (MMSE) and the HVLT when compared to age equated elderly in the UK (Hogervorst, 2011)). For instance, the Korean version of the HVLT (K-HVLT) was investigated in Korean MCI and AD patients (Baek, 2011). The total score of this HVLT showed correlations with the MMSE, Clinical Dementia Rating (CDR), Global Deterioration Scale (GDS), and Story Recall Test (SRT), but also revealed significantly different levels of memory performance in MCI and AD patients compared to a control group (mean score 20.6 for controls; 16.3 for MCI, and 12.4 for AD, $p<0.001$). Similar to the studies mentioned earlier (Hogervorst, 2011), controls reached a lower average score on the total immediate recall when compared to other control cohorts mentioned earlier (also see table 7). However, average scores for the MCI and AD cases were quite similar to the earlier mentioned studies (see above).
Similarly, the Spanish version of the HVLT total recall (Gomez-Tortosa, 2012) also showed different levels of performance among different diagnostic groups (11.7 for MCI, 9.63 for AD and 17.7 for controls). However, here average HVLT total immediate recall scores for controls were even 3-4 points lower than those from the Korean study (so around 6-7 points lower than those of other studies investigating controls in table 8). Many participants in this study had low levels of education (72%). This perhaps further reflected the much lower cut-off scores required per diagnostic group in that study. An HVLT total immediate recall cut-off score of <=14 words demonstrated a 70.1% sensitivity and 73.7% specificity when discriminating aMCI cases from controls, and a score of <=11 words recalled had a 79.2% sensitivity and 91.9% specificity, when differentiating AD cases from controls. Slight differences in age and/or education between cases and controls between and within cohorts as mentioned above may result in different results reported. Alternatively, this lower cut-off score for optimal specificity could perhaps suggest inadequate adaptation of the word lists to local knowledge. As stated in the previous paragraph, adequate back translation and adaptation to local knowledge may go some way in solving these issues.

3.3.5 Comparing the HVLT with other memory tests

Several perhaps more commonly used verbal learning tests were compared to the HVLT. For instance, the California Verbal Learning Test (CVLT, mentioned earlier) is also used in the screening of cognitive impairment and it showed strong correlations with the HVLT (Lacritz, 2001). While the authors summarized that the HVLT may not always be challenging enough, nevertheless, the HVLT was suggested to be a superior multidimensional brief verbal learning assessment when compared to the CVLT, as it took less time and training to use. In addition, the CVLT as discussed before also is affected by demographic factors. For instance, in Norman's study (Norman, 2000), age, education, ethnicity, and gender were also found to be significant predictors of CVLT total recall performance among both Caucasians and Africa American populations. Another comparative study between the HVLT and the Story Recall test (SRT) (Baek, 2011) also concluded that although the SRT was well correlated with the HVLT, the HVLT was less influenced by education and would thus also be deemed superior.

3.4 Discussion

In conclusion, the HVLT has been shown to be an effective instrument in the screening of MCI and mild dementia with a high level of sensitivity and specificity. Furthermore, the HVLT could play a role in treatment studies in MCI and mild dementia patients as its baseline screening assessment could be included in the assessment and save money and time.

However, the effect of demographic factors on verbal memory performance remains to be debated. Ethnic differences reported in this review (Friedman, 2002; Hogervorst, 2011; Schwartz, 2004) were probably confounded by systematic differences in exposure to vocabulary, health status and educational levels. Despite these differences, Chinese and rural Indonesian elderly did not require specific cut-off scores for MCI and mild dementia when compared to our UK cohorts, but some of the words in our studies had been changed to fit regional knowledge. To control for some of the possible health status effects, age adjusted norms for the HVLT may be important for early onset AD (<65), as well as for those with advanced age (>80) (Vanderploeg, 2000). As discussed, the

Chinese version of the HVLT using age strata resulted in a 4 points difference on the cut-off score (18.4 VS 14.5) to obtain maximum discriminative capacity for these groups (Shi, 2012).

The HVLT not only has the ability to differentiate MCI from controls, but can also distinguish between different stages of cognitive impairment which is useful in treatment and diagnostic assessments. A revised and copyrighted version of the HVLT(-R) added a delayed recall (DR) and delayed recognition trial which demonstrated good reliability (Benedict 1998). The total immediate recall (IR) trials were published in the public domain (Brandt, 1991) and so whether these are copyrighted could be debated. One study showed significantly worse HVLT IR mean scores for the MCI progression group when compared to the MCI stable group (15.2 vs 16.7, $p=0.001$), whereas an even greater difference was found between groups on the HVLT DR mean scores (1.8 vs 3.6, $p<0.0001$) (Gomez-Tortosa, 2012). Others reported that DR was less susceptible to educational confounding effects in analyses of another similar word learning test (Prince, 2003). On the other hand, studies reported that the HVLT total immediate recall score proved to be useful in discriminating moderate to severe AD and mild AD from controls (with average scores of 8.8 for moderate to severe AD, 14.0 for mild AD and 26.0 for controls) without being confounded by educational effects (Foster, 2009) and using the total immediate recall only would save time in assessments. However, as no significant difference between mild AD and moderate to severe AD in IR scores was detected (Foster, 2009) perhaps other tests and including the DR should be used to further discriminate between these stages.

Lastly, the HVLT was found to distinguish between dementia with AD from that with Lewy Bodies (DLB) (McLaughlin, 2012), and perhaps Parkinson's (PD) and Huntington's (HD) disease (Aretouli, 2010). The HVLT showed its superiority in distinguishing those with executive dysfunction from healthy controls with no executive impairment (16.9 vs 15.0, $p=0.02$) (Tremont, 2010). This is perhaps reflective of its ability to also distinguish between CVD (vascular cognitive impairment/dementia, such as VCI/VaD) versus AD and controls as mentioned previously (Shapiro, 1999; Hogervorst, 2002; Gaines, 2006). VCI/VaD usually present with executive function

impairment before memory problems becomes evident. These findings elucidated an even wider range of utility of the HVLT in future studies.

In sum, the HVLT is a useful test which is available in the public domain and which may have a wide range of applicability, from diagnosing MCI, CVD, DLB and AD, to tracking treatment effects.

3.5 Reference

Alzheimer's Association (2010). 2010 Alzheimer's disease facts and figures. Alzheimers Dement. 6: 158-194.

Alzheimer's Association. (2014). 2014 Alzheimer's disease facts and figures. Alzheimer's & Dementia. 10(2): 4-67.

Aretouli E & Brandt J (2010). Episodic Memory in Dementia: Characteristics of New Learning that Differentiate Alzheimer's, Huntington's, and Parkinson's Diseases. Archives of Clinical Neuropsychology 25:396–409.

Baek MJ, Hyun JK , Hui JR , Seoung HL , Seol HH , Hae RN , Young HC, Chey JY & Kim SY (2011). The usefulness of the story recall test in patients with mild cognitive impairment and Alzheimer's disease, Aging, Neuropsychology, and Cognition: A Journal on Normal and Dysfunctional Development, 18(2): 214-229.

Benedict RHB & Zgalijardic DJ (1998). Practice effects during repeated administration of memory tests with and without alternate forms. Journal of Clinical and Experimental Neuropsychology, 20: 339-352.

Brandt J (1991). The Hopkins Verbal Learning Test: Development of a new memory test with six equivalent forms. Clinical Neuropsychologist, 5(2): 125-142.
Petersen RC (2004). Mild cognitive impairment as a diagnostic entity. Journal of Internal Medicine, 256: 183-187.

Cherner M, Suarez P, Lazzaretto D, Fortuny LA., Mindt MR, Dawes S, Marcotte T & Heaton R (2007). Demographically corrected norms for the Brief Visuospatial Memory Test-revised and Hopkins Verbal Learning Test-revised in monolingual Spanish speakers from the U.S.-Mexico border region. Archives of Clinical Neuropsychology, 22 (3): 343-353.

De Jager CA, Hogervorst E, Combrinck M & Budge MM (2003). Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. Psychological Medicine, 33:1039-1050.

De Jager CA, Schrijnemaekers AMC, Honey TEM & Budge MM(2009). Detection of MCI in the clinic: evaluation of the sensitivity and specificity of a computerised test battery, the Hopkins Verbal Learning Test and the MMSE. Age and Ageing, 38(4): 455-460.

Frank RM and Byrne GJ (2000). The clinical utility of the Hopkins Verbal Learning Test as a screening test for mild dementia. Int. J. Geriat. Psychiatry, 15: 317–324.

Friedman, MA, Schinka, JA, Mortimer JA. & Borenstein GA (2002). Hopkins Verbal Learning Test - Revised: Norms for Elderly African Americans. The Clinical Neuropsychologist, 16(3): 356- 372.

Foster PS, Valeria D, Crucian GP, Rhodes RD, Shenal BD & Heilman KM (2009). Verbal learning in Alzheimer's disease: Cumulative word knowledge gains across learning trials. Journal of the International Neuropsychological Society, 15: 730 – 739.

Gaines JJ, Shapiro A, Alt M & Benedict RHB (2006). Semantic Clustering Indexes for the Hopkins Verbal Learning Test-Revised: Initial Exploration in Elder Control and Dementia Groups, Applied Neuropsychology, 13 (4): 213-222.

Gomez-Tortosa E, Mabillo-Ferna¡ndez I, Guerrero R, Montoya J, Alonso A & Sainz MJ (2012). Outcome of Mild Cognitive Impairment Comparing Early Memory Profiles. The American Journal of Geriatric Psychiatry 20(10) : 827-35.

Gonza´lez-Palau F, Franco M, Jime´nez F, Parra E, Bernate M & Solis A (2013). Clinical Utility of the Hopkins Verbal Test-Revised for Detecting Alzheimer's Disease and Mild Cognitive Impairment in Spanish Population. Archives of Clinical Neuropsychology, 28:245–253.

Hester RL, Kinsella GJ, Ong B & Turner M (2004). Hopkins Verbal Learning Test: Normative data for older Australian adults. Australian Psychologist, 39(3): 251 – 255.

Herlitz A, Lars-Göran N & Bäckman L (1997). Gender differences in episodic memory. Memory & Cognition, 25 (6): 801-81.

Hogervorst E (1998). Age-related decline and cognition enhancers. Neuropsych publishers: Maastricht.

Hogervorst E, Combrinck M, Lapuerta P, Rue J, Swales K, Budge M (2002). The Hopkins Verbal Learning Test and screening for dementia.Dement Geriatr Cogn Disord,13(1):13-20.

Hogervorst E, Mursjid F, Irawati IR, Prasetyo S, Mochtar N, Ninuk T, Bandelow S, Kusdhany LS,, & Rahardjo TBW (2011). Validation of Two Short Dementia Screening Tests in Indonesia. Vascular Dementia: Risk Factors, Diagnosis and Treatment, 235-256.

Hogervorst E, Rahardjo TB, Jolles J, Brayne C & Henderson VW (2011). Gender differences in verbal learning in older participants. Aging Health, 8 (5): 493-507.

Kang YW & Na DL (2003). Seoul neuropsychological screening battery. Seoul, Korea: Human Brain Research & Consulting Co.

Kuslansky G, Katz M, Verghese J, Hall CB, Lapuerta P, LaRuffa G & Lipton RB (2002). Detecting dementia with the Hopkins Verbal Learning Test and the Mini-Mental State Examination Archives of Clinical Neuropsychology,19(1):89-104.

Lacritz LH & Cullum CM (1998). The Hopkins Verbal Learning Test and CVLT: A Preliminary

Comparison. Archives of Clinical Neuropsychology, 13(7): 623–628.

Lacritz LH, Cullum CM, Weiner MF & Rosenberg RN (2001). Comparison of the Hopkins Verbal Learning Test-Revised to the California Verbal Learning Test in Alzheimer's Disease, Applied Neuropsychology, 8, (3): 180-184.

Lu Y, Zhao W (2001). Clinical study on Chinese herbal, Heart－Regulating Formula and Kidney－Tonifying Formula in improving cognitive ability in Alzheimer's disease. Modern Rehabilitation, 11: 46-47.

McLaughlin NCR, Chang AC & Malloy P (2012). Verbal and Nonverbal Learning and Recall in Dementia with Lewy Bodies and Alzheimer's Disease, Applied Neuropsychology Adult, 19(2): 86-89.

Norman MA, Jovier DE, Walden SM & Heaton RK (2000). Demographically Corrected Norms for the California Verbal Learning Test. Journal of Clinical and Experimental Neuropsychology, 22(1):80-94.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, & Kokem E (1999). Mild cognitive impairment: Clinical characteristics and outcome. Archives of Neurology, 56(3): 303-308.

Proust-Lima C, Amieva H, Letenneur L, Orgogozo JM, Jacqmin-Gadda H & Dartigues JF(2008). Gender and Education Impact on Brain Aging: A General Cognitive Factor Approach. Psychology and Aging, 23 (3): 608-620.

Prince M, Acosta D, Chiu H, Scazufca M & Varghese M (2003). Dementia diagnosis in developing countries: a cross-cultural validation study. The Lancet, 2003, 361(9361): 909 – 917.

Riberiro F, Guerreiro M, & DeMendonca A (2007). Verbal learning and memory deficits in mild cognitive impairment. Journal of Clinical and Experimental Neuropsychology, 29(2): 187-197.

Shapiro AM, Benedict RHB, Schretlen D & Brandt J (1999). Construct and Concurrent Validity of the Hopkins Verbal Learning Test – Revised. The Clinical Neuropsychologist, 13 (3): 348-358.

Shi J, Tian J, Wei M, Miao Y & Wang Y (2012). The utility of the Hopkins Verbal Learning Test (Chinese version) for screening dementia and mild cognitive impairment in a Chinese Population. BMC Neurology, 12:136.

Schrijnemaekers A MC, De Jager CA; Hogervorst E & Budge MM (2006). Cases with Mild Cognitive Impairment and Alzheimer's Disease Fail to Benefit from Repeated Exposure to Episodic Memory Tests as Compared with Controls. Journal of Clinical and Experimental Neuropsychology, 28(3):438 – 455.

Schwartz BS, Thomas AG, Karen IB, Walter FS, Gregory G, Meghan R, Bressler J, Shi W &

Bandeen-Roche K (2004).Disparities in cognitive functioning by race/ethnicity in the Baltimore Memory Study. Environ Health Perspect, 112(3): 314–320.

Tanaka T (2005). Gender and ethnic differences on select verbal and visuospatial measures among older European and Japanese Americans. Pacific Graduate School of Psychology, 123: 3438

Tracy JI, Ahmed N, Khan W & Sperling MR (2007). A test of the efficacy of the MC Square device for improving verbal memory, learning and attention. International Journal of Learning Technology,3(2):183-202.

Tremont G, Miele A, Smith MM & Westervelt HJ (2010). Comparison of verbal memory impairment rates in mild cognitive impairment, Journal of Clinical and Experimental Neuropsychology, 32(6): 630-636.

Trenerry RM, Clifford JR, Cascino GD, Sharbrough FW & Ivnik RJ (1995). Gender differences in post-temporal lobectomy verbal memory and relationships between MRI hippocampal volumes and preoperative verbal memory. Epilepsy Research, 20(1): 69-76.

Vanderploeg RD, Schinka JA, Jones T, Small BJ, Graves AB & Mortimer JA (2000). Elderly Norms for the Hopkins Verbal Learning Test-Revised. The Clinical Neuropsychologist, 14(3): 318-324.

Xu X, Dai J, Hogervorst E, Xiao S (2012). Sensitivity of the Chinese version of Hopkins Verbal Learning Test and Mini-Mental State Examination to Dementia and Demographics. The 15th asia-Pacific Regional Conference of Alzheimer's Disease.

Yasar A, Zhou J, Varadhan R & Carlson MC (2008).The Use of Angiotensin-converting Enzyme Inhibitors and Diuretics Is Associated With a Reduced Incidence of Impairment on Cognition in Elderly Women Clinical Pharmacology & Therapeutics,84(1): 119–126.

Table 6. Demographics of the reviewed studies

Study		Brandt (1991)[6]	Benedict (1998)[43]	Lacritz (1998) [34]	Shapiro (1999) [7]	Frank (2000)[9]	Lacritz (2001) [35]	Hogervorst (2002) [8]	Friedman (2002) [22]	De Jager (2003) [10]	Kuslansky (2004) [16]	Hester (2004) [23]
Setting			Community and others			Clinic		Community	Community	Community	Community	Community
Sample Size	**NCI**	18	541	25	59	37 15		114	237	51	323	203
	MCI	3 Amnesic								29		
	Dementia	45 AD			55 AD	34 Va D 26	40 AD	82		60 AD 12 CVD	70	
Mean Age	**NCI**	69.4		70.7	75.3	73.6				75	78.6	73.1
	MCI	77			76.1	73.1	73.4			76		
	Dementia	73.6			76.1	73.1				AD:77 CVD: 75	82	
	Total		48.1			74.7		75	60-84			
Gender (Female%)			63.0%			62.5%		44.4%		50.7%	36.4%	55.2%
Education (years)			13.8	16.2	11.5	11.4 8.5	13.7	11	<=12 years(115); 12 years(42); >12 years(22)	12	12.3	11.1
Ethnicity		**US**	85% Caucasian,14% African, 1% others			Caucasian		Caucasian	African American	UK	mixed (61.8% Caucasian)	Australian

Study		Schrijnemaekers (2004) [11]	Gaines (2006) [33]	Cherner (2007) [21]	Jager (2009) [20]	Foster (2009) [37]	Aretouli (2010) [32]	Baek (2011) [38]	Gomez-Tortosa (2012) [39]	Shi (2012) [30]	McLaughlin (2012) [40]	Gonzalez-Palau (2013) [31]
Setting		Community	Clinic	Community	Clinic	Clinic	Clinic	Clinic	Cohort	Clinic	Clinic	Community + Clinic
Sample Size	**NCI**	54	30	125	98	31				249		109
	MCI	19			21			112	DI<8:103; DI≥8:107	134		132
	Dementia	28	61			28		97 AD		97	22 DLB; 32 AD	54
Mean Age	**NCI**	76	63.5			65.7				67.1		81.9
	MCI	76.2			77.2			69.1		69.9		82
	Dementia	77.2	72.6		82	74.7		73.5		71.1	DLB:77.9 AD:78.9	83.4
	Total	76.4		37.5			63.6		72.3			
Gender (Female%)		48.5%	62.3%	42.5%			49.4%		64.30%	58.50%	66.70%	74.80%
Education (years)		18.2	12.4	9.7		14	14.7	11.1	72.4% below level 2 (out of 5)	11	12.5	8.3
Ethnicity		Caucasian	mixed (75.8% Caucasian)	Mexican decent					Korean Spanish	Chinese	US	Spanish

Table 7. The discriminant ability of the HVLT in differentiating between diagnostic groups in the reviewed studies which reported AUC and optimal cut-off scores using ROC

Study	Aim of Comparison	HVLT total recall performance			
		AUC (95% CI)	Optimal Cut-off	Sensitivity	Specificity
Brandt (1991) [6]	NCI vs Amnesic & Dementia		19/20	0.94	1.0
Frank (2000) [9]	NCI VS mild Dementia	-	18	0.96	0.8
Hogervorst (2002) [8]	NCI VS Dementia	0.97 (0.95-0.99)	14.5 19.5	0.87 0.95	0.98 0.77
De Jager (2003) [10]	NCI VS MCI VS AD VS CVD	0.88 0.84	15.5 (MCI VS AD) 14.5 (CVD VS AD)	0.91 0.82	0.69 0.75
Kuslansky (2004) [16]	NCI VS Dementia	0.89	<16	0.83	0.83
Schrijnemaekers (2004) [11]	NCI VS MCI VS AD		24.5 (NCI VS MCI) 16.5 (MCI VS AD)	0.82 0.79	0.79 0.96
De Jager (2009) [20]	NCI VS MCI	0.9	25.5	0.79	0.95
Shi (2012) [30]	NCI VS MCI VS Dementia	0.98 0.79	15.5 (NCI vs Dementia) 21.5 (NCI vs MCI)	0.95 0.69	0.93 0.71
Gonza´lez-Palau (2013) [31]	NCI VS AD	0.95 (0.92-0.98)	13	0.96	0.85
Aretouli (2010) [32]	AD VS HD VS PD	0.77 (0.65-0.89) 0.64 (0.48-0.80) 0.66 (0.49-0.83)	12.5 (AD VS HD) 12.5 (AD VS PD) 13.5 (PD VS HD)	0.97 0.72 0.87	0.52 0.52 0.44

Notes: NCI=No Cognitive Impairment; MCI=Mild Cognitive Impairment; AD=Alzheimer' Disease; CVD= Cerebral Vascular Disease; HD= Huntington's Disease; PD=Parkinson's Disease.

Table 8. Comparison of the HVLT immediate and delay recall performance between different groups

Study	Aim of Comparison	Comparing Group	HVLT performance		Significance
			IR	DR	
Lacritz (1998) [34]	HVLT-R VS CVLT	HVLT	26.3 (4.9)	10.2 (1.8)	IR: r=0.74, p<0.001; DR: r=0.65, p<0.001
		CVLT	50.2 (9.7)	11.9 (2.5)	
Shapiro (1999) [7]	NCI VS AD	NCI	24.8 (5.1)	-	F=164.8, p<0.001
		AD	12.2 (5.3)	-	
	NCI VS VaD	NCI	24.6 (5.5)	-	F=56.4, P<0.001
		VaD	14.5 (5.8)	-	
Lacritz (2001) [35]	HVLT-R VS CVLT	HVLT	11.4 (3.5)	0.6 (1.3)	IR: r=0.36, p=0.02; DR: r=0.62, p<0.001
		CVLT	19.2 (6.9)	1.2 (2.0)	
Gaines (2006) [33]	VaD VS AD	NCI	25.3 (4.9)	8.9 (2.1)	p<0.05
		VaD	15.1 (4.8)	2.9 (2.5)	
		AD	12.2 (4.8)	1.3 (1.5)	
Cherner (2007) [21]	Demographic correction	Age, education , and gender difference	25.2 (4.3)	8.4 (2.4)	IR: r=0.36, p<0.001 (education); DR: r=0.43, p<0.001 (education);
Foster (2009) [37]	NCI VS Mild AD VS mod AD	NCI	26.0 (9.6)	4.4 (2.2)	IR: F=54.47, p<0.0001
		mild AD	14.0 (1.5)	4.7 (2.5)	
		moderate AD	8.8 (1.0)	1.0 (2.1)	
Baek (2011) [38]	NCI VS MCI VS AD	NCI	20.6 (4.3)	6.4 (2.1)	IR: F=66.12, p<0.001; DR: F=81.6, P<0.001
		MCI	16.3 (4.3)	3.4 (2.5)	
		AD	12.4 (4.1)	1.4 (2.1)	
McLaughlin (2012) [40]	DLB VS DAT	DLB	2.5 (1.8)	1.2 (2.0)	IR: p<0.04; DR: p=0.01
		AD	1.6 (1.1)	0.0 (0.3)	
Gómez-Tortosa (2012) [39]	Baseline	MCI (DI<8)	15.4 (3.0)	2.3 (1.9)	IR: p<0.001; DR: p<0.0001
		MCI (DI>=8)	16.8 (3.0)	3.5 (1.9)	
	48 ±12 Months	MCI (stable)	16.7 (3.0)	3.6 (1.8)	IR: p=0.001;

	follow-up	MCI (progression)	15.2 (3.1)	1.8 (1.9)	DR: p<0.0001

Notes: CVLT=California Verbal Learning Test; IR=Immediate Recall; DR= Delayed Recall; VaD= Vascular Dementia; AD= Alzheimer' Disease; DLB= Dementia with Lewy Bodies; DI= Discrimination Index based on HVLT performance.

Table 9. Normative data for the HVLT IR and DR performance using age and education strata

Study	Stratification						Sample size	HVLT, mean (SD)	
	Age, years		Education, years		Gender, n				
	Mean (SD)	Range	Mean (SD)	Range	Male	Female		IR	DR
Benedict (1998) [43]	24.2 (4.6)	17-30	13.8 (2.1)	8-18	46	56	102	29.4 (3.7)	10.6 (1.6)
	42.1 (6.5)	31-54	13.8 (1.9)	10-20	79	156	235	28.8 (3.8)	10.3 (1.7)
	61.9 (4.3)	55-69	13.8 (2.6)	6-20	50	79	129	27.5 (4.3)	9.8 (1.8)
	75.2 (4.5)	70-88	13.4 (2.9)	5-20	25	50	75	25.2 (5.5)	8.7 (2.8)
Friedman (2002) [22]		60-71		<12	37	30	67	16.9 (3.2)	6.5 (1.5)
				12	11	16	27	18.6 (2.5)	6.7 (1.4)
				>12	6	11	17	20.5 (4.7)	6.8 (2.5)
		72-84		<12	49	57	106	14.9 (4.2)	5.6 (2.0)
				12	4	11	15	18.5 (3.6)	7.0 (2.0)
				>12	1	4	5	17.8 (5.7)	5.2 (3.1)
Hester (2002) [23]		60-69		<=10			29	20.0 (5.5)	6.3 (3.3)
				>10			35	2.6 (4.8)	8.4 (2.9)
		70-79		<=10			63	19.4 (5.8)	6.4 (3.5)
				>10			45	20.2 (4.6)	7.3 (2.7)
		80-89		<=10			15	17.4 (5.2)	5.4 (3.1)
				>10			16	21.1 (4.6)	5.4 (2.6)

4 CHAPTER 4 STUDY AIMS & HYPOTHESIS

In this chapter we will describe the study aims and hypotheses which originate from our literature review and which form the basis of this thesis.

4.1 Investigating usefulness of the Hopkins Verbal Learning Test (HVLT) in discriminating between controls, Mild Cognitive Impairment (MCI) and dementia in two community-based populations in Shanghai

4.1.1 Aims

i. To assess the concurrent validity of the Mandarin version of the HVLT compared to the MMSE;

ii. To investigate the discriminant ability of the HVLT in detecting MCI and dementia among community-dwelling elderly in Shanghai;

iii. To investigate the sensitivity of the HVLT to demographic factors such as age, gender and education compared to the MMSE.

4.1.2 Hypothesis

iv. The HVLT will reveal good concurrent validity compared to the MMSE;

v. The HVLT will show good discriminant validity in differentiating between NCI and MCI/Dementia

vi. The HVLT will not be influenced by demographic factors, but the MMSE is.

4.2 Investigating the Hopkins Verbal Learning Test (HVLT) in detecting dementia in an institutionalized population in Shanghai

4.2.1 Aims

To investigate the discriminant ability of the HVLT in detecting MCI and dementia among institutionalized elderly with dementia or psychiatric disorders in Shanghai;

4.2.2 Hypothesis

The HVLT will reveal good discriminant validity in detecting dementia among institutionalized elderly and will not be influenced by demographic factors, such as age, gender and education, compared to the MMSE.

4.3 Detecting cognitive impairment among elderly using physiological, psychological and other indicators

4.3.1 Aims

i. To investigate which demographic/physiological/psychological variables cluster together when detecting cognitive impairment and frailty;

ii. To categorize frailty and dependency into different categories in order to facilitate future interventions.

4.3.2 Hypothesis

Cognitive impairment and physical dysfunction will be categorized into different components.

4.4 Detecting functional disability among elderly using physiological, psychological and other indicators

4.4.1 Aims

To investigate which demographic/physiological/psychological variables cluster together when detecting dependency (defined as impairment at least one section on either the IADL or the ADL.

4.4.2 Hypothesis

Different frailty phenotypes will present with different types of measurements (physiological and psychological).

4.5 A phenotype of frailty among elderly in a community-based population in Shanghai

4.5.1 Aims

i. To build up a model of frailty among elderly using the combinations of the most common assessments over all criteria reported in the past literatures, and to report the prevalence of frailty in a community setting;

ii. To investigate the association among frailty, functional disability and cognitive impairment. To examine to which extent do frailty overlap with functional disability and cognitive impairment.

4.5.2 Hypothesis

i. The indicators been applied in the past studies also applies in the current study;

ii. The prevalence of frailty in the current study is consistent with the figures reported in the past literatures;

iii. There is a strong overlapping between frailty, functional disability and cognitive impairment. Subjects who present frail status are more prone to be cognitive impaired and functional disabled.

4.6 Demographic risk factors associated with cognitive impairment

4.6.1 Aims

To investigate the influence of demographic and risk factors such as age, gender, education, and occupation on cognitive impairment.

4.6.2 Hypothesis

Participants who are older and less educated, whose main occupation was manual, have higher chance of being cognitive impaired and frail.

4.7 Lifestyle risk factors associating cognitive impairment

4.7.1 Aims

To investigate the influence of lifestyle risk factors such as smoking/alcohol history, exercised frequency, and in particular, food consumption frequency on cognitive impairment.

4.7.2 Hypothesis

i. Participants with smoking/alcohol history and less exercise are at higher risk of cognitive impairment;

ii. Intake of food such as fruit/juice, vegetables (green and orange/red) lower the cognitive impairment risk;

iii. Intake of tofu increases the risk of being cognitive impairment.

5 CHAPTER 5 METHODOLOGY

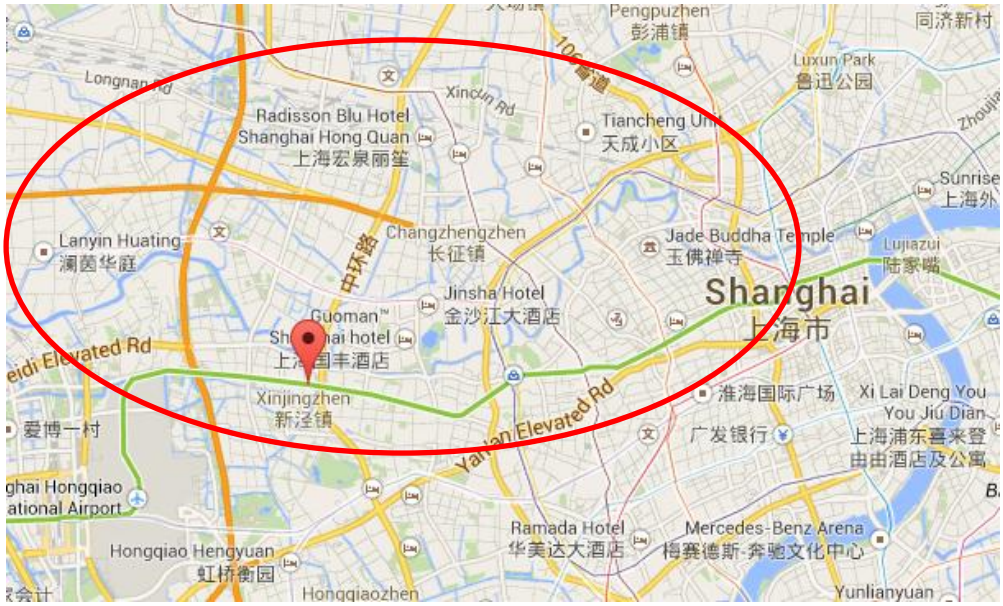
5.1 Project design and data collection

5.1.1 Shanghai 2011 project

5.1.1.1 Testing areas and participants

We measured cognitive function and risk factors for possible dementia in Shanghai, China. A total of 521 participants were investigated in urban sites (North Xin Jing District) in Shanghai. The study was carried out between June 1 and August 31, 2011, All 50 to 95-year old persons born between June 1, 1916, and August 31, 1961, and registered for census purposes in Shanghai were invited to take part in the study.

Figure 1. Testing area in North Xin Jing, Shanghai, China



Ethical approval (Shanghai Jiao Tong University, China, and Loughborough University, UK), governmental, and local permits had all been obtained before study onset.

5.1.1.2 Before test administering

Prior to the study all elders and staff at local community health centres had been informed of the study and subsequently forwarded this information to potential participants. Interested participants were asked to bring their caregiver (if any) and to arrive in the morning between 8-11 am the local health centres at agreed dates for potential participation in the study. None of the elderly approached

refused participation after they had been given information about the study by trained research assistants (RAs) and hence all signed the informed consent forms. No monetary incentives was offered, but participants at the community health centre were given lunch.

5.1.1.3 Clinical interviewer training

In collaboration with the Chinese scientists from Shanghai Jiaotong University, 5 clinicians, 7 RAs and 1 experienced Field Coordinators were fully trained in all aspects integral to the process of testing participants. This included informed consent taking, test administering and scoring. The author of this thesis presented the aims and procedures of the study to all research staff and collaborators at Shanghai Jiaotong University at study onset. Pilot testing was carried out and detailed observations were recorded by the author and feedback to the research team was given with further adjustment made when necessary.

5.1.1.4 Procedure

5.1.1.4.1 Translation and testing procedure

To ensure that the correct meaning of words was delivered during translating questions from English to the local language (Mandarin), multiple forward and backward translations were performed and the test pack was proof-read by members of the scientific staff in both China and Britain. Back translation was done successfully for all the testes and questionnaires, which were all well tolerated in this study.

Test sessions were announced beforehand in general community meetings. Testing was done by the trained and supervised RAs between 8-11 am to avoid the effects of heat and time of day. Participants were communally talked to by the supervisor and told about the study, its aims and procedures, as well as time and other commitments required for participation. Any questions were answered. If the individuals were willing to participate, they were read the information for volunteers clearly and slowly, the informed consent sheet was then signed by both participants and

their carer if present and the participant was allocated a participant number. Consent and contact details were then requested from the participants and their carer for any follow-up contact.

5.1.1.4.2 Questionnaire test pack

The questionnaire and test pack consisted of 4 sections which the RA followed in a pre-defined order. The questions assessed in this thesis included demographic, self and caregiver reported health and cognitive complaints, as well as objective cognitive and functional assessment measures. All questions and measures were presented verbally by the RA.

After the majority of the questionnaire was completed assessing demographics, health and lifestyle, the cognitive measures using the Hopkins verbal Learning Test (HVLT) and the MMSE (Folstein, 1975) were completed, followed by a functional ability assessment using the ADL (Mahoney & Barthel, 1965). The participants was then asked to recall the word list from the HVLT for the delayed recall (DR) score, after approximately 30 minutes after initial exposure.

Each testing session lasted between 45 minutes and 60 minutes depending on the cognitive function of the participant.

5.1.1.4.2.1 Mini Mental Status Examination (MMSE)

The Mini Mental Status Examination (MMSE) (Folstein et al. 1975) is commonly used worldwide to measure cognitive function. It consists of a series of questions designed to measure change in cognitive status and to differentiate between normal age-related cognitive impairment and the pathological cognitive dysfunction that occurs in dementia. It measures 5 cognitive domains: orientation, registration (immediate memory), short-term memory, attention and calculation and language. A score of 23/24 has been considered as the most optimal cut-off point for cognitive impairment.

5.1.1.4.2.2 Hopkins Verbal Learning Test (HVLT)

The HVLT (Brandt, 1991) is widely used to detect memory decline. It is a word learning test consisting of 12 words from 3 low frequency categories. It has 6 parallel versions but in our studies,

version A was used. Words from these 3 categories ('human shelter', 'animals' and 'precious stones') were repeated 3 times for the total immediate recall (IR). Delayed recall (DR) was subsequently obtained after approximately 20 minutes without prompting. In the current project, the HVLT was utilised as the screening tool for possible MCI and dementia. This was suggested by De Jager (2003) that the HVLT has the optimal discriminant ability in detecting MCI and dementia comparing to all the other cognitive tests.

5.1.1.4.2.3 Possible dementia/Mild Cognitive Impairment (MCI) in the current study

After cognitive test, an extensive medical examination was conducted by the clinicians, which led to a consensus diagnosis of dementia. Dementia and MCI were diagnosed according to standard clinical diagnostic criteria, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; The American Psychiatric Association, 1994) and the revised Petersen's diagnostic algorithm (Petersen, 2004), respectively.

Using a combination of cognitive tests and clinical investigations, three groups consisting of no cognitive impairment (NCI), mild cognitive impairment (MCI) and dementia were stratified. In further analysis, MCI and dementia were combined together as cognitive impairment (CI).

5.1.1.4.2.4 Functional ability measures

Functional ability was measured using the Barthel Activity of Daily Living (ADL, Mahoney and Barthel, 1965) and Instrumental (IADL, Lawton, 1969). The ADL was developed to examine participant's basic functional status. It tests ten items including the ability to independently feed oneself, bathe, groom oneself, control of bowels and bladder, toilet use, transfers, mobility on level surfaces and stairs. It has a point value for each section and a higher score means the patient is more independent (0 means unable to handle, 5 means needs help, and 10 means independent function). It is suggested that intact ADL is associated with MCI (Petersen, 1999) and subsequently can be used to detect the deterioration from MCI to dementia. In addition, this reported that the cognitive impaired group is more prone to be ADL disabled (Perneczky, 2006).

The IADL assesses participant's complex functional aptitude. On the IADL, 8 section were examined including ability in using telephone, shopping, food preparation, housekeeping, responsibility for own medication, handling finances, laundry and travelling with transportation. It has a point value for each question, with a higher score representing a better performance (0 means unable to handle/ needs help, and 1 means independent function). Weintraub et al. (1982) suggested that the IADL has been found to be strongly associated with cognitive impairment. In addition it was proved to be cross-culture applicable when tested out in Asian populations (Ng, 2006).

Both the ADL and IADL scale was confirmed to be able to detect functional limitations related to cognitive impairment. In the present study, if participants indicated that they were unable to perform at least one of the listed tasks independently, they were considered as IADL or ADL disabled.

5.1.1.4.2.5 Demographics and lifestyle questions

General demographics about the participants covered a wide variety of information (e.g. age, gender, education, occupation, and living status). Following from this, lifestyle questions, e.g. leisure activities, smoking and drinking frequency, and the food frequency questionnaire (FFQ) were also surveyed using standard questionnaires.

The FFQ is a standardized questionnaire investigating participant's dietary consumption habit and frequency (Frankenfeld, 2004). On the FFQ, consumption of food such as bread, rice, fruit/juice, green vegetables, orange/red vegetables, meat, tofu, tempe, were surveyed based on three types of frequencies, daily, weekly and monthly. In the current project, food intake frequency were calculated on a weekly basis (calculated from daily, weekly and monthly, e. orange/ g. food intake 1 time/day= 4 times/week; food intake 1 time/month= 0.25 times/week). This included the types of food of interested in the project: fruit/juice, green vegetables, red vegetables, and tofu.

Previously, it was concluded that intake of fruit/juice and vegetables significantly reduces the risk of being demented (Barberger-Gateau, 2007). However the effect of tofu on cognition remained debatable. Several authors suggested that higher tofu consumption is associated with poorer cognitive performance (White, 2000; Hogervorst, 2008). In contrast, tofu intake was reported to be positively related to cognitive ability (Hogervorst, 2011), but only among younger elderly (mean age 65 years). There are also some studies reporting no association between tofu intake and cognition, especially among older elderly people (Franco, 2005; Hogervorst, 2011). Therefore it is unclear whether consumption of tofu exerts positive or negative impact on elderly's cognitive function which could be an early sign for dementia.

5.1.2 The HVLT and MMSE among Institutional Patients in Shanghai

5.1.2.1 Testing areas and participants

We measured cognitive function and risk factors for possible dementia in Shanghai, China. A sample of institutionalized 47 elderly non-disabled patients above 60 years of age was included for this study. The study was carried out between December, 2011 and January, 2012. Participants were all in good physical condition, without chronic systematic disease and had no severe visual or hearing problems. All were able to participate in the study. Ethical approval (Shanghai Jiao Tong University, China, and Loughborough University, UK), governmental, and local permits had all been obtained before study onset.

5.1.2.2 Before test administering

As been described above in section 4.1.1.2

5.1.2.3 Clinical interviewer training

As been described above in section 4.1.1.3

5.1.2.4 Questionnaire test pack

As been described above in section 4.1.1.4.2

5.1.3 Frailty project

5.1.3.1 Testing areas and participants

We measured cognitive function, physical function and risk factors for possible frailty cases in Shanghai, China. A total of 170 participants were investigated in urban sites (Chang Ning District) Shanghai. The study was carried out between May 1, 2012 and July 31, 2012. All 50 to 95-year old persons born between May 1, 1917, and July 31, 1962, and registered for census purposes in Shanghai were invited to take part in the study.

Figure 2. Testing area in Changning District, Shanghai, China

Ethical approval (Shanghai Jiao Tong University, China, and Loughborough University, UK), governmental, and local permits had all been obtained before study onset.

5.1.3.2 Before test administering

As been described above in section 4.1.1.2

5.1.3.3 Clinical interviewer training

As been described above in section 4.1.1.3

5.1.3.4 Procedure

5.1.3.4.1 Translation and Testing Procedure

Translation and informed consent signing procedures are as have been described above in section 4.1.1.4.1

5.1.3.4.2 Questionnaire test pack

The whole investigation included both physiological and psychological assessments. Participants were surveyed for demographics (e.g.: age, gender, education, living circumstances), and other variables (such as health and lifestyle) using standardized questionnaires. Cognitive and physical status was assessed thereafter. In our study frailty was assessed by using the most common physiological and psychological assessments over all criteria reported in the past literature. Physiological symptoms were measured by assessment of muscle strength (grip strength and the Timed Up and Go (TUG) or Get-Up and Go (GUG) test), gait speed (15 feet walking test), balance (Berg Balance scale), and body mass index. In addition we assessed incontinence through the ADL questionnaires. However we left out the assessment of depression status in the current study. This is because the direct association between depression and frailty is not entirely clear. Therefore we omit the questionnaire on depression to shorten the time taken in administering the tests, so as to avoid the exhaustion on participants caused by time-consuming test package.

By doing these, we identified the best combination of mental and psychological and physiological components of frailty, to review risks for consequences (dependency, poor health, falls and hospitalisation).

Each test package took roughly 100 minutes in total: 30 minutes for the questionnaire survey, 20 minutes for psychological assessment and 40 minutes for physiological assessment, with two short breaks of 10 minutes in between these procedures.

5.1.3.4.2.1 Physiology assessments

5.1.3.4.2.1.1 Upper body strength—grip strength

Loss of grip strength is strongly associated with increasing chronological age (Bassey, 1993). Lower grip strength is associated with incident as well as prevalent disability and can be predictive of morbidity and mortality (Rantanen, 1999). Rantanen (1999) examined whether hand grip strength could be a useful predictor of age related disability, and found that midlife hand grip strength was highly predictive of functional limitations and disability 25 years later. Good muscle strength in midlife may protect people from old age disability by providing a greater safety margin above the threshold of disability.

5.1.3.4.2.1.2 Gait speed—15 feet walking test

Gait Speed is widely used as a standard in rehabilitation reflecting muscle strength and is usually assessed by a 15 feet walking test. This assesses how long it will take for a participant to walk at his/her own pace for a distance of 15 feet. Rest can be taken using the chairs at any time when needed.

5.1.3.4.2.1.3 Lower body strength—Timed-Up-and-Go (TUG) test

We need prognostic tools that help identify individuals with an increased risk of loss of lower body strength. The TUG is a modified, timed version of the "Get- Up and Go" test (Mathias, 1986). The TUG is an observational rating scale of fall risk using a score from 1 to 5. It is an assessment that should be conducted as not only part of a routine evaluation, but also part of the treatment when dealing with older persons. Its purpose is to detect "fallers", to identify those who need evaluation and to measure the lower body strength. The TUG test was examined in a community-based study in America (Shumway, 2000) and proved to be a strong identifier for falls (sensitivity 87%, specificity 87%). Furthermore, another community-based study conducted among elderly in Ireland (Donoghue, 2012) concluded that lower score on the TUG test is associated with lower level of cognitive performance including executive function, attention and memory. The results indicate that

the TUG can be used to predict risk of being frail and cognitive impaired which could be a sign of dementia.

In the present study, the TUG was tested by taking the time that a participant takes to rise from a chair, walk three metres, turn around, walk back to the chair and sit down. Participant's ability to stand up without physical assistance (i.e. touching the chair armrest) was recorded, subsequently followed by 3 trials of tests. Average time taken was calculated as the final score.

5.1.3.4.2.1.4 Postural stability—Berg body balance test

Falls and fall-related injuries are a major public health problem for the elderly. An important component of falls research is the development of objective, quantitative measures of balance and mobility. Balance is critical in the normal performance of physical activities, and impaired balance is an important risk factor for falls in older people. It has been found that loss of balance increases the risk for falling (American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel of Falls Prevention, 2001). The Berg balance test was developed as a clinical performance-oriented measure of functional balance specifically in elderly (Berg, 1989). It was found to be strongly related to the TUG test (r=-0.81) (Podsiadlo, 1991) in detecting basic functional mobility for frail elderly. Furthermore, good discriminative ability of the Berg balance test was indicated in predicting falls in a community-based prospective study (Berg, 2008).

In the present study, the Berg balance test which contains 14 sections of static and dynamic functional balance tasks was administered. The items being tested on the Berg balance test include sitting to standing, standing unsupported, standing to sitting, sitting unsupported, transfers, standing unsupported with eyes closed, standing unsupported with feet together, reaching forward with arms stretched while standing, reaching forward to place a ring around a standing stick, picking up objects from floor, looking behind while standing with feet fixed, turning 360 degrees, alternating placing foot on step, tandem stance, and standing on one leg. On each task, score ranges from 0-4, and a higher score represents better performance.

5.1.3.4.2.2 Assessment of cognitive function

5.1.3.4.2.2.1 Mini Mental Status Examination (MMSE)

As been described above in section 4.1.1.4.2.1.

5.1.3.4.2.2.2 Hopkins verbal Learning Test (HVLT)

As been described above in section 4.1.1.4.2.2.

5.1.3.4.2.2.3 Possible dementia/cognitive impairment in the current study

As been described above in section 4.1.1.4.2.3.

5.1.3.4.2.2.4 Functional ability measures

As been described above in section 4.1.1.4.2.4.

5.1.3.4.2.2.5 Demographics and lifestyle questions

As been described above in section 4.1.1.4.2.5.

5.1.3.5 Operational definition of frailty

Table 10. Operationalizing a Phenotype of Frailty

Measurement	Description of characteristic
BMI	Less than 21 kg/m^2
Grip strength	Lowest 20%, adjusted for gender
TUG (Get up)	Get up with assistance or unable to get up
TUG (walk) score	Lowest 20%, adjusted for gender
15 feet gait speed (lowest 20%)	Lowest 20%, adjusted for gender
Balance (lowest 20%)	Lowest 20%, adjusted for gender
Low physical activity	Exercise less than once per week
Presence of Frailty	Positive for frailty phenotype: ≥ 3 criteria present Pre-frail: 1 to 3 criteria present Robust: 0 criterion present

Operationalization of the frailty phenotype is summarized as a result of the previous studies reviewed in the current thesis (see chapter 2).

We identified a phenotype of frailty by the presence of three or more of the following components of potential frailty:

1) Low BMI as measured by this algorithm:

$$BMI = \text{Weight (kg)}/\text{Height (m)}^2$$

2) Weakness (upper and lower body): grip strength in the lowest quintile, adjusted for gender; and TUG get up with assistance or unable to get up

3) Slowness (lower body): TUG score in the lowest quintile, adjusted for gender; and 15 feet gait speed in the lowest quintile, adjusted for gender;

4) Poor balance: Berg Balance test score in the lowest quintile, adjusted for gender;

5) Low physical activity: exercise less than once per week.

An individual with 4 or more present frailty components out of a total of 7 was considered to be ‘frail’, whereas equal or less than 3 characteristics were hypothesized to be ‘pre-frail’. Those with no present frailty components were considered as robust.

Cognitive impairment status in the current analysis was measured by the HVLT and the MMSE by applying an optimal cut-off score been used to differentiating MCI from NCI in the current thesis (see chapter 6, section 6.1.2, table 12). Functional disability was measured by the ADL and IADL (see chapter 5, section 5.1.1.4.2.4, functional measures).

5.2 Statistical analyses

The following section describes the statistical methods used to assess the area of interested described so far in the thesis. For all analyses, a p-value of less than 0.05 was considered significant and analyses were performed in SPSS version 19.0.

5.2.1 Descriptive data of demographics, cognitive function, functional status and lifestyle

Descriptive analyses were performed for the whole group and within each cognitive group giving frequencies and percentages for demographic variables. The analyses were done using Chi Square for percentages (e.g. for gender) and using Mann Whitney U tests for continuous data. The demographics variables were gender, age, education, occupation and living status (whom the participants was living with and whether this was an institution or the community) the sample was described for cognitive scores on the MMSE and HVLT (immediate recall, IR) as well as functional status (ADL) and proxy measures by the clinician.

5.2.2 Receiver Operating Curves (ROC) Analysis to establish optimal HVLT and MMSE cut-off score to detect MCI and dementia

The receiver operating characteristic (ROC) was employed to select optimal MCI/Dementia discriminant models by illustrating the performance of a binary classifier system (which was demonstrated in the Shanghai 2011 project and the Institutionalized study as normal controls with no cognitive impairment (NCI) vs mild cognitive impairment (MCI) or NCI vs Dementia. The ROC plotted the fraction of true positives out of the total actual positives (TPR = true positive rate) vs. the fraction of false positives out of the total actual negatives (FPR = false positive rate). The optimal cut-off scores for each cognitive test (HVLT and MMSE) were identified by choosing the score that maximized the sensitivity and specificity. Area Under Curve (AUCs) was subsequently compared in order to determine the cognitive test with superior discriminant ability[1].

[1]. Hanley JA & McNeil BJ. A method of comparing the areas under receiver operating characteristics curves derived rom the same cases. Radiology 148:839-843, September 1983

All analyses were subsequently stratified by gender (female vs. male), education (no or primary level vs. secondary and above), and age (≤65, 66-79 and ≥80 years of age) to further explore the difference on cut-off scores as well as the changes in sensitivity and specificity.

5.2.3 Logistic regression to confirm the specific HVLT and MMSE cut-off scores in predicting MCI and dementia

After the optimal cut-off scores for the HVLT (IR) was generated, logistic regression (Backward conditional) was performed using the Cut-off scores of the HVLT with the optimal balance between sensitivity and specificity (as obtained with the ROC curve analyses) as the dependent variables. In these analyses, variables such as MCI (yes/no), dementia (yes/no), and potential confounds (age, gender and education) as independent variables. These analyses examined whether the HVLT cut-off scores needed to be modified according to participant demographics (age, gender and education). The same analyses were performed for the MMSE for comparison.

5.2.4 Factor Analysis to assess which variables cluster together to detect cognitive impairment and functional disability

5.2.4.1 Research questions and areas of interest

Principle Component Analysis (PCA), a particular method of Factor Analysis (FA) was employed to explore the method in which variables clustered together, to what extent they correlated with each other, and the underlying constructs of these combinations. In the current study, we examined whether physical measurement, psychological measure and demographic factors grouped together in determining Cognitive Impairment (CI) and functional disability. PCA was used to assess the discriminatory value of these variables.

5.2.4.2 Definition of outcome measurements

In the present analyses, CI and functional disability were the outcome variables. CI included the clinically defined MCI (according to Petersen, 1999) and dementia (according to DSM-IV criteria) participants.

Functional disability was determined using IADL and ADL as proxy variables of (in) dependent functioning. In the present study, if participants indicated that they were unable to perform at least one of the listed tasks independently, they were considered as IADL or ADL disabled and subsequently categorized into the 'functional disabled group.

5.2.4.3 Nature of the sample

The portion of the total population whom met the basic criteria for CI was identified by combing the MCI and dementia group together, due to the small sample of dementia cases (33 out of 521). Therefore assessing this proportion of the sample in isolation, as opposed to the entire sample which would include both CI and NCI cases, allowed more sensitive investigation of the possible components of CI the variables measured [2].

5.2.4.4 Assumptions

In order to be able to justifiably use any method of FA, the data must meet the following assumptions (Field, 2005):

i. data must be of at least ordinal level measurement;
ii. variables should be normally distributed;
iii. relationship between variables should be linear (i.e. the variables must be continuous);
iv. at least 100 participants should be have been tested;
v. there should be more participants than extracted components (at least 2:1), but as this is exploratory analysis, this was not known until after analysis was performed.

This data set met all above assumptions and therefore FA was applicable.

[2]. This was checked during preliminary analysis with the whole sampe (N=170). Preliminary factor analysis extracted two components, a highly loading first component with a very high eigenvalue (explained 48% of the variance) whereas another component explained much less of the total variance (13%). The analysis was therefore not discriminatory enough for the nature of the data. This could have been due to the inclusion of cognitively intact, MCI and dementia cases in the entire sample. Thus the analysis was not sensitive enough to identify cognitive impairment.

5.2.4.5 Suitability of data for FA (preliminary analysis)

5.2.4.5.1 Preliminary analysis

To examine the suitability of the data for FA, preliminary analysis was performed. The sample was of adequate size. Nevertheless due to the nature of the data, not all questions were answered by all participants. Therefore although the preferable method of exclusion of missing cases is 'exclude cases list wise', this method could have resulted in a significant reduction in the sample size. Cases were excluded pairwise in the current analysis as it ensured the adequate sample size for FA.

5.2.4.5.2 Normality of data

Distribution histograms were plotted to check the data were not skewed and were normally distributed.

5.2.4.5.3 Correlation between variables

Multi co-linearity and singularity were checked using the determinant (a critical value which gives an indication of the correlation between variables) the determinant should be greater than 0.00001 as if this value is 0, a solution could not be reached and FA is not appropriate. Checking for singularity, assess if two variables are perfectly correlated, was checked by considering the removal of variables which correlate too high with each other ($r>0.9$). Different absolute value cut-offs have been suggested for the minimum absolute values for correlations between variables (Field, 2005; Pallant, 2005b). The more stringent rule involves considering the removal of absolute values below $r=0.4$. This would result in analyses that narrowed down the variables and the components they loaded onto. However, during preliminary checking, a $r=0.4$ would not allow the nature sharing of some variables between different components as it resulted in most variables only loading onto one component. Hence as Pallant (2005b) suggested, an absolute value cut-off of $r=0.3$ was used in further analysis.

5.2.4.5.4 Factorability of the data

The factorability was assessed via two standard methods:

i. Bartlett's test of sphericity tests the null hypothesis, for which the correlation matrix would be an identify matrix and all correlation coefficients would be 0. Bartlett's test of sphericity needed to be statistically significant ($p<0.05$) to inform that the R-matrix was not an identity matrix and that there was actually relationship between variables.

ii. Kaiser-Meyer-olkin (KMO) (values range from 0-1) is a measure of sampling adequacy. It tests the amount of variance within the data that can be explained by the components. Guidelines (Tabachnic & Fidell, 2001) state that a value of 0.6 is considered to be the minimum value for a good FA[3].

5.2.4.5.5 Criteria employed to determine numbers of extracted components

Components extraction was used to determine the smallest number of components that could best be used to account for the inter-correlation between variables. The aim was to find a simple solution with as few factors as possible (specificity) but still explaining as much of the variance in the data as possible. Several methods were used to determine the number of components to be retained after preliminary analysis and before factor rotation.

The proportion of total variance and the variance due to each of the extracted factors was examined using Kaiser's criterion—only components with an eigenvalue of above 1 were retained for further analysis. For further confirmation of the number of retained components, parallel analysis was performed using Monte Carlo PCA for FA (Watkins, 2000) for randomly generated dataset. This method increases confidence in results and reduced subjective interpretation of an objective analytical method (Franklin, 1995).

5.2.4.5.6 Factor rotation

Rotation maximised the loading of each variable onto one extracted component. It provides a clear indication of which specific variables are more strongly correlated to which component. Rotations performed are either orthogonal rotations (Varimax method), which assume that the underlying

[3]. Kaiser (1974) reported that 0.5-0.7 =mediocre; 0.7-0.8= good; 0.8-0.9 and above=superb

construct are independent or uncorrelated, or oblique rotations (direct oblim method), which allows for the underlying construct or components to be correlated.

5.2.5 A phenotype of frailty among elderly in a community-based population in Shanghai

5.2.5.1 Calculate the lowest quintile for physical measurements for frailty

Lowest quintile of the grip strength, TUG scores, 15 gait speed and Berg balance test scores was calculated by ranking cases. By selecting assigning rank to low ties, a new variable displaying the ranking in percentage for each measurement was generated in the dataset. The lowest 20% of each measurement was subsequently identified, adjusting for gender (Fried, 2001).

5.2.5.2 Chi-square analysis to investigate the prevalence of frailty across different age groups, education levels, functional and cognitive status

Chi-square analysis was performed to investigate the percentage of demographic, functional and cognitive status. Functional disability was classified by the ADL and IADL. Those who fail at least one test were considered as functional disabled.

5.2.6 Demographic and lifestyle risk factors for cognitive impairment

5.2.6.1 Correlations between demographic and lifestyle variables

Various literature driven associations between demographic and lifestyle variables were assessed using ANOVA (for continuous, interval level data) and Chi-Square (for categorical data which is either ordinal or nominal), using participants' cognitive status (NCI vs. CI group).

All analyses were subsequently stratified by age splits (≤65, 66-79, and ≥80 years of age), education (no or primary vs. secondary and above), gender (female vs. male), and profession (no job or manual vs. non-manual) to further investigate the performance on the HVLT IR and DR in these groups.

5.2.6.2 Logistic Regression

In the current study, cognitive impairment, as the dependent variable, was used in the logistic regression model. Cognitive impairment was categorized according to the HVLT total recall (IR) performance. The optimal cut-off score of the HVLT in discriminating between NCI and CI cases was generated by applying ROC (19/20 in the current study). Subsequently, a HVLT score of equal or less than this cut-off score (≤19 in the current study) was defined as "higher risk of cognitive impairment" and a HVLT score of above this cut-off score (>19) was defined as "lower risk of cognitive impairment".

Binomial Logistic Regression was employed as it can statistically predict category membership based on groups of participants. Logistic regression was used as this part of the study aimed at assessing whether certain demographic/physiological variables could predict cognitive impairment, i.e. the odd ratio of a particular outcome.

5.2.6.2.1 Demographic risk factors for cognitive impairment

In the current study, demographic variables of age, gender, education, and occupation were added into the regression equation using the 'Enter' method which some believe in the most appropriate methods for theory testing where previous research exists and it is not as influenced by random

variation or as un-replicable as stepwise methods (Field, 2005). Afterwards, analysis was repeated using age stratification to investigate the predictive value of the significant risk factors on cognitive impairment across different age groups.

5.2.6.2.2 Lifestyle risk factors for cognitive impairment

Lifestyle variables such as smoking/alcohol history, exercise frequency, and weekly consumption of various types of food (fruit/juice, green vegetables, orange/red vegetables and tofu) were put into the mode using the same method as described above in section 5.3.2.2.1. Subsequently, logistic regression analyses were performed in 3 steps stratified by participant's dietary habits (vegetarian or non-vegetarian). In step 1, only food intake habits (fruit/juice, green vegetables, orange/red vegetables and tofu) were put into the model; in step 2, other lifestyle variables such as smoking/alcohol history and exercise frequency were added into the model to see whether the effect of various food consumption was mediated; in step 3, all demographic variable, such as age, gender, educational level or profession, were also added into the model.

5.2.6.2.3 The association between tofu intake and cognitive impairment

Binomial logistic regression was performed to assess the predictive value of tofu consumption on cognitive impairment, controlling for demographic and other dietary variables including age, gender, education, being vegetarian (yes or no), weekly intake of fruit/juice, green vegetables and orange/red vegetables. Analyses were also stratified by median age split (68 years of age). All data analyses were performed using SPSS 21.0., using a p value of <0.05 for significance.

5.2.6.3 Linear Regression

Linear regression analysis was employed to investigate the effect of tofu on HVLT performance using the HVLT IR scores (continuous data) as the dependent variable, adjusting for demographic and other dietary variables, including age, gender, education, being vegetarian (yes or no to eating meat), weekly intake of fruit/juice, green vegetables and orange/red vegetables.

6 CHAPTER 6 THE HVLT AND THE MMSE IN DISCRIMINATING MCI AND DEMENTIA CASES FROM NCI IN COMMUNITY AND INSTITUIONALIZED SETTINGS

6.1 Shanghai 2011 data analysis results of A Community-dwelling Sample

6.1.1 Descriptive data of the whole sample and different diagnostic groups

Table 11. Demographic data and scores on neuropsychological tests

	Whole (N=521)	NCI (N=406)	MCI (N=82)	Dementia (N=33)	P value
Age	67.5±10.3	65.7±9.7	71.3±10.2	79.8±6.0	<0.001
Education (below Primary School level)	31.1% (162)	22.9% (93)	46.3% (38)	93.9% (31)	<0.001
Years of Education	8.4±4.3	9.3±3.9	7.0±4.1	2.3±3.1	<0.001
Gender (male %)	45.5% (237)	47.0% (191)	42.7% (35)	33.3% (11)	NS
Occupation (no job or manual %)	66.8% (348)	65.8% (267)	58.5% (48)	100% (33)	<0.001
History of Smoke (Yes %)	24.8% (129)	25.4% (103)	20.7% (17)	27.3% (9)	NS
History of Alcohol (Yes %)	15.7% (81)	16.4% (66)	14.8% (12)	9.1% (3)	NS
Diet (Vegetarian mainly)	53.0% (276)	49.8% (202)	53.7% (44)	90.9% (30)	0.002
MMSE total score	26.6±5.2	28.2 ±3.2	24.5±3.4	12.9±6.6	<0.001
HVLT total score	22.4±9.0	25.4±7.1	13.8±5.6	6.8±6.1	<0.001

NS=Not Significant

The dementia group was on average 10 years older than those without dementia and also had a lower educational level than the other 2 groups.

Interestingly, 100% of the group with dementia used to be manually workers whereas the other 2 groups had an equal proportion of people who used to work manually or intellectually. Also, the percentage of vegetarians in the dementia group was almost twice as high as (90.9%) as that in the other two groups (see table 11).

6.1.2 The discriminant ability of the HVLT and the MMSE in detecting MCI from NCI

6.1.2.1 The discriminant ability of the HVLT and MMSE in detecting MCI before age, gender and education stratification

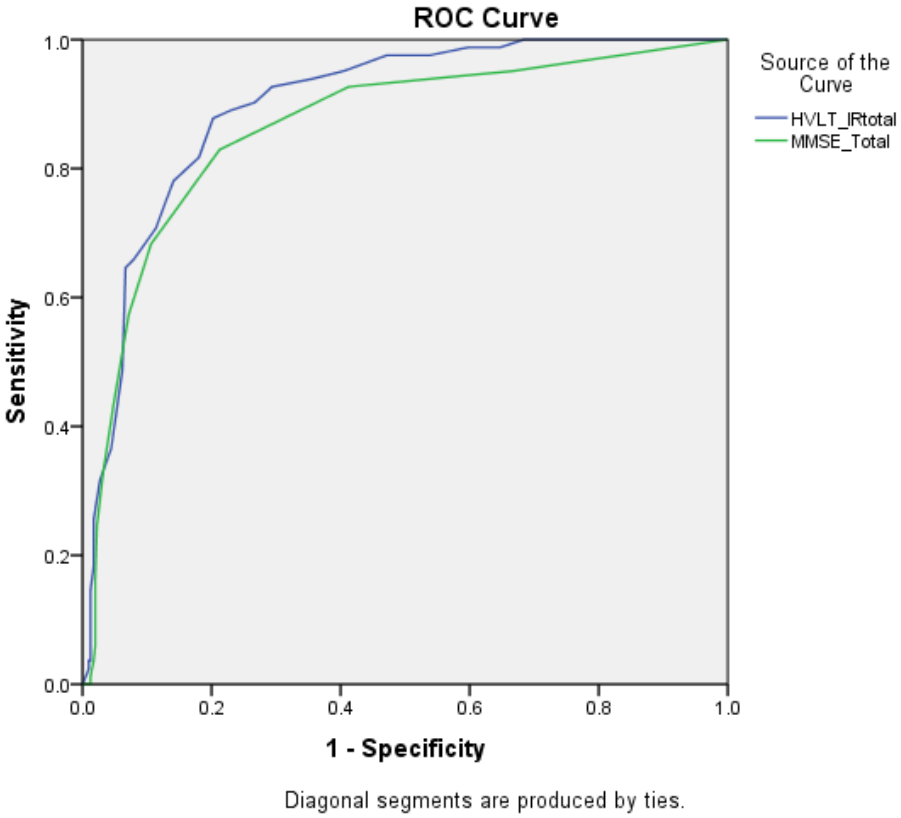


Figure 3. Receiver operating characteristic curve for the HVLT and MMSE total score in detecting MCI

Table 12. Area Under Curve (AUC), optimal cut-off scores, SE, SP, PPV and NPV of HVLT and MMSE in discriminating MCI from NCI in the whole group

Test	AUC (95% CI)	Cut-Off	SE	SP	p value
MMSE	0.86 (0.82-0.91)	27/28	82.9%	78.8%	NS
HVLT	0.90 (0.87-0.93)	19/20	87.8%	79.8%	

NS=Not Significant

The HVLT and MMSE both showed good discriminative capacity in MCI screening. Among the whole sample, by applying an optimal cut-off of 27/28, the MMSE rendered good sensitivity (82.9%) and specificity (78.8%). Slightly better sensitivity (87.8%) and specificity (79.8%) of the HVLT was seen using a cut-off of 19/20 (see table 12).

6.1.2.2 The discriminant ability of the HVLT and MMSE in detecting MCI after age, gender and education stratification

Table 13. Area Under Curve (AUC), optimal cut-off scores, SE, SP, PPV and NPV of HVLT and MMSE in discriminating MCI from NCI using age, gender and education stratification

Comparing Group			AUC (95% CI)	Cut-off	SE	SP
Gender	Male (N=226)	MMSE	0.94 (0.91-0.98)	27/28	88.60%	85.80%
		HVLT	0.92 (0.86-0.97)	19/20	85.70%	84.70%
	Female (N=262)	MMSE	0.80 (0.72-0.88)	27/28	78.70%	72.60%
		HVLT	0.88 (0.84-0.92)	19/20	89.40%	95.30%
Age	≤65 (N=274)	MMSE	0.86 (0.78-0.94)	27/28	75.90%	84.20%
		HVLT	0.89 (0.84-0.94)	19/20	82.80%	83.00%
	66-79 (N=115)	MMSE	0.88 (0.81-0.95)	26/27	74.30%	86.00%
		HVLT	0.92 (0.88-0.97)	18/19	88.60%	82.50%
	≥80 (N=99)	MMSE	0.75 (0.62-0.87)	26/27	88.90%	71.70%
		HVLT	0.81 (0.69-0.92)	17/18	83.30%	69.60%
Education	≤Primary (N= 131)	MMSE	0.84 (0.75-0.92)	25/26	76.30%	88.90%
		HVLT	0.87 (0.81-0.93)	18/19	86.80%	78.90%
	>Primary (N=357)	MMSE	0.86 (0.80-0.92)	27/28	79.50%	81.70%
		HVLT	0.90 (0.85-0.94)	20/21	88.60%	78.80%

After stratification by age (using a median split of 65), gender and education (using a primary school level as the split), better discriminative capacity was seen in the HVLT comparing to the MMSE (see table 13).

Although the cut-off scores of the HVLT and MMSE remained the same (27/28 for MMSE and 19/20 for HVLT) after gender stratification, the MMSE was found to have superior discriminative capacity among males, while the HVLT showed an advantage in detecting MCI among females.

With regards to age stratification, the HVLT showed better discriminative value than the MMSE in all three age groups, whereas larger differences for tests were found in relation to an advanced age (ROC AUC: 0.81 vs 0.75 among those who are older than 80 years of age; ROC 0.92 vs 0.88 for those aged from 65 to 80 and ROC 0.89 vs 0.86 among those aged below 65 years of age). Using only primary levels of schooling obtained vs. more than that for educational stratification, the HVLT revealed superior differentiating ability compared to the MMSE for both lower and higher education groups (ROC 0.90 vs 0.86 in less educated group, and 0.87 vs 0.84 in higher educated group).

Stepwise backward conditional logistic regression was performed using the HVLT and MMSE optimal cut-off scores (recoded as below '0' or equal or above '1' the HVLT cut-off score of 19.5 and MMSE cut-off score of 27.5). Results indicated that MCI (y/n) was the only significant predictor for HVLT performance ($p<0.001$), correctly classified 80.2% of the whole sample. With regards of the MMSE, MCI (y/n) ($p<0.001$), age ($p<0.001$), gender ($p=0.04$) and education ($p=0.04$) were all strong indicators for a MMSE performance lower than 23.5 (correctly classified 78.1%).

6.1.3 The discriminant ability of the HVLT and the MMSE in detecting dementia from NCI

6.1.3.1 The discriminant ability of the HVLT and MMSE in detecting dementia before age, gender and education stratification

Figure 4. Receiver operating characteristic curve for the HVLT and MMSE total score in detecting dementia

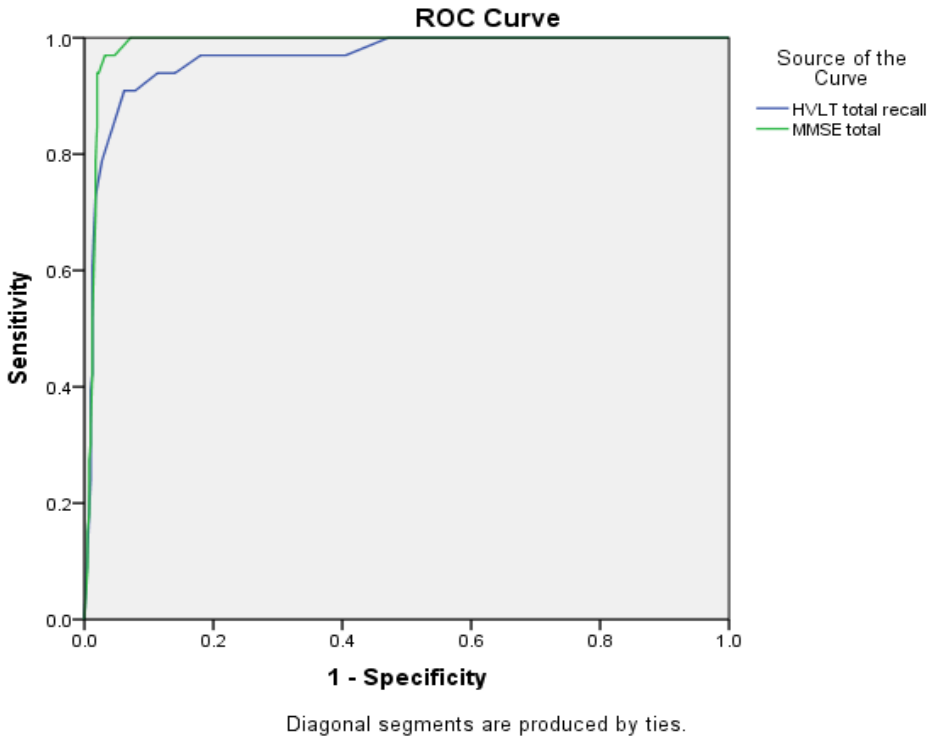


Table 14. Area Under Curve (AUC), optimal cut-off scores, SE, SP, PPV and NPV of HVLT and MMSE in discriminating dementia from NCI in the whole group

Test	AUC (95% CI)	Cut-Off	SE	SP	*p* value
MMSE	0.99 (0.98-1.00)	23/24	97.0%	96.8%	NS
HVLT	0.97 (0.94-0.99)	13/14	90.9%	93.8%	

NS=Not Significant

The MMSE and the HVLT demonstrated equivalent discriminant ability in differentiating between NCI and dementia. Applying a cut-off score of 23/24, the MMSE rendered an optimal balance between sensitivity (97.0%) and specificity (96.8%), whist 90.9% sensitivity and 93.8% specificity was gained accompanying the HVLT cut-off score of 13/14 (see table 14).

6.1.3.2 The discriminant ability of the HVLT and MMSE in detecting dementia after age, gender and education stratification

Table 15. Area Under Curve (AUC), optimal cut-off scores, SE, SP, PPV and NPV of HVLT and MMSE in discriminating dementia from NCI using age, gender and education stratification

Comparing Group			AUC (95% CI)	Cut-off	SE	SP
Gender	Male (N=202)	MMSE	1.00 (1.00-1.00)	19/20	100%	100%
		HVLT	0.99 (0.99-1.00)	13/14	100%	97.4%
	Female (N=237)	MMSE	0.97 (0.95-0.99)	23/24	95.5%	94.4%
		HVLT	0.94 (0.90-0.99)	13/14	86.4%	90.7%
Age	≤65 (N=245)	MMSE	Not Applicable			
		HVLT				
	66-79 (N=148)	MMSE	1.00 (0.99-1.00)	25/26	100%	93.0%
		HVLT	0.98 (0.96-1.00)	16/17	94.1%	89.5%
	≥80 (N=46)	MMSE	0.75 (0.62-0.87)	20/21	100%	82.6%
		HVLT	0.81 (0.69-0.92)	13/14	93.8%	78.3%
Education	≤Primary (N= 124)	MMSE	0.96 (0.92-1.00)	13/14	100%	99.7%
		HVLT	0.93 (0.88-0.98)	9/10	100%	99.4%
	>Primary (N=315)	MMSE	1.00 (0.99-1.00)	25/26	100%	88.9%
		HVLT	1.00 (0.99-1.00)	13/14	90.3%	88.9%

From table 15 we can see that a stable cut-off score of the HVLT total recall was revealed (13/14), regardless of age and gender, whereas the MMSE showed a higher cut-off scores in females (23/24) compared to males (19/20).

In terms of the age split, no valid observation was applied among those aged less or equal to 65 years due to there not being any dementia case in that age group. A 5-point discrepancy in the MMSE cut-off score was seen, whereas the HVLT only showed a 3-point difference between the younger and older group (16/17 for 66-79 age group, and 13/14 for 80 years and above age.

Both the MMSE and the HVLT revealed different levels of educational difference to impact on scores. While a 4-point lower HVLT cut-off score was seem among less educated participants (9/10 vs 13/14), a huge gap (of 12 points) on the MMSE cut-off scores was illustrated between less educated and more highly educated participants (13/14 and 25/26 respectively). Again stratification was based on having obtained primary schooling vs. more.

Backward conditional logistic regression was performed using the HVLT and MMSE optimal cut-off scores (recoded as below '0' or equal or above '1' the HVLT cut-off score of 13.5 and MMSE cut-off score of 23.5). Results showed that for the HVLT, dementia (y/n) ($p<0.001$) and age ($p=0.02$) were the significant predictors (correctly classified rate 92.7%). For the MMSE, apart from dementia (y/n) ($p<0.001$) being the significant predictor, age ($p<0.001$), gender ($p=0.04$) and education ($p=0.01$) all strongly predicted MMSE performance below the cut-off score of 23.5 (correct classification 97.6%). This indicates that the MMSE is more heavily influenced by demographic factors such as age, gender and education, whereas limited or no impact of these factors was found on the HVLT cut-offs.

In the next results section we describe the validity of the HVLT and MMSE in MCI assessment in the community dwelling elderly (n=157) not included in the previous sample who had a more in depth assessment including a physical frailty screening. Due to the very limited sample size of dementia cases in this study (n=13), no analysis was performed to assess the validity of these cognitive tests in screening for dementia.

6.2 Dementia and frailty screening validity analysis results in a community-dwelling sample (n=170)

6.2.1 Descriptive data of the whole sample and different diagnostic groups

Table 16. Demographic data and scores on neuropsychological tests

	Whole (N=170)	NCI (N=115)	MCI (N=42)	Dementia (N=13)	P value
Age	73.2±10.1	71.6±7.8	77.9±7.8	79.7±7.9	<0.001
Education (below Primary School level)	40.0% (68)	21.7% (25)	78.6% (33)	76.9% (10)	<0.001
Years of Education	7.4±4.7	9.2±3.7	3.6±3.7	3.8±5.8	<0.001
Gender (male %)	45.0% (322)	45.2% (52)	28.6% (12)	23.1% (3)	0.08[a]
Occupation (manual %)	56.5% (96)	47.8% (55)	78.6% (33)	61.5% (8)	0.003
History of Smoking (Yes %)	22.9% (39)	26.1% (30)	16.7% (7)	15.4 (2)	NS
History of Alcohol use (Yes %)	18.2% (31)	20.0% (23)	14.3% (6)	15.4% (2)	NS
Living Area (Rural %)	11.8% (20)	11.3% (13)	11.9% (5)	15.4% (2)	NS
MMSE total score	17.3±6.6	27.2 ±2.7	19.9±4.7	15±4.6	<0.001
HVLT total score	14.28±6.2	16.7±5.4	10.1±4.2	6.1±4.0	<0.001

[a]= trend level significance; NS=Not Significant

The NCI group was on average younger and higher educated than the other two groups. Gender and smoking/alcohol consumption history did not differ across the 3 groups. Interestingly, equivalent proportions between manual and non-manual occupations before retirement were seen in NCI group whereas the majority of the other two groups used to be manual workers. On the MMSE and HVLT performance, significant between-group differences were seen (see table 16).

6.2.2 The discriminant ability of the HVLT and the MMSE in detecting MCI from NCI

6.2.2.1 The discriminant ability of the HVLT and MMSE in detecting MCI before age, gender and education stratification

Figure 5. Receiver operating characteristic curve for the HVLT and MMSE total score in detecting MCI

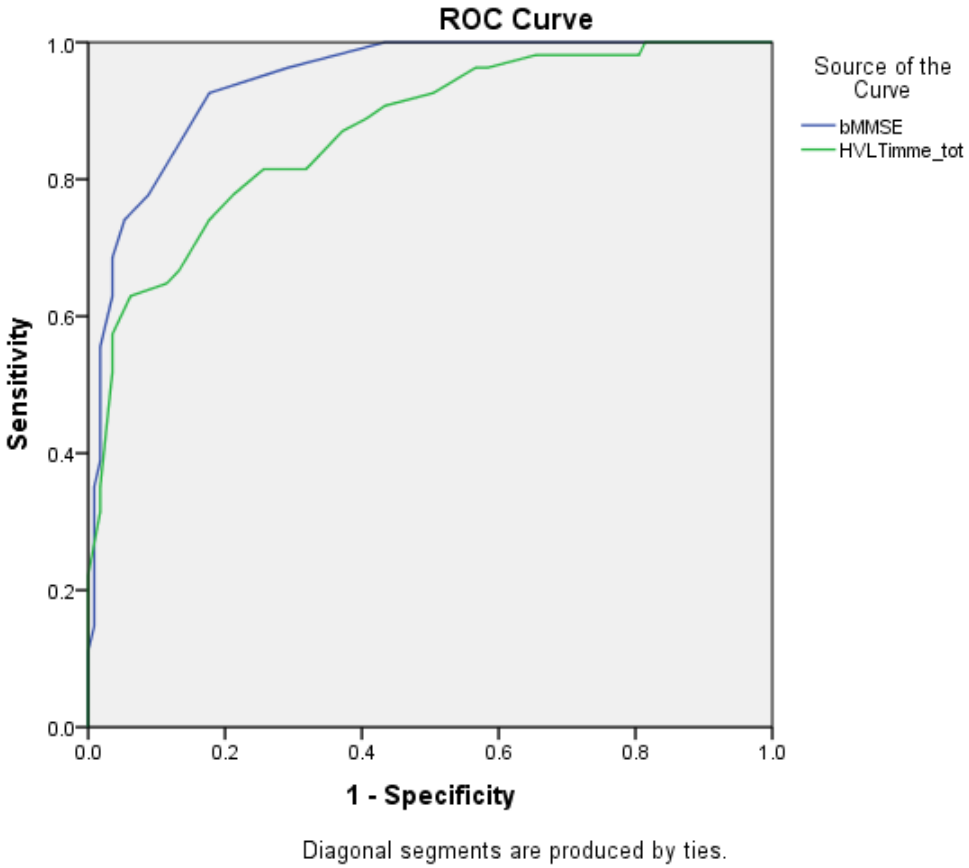


Table 17. Area Under Curve (AUC), optimal cut-off scores, SE, SP, PPV and NPV of HVLT and MMSE in discriminating MCI from NCI in the whole group

Test	AUC (95% CI)	Cut-Off	SE	SP	p value
MMSE	0.94 (0.91-0.98)	24/25	85.2%	86.7%	0.01
HVLT	0.87 (0.81-0.93)	15/16	77.8%	78.8%	

The MMSE showed better discriminant ability than the HVLT in differentiating between MCI and NCI. Applying a cut-off score of 24/25, the MMSE rendered a good sensitivity of 85.2% and a specificity of 86.7%, whilst only 77.8% sensitivity and 78.8% specificity were gained accompanying a HVLT cut-off score of 15/16.

The cut-off scores on the cognitive tests used in this study were lower than those obtained in the previous study.

The HVLT cut-off score is 4 points lower (15/16 vs 19/20) whereas the MMSE cut-off is 3 points lower (24/25 vs 27/28). This could be because of an older mean age of the whole sample in this study compared to the previous study (73.2 vs 67.5 years) and the fact that fewer years of education were obtained by the participants in this study compared to the previous study (7.4 vs 8.4) (see table 17).

We further stratified the data according to demographic factors such as gender, age and education.

6.2.2.2 The discriminant ability of the HVLT and MMSE in detecting MCI after age, gender and education stratification

Table 18. Area Under Curve (AUC), optimal cut-off scores, SE, SP, PPV and NPV of HVLT and MMSE in discriminating MCI from NCI using age, gender and education stratification

Comparing Group			AUC (95% CI)	Cut-off	SE	SP
Gender	Male (N=64)	MMSE	0.97 (0.94-1.00)	25/26	100%	92.0%
		HVLT	0.79 (0.64-0.94)	15/16	72.7%	78.0%
	Female (N=93)	MMSE	0.91 (0.85-0.97)	25/26	86.7%	74.6%
		HVLT	0.79 (0.64-0.93)	16/17	76.7%	74.6%
Age	65 and less (N=39)	MMSE	0.94 (0.86-1.00)	26/27	100%	75.8%
		HVLT	0.93 (0.85-1.00)	17/18	100%	75.8%
	66-79 (N=81)	MMSE	0.92 (0.85-0.98)	24/25	94.1%	79.0%
		HVLT	0.79 (0.67-0.92)	16/17	76.5%	69.4%
	80 and above (N=37)	MMSE	0.95 (0.86-0.97)	21/22	73.7%	100%
		HVLT	0.80 (0.66-0.95)	14/15	73.7%	88.9%
Education	≤Primary (N= 58)	MMSE	0.86 (0.76-0.96)	24/25	100%	99.7%
		HVLT	0.81 (0.70-0.92)	13/14	60.6%	100%
	>Primary (N=99)	MMSE	0.93 (0.87-0.99)	26/27	100%	76.1%
		HVLT	0.85 (0.73-0.97)	14/15	75.0%	83.0%

Both the MMSE and the HVLT cut-off scores remained relatively stable regardless of gender. After the age stratification, the only difference in the cut-off scores was found among the participants who were aged 80 and above: The MMSE cut-off score was 5 points lower than in the youngest group and 3 points lower than in the middle group. The HVLT cut-off was 3 points lower than in the youngest group and 2 points lower than in the middle group.

Both the MMSE and the HVLT revealed slight different levels of educational differences to impact on scores. Whist there was only a 1-point lower HVLT cut-off score seen among less educated participants (13/14 vs 14/15), a 2-point gap on the MMSE cut-off scores was shown between less educated and more highly educated participants (24/25 and 26/267 respectively) (see table 18).

The results indicate that both the HVLT and the MMSE were influenced by age, slightly influenced by education, but not by gender. The result was slightly at disparity with the results from our previous study with a larger sample size and where age was found to have a very limited impact on the HVLT. However, both studies revealed a larger impact of age and education on the MMSE scores.

In the next section, we describe the same analyses for institutionalised elderly (n=47) to further investigate discriminative capacity for our cognitive tests in elderly with psychiatric disorders and those with dementia

6.3 Sensitivity of the Chinese version of Hopkins Verbal Learning Test and Mini-Mental State Examination to dementia and demographics in an institutionalized setting

6.3.1 Descriptives of the whole sample and different diagnostic groups

Table 19. Demographic data and scores on neuropsychological tests

	Whole group (N=47)	Dementia (N=9)	Not Dementia (N=38)	P Value
Age	74.6±8.0	80.6±7.0	73.2±7.6	0.01
Gender (Female %)	77.0% (36)	66.7% (6)	78.9% (30)	NS
Years of Education	9.7±4.6	9.9±4.3	9.1±5.7	NS
Illiterate %	8.5% (4)	11.1% (1)	7.9% (3)	NS
University/above %	21.3% (10)	11.1% (1)	23.7% (9)	
Profession (Manual %)	46.8% (22)	33.3% (3)	50.0% (19)	NS
HVLT total score	12.2±6.2	9.1±6.3	12.9±6.0	0.01
MMSE total score	20.4±6.2	16.6±5.6	21.3±6.1	0.04

NS=Not Significant

From table 19 we can see that people with dementia are almost 8 years older than those without (81 vs. 73, p=0.01). Yet no other significant difference was found in gender, education, profession, and living area. When it comes to cognitive performance, comparing to non-demented participants, dementia patients scored 4 points lower on the HVLT immediate total recall (9 vs. 13, p=0.01) and 4 points lower on the MMSE total score (17 vs. 21, p=0.04).

6.3.2 Demographic factors influenced HVLT and MMSE performance

Table 20. Linear regression analysis between HVLT & MMSE performance at baseline and significantly associated demographic variables (with age, gender, years of education, living area and marital status all entered as independent variables)

		B	S.E.	β	p	B	S.E.	β	p	R2 (adjusted)
HVLT	Education (years)	0.67	0.18	0.49	<0.001					0.23
MMSE	Education (years)	0.58	0.18	0.43	0.003					
	Profession					0.99	0.21	0.73	0.003	0.3

Including the whole group showed that both HVLT total recall and MMSE performance had strong associations with years of education, whereas no age or gender effect was revealed. However, the type of profession people had before retirement was strongly related to the MMSE test result, which independently explained 13% of the variance (adjusted) on this test (see table 20).

Figure 6. Receiver's Operational Curve of the HVLT and the MMSE in detecting dementia

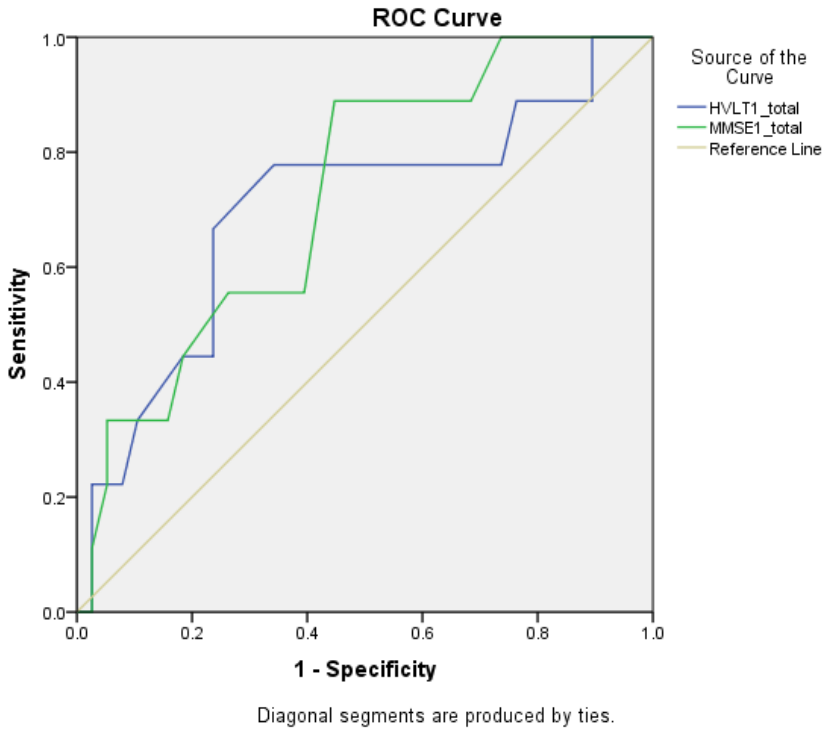


Table 21. AUC, sensitivity and specificity of the optimal cut-off points for the HVLT and MMSE in discriminating between demented and not demented patients

Test	AUC (95% CI)	Cut-Off	SE	SP	p value
MMSE	0.72 (0.55-0.90)	20/21	89.2%	55.5%	NS
HVLT	0.70 (0.49-0.91)	10/11	78.0%	66.0%	

By plotting the sensitivity and 1-specificity for each score on HVLT and MMSE performance, the ROC curves were generated to discriminate between dementia patients and controls (Fig. 6). Using the established cut-off scores, a list of screening criteria for dementia was summarized in table 20.

Using a cut-off point of 9/10, the HVLT total recall showed a good specificity (76%) with moderate sensitivity (66.7%) With regards to the MMSE, 89% sensitivity was rendered using a cut-off of 20/21 (Specificity 55%) (table 21). This indicates a better balanced sensitivity and specificity when using the HVLT .

These analyses all indicate that the HVLT and MMSE can be used to screen for dementia using different cut-offs based on age mainly. The HVLT adds to the discriminative capacity of this screening instrument as the MMSE is susceptible to effects of education. Similar findings were reported for Shi (2012) in Beijing.

In the next section we describe how cognitive impairment relates to functional disability as well as frailty.

7 CHAPTER 7 COGNITIVE IMPAIRMENT, FUNCTIONAL DISABILITY AND FRAILTY IN A COMMUNITY-DWELLING ELDERLY SAMPLE

7.1 Possible demographic, physical, psychological and lifestyle variables in determining cognitive impairment (CI)

7.1.1 Descriptive data of the whole sample and different diagnostic groups

The NCI group was on average younger and more highly educated than the other two groups. Gender and smoking/alcohol history as measure by asking a question 'Do you have a history of smoke/alcohol' (see appendix) did not differ across 3 groups. Interestingly, equivalent proportions between manual and non-manual occupations before retirement were seen in NCI group whereas the majority of the other two groups used to be manual workers. On the MMSE and HVLT performance, significant between-group differences were seen (see table 16).

7.1.2 Factor analysis to assess which variables cluster together in determine cognitive impairment

7.1.2.1 Suitability of data for FA (part 1 summary)

Initially the factorability of 11 variables was examined (age, years of education, grip strength, get-up-and-go seconds, 15 feet gait seconds, MMSE total score, HVLT IR total score, HVLT DR total score, ADL total score, Balance total score and BMI). Based on the poor correlation with other variables, it was decided that the variable of BMI should be removed.

7.1.2.2 Sample size and variable left in the analyses

The sample size for the remaining 10 variables were between n=136 and n=170 (mean n= 161), providing a ratio of 16 cases per variable, which is adequate for PCA. However, as the mean sample size is not very large, communalities before extraction were assessed. Field (2005) suggests that for a sample size between 100 and 200 participants, communalities before extraction of each variable should be >0.5. The communalities before extraction for the 10 variables were all greater than 0.5 and therefore the sample size were not considered problematic.

7.1.2.3 Normality of data

Distribution histograms were performed and indicated that the variables were normally distributed. There was no extreme outlier that skewed the distribution curve.

7.1.2.4 Correlations between variables

The analyses output for correlation matrixes between variables were examined. All variables were significantly correlated with each other and for most variable correlations, the absolute value was adequate (r>0.3) without being too high (r>0.9), hence no singularity was observed (see table 22).

Table 22. Correlations between the variables

	Grip strength	TUG score	15 feet gait score	MMSE score	HVLT IR score	HVLT DR score	Balance	Age	Years of Education
TUG score	-.231**								
15 feet gait score	-.319**	.711**							
MMSE score	.405**	-.328**	-.317**						
HVLT IR score	.328**	-.278**	-.276**	.618**					
HVLT DR score	.319**	-.243**	-.220**	.655**	.710**				
Balance score	.290**	-.106	-.254**	.297**	.272**	.243**			
Age	-.413**	.379**	.445**	-.491**	-.391**	-.457**	-.401**		
Years of education	.348**	.313**	-.257**	.652**	.454**	.529**	.211*	.371**	
ADL total score	-.243**	.216**	.281**	-.444**	-.303**	-.225**	-.753**	.289**	-.289**
**. Correlation is significant at the 0.01 level (2-tailed).									
*. Correlation is significant at the 0.05 level (2-tailed).									

7.1.2.5 Factorability of the data

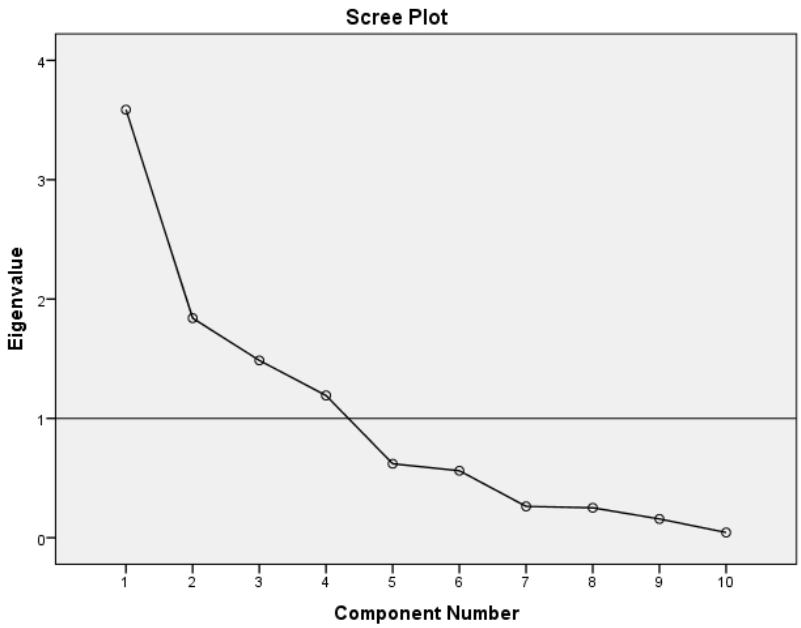
Bartlett's test of sphericity was statistically significant (χ^2=602.98, p<0.001) and the KMO critical value (KMO=0.81) was good (Field, 2005), both indicating good factorability.

7.1.2.6 Factor extraction

The initial eigenvalues showed that the first four components (with eigenvalues greater than 1) explained 36%, 18%, 15% and 12% of the variance respectively, with a total variance of 81%. The

fifth to tenth components all had less than 1 and in total only explained 19% of the variance. Hence only the first four components were considered. On further examination of the screen plot, the extraction of four components was supported (see Fig 7).

Figure 7. Screen plot to determine the number of extracted components



In the screen plot, the horizontal dotted line shows the components above and below the cut-off of eigenvalue =1, the component numbers of the x axis refers to the number of extracted components which are plotted on the graph against the eigenvalue.

7.1.2.7 Factor rotation

Under the assumption that the components extracted may be correlated with each other, oblique rotation was use (direct oblim method). The correlations between four components was less than the theoretically based value of 0.3 (a value of 0.3 or above indicates a strong correlation). This indicates that in the current sample, the overlap between components was not substantial, and that the components were relatively independent. Hence it was decided that the PCA would be employed to determine the correlation between these components.

Table 23. Correlation between the four components in factor analysis

Component Correlation Matrix[a]

Component	1	2	3	4
1	1.000	.026	.225	.270
2	.026	1.000	.116	.147
3	.225	.116	1.000	.193
4	.270	.147	.193	1.000

Extraction Method: Principal Component Analysis.
Rotation Method: Oblimin with Kaiser Normalization.

7.1.2.8 Extracted components

Varimax orthogonal rotation was employed on the ten variables in the final stage of the analyses. The four extracted components (table 24) explained a total of 81% of the variance which was the same as been indicated in the earlier part.

It is noted that the variance explained by the four components are more evenly distributed now. All variables in the analysis had primary loadings more than 0.5. See table 24 for the factor-loading matrix after the final solution.

Table 24. Total variance explained before and after rotation [a]

Component	Initial Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	3.587	35.866	35.866	2.339	23.385	23.385
2	1.840	18.403	54.269	2.129	21.295	44.680
3	1.486	14.857	69.126	1.851	18.507	63.187
4	1.192	11.923	81.049	1.786	17.862	81.049
5	.620	6.197	87.246			
6	.561	5.610	92.856			
7	.263	2.626	95.482			
8	.251	2.509	97.991			
9	.157	1.573	99.563			
10	.044	.437	100.000			

[a.] principle component analysis; rotation method=varimax; analyses was only for Cognitive impairment (CI) vs. No Cognitive impairment (NCI).

Table 25 shows the variables which load onto the four extracted components. The highest loading variables with absolute values greater than 0.3 are highlighted.

Table 25. Pattern/ structure coefficients

	Component				Communalities After extraction
	1	2	3	4	
Grip strength	**.728**	-.169	-.083	.233	.620
TUG score	-.131	**.966**	.007	-.073	.957
15 feet gait score	-.180	**.958**	-.021	-.104	.962
MMSE total score	**.713**	-.172	**.414**	.248	.771
HVLT IR score	-.111	-.066	**.909**	.173	.874
HVLT DR score	.211	.064	**.881**	.030	.825
ADL total score	-.100	**.366**	-.207	**-.819**	.857
Balance score	.163	.068	.073	**.905**	.856
Age	**-.736**	.265	.078	-.294	.705
Years of Education	**.784**	.048	.123	-.216	.678

The strongest variables (greater than 0.3) on the components and the possible underlying theoretical structure they measure were as follows:

Table 26. The component found by the principle component analysis and the loading variables [a]

Component 1	Component 2	Component 3	Component 4
Years of Education	HVLT IR Total Score	TUG speed	Berg's Balance Score
Age	HVLT DR Total Score	15 feet gait speed	
Grip Strength	MMSE Total Score		
MMSE Total Score			

[a]. Variables are listed in descending order based on the strength of the component loading.

This suggest that there is i) a group of participants with general frailty characterised by an older age and lower education, with poor global cognitive function and frailty; ii) a group with mainly cognitive impairments; iii) there is a group characterised with difficulties in getting out and about; and iv) a group with mainly balancing issues (see table 26).

One could hypothesise that there are different pathways leading to these categories of elderly, e.g. general deprivation (low childhood education) and older age leading to frailty for i); early dementia for iii); morbidity; for iii); vision problems, stroke or medication overuse leading to balance disorders for iv).

This may also lead to a model with different more focused treatments, such as: general activities for group i), including social stimulation in community centres); cognitive stimulation and strength exercises earlier found to improve cognitive impairment and dementia (Hogervorst, 2012) for group ii); aerobic exercises (swimming, dancing, walking after strength exercises to build up muscle mass and lung capacity for group iii);and yoga and other strengthening exercises to improve balance and reduce the risk for falls for group iv).

We then analysed how these variables determined cognitive impairment (see table 27).

7.1.3 Combinations of measurements in determining different phenotypes of CI

Table 27. AUCs, Cut-off scores, sensitivity and specificity of each variable for cognitive impairment

Variables	AUC (95% CI)	Cut-off Score	Sensitivity	Specificity
Grip Strength	0.79 (0.71-0.88)	11.8	0.83	0.66
Balance	0.68 (0.59-0.78)	53/54	0.78	0.52
15-feet gait	0.82 (0.75-0.89)	4.4	0.71	0.69
TUG-walk	0.77 (0.69-0.85)	12.7	0.52	0.85
HVLT (IR)	0.87 (0.81-0.93)	15/16	0.78	0.79
HVLT (DR)	0.87 (0.81-0.92)	5/6	0.85	0.74
MMSE	0.94 (0.91-0.98)	25/26	0.93	0.82

Cognitive scores obviously had good predictive value in predicting group membership but the 15 feet gait test and grip strength also predicted group membership reasonably well, suggesting some overlap between cognitive and physical frailty as assessed by fitness and grip strength.

Table 28 reflects this in more detail, showing that more than half of participants scored under the cognitive score (MMSE) OR did worse on the grip strength test, with many being over 78 years of age and having had low education. Less than about a third did badly on both tests. The highest second percentage of the participants who fulfilled all the conditions was the cognitive impairment group indicative of dementia (22.9%). Much lower percentages of people had either physical or balance related aspects affecting activities of daily life suggesting more physical aspects of frailty (11-15%).

Table 28. Four main categories for cognitive impairment and the percentage of participants fulfilling at least 1 of the conditions

	% fulfil at least 1 condition (no.)	% fulfil all the conditions (no.)
Cognitive Impairment +Physical Frailty (CI+PF)		
Grip Strength <11.8 MMSE <25	57.7% (98)	28.8% (49)
*. Plus age >78 and years of education <6	65.9% (112)	14.7% (25)
Physical Frailty-fitness (PF-f)		
TUG >12.7 15 feet gait >4.4	78.2% (133)	8.2% (14)
Cognitive Impairment (CI)		
MMSE <25 HVLT IR <15 HVLT DR <5	57.1% (97)	22.9% (39)
Physical Frailty-balance (PF-b)		
Balance <53	42.4% (72)	11.2% (19)
All components		4.1% (7)

Median split of age (78 years of age) and lower level of education (less than 6 years) were added into the model to further explore whether they increase the risk of being cognitive impaired.

These latter two groups are, however, regarded at “high risk of cognitive impairment” group as they have poor endurance, leg strength, and slowness possibly related to lower level of physical activity which is a risk factor for later life dementia. The last group with balance issues also has an increased risk for falls which increases risk for dementia by a factor 3.

From table 28 we can see that the highest percentage of the participants who fulfilled all the conditions lie in these two groups: cognitive impairment with physical frailty group (14.7%) and cognitive impairment group (22.9%). This further affirms that the cognitive assessments, such as the MMSE and HVLT, other than physical measurements, are important in the assessment of elderly.

In addition, 78.2% of the physical frailty-fitness group (PF-f) fulfilled at least 1 condition, with a total of 8.2% in this group fulfilling all of the conditions. This group is regarded as possibly at high risk of dependence as they have poor endurance, slowness and lower level of physical activity.

Similarly, there are 42.4% of the physical frailty-balance group fulfilling at least one condition, accompanying with 11.2% fulfilling all the conditions. Balance is also an important factor is predicting disability. Elderly losing balance have higher risk of incident fall, which will cause functional disability so as gives rise to larger chance of having dementia. In this cohort, 4.1% of the whole sample had an older age, less education, slowness, cognitive impairment and poor balance. All these 7 participants were diagnosed as CI in the present study.

In sum, all these factors are considered to be the major contributing elements to cognitive impairment which is an important component in diagnosing frailty but also dementia according to DSM-IV criteria.

7.2 Possible demographic, physical, psychological and lifestyle variables in determining functional disability

7.2.1 Factor analysis to assess which variables cluster together in determine functional disability

7.2.1.1 Suitability of data for FA (part 1 summary)

Initially the factorability of 10 variables was examined (age, years of education, grip strength, get-up-and-go seconds, 15 feet gait seconds, MMSE total score, HVLT IR total score, HVLT DR total score, Balance total score and BMI). Based on the poor correlation with other variables, it was decided that the variable of BMI should be removed.

7.2.1.2 Sample size and variable left in the analyses

The sample size for the remaining 9 variables were between n=136 and n=170 (mean n= 161), providing a ratio of 16 cases per variable, which is adequate for PCA. However, as the mean sample size is not very large, communalities before extraction were assessed. Field (2005) suggests that for a sample size between 100 and 200 participants, communalities before extraction of each variable should be >0.5. The communalities before extraction for the 10 variables were all greater than 0.5 and therefore the sample size were not considered problematic.

7.2.1.3 Normality of data

Distribution histograms were performed and indicated that the variables were normally distributed. There was no extreme outlier that skewed the distribution curve.

7.2.1.4 Correlations between variables

The analyses output for correlation matrixes between variables were examined. All variables were significantly correlated with each other and for most variable correlations, the absolute value was adequate (r>0.3) without being too high (r>0.9), hence no singularity was observed (see table 29).

Table 29. Correlations between the variables

	Grip strength	TUG score	15 feet gait score	MMSE score	HVLT IR score	HVLT DR score	Balance	Age	Years of Education
TUG score	-.231**								
15 feet gait score	-.319**	.711**							
MMSE score	.405**	-.328**	-.317**						
HVLT IR score	.328**	-.278**	-.276**	.618**					
HVLT DR score	.319**	-.243**	-.220**	.655**	.710**				
Balance score	.290**	-.106	-.254**	.297**	.272**	.243**			
Age	-.413**	.379**	.445**	-.491**	-.391**	-.457**	-.401**		
Years of education	.348**	.313**	-.257**	.652**	.454**	.529**	.211*	.371**	
**. Correlation is significant at the 0.01 level (2-tailed).									
*. Correlation is significant at the 0.05 level (2-tailed).									

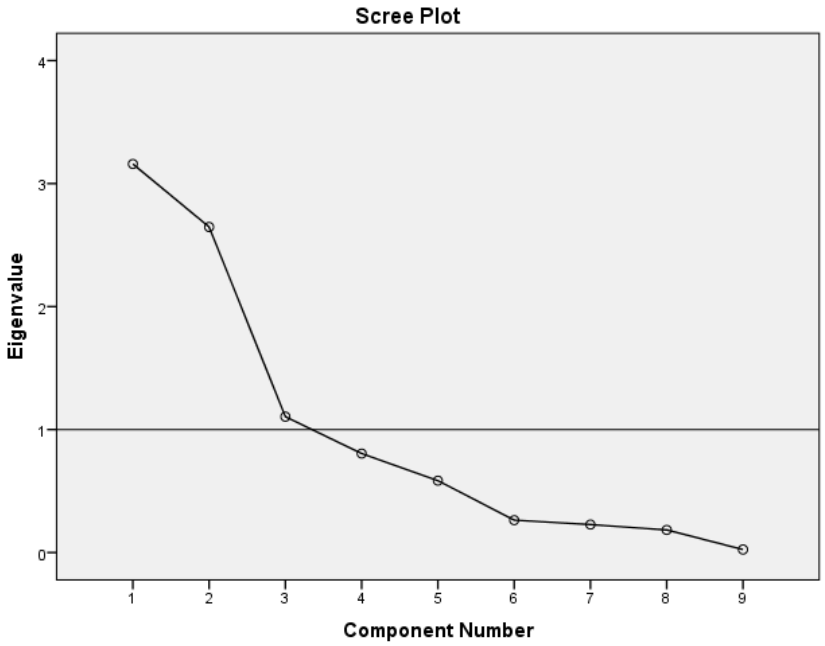
7.2.1.5 Factorability of the data

Bartlett's test of sphericity was statistically significant (χ^2=122.531, p<0.001) and the KMO critical value (KMO=0.68) was moderately good (Field, 2005), both indicating good factorability.

7.2.1.6 Factor extraction

The initial eigenvalues showed that the first three components (with eigenvalues greater than 1) explained 35%, 18%, 29% and 12% of the variance respectively, with a total variance of 77%. The forth to ninth components all had less than 1 and in total only explained 23% of the variance. Hence only the first three were considered. On further examination of the scree plot, the extraction of three components was supported (Fig 8).

Figure 8. Screen plot to determine the number of extracted components



In the screen plot, the horizontal dotted line shows the components above and below the cut-off of eigenvalue =1, the component numbers of the x axis refers to the number of extracted components which are plotted on the graph against the eigenvalue.

7.2.1.7 Factor rotation

Under the assumption that the components extracted may be correlated with each other, oblique rotation was use (direct oblim method). A correlation of 0.213 between three components indicates that in the current sample, the overlap between components was not substantial, and that the components were relatively independent. Hence it was decided that the PCA would be employed to determine the correlation between these components.

Table 30. Correlation between the three components in factor analysis

Component Transformation Matrix[a]

Component	1	2	3
1	-.697	.572	.432
2	.666	.739	.096
3	-.265	.355	-.897

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.

7.2.1.8 Extracted components

Varimax orthogonal rotation was employed on the nine variables in the final stage of the analyses. The three extracted components (table 31) explained a total of 81% of the variance which was the same as been indicated in the earlier part.

It is worthwhile reported that the variance explained by the three components are more evenly distributed now. All variables in the analysis had primary loadings more than 0.5. See table 31 for the factor loading matrix after the final solution.

Table 31. Total variance explained before and after rotation

Component	Initial Eigenvalues			Rotation Sums of Squared Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	3.159	35.103	35.103	2.788	30.979	30.979
2	2.647	29.411	64.514	2.620	29.115	60.094
3	1.105	12.277	76.791	1.503	16.697	76.791
4	.805	8.944	85.735			
5	.584	6.494	92.229			
6	.264	2.929	95.157			
7	.227	2.527	97.685			
8	.184	2.042	99.727			
9	.025	.273	100.000			

Table 32 shows the variables which load onto the four extracted components. Highest loading variables with absolute values greater than 0.3 are highlighted.

Table 32. Pattern/ structure coefficients

	Component			Communalities After extraction
	1	2	3	
Age	**.080**	-.062	**-.864**	.758
Years of education	.203	**.576**	.031	.374
Grip strength	-.180	.226	**.773**	.680
TUG score	**.945**	.088	-.130	.917
15-feet gait score	**.970**	-.062	-.035	.945
MMSE score	.090	**.863**	.288	.836
HVLT IR score	-.165	**.837**	.160	.753
HVLT DR score	-.114	**.881**	.000	.789
Balance score	**-.909**	-.007	.176	.858

The strongest variables (greater than 0.3) on the components and the possible underlying theoretical structure they measure were as follows:

Table 33. The component found by the principle component analysis and the loading variables [a]

Component 1	Component 2	Component 3
Age	Years of education	Age
TUG score	MMSE score	Grip strength
15 feet gait score	HVLT IR score	
Balance Score	HVLT DR score	

[a]. Variables are listed in descending order based on the strength of the component loading.

In sum, data suggest that there is a there is an older group with lower educational level and cognitive impairments: a group with dementia/CI; an older group of participants with general frailty characterised by slowness and lower body strength; and an older group with mainly grip strength issue. (see table 33).

We then explored the specific cut-off scores for each measurement (table 34) and subsequently investigated the percentage of participants who fulfilled these functional disability related factors based on the three categories of functional disability established in table 35.

7.2.2 Combinations of measurements in determining phenotypes of functional disability

Table 34. AUCs, Cut-off scores, sensitivity and specificity of each variable for functional disability

Variables	AUC (95% CI)	Cut-off Score	Sensitivity	Specificity
Grip Strength	0.81 (0.72-0.89)	6.6	0.86	1.58
Balance	0.83 (0.72-0.94)	51/52	0.81	0.59
15-feet gait	0.90 (0.84-0.96)	5.4	0.84	0.85
TUG	0.88 (0.82-0.95)	12.5	0.87	0.76
HVLT (IR)	0.73 (0.61-0.84)	17/18	0.78	0.56
HVLT (DR)	0.76 (0.67-0.86)	6/7	0.87	0.59
MMSE	0.81 (0.72-0.89)	21/22	0.86	0.51

Table 35. Three Main Categories for IADL/ADL disability and the percentage of participants fulfilling at least 1 of the conditions

	% fulfil at least 1 condition (no.)	% fulfil all the conditions (no.)
Physical Frailty- lower body (PF-lb)		
Age >78 TUG score >12.5 15 feet gait score >5.4 Balance score <52	50.6% (86)	10.0% (17)
Cognitive Impairment Frailty (CI)		
Years of education <6 MMSE score <22 HVLT IR score <18 HVLT DR score <7	73.5% (125)	18.2% (31)
Physical Frailty-upper body (PF-ub)		
Age >78 Grip Strength <6.7	43.5% (74)	14.7% (25)
All components		5.3% (9)

From table 35 it is evident that the highest percentage of participants fulfilled either at least 1 condition or all the conditions are in the cognitive impairment frailty group. These four measurements, years of education, MMSE score, HVLT IR score and HVLT DR score, are the biggest contributing factors to elderly who are IADL/ADL disabled.

On the other hand, lower level of upper body and lower body are the other two elements in detecting disability. 14.7% of the upper body frailty group and 10% of the lower body frailty fulfilled all the conditions, whereas very close percentage of these two groups fulfilled at least 1 condition (50.6% for lower body frailty group, 43.5% for upper body frailty group respectively).

Interestingly, among these 9 participants (5.3%) who fulfilled all the conditions, 6 were also among the 7 participants who fulfilled all the conditions for cognitive impairment (see section 6.4.3, table 28).

These finding concurs with the conclusion from another community-based study (Avila-Funes, 2011) that not only low level of physical activity, but also cognitive ability are essential as part of the frailty phenotype, contributing to build up a more comprehensive and accurate frailty profile.

From section 6.4.3 and section 6.4.5 we noticed that there are some similarities between the patterns of CI and functional disability. However it still remains unclear how to establish the frailty phenotypes and what cut-offs to use. In the next section (6.5), a phenotype of frailty was formed using our indicators and the important physical indicators reported in the past literature (see chapter 2, literature review for frailty which did include BMI), followed by the analysis on the overlapping of frailty with cognitive impairment and functional disability.

7.3 A phenotype of frailty among elderly in a community-based population in Shanghai

7.3.1 Operationalizing a phenotype of frailty

Table 36. Operationalizing a phenotype of frailty

	Female	Male
BMI	<21	
Grip strength (lowest 20%)	<4.2	<11.2
TUG (Get up)	Get up with assistance or unable to get up	
TUG (walk) score (lowest 20%)	<9.1	<8.4
15 feet gait speed (lowest 20%)	<3.57	<3.1
Balance (lowest 20%)	<50	<49
Low physical activity	Exercise less than once per week	
Presence of Frailty	Positive for frailty phenotype: ≥ 3 criteria present Pre-frail: 1 or 3 criteria present Robust: 0 criterion present	

The lowest quintile of grip strength, TUG scores, 15-feet gait speed and Berg balance test were adjusted for gender as suggested by Fried (2001). An individual with 4 or more present frailty components out of a total of 7was considered to be 'frail', whereas equal or less than 3 characteristics were hypothesized to be 'pre-frail'. Those with no present frailty component were considered as robust.

Using Shanghai Frailty project data, we identified the number of frailty characteristics present, as per definitions described in chapter 5, section 5.1.2.5. Subjects who had 4 and above valid data for frailty components among the7 characteristics were included in the analyses. 2 cases were excluded due to insufficient evaluable components.

Table 37. Association of demographic, functional and cognitive characteristics with frailty status

Factor	Total (n=168)	Robust (n=62)	Prefrail (n=82)	Frail (n=24)	p value
Age					
≤65	41 (24.4%)	16 (25.8%)	21 (25.6%)	4 (16.7%)	0.03
66-79	83 (49.4%)	35 (56.5%)	40 (48.8%)	8 (33.3%)	
≥80	44 (26.2%)	11 (17.7%)	21 (25.6%)	12 (50.0%)	
Gender					
Male	102 (60.7%)	35 (56.5%)	50 (61.0%)	17 (70.8%)	NS
Female	66 (39.3%)	27 (43.5%)	32 (39.0%)	7 (29.2%)	
Education					
≤Primary level	102 (60.7%)	25 (40.3%)	57 (69.5%)	20 (83.3%)	0.03
Secondary and above	66 (39.3%)	37 (59.7%)	25 (30.5%)	4 (16.7%)	
ADL/IADL					
Fully independent	108 (64.3%)	56 (90.3%)	50 (61.0%)	2 (8.3%)	0.004
fail at least one task	60 (35.7%)	6 (9.7%)	32 (39.0%)	22 (91.7%)	
MMSE					
>24	104 (61.9%)	44 (71.0%)	52 (63.4%)	8 (33.3%)	0.01
≤24	64 (38.1%)	18 (29.0%)	30 (36.6%)	16 (66.7%)	
HVLT IR					
>15	98 (58.3%)	40 (64.5%)	54 (65.9%)	4 (16.7%)	0.002
≤15	70 (41.7%)	22 (35.5%)	28 (34.1%)	20 (83.3%)	

NS=Not Significant

Participant's frailty status significantly differentiate between different age groups (p=0.03), education levels (p=0.03), ADL/IADL abilities (p=0.004) and cognitive abilities as measured by the MMSE (p=0.01) and the HVLT (IR, p=0.002). However, there is no gender difference in the frailty status (p=0.3)

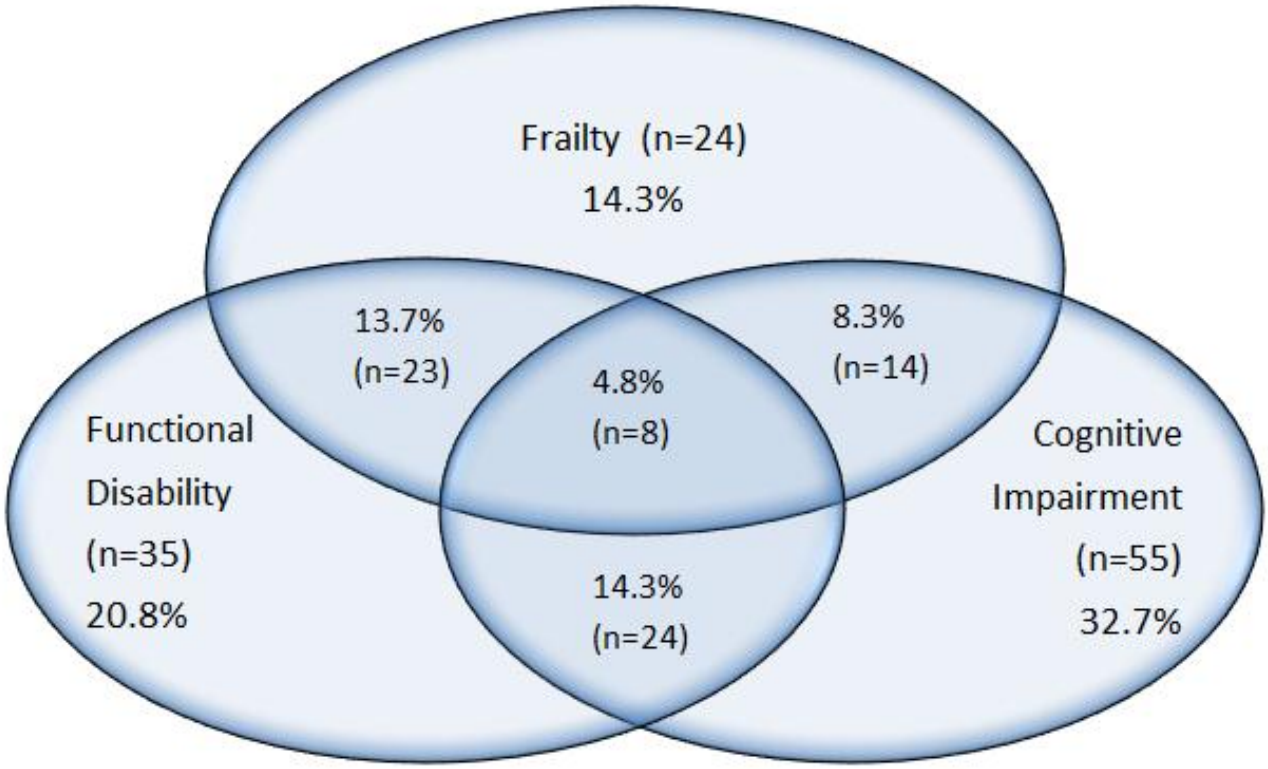
From table 37 we can see that 50% of the frailty group are older than 80 years of age (12 out of 24), compared to 16.7% being equal or younger than 65 years of age. A difference in the educational level by frailty status was also seen. Whilst 59.7% of the robust group are highly educated (secondary level and above), the majority of the pre-frail group (69.5%) and frail group (83.3%) are less educated (no or primary level).

When it comes to the functional measures, 90.3% of the robust group are fully independent indicated by the ADL and IADL, compared to 61% of the pre-frail group indicating no ALD/IADL dependency. This trend further extended to the frail group where only 8.3% (2 out of 24) were able to be fully independent.

With regard to the cognitive measures, significant differences in the MMSE and the HVLT performance across the 3 frailty status groups were revealed. By applying a MMSE cut-off score of 24, a HVLT (IR) cut-off score of 15 in distinguishing MCI from NCI (see chapter 6, section 6.2.2, table 16), 66.7% and 83.3% of the frail group failed the MMSE and the HVLT, respectively.

From the above, we can conclude that participants in the frail group are more prone to be older, less educated, with functional disability, and cognitive impairment.

Figure 9. Venn diagram demonstrating extent of overlap of frailty with functional disability[1] and cognitive impairment[2]



[1]. Functional disability is measure by the IADL and ADL. Those who failed at least one task on either tests were considered as functional disabled;

[2]. Cognitive impairment included MCI and dementia cases (see chapter 6 section 6.4.1, table 21)

Fig 9 displays the extent of overlap between frailty, functional disability and cognitive impairment. 14.3% (n=24) of the whole sample (n=168) are both functional disabled and cognitive impaired. 8.3% (n=14) are frail and cogntive impaired at the same time. 13.7% (n=23) are functional disabled accompanying present frailty. Interestingly, in total 24 subjects categorized as ‘frail’ in the current sample, of whom the majority (95.8%) are also identified as functional disabled. Overall, only 4.8% of the current sample (n=8) display all 3 present conditions: frail, cognitive impaired, and functional disabled.

To further look into these 8 cases who present all 3 conditions as indicated in Fig. 9 and to compare this result with our previous results (see chapter 6, section 6.4.3, table 28 and section 6.4.5, table 35), an intersting finding is revealed. Among these 8 cases who fulfiled all the conditions, 6 of them also met the characteristics for CI and functional disability.

8 CHAPTER 8 DEMOGRAPHIC RISK FACTORS ASSOCIATED WITH COGNITIVE DECLINE

8.1 Distribution of demographic characteristics and HVLT performance in CI and NCI groups

Table 38. Demographic risk factors and the HVLT performance stratified by cognitive status

	CI Group	NCI Group	Critical Value	p Value
N (%) of total sample	115 (22.1%)	406 (77.9%)	~	~
Demographic Risk Factors				
Age Group			22.17	<0.001
≤ 65 years	29 (25.2%)	245 (60.3%)		
65-79 years	33 (28.7%)	115 (28.3%)		
≥80 years	53 (46.1%)	46 (11.3%)		
Gender			1.79	NS
Male	46 (40.0%)	191 (47.0%)		
Female	69 (60.0%)	215 (53.0%)		
Education			57.6	<0.001
No or primary level	69 (60.0%)	93 (22.9%)		
Secondary and above level	46 (40.0%)	313 (77.1%)		
Profession			7.0	0.01
No Job or Manual	81 (70.4%)	267 (65.8%)		
Non Manual	34 (29.6%)	139 (34.2%)		
HVLT Performance				
HVLT IR	11.8 ± 6.6	25.4 ± 7.1	18.4	<0.001
HVLT DR	1.4 ± 2.5	8.6 ± 3.6	24.3	<0.001

NS=Not Significant

From table 38 we can see that participants in the CI group were more likely to be older (60% equal or older than 80 years), less educated (60%), and manual workers (70.4%). Furthermore, there was a 13- point difference between CI and NCI groups on the HVLT IR performance (12 vs. 25) whereas an 8-point difference was observed on the HVLT DR performance between these 2 groups (1 vs. 9). However, equivalent proportion of gender in NCI and CI groups was shown in the current study (60% female in CI group and 53% female in NCI group).

Subsequently, more analyses were employed to investigate the HVLT both IR and DR performance in CI and NCI groups, stratified by different demographic characteristics, such as age (≤65 vs. 66-79 vs. ≥80 years of age), education (no or primary level vs. secondary and above), gender (male vs. female) and profession (no job or manual vs. non manual).

Table 39. The HVLT IR and DR performance in NCI and CI groups stratified by demographic characteristics

			NCI Group	CI Group	Critical Value	p Value
Age	**≤65**	N (%)	245 (60.3%)	29 (25.2%)		
		HVLT IR	26.6 ± 6.6	16.4 ± 4.3	11.4	<0.001
		HVLT DR	9.1 ± 1.4	2.0 ± 2.7	10.7	<0.001
	66-79	N (%)	115 (28.3%)	33 (28.7%)		
		HVLT IR	24.8 ± 6.2	14.8 ± 6.1	14.8	<0.001
		HVLT DR	8.1 ± 3.6	1.5 ± 2.2	14.0	<0.001
	≥80	N (%)	46 (11.3%)	53 (46.1%)		
		HVLT IR	20.5 ± 9.5	12.4 ± 5.8	5.0	<0.001
		HVLT DR	7.1 ± 3.9	1.0 ± 2.6	8.4	<0.001
Gender	**Male**	N (%)	191 (47.0%)	46 (40.0%)		
		HVLT IR	26.2 ± 6.4	11.7 ± 7.0	13.6	<0.001
		HVLT DR	9.1 ± 3.0	1.0 ± 2.4	19.5	<0.001
	Female	N (%)	215 (53.0%)	69 (60.0%)		
		HVLT IR	24.7 ± 7.6	11.9 ± 6.3	12.6	<0.001
		HVLT DR	8.1 ± 4.0	1.4 ± 2.5	15.5	<0.001
Education	**No or primary level**	N (%)	93 (22.9%)	69 (60.0%)		
		HVLT IR	23.8 ± 8.4	10.2 ± 6.6	11.2	<0.001
		HVLT DR	8.0 ± 3.7	1.3 ± 2.6	13.2	<0.001
	Secondary and above	N (%)	313 (77.1%)	46 (40.0%)		
		HVLT IR	25.8 ± 6.6	14.2 ± 5.8	11.3	<0.001
		HVLT DR	8.4 ± 3.6	1.4 ± 2.4	18.1	<0.001
Profession	**No Job or Manual**	N (%)	267 (65.8%)	81 (70.4%)		
		HVLT IR	25.6 ±7.6	10.6 ± 6.7	16.0	<0.001
		HVLT DR	8.1 ± 3.6	1.3 ± 2.4	21.4	<0.001
	Non Manual	N (%)	139 (34.2%)	34 (29.6%)		
		HVLT IR	25.7 ± 6.1	14.7 ± 5.0	11.7	<0.001
		HVLT DR	8.4 ± 3.6	1.8 ± 2.7	9.2	<0.001

From the above table we can conclude that CI group shows significant worse performance on the HVLT IR and DR tests than the NCI group, independent of participant's age group, gender, educational level and profession.

Initially, a 10-point difference on the HVLT IR results between NCI and CI group was shown in the ≤65 and 66-79 age groups The difference was 7-8 points in the older group (≥80 years of age). In contrast, the difference between the CI and NCI group on the HVLT DR performance remained relatively stable over age, where a 6-7 point difference was shown in all three age groups.

In gender groups, males demonstrated a 1-point better performance on both the HVLT IR and DR tests than females in NCI group only (26 vs. 25 on IR, and 9 vs. 8 on DR respectively) whereas equivalent performance in males and females on both the IR and DR were shown in the CI group (12 on IR and 1 on DR).

In education groups, higher educated participants (secondary level and above) from NCI group and CI group manifested a 2-point and a 4-point superior performance than those who were less or not educated (no or primary level) (25 vs. 23 in NCI group and 14 vs. 10 in CI group). Nevertheless this educational difference disappeared on the HVLT DR test where participants from different educational levels performed equally in both NCI and CI groups (8 in NCI group and 1 in CI group).

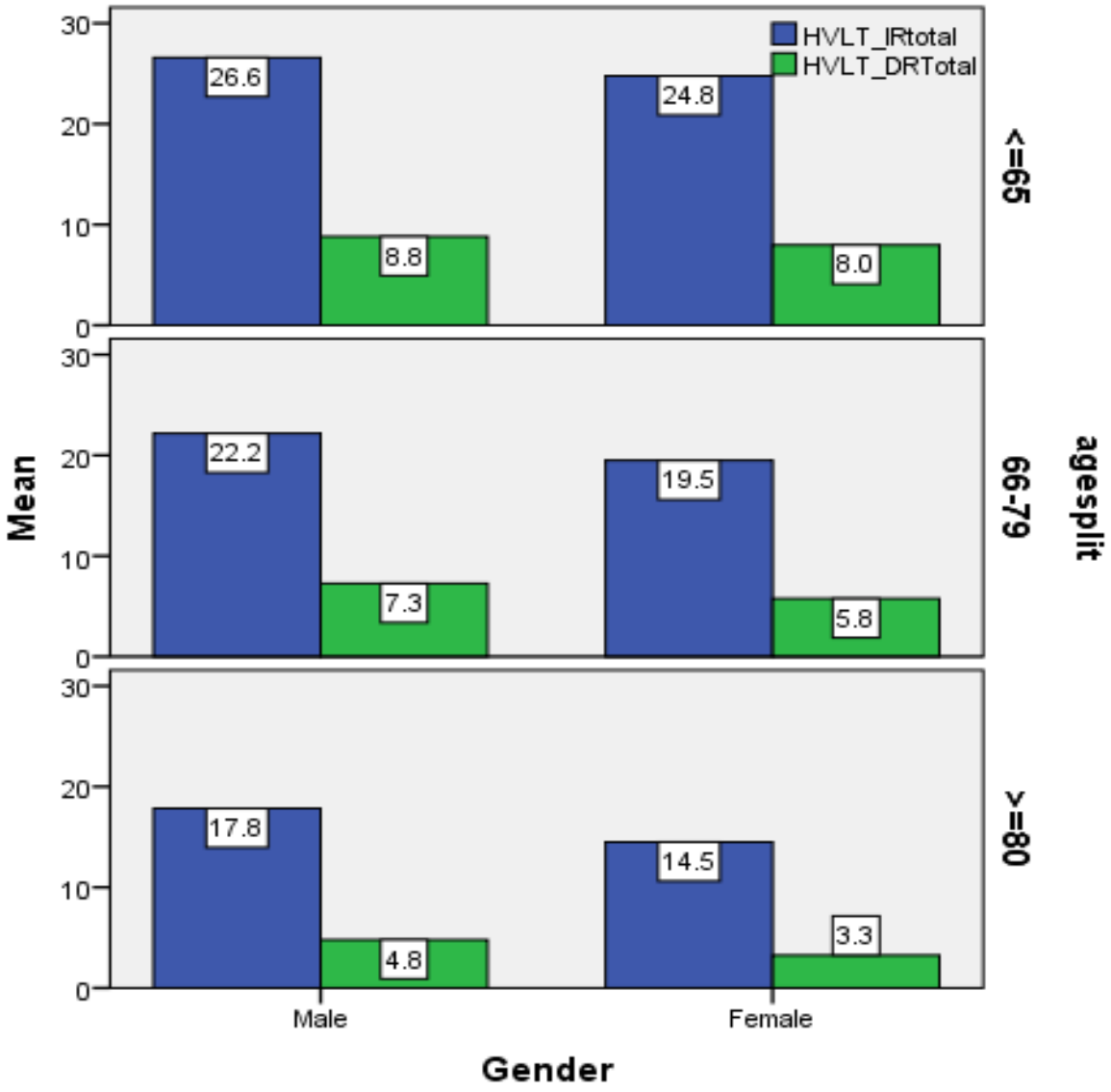
In profession groups, noticeably, there was a 4-point difference on the HVLT IR performance between no job or manual workers and non-manual workers in the CI group (11 vs. 15). However, there was no other significant difference between these 2 groups elsewhere.

In the following results, interactions between different demographic characteristics on the HVLT IR and DR performance were further examined to investigate whether gender and educational differences on cognitive performance could be explained by other variance, i.e., that derived from differences in age and profession.

8.2 Demographic difference on the HVLT performance

8.2.1 Gender difference on the HVLT IR and DR performance stratified by age, education and profession

Figure 10. The HVLT IR and DR performance in male and female groups stratified by age groups (≤ 65, 66-79, and 80 years of age)



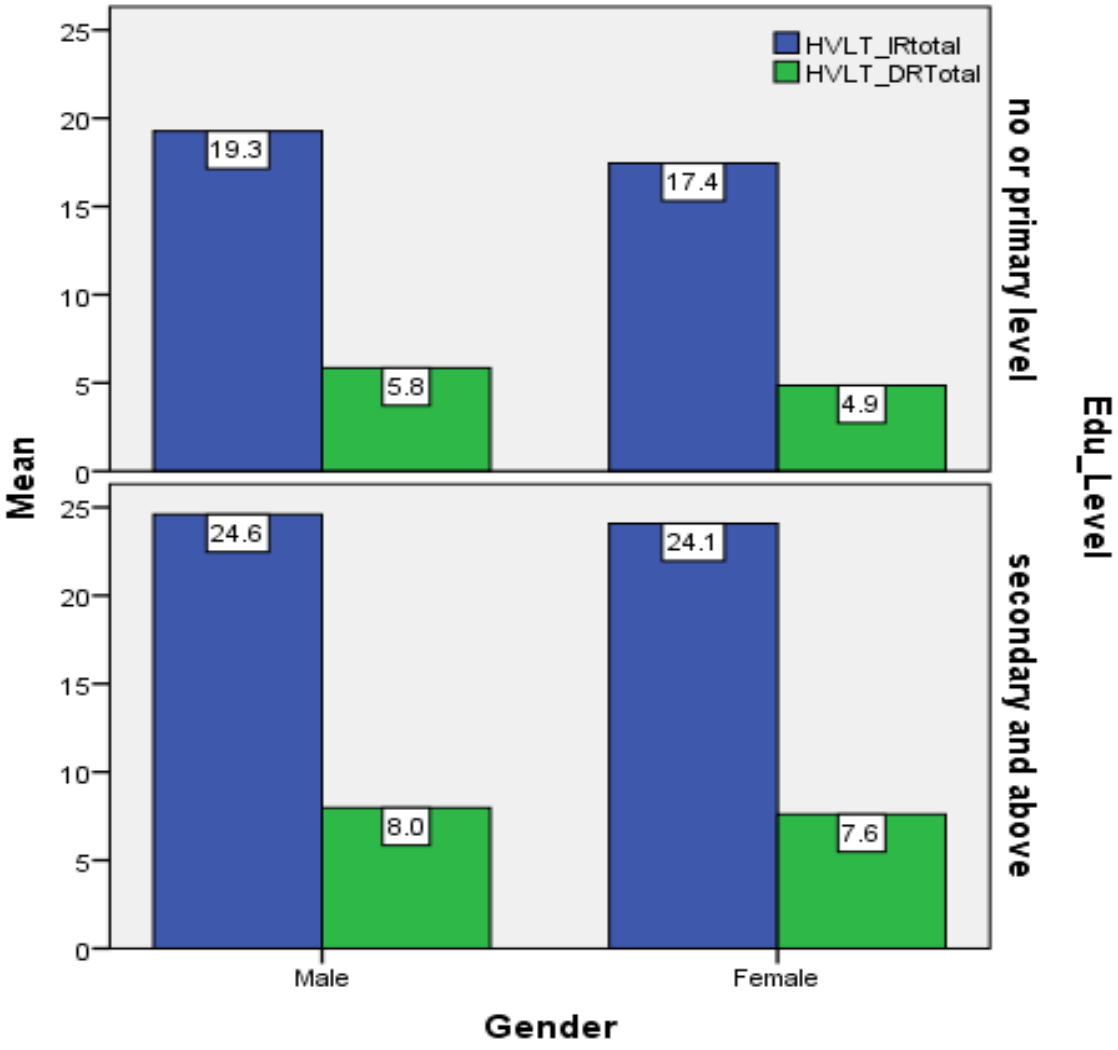
Bar graphs display the difference between males and females on the HVLT IR and DR performance in three age groups, ≤65, 66-79, and ≥80 years of age. On the HVLT IR performance, a 2-point gender difference on test results was observed in the youngest age group (≤65 years of age) where males demonstrated significantly better performance than females (27 vs. 25, p=0.04) after controlling for education and profession. However, in the other two age groups, gender differences were not significant, while a trend superior performance in males comparing to females was revealed (p=0.09 in 66-79 age group, and p=0.07 in ≥80 age group respectively, controlling for education and profession).

In contrast, although a trend of higher HVLT DR scores were shown in males compared to females in all three age groups, the differences were not significant after adjusting for education and profession.

These results reveal that in general, males showed superior memory performance (especially short term memory) than females, regardless of their age. Nevertheless, this difference is more significant in the younger group (≤65 years of age).

Afterwards, additional analysis was performed to investigate whether this gender difference was caused by different levels of education obtained.

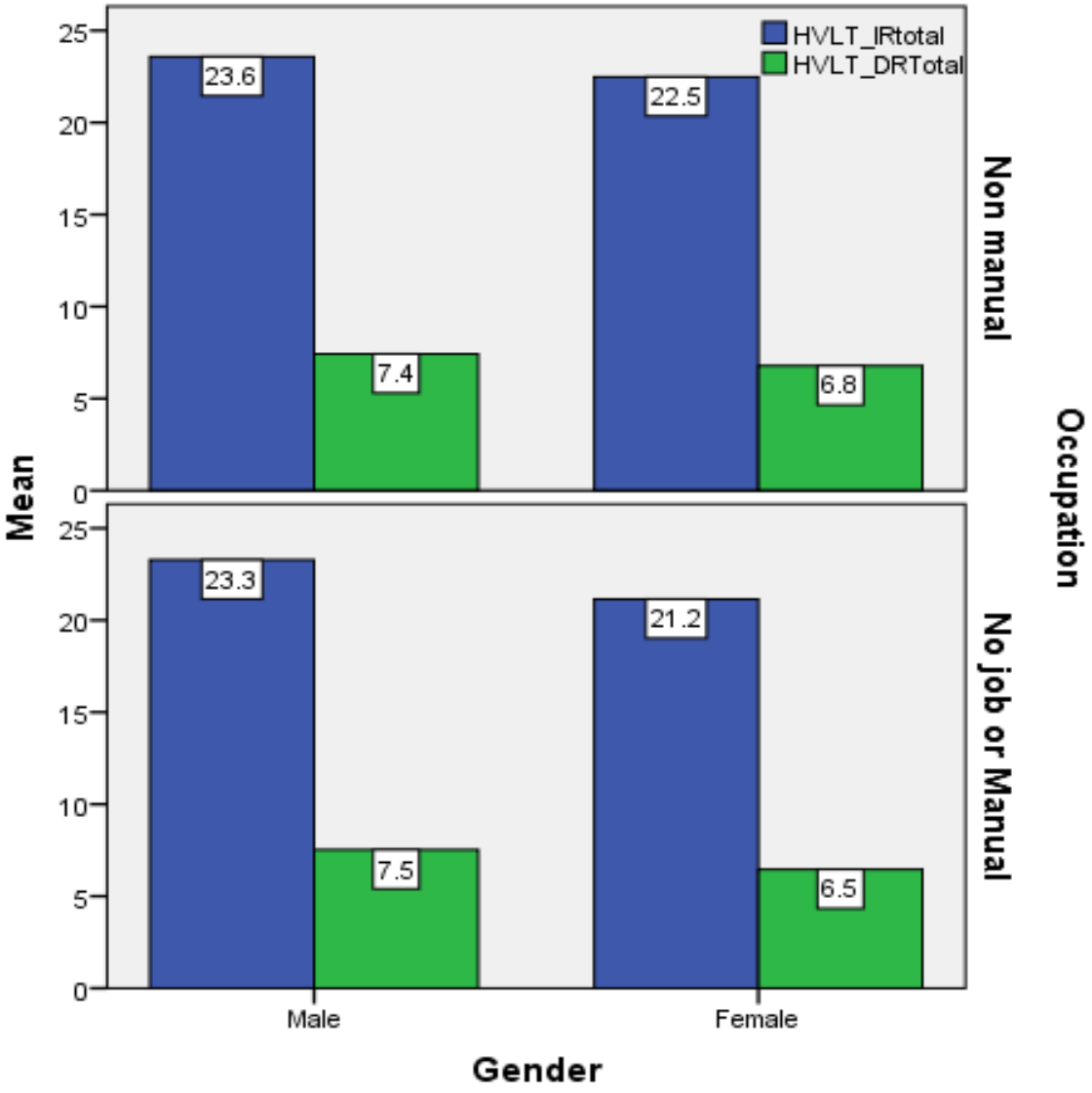
Figure 11. The HVLT IR and DR performance in male and female by educational split (no or primary level vs. secondary and above level)



After educational stratification, a 2-point HVLT IR score difference and a 1-point DR score difference was shown in the less educated group (no or primary level). After controlling for age, ANOVA analyses indicated a trend for significant differences between males and females (p=0.06 for IR scores and p=0.07 for DR scores, adjusting for age and profession).

However, this gender difference did not extend to the higher educated group (secondary and above), where males and females demonstrated equivalent performance on both HVLT IR and DR tests.

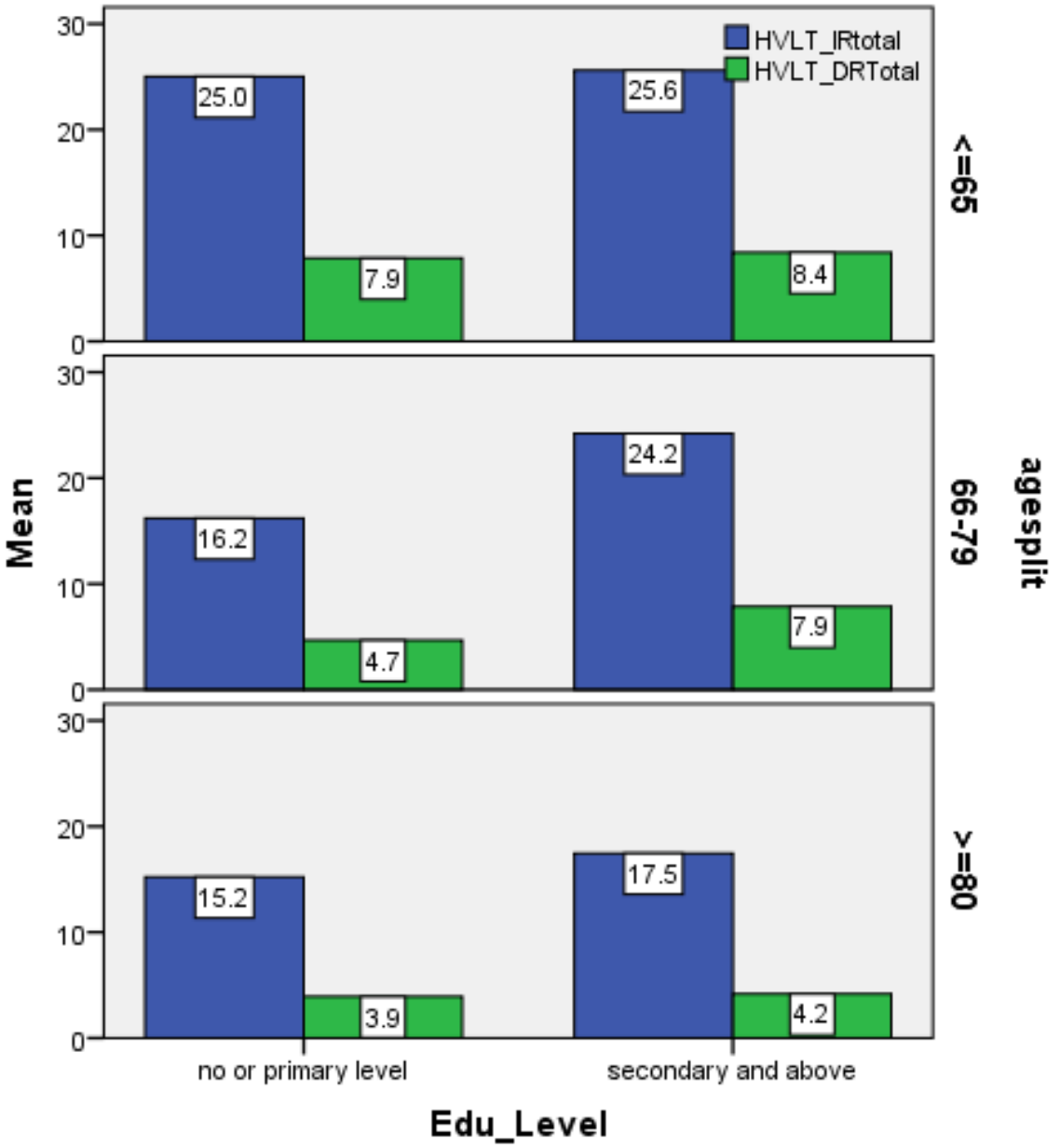
Figure 12. The HVLT IR and DR performance in male and female stratified by profession split (no job or manual vs. non manual)



Equivalent performances on the HVLT IR and DR tests were shown between male and female in both no job or manual profession, and in non-manual profession groups. After controlling for age and education, there was no significant gender difference (p=0.12 in no job or manual group, and p=0.1 in non-manual group). This indicated that there is no significant interaction between gender and profession on memory outcomes.

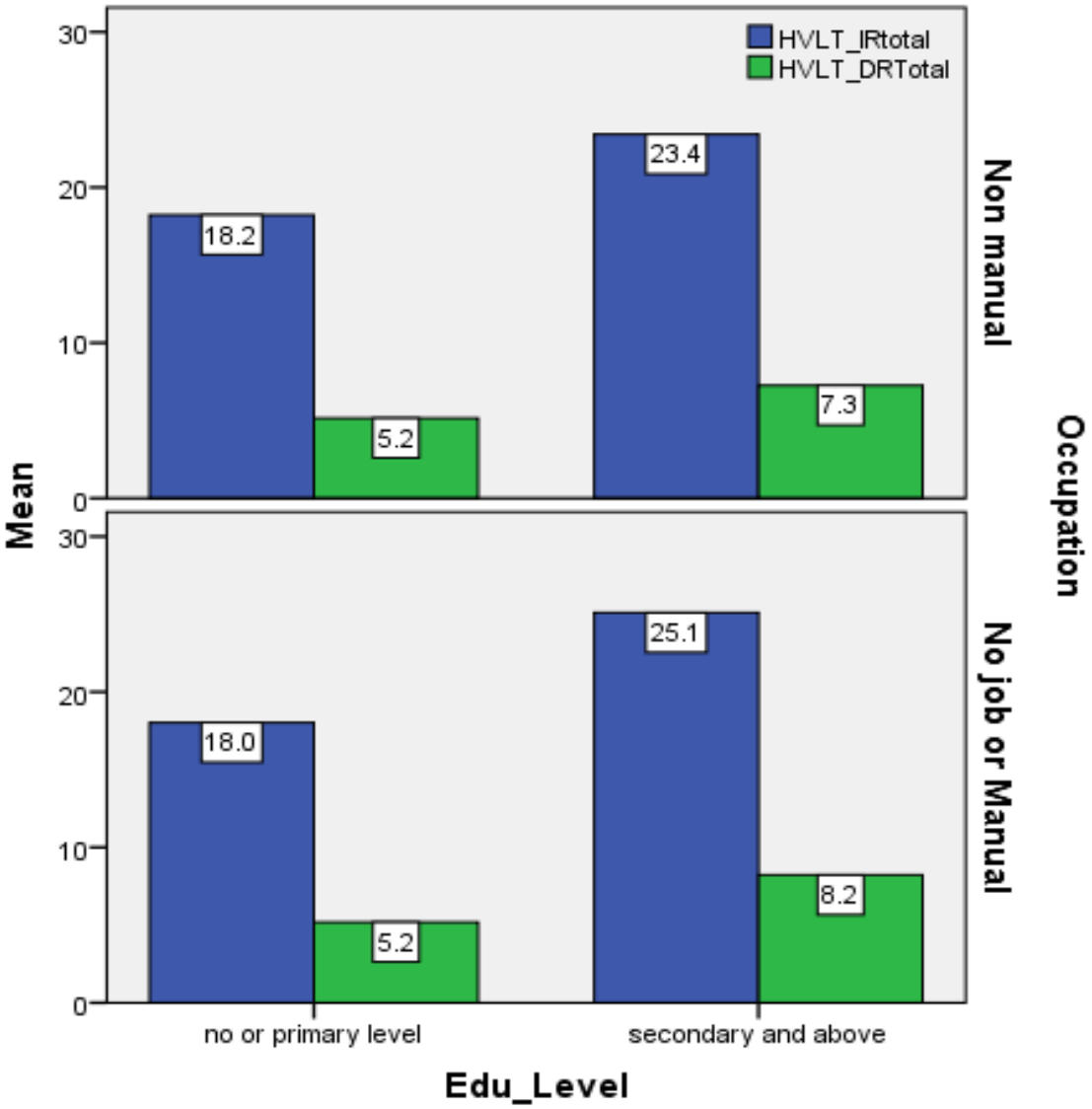
8.2.2 Educational difference on the HVLT IR and DR performance stratified by age and profession

Figure 13. The HVLT IR and DR performance in less educated (no or primary level) and higher educated (secondary and above) groups stratified by age split (≤65, 66-79, and ≥80 years of age)



Equivalent performance on both HVLT IR and DR tests between less educated (no or primary level) and higher educated (secondary and above) groups were indicated in the younger group (≤65 years of age) (25vs. 26 on IR, p=0.31; 8 on DR, p=0.29, adjusted for gender and profession). Nevertheless, an 8-point HVLT IR score difference and a 3-point DR score difference was observed between less and higher educated participants in the 66-79 age group, where significant superior memory performance was found among higher educated participants ($p<0.001$ for both IR and D, controlled for gender and profession). However, this significance was gone when comparing the HVLT IR and DR performance in the older age group (≥80 years of age) (15 vs. 18 on IR, p=0.72; 4 on DR, p=0.89 respectively, controlled for gender and profession).

Figure 14. The HVLT IR and DR performance in less educated (no or primary level) and higher educated (secondary and above) groups stratified by profession split (no job or manual vs. non manual)



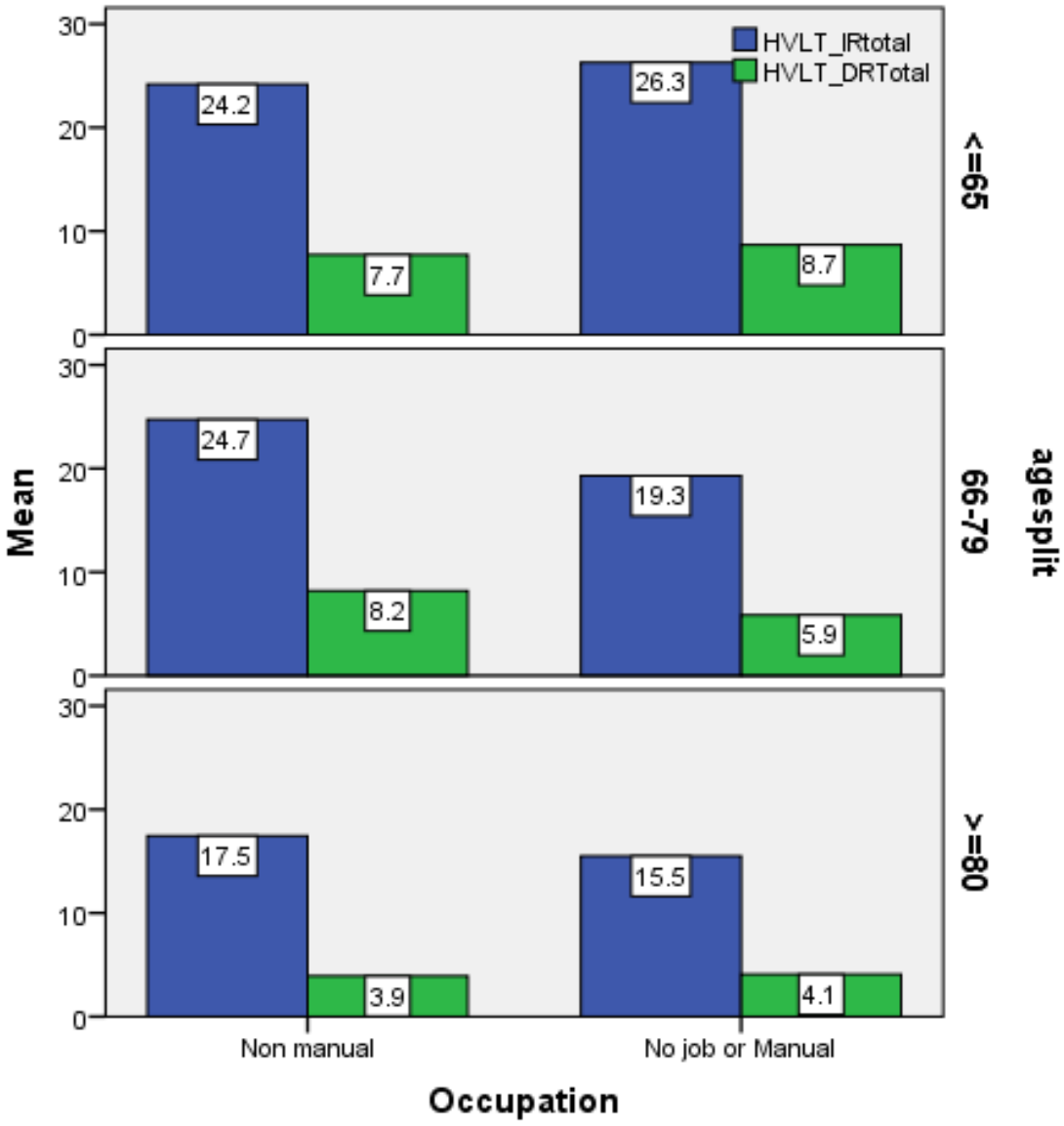
A 5-point HVLT IR score difference was observed between less and higher educated groups in non-manual profession group (18 vs. 23). After controlling for age and gender, the difference was found to be significant ($p=0.04$). In contrast, although a 7-point educational difference on IR test was seen in no job or manual profession group, this difference was not significant after adjusting for age and gender ($p=0.1$). This is due to the significant effect of age ($p<0.001$). In non-manual groups, mean ages for less educated and higher educated group were 70 and 66 years, respectively ($p=0.08$), whereas in no job or manual profession group, mean ages for less and higher educated groups were 75 and 63 years, respectively ($p<0.001$).

However, there was no significant educational difference on the DR performance after controlling for age and gender ($p=0.22$ for non-manual group and $p=0.10$ for no job or manual group).

From the above results we can see that there is a significant educational effect on the total recall performance in the non-manual profession group, whilst the difference in the no job or manual profession group can be explained by the age difference. Nevertheless there is no significant educational effect on DR performance in both professional groups.

8.2.3 Profession difference on the HVLT IR and DR performance stratified by age groups

Figure 15. The HVLT IR and DR performance in no job or manual profession, and non-manual profession groups by age split (≤65, 66-79, and ≥80 years of age)



Among older adults (>65 years of age), non-manual profession participants performed equivalent or better on both HVLT IR and DR tests compared to no job or manual profession participants. Yet the difference was not significant after controlling for gender and education ($p=0.18$ in 66-79 age group, and $p=0.73$ in ≥80 age group for IR; $p=0.18$ in 66-79 age group, and $p=0.66$ in ≥80 age group for DR).

In contrast, no job or manual profession group manifested significantly better IR performance than the non-manual group in the younger age group (≤65 years of age) (26 vs. 24, $p=0.01$ after controlling for gender and education). Additionally, significantly better DR performance was also seen in no job or manual group compared to the non-manual group in the younger age-group (9 vs. 8, $p=0.04$ after controlling for gender and education).

This result is consistent with the above results (Fig. 12 and Fig. 14) where significant gender and educational effect on both IR and DR performance on the HVLT were found, which explains the numerically better (but not statistically significant differences on the-) memory performance in non-manual group compared with the no job or manual group in the older age groups.

8.3 Demographic variables in predicting cognitive impairment

8.3.1 The discriminant ability of the HVLT (IR) score in differentiating CI from NCI

Figure 16. Receiver Operating Characteristics (ROC) curve for the HVLT (IR) in detecting CI from NCI

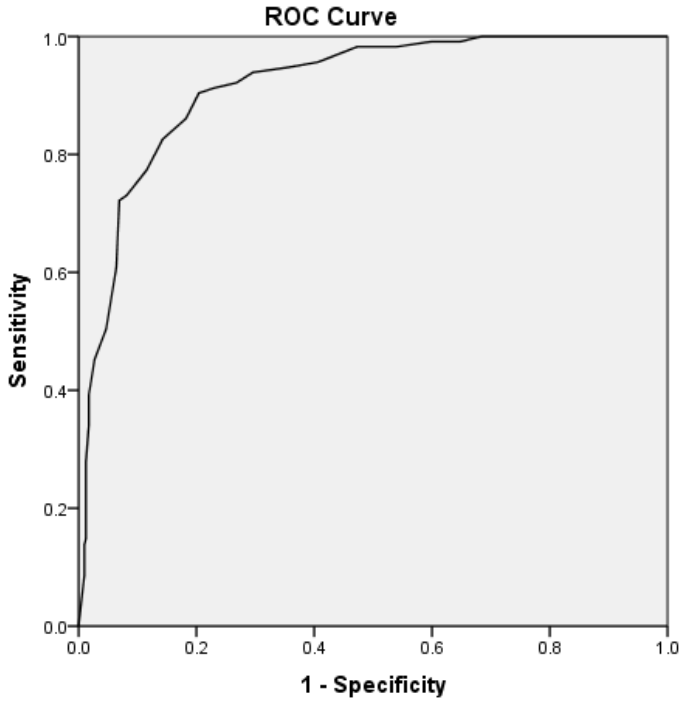


Table 40. Area Under Curve (AUC), optimal cut-off scores, SE and SP of the HVLT (IR) scores in discriminating MCI from NCI in the whole group

	AUC (95% CI)	Cut-off score	SE	SP
HVLT IR	0.92 (0.89-0.94)	18/19	86.1%	81.8%
		19/20	90.0%	79.6%

Excellent discriminant ability of the HVLT IR was revealed in differentiating CI from NCI. Applying an optimal cut-off score of 19/20, 90.0% SE and 79.6% SP was obtained. Alternatively, a cut-off score of 18/19 provided with a better SP of 81.8% accompanied with a decreased SE of 86.1%.

In the following analyses, the HVLT cut-off score of 19/20 was employed to investigate the predictive value of demographic characteristics on cognitive performance.

8.3.2 Logistic regression analysis in examining the predictive ability of age, gender, education and profession in detecting cognitive performance

Firstly, logistic regression analysis was employed using the 'Enter' method with a HVLT IR cut-off score of 19/20 in differentiating CI from NCI as the dependent variables and demographic variables as predictors. These included age, gender, education and occupation. Subsequently, these variables were entered as predictors for cognitive impairment, stratified by the age split as suggested by Shi (2012).

A total of 521 cases were included in the analysis and the full model significantly predicted cognitive status.

Table 41. Logistic regression analyses to assess possible demographic risk factors for cognitive impairment

Variables Entered	B	S.E.	Exp (B)	Sig.	95% CI for Exp (B)
Diagnosis (CI vs. NCI)	3.46	0.37	31.83	<0.001	15.44-65.62
Age (continuous)	0.07	0.03	1.07	0.009	1.02-1.14
Education Group					
No or primary level vs. Secondary and above level	0.15	0.31	1.16	NS	0.63-2.14
Gender					
Male vs. Female	-0.60	0.25	0.55	0.02	0.34-0.89
Profession					
No job or manual vs. non manual	0.13	0.27	1.14	NS	
Constant	-6.62	2.40	0.001	0.006	

B= standardized beta; S.E. = standard error; Sig= significance level; Exp (B) = change in predicted odds of CI for each change in predictor variable; 95% CI= 95% confidence interval for Exp (B); [a] = trend level significance; NS=Not Significant

Table 41 shows the logistic regression analyses to investigate potential risk factors for cognitive impairment. Age and gender were significant predictors for worse cognitive performance (HVLT ≤19), independent of diagnosis (NCI or CI). Accompanying an advanced age, higher risk of worse cognitive performance was also shown (OR= 1.07, 95%CI= 1.02 to 1.14, p=0.009).

Males have a lower risk of being cognitively impaired than females (OR=0.55, 95%CI=0.34-0.89, p=0.02). However, education and profession were found to not be significant predictors for cognitive impairment, independent of participant's diagnosis.

Table 42. Logistic regression analyses to assess demographic risk factors for cognitive impairment, stratified by age groups (⩽65, 66-79 and ⩾80 years of age)

Age Split	Variables Entered	B	S.E.	Exp (B)	Sig.	95% CI for Exp (B)
≤65 years of age	Diagnosis CI vs. NCI	3.20	0.54	24.49	<0.001	8.52-70.40
	Age	0.09	0.05	1.10	0.07[a]	0.99-1.22
	Education Equal or less than primary vs. Secondary and above	0.30	0.51	1.34	NS	
	Gender Male vs. Female	-0.69	0.35	0.73	0.04	0.25-1.00
	Profession No job or manual vs. non manual	-0.32	0.34	0.73	NS	
66-79 years of age	**Diagnosis** CI vs. NCI	4.91	1.17	135.53	<0.001	13.69-1343.28
	Age	-0.01	0.06	0.99	NS	
	Education Equal or less than primary vs. Secondary and above	0.38	0.58	1.46	NS	0.47-4.51
	Gender Male vs. Female	-0.36	0.46	0.70	NS	
	Profession No job or manual vs. non manual	0.42	0.52	1.53	NS	
≥80 years of age	**Diagnosis** CI vs. NCI	4.43	0.95	83.49	<0.001	12.86-541.93
	Age	0.12	0.06	1.13	0.04	1.00-1.27
	Education Equal or less than primary vs. Secondary and above	0.13	0.73	1.14	NS	
	Gender Male vs. Female	-0.65	0.56	0.52	NS	
	Profession	1.31	0.86	3.72	NS	

	No job or manual vs. non manual					

B= standardized beta; S.E. = standard error; Sig= significance level; Exp (B) = change in predicted odds of cognitive impairment for each change in predictor variable; 95% CI= 95% confidence interval for Exp (B); [a]= trend level significance; NS=Not Significant

Table 42 demonstrates the predictive value of diagnosis, age, education, gender and profession in detecting cognitive impairment, stratified by age groups. It is explicit that participant's diagnosis is the most significant predictor for cognitive impairment across three age groups. In the younger age group (≤65 years of age), gender is the most significant predictor for cognitive impairment, as males have lower risk of cognitive impairment (OR=0.73, 95% CI= 0.25-1.00, p=0.04). In addition, age shows a trend of its significant predictive ability (p=0.07). In the middle age group (66-79 years of age), only the diagnosis is the strong predictor for cognitive impairment (OR=135.53, 95% CI=13.69-1343.28, p<0.001). However in the advanced age group (≥80 years of age), in addition to the diagnosis, age also shows its significant predictive value in detecting worse cognitive performance (p=0.04) whilst all the other variables revealed no significant predictive value.

In conclusion, demographic characteristic, such as age, gender can be predictors for cognitive impairment indicative of dementia. Among elderly in relatively younger age group (i.e. ≤65years of age), gender is a significant predictor for low cognitive ability as males tend to perform better on the cognitive test than females. Nevertheless, accompanying an advanced age, only age is the most significant predictor for dementia, independent of diagnosis.

Better cognitive performance among males than females was also reported in another study (Hogervorst, 2012), in which author explored several possible reasons to conclude for this gender difference. It was suggested that males have better performance on cognitive tests may be because of their better health status and survival bias.

9 CHAPTER 9 LIFESTYLE RISK FACTORS ASSOCIATED WITH COGNIITVE DECLINE

9.1 Lifestyle characteristics in predicting cognitive impairment

9.1.1 Distribution of lifestyle factors among CI and NCI participants

Table 43. Descriptives of lifestyle risk factors stratified by cognitive status

	CI Group	NCI Group	Critical Value	p Value
N (%) of total sample	115 (22.1%)	406 (77.9%)	~	~
Lifestyle Risk Factors				
Smoking History				
Yes	26 (22.6%)	103 (25.4%)	0.37	NS
No	89 (77.4%)	303 (74.6%)		
Alcohol History				
Yes	15 (13.0%)	66 (16.3%)	0.7	NS
No	100 (87.0%)	340 (83.7%)		
Dietary habit				
Vegetarian				
Yes	74 (64.3%)	202 (49.8%)	7.66	0.006
No	41 (35.7%)	204 (50.2%)		
Type of food (times/week)				
tofu	1.6 ± 1.5	1.8 ± 1.6	1.5	NS
Fruit/juice	2.7 ± 1.9	2.7 ± 1.9	0.08	NS
Vegetables	8.7 ± 4.4	9.9 ± 3.4	2.7	0.007
Meat (white meat/red meat)	3.7 ± 2.7	2.8 ± 2.3	-3.5	0.001
Exercise				
Less than once per week	51 (44.3%)	157 (38.7%)	1.27	NS
More than once per week	64 (55.7%)	249 (61.3%)		

NS=Not Significant

Among all the lifestyle risk factors, such as smoking history, alcohol history, dietary habits including vegetarian (yes or no), tofu intake per week, fruit/juice intake per week, vegetables intake per week, and exercise frequency per week, only dietary habits significantly differentiate between CI and NCI groups. In CI group, higher proportion of vegetarian participants was seen (64.3%) whereas equivalent percentages of vegetarian and non-vegetarian subjects were found in NCI group ($p=0.006$). Furthermore, it was found that the NCI group eat vegetables more frequently than CI group (10 vs. 9 times per week, 0.007), whereas CI group eat meat more frequently than NCI group (4 vs. 3 times per week, $p=0.001$).

These results implicated that lifestyle factors such as dietary habits may be important risk/protective factors for cognitive impairment. However more analyses need to be done to further investigate the influence of these factors on cognitive impairment.

9.1.2 Logistic regression in examining the predictive ability of lifestyle risk factors

Logistic regression analyses were subsequently performed in 2 steps. The HVLT cut-off score (≤19 or >19) was entered as dependent variable and diagnosis (NCI or CI), along with lifestyle variables such as smoking history (yes/no), alcohol history (yes/no), vegetarian (yes/no), exercise less than once per week (yes/no) were entered as categorical independent variables. In step 2, demographic variables such as age, educational level, gender and profession were added into the regression model to assess whether these factors mediated the possible effects of lifestyle variables on worse cognitive performance.

Table 44. Logistic Regression Analyses to assess possible demographic and lifestyle risk factors for cognitive impairment

Variables Entered	B	S.E.	Exp (B)	Sig.	95% CI for Exp (B)
Significant variables in Step 1					
Diagnosis (CI vs. NCI)	3.63	0.35	37.70	<0.001	19.02-74.73
Smoking History					
No vs. Yes	-0.75	0.31	0.47	0.02	0.26-0.88
Diet habit					
Vegetarian vs. Non Vegetarian	0.72	0.24	2.05	0.003	1.57-3.28
Constant	-0.90	0.19	0.41	<0.001	
Significant variables in Step 2					
Diagnosis (CI vs. NCI)	3.37	0.36	29.17	<0.001	14.43-58.94
Age	0.05	0.01	1.05	<0.001	1.02-1.08
Dietary Habit					
Vegetarian vs. Non Vegetarian	0.84	0.25	2.31	0.001	1.42-3.75
Constant	-4.59	0.89	0.01	<0.001	

B= standardized beta; S.E. = standard error; Sig= significance level; Exp (B) = change in predicted odds of CI for each change in predictor variable; 95% CI= 95% confidence interval for Exp (B); [a]= trend level significance

Table 44 displays the significant predictor for cognitive impairment. In step 1, smoking history (yes), vegetarian (yes) were significant predictors for worse cognitive performance, independent of participant's cognitive status. Absent smoking history, reduced the odds of deteriorating cognitive function by a factor of 0.47 (95% CI=0.26-0.88, p=0.02). In addition, being a vegetarian also increase the risk of cognitive impairment (OR=2.05, 95% CI=1.57-3.28, p=0.003).

After putting in demographic variables such as age, education, gender and profession, whilst age and educational level were proven to be significant predictors, the predictive ability of smoking history was not significant anymore. In contrast, being vegetarian, independent of participant's diagnosis and age, remained as a strong predictor for cognitive impairment (OR=2.31, 95% CI=1.42-3.75, p=0.001)

It is an interesting finding that being vegetarian is not good for elderly's cognitive function. Therefore, it is important to further investigate the effect of different patterns of intake of food on cognitive performance, especially whether there is a difference on demographic as well as lifestyle variables, especially food intake patterns between vegetarian and non-vegetarian participants.

9.2 Demographic and lifestyle differences between vegetarian and non-vegetarian groups

9.2.1 Demographic difference between vegetarian and non-vegetarian groups

Table 45. Demographic characteristics and HVLT performance among vegetarian and non-vegetarian subjects

	Vegetarian	Non-vegetarian	Critical Value	p Value
N (%) of total sample	245 (47.0%)	276 (53.0%)	~	~
Demographic Factors				
Age Group			3.45	NS
≤ 65 years	130 (53.1%)	144 (52.2%)		
66-79 years	76 (31.0%)	72 (26.1%)		
≥80 years	39 (15.9%)	60 (21.7%)		
Gender			1.29	NS
Male	105 (42.9%)	132 (47.8%)		
Female	140 (57.1%)	144 (52.2%)		
Education			1.22	NS
No or primary level	82 (33.5%)	80 (29.0%)		
Secondary and above level	163 (66.5%)	196 (71.0%)		
Profession			11.7	0.001
No Job or Manual	182 (74.3%)	166 (60.1%)		
Non Manual	63 (25.7%)	110 (39.9%)		
HVLT Performance				
HVLT IR	24.3 ± 9.4	20.7 ± 8.3	-4.54	<0.001
HVLT DR	7.9 ± 4.3	6.1 ± 4.6	-4.66	<0.001

NS=Not Significant

From table 45 we found that among all the demographic characteristics, only profession differentiate between vegetarian and non-vegetarian groups (p=0.001). Whilst 74.3% of the vegetarian group had no job or manual profession, a lower percentage of non-vegetarian groups had no job or a manual job (60.1%).

Noticeably, when it comes to the HVLT IR and DR performance, a significant difference was seen between these 2 groups. Overall, vegetarian participants scored 3 points higher than non-vegetarian participants on IR tests (24 vs. 21, $p<0.001$). A 2-point better performance on the DR trial was found among vegetarian subjects comparing to non-vegetarian subjects (8 vs. 6, $p<0.001$).

In general, demographics do not significantly differentiate between vegetarian and non-vegetarian groups. Therefore in the next section we furthermore examine the differences on lifestyles, dietary habits in particular, between these 2 groups.

9.2.2 Differences in lifestyle variables between vegetarian and non-vegetarian groups

Table 46. Lifestyle characteristics among vegetarian and non-vegetarian subjects

	Vegetarian Group	Non-vegetarian Group	Critical Value	p Value
N (%) of total sample	245 (47.0%)	276 (53.0%)	~	~
Lifestyle Factors				
Smoking History			0.005	NS
Yes	61 (24.9%)	68 (24.6%)		
No	184 (75.1%)	208 (75.4%)		
Alcohol History			8.56	0.004
Yes	26 (10.6%)	55 (19.9%)		
No	219(89.4%)	221 (80.1%)		
Exercise Frequency			1.52	NS
Less than once per week	105 (42.9%)	103 (37.3%)		
More than once per week	140 (57.1%)	173 (62.7%)		
Diet Habit (times/week)				
Fruit/Juice	3.9 ± 2.0	2.3 ± 1.7	2.82	0.005
Vegetables	9.7 ± 3.7	9.5 ± 3.7	0.55	NS
Green vegetables	7.5 ± 3.2	5.9 ± 3.8	2.21	0.04
Orange/Red vegetables	2.2 ± 2.1	2.1 ± 2.0	0.23	NS
Tofu	1.7 ± 1.4	1.2 ± 1.4	2.3	0.02

NS=Not Significant

No significant difference in smoking history and exercise frequency was found between vegetarian and non-vegetarian groups, except for alcohol history. Non-vegetarian group showed higher percentage of people who had an alcohol use history (19.9%) comparing to the vegetarian group (where 10.6% had an alcohol use history).

However, on weekly food intake frequency, vegetarian participants were found to eat more fruit/juice than non-vegetarian people (4 times/week vs. 2 times/week, p=0.005). In addition, regarding vegetable intake, although an equivalent intake of orange/red vegetables was found in both groups (2 times/week), vegetarian subjects ate more green vegetables than non-vegetarian subjects (8 times/week vs. 6 times/week, p=0.04). Furthermore, vegetarian subjects ate more soy products, such as tofu (2 times/week vs. 1 time/week among non-vegetarian subjects, p=0.02). Tempe is not a very popular type of food in China, in our survey, we found that most of participants only ate tempe occasionally (less than once/month). Therefore intake of tempe was excluded from the current analyses.

It was clearly observed that there is a food habit difference between vegetarian and non-vegetarian subjects. It remains unclear that to what extent these dietary habits differences exerted effects on cognitive performance. Therefore in the following section, we investigated the predictive value of different patterns of food intake on cognitive impairment as defined by the HVLT split, using a cut-off score of 19/20. In the first step, dietary habits, including fruit/juice intake, green vegetables intake, orange/red vegetables intake, and tofu intake were entered as predictors. In step 2, other lifestyle variables such as smoking history, alcohol history and exercise frequency were added into the model to investigate whether these factors mediate the effect of predictors in step 1. In the final step, diagnosis and demographic variables such as age, gender, educational level and profession were added into the regression model.

9.2.3 Lifestyle risk factors in predicting cognitive impairment so as to compare to demographic risk factors, stratified by dietary habits (vegetarian vs. non-vegetarian)

Table 47. Logistic regression analyses of lifestyle and demographic risk factors in predicting cognitive impairment

	Vegetarian					Non-Vegetarian				
Variables Entered	B	S.E.	Exp (B)	Sig.	95% CI for Exp (B)	B	S.E.	Exp (B)	Sig.	95% CI for Exp (B)
Significant variables in Step 1										
Fruit/Juice	0.11	0.09	1.11	NS		-0.12	0.07	0.89	0.09[a]	0.78-1.02
Green Vegetables	-0.11	0.04	0.9	0.01	0.83-0.98	-0.23	0.05	0.8	<0.001	0.73-0.87
Constant	-0.06	0.45	0.95	NS		1.76	0.49	5.83	<0.001	
Significant variables in Step 2										
Green Vegetables	-0.12	0.04	0.89	0.008	0.82-0.97	-0.23	0.04	0.8	<0.001	0.73-0.87
Constant	1.35	0.33	3.87	<0.001		-0.18	0.33	0.83	NS	
Significant variables in Step 3										
Green Vegetables	-0.13	0.05	0.88	0.008	0.79-0.97	-0.24	0.05	0.79	<0.001	0.72-0.87
Age	0.09	0.02	1.09	<0.001	1.05-1.13	0.03	0.02	1.03	0.02	1.01-1.07
Education										
No or primary vs. Secondary and above	-0.67	0.43	0.51	NS	0.22-1.18	-0.78	0.35	0.46	0.03	0.23-0.92
Constant						-0.17	0.02	0.84	NS	

B= standardized beta; S.E. = standard error; Sig= significance level; Exp (B) = change in predicted odds of cognitive impairment for each change in predictor variable; 95% CI= 95% confidence interval for Exp (B); [a]= trend level significance; NS=Not Significant

Table 47 demonstrates the significant predictors for cognitive impairment in 3 steps. In step 1, intake of green vegetable was the only significant protective factor in both vegetarian and non-vegetarian groups, whereas there was a trend for intake of fruit/juice to reduce the risk of cognitive impairment (OR=0.89, 95% CI=0.78-1.02, p=0.09). However this trend of significance of fruit/juice intake disappeared in step 2 when entering other lifestyle risk factors, such as smoking history, alcohol history and exercise frequency, leaving intake of green vegetables as the only significant predictor. Furthermore, in step 3, after putting in demographic variables, whilst the significant predictive value of green vegetables intake remained, age revealed its significant predictive ability in both vegetarian and non-vegetarian groups. Interestingly, education was proven as an important predictor for cognitive decline in non-vegetarian group. Higher educated non-vegetarian people are less likely to be at risk of long term cognitive deterioration (OR=0.46, 95% CI=0.23=0.92, p=0.03).

Age proved its significant ability in predicting cognitive impairment. Therefore in the following results we furthermore investigate these lifestyle risk factors in different age groups (≤65, 66-79, and ≥80 years of age).

Table 48. Food frequency risk factors in predicting cognitive impairment, stratified by different age groups

		Vegetarian					Non-Vegetarian				
	Variables Entered	B	S.E.	Exp (B)	Sig.	95% CI for Exp (B)	B	S.E.	Exp (B)	Sig.	95% CI for Exp (B)
≤65 years of age	**Fruit/Juice**	0.22	0.17	1.24	NS	0.89-1.74	-0.22	0.12	0.8	0.07[a]	0.63-1.02
	Green Vegetables	-0.18	0.08	0.84	0.03	0.71-0.99	-0.25	0.07	0.78	<0.001	0.68-0.89
	Tofu	0.54	0.27	1.67	0.07[a]	0.95-2.94	-0.13	0.14	0.88	NS	0.66-1.16
	Constant	-0.85	0.78	0.43	NS		2.11	0.74	8.24	0.004	
66-79 years of age	**Green Vegetables**	-0.06	0.07	0.94	NS	0.82-1.07	-0.23	0.09	0.8	0.01	0.66-0.96
	Constant	0.03	0.51	1.03	NS		1.07	0.69	0.81	0.02	
≥80 years of age	**Green Vegetables**	-0.1	0.12	0.99	NS	0.79-1.24	-0.2	0.1	0.82	0.05[a]	0.67-1.00
	Constant	0.34	0.88	1.4	NS		-0.21	0.09	0.81	0.02	

B= standardized beta; S.E. = standard error; Sig= significance level; Exp (B) = change in predicted odds of cognitive impairment for each change in predictor variable; 95% CI= 95% confidence interval for Exp (B); [a]= trend level significance; NS= Not Significant

In table 48 we found that in the youngest elderly group (≤65 years of age), intake of green vegetables is a strong predictor for cognitive impairment in both vegetarian and non-vegetarian groups (in vegetarian group, OR=0.84, 95%CI= 0.71-0.99, p=0.03; in non-vegetarian group, OR=0.78, 95% CI=0.68-0.89, p<0.001). Apart from this, there was a trend that high intake of tofu could be a risk factor for cognitive impairment in the vegetarian group (OR=1.67, 95% CI=0.95-2.94, p=0.07).

In the middle age elderly group (66-79 years of age), green vegetable intake remained independent as the only significant protective variable, but only in non-vegetarian group (OR=0.80, 95% CI=0.66-0.96, p=0.01) whereas in the oldest elderly group (≥80 years of age), only intake of green vegetables revealed a trend in reducing the risk of cognitive impairment (OR=0.82, 95% CI=0.67-1.00, p=0.05).

From the above results we found that high intake of tofu in the younger vegetarian group might be a risk factor to predict cognitive impairment. However it is still not entirely explicit to what extent tofu intake was associated with elderly's cognitive performance, especially memory. In the next section we describe the association between tofu intake and memory performance as measured by the HVLT IR and DR tests. Intake of tofu was categorized into a binary variable, with 'yes' meaning presence of intake of tofu, and 'no' meaning absence of intake of tofu.

9.2.4 Association between tofu intake and risk of cognitive impairment in elderly

Table 49. Descriptives on demographic, lifestyles and HVLT performance in 'eat tofu' and 'do not eat tofu' groups

	Eat tofu	Do not eat tofu	Critical Value	p Value
N (%) of total sample	445 (85.4%)	76 (14.6%)	~	~
Demographic Factors				
Age Group			3.01	NS
≤ 65 years	241 (54.2%)	33 (43.4%)		
66-79 years	122 (27.4%)	26 (34.2%)		
≥80 years	82 (18.4%)	17 (22.4%)		
Gender			3.56	0.06[a]
Male	210(47.2%)	27 (35.5%)		
Female	235 (52.8%)	49 (64.5%)		
Education			7.70	0.007
No or primary level	128 (28.8%)	34 (44.7%)		
Secondary and above level	317 (71.2%)	42 (55.3%)		
Profession			2.70	NS
No Job or Manual	291 (65.4%)	57 (75.0%)		
Non Manual	154 (34.6%)	17 (25.0%)		
Lifestyle Factors				
Smoking History				
Yes	116 (26.1%)	13 (17.1%)	2.80	NS
No	329 (73.9%)	63 (82.9%)		
Alcohol History				
Yes	72 (16.2%)	9 (11.8%)	0.99	NS
No	373 (83.8%)	67 (88.2%)		
Exercise Frequency				
Less than once per week	175 (39.3%)	33 (43.4%)	0.49	NS
More than once per week	270 (60.7%)	43 (56.6%)		
Vegetarian				
Yes	192 (43.1%)	53 (69.7%)	18.41	<0.001
No	253 (56.9%)	23 (30.3%)		
Diet habit (times/week)				

Fruit/Juice	2.8 ± 1.9	2.3 ± 1.8	-2.00	NS
Green Vegetables	7.7 ± 3.2	5.9 ± 3.5	-4.13	<0.001
Orange/Red Vegetables	2.2 ± 2.1	2.0 ± 2.1	-0.78	NS
HVLT Performance				
HVLT IR	22.2 ± 8.3	23.3 ± 9.8	0.98	NS
HVLT DR	6.9 ± 4.5	7.3 ± 4.5	0.67	NS

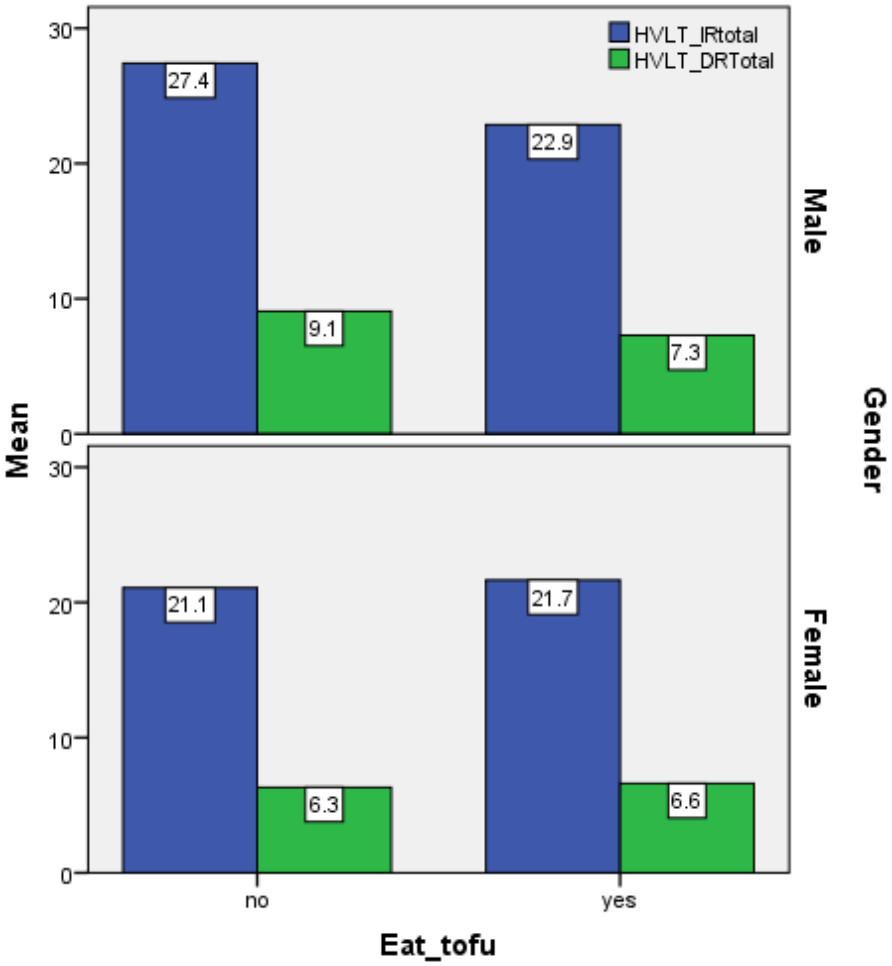
[a]= trend level significance; NS= Not Significant

There was a trend for males to be more likely to eat tofu (p=0.06). Also, those who ate tofu were more likely to be higher educated (secondary and above, p=0.007) and vegetarian (p<0.001), and eat more green vegetables (8 vs. 6 times per week, p<0.001).

In the next section, we analysed the effect of tofu intake status (yes or no) on the HVLT IR and DR performance, stratified by the significant factors listed above in table 49 (i.e. gender, education, and dietary habits(vegetarian or non-vegetarian).

9.2.4.1 Impact of tofu intake status on the HVLT IR and DR performance stratified by gender

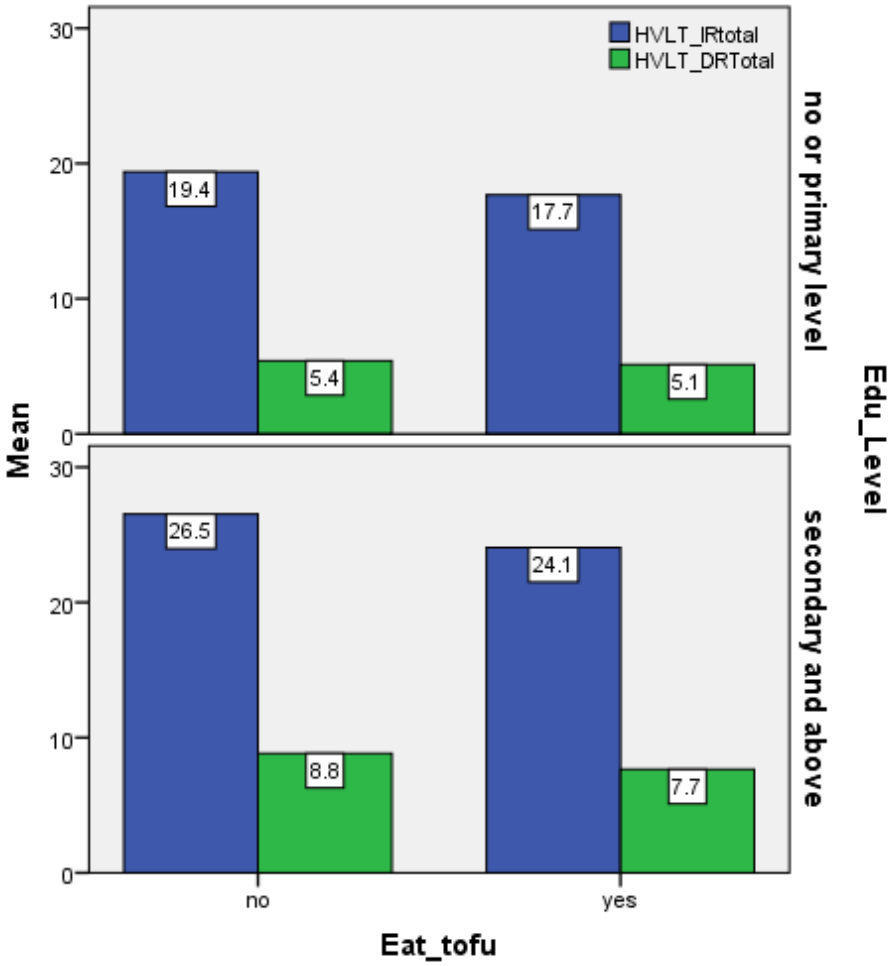
Figure 17. The HVLT IR and DR performance among those who eat tofu and who do not, stratified by gender



Among males, those who did notate tofu performed significantly better on the HVLT IR test than those who ate tofu after controlling for age, education and profession (27 vs. 23, p=0.01), following by a trend of better DR performance (9 vs. 7, p=0.05). However there was no significant effect of tofu on memory among females.

9.2.4.1 Impact of tofu intake status on the HVLT IR and DR performance stratified by gender

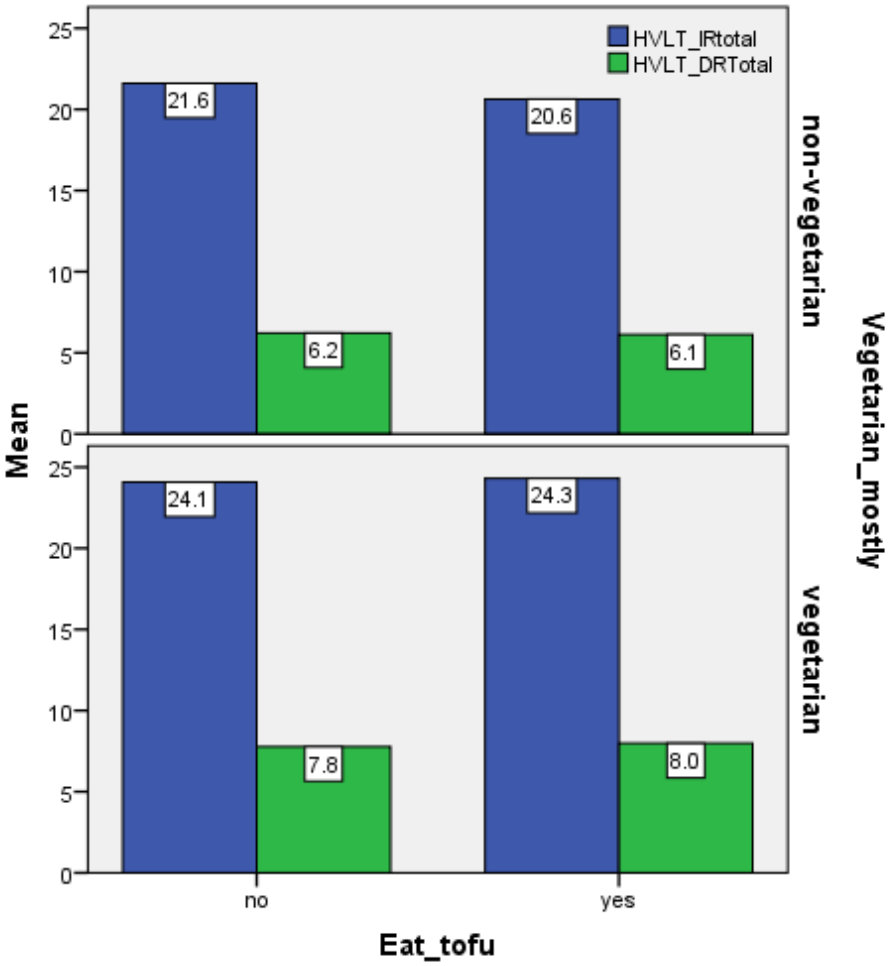
Figure 18. The HVLT IR and DR performance among those who eat tofu and who do not, stratified by education



Among those who were higher educated (secondary and above), those who did not eat tofu performed significantly better on IR test than those who did after controlling for age, gender and profession (27 vs. 24, p=0.03), followed by a trend of higher DR scores as well (9 vs. 8, p=0.06). However there was no significant difference on either HVLT IR or DR test between participants who ate tofu and who did not among those who were less educated (no or primary level).

9.2.4.2 Impact of tofu intake status on the HVLT IR and DR performance stratified by dietary habits (vegetatian vs. non-vegetarian)

Figure 19. The HVLT IR and DR performance among those who eat tofu and who do not, stratified by dietary habits (vegetarian vs. non-vegetarian)



On both the HVLT IR and DR trials, elderly who ate tofu in vegetarian and non-vegetarian groups performed equivalently after controlling for age, gender, education and profession (p=0.72 in vegetarian group and p=0.23 in non-vegetarian group).

Overall, gender and educational level, rather than dietary habits (vegetarian or non-vegetarian), exerted a significant impact on cognitive performance between those who ate tofu and who did not. However these impacts only existed among people with certain characteristics (i.e. who were male and higher educated elderly).

In the next section we analysed the predictive ability of tofu intake on cognitive impairment, whilst controlling for other potential covariates. Linear regression analysis was employed to investigate the effect of tofu on HVLT performance using the HVLT IR scores (continuous data) as the dependent variable, adjusting for demographic and other dietary variables, including age, gender, education, being vegetarian (yes or no to eating meat), weekly intake of fruit/juice, green vegetables and orange/red vegetables. Binomial logistic regression was subsequently performed to assess the predictive value of tofu consumption on cognitive impairment (as defined by a HVLT IR score of ≤19), adjusting for demographic and other dietary variables such as age, gender, education, being vegetarian (yes or no to eating meat), weekly intake of fruit/juice, green vegetables and orange/red vegetables. Analyses were also stratified by median age split (68 years of age).

9.3 Effect of tofu on cognitive function among community-dwelling elderly in Shanghai, China

9.3.1 Introduction

Soy products containing isoflavones, such as tofu, are common foods consumed in Asian countries. However, the effects of soy products on cognition remain debatable. Several authors suggested that higher soy consumption is associated with worse cognitive performance in Asian populations over the age of 65 years (White, 2000; Rice, 2000; Hogervorst, 2008). For instance, high tofu consumption was associated with worse memory using the Hopkins Verbal Learning Test (HVLT) [4] in a community-based study conducted in Indonesia (Hogervorst, 2008). This negative association of tofu and global cognitive function was also reported in two longitudinal studies in US among Japanese Americans (White, 2000; Rice, 2000). On the other hand, Greendale (2012) reported a better performance on cognitive tests measuring processing speed in a longitudinal study conducted in the US among Asian females during and after menopausal transition with high phytoestrogen intake. Similarly, genistein, the most potent isoflavone or phytoestrogen was reported to be positively related to cognitive ability among middle-aged participants, but had negative associations in elderly subjects (Soni, 2014; Hogervorst, 2009). There are also some studies reporting no association between soy consumption and cognition, especially among older European and American elderly people (Franco, 2005; Hogervorst, 2011; Soni, 2014). Age, gender, type of test used for assessment, level of consumption, ethnicity, being an equol producer and/or type of product consumed may explain some of the differences found.

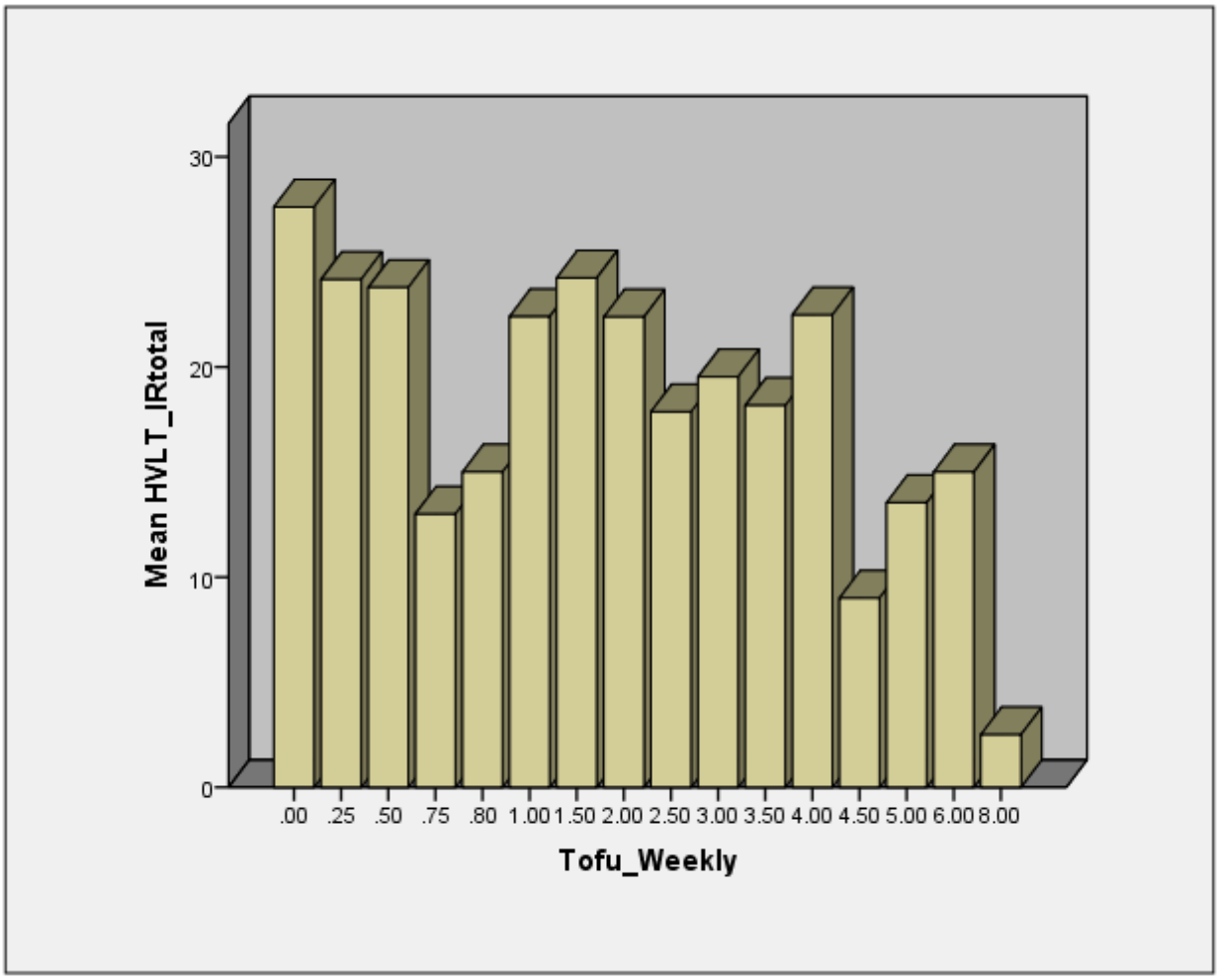
Intervention studies also reported different results of soy isoflavones on cognitive function. Improvement of cognitive function, including attention (Duffy, 2003; Casini, 2006), language (Kritz-Silverstein, 2003; Gleason, 2009), executive function (Kritz-Silverstein, 2003; Casini, 2006) and visual memory (Duffy, 2003; Gleason, 2009; Thorp, 2009; Henderson, 2012) were reported after daily soy supplement interventions (ranging from (60-2000 mg/day, 1.5-6 months total duration). Yet no effect of isoflavone intake on cognitive function was reported with soy

supplementation interventions ranging from 60-160 mg/day, within a total duration of intervention period from 4 to 12 months (Kreijkamp-Kaspers, 2004; Fournier, 2007; Ho, 2007; Basaria, 2009; Maki, 2009). Noticeably, among all the reported intervention studies mentioned, only one of these was conducted in an Asian sample (Hong Kong, Ho, 2007), whereas all the other studies were conducted in Western countries.

The relatively low treatment dosage here may have had no effect because the Asian participants would have already consumed more daily isofalvones (Yesufu, 2009). Soy product intake is generally relatively higher in Asian countries which may affect isoflavone metabolism and/or their subsequent effect on the brain. Only very few studies looked into the effect of tofu on cognition among Chinese elderly people in community settings. In a recent study no association of tofu and cognitive function was found in Chinese elderly (Gao, 2013). However, this study was conducted among elderly above 90 years of age and survival bias may have played a role. Hence, the current study further explored the association between tofu intake and cognitive ability among community-dwelling elderly people in Shanghai, China. We used the same memory test earlier found to be sensitive to phytoestrogen intake and that found in saliva samples (Hogervorst, (2008, 2009, 2011)). This test was also found to have very good sensitivity and specificity for dementia, in particular for its early stages (Hogervorst (2002, 2011); De Jager, 2003; Schrijnemaekers, 2006). Because inter-rater reliability for dementia is often 'moderate at best (Hogervorst, 2000) and many older people who were thought to have mild cognitive impairment will reverse to normal function (Schrijnemaekers, 2006), in this study we used the cut-off for that test which best indicated early dementia rather than the clinical diagnoses.

9.3.2 The predictive value of tofu intake on cognitive impairment

Figure 20. Relationship between mean HVLT IR score and weekly Tofu intake



A bar graph showed an overall trend for increasing weekly tofu intake to be negatively and linearly associated with subject's worse performance on the HVLT IR test (Fig 20).

Linear regression analysis was employed to investigate the predictive value of tofu intake on cognitive impairment.

Table 50. Linear regression analyses in 2 steps: step1, controlled for age, gender and education; step 2, for food intake habits

	HVLT (IR)			
	Step 1		Step 2	
	β	p Value	β	p Value
Tofu (weekly)	-0.11	0.009	-0.10	0.01
Age	-0.34	<0.001	-0.31	<0.001
Gender	-0.05	NS	-0.03	NS
Education	0.27	<0.001	0.3	<0.001
Vegetarian	-	-	0.16	<0.001
Fruit/Juice (weekly)	-	-	0.06	NS
Green Vegetables (weekly)	-	-	0.17	<0.001
Orange/Red Vegetables (weekly)	-	-	0.004	NS

NS= Not Significant

Linear regression models (see table 51) demonstrated that weekly tofu intake was negatively associated with immediate recall memory on the HVLT (IR) after controlling for demographic (age, gender and education) and other food intake variables (being vegetarian, weekly intake of fruit/juice, green vegetables and orange/red vegetables). Eating meat (not being vegetarian) was independently associated with better memory function, as was consumption of green vegetables (table 51).

A logistic regression model using possible dementia as a binary outcome investigated the predictive value of weekly tofu intake, controlling for demographic variables and other types of food consumed weekly. These analyses indicated that there was a trend for weekly tofu intake to increase the risk for CI by 20% (OR=1.20, p=0.08) after adjusting for age, gender, education, vegetarian habits, and weekly intake of fruit/juice, green/orange/red vegetables. In our previous study (Hogervorst, 2008) tofu intake was mainly negatively associated with dementia risk and worse

memory performance among 'older' elderly (>68 years of age). Therefore, in the current study stratification using a median age split (68 years of age) was applied.

Table 51. Logistic regression analyses stratified for age using the median split (68 years of age), controlled for age, gender and education in step 1, and dietary habits in step 2

	<68 years of age		≥68 years of age	
	Step 1	Step 2	Step 1	Step 2
	Odd Ratio (95% CI), p value			
Weekly Tofu intake	NS	NS	1.24 (0.97-1.57), p=0.08[a]	1.27 (0.99-1.64), p=0.04
Age	NS	NS	1.10 (1.01-1.18), p=0.02	NS
Education	0.90 (0.84-0.96), p=0.002	0.87 (0.81-0.94), p<0.001	0.85 (0.76-0.94), p=0.001	0.83 (0.74-0.93), p=0.001
Gender (Male)	NS	NS	0.49 (0.27-0.90), p=0.02	0.54 (0.28-1.04), p=0.06[a]
Being Vegetarian	-	NS	-	3.80 (1.87-7.70), p<0.001
Weekly fruit/juice intake	-	NS	-	NS
Weekly green vegetables intake	-	0.83 (0.75-0.92), p<0.001	-	0.81 (0.73-0.89), p<0.001
Weekly orange/red vegetables intake	-	NS	-	NS

[a]= trend for significance; NS= Not Significant;

From table 52 we can see that among younger participants, there was no significant effect of tofu on cognitive impairment, whereas increased risk of almost 30% was seen for being cognitive impaired with a higher tofu intake among older elderly (≥68 years of age) (OR=1.27, 95% CI=0.99-1.64, p=0.04) after adjusting for all the other covariates. Not being vegetarian (eating meat) increased risk for cognitive impairment almost 4-fold while, eating green vegetables reduced the risk by almost 20%. Education, but not gender or age reduced the risk independently.

10 CHAPTER 10 DISCUSSION

10.1 The optimal HVLT cut-off scores in differentiating dementia and MCI cases from NCI

Both the HVLT and the MMSE revealed excellent discriminant ability in differentiating MCI cases from NCI. Applying a MMSE cut-off score of 27/28, a 79.3% correct classification was obtained (sensitivity 82.9%, specificity 78.7%). With a HVLT cut-off score of 19/20 for IR, a slightly higher correct classification rate of 81.1% was achieved (sensitivity 87.8%, specificity 79.8%). After applying a gender, age and educational stratification, a larger discrepancy on the MMSE cut-off scores were seen compared to the HVLT, indicating that the HVLT is more independent of the influence of demographic factors.

With regards of the discriminant ability of both tests in distinguishing dementia cases from NCI, a MMSE cut-off score of 23/24 rendered 97% sensitivity and 96.8% specificity, with a correct classification rate of 96.8%, whist 90.9% sensitivity and 93.8% specificity accompanied a HVLT cut-off score of 13/14 (correct classification 93.6%). After age, gender and education stratification, an up-to 12 points discrepancy on the MMSE cut-off scores was seen between less educated (no or primary level of education) and more educated (beyond primary level of education) subjects (13/14 vs. 25/26), whereas only a 4-point difference was seen on the HVLT (9/10 vs. 13/14). This indicates that the HVLT is culturally applicable across different ethnicities and not as affected as the MMSE by education.

It has been widely known that the MMSE may be biased against demographic variables such as age, education and ethnicity (Brown. 2003; Marcoulos, 2003; Anderson, 2007; Moraes, 2010), whereas the HVLT is less- or not- affected (Hogervorst, 2002). Other advantages of the HVLT have also been summarized in various studies, i.e. it has no ceiling effect comparing to the MMSE (Hogervorst, 2002) and allows repeating testing within a short period of time (Krebs, 1994).

Results from the present study are consistent with previous studies done in Oxford, United Kingdom in a community-dwelling elderly population (Hogervorst, 2002) where a HVLT cut-off score of 14/15, a MMSE cut-off score of 24/25 rendered the optimal balance between sensitivity and specificity in detecting dementia from controls.

Furthermore, comparing the current HVLT cut-off scores with another study previously been conducted in China (Shi, 2012), the HVLT cut-off scores were 2 points lower than theirs in differentiating dementia and MCI cases from controls. In this study, A HVLT cut-off score of 15/16 and 21/22 was applied to distinguish between dementia and MCI patients and controls, respectively. After applying an age stratification (50-64 age group vs. 65-80 age group), a 4-point difference for age adjusted HVLT cut-off scores was reported (18/19 vs. 14/15). Similarly, an age split was also performed in the present study. However, as there was no dementia case in the 65 years and younger age group, no valid HVLT cut-off score was obtained. When comparing the 65-80 age group, our HVLT cut-off is 2 points higher than theirs (16/17 vs. 14/15).

This may be due to the study setting difference. As participants in Shi's study were drawn from a memory clinic setting, a large dementia base rate was seen as expected (40.9% in Shi's study vs. 6.4% in the present study). In addition, the mean ages among control, MCI, and dementia cases are more equivalent with a small gap (67, 70 and 71 respectively), whereas in our study, the mean age of NCI group was roughly 6 years younger than the MCI group (66 and 71 years of age respectively), and 15 years younger than dementia group (80 years of age).

One limitation of the present study is that the sample size of dementia cases is small, because of its setting (community base). Thus its generalization ability to clinical utility is limited. In addition, there is no younger dementia case (less or equal than 65 years of age) in our study, resulting in no applicable HVLT and MMSE age adjusted cut-off scores for this group.

The main implication of the present study is that further studies need to be done to investigate the specific age adjusted HVLT cut-off scores in Asian population and to compare these with Western-based studies to verify its cross-cultural feasibility.

10.2 Frailty prevalence in community-dwelling elderly population and its association with dementia

10.2.1 Prevalence of frailty in community-dwelling elderly population

Accompanying an ageing population, there is a globally growing concern about frailty. This term has been known for decades, yet still remains lacking a consensus definition and solid diagnostic criteria (Abellan, 2008).

Frailty, as a clinical entity of ageing syndromes, should be differentiated from the normal ageing process. According to Collard (2012), the prevalence of frailty in the community ranged from 4.0% (Cawthon, 2007) to 59.1% (Metzelthin, 2010) with a substantial variation. This is due to the varied definition of frailty. In addition, age and gender were also considered as important risk factors for frailty. Frailty rate increased gradually with an advanced age, from 4% in the 65-69 age group, to 26% in the 85 and above age group (Clegg, 2013). Furthermore, higher prevalence of frailty was found in females comparing to males (9.6% vs. 5.2%) (Collard, 2012; Clegg, 2013).

Currently, most of the research projects on frailty are conducted in Western countries including America, Canada European and Australia (Strawbridge, 1998; Fried, 2001; Cawthon, 2007; Avila-Funes, 2008; Santos-Eggiman, 2009; Metzelthin, 2010; Song, 2010; Wong, 2010), with a very limited numbers of studies having been conducted in Asian areas (Chen, 2010). Therefore it is essential that more results from the Asia population investigating the prevalence of frailty are discussed and compared.

In the present study, 14.3% of the whole sample fulfilled all the frailty characteristics which includes low BMI (<21 kg/m^2), weak grip strength (measured by grip strength, lowest quintile adjusted for gender), slowness and poor endurance (measured by 15-feet gait speed and TUG test, adjusted for gender), poor balance (measured by Berg balance test, adjusted for gender), and low levels of physical activity (exercise less than once per week). This percentage is higher comparing to the only existed Asian community- based study in which a frailty rate of 4.9% using Fried Frailty

Index (FFI) was reported (Chen, 2010). This rate is also higher than the figure from Fried's study (of 6.9%, Fried, 2001), nevertheless significantly smaller than another study in European using the FFI (Santos-Eggiman, 2009). However, the pre-frailty rate in Chen's study and Fried's study is also similar to our results (40%, 46.6% and 43.5% respectively).

However when comparing to the Western-based studies, the rates of frailty in our study and Chen's study are at the lowest percentile among all 21 studies presented in Collard's report (2012). Frailty rates ranged from 6.5% in Italy (Ble, 2006) to 59.1% in the Netherlands (Metzelthin, 2010) in studies from European countries. In America, frailty rates varied from 4.2% (Kiely, 2009) to 44% (Ma, 2009). In Canada, the rate ranged from 5.3% (Gutman, 2001) to 22.7% (Song, 2010) and in Australia from 9.4% and 15.2% as was reported in Blyth's (2008) and Hyde's (2010) studies. The reason for this wide variation in prevalence rates is not entirely clear, i.e. whether there is any ethnic difference in frailty phenotypes and the applicability of the frailty indicators as developed by Fried (2001).

10.2.2 Association between frailty and cognitive impairment

It has been widely reported that cognitive impairment is associated with frailty (Avila-Funes, 2009; Mitnitski, 2011; Kulmala, 2013). Furthermore, it is reported that frail persons are at high risk of developing dementia, hence poor cognition can assist in predicting the phenotype of frailty (Avila-Funes, 2009). Being frail with cognitive impairment increased the risk of developing dementia by almost 5 times compared to being frail without cognitive impairment (OR=4.98, 95% CI=2.17-11.41 vs. OR=0.74, 95% CI=0.27-2.07) (Avila-Funes, 2009). Furthermore, Kulmala (2013) suggested that cognition impairment should be considered to be included in the definition of frailty.

The present study explored various predictors of cognitive impairment and frailty and found an association between them. By applying PFA, all physical and psychological predictors were categorized into different groups, together to form the different phenotypes of cognitive impairment and frailty. Where those with cognitive impairment were the largest groups, those with purely physical frailty were less common. However, their phenotypes (less fitness, balance problems) could also lead to cognitive impairment due to reduced levels of exercise and an increased risk of falls.

From table 26 and table 33 we can see that people who perform worse on the physical tests risk of frailty are also at risk of CI. This group of people can be described as: age above 79 years, education equal or less than primary level, having poor balance (scored less than 52), a lower score on the TUG test (<12.5) and 15 feet gait speed test (<4.4).

The discrepancy on the grip strength assessment as a predictor for cognitive impairment or frailty is evident in our two studies. In a community-based study conducted in UK (Syddall, 2003), grip strength was proven to be a strongly marker that could independently predict frailty. In the present study, by applying a backward conditional logistic regression, grip strength less than 6.6 kg significantly predicted frailty, independent of all the other indicators ($p<0.001$), correctly classified 79.3% of the whole sample (OR=7.6, 95% CI=3.4-17.3). Others found grip strength to be a strong

predictor of dementia. In contrast, the ability of grip strength in our studies to predict CI was less. Grip strength less than 11.8 was only a marginally significant predictor (p=0.07) for cognitive impairment, whilst there were also other more significant markers, such as the MMSE (p<0.001), HVLT IR score (p=0.005), and low education (p=0.002) (correct classification 93.8%).

The MMSE has been widely used to predict frailty, in addition to the other commonly used physical indicators mentioned above, such as grip strength, TUG, 15 feet gait and balance. The MMSE cut-off score for frailty is 3 points lower than for CI (22 vs. 25). A MMSE cut-off score of 25 for CI is consistent with our earlier results from the Shanghai 2011 project (see chapter 6, section 6.2.2, table 15) and another community-based study in Finland (Kulmala, 2013). However, the MMSE cut-off score for frailty in the present study is lower than the result from another community-based study in France (Avila-Funes, 2009). In this study, the MMSE mean score for the frail group was 26.9, which is at less than 1-point difference compared to the non-frail group (27.5). In another longitudinal study in Jerusalem (Jacobs, 2011), CI as measured by the MMSE (cut-off score of ≤ 24) was strongly associated with being frailty (OR=3.77 (95% CI=1.42-9.99). However in the present study, the MMSE did not independently predict frailty (p=0.15).

In contrast, a 3-point lower HVLT IR cut-off score, and a 2-point HVLT DR cut-off score were revealed in predicting CI compared to frailty (15 vs. 18 and 5 vs. 7, respectively). The HVLT is not commonly used in adjunction with other measures to predict frailty, as the association between frailty and poor memory has not been reported before. The present study included the memory domain in predicting frailty as a first attempt. The logistic regression was conducted and the HVLT IR and DR scores did not independently predict frailty. Nevertheless, after combining three cognitive indicators together (MMSE score <22, HVLT IR score <18 and HVLT DR score <7) as individual cognitive markers, this significantly predicted frailty (OR=2.8, 95% CI= 0.43-8.46, p=0.003).

Although there is evidence that cognitive impairment is strongly associated with frailty, it remains unclear whether poor memory is a significant single marker for frailty. From our current results, the HVLT needs to be used in conjunction with other cognitive measures (e.g. MMSE) in order to achieve better frailty predictive ability. Therefore further studies need to be done to investigate the role of memory in frailty.

10.3 Direct adverse consequences and long term health outcomes, and possible intervention methods of frailty

Figure 21. Schema for indicators of frailty

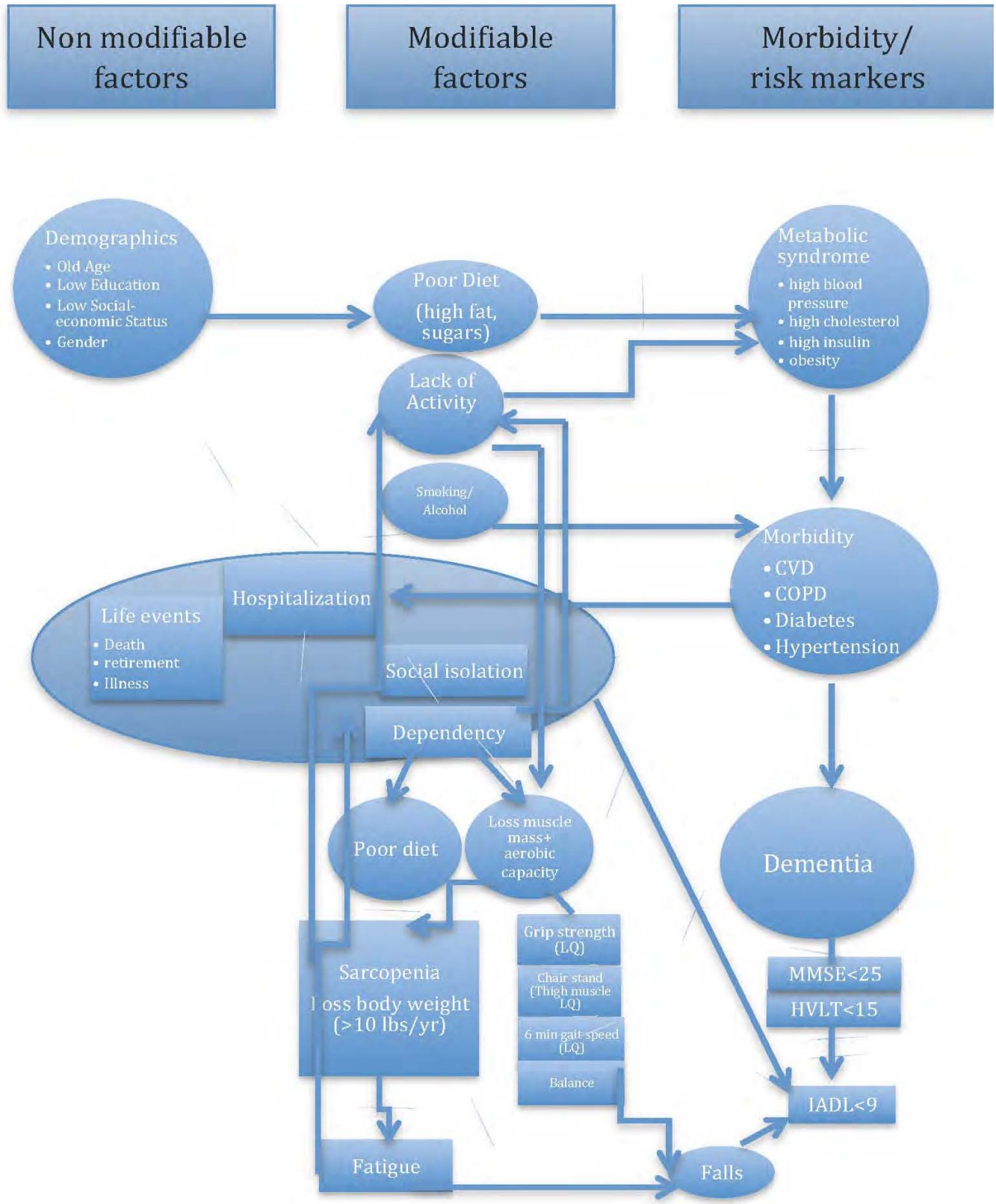


Figure 22. Significant predictors from the present study, direct adverse consequences, long term adverse health outcomes, possible intervention methods for 3 different frailty phenotype

Frailty is thought to be a common condition in the elderly and it may be considered as a state of high vulnerability preceding the onset of overt disability. After investigating key symptoms and risk factors for frailty, it is mandatory for us to develop a rehabilitation program for the elderly subjects at high risk and reduce the risk for morbidity and disability.

Exercise has been implicated as effective for improving cognitive functioning in older adults, yet the results are inconsistent as little or no overall cognitive effect was seen in Clifford's review (2009) which suggests that moderating or mediating factors are involved in this process. Furthermore, other studies highlighted the protective role of regular physical activity in reducing the risk of cognitive impairment and dementia. Most prospective intervention studies of exercise and cognitive function focused on aerobic-based exercise training by highlighting that aerobic-based exercise training enhances both brain structure and function (Kramer, 1999; Fabre, 2002; Colcombe, 2003; Heyn, 2004). They suggested that long-term moderate-intensity aerobic exercise could reliably reverse age-related cognitive impairment. They also found out that some specific aerobic exercises have great positive influence on cognitive and brain function. The effect of aerobic exercise training was considered to be on central- rather than on peripheral -function by promoting increased cerebral metabolic activity (Dustman, 1984).

Loss of strength is also strongly associated with falls among older people, thus prompting the investigation of muscle weakness as a contributor to disability and hospitalization in frail elderly. Fried (2001) defined frailty as a physiological syndrome characterized by decreased reserve and resistance to stressors. However, muscle strength could be improved in older people especially when their muscles are significantly overloaded by training exercises (Charette, 1991). Fiatarone (1994) was the first one who reported a remarkable exercise effect on functional ability in frail elderly, recommending high-intensity resistance exercise training as a feasible and effective means to contradict muscle weakness and physical frailty in elderly.

Progressive resistance training (PRT) is defined as a strength-training program in which participants exercised their muscles against an external force that was set at a specific intensity for each participant, and this resistance was adjusted throughout the training programme. Consistent evidence has accumulated to show that PRT has a broad range of benefits for older adults (Borst, 2004; Layne, 1999; Trappe, 1999), including reduce physical frailty and a delay of physical dependence. It is widely accepted as an appropriate modality for treating sarcopenia and muscle weakness which are amenable for improvement. Some studies reported that resistance training may prevent both physical and cognitive impairment among older people (Liu-Ambrose, 2012).

Yoga is an ancient Indian science and way of life that has been described as a training process in awareness, produces definite changes in perception, attention and cognition. As a part of the mind-body therapy, yoga was reported by an increasing number of empirical studies for its treatment of mental disorders, such as depression and anxiety (Chan, 2009). Ross (2010) suggested that yoga is effective at improving a variety of health-related outcome measures. In addition, some studies reported an improvement of attention after yoga practise in patients with multiple sclerosis (Velikonja, 2010; Prakash, 2011). However, there are other authors suggested that yoga exercise failed to produce any cognitive improvement. Oken (2006a, 2006b) reported no relative improvements of cognitive function among healthy seniors in the yoga, but those in the yoga group showed significant improvement in fatigue and quality of life. Also because of its effect in improving balance it may reduce the risk for falls which by itself increases the risk for dementia. As such, yoga might be good treatment for our balance phenotype to prevent disability and dependence.

10.4 Association between tofu consumption with cognitive function among elderly

In the present study, higher intake of tofu was negatively associated with immediate memory performance on the HVLT. Furthermore, among elderly who were 68 years of age or older, tofu intake was a significant risk factor which increased the risk of cognitive impairment, independent of the other covariates, including demographic variables and other dietary habits. Similar results could be found in another earlier study conducted in Indonesia, where high tofu intake was associated with poor memory using the same test (Hogervorst, 2008). The authors also reported that tempe intake, a fermented whole soybean food was significantly related to better memory (Hogervorst, 2008; Hogervorst, 2011). However, tempe is not a popular type of food in China and only very limited number of participants reported to eat tempe (5 out of 521, less than 1% of the whole sample), hence consumption of tempe was not included in the current analyses. Tempe, similar to green vegetables, contains folate which reduces homocysteine, a risk factor for dementia and cognitive decline (Smith, 2008). Not being vegetarian, e.g. eating meat in elderly was associated with a four-fold increase in risk of dementia. Earlier studies noted that meat eaters had a doubled risk of dementia (Giem, 1993). This may be because meat contains saturated fats, which is a risk factors for cardiovascular disease, and risk factors for cardiovascular disease are risk factors for dementia (Hogervorst, 2012). However, meat also contains cobalamin which can further help reduce homocysteine levels (Smith, 2008). This means that a well-balanced diet with little protein, such as tofu and meats, but plenty of vegetables are probably best suited for elderly to prevent dementia. On the other hand in Indonesia, high green vegetable consumption was associated with increased dementia risk (Hogervorst, 2008), which was possibly due to pollution and heavy use of pesticides. Hence, moderation of overall food intake is probably best advised, similar to earlier advice regarding the consumption of fatty (polluted) fish.

There were several limitations to the current study. Firstly, the results from the current study may have limited representativeness. One of these the overall poor socioeconomic status (SES) of the cohort investigated (the current sample was drawn from a relatively underdeveloped area in Shanghai, China). SES, however, was not different for those with cognitive impairment and those without. Because the present study was conducted in a cross-sectional community setting, it is not possible to examine whether elderly who eat more tofu actually deteriorated cognitively. A follow-up study thus needs to be performed, In addition, the current sample was constituted of Chinese elderly only. Therefore results might not apply to Western countries as several earlier studies did not find these types of associations in non-Asian populations. Lastly, it may well be that lower quantities of tofu consumption do not lead to cognitive impairment and an optimal dosage needs to be investigated to maintain optimal health and cognitive function in the elderly. Our graphs in China and Indonesia did not suggest optimal intakes of tofu for elderly, although for those of middle-age optimal levels of genistein associated with better cognitive function were detected in Indonesia (Hogervorst, 2009). This may be associated with its estrogenic effects on brain function, which may be positive in middle-aged people but which may worsen pathology in the old. In sum, further research needs to investigate whether tofu really is associated with worse cognitive function and increased risk for dementia in those over 68 years of age and whether a balanced diet and exercise particularly in midlife can affect this risk in later life (Clifford, 2009)

11 CHAPTER 11 CONCLUSION AND FUTURE IMPLICATIONS

In conclusion, before age, gender and educational stratification, the HVLT is equivalent to the MMSE in distinguishing MCI and dementia from NCI in a community-based sample in China. To differentiate between NCI and MCI, applying a cut-off score of 19/20 on the HVLT IR recall, 87.8% SE and 79.8% SP was obtained, comparing to slightly lower SE (82.9%) and SP (78.8%) accompanying with a MMSE cut-off score of 27/28. To detect dementia from NCI, a HVLT IR cut-off score of 13/14 rendered 90.9% SE and 93.8% SP, whereas a MMSE cut-off score of 23/24 obtained 97.0% SE and 96.8% SP.

However, after stratification, the HVLT indicated having superior psychometric properties compared to the MMSE. The HVLT is less or not influenced by gender and educational level (no or primary level of education vs. secondary and above level of education), compared to the MMSE which is more affected by these 2 factors. Both the HVLT and the MMSE are affected by the impact of age, when differentiating between dementia and NCI as the cut-off scores for both tests decreased with increasing age. In addition, to detect dementia from not dementia cases in an institutionalized sample, the cut-off scores of the HVLT and the MMSE both drop 3 points, due to the study setting difference (10/11 for the HVLT and 20/21 for the MMSE).

Furthermore, when applying physical, psychological and demographic indicators to build up different patterns of cognitive impairment (CI, including both MCI and dementia) and functional disability (as defined by failing at least one task on either the ADL or IADL test), 4 components for CI and frailty (cognitive impaired +physically limitations; cognitive impairment only; physical limitations-fitness; and physical limitations-balance) as well as 3 components for functional disability (cognitive impairment, physical limitations-lower body; and physical limitations-upper body) were identified. Subsequently, a phenotype of frailty was formed by combining potential frailty characteristic together (adjusted for gender).

To predict cognitive impairment (defined as a HVLT IR score ≤19), demographic risk factors, such as an advanced age and lower education (no or primary level) increase the risk of being cognitive impaired.

Lifestyle risk factors were also investigated. The most stable and significant risk factors after controlling for covariates to predict cognitive impairment were dietary habits (lower green vegetables intake and higher tofu intake).

The largest limitation of the current studies is that the sample size is relatively small, especially for the frailty project (n=170). Thus the results may be of limited generalization ability for other community-based studies. Secondly, two of the studies are community-based. Therefore the results may not apply to other settings (e.g. clinical settings). However, we did also have data from a clinical setting.

It is explicit from our data that frailty is strongly associated with functional disability and cognitive impairment as these three deficits overlap each other largely.

Moving forward, it is suggested that the utility of the HVLT should be applied in the communities in China as a screen tool for dementia. Additionally, the association of frailty, functional disability and cognitive impairment needs to be further explored in future studies with larger sample size, ideally with more analysable follow-up data in Asian countries to investigate the predictability of frailty in detecting disability, co-morbidity, and mortality.

Finally, as there is few research examining the intervention of physical and nutritional (soy product intake) on frailty in Asian countries, it is strongly suggested that potential physical and nutritional intervention for frailty needs to be investigated among elderly people, especially in Asian countries, to examine its long-term effect on frailty, on both functional and cognitive dimensions.

12 REFERENCES

Abellan van Kan, G (2009). Epidemiology and consequences of sarcopenia
The journal of nutrition, health & aging, 13 (8): 708.

American Geriatrics Society, British Geriatrics Society, and American Academy of Orthopaedic Surgeons Panel of Falls Prevention (2001). Guidelines for the prevention of falls in older persons. J Am Geriatr Soc.49:664-672.

Avila-Funes JA, Pina-Escudero SD, Aguilar-Navarro S, Gutierrez-Robledo LM, Ruiz-Arregui L, Amieva H. Cognitive impairment and low physical activity are the components of frailty more strongly associated with disability. J Nutr Health Aging 2011; 15(8):683-689.

Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, et al (2007). Dietary patterns and risk of dementia: the Three-City cohort study. Neurology, 69: 1921–1930.

Basaria S, Wisniewski A, Dupree K, et al (2009). Effect of high-dose isoflavones on cog-nition, quality of life, androgens, and lipoprotein in post-menopausal women.J Endocrinol Invest,32:150–5.

Blyth FM, Rochat S, Cumming RG, Creasey H, Handelsman DJ, Le Couteur DG, Naganathan V, Sambrook PN, Seibel MJ, Waite LM. Pain, frailty and Comorbidity on older men: the CHAMP study. Pain 2008; 140:224–30.

Borst, SE. (2004). Interventions for sarcopenia and muscle weakness in older people. Age Ageing 33, 548–555.

Casini ML, Marelli G, Papaleo E, Ferrari A, D'Ambrosio F, Unfer V (2006). Psychological assessment of the effects of treatment with phytoestrogens on postmenopausal women: a randomized, double-blind, crossover, placebo-controlled study. Fer-til Steril, 85:972–8.

Cawthon PM, Marshall LM, Michael Y, et al; Osteoporotic Fractures in Men Research Group. Frailty in older men: prevalence, progression, and relationship with mortality. J Am Geriatr Soc. 2007; 55(8):1216-1223

Clifford A, Yesufu UA, Edwards A, Bandelow S & Hogervorst E (2009).Maintaining cognitive health in elderly women: an invited review. Aging Health, 5: 655–670.

Chan D. and Woollacott M. (2007). Effects of level of meditation experience on attentional focus: is the efficiency of executive or orientation networks improved? Journal of Alternative and Complementary Medicine, 13 (6): 651–657.

Charette, S. L., L. McEvoy, G. Pyka, et al (1991). Muscle hypertrophy response to resistance training in older women. J. Appl. Physiol. 70:1912-1916.

Chen CY, Wu SC, Chen LJ, Lue BH. The prevalence of subjective frailty and factors associated with frailty in Taiwan. Arch Gerontol Geriatr 2010, 50:S43–7

Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. (2013). Frailty in elderly people. Lancet, 381: 752–62

Colcombe, S., Kramer, A.F., 2003. Fitness effects on the cognitive function of older adults: a meta-analytic study. Psychol. Sci. 14, (2), 125–130.

Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. (2012). Prevalence of frailty in community-dwelling older persons: a systematic review, J Am Geriatr Soc, 60: 1487-1492.

De Jager C. A., Hogervorst E., Combrink M. and Budge M. M. (2003). Sensitivity and specificity of neuropsychological tests for mild cognitive impairment, vascular cognitive impairment and Alzheimer's disease. Psychological Medicine, pp 1039-1050.

Duffy R, Wiseman H, File SE (2003). Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. Pharmacol Biochem Behav, 75:721–9.

Dustman RE, Ruhling RO, Russell RM, et al. (1984). Aerobic exercise training and improved neuropsychological function of older individuals. Neurobiol Aging, 5:35–42.

Fabre, C, Chamari, K, Mucci, P, Masse-Biron, J, Prefaut, C., (2002). Improvement of cognitive function by mental and/or individualized aerobic training in healthy elderly subjects. Int. J. Sports Med. 23, 415–421.

Fiatarone MA, O'Neill EF, Ryan ND, et al. (1994). Exercise training and nutritional supplementation for physical frailty in very elderly people. N. Engl J Med, 330:1769–1775.

Fournier LR, Ryan Borchers TA, Robison LM (2007). The effects of soy milk and isoflavone supplements on cognitive performance in healthy, postmenopausal women. J Nutr Health Ageing, 11: 155–64.

Frankenfeld CL, Lampe JW, Shannon J, Gao DL, Ray RM, Prunty J, et al (2004). Frequency of soy food consumption and serum isoflavone concentrations among Chinese women inShanghai. Public Health Nutr, 7: 765–772.

Franco OH, Burger H, Lebrun CE, et al (2005). Higher dietary intake of lignans is asso-ciated with better cognitive performance in postmenopausal women. J Nutr;135:1190–5.

Fried LP, Tangen CM, Walston J et al (2001). Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci; 56A:146–156.

Gao L, Dong B, Qiu KH, Xiang D (2013). Association between cognitive impairment and eating habits in elderly Chinese subjects over 90 years of age. Journal of International Medical Research, 41: 1362-1369.

Giem P, Beeson WL, Fraser GE (1993). The incidence of dementia and intake of animal products: preliminary findings from the adventist health study. Neuroepidemiology, 12:28-36.

Gleason CC, Carlsson J. Barnet et al (2009). A preliminary study of the safety: feasibility and cognitive efficacy of soy isoflavone supplements in older men and women. Age and ageing, 38(1):86–93.

Greendale G, Huang M, Leung K, et al (2012). Dietary phytoestrogen intakes and cognitive function during the menopause transition: results from the SWAN phytoestrogen study. Menopause, 19(8):894–903.

Gutman GM, Stark A, Donald A, Beattie BL (2001). Contribution of self-reported health ratings to predicting frailty, institutionalization, and death over a 5-year period. Int Psychogeriatr, 13(1): 223-231.

Henderson VW, St John JA, Hodis HN, et al (2012). Long-term soy isoflavone supple-mentation and cognition in women: a randomized, controlled trial. Neurology, 78(23):1841-8.

Heyn PC, Abreu BC, Ottenbacher KJ. (2004). the effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis. Arch Phys Med Rehabil 85:1694–1704.

Ho SC, Chan AS, Ho YP, et al (2007). Effects of soy isoflavone supplementation on cognitive function in Chinese postmenopausal women: a double-blind, randomized, controlled trial. Menopause, 14:489–99.

Hogervorst E, Sadjimim T, Yesufu A, Kreager P, Rahardjo TB (2008). High tofu intake is associated with worse memory in elderly Indonesian men and women. Dement Geriatr Cogn Disord, 26(1):56–7.

Hogervorst E, Kushandy L, Angrianni W (2009). Different forms of soy processing may determine the positive or negative impact on cognitive function of Indonesian elderly. In: Hogervorst, Henderson, Gibbs, Brinton RD, editors. In: Hormones,Cognition and Dementia. Edinburgh: Cambridge University Press; p.121–32.

Hogervorst E, Mursjid F, Priandini D (2011). Borobudur revisited: soy consumption may be associated with better recall in younger, but not in older, rural Indonesian elderly. Brain Re, 1379:206–12.

Hogervorst E, Clifford A, Stock J, Xin X, Bandelow S (2012). Exercise to prevent cognitive decline and Alzheimer's disease: for whom, when, what and (most importantly) how much? J Alzheimers Dis Parkinsonism, 2:e117. doi:10.4172 /2161-0460.1000e117.

Hyde Z, Flicker l, almeida OP, Hankey GJ, McCaul Ka, Chubb SA, yeap BB (2010) Low free testosterone predicts frailty in older men: the Health in Men study. J Clin endocrinol Metab; 95:3165-72.

Kiely DK, Cupples LA, Lipsitz LA (2009). Validation and comparison of two frailty indexes: The MOBILIZE Boston Study. J Am Geriatr Soc; 57:1532–1539.

Kramer, A.F., Hahn, S., Cohen, N.J., Banich, M.T., McAuley, E., Harrison, C.R., Chason, J., Vakil, E., Bardell, L., Boileau, R.A., Colcombe, A. (1999). Ageing, fitness and neurocognitive function. Nature 400, 418–419.

Kreijkamp-Kaspers S, Kok L, Grobbee DE, et al (2007). Dietary phytoestrogen intake and cognitive function in older women. J Gerontol A-Biol, 62:556–62.

Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, Bressel MAB (2003). Isoflavones and cognitive function in older women: the Soy and Postmenopausal Health in Aging (SOPHIA) Study. Menopause, 1: 0–19, 6.

Jacobs JM, Cohen A, Ein-Mor E, Maaravi Y, Stessman J. (2011). Frailty, cognitive impairment and mortality among the oldest old. J Nutr Health Aging; 15(8):678-682.

Layne, J.E., Nelson, M.E. (1999). The effects of progressive resistance training on bone density: a review. Med. Sci. Sports Exerc. 31, 25–30.

Liu-Ambrose T, Khan KM, Eng JJ, et al. (2004). Resistance and agility training reduce fall risk in women aged 75 to 85 with low bone mass: a 6-month randomized, controlled trial. J Am Geriatr Soc; 52:657-65.

Maki PM, Dennerstein L, ClarkM. Guthrie J, Lamontagne P, Fornelli D, et al (2011). Premenopausal use of hormone therapy is associated with enhanced memory and hippocampal function later in life. Brain Re, 1379:232–43.

Ma SL, Oyler J, Glavin S, et al (2009). Self-reported frailty is associated with low calcaneal bone mineral density in a multiracial population of community dwelling elderly. Osteoporos Int, 20:1837–1846.

Metzelthin SF, Daniels R, vanRossum E, et al. (2010). The psychometric properties of three self-report screening instruments for identifying frail older people in the community. BMC Public Health, 10:176.

Mitiniski A, Nader F AND Rockwood K (2011). A Multistate Model of Cognitive Dynamics in Relation to Frailty in Older Adults. Ann Epidemiol, 21: 507–516.

Oken BS, Zajdel D., Kishiyama S., Flegal K., Dehen C., Haas M., Kraemer DF., Lawrence J. & Leyva J. (2006) Randomized, controlled, six-month trial of yoga in healthy seniors: effects on cognition and quality of life. Alternative Therapies in Health and Medicine 12: 40–47.

Podsiadlo D, Richardson S (1991). Division of Geriatrics, Royal Victoria Hospital, McGill University, Montreal, Quebec, Canada. Journal of the American Geriatrics Society, 39(2):142-148.

Prakash, R.S., Patterson, B., Jannssen, A., Abduljalil, A., Boster, A. (2011). Physical activity associated with increased resting-state functional connectivity in multiple sclerosis. Journal of the International Neuropsychological Society, 17: 986–97.

Rice MM, Graves AB, McCurry SM, et al (1999). Third international symposium on therole of soy in preventing and treating chronic disease, Washington, DC, Oct31–Nov 3,130: 676.

Ross A. and Thomas S. (2010). The health benefits of yoga and exercise: a review of comparison studies. Journal of Alternative and Complementary Medicine, 16 (1): 3–12.

Santos-Eggimann B, Cuenoud P, Spagnoli J, et al. (2009). Prevalence of frailty in middle- aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci; 64A:675–681.

Shumway-Cook A, Brauer S, Woollacott M (2000). Predicting the probability for falls in community-dwelling older adults using the Timed Up & Go Test. Phys Ther, 80:896-903.

Smith AD. (2008). The worldwide challenge of the dementias: a role for B vitamins and homocysteine? Food Nutr Bull 29: S143-172.

Song X, Mitnitski A, Rockwood K. (2010). Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. J Am Geriatr Soc, 58:681–687.

Soni M, Rahardjo TBW, Soekardi R, Sulistyowati Y, L, Yesufu-Udechuku A, Irsan A, Hogervorst E (2014). Phytoestrogens and cognitive function: a review. Maturitas, 77 (3): 209–220.

Syddall H, Cooper C, Martin F, Briggs R, Sayer AA (2003). Is grip strength a useful single marker of frailty? Age Ageing, 32: 650-656.

Thorp A, Sinn N, Buckley J, et al (2009). Soya isoflavone supplementation enhances spatial working memory in men. Brit J Nutr, 102(9):1348–54.

Trappe S., Williamson, D., Godard, M. (2002). Maintenance of whole muscle strength and size following resistance training in older men. J. Gerontol. A Biol. Sci. Med. Sci. 57, B138–B143.

Velikonja O, Curic K, Ozura A, Jazbec SS (2010). Influence of sports climbing and yoga on spasticity, cognitive function, mood and fatigue in patients with multiple sclerosis. Clin Neurol Neurosurg, 112:597-601.

White LR, Petrovitch H, Ross GW, et al (2000). Brain aging and midlife tofu consumption. J Am Coll Nutr, 19:242–55.

Wong C, Weiss D, Sourial N et al. Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: a cross-sectional study. Aging Clin Exp Res 2009. In press.

Yesufu, A., Rahardjo, T-B, Hogervorst, E. (2011). Soy, Tofu and Brain Function in the Elderly. In: theInternational Handbook of Behavior, Diet and Nutrition. Springer-Verlag: London.

APPENDICES

Appendix 1. Test package for Shanghai 2011 project (English Version)

HOPKINS VERBAL LEARNING TEST VERSION A (we have this version in our test battery as well where the words are presented verbally. The recognition component can also be programmed for a reaction time and % correct response.

Instructions for face to face testing:

Trial 1:
'Listen carefully while I read a list of words. Try your very best to memorize as many of these words as you can. When I stop, you are to say back as many of the words as you can, in any order that you wish. Ready?' Read the words at the rate of one word every 2 seconds (1 sec between words). After reading the entire list to the patient, have the patient recall them. Check off the words the patient recalls on the form. If a word is said that is not in the list, write that word on the form but say nothing to the patient about the word not being on the list. If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words. If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

Trial 2:
'That was a good beginning. Now, I'm going to read the same list again. When I stop, I want you to tell me as many words as you can remember; including the words you said the first time. It does not matter in what order you say them. Just say as many words as you can remember whether or not you said them before. Ready?' Read the words at the rate of one word every 2 seconds. Then have the patient recall them. Check off the words that the patient recalls on the form. If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words. If not, move on to trial 3. Later, record the number of words that were correctly repeated on the summary form.

Trial 3:
'Very good. I'm going to read the list again. Again, listen carefully and try to remember as many words as you can whether or not you said them before. Ready?' Continue to follow recording procedures from trials 1 & 2. Note that each *learning* and recall trial should last about 1 minute.

Delayed recall.

For researcher: This part is asked after all tests are done. Do not read the list again. Check the words the patient recalls.

<u>Delayed Recall (D)</u> PART IS ON THE LAST PAGE

Words to Mention		**Trial 1**		**Trial 2**		**Trial 3**	
		Correct (√)	**Incorrect word**	**Correct (√)**	**Incorrect word**	**Correct (√)**	**Incorrect word**
1	Lion						
2	Emerald						
3	Horse						
4	Tent						
5	Sapphire						
6	Hotel						
7	Cave						
8	Opal						
9	Tiger						
10	Pearl						
11	Cow						
12	Hut						
	TOTAL						

Refused to attempt word list recall Total recall (0 to 36)

MINI MENTAL STATE EXAMINATION (MMSE)
is available online
http://ncemi.org/shared/etools_c/etools_c.pl?cmd=run&resource_fn=edecision_mini_mental_status_exam.xml

Respondent's Name	:	Interviewer Name	:
Respondent's Age	:	Interview Date	:
Education	:	Finish Time	:

Max. Score | Elderly

F4.1 Orientation

5 ( ) What is the (day) (date) (month) (year) (season)?

5 ( ) Where are we: (street) (house number) (town) (village) (province)?

F4.2 Registration

3 ( ) Interviewer name 3 objects: 1 second to say each. Then ask the respondent to repeat all 3 after you have said them. Give 1 point for each correct answer. If still incorrect, repeat them until he learns all 3. Count trials and record (**House – Child – Rice**).
Trials _____

F4.3 Attention and Calculation

5 ( ) Ask the subject to begin with 20 and count backwards by 3. Give 1 score for each correct answer. Stop after five subtractions (20, 17, 14, 11, 8, 5, 2). Other alternative is to spell the word "world" backwards (d-l-r-o-w).

For Illiterate Respondents:
Ask respondent to name days in week from first day (Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday). Then ask respondent to name it backwards (Sunday, Saturday, Friday, Thursday, Wednesday, Tuesday, Monday).

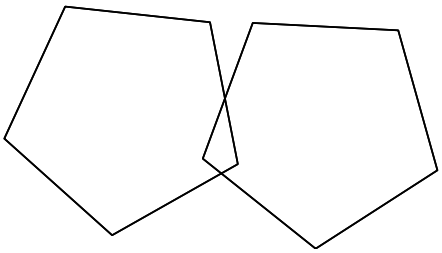
F4.4 Recall

3 ( ) Ask for the three words you previously asked him to remember. One point for each correctly recalled

F4.5 Language

9 ( )
a. What is the name of these things? (Show 2 things, e.g. pencil and wrist watch) .....(2 points)
b. Repeat the following sentence: If not, and or but' ..... (1 point)
c. Follow a 3 stage command: ..... . (3 points)
- Take this paper in your right hand,
- fold it in half and
- put it on the floor.

d. Read and obey the following: "Close your eyes" ..... (1 point)
   If illiterate just say „Close your eyes"
e. Write a sentence ..... (1 point)
   If illiterate ask to draw a house
f. Copy the following drawing ..... (1 point)



Total Score ( ) Mark elderly respondent level of consciousness on the line below with an x:

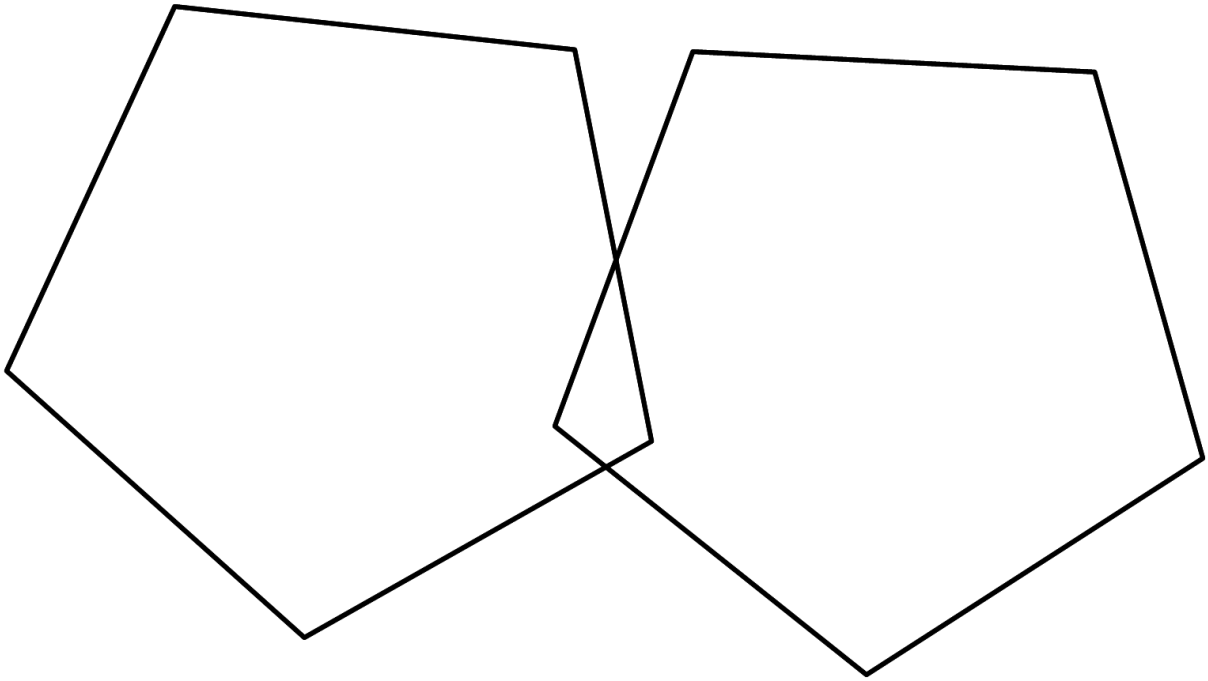
Fully conscious Somnolent Stupor Coma

24 or less : High likelihood of dementia
25 – 30 : Normal aging or borderline dementia

Finish time:
Interview place:

Observation Column: Record condition during interview (respondent conditions, respondent reactions to questions or instructions).

Show this drawing, and then ask respondent to close her/his eyes then open and copy this drawing.



Close Your Eyes

HOPKINS VERBAL LEARNING TEST VERSION A (Part D)

For researcher: This part is asked after all other tests are done by respondent/participant. Do not read the list again. Check each word that the patient recall, record all incorrect words on the form.

Tell the patient, **'I read you a list of words and you practiced remembering the words. Now tell me as many words as you remember.'**

	Words to recall	Correct (√)	Record all words not on the original list
1	Lion		
2	Emerald		
3	Horse		
4	Tent		
5	Sapphire		
6	Hotel		
7	Cave		
8	Opal		
9	Tiger		
10	Pearl		
11	Cow		
12	Hut		
	TOTAL		

Total recall:

/12

Appendix 2. Test package for Shanghai 2011 project (Mandarin)

一、一般资料

在划线处填入结果。

（一）人口学资料

R1 姓名：

R2 性别：1. 男　2. 女　□

R3 身份证生日：_____年___月___日　□□□□□□□□

R4 年龄：____岁　□□□

R5 民族：　□

1. 汉族 2. 回族 3. 藏族 4. 维吾尔族 5. 蒙古族 6. 其他

R6 受教育年数：_____年　□□

R7 文化程度：1.文盲 2.小学 3.初中 4.高中或中专 5.大专 6.大学或以上　□

R8 职业：是否离退休：1.是 2.否　□

R9 职业性质：1. 脑力劳动　2. 体力劳动　□

R10 长期居住地：1.城市 2.乡镇 3.农村　□

（二）生活习惯

S10 吸烟史：1.有 2.无 □

S11 持续:___年 □□

S20 饮酒史：1.有 2.无 □

S21 持续:___年 □□

S30 饮茶史：1.有 2.无 □

S31 持续:___年 □

S40 运动（每次锻炼 20 分钟以上的天数）：1.有 2.无 □

S41 运动频率: □

1. 偶尔 2. 每周 1-3 天 3. 每周 4-6 天 4. 每日

S50 业余爱好：1.有 2.无 □□

S51 持续:___年 □□

S60 饮食习惯： 1.素食为主 2.荤食为主 3.荤素搭配 □

二、神经心理测验

（一）霍普金斯词语学习测试

指导语

测试 1:

‘下面我讲连续朗读 12 个词语。朗读过程中请您仔细听并努力记忆尽可能多的词语. 当我停下的时候**, 请您说出您所能回忆出的词语,忽略它们的先后顺序. 您准备好了吗?’** 按照每 2 秒钟一个词语的速度进行朗读(词语中间有一秒间隙）. 当将所有词语朗读完毕后,示意被试开始复述，同时在表格上记录被试的复述情况。如果被试说出受测词语之外的词，请将这个词语记录在表格上，但不要提醒被试。如果被试在停顿 15－20 秒之后没有说出其它词语, 询问被试是否还能继续进行复述。如果不能，开始第二轮测试。事后可以在小结表格中计算被试几轮测试中每次均正确复述的词语数量。

测试 2:

‘刚才那是一个很好的开始。现在，我将朗读同一份词语列表。当我停下的事后，请您尽可能多的复述出我朗读过的词语，包括您在第一轮测试中已经复述过的词语，并且忽略它们的先后顺序。只要尽力复述尽可能多的词语，无论您之前是否已经复述过了。您准备好了吗?’ 仍然按照每 2 秒钟一个词语的速度进行朗读。然后请被试进行复述。同时在表格上记录被试的复述情况。如果被试在停顿 15－20 秒之后没有说出其它词语,询问被试是否还能继续进行复述。如果不能，开始第三轮测试。事后可以在小结表格中计算被试几轮测试中每次均正确复述的词语数量。

测试 3:

‘非常好. 现在我将要再次朗读同一份词语列表。请仔细听并努力回忆起尽可能多的词语，无论您之前是否已经复述过它们. 您准备好了吗?’ 按照第一、二轮测试的程序进行朗读和复述，并继续在表格上记录被试的复述情况。

＊注意：每次“学习”和复述的流程需持续大约 1 分钟

受测词语		测试 1		测试 2		测试 3	
		正确 (√)	错误词语	正确 (√)	错误词语	正确 (√)	错误词语
1	狮子						
2	绿宝石						
3	马						
4	帐篷						
5	蓝宝石						
6	旅馆						
7	洞穴						
8	猫眼石						
9	老虎						
10	珍珠						
11	奶牛						
12	棚子						
	总计						

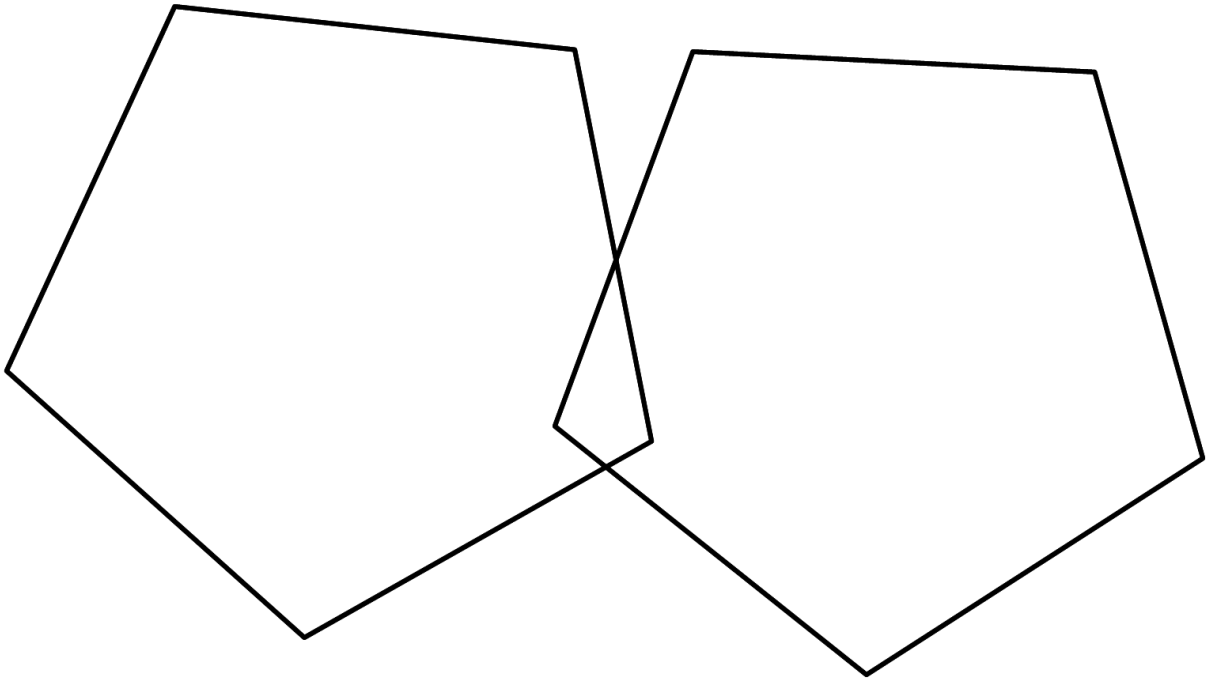
总分= 0~36

（二）简明精神状态检查(MMSE)

编号	评价项目	回　答	得分
	（1）请您告诉我：		
M1	现在是哪一年？		1　0
M2	现在是什么季节？		1　0
M3	现在是几月份？		1　0
M4	今天是几号？		1　0
M5	今天是星期几？		1　0
M6	这是什么城市（城市名）？		1　0
M7	这是什么区（城区名）？		1　0
M8	这是什么街道？		1　0
M9	这是第几层楼？		1　0
M10	这是什么地方？		1　0
	（2）现在我告诉您三样东西的名称，我说完后您重复一遍记住，过一会儿还要问您。“皮球”、“国旗”、“树木”。请您重复（仔细说清楚，每样东西用一秒钟，如果患者不能完全说出，可以重复，最多六遍，但记第一遍得分）。		
M11	皮球		1　0
M12	国旗		1　0

M13	树木 1　0		1　0
	（3）现在请您算一算，从 100 中减去 7，所得的数再减 7，一直算下去，将每减一个 7 后的答案告诉我，直到我说“停”为止（每一个正确答案 1 分，如果上一个错了，如 100-7=90，下一个对，如 90-7=83，第二个仍给分）。		
M14	100-7=93		1　0
M15	93-7=86		1　0
M16	86-7=79		1　0
M17	79-7=72		1　0
M18	72-7=65		1　0
	（4）现在请您说出刚才我让您记住的是哪三样东西？		
M19	皮球		1　0
M20	国旗		1　0
M21	树木		1　0
	（5）命名		
M22	（检查者出示手表）请问这是什么？		1　0
M23	（检查者出示铅笔）请问这是什么？		1　0

M24	（6）请您跟我说“吃葡萄剥葡萄皮，不吃葡萄不剥葡萄皮”		1 0
M25	（7）请您念一念这句话“请您闭上眼睛”，并按这句话的意思去做。	（请出示下页句子）	1 0
	（8）我给你一张纸，请您按照我说的做：“用右手拿起这张纸，双手把它对折起来，放在您的左腿上”。		
M26	右手拿纸		1 0
M27	双手对折		1 0
M28	放在左腿上		1 0
M29	请您写一个完整的句子（由患者自己写，必须有主语、谓语，有一定的内容。语法、标点、拼写错误可以忽略）	（请写于表格下面空白处）	1 0
M30	请您照着这个样子把它划下来（必须划出 10 个角，两个五边形交叉，交叉图形呈四边形方能得分，线条不平划可以忽略）	（请绘于下页图形下面空白处）	1 0
M31	**总分（最高 30 分）：**		



请您闭上眼睛

霍普金斯词语学习测试—延迟记忆

主试请注意: 这一部分的测试在以上所有测试都已完成的情况下进行的。请检查被试的以上复述情况，不要立即朗读词语。

受测词语		测试正确 (√)	错误词语
1	狮子		
2	绿宝石		
3	马		
4	帐篷		
5	蓝宝石		
6	旅馆		
7	洞穴		
8	猫眼石		
9	老虎		
10	珍珠		
11	奶牛		
12	棚子		
	总计		

总分= /12

Appendix 3. Shanghai 2011 project informed consent (Mandarin)

北新泾社区痴呆症早期筛查及干预研究

知情同意书

研究者（正楷）： _____ **受访者编号：**

研究中心地址：

尊敬的受访者：

我们邀请您参加**北新泾社区痴呆症早期筛查及干预研究**。该研究由上海市慈善基金会资助，为慈善公益项目。在您和您的家人参加研究前，请仔细阅读下面信息。如果您有不清楚的地方或您想了解更多信息，请向我们咨询。

[研究目的]

本研究将开展社区老年痴呆症的早期筛查，建立社区早期识别老年痴呆的方法和技术，并在社区开展早期干预治疗，为老年痴呆症的三级预防提供科学依据。

[研究过程概述]

本研究需要对受访者进行体格检查、认知功能、情绪状态等相关评估。这些评估和检查都是免费的。

[参与原则]

参加此研究完全是自愿的，您和您的监护人可以自愿决定是否参加，在研究中的任何时间您都可以退出研究。我们将为您提供适当的误工、误餐或交通补贴。

[研究内容知晓权]

您的身份等隐私资料将严格保密，除研究者外，任何第三方都不会知道您的身份等隐私资料。您参加研究意味着允许研究者使用研究获得的信息。

我已知晓本研究的有关介绍，研究者已向我作了详细的说明。我和我的监护人认真详细的阅读（或告知）了这些内容，并且自愿参加本研究，愿意与研究医生合作，按要求参加有关检查与随访。

受访者签名：签名（正楷）_____签名：_____日期：

法定监护人：签名（正楷）_____签名：_____日期：

研究者签名：_____ 日期：

Appendix 4. Data sharing agreement for Shanghai 2011 project

1. Requesting party

Name	Role	Contact
Xu Xin,	PhD student, School of Sport, Exercise and Health Sciences, Loughborough University, UK	Email: Xu.X@lboro.ac.uk

2. Provider

Name	Role	Contact
Xiao Shifu	Professor and Director, Department of Geriatric Psychiatry, Shanghai Mental Health Centre, Shanghai Jiaotong University	Email:xiaoshifu@msn.com Tel:+86 21 64387250 ext. 3441 (office) +86 13818246156 (mobile)

3. Data required

Requirements
Provide details of the data to be provided, including the data source and the list of data items within the data set, highlighting any sensitive and/or identifiable items. The Requesting party must liaise with the Supplying party to ensure that the required Data are correctly identified.

4. Purpose

Use of data	Specific conditions of use
Xu Xin's PhD project-- Predicting and Diagnosing Frailty in Community-dwelling Elderly People Using Physical, Psychological and Other indicators	

5. Retention period

Date from	Date to
10-07-2013	10-07-2014

I agree that my project will use the requested data from "Dementia Screening and Early Intervention among Elderly in a Shanghai Community Setting (2011)".

I agree that both *myself and my collaborators* will abide by the terms and conditions *summarised in the next page.*

I agree that failure to comply with these terms and conditions will result on any future data sharing applications *from me/or my collaborators* being refused by the provider.

Signature of **main applicant:** .....

Name in block capitals: XU XIN

Date: 10-07-2013

Signature of the **Provider**: Xiao Shifu

Name in block capitals: .....

Date: 2013.7.11

Summary of Data Sharing terms and conditions

Data usage and security

- Data must be used only for the specified research project.
- Data cannot be used by persons not mentioned in the application or distributed to third parties.
- Users will NOT have sole and exclusive access to their required dataset.
- Data errors must be notified to the Researchers.
- Data users must work under the Data Protection Scheme that operates in their country.
- Secure data access must be ensured by using secure networks, passwords, firewalls and/or highly encrypted devices.
- Data users working on the same project should use a shared drive for exchanging files, and avoid the use of memory sticks or attachments in e-mails.
- Data users must be aware that the data may allow individuals to be identified. Therefore, it will be the data user's responsibility to ensure that the participants' identity is not disclosed under any circumstances.
- It is forbidden to match or attempt to match individual records to any other data.
- On completion of the project, all electronic copies of the data must be deleted.
- There can be no more copies of the data than is reasonable for backing up work.

Publications

- The name of the Study must be included in the title or subtitle of publications.
- A suitable note of acknowledgement should be added.
- If the project has received significant input from the Study Researcher then s/he may also be included as an author.

Appendix 5. Shanghai 2012 Frailty project physical test package

Physical Assessment Recording Sheeting

Shanghai 2012 Frailty Project

Xu X, Hogervorst E, 2012

Participation Number: _____

Gender: Female □ Male □

Age: _____

Height: _____cm

Weight: ____kg

BMI: _____

Instructions for Grip strength Assessment

1. Stand up.

2. Hold the grip dynamometer in one hand with your arm rest next to your thigh

3. Adjust the grip dynamometer so the grip is between fingers and palm at the base of the thumb.

4. Hold firmly and begin to squeeze as much as possible foe 3 seconds - you should be aiming for maximal force.

*** There will be one practice trial; best of three attempts with 30 seconds rest between are recorded.*

Attempt 1: _____kg

Attempt 2: _____kg

Attempt 3: _____kg

Best Attempt: ____kg

Instructions for the combination test of Get-Up-and-Go and 15-feet walking test:

1. Have the person sit in a straight-backed chair (position A).

2. Ask the person to stand up from the chair and stand still momentarily.

3. Have the person walk a short distance (3 meters) to position B.

4. Have the person turn around, walk back to position A, and sit down again.

5. Note down the time.

5. Ask the person to stand up again and walk a distance of 15 feet (4.57 metres approximately) to position C

6. Note down the time.

**Timing begins when the person starts to rise from the chair and ends when he or she returns to the chair and sits down.*

***The person should be given 1 practice trial and then 3 actual trials. The times from the three actual trials are averaged.*

Timed-Up-and-Go test

Instruction: When I say 'go', I want you to stand up and walk to Chair B, turn and then walk back to chair A and sit down again. Please walk at your maximum pace speed.

Able to get up: Without support □ ***With support*** □ ***Unable to get up*** □

Trial 1: _____ Trial 2:_____ Trial 3:_____

Average time to complete _____seconds

15-feet walking test

Instruction: When I say 'go', I want you to stand up and walk to the chair C, turn and then walk back. Please walk at your maximum pace speed.

Trial 1: _____ Trial 2:_____ Trial 3:_____

Average time to complete _____seconds

Instructions for Berg Balance Test

Scoring: A five-point scale. Score for each question ranges from 0-4. “0” indicates the lowest level of function and “4” the highest level of function.

Total Score = 56

Please document each task and/or give instructions as written. When scoring, please record the lowest response category that applies for each item.

In most items, the subject is asked to maintain a given position for a specific time. Progressively more points are deducted if:

- the time or distance requirements are not met
- the subject’s performance warrants supervision
- the subject touches an external support or receives assistance from the examiner

Subject should understand that they must maintain their balance while attempting the tasks. The choices of which leg to stand on or how far to reach are left to the subject. Poor judgment will adversely influence the performance and the scoring.

Equipment required for testing is a stopwatch or watch with a second hand, and a ruler or other indicator of 2, 5, and 10 inches. Chairs used during testing should be a reasonable height. Either a step or a stool of average step height may be used for item # 12.

SITTING TO STANDING

INSTRUCTIONS: Please stand up. Try not to use your hand for support.

( ) 4 able to stand without using hands and stabilize independently

( ) 3 able to stand independently using hands

( ) 2 able to stand using hands after several tries

( ) 1 needs minimal aid to stand or stabilize

( ) 0 needs moderate or maximal assist to stand

STANDING UNSUPPORTED

INSTRUCTIONS: Please stand for two minutes without holding on.

( ) 4 able to stand safely for **2 minutes**

( ) 3 able to stand 2 minutes with supervision

( ) 2 able to stand 30 seconds unsupported

( ) 1 needs several tries to stand 30 seconds unsupported

( ) 0 unable to stand 30 seconds unsupported

** If a subject is able to stand 2 minutes unsupported, score full points for sitting unsupported. Proceed to item #4.

SITTING WITH BACK UNSUPPORTED BUT FEET SUPPORTED ON FLOOR OR ON A STOOL

INSTRUCTIONS: Please sit with arms folded for 2 minutes.

( ) 4 able to sit safely and securely for **2 minutes**

( ) 3 able to sit 2 minutes under supervision

( ) 2 able to able to sit 30 seconds

( ) 1 able to sit 10 seconds

( ) 0 unable to sit without support 10 seconds

STANDING TO SITTING

INSTRUCTIONS: Please sit down with minimal use of hands.

( ) 4 sits safely with minimal use of hands

( ) 3 controls descent by using hands

( ) 2 uses back of legs against chair to control descent

( ) 1 sits independently but has uncontrolled descent

( ) 0 needs assist to sit

TRANSFERS (Arrange another chair)

INSTRUCTIONS: Please sit to the chair on your left/right, with minimal use of hands. (5 seconds later) Please sit back to the original chair, with minimal use of hands.

( ) 4 able to transfer safely with minor use of hands

( ) 3 able to transfer safely definite need of hands

( ) 2 able to transfer with verbal cuing and/or supervision

( ) 1 needs one person to assist

( ) 0 needs two people to assist or supervise to be safe

STANDING UNSUPPORTED WITH EYES CLOSED

INSTRUCTIONS: Please stand, close your eyes and stand still for 10 seconds.

( ) 4 able to stand **10 seconds** safely

( ) 3 able to stand 10 seconds with supervision

( ) 2 able to stand 3 seconds

( ) 1 unable to keep eyes closed 3 seconds but stays safely

( ) 0 needs help to keep from falling

STANDING UNSUPPORTED WITH FEET TOGETHER

INSTRUCTIONS: Please open your eyes, place your feet together and stand without holding on.

( ) 4 able to place feet together independently and stand **1 minute** safely

( ) 3 able to place feet together independently and stand 1 minute with supervision

( ) 2 able to place feet together independently but unable to hold for 30 seconds

( ) 1 needs help to attain position but able to stand 15 seconds feet together

( ) 0 needs help to attain position and unable to hold for 15 seconds

REACHING FORWARD WITH OUTSTRETCHED ARM WHILE STANDING (place a ruler on the wall)

INSTRUCTIONS: Lift arm to 90 degrees. Stretch out your fingers and reach forward as far as you can.

*(**Examiner places a ruler at the end of fingertips when arm is at 90 degrees. Fingers should not touch the ruler while reaching forward. The recorded measure is the distance forward that the fingers reach while the subject is in the most forward lean position. When possible, ask subject to use both arms when reaching to avoid rotation of the trunk.)*

( ) 4 can reach forward confidently **25 cm (10 inches)**

( ) 3 can reach forward 12 cm (5 inches)

( ) 2 can reach forward 5 cm (2 inches)

( ) 1 reaches forward but needs supervision

( ) 0 loses balance while trying/requires external support

PICK UP OBJECT FROM THE FLOOR FROM A STANDING POSITION

INSTRUCTIONS: Pick up the object, which is in front of your feet.

( ) 4 able to pick up slipper safely and easily

( ) 3 able to pick up slipper but needs supervision

( ) 2 unable to pick up but reaches 2-5 cm (1-2 inches) from slipper and keeps balance independently

( ) 1 unable to pick up and needs supervision while trying

( ) 0 unable to try/needs assist to keep from losing balance or falling

TURNING TO LOOK BEHIND OVER LEFT AND RIGHT SHOULDERS WHILE STANDING

INSTRUCTIONS: Turn to look directly behind you over toward the left shoulder. Repeat to the right. (Examiner may pick an object to look at directly behind the subject to encourage a better twist turn.)

( ) 4 looks behind from both sides and weight shifts well

( ) 3 looks behind one side only other side shows less weight shift

( ) 2 turns sideways only but maintain balance

( ) 1 needs supervision when turning

( ) 0 needs assist to keep from losing balance or falling

TURN 360 DEGREES

INSTRUCTIONS: Turn completely around in a full circle. Pause. Then turn a full circle in the other direction.

( ) 4 able to turn 360 degrees safely in **4 seconds** or less

( ) 3 able to turn 360 degrees safely one side only 4 seconds or less

( ) 2 able to turn 360 degrees safely but slowly

( ) 1 needs close supervision or verbal cuing

( ) 0 needs assistance while turning

PLACE ALTERNATE FOOT ON STEP OR STOOL WHILE STANDING UNSUPPORTED

INSTRUCTIONS: Place each foot alternately on the stool. Continue until each foot has touched the stool four times.

( ) 4 able to stand independently and safely and complete 8 steps in **20 seconds**

( ) 3 able to stand independently and complete 8 steps in > 20 seconds

( ) 2 able to complete 4 steps without aid with supervision

( ) 1 able to complete > 2 steps needs minimal assist

( ) 0 needs assistance to keep from falling/unable to try

STANDING UNSUPPORTED ONE FOOT IN FRONT

INSTRUCTIONS: (DEMONSTRATE TO SUBJECT) Place one foot directly in front of the other. If you feel that you cannot place your foot directly in front, try to step far enough ahead that the heel of your forward foot is ahead of the toes of the other foot. (To score 3 points, the length of the step should exceed the length of the other foot and the width of the stance should approximate the subject's normal stride width.)

( ) 4 able to place foot tandem independently and hold 30 seconds

( ) 3 able to place foot ahead independently and hold 30 seconds

( ) 2 able to take small step independently and hold 30 seconds

( ) 1 needs help to step but can hold 15 seconds

( ) 0 loses balance while stepping or standing

STANDING ON ONE LEG

INSTRUCTIONS: Please stand in the normal stands. Please stand on one leg as long as you can without holding on.

( ) 4 able to lift leg independently and hold **> 10 seconds**

( ) 3 able to lift leg independently and hold 5-10 seconds

( ) 2 able to lift leg independently and hold L 3 seconds

( ) 1 tries to lift leg unable to hold 3 seconds but remains standing independently.

( ) 0 unable to try of needs assist to prevent fall

ITEM DESCRIPTION SCORE (0-4)

1. Sitting to standing _____

2. Standing unsupported _____

3. Sitting unsupported _____

4. Standing to sitting _____

5. Transfers _____

6. Standing with eyes closed _____

7. Standing with feet together _____

8. Reaching forward with outstretched arm _____

9. Retrieving object from floor _____

10. Turning to look behind _____

11. Turning 360 degrees _____

12. Placing alternate foot on stool _____

13. Standing with one foot in front _____

14. Standing on one foot _____

TOTAL (maximum 56) _____

( ) TOTAL SCORE (Maximum = 56)

Appendix 6. Shanghai 2012 Frailty project psychological and lifestyle test package

Note to Investigators: This HSQ can be used in its entirety but you can also remove some of the questions if you know they are not relevant to your study.

As a volunteer participating in a research study, it is important that you are currently in good health and have had no significant medical problems in the past. This is (i) to ensure your own continuing well-being and (ii) to avoid the possibility of individual health issues confounding study outcomes.

Please complete this brief questionnaire to confirm your fitness to participate:

HEALTH STATUS

Important for respondent is they are healthy and never experienced serious illness in the past. This is to confirm (i) their own health, and (ii) to avoid possibility of health problems as confounding factor in study result. Complete this questionnaire fully and clearly to assert the ability to become a participant. Explain clearly and comprehensively whether you have health problems, no serious problems, or in good maintenance (controlled).

F 1 Health Complaint

		Participant		Caregiver	
<u>At present</u>, do you have any health problem for which you are:		Yes **(1)**	No **(0)**	Yes **(1)**	No **(0)**
a	On medication, prescribed or otherwise (incl traditional medicine): number of medications used in total, in separate section	☐	☐	☐	☐
b	Attending your doctor, health provider or traditional healer:	☐	☐	☐	☐
<u>In the past two years</u>, have you had any illness which require you to (write down which one):		☐	☐	☐	☐
c	Consult your doctor health provider or traditional healer	☐	☐	☐	☐
d	Attend a hospital outpatient department or health center	☐	☐	☐	☐
E	Be admitted to hospital	☐	☐	☐	☐

<u>If 'no' to above questions then skip next section F2 and continue with Health Survey on page 2)</u>

F 2 Medical examination and history based on Cambridge Mental Disorders of the Elderly Examination (Roth, 1984)

Have you been told by a doctor that you have (had)		Yes(1)	No(0)
1	High blood pressure	☐	☐
2	A heart attack	☐	☐
3,4	A stroke or TIA	☐	☐
5a	Diabetes (sugar)	☐	☐
5b	If you have diabetes, do you take medication (insulin)?	☐	☐
6a	Dementia	☐	☐
6b	Another neurological problem (e.g. Parkinson)? If yes, what…….	☐	☐
7	Problems with alcohol or drugs	☐	☐
8a	Do you use hormone therapy?	☐	☐
8b	If yes, which of the following:	☐	☐
	Estrogens	☐	☐
	Thyroid	☐	☐
	Testosterone	☐	☐
	Soy/phytoestrogens supplements	☐	☐
	Viagra	☐	☐
9	Are you using medication prescribed by a doctor:	☐	☐
	To be calm, to be able to sleep	☐	☐
	To not be depressed	☐	☐

F 3 Life style questions related to health

F 3.1 Have you EVER smoked?

Yes	1
No	2

F 3.2 Are you a REGULAR smoker?

Yes	1
No	2

F 3.3 How much do you smoke? (*Choose amount of cigarettes and one time frame which respondent remember easily*)

	Amount	Yes
Amount per day	..... cigarettes	1
Or per week	..... cigarettes	1
Or per month	..... cigarettes	1

F 3.4 Which alcohol do you consume?

Beer	☐	1
Wine	☐	2

Spirits	☐	3
None now	☐	0
None ever	☐	4

F 3.5 Have people said you have a problem with alcohol or drugs (marijuana, amphetamine/calming drugs):

Yes, now (1) ☐	Yes, in the past (2) ☐	No, never (3) ☐

F 4 Food Consumption

How much do you consume the following food item		Do you eat it daily? *If yes, ask how many times a day and continue to the next food item*			Days in a week	Days in a month
		Yes, how many times a day		No		
A1	Rice	1	.....	2		
A2	Bread	1	.....	2		
A3	Other : pasta, mie etc.					
b	Fruit/juice					
c	Orange/red colored vegetables	1	.....	2		
d	Green vegetables	1	.....	2		
E1	Fish:	1	.....	2		
E2	Is that fatty sea fish like tuna/ mackerel/ herring/ salmon?	1	.....	2		
f	Tempe					
g	Tahu/tofu	1	.....	2		
h	Soy milk, other soy product	1	.....	2		
i	Turmeric as jamu (herbal medicine)	1	.....	2		
j	Tumeric as spices	1	.....	2		
k	Tumeric as raw vegetables	1	.....	2		
l	White meat (chicken)	1		2		
M	Red meat (beef/lamb/veal)	1		2		

F 5 Do you have hobbies?

None	0
Yes	1

F 6 Activities of Daily Living

No	Function	Points	Criteria
F6.1	Defecation control	0	Irregular/incontinence
		1	Incontinence sometimes (once a week)
		2	Continence
F6.2	Urinate control	0	Incontinence or using catheter and uncontrolled
		1	Incontinence sometimes (max. 1x24 hour)
		2	Independent
F6.3	Ability to clean themselves (wash the face, to comb, brush the teeth)	0	Need help
		1	Independent
F6.4	Toilet use. To go to and from toilet (take off and wear trousers, wipe, flush)	0	Dependent
		1	Need help in some activities but independent in others.
		2	Independent
F6.5	Eat	0	Unable
		1	Need someone to cut the food
		2	Independent
F6.6	Change position from lie down to sit up	0	Unable
		1	Need help to sit (2 persons)
		2	Help from 1 person
		3	Independent
F6.7	Mobility/walking	0	Unable
		1	Use wheel chair
		2	Walk with help from 1 person/walker
		3	Independent
F6.8	Get dressed (put clothes on)	0	Dependent
		1	Partly dependent (e.g. buttoning shirt)
		2	Independent
F6.9	Climb up and down stairs	0	Unable
		1	Need help from others
		2	Independent (climb up and down)
F6.10	Take a bath	0	Dependent
		1	Independent
	Total score		Criteria

ADL Score: 20: Independent; 12 – 19: Lightly dependent; 9 – 11: Moderately dependent; 5 – 8 : Heavily dependent; 0 – 4: Totally dependent

F 7. Instrumental Activities of Daily Living (IADL)				
No	**Activities**	**Point**	**Criteria**	
F7.1	Extending message/using the telephone	0	I am unable to use the phone	
		1	I am capable of answering phone but unable to operate it)	
		2	I am able to operate telephone	
F7.2	Shopping	0	I am unable to do any shopping	
		1	I am capable of purchasing up to 3 items, otherwise I need help.	
		2	I do my shopping independently	
F7.3	Preparing meal	0	I am unable to cook	
		1	I am able to cook if the ingredients are ready or to warm cooked food	
		2	I cook independently	
F7.4	Housekeeping	0	I am unable to do the housekeeping	
		1	I am able to do light tasks (sweeping, make the bed) only, but otherwise need help.	
		2	I do the housekeeping independently (capable to do all household tasks including mopping and washing clothes)	
F7.5	Washing clothes	0	I am unable to was my clothes	
		1	I am able to wash light clothes or ironing, but otherwise need help	
		2	In do my washing independently (using washing machine included)	
F7.6	Utilization of transportation means	0	I am unable to travel with any transportation mean	
		1	I travel on public transportation/taxi or private car if I am helped/accompanied by other	
		2	I travel independently	
F7.7	Responsibility of own medication/preparing own medication	0	I need help from others to prepare and consume my medication.	
		1	I am able to take it if medication is previously prepared	
		2	I take my medication independently (I am able to prepare my own medication according to prescribed dose and time)	
F7.8.	Ability to handle finances	0	I am incapable at handling my own finances	
		1	I am able to arrange my daily purchases, but need help with banking/major purchasing	
		2	I am able to manage financial problems (household budget, pays the rent, receipt, bank matters) or to monitor my income.	
	Total score			

IADL score: 9 – 16: Independent; 1 – 8: Needs help; 0: Unable

F 8. HOPKINS VERBAL LEARNING TEST VERSION A (we have this version in our test battery as well where the words are presented verbally. The recognition component can also be programmed for a reaction time and % correct response.

Instructions for face to face testing:

Trial 1:

'Listen carefully while I read a list of words. Try your very best to memorize as many of these words as you can. **When I stop, you are to say back as many of the words as you can, in any order that you wish. Ready?'** Read the words at the rate of one word every 2 seconds (1 sec between words). After reading the entire list to the patient, have the patient recall them. Check off the words the patient recalls on the form. If a word is said that is not in the list, write that word on the form but say nothing to the patient about the word not being on the list. If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words. If not, move on to trial 2. Later, you can record the number of words that were correctly repeated on the summary form.

Trial 2:

'That was a good beginning. Now, I'm going to read the same list again. When I stop, I want you to tell me as many words as you can remember, including the words you said the first time. It does not matter in what order you say them. Just say as many words as you can remember whether or not you said them before. Ready?' Read the words at the rate of one word every 2 seconds. Then have the patient recall them. Check off the words that the patient recalls on the form. If the patient does not produce any words for 10-15 seconds, ask the patient if he/she can remember any more words. If not, move on to trial 3. Later, record the number of words that were correctly repeated on the summary form.

Trial 3:

'Very good. I'm going to read the list again. Again, listen carefully and try to remember as many words as you can whether or not you said them before. Ready?' Continue to follow recording procedures from trials 1 & 2. Note that each *learning* and recall trial should last about 1 minute.

Delayed recall.

For researcher: This part is asked after all tests are done. Do not read the list again. Check the words the patient recalls.

<u>Delayed Recall (D)</u> PART IS ON THE LAST PAGE

Words to Mention		Trial 1		Trial 2		Trial 3	
		Correct (√)	**Incorrect word**	**Correct (√)**	**Incorrect word**	**Correct (√)**	**Incorrect word**
1	Lion						
2	Emerald						
3	Horse						
4	Tent						
5	Sapphire						
6	Hotel						
7	Cave						
8	Opal						
9	Tiger						
10	Pearl						
11	Cow						
12	Hut						
	TOTAL						

Refused to attempt word list recall Total recall (0 to 36)

F 9. MINI MENTAL STATE EXAMINATION (MMSE)
is available online
http://ncemi.org/shared/etools_c/etools_c.pl?cmd=run&resource_fn=edecision_mini_mental_status_exam.xml

Respondent number :
Respondent's Age : Interview Date :
Education : Finish Time :

F9.1 Orientation

5 ( ) What is the (day) (date) (month) (year) (season)?

5 ( ) Where are we: (street) (house number) (town) (village) (province)?

F9.2 Registration

3 ( ) Interviewer name 3 objects: 1 second to say each. Then ask the respondent to repeat all 3 after you have said them. Give 1 point for each correct answer. If still incorrect, repeat them until he learns all 3. Count trials and record (**House – Child – Rice**).
Trials _____

F9.3 Attention and Calculation

5 ( ) Ask the subject to begin with 20 and count backwards by 3. Give 1 score for each correct answer. Stop after five subtractions (20, 17, 14, 11, 8, 5, 2). Other alternative is to spell the word "world" backwards (d-l-r-o-w).

For Illiterate Respondents:
Ask respondent to name days in week from first day (Monday, Tuesday, Wednesday, Thursday, Friday, Saturday, Sunday). Then ask respondent to name it backwards (Sunday, Saturday, Friday, Thursday, Wednesday, Tuesday, Monday).

F9.4 Recall

3 ( ) Ask for the three words you previously asked him to remember. One point for each correctly recalled

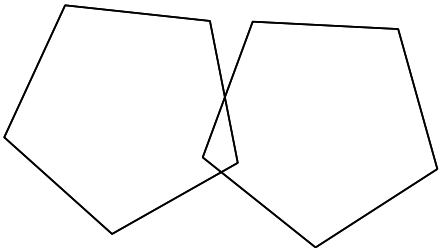
F9.5 Language

9 ( )

a. What is the name of these things? (show 2 things, e.g. pencil and wrist watch)…….. (2 points)
b. Repeat the following sentence: If not, and or but'
.....(1 point)
c. Follow a 3 stage command: ……..…..... (3 points)
   - Take this paper in your right hand,
   - fold it in half and
   - put it on the floor.
d. Read and obey the following: "Close your eyes"……. (1 point)

If illiterate just say „Close your eyes“

e. Write a sentence…….... (1 point)
   If illiterate ask to draw a house
f. Copy the following drawing ……... (1 point)



Total ( ) Score

Mark elderly respondent level of consciousness on the line below with an x:

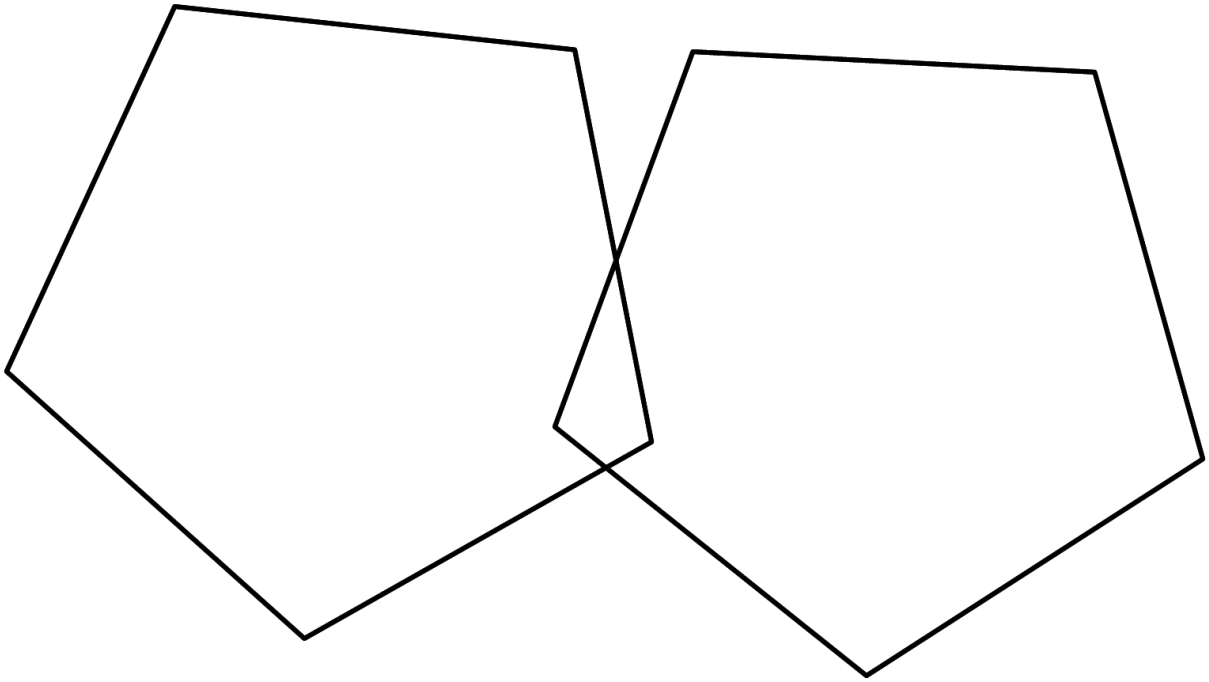
Fully conscious Somnolent Stupor Coma

24 or less : High likelihood of dementia
25 – 30 : Normal aging or borderline dementia

Finish time:
Interview place:

Observation Column: Record condition during interview (respondent conditions, respondent reactions to questions or instructions).

Show this drawing, and then ask respondent to close her/his eyes then open and copy this drawing.



Close Your Eyes

F 10 HOPKINS VERBAL LEARNING TEST VERSION A (Part D)

For researcher: This part is asked after all other tests are done by respondent/participant. Do not read the list again. Check each word that the patient recall, record all incorrect words on the form. Tell the patient, **'I read you a list of words and you practiced remembering the words. Now tell me as many words as you remember.'**

	Words to recall	**Correct (√))**	**Record all words not on the original list**
1	Lion		
2	Emerald		
3	Horse		
4	Tent		
5	Sapphire		
6	Hotel		
7	Cave		
8	Opal		
9	Tiger		
10	Pearl		
11	Cow		
12	Hut		
	TOTAL		

Total recall:

/12

Appendix 7. Shanghai 2012 Frailty project Informed Consent

A Multi-cultural Investigation for Risk Factors of Frailty Using Physiological and Psychological Assessments

Participant Information Sheet

Investigator: PhD student Xu Xin, School of Sport, Exercise and Health Sciences,

mail to:X.Xu@lboro.ac.uk

Supervisor: Professor Eef Hogervorst, Department of Human Sciences,

mail to:E.Hogervorst@lboro.ac.uk

Professor Shifu Xiao, Shanghai Mental Health Centre

Mail to: xiaoshifu@msn.com

What is the purpose of the study?

In this study, we aim in establishing a model to predict frailty where demographical factors such as an older age, low education and socioeconomic status, as well as poor health, low physiological capacity, disability, nutritional factors and a lack of activity are related to different objective physical and psychological parameters used to establish frailty in elderly.

Who is doing this research and why?

Xu Xin will be primarily responsible for the day-to-day running of the study.

Prof. Hogervorst and Prof. Xiao will supervise the research.

Are there any exclusion criteria?

If you have a chronic disease or any disability that prevents you from doing light exercise (e.g. balance, walking), you may be advised not to participate.

Once I take part, can I change my mind?

Yes. After you have read this information and asked any questions you may have we will ask you to complete an Informed Consent Form, however if at any time, before, during or after the sessions you wish to withdraw from the study please just contact the main investigator. You can withdraw at any time, for any reason and you will not be asked to explain your reasons for withdrawing.

Will I be required to attend any sessions and where will these be?

Yes. You will be contact to see if you could come to our laboratory for the assessment in Wavy Top building in Loughborough University.

When you are unable to come to the clinic, you will be visited at home by trained research assistants.

How long will it take?

The whole assessment takes roughly 100 minutes in total: 30 minutes for the questionnaire survey, 20 minutes for psychological assessment and 40 minutes for physiological assessment, with two short breaks of 10 minutes between these procedures.

Is there anything I need to do before the sessions?

We will ask you to abstain from drinking alcohol 10 hours before you visit us and to arrive on time and well rested.

Is there anything I need to bring with me?

Please bring your reading glasses and hearing aids where necessary.

What type of clothing should I wear?

Clothing should be loose to allow light physical exercise.

What will I be asked to do?

1) At the beginning of the session you will be asked to read this information letter to make sure you are eligible to take part in the study. If you are eligible to participate and you would like to participate then you will be asked to sign a consent form;
2) Your height, weight, BMI and arm muscle area will be measured;
3) You will be invited to complete a questionnaire regarding your person information, food habit, daily functioning and health;
4) After a short break, you will be invited to the psychological assessment which consists of two tests. It will last approximately 20 minutes;
5) After a short break, you will be invited to the physiological assessment which consists of three different tests. It will last about 40 minutes.

What personal information will be required from me?

Demographics including your age, gender, ethnicity, educational level, living circumstance will be surveyed. Your health situation, nutrition facts and lifestyle including smoking frequency and alcohol intake will be surveyed. Your identity will not be revealed and is kept away from your data.

Are there any risks in participating?

In the physiological assessment your muscle strength and heart/lung capacity as well as your control of balance will be measured. Though these tests are well tolerated by people,

Some muscle strain and fatigue may occur.

Will my taking part in this study be kept confidential?

The confidentiality of data collected is ensured. All personal information is anonymized. You will be assigned a reference number and data will be stored against this number. We will maintain separate lists of people who have taken part in their research.

Data storage will adhere to the Data Protection Act so that no participant's confidentiality will be breached. All research data will be stored securely in a locked filing cabinet.

What will happen to the results of the study?

The findings of the study will form part of a PhD thesis. In addition, the results might be presented at a scientific conference and will be published in a scientific journal. However, your individual data will not be revealed.

What do I get for participating?

You will receive a copy of our report if you wish to read about our findings.

I have some more questions who should I contact?

Please contact Xu Xin, E-mail: X.Xu@lboro.ac.uk . Tel: 07761 324 384.

What if I am not happy with how the research was conducted?

The University has a policy relating to Research Misconduct and Whistle Blowing which is available online at http://www.lboro.ac.uk/admin/committees/ethical/Whistleblowing(2).htm. Please ensure that this link is included on the Participant Information Sheet.