UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HUMAN DEVELOPMENT AND HEALTH

RELATIONSHIP BETWEEN SIZE AT BIRTH, SOCIOECONOMIC POSITION AND CARDIOMETABOLIC RISK FACTORS ACROSS THE LIFECOURSE WITH COGNITION AND DEPRESSION IN LATE LIFE

Mysore Studies of **N**atal effect on **A**geing and **H**ealth (MYNAH)

By

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ABSTRACT

FACULTY OF MEDICINE, HUMAN DEVELOPMENT AND HEALTH

Doctor of Philosophy

RELATIONSHIP BETWEEN SIZE AT BIRTH, SOCIOECONOMIC POSITION AND CARDIOMETABOLIC RISK FACTORS ACROSS THE LIFECOURSE WITH COGNITION AND DEPRESSION IN LATE LIFE

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Background: There is limited and inconsistent evidence, mainly from high income countries, indicating that growth restriction in utero may lead to lower cognition and a higher risk of depression in late life, either through impaired brain development or adverse metabolic programming.

Methods: Between 2013-15, I examined associations of size at birth with cognition and depression among 721 men and women (55-80 yrs) whose size at birth had been recorded at Holdsworth Memorial Hospital, Mysore, South India. Approximately 20 yrs ago, a subset (n=522) of them had assessments for cardiometabolic disorders in midlife. In my study, cognitive function and depression were measured using a culturally adapted and validated 10/66 battery of cognitive tests and the Geriatric Mental State examination respectively. A reliable informant was interviewed for the evidence of cognitive decline and functional impairment of the participants. Other investigations included a structured assessment for sociodemographic and lifestyle factors; blood tests (for glucose tolerance, insulin resistance, diabetes, dyslipidemia, anaemia, B12 and folate deficiency, and hyperhomocysteinaemia), physical health assessments (for hypertension, coronary heart disease and stroke) and a genetic assay for Apoε lipoprotein.

Results: Age was inversely and independently associated with cognition in late life, women had higher cognitive function than men. Those who were heavier at birth had higher composite cognitive score [0.12 SD per SD birth weight 95% CI (0.05, 0.19) p=0.001] in late life. Other lifecourse factors independently related to cognition were (positively) maternal educational level and participants' own educational level, adult leg length, body mass index (BMI) and socioeconomic position; and (negatively) diabetes in midlife and, current stroke and depression. The association of birth weight with cognition was independent of midlife and current cardiometabolic risk markers, was possibly mediated by attained educational level of the participants, and was attenuated after adjustment for all lifecourse factors [0.08 SD per SD birth weight (95% CI -0.01, 0.18) p=0.07)]. The greatest attenuation occurred after adjusting for indicators of the childhood environment (maternal education and adult leg length). Birth weight and markers of a better childhood environment were positively related to late life cognitive function, indicating the persistence of the effect of these exposures into late life. Findings from this study are consistent with the 'cognitive reserve', but not the 'fetal cardiometabolic programming' pathway of cognitive ageing.

Those who were heavier at birth had lower rates of depression and this was of borderline significance [OR=0.82 per SD birth weight 95%CI (0.68, 1.00) p=0.09]. In a multiple regression model, factors independently associated with depression were (negatively) being married, current leg length, socioeconomic position, physical activity and haemoglobin, and (positively) Apoε4 genotype, stroke and current homocysteine level. After adjusting for lifecourse factors, birth weight was unrelated to depression.

Conclusion: With the caveat that causality cannot be assumed from observational cohort data, better childhood environment, higher attained education and socioeconomic status, and better current nutritional status may be protective against late life depression. Further studies are required to elucidate the Developmental Origins of Health and Disease (DOHaD) mechanisms of brain ageing.

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Declaration of Authorship

I, **MURALIKRISHNA TIPTUR NAGARAJ** declare that this thesis and the work presented in it are my own and has been generated by me as the result of my own original research.

RELATIONSHIP BETWEEN SIZE AT BIRTH, SOCIOECONOMIC POSITION AND CARDIOMETABOLIC RISK FACTORS ACROSS THE LIFECOURSE WITH COGNITION AND DEPRESSION IN LATE LIFE

I confirm that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

5. I have acknowledged all main sources of help;

6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

7. Either none of this work has been published before submission, or parts of this work have been published as: [please list references below]:

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Publications are listed overleaf

Publications

Krishna M, Kumaran K, Veena SR, Krishnaveni GV, Karat SC, Coakley P, Nagaraj K, Stein C, Paul BDR, Prince M, Osmond C, Fall CHD. Cohort Profile: The 1934–1966 Mysore Birth Records Cohort in South India. International Journal of Epidemiology. 2015;44(6):1833-41.

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Author's Contribution

I designed this study and prepared the study protocol with guidance from Prof CHD Fall, Prof C Osmond and Prof M Prince.

I led the research team and supervised the retracing and recruitment process for this study. I trained the team in conducting blood investigations, anthropometry, physical and cognitive assessments. I conducted inter-observer variability studies for anthropometric examination and cognitive tests. I was responsible for running the clinics, obtaining consent and, conducting neurological and mental health examination of all the study participants. At the end of the clinics, I provided detailed feedback and clinical advice to all the participants and their family members. I ensured safe collection of blood samples and storage at the research unit.

I have personally checked the data collected for all the participants and supervised data management. I was in-charge of data cleaning and processing. With help from Mrs P Coakley, I ran the 10/66 diagnostic algorithms. I conducted the statistical analyses required for the thesis, and interpreted the results, with training and supervision from Prof C Osmond, Prof CHD Fall, Dr GV Krishnaveni and Ms C Di'Gravio.

I typed and prepared the manuscript. Mr Chetan R helped me in formatting the manuscript.

List of Abbreviations

AD	Alzheimer's Disease
AH4	Alice Heim Test Version 4
ARDSI	Alzheimer's and Related Disorders Society of India
BIA	Bio Impedance Analysis.
BCS	British Cohort Study
BMI	Body Mass Index.
BP	Blood Pressure.
CCMB	Centre for Cellular and Molecular Biology
CERAD	Consortium to Establish a Registry for Alzheimer's Disease.
CHD	Coronary Heart Disease.
CINAHL	Cumulative Index to Nursing and Allied Health Literature
COWAT	Controlled Word Association Test
COPD	Chronic Obstructive Pulmonary Disorder
COSMIC	Cohort Studies of Memory in an International Consortium
CR	Cognitive Reserve
CSI	Church of South India
CSI'D'	Community Screening Instrument for Dementia
DOHAD	Developmental Origins of Health and Disease
DSM IV	Diagnostic Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EURO-D	EURO Depression Scale
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GBD	Global Burden of Disease
GMS	Geriatric Mental State Examination.
HAS-D	History and Aetiology Schedule for diagnosis of Dementia
HDL	High Density Lipoprotein.
HIC	High Income Countries.
HMH	Holdsworth Memorial Hospital.
HOMA	Homeostasis Model Assessment.
OR	Odds Ratio
PEF	Peak Expiratory Flow
ICDS	Integrated Child Development Service
IDF	International Diabetic Federation
IOV	Inter Observer Variability
LDL	Low Density Lipoprotein
LEU	Lifecourse Epidemiology Unit
LMIC	Low and Middle-Income Country
LMP	Last Menstrual Period
MCS	Millennium Cohort Study
mhGAP	Mental Health Gap Action Programme
MMSE	Mini Mental State Examination
MCI	Mild cognitive Impairment
MRC	Medical Research Council
MYNAH	Mysore Studies of Natal Effects of Ageing and Health
NART	National Adult Reading Test
NCDS	National Child Development Study
NCD	Non-Communicable Disorders
NCEP	National Cholesterol Education Program
NEUROEX	Neurological Examination
NPHCE	National Programme for Health Care of the Elderly
NPI-Q	Neuro Psychiatric Inventory Questionnaire

List of Abbreviations	
OH	Orthostatic Hypotension
PRISMA	Preferred Reporting Items for Systematic Reveiws and Meta-Analyses
RR	Relative Risk
SEP	Socioeconomic position
SLI	Standard of Living Index.
SPSS	Statistical Package for the Social Sciences
SSRI	Selective Serotonin Re-uptake Inhibitors
STROBE	Reporting of OBservational Studies in Epidemiology
TSH	Thyroid Stimulating Hormone.
UKNEQAS	United Kingdom National External Quality Assessment Service.
WHO	World Health Organisation.
WHO DAS	WHO Disability Assessment Schedule.
WHO SAGE	WHO Studies of AGEing
WLMR	Word List Memory Recall

1. Introduction

1.1 Global population ageing

Demographic ageing is a global phenomenon. Countries are at various stages of demographic ageing: the share of the 60+ population ranges from under 5% in a number of African and Gulf countries to more than 20% in several European and East Asian countries (United Nations.,2015). Demographic ageing has picked up momentum in low income countries of Asia, Latin America and Africa. Soon, there will be a sharp increase in the number of older people in low- and middle- income countries (LMIC). This makes the task of meeting the needs of the older people a more challenging and an urgent one (United Nations.,2015).

Population ageing has given rise to increased awareness of its implications for society. It is important to note that this rapid demographic change is happening along with fast paced social restructuring that accompanies economic development. Regardless of the effect of population ageing on the economy, this will lead to increased need for care and support of older adults, at a time when, in LMIC societies, traditional family based care is becoming less the norm than in the past. In addition, a higher share of older people negatively affects the resource poor health and social care systems in these countries (The Dementia India Report.,2010).

1.2 Ageing in India

With 1.21 billion inhabitants counted in its 2011 census, India is the second most populous country in the world. Currently, the 60+ population accounts for 8% of India's population, translating into roughly 93 million people. By 2050, the share of the 60+ population is projected to climb to 19%, or approximately 323 million people. The share of the "oldest old", or the population aged 80 and over, is also projected to increase from 1% to 3% (The Registrar General of India.,2011; United Nations.,2015). The elderly dependency ratio (the number of people aged 60 and older per person aged 15 to 59) will rise dramatically from 0.12 to 0.31 (United Nations.,2015).

India is going through rapid economic transition alongside demographic ageing. It is also experiencing a breakdown of the traditional extended family structure. Currently, India's older people are largely cared for privately, but these family networks are coming under stress from a variety of sources. The rapid rise of India's older adult population, coupled with

changing family structures and limited social provisions, presents policy makers with pressing economic, health, and social challenges (Central Statistics Office India.,2006; Central Statistics Office India.,2011).

Several forces are driving India's changing age structure, including an upward trend in life expectancy and falling fertility. An Indian born in 1950 could expect to live for 37 years, whereas today India's life expectancy at birth has risen to 65 years; by 2050 it is projected to increase to 74 years. Fertility rates in India have declined sharply, from nearly 6 children per woman in 1950 to 2.6 children per woman in 2010 (Central Statistics Office India.,2011).

1.3 Ageing and chronic non-communicable disorders

A key finding from the Global Burden of Disease (GBD) report is that chronic non-communicable diseases (NCDs) are rapidly becoming the dominant causes of ill health in all LMIC regions except Sub-Saharan Africa (Lozano et al.,2012). As India's population ages, they will be living to an age where non-communicable diseases manifest. Insufficient health care services to support them adequately further adds to the burden (National Programme for the Health Care of Elderly NPHCE India.,2011). Older people frequently have multiple health conditions such as chronic physical diseases co-existing with mental or cognitive disorders, the effects of which may combine together in complex ways leading to disability and needs for care. However, studies from both high-income countries and low- and middle-income countries concur that, among older people, cognitive impairment and dementia make the largest contribution to needs for care, much more so than other types of impairment and other chronic diseases (Sousa et al.,2009; Sousa et al.,2010; Aguero Torress et al.,2002; Wolf et al.,2005).

Of the chronic NCDs, dementia and cognitive impairment are the leading contributors to disability, and, particularly, dependence among older people worldwide (World Alzheimer's Report.,2009). While older people can often cope well, and remain reasonably independent even with marked physical disability, the onset of cognitive impairment quickly compromises their ability to carry out activities of daily living leading to dependence on care givers. As cognition worsens, people living with dementia will have greater difficulty in meeting their basic personal care needs and this intensifies the need for support from caregivers and continues until their death. The caregivers experience practical (hours spent care giving detracting from other activities, particularly leisure and socialising), psychological (emotional strain, leading to a high prevalence of anxiety and depression), and economic (increased

costs, coupled with giving up or cutting back on work to care) strain from providing care (World Alzheimer Report.,2014).

1.4 Prevalence and estimates of dementia from India

Studies on dementia prevalence are scattered around India but predominantly in the south (6 studies in south region and single studies from the west, east, and northern regions). More than 42,000 older people were studied in eight centres across India, and wide variations in estimates were reported. Prevalence of dementia reported from Indian studies range from 0.6 % to 3.5% in rural areas and 0.9% to 4.8 % in urban areas. The difference in reported prevalence could be explained by lack of sensitive and specific local measures of assessment, methodological differences in the studies and a host of genetic, sociocultural and environmental factors (The Dementia India Report.,2010).

Presently, an estimated 3.7 million Indian people aged over 60 have dementia (2.2 million women and 1.5 million men) (The Dementia India Report.,2010). The number of people with dementia is increasing every year because of the steady growth in the older population and stable increment in life expectancy resulting in an estimated increase of twofold by 2030 and threefold by 2050 (The Dementia India Report.,2010). It is estimated that rates of prevalence of dementia will double every 5 years in India, and therefore India will have one of the largest numbers of older adults with this problem. There is a growing realisation that the care of older adults with disabilities makes enormous demands on their carers (The Dementia India Report.,2010; NPHCE India.,2011).

1.5 Pathophysiology of cognitive ageing and dementia

1.5.1 The spectrum of cognitive aging

Normal Cognitive Ageing (cognitive changes as a normal process of brain aging) has been well documented in the scientific literature (Harada et al.,2013). Some cognitive abilities, such as vocabulary are resilient to brain aging and may even improve with age. Other abilities, such as conceptual reasoning, memory, and processing speed decline gradually over time (Mielke and Kessler.,2006). However, there is significant heterogeneity among older adults in the rate of decline in some abilities, such as measures of perceptual reasoning and processing speed (Wisdom et al.,2012). Mild cognitive impairment (MCI) is the stage between the expected cognitive decline of normal aging and the more serious decline of dementia. It can involve problems with memory, language, thinking and judgment

that are greater than normal age-related changes and do not seriously impact daily functioning (Petersen.,2016). Dementia is a syndrome characterised by significant and progressive cognitive decline in one or more cognitive domains with interference in independence of activities of daily living, not exclusively during delirium and not better explained by any other mental disorder (Knopman and Petersen.,2014; American Psychiatric Association.,2000)

1.5.2 Cognitive reserve and Intelligence

One theory for how certain activities may prevent age-associated cognitive decline is the theory of cognitive reserve. The cognitive reserve hypothesis posits that some individuals have a greater ability to withstand pathologic changes to the brain, such as accumulation of amyloid protein due to greater brain reserve (Harada et al.,2013). This hypothesis holds that higher levels of education, participation in certain activities, higher socioeconomic status, and baseline intelligence protect against the clinical manifestations of brain disease. Passive reserve refers to characteristics such as brain volume and the number of neurons and synapses present. Active reserve refers to the brain's potential for plasticity and reorganisation in neural processing, allowing it to compensate for neuropathologic changes (Medaglia et al.,2017).

Fluid and crystallized intelligence are factors of general intelligence (g), originally identified by Raymond Cattell (Cattell.,1963). *Fluid* intelligence or *fluid reasoning* is the capacity to reason and solve novel problems, independent of any knowledge from the past (Cattell., 1971). It is the ability to analyse novel problems, identify patterns and relationships that underpin these problems and the extrapolation of these using logic. It is necessary for all logical problem solving. Fluid reasoning includes inductive reasoning and deductive reasoning. *Crystallised* intelligence is the ability to use skills, knowledge, and experience. It does not equate to memory, but it does rely on accessing information from long-term memory. Crystallised intelligence is one's lifetime of intellectual achievement, as demonstrated largely through one's vocabulary and general knowledge. This improves somewhat with age, as experiences tend to expand one's knowledge. Crystallised intelligence is indicated by a person's depth and breadth of general knowledge, vocabulary, and the ability to reason using words and numbers. It is the product of educational and cultural experience in interaction with fluid intelligence. Crystallised and fluid intelligence are believed to be separate neural and mental systems. However, they are correlated with each other and the overall IQ score is based on a combination of these. For example, the Wechsler Adult Intelligence Scale measures fluid intelligence on the performance scale and

crystallized intelligence on the verbal scale (Wisdom et al.,2012).

1.5.3 Pathology of dementia

Despite dementia being considered as “the epidemic of our century”, little is known about the pathophysiology of this condition. Alzheimer's disease is the most common type of dementia followed by vascular dementia (O’Brien and Thomas.,2015). Neurodegenerative changes are known to begin several years before the manifestation of dementia (O’Brien and Thomas.,2015). Pathogenesis of dementia in unclear, but two theories: amyloid cascade theory and vascular theory, attempt to provide an explanation for its origins. The former is thought to be more relevant to Alzheimer's disease and latter to vascular dementia (De-Paula et al.,2012; O’Brien and Thomas.,2015).

a) Amyloid cascade theory: Medial temporal lobes and the associated neocortical structures in the brain are most commonly affected structures in Alzheimer's disease (De-Paula et al.,2012). The pathological hallmark of this disease is the presence of neuritic plaques and neurofibrillary tangles in the brain (mainly in medial temporal lobes). While neuritic plaques are as a result of accumulation of amyloid-beta peptides, the neurofibrillary tangles due to hyperphosphorylation of Tau protein in neurons (Deng et al.,2013).

According to this hypothesis, the overproduction of amyloid-beta peptide is a result of the disruption of homeostatic processes that regulate its breakdown by beta-secretase and gamma-secretase. The neurotoxin potential of this peptide is because it accelerates aggregation of insoluble protofibrils and oligomers, resulting in neuritic plaques (Selkoe and Hardy.,2016). These processes, in addition to a reduction of amyloid-beta clearance, leads to the extracellular accumulation of this amyloid-beta peptide in the brain, and the consequent activation of neurotoxic cascades that ultimately results in neuronal dysfunction and cellular death (De-Paula et al.,2012; Deng et al.,2013; Slekoe and Hardy.,2016).

b) Vascular theory: Cardiometabolic disorders like obesity, diabetes, hypertension, dyslipidemia, coronary heart diseases, and the sedentary lifestyle produce several vascular changes such as the thickening of the capillary basal membrane and the accumulation of collagen in the vascular endothelium (O’Brien and Thomas.,2015, Chui and Ramirez-Gomez.,2015).

These vascular changes lead to several types of pathologies in the brain: atherosclerosis of small and larger vessels, infarcts in cortical and subcortical areas including lacunar infarcts, whiter matter lesions also called as leukoriasis, gliosis, demyelination, microvascular brain haemorrhages and amyloid angiopathy (Gorelick et al.,2011; Snyder et al.,2015; Chui and Brown.,2007). These brain pathologies are known to accumulate over the lifecourse resulting in reduced perfusion of the brain, neuronal loss, cerebral atrophy and accumulation of phosphorylated tau and beta-amyloid proteins.

The above pathologies are not mutually exclusive or disease specific, but shared by both vascular dementia and Alzheimer's disease. However, the mechanistic link between the two in unclear (Custodio et al.,2017). The pathology described in the above sections occurs as a continuum for normal cognitive ageing through mild cognitive impairment to dementia.

1.6 Impact of dementia

1.6.1 Disability, dependency and mortality

The World Alzheimer's Report highlights the importance of comorbidity in the causation of disability and dependence. Persons with dementia often have serious comorbid physical health problems and both contribute to disability and need for care (World Alzheimer's Report.,2009). The 10/66 Dementia Research Group has assessed the impact of dementia, depression and physical impairment on dependence in LMIC countries: urban and rural sites in Cuba, Dominican Republic, Venezuela, Peru, Mexico, China and India. Those with needs for care were characterised by comorbidity between dementia (cognitive impairment) and physical and mental disorders. Dementia emerged as the leading independent cause of both disability and dependency, followed by limb weakness, stroke, depression, eyesight problems and arthritis. Neither ischaemic heart disease nor hypertension, or even chronic obstructive pulmonary disease was associated with disability or dependency. Dementia has a disproportionate impact on capacity for independent living (Sousa et al.,2009; Sousa et al.,2010).

Studies from LMIC settings have found increased mortality risk for older persons with dementia when compared to higher income countries (Prince et al.,2012). The global age standardised death rate for dementia is 6.7 per 100,000 for men and 7.7 per 100,000 for women. For India, the dementia mortality rate is much higher at 13.5 per 100,000 men and 11.1 per 100,000 women (Lozano et al.,2012). The only study from India, conducted in

Chennai, investigated predictors of mortality among older people living in the community. The study reported a higher risk of mortality (2.3 times) for older people who received a diagnosis of dementia at the baseline survey and risk of mortality was linearly associated with the severity of cognitive impairment (Jotheeswaran et al.,2010).

1.6.2 Caregiver burden

Cares giving in India like elsewhere in a LMIC setting is associated with substantial economic disadvantage. The economic vulnerability of families who care for people with dementia in India is indeed overwhelming, particularly for the families who live below the poverty line. Studies from India indicate that 23% of caregivers (17% primary caregivers and additional 6% of other caregivers) cut back on work and nearly a quarter of all caregivers suffer economic losses as they are unable to fulfil their work responsibilities. In India, despite larger, extended families, the economic strain on family caregivers is substantial. Paid care workers are becoming common in some cities, adding to the economic burden. Moreover, compensatory benefits are practically non-existent (NPHCE India.,2011; The Dementia India Report.,2010).

The 10/66 study in India observed that families from the poorest sections of the society were likely to use expensive private medical services, and spend more than 10% of the per capita Gross Domestic Product on health care further pushing them into impoverishment (Prince et al.,2013). Unfortunately, in India, currently, the provisions for financial support as a welfare measure or benefit for caregivers in taxation is meagre. While formal health insurance is predominantly an urban phenomenon, only few older people in India receive government or occupational pension and the income security for those with dementia is marginal (The Dementia India Report.,2010; NPHCE India.,2011).

1.6.3 Economic costs

The total estimated worldwide costs of dementia were US$ 604 billion in 2010, equivalent to 1% of the world's gross domestic product. Low-income countries accounted for just under 1% of total worldwide costs (but 14% of the prevalence of dementia), middle-income countries for 10% of the costs (but 40% of the prevalence of dementia) and high-income countries for 89% of the costs (but 46% of the prevalence of dementia).

About 70% of the global costs occurred in just two regions: Western Europe and North America. These discrepancies are accounted for by the much lower costs per person in

lower income countries – US$ 868 in low-income countries, US$ 3,109 in lower-middle-income, US$ 6,827 in upper-middle-income, and US$ 32,865 in high-income countries. The costs are driven mainly by social care needs; health care costs account for a small proportion of the total, given the low diagnosis rate, limited therapeutic options, and the underutilisation of health care services (WHO.,2012; Prince et al.,2013).

The World Alzheimer Report 2010 tentatively estimated an 85% increase in costs to 2030, based only on predicted increases in the numbers of people living with dementia. Costs in LMICs including India are likely to rise faster than in high income countries due to demographic and social changes that reduce the availability of family members to provide care (World Alzheimer Report.,2010).

In India, with an estimated 3.7 million persons with dementia, the total societal cost of dementia is estimated to be US$ 3.415 billion (INR 147 billion). The total cost per person with dementia is US$ 925 (INR 43,285). With the recognition that as the disease progresses, the costs also increase, estimates indicate that, during the average 7 years of life for a person with dementia, the total cost of care would be about INR 960,000. Considering the recent estimates by Alzheimer's Disease International, India is currently spending nearly 150,000 million INR per year for care of persons with dementia. It is predicted that the number of persons with dementia would double by 2030 (3.69 million to 7.61 million), the immediate consequence would be that the cost of care would also double, with two-thirds or more of this huge burden met by individual households (The Dementia India Report.,2010).

1.7 Limited research in cognitive ageing in India

Although neurocognitive disorders are the second highest source of burden after tropical diseases, research in India is minimal (The Dementia India Report.,2010). Research into cognitive ageing has until recently been confined to developed countries, principally Europe and the United States of America. Equity alone demands that the distribution of the research effort should more adequately reflect the geographical distribution of late life neurocognitive disorders.

In the last 15 years, the data on dementia prevalence in India have expanded considerably. Ageing studies to date in India are limited to examining prevalence of cognitive impairment and dementia in different geographical areas and their associations with sociodemographics and other NCDs (The Dementia India Report.,2010; Prince et al.,2009). Studies from India

have documented advancing age, rural residence, widowhood, lower educational level, lower socioeconomic status, and positive family history as risk factors for cognitive impairment and dementia (Das et al.,2012). Some studies have found smoking, Apoε4 genotype, stroke, diabetes and hypertension as risk factors of dementia (Shaji et al.,1996: Saldanha et al.,2010; Das et al.,2007; Das et al.,2012). In addition to reporting the prevalence of dementia and Mild Cognitive Impairment, population based research from the 10/66 Dementia Research Group in south India has provided prevalence rates for other NCDs and their impact on mortality, disability and caregiver burden in late life (Albanese et al., 2011). Two Incidence studies of dementia, both from north India have reported an incidence of 4.7 per 1000 person-years and 5.3 per 1000 person-years respectively (Chandra et al.,2001; Raina et al.,2009).

There are limited data from longitudinal studies examining lifecourse risk factors (e.g. growth and development in early life, and cardiometabolic disorders and socioeconomic position in midlife) for cognitive ageing in LMIC settings including India. Well-designed lifecourse epidemiological research can generate awareness, inform policy, and encourage service development (Prince et al.,2008).

1.8 Developmental Origins of Health and Disease (DOHaD)

The 'Developmental Origins of Health and Disease (DOHaD)' hypothesis, a more recent term for the concept initially proposed and called 'Fetal Origins of Adult Disease or the Barker's hypothesis' in the 1990s, postulates that exposure to adverse environmental influences during critical periods of development and growth (reflected in lower birth weight) causes impaired development of key metabolic tissues leaving a lifelong vulnerability to cardiometabolic disease (Barker.,2007). Barker proposed that the association between small size at birth and disease in later life reflects the permanent effects of fetal undernutrition (Barker et al.,1993; Barker.,2007). Fetal undernutrition could occur because the mother is undernourished or because the materno-fetal supply line (uterine blood flow, placenta) is suboptimal. The fetus depends on the transfer of nutrients from the mother and adapts to an inadequate supply of nutrients in various ways: prioritisation of brain growth at the expense of other tissues, such as the abdominal viscera; reduction in the secretion of and sensitivity to the fetal growth hormones (for example, insulin); and upregulation of the hypothalamo-pituitary-adrenal (stress) axis (Gluckman et al.,2008). Barker proposed that, although they occur in response to a transient phenomenon of fetal undernutrition, these changes become permanent or *programmed* because they occur during critical periods of early plasticity. Programmed changes may include different tissues, producing a variety of metabolic effects,

which could lead directly to adult cardiovascular disease or render the individual more susceptible to the adverse cardiometabolic effects of environmental stressors, such as smoking and obesity in later life. Subsequent research in experimental animals has confirmed that it is possible to program high blood pressure and diabetes by manipulating the nutrition of the mother during pregnancy (Duque-Guimaraes and Ozanne., 2013).

Developmental neuroplasticity is a general term referring to changes in neural connections during development as a result of environmental interactions as well as neural changes induced by learning (Kolb.,1995) This is specific to the change in neurons and synaptic connections as a consequence of developmental processes. A child creates most of these connections from birth to early childhood. During development, the central nervous system acquires information via endogenous or exogenous factors as well as learning experiences. In acquiring and storing such information, the plastic nature of the central nervous system allows for the adaptation of existing neural connections in order to accommodate new information and experiences, resulting in developmental plasticity. This form of plasticity that occurs during development is the result of three predominant mechanisms: synaptic and homeostatic plasticity, and learning (Kolb and Gibb., 2011).

2. Risk factors for cognitive ageing

The greatest risk factors for cognitive impairment and dementia in late life are older age, lower educational attainment, family history, and genetic susceptibility genes, such as the Apolipoprotein ε4 allele (World Alzheimer Report.,2014; The Dementia India Report.,2010).

2.1 Age and gender

The prevalence of dementia increases steadily with age and a higher prevalence is seen among older women than men. The larger proportion of older women than men who have dementia can be explained by the fact that women live longer in India (WHO SAGE National Report for India.,2013). In general, studies of age-specific prevalence and incidence of dementia among older people show no significant difference between women and men. It may therefore appear that gender is not a risk factor for cognitive decline and dementias among older people (World Alzheimer Report.,2014; The Dementia India Report.,2010).

2.2 Genetic factors

The Apoε4 allele represents a major risk factor for cognitive impairment, cognitive decline and dementias in late life (Small et al.,2004). The frequency of Apoε4 allele in Indian population is lower than the west and ranges from 0.073-0.133. However, the strength of the association between Apoε4 allele and dementia in the Indian population is not significantly different to the west (Ganguli et al.,2000; Thelma et al.,2001). Apoε4 genotype increases the risk for Alzheimer's dementia by 3 to 10-fold (Small et al.,2004). The average risk for developing dementia at the age of >65 years is about 15%. However, in carriers of an Apoε4 allele, this increases to 30% and in individuals without an Apoε4 allele, it is only 9%. The adjusted odds of age related cognitive decline, cognitive impairment, and dementia in Apoε4 carriers are 3.0 (95% CI 1.2-7.3), 3.7 (95% CI 2.3-6.0) and 5.6 (95% CI 3.6-8.9) respectively when compared to non-carriers (Rosich-Estrago et al.,2004). Apolipoproteinε plays important roles in lipoprotein metabolism as well as regulating synaptic plasticity and repair (Bu.,2009), and the Apoε gene is a known susceptibility gene for both sporadic and familial Alzheimer's disease. Previous studies have shown an association between Apoε4 allele and brain anomalies including hippocampal atrophy, increased cerebral beta-amyloid deposition, cerebral hypometabolism and increased white matter hyperintensity burden (Schilling et al., 2013). Apoε4, a susceptibility gene for dementia, plays an important role in the regulation of synaptic plasticity of hippocampus (Liu et al.,2015).

Some studies have shown that the severity of cognitive problems and rate of progression of dementia were greater in carriers of the Apoe ε4 allele compared to non-carriers (Mielke et al.,2011; Beeri et al.,2006; Helzner et al.,2009; Martias et al 2005; Craft et al 1998; Frisoni et al.,1995). Genetic testing has a role in the diagnosis of familial early-onset Alzheimer's disease, however it adds little to the diagnosis of sporadic Alzheimer's Disease. The use of predictive gene testing, including Apoε4 is not recommended particularly as there is no known preventative or curative measure available.

However, none of the above risk factors can be modified by medical interventions or by individual behaviour. In the following sections of this chapter, I have provided a summary of studies that have examined the relationship of various modifiable cardiometabolic and other lifestyle risk factors with cognitive function in late life.

2.3 Cardiometabolic risk factors

2.3.1 Diabetes

There have been numerous longitudinal studies testing for a prospective association of diabetes with the onset of cognitive impairment and dementia in late life. These have been summarised in four systematic reviews (Cheng et al.,2012; Gudala et al.,2013; Roberts et al.,2014; World Alzheimer Report.,2014). In general, most studies have shown lower cognitive performance, an increased rate of cognitive decline and an increased risk for dementia in those with diabetes. The association between diabetes and dementia has been shown across countries, continents and ethnic groups (World Alzheimer Report.,2014).

Further, a recent meta-analysis demonstrated that individuals with Mild Cognitive Impairment and diabetes were more likely to progress to dementia than individuals with Mild Cognitive Impairment and no diabetes (Cooper et al.,2015). Evidence suggests diabetes increases risk for late life cognitive impairment by not only through vascular pathways but also through interactions of other biological mechanisms related to diabetes itself, such as insulin resistance and inflammation (Mushtaq et al.,2014; Ferreira et al.,2014).

In older adults with diabetes, poor glycaemic control is an important predictor of cognitive decline. Complications from diabetes resulting from poor glycaemic control like diabetic retinopathy, diabetic foot, cerebrovascular and cardiovascular disease are all associated with an increased risk of dementia (Parikh et al.,2011). However, those with better glycaemic control have a reduced incidence of cognitive decline and dementia. Rapid improvement in

glycaemic control (falling HbA1c levels from a high baseline level) is known to be associated with worse cognitive outcomes when compared with those with stable, good or poor control, and hypoglycaemic episodes in those with diabetes is a reliable predictor of the onset of dementia (Ravone-Springer et al.,2014; Luchsinger et al.,2011). Therefore, a cautious approach in optimising glycaemic control whilst avoiding hypoglycaemia is necessary to improve cognitive outcomes in this population. Findings on the impact of particular treatments for diabetes (e.g. different types of oral hypoglycaemic drugs and insulin) are inconsistent between studies. Management of cardiovascular comorbidities is important, with studies suggesting that the incidence of dementia may be lower among those with diabetes who are also treated with statins (Feil et al.,2011). Comorbid hypertension increases the risk of dementia among people with diabetes, and treatment for hypertension may reduce the risk (Feil et al.,2011).

2.3.2 Obesity

Several prospective epidemiological studies have been conducted to test the associations of BMI in mid and late life with incident dementia. Three systematic reviews of studies examining this association were identified: Gorsope and Dave 2007, Beydoun et al 2008 and Anstey et al 2011. The most recent of these, by Anstey and colleagues is the most comprehensive and useful, in distinguishing between studies of the effects of midlife and late life obesity, and their effects upon dementia. I have provided a summary of key findings from this review. It included 15 prospective studies examining the relationship between body mass index (BMI) and dementia, 4 studies of midlife and 11 of late life exposures, with follow-up periods ranging from 3 to 36 years. BMI in late life was not associated with dementia. However, pooled relative risks from meta-analyses indicated positive associations between BMI in midlife and dementia risk. Those who were overweight in midlife had around a 30% increased risk of dementia compared with those with normal BMI [RR=1.26, 95% CI (1.10,1.44)] while those who were obese had up to twice the risk [RR=2.04 95% CI (1.59,2.62)] There is a suggestion by the authors of a ‘U-shaped’ association in that those with a low BMI in midlife were also at twice the risk of developing dementia compared with those with a normal BMI [RR=1.96, 95% CI(1.32-2.92)]

Three important population based studies published since this systematic review have provided further conflicting findings. In the Finnish, Cardiovascular Risk Factors, Aging and Dementia study, there was a positive association between midlife obesity, but not overweight, and incident dementia [RR 2.44, 95% CI (1.18,5.06)]. This association diminished and not was statistically significant after controlling for other cardiovascular risk

factors and Apoε4 genotype (Kivipelto et al.,2005). In the Prospective Population Study of Women in Sweden there was no association between BMI and incident dementia after 32 years of follow-up from mid- to late life (Gustafson et al.,2009). No association between midlife BMI or weight and dementia incidence was detected in the Honolulu Asia Aging Study after 32 years of follow-up (Stewart et al.,2005). A recent, large, retrospective cohort study found a lower risk for dementia among those who were overweight even in midlife, while those who were underweight had an elevated risk (Qizilbash et al.,2015). In summary, the evidence regarding an association between midlife obesity and incident dementia is weak and conflicting.

Declining BMI in late life is associated with increased cognitive impairment and risk of incident dementia. Being overweight and, even possibly being obese in late life has been associated with reduced risk of dementia (Luchsinger et al.,2007; Fitzpatrick et al.,2009; Barnes et al.,2009; Dahl et al.,2008; Gustafson and Luchsinger., 2013; Luchsinger et al.,2013). More contemporaneous associations between level of BMI and cognitive impairment in late life have led to conflicting findings which appear to be accounted for by accelerated late life weight loss in the years preceding the clinical onset of dementia.

Waist circumference is less often measured than BMI in prospective, longitudinal epidemiological studies of the association with cognitive impairment and onset of dementia in late life. This exposure was not assessed in the above mentioned systematic reviews. There is limited evidence from three population based studies (Prospective Population Study of Women in Sweden, Kaiser Permanente study, New York study) that examined the relationship between central obesity and dementia risk (Gustafson et al.,2009; Whitmer et al.,2008; Luchsinger et al.,2012). However, the results from these studies are more consistent than studies examining the relationship between BMI and dementia. A positive, prospective association between a waist-to-hip ratio greater than 0.8 and greater dementia risk was found in all the three studies. Those with highest central obesity in midlife were almost two to three times more likely to have been diagnosed with dementia three decades later independent of BMI. Because central obesity is a better indicator of associated metabolic changes than BMI, these findings support the hypothesis that any link between adiposity and cognitive disorders in late life may be best understood as a continuum through type 2 diabetes, possibly mediated through insulin resistance and hyperinsulinaemia (Luchsinger and Gustafson.,2009).

In conclusion, there is currently insufficient evidence to confirm an association between midlife BMI/adiposity and dementia in late life. Decline in BMI from mid- to late life appears

to be a stronger predictive factor than midlife obesity. Clarification of the nature of this association is complicated by the decline in BMI that accompanies dementia and in its preclinical stages by up to a decade. The possibility that central obesity in midlife rather than BMI as a future dementia risk warrants further research.

2.3.3 Hypertension

The association between blood pressure and late life neurocognitive disorders is complex, nonlinear and age dependent. There is particularly strong evidence for an association of midlife hypertension with incident dementia in late life (Launer et al.,2000; Freitag et al.,2006; Kivipelto et al.,2002; Ronnemaa et al.,2011). Meta-analyses of longitudinal, and cross-sectional studies, including a Cochrane review, have not indicated a consistent relationship between hypertension across life and cognition in late life. These studies indicate the raised blood pressure in midlife is associated with an increased risk of cognitive impairment, cognitive decline and dementia 10 to 20 years late. However, by the time cognitive impairment is manifest, blood pressure levels are relatively low, although this has not been a universal finding (Power et al.,2011; McGuinness et al.,2009; Shah et al.,2009; Guanet al.,2011; Sharp et al.,2011).

Similar to data on the link between obesity and cognitive decline/dementia, some studies demonstrate that hypertension in late life may be protective against cognitive decline. These population based studies of older adults have demonstrated that those at risk of cognitive decline had a greater increase in systolic blood pressure followed by a greater decrease when compared to those who did not. This inverse association may reflect a decline in blood pressure that occurs in the prodromal stage of dementia and or a feature of a more general metabolic change associated with neurodegeneration (Kennelly et al.,2009; Corrada et al.,2014).

A systematic review of meta-analyses, randomised controlled trials and observational studies by Rouch and colleagues indicate that treatments of hypertension may reduce the risk of cognitive decline in late life (Rouch et al.,2015). This review included 18 longitudinal studies, 11 randomised controlled trials, and 9 meta-analyses assessing the effect of antihypertensive medication on cognitive impairment or cognitive decline (n=1,346,176). Of the 11 longitudinal studies that assessed the effect of antihypertensive medication on incidence of dementia, three studies did not find a significant protective effect. Four randomised controlled trials showed a potentially preventive effect of antihypertensive drugs on the incidence of dementia or cognitive decline, with a 55 % reduction in dementia risk (3.3

vs. 7.4 cases per 1,000 patient years; $p < 0.001$) and with a 41% reduction in cognitive decline associated with stroke and 19% reduction in cognitive decline. However, a meta-analysis of 14 longitudinal studies examining the relationship between antihypertensive medication use and the incidence of dementia or cognitive decline concluded the opposite. There were no significant differences in incidence of dementia [RR=0.90 95% CI (0.79,1.03)], cognitive decline [RR=0.97 95% CI (0.92–1.03)] and cognitive impairment [RR=0.97 95% CI (0.92–1.03) between subjects with (n=32,658) and without (n=36,905) antihypertensive medication use. Treatment for hypertension was not protective of cognitive decline in late life (Chang-Quan et al.,2011). The conflicting results from these meta-analyses may be due to methodological considerations. The lack of homogeneity across study designs, patient populations, exposures, outcomes, and duration of follow-up are the most important methodological limitations that might explain the discrepancies in findings between these studies.

In conclusion, studies examining the association of hypertension with the cognitive function in late have demonstrated clearly the importance of a lifecourse perspective. There is strong and consistent evidence for an association of midlife hypertension with dementia in late life. Hypertension in late life is not associated, or is even inversely associated with incident dementia because of the decline in blood pressure levels that precedes the clinical onset of dementia. There is inconsistent evidence on possible cognitive benefit of antihypertensive medication.

2.3.4 Hyperlipidemia (elevated cholesterol)

The role of total cholesterol levels in the aetiology of late life cognitive impairment remains controversial with some studies but not others suggesting that high midlife cholesterol levels predict increased risk of cognitive impairment and dementia in late life. Systematic reviews of prospective studies have found mixed results for the relationship between both midlife and late life high cholesterol levels and dementia, including no association between cholesterol levels and dementia (Anstey et al.,2008; Kivipelto and Solomon.,2006). In a systematic review of 18 prospective studies (n=14,331) by Anstey and colleagues with follow-up ranging from 3 to 29 years' consistent associations between high midlife total cholesterol and increased risk of dementia was found. There was no evidence supporting an association between late life total cholesterol and cognitive impairment and dementia. There was no relationship between midlife and late life total cholesterol and cognitive decline.

Older adults with dementia have normal or relatively lower levels of total cholesterol. Epidemiological studies examining the cholesterol-dementia relationship over 26 year and 32-year follow-up periods, showed that those who went on to develop dementia had a greater decline in cholesterol levels prior to incident cognitive impairment (Stewart et al., 2007; Mielke et al.,2010). Some observational studies have suggested that statin medications used to control cholesterol levels may reduce the risk of dementia (McGuinness et al.,2009; Muangpaisan and Brayne.,2010; Beri et al.,2009). However, a Cochrane review and two other systematic reviews found no or inconsistent evidence that use of statins reduces risk (McGuinness et al.,2009; Richardson et al., 2013; Ligthart et al.,2010).

2.3.5 Coronary heart disease

Coronary heart disease (CHD), the most common type of heart disease, is one of the major causes of death worldwide (Opie et al.,2006). The relation between CHD and cognitive ageing is complex and difficult to confirm because of strong competing risks of death. Several studies have showed that CHD is associated with an increased risk of cognitive impairment, decline and dementias in late life (Newman et al.,2005; Roberts et al.,2010), whereas other studies have found no such associations (Knopman et al.,2005; Petrovitch et al.,1998). The Rotterdam Study showed that unrecognised myocardial infarction was associated with increased risk of dementia, whereas recognised myocardial infarction was not (Ikram et al.,2008). Atherosclerosis is a shared aetiological factor for both CHD and dementia, and this may explain the increased risk of dementia in those with CHD (Justin et al.,2013; Duron and Hanon.,2008). In addition, reduced cardiac function, diminished cerebral blood flow and emboli from CHD are other possible mechanisms linking CHD with dementia (Muqtadar et al.,2012; Justin et al.,2013; Duron and Hanon.,2008).

2.4 Smoking

Several systematic reviews, meta-analyses and longitudinal studies have found strong evidence that current smoking increases the risk of cognitive decline and possibly dementia (Prince et al.,2014; Plassman et al.,2010; Lee et al.,2010; Anstey et al.,2007; Cataldo et al.,2010; Peters et al.,2008; Beydoun et al.,2014; McKenzie et al.,2014; Zhong et al.,2015). The Honolulu Asia Ageing study examined the impact of smoking in midlife and cognitive impairment and dementia in late life (Tyas et al.,2003). Adjusting for age, education and Apoε4 genotype, the risk of dementia in smokers increased with pack-years of smoking at medium [OR=2.18, 95%CI (1.07-4.69)] and heavy [OR=2.40 95%CI (1.16-5.17)] smoking

levels. Very heavy smoking was not associated with dementia [OR=1.08; 95% CI(0.43-2.63)]. The lack of association in very heavy smokers may be due to a survivor effect. Number of pack-years in midlife was correlated inversely with late life cognitive function and positively with dementias in a dose-response manner. Rusanen and colleagues report from a large multi-ethnic cohort that heavy smoking in middle-age doubled the risk of dementia in late life (Rusanen et al.,2011).
Smoking contributes to atherosclerosis, and has been related to cerebral small vessel disease (van Dijk et al.,2008; Messner and Bernhard.,2014). Additionally, tobacco contains many neurotoxins, which might cause direct neuronal damage (Treweek et al.,2009). However, the exact mechanisms underlying the relation between smoking and dementia require further investigation. Quitting smoking may reduce the associated risk to levels comparable to those who have not smoked (World Alzheimer Report.,2014; McKenzie et al.,2014; Zhong et al.,2015; Sabia et al.,2012).

2.5 Alcohol

Meta-analyses of prospective and case control studies of older adults suggest small or moderate alcohol consumption may decrease the risk of cognitive decline and dementia (Ilomaki et al., 2015; Anstey et al.,2009; Peters et al.,2008; Neafsey and Collins.,2011).The most recent systematic review by Ilomaki and colleagues included 45 longitudinal studies examining the relationship between drinking alcohol and cognitive function, decline and dementia risk in late life reports that light to moderate drinking may decrease the risk of dementia [RR=0.74; 95%CI (0.61-0.91)] whereas heavy to excessive drinking does not affect the risk [RR=1.04; 95%CI (0.69-1.56] respectively. The findings from this systematic review are similar to previous systematic reviews listed above (Anstey et al.,2009; Peters et al.,2008; Neafsey and Collins.,2011). At least in population based epidemiological studies, low to moderate alcohol use is associated with reduced risk of incident dementia. The systematic review by Peters and colleagues conducted a subgroup evaluation to examine specific dementia type, alcohol type, gender and Apoε4 status in detail, which suggests that the protective effects are more likely with wine consumption and in the absence of an Apoε4 allele (Peters et al.,2008). Although alcohol may be associated with less incident dementia, it is difficult infer causality. It is well recognised that men and women who drink alcohol sensibly also moderate themselves to live healthier lives both in physical, dietary and mental domains (Peters et al.,2008).

There are some important limitations in the published literature in this field. Publication bias may have resulted in negative studies not being published. The different studies vary in

population, assessment, follow-up, classification of alcohol use with some studies not specifying the amount of alcohol in a 'standard drink' and not reporting the patterns of drinking. Also, related to this is the repeated finding that it is the low to moderate levels of alcohol that are protective despite the amounts included in this category varying widely between studies. With respect to alcohol intake, the amount of detail reported regarding the collection of these data also varies widely with some studies collecting data on recent consumption to some assessing consumption further back in time or lifetime abstinence/change in consumption and with the 'non-drinker' reference category.

There are many mechanisms proposed to explain a neuroprotective effect of alcohol. They include antioxidant properties of the flavenoids in wine, increasing levels of HDL cholesterol and fibrinolytic factors leading to lower platelet aggregation, cardiovascular protection and possibly lower risk of stroke/ischaemia (Rimm et al.,1999; Agarwal.,2002). In summary, mild to moderate alcohol intake is associated with less incident dementia in late life, at least in Western populations. The evidence is not strong enough, however, to suggest those who do not drink should start drinking, especially when weighed against the potential negative effects of excessive alcohol consumption, such as an increased risk of falls among older adults (Stahre et al.,2014).

2.6 Physical activity

Several systematic reviews and meta-analyses of nearly 20 prospective, longitudinal, and cross-sectional studies, as well as randomised controlled trials, have shown that a higher level of physical activity even in some cases, mild physical activity such as walking is associated with a decreased risk of cognitive impairment and/or improved cognitive function in late life (Lee et al.,2010; Beydoun et al.,2014; Rolland et al.,2008; Hamer and Chida., 2009; Paterson, and Warburton.,2010, Lautenschlage et al.,2008; Sofi et al.,2011; Blondell et al.,2014; Ahlskog et al.,2011; Colcombe and Kramer.,2003; Smith et al.,2010; Bherer et al.,2013). However, most of these studies had relatively short follow-up, and studies with long follow-up periods have yielded inconsistent results (Rovio et al.,2005; Morgan et al.,2012).

Physical activity is inversely associated with cerebrovascular and cardiometabolic disorders, and could therefore also reduce the risk of cognitive decline and dementia in late life. (Berlin and Colditz.,1990; Helmrich et al.,1991). Physical activity is also known to have a direct neuroprotective effect as it improves cerebral perfusion and increases neurogenesis (van Praag et al.,1999; Pereira et al.,2007). Several randomised controlled trials and a

Cochrane review of such trials have found that inactive, but otherwise healthy, older adults who begin an exercise program experience significantly improved cognitive function (Angevaren et al.,2008; Barnes et al.,2013). Studies most consistently demonstrate that exercise must be regular and tend toward the more vigorous side for positive effect on cognition. (Paterson and Warburton.,2010; Lautenschlager et al.,2008; Sofi et al.,2011; Blondell et al.,2014; Colcombe and Kramer.,2003). Due to the heterogeneous nature of these studies, it is not possible to inform the optimal duration of the physical activity, the type and intensity of the exercise, and in what period during a person's lifespan it should occur to maximise potential protective effects.

2.7 Nutrition

Lower levels of haemoglobin and anaemia are well established risk factors for lower cognitive function and dementia in late life (Andro et al.,2013). A systematic review of 43 population based studies found no differences in cognitive function and rates of dementia between older adults who were vegetarians when compared to those who were non-vegetarians (Cao et al.,2016). There was no relationship between amount of intake of fish, fruits and vegetables with cognitive function or dementia in this review.

Though there has been consistent evidence for a direct association of folate levels with cognition and an inverse association with dementia (Araujo et al.,2015; Raman et al.,2007), the relationship between B12 and cognition in late life has been controversial and findings from several systematic reviews are in conclusive (Moore et al.,2012; O'Leary et al.,2012; Raman et al 2007). The inconsistent finding from studies examining the relationship between nutritional factors with cognition in late life are due to a variety of reasons. They include heterogeneity in populations and dietary composition, possibility of reverse causality and inconsistency in nutrient assays (for e.g. B12).

2.8 Conclusions

In summary, the strongest evidence for possible causal associations with late life cognitive impairment and dementia are those of hypertension in midlife, and smoking and diabetes across the lifecourse. There is particularly strong and consistent epidemiological evidence that hypertension in midlife increases the risk of dementia. Diabetes both in mid- and late life is associated with an increased risk of cognitive impairment, decline and dementia in late life. There is weak and inconsistent evidence that obesity and hypercholesterolaemia in midlife may increase the risk of dementia. Hypertension, obesity and hypercholesterolaemia

in late life are not associated with impaired cognitive functioning or dementia. However, a decline in blood pressure level, BMI and total cholesterol precedes and predicts the onset of dementia, by five to 15 years. The relationship between cardiometabolic risk factors and cognition in late life is complex and highlights the importance of a lifecourse approach to better understand these associations.

3. Size at birth and cognitive ability in late life: A systematic review

3.1 Background

3.1.1 Developmental Origins of Health and Disease (DOHaD) pathways of cognitive ageing

Neurocognitive disorders are a major cause of disability and mortality in late life and are associated with high costs for health systems and society (Lim et al.,2012; World Alzheimer Report.,2014). For late-life neurocognitive disorders, as for other late-life chronic diseases, there is an increased interest in the relevance of DOHaD hypothesis with two plausible pathways to cognitive ageing: (a) by a direct effect of reduced intrauterine nutrition (reflected in birth size) on fetal brain development leading to reduced cognitive reserve and decreased cognitive ability *or* (b) programming of metabolism in very early life by under-nutrition leading to increased risk mediated through cardiometabolic disorders (Whalley et al.,2006).

Quality of nutrition during intra-uterine development, reflected crudely in size at birth, is an important determinant of lifelong function, health and disease risk (Barker D et al.,1993). Birth weight and head circumference at birth are indicators of intrauterine growth and brain development respectively (Epstein & Epstein.,1978; Gunnell.,2002). Larger birth weight, the most widely researched birth size measure, is associated with better cognitive function and higher intelligence from infancy through the third decade of life in several populations and countries independent of social background (Gu et al.,2017; Shenkin et al.,2004; Grove et al.,2017). This association of birth weight with cognition occurs across the whole spectrum of birth weight rather than being confined to an extreme group. However, the strength of this association is known to diminish as individuals reach middle age, and associations with growth in early life may not persist beyond midlife (Grove et al.,2017).

In a systematic review, Grove and colleagues examined the relationship between birth weight and general cognitive ability in non-clinical adult populations (Grove et al.,2017). This included 1,122,858 participants aged between 18 to 78 years, from 19 studies. Of these only eight could be included in a random-effects meta-analysis, and three were in those aged 60 yrs and above. There was a modest association of birth weight with cognitive ability; with each kilogram increase in birth weight there was a 0.13 SD increase in general intelligence (95% CI: 0.07, 0.19) in those aged less than 60 yrs, independent of gestational age and parental social class at birth. However, the effect size was much lower and not statistically significant in those aged 60 years and above [0.07 SD, 95% CI (-0.02, 0.16)]. In addition to

the small number of studies, the authors did not consider other birth size parameters (like head circumference, length at birth and ponderal index) which are known to be associated with cognitive ability in this age group (Gale et al.,2003; Shenkin et al.,2009; Zhang et al.,2009). While birth weight was not a reliable predictor of cognitive ability or decline beyond midlife in this review, it would be premature to conclude that prenatal environment is not associated with cognitive ability in late life.

3.2 Aims

The aim of this systematic review was to locate, appraise and synthesise studies investigating the relationship between size at birth and cognitive ability in late life.

3.3 Materials and methods

It was conducted according to the Cochrane guidelines for systematic reviews of observational studies, and adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance (Moher et al.,2015).

3.3.1 Inclusion and exclusion criteria

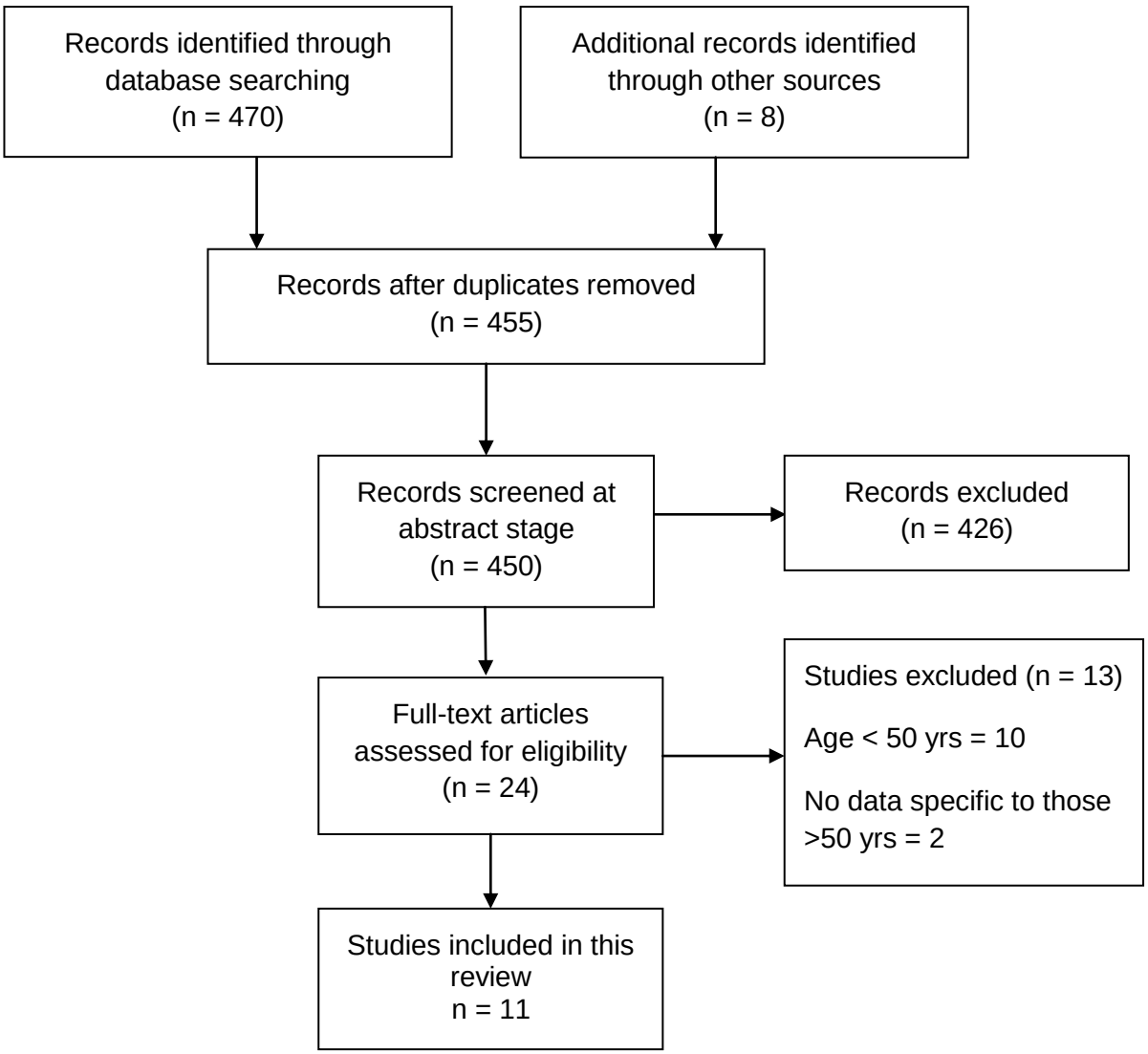
Cross-sectional or longitudinal studies examining the relationship between *any* birth size parameter (birth weight, birth length, head circumference and ponderal index) and performance on *any* cognitive function test in adults aged 50 years and above were eligible for inclusion. Studies were excluded if they examined the association of birth size with mental disorders (e.g. depression) or physical health (e.g. frailty) without reporting measurements of cognitive performance, or were purely qualitative in nature.

3.3.2 Identification and selection of studies (Figure 3.1)

Searches were undertaken by two independent researchers (Murali Krishna and Michelle Madden) in the following databases: MEDLINE, Embase, PsychINFO and CINAHL. Databases were searched from their inception to March 2017. Two reviewers (Murali Krishna and Steve Jones) independently screened all the potential studies against the inclusion criteria. Disagreements were resolved by discussion. The population search terms (both MeSH terms and text words) for *exposure* included “birth weight, birth size, birth length, ponderal index, growth in utero, fetal growth, fetal development, fetal growth retardation, intrauterine growth, prenatal nutrition, fetal origins hypothesis” *and* for outcome

included “cognition, memory, attention, recall, intelligence, brain function, and dementia". Where available, limits appropriate to participants (human studies), age (above 50 years) and study design (cohort studies, observational studies, and longitudinal studies) were applied. No date or language restrictions were applied (Appendix 1 illustrates the search strategy for this systematic review). Experts in the field were contacted for any ongoing and unpublished studies. Authors were contacted for additional information when indicated. Reference lists of included studies were scanned for additional relevant publications. Citation searches were also conducted on key papers. The International Journal of Geriatric Psychiatry, Journal of Alzheimer's Disease and Dementia, and Journal of Developmental Origins of Health and Disease were manually searched from March 2015 to March 2017.

Figure 3.1 Flow diagrams illustrating the process of selection of eligible studies for this systematic review



3.3.3 Data extraction and analyses

A data extraction form was created and piloted (Appendix 2). Data were extracted on all measurements of size at birth, scores on cognitive function tests (both for individual domains and composite scores) and any other relevant key data. The quality of eligible studies was evaluated using the Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE) checklist (von Elm et al.,2008) (Appendix 3). Two independent researchers (Murali Krishna and Steve Jones) undertook data extraction and quality assessment. Disagreements were resolved by consensus. If it was feasible to conduct a meta-analysis, it was planned to provide an estimate of combined effect size. If sufficient numbers of eligible studies were retrieved, it was planned to evaluate publication bias by a funnel plot analysis.

3.4. Results

3.4.1 Selection of studies

Selection process for this systematic review was conducted in accordance with the PRISMA guidelines - Preferred Reporting Items for Systematic Reveiws and Meta-Analyses (Moher et al.,2015). Figure 3.1 outlines the results of the search process. Of the 455 selected studies, 11 met the eligibility criteria for this review.

3.4.2 Key characteristics (table 3.1)

a) Setting and design: The studies were published between 1996 and 2014, and included community dwelling men and women who volunteered to participate. Two studies had a cross sectional design (Erickson et al.,2010; Zhang et al.,2009), while others were longitudinal follow-ups of established cohorts. Of the 11 studies, nine were cohort studies in which participants were matched to their birth records. The other two were community based cohorts from the USA, set up for examining cardiovascular disorders and birth weight was self-reported by the participants.

b) Demographics: The sample size ranged from 130 to 6,875 and participants were aged between 50 to 89 yrs. While Raikkonen et al included men only, Erickson et al included women only (Raikkonen et al.,2013; Erickson et al.,2010).

Table 3.1 Key characteristics of the studies included in this systematic review

First author, year and country	Population and setting	Study design	Sample size, gender and age	Exclusion criteria	Early life exposures	Cognitive outcomes
Martyn 1996 UK	Men and women born in Hertfordshire, Sheffield or Preston between 1920-1943	Longitudinal follow-up of a birth cohort	N=1576 (% F unclear) Mean 61 (2.1) yrs	Those born before 38 weeks of gestation	Birth weight, length, head circumference, gestational age, maternal age, parity and paternal occupation	Alice Heim intelligence test Mill Hill Vocabulary test
Raikkonen 2013 Finland	Men born Helsinki between 1934-44 and performed compulsory military service	Longitudinal follow-up of the Helsinki birth cohort	N=931 (0% F) Mean 68 (2.5) yrs	Those not living in Helsinki	Birth weight, length, head circumference, gestational age,maternal age, parity and height	Finnish Defense Forces basic Intellectual Ability Test
Shenkin 2009 UK	Men and women born in one hospital in Edinburgh UK between 1921-1926	Longitudinal follow-up of a birth cohort	N=130 (71% F) Mean 78 (1.4) yrs 75-81 yrs	dementia deafness	Birth weight, length, head circumference, gestational age, maternal age, parity and height	Controlled Word Association Test Murray House Test Raven's Matrices Test National Adult Reading Test
Gale 2003 UK	Men and women born in Jessop Hospital for Women in Sheffield	Longitudinal follow-up a stratified sample of a birth cohort.	N=215 (46% F) Mean 70 (2.0) yrs 66-75 yrs	dementia deafness	Birth weight, length, head circumference, gestational age, and parental occupation	Alice Heim Intelligence Test, Weschler logical memory test
Costa 2011 USA	Men and women from Minneapolis and Washington	Longitudinal follow-up of a community cohort	N=6785 (56% F) Mean 59 (5.6) yrs 54-73 yrs	Coronary heart disease, stroke, prematurity non-white	Birth weight by recall and non-hospital records	Delayed Word Recall test, Digit Symbol Test Word Fluency Test
Skogen 2013 Norway	Men and women from Bergen born between 1925-1927	Longitudinal follow-up of a birth cohort	N=346 (55% F) 72-74 yrs	None reported	Birth weight, length, head circumference, maternal age and parity, parental occupation	Kendrik Object Learning test. Trail making test, Digit Symbol Test, Block Design, Controlled Word Association Test

Table 3.1 Key characteristics of the studies included in this systematic review (continued)

First author, year and country	Population and setting	Study design	Sample size, gender and age	Exclusion criteria	Early life exposures	Cognitive outcomes
Hyvarinen 2009 Finland	Men and women living in Helsinki and matched to birth records	Longitudinal follow-up of a randomly selected subsample in a birth cohort	N=1243 (53% F) 60-66 yrs	Major physical disabilities and poor vision	Birth weight	Beck's Depression Inventory, Battery of cognitive tests (for reaction time, attention, working memory and associate learning)
Zhang 2009 China	Men and women born in Beijing between 1921-1954	Retrospective birth cohort, cross sectional design	N=2062 (48% F) 50-82 yrs	Not reported	Birth weight, length, head circumference, maternal age and parity, gestational age, parental occupation.	Fluid object memory test,Verbal fluency, Weschler intelligence test
de Rooij 2010 Netherlands	Men and women born between 1944-1945 from the Dutch Famine Birth Cohort	Longitudinal follow-up of a birth cohort	N=737 (53% F) 56-59 yrs	Mental disorders	Birth weight, head circumference, gestational age, placental area and occupation of head of the household	Alice Heim test Stroop test Paragraph Encoding and Recall Mirror drawing test
Muller 2014 Iceland	Men and women from Reykjavik born between 1907-1935	Longitudinal follow-up of a randomly selected subjects from a birth cohort	N=1254 (57% F) Mean 76 (5) yrs 69-81 yrs	Dementia and prematurity	Birth weight and length	California Verbal Learning Test,Figure Comparison Test Digit symbol and Stroop Test,Spatial Working Memory test
Erickson 2010 US	Women living in Rancho Bernado	Cross-sectional	N=292 55-89 yrs Median 71 yrs	Not reported	Birth weight (self reported)	Blessed Dementia Scale Trail Making Test Verbal Fluency Heaton Visual Memory Test

c) Factors at birth: Birth weight was a universally available measurement of birth size across all the studies. In two studies (Costa et al.,2011; Erickson et al.,2010), both from the USA, birth weight was obtained by recall and non-hospital records (such as family diaries and birth certificates), and did not provide any other information related to birth. All other studies were based on the birth weight obtained from obstetric records. As a measurement of birth size, only birth weight was available from obstetric records in Hyvarinen et al, while Muller et al had an additional measurement of length at birth. In addition to birth weight, length at birth, head circumference and gestational age were available from the maternity records in other studies (Martyn et al.,1996; Raikkonen et al.,2013; Shenkin et al.,2009; Gale et al.,2003; Zhang et al.,2009; de Rooij et al.,2010).

   Parental occupation as an indicator of socioeconomic position at birth was available from obstetric records in some studies (Martyn et al.,1996; Zhang et al.,2009; Gale et al.,2003; and Skogen et al.,2013), while occupation of the head of the household was available from maternity records from de Rooij 2010 et al. Information about parental education at birth, an important determinant of growth and development of the offspring was not available in any of the studies.

d) Cognitive outcomes: All studies examined memory and attention, while most studies (n=9) had a measure of verbal fluency as cognitive outcomes (table 3.1). Additional cognitive domains were examined in most of the studies. They include: logical, verbal and numerical reasoning in Martyn et al; processing speed and executive function in Muller et al; general intelligence and selective attention in de Rooij et al; processing speed, selective attention, visuospatial performance, and motor skills in Skogen et al; verbal, arithmetic and visual spatial reasoning in Raikkoken et al; visuospatial tracking and attention in Erickson et al; verbal-non verbal reasoning and executive function in Shenkin et al 2007; intelligence in Zhang et al; reaction time and attention in Hyvarinen et al and intelligence in Gale et al. None of the studies had cognitive impairment, and dementia as outcomes, while, Hyvarinen et al. had a measure of depressive symptoms. Unadjusted outcomes that are missing in table 3.2 were not provided by the authors

e) Confounding factors: The association of birth size with cognitive outcomes was adjusted for a range of confounding factors, in most of the studies. They include: gestational age, maternal age and parity, indicators of socioeconomic position at birth, attained educational level, social class of participants and cardiometabolic risk factors.

However, these studies do not provide information as to why these factors were thought to be confounding and /or were important as covariates.

f) Analyses: The strength of association of birth size parameters with cognitive outcomes was examined and reported differently across studies (table 3.2). In addition, many of the eligible studies were relatively small, from diverse population groups, both exposures and outcome measures for cognitive function were multiple and heterogeneous. Therefore, it was not possible to conduct a meta-analysis or evaluate for publication bias.

3.4.3 Quality of reporting

The quality of reporting of the studies as assessed by the STROBE check list was good to excellent. At least 18 of the 22 items (range 18 to 22) from this checklist were reported. None of the authors reported how the study size was derived. While some (n=4) did not report the efforts made to address potential sources of bias, some (n=3) did not discuss the generalisability (external validity) of the study results. Degree of overall bias as estimated from the STROBE check list for individual studies is provided in table 3.2.

3.5 Summary of eligible studies (tables 3.1 and 3.2)

3.5.1 Seven studies that showed an association of size at birth with cognitive function in late life

a) Martyn et al 1993: examined the relation between birth size and cognitive function in 1576 men and women born in Hertfordshire, Sheffield, or Preston in the UK between 1920 and 1943. They were aged 60.9 yrs (SD 2.1 yrs) and cognitive assessments included AH4 (Alice Heim) test for intelligence quotient and Mill Hill vocabulary test. Scores on the intelligence test were higher in those who had a larger head circumference at birth, but were not related to birth weight and length at birth. After adjusting for gestational age, education and socioeconomic position at birth, the score of AH4 test rose by 3.7 for each inch increase in biparietal head diameter at birth (p=0.008). Measurements of birth size were not associated with cognitive decline, (estimated by the difference between score on AH4 test and Mill Hill vocabulary test). Analyses were not adjusted for education and cardiometabolic disorders in this study.

Table 3.2 Effect sizes, confounders and risk of bias in the studies included in this systematic review

Study (yr) Birth parameter (units)	Cognitive test	Unadjusted correlation			Adjusted correlation			Confounders	Risk of Bias
		Coefficient	SE	p	Coefficient	SE	P		
Zhang (2009) Ponderal Index (kg/m^3)	Immediate Recall			NR	NR	NR	0.50	Gestational age, parity and paternal occupation at birth; drinking milk during childhood; age, sex, cardiometabolic risk factors, socioeconomic position and occupation in adult life	Low
	Delayed Recall			NR	NR	NR	0.77		
	Cumulative score	OR= 1.5*	NR	0.02	OR= 1.26	NR	0.30		
de Rooij (2010) ** Birth weight (gms)	Alice Heim (reaction time)	ρ = 0.03		ns	NR	NR	NR	No adjustments were made Spearman correlation coefficients were reported for birth weight and cognitive outcomes	Medium
	Alice Heim score	ρ = 0.06		ns	NR	NR	NR		
	Stroop test	ρ = -0.01		ns	NR	NR	NR		
	Stroop score	ρ = 0.03		ns	NR	NR	NR		
	Memory Immediate recall	ρ = 0.01		ns	NR	NR	NR		
	Retrieval	ρ = -0.02		ns	NR	NR	NR		
	Mirror errors	ρ = -0.07		ns	NR	NR	NR		
	Mirror rounds	ρ = 0.06		ns	NR	NR	NR		
	Mirror errors per rounds	ρ = -0.08		ns	NR	NR	NR		
Costa (2011) Birth weight (gms)	Word fluency			NR	β= 0.75	0.3	0.004	Age, sex, education, race, social class, education, smoking, alcohol, BMI and self-reported cardiometabolic risk factors (diabetes, hypertension, LDL and HDL cholesterol) and history of stroke	High
	Delayed word recall			NR	β= 0.03	0.03	ns		
	Digit symbol			NR	β= -0.07	0.25	ns		
Martyn (1993) Head circumference (inches)	Alice Heim Test			NR	NR	NR	0.008	Social class at birth, age, sex and for individual datasets.	Medium
	Decline			NR	NR	NR	0.85		
	Divided attention			NR	β= -3.8	1.38	0.005		
	Association learning			NR	β= -1.5	0.71	0.04		

NR= Not reported ns=not significant but values not provided OR=Odds ratio ρ= correlation coefficient β=effect size from regression analyses r=rho * Odds ratio for lower cognition defined as cumulative score lower than 10 percentile ** values only for those exposed to famine in utero

Table 3.2 Effect sizes, confounders and risk of bias in the studies included in this systematic review (continued)

Study (yr) Birth parameter (units)	Cognitive test	Unadjusted correlation			Adjusted correlation			Confounders	Risk of Bias
		Coefficient	SE	p	Coefficient	SE	p		
Hyvarinen (2009) Birth weight (kgs)	Association learning			NR	NR	NR	ns	Gestational age, sex, age and education (history of heart disease, depression and self-reported health status also considered but not included in adjusted model)	Low
	Simple reaction time			NR	NR	NR	ns		
	Choice reaction time			NR	NR	NR	ns		
	Working memory hit rate			NR	NR	NR	ns		
	Working memory reaction time			NR	NR	NR	ns		
Raikkonen (2013) Birth weight (SD)	IQ (Finnish Defense Forces)	β= 1.04	0.51	0.04*	β= 1.31	0.64	0.04	Gestational age and parity at birth; breastfeeding in childhood; education, social class, height, history of heart disease and stroke	Medium
	Decline	r = 0.07	0.04	0.04	r= 0.08	0.04	0.06		
Erickson (2010) Birth Weight (lbs)	Buschke total			NR	β= -0.08		0.77	Age and education	Medium
	Buschke LTM			NR	β= -0.08		0.83		
	Buschke STM			NR	β= 0.00		0.97		
	Heaton visual copying			NR	β= 0.05		0.63		
	Heaton visual LTM			NR	β= -0.00		0.99		
	Heaton visual STM			NR	β =0.07		0.22		
	MMSE total			NR	β= 0.03		0.57		
	Serial 7's			NR	β= 0.08		0.04		
	World backward			NR	β= -0.00		0.89		
	Trails B			NR	β= 2.23		0.18		
	Category fluency			NR	β= 0.08		0.59		
	Blessed Dementia Scale			NR	β= 0.05		0.16		

NR: Not reported ns: not significant but values not provided SE: Standard error OR: Odds ratio ρ: correlation coefficient LTM: Long term memory STM: Shot term memory β=effect size from regression analyses SE: Standard error r: rho

Table 3.2 Effect sizes confounders and risk of bias in the studies included in this systematic review (continued)

Study (yr) Birth parameter (units)	Cognitive test	Unadjusted correlation			Adjusted correlation			Confounders	Risk of Bias
		Coefficient	SE	p	Coefficient	SE	p		
Skogen (2013) Birth weight (kgs)	Mini Mental State Examination	β= -0.03	0.09	Ns	β= 0.05	0.09	ns	Age and sex	Medium
	Digit symbol	β= -0.12	0.44	Ns	β = -0.03	0.45	ns		
	Kendrick	β= -0.24	0.79	Ns	β= -0.14	0.78	ns		
	Object learning	β= 0.85	0.55	Ns	β= 0.91	0.55	ns		
	Trail making A	β= 2.44	2.94	Ns	β= 2.01	2.97	ns		
	Block Design	β= -0.23	0.21	Ns	β= -0.26	0.21	ns		
	Composite score	β= 0.01	0.1	Ns	β= 0.02	0.1	ns		
Muller (2014)*** Ponderal Index (kg/m^3)	Memory			NR			NR	Age and sex	Medium
	Processing speed			NR	β= -0.012	NR	0.008		
	Executive function			NR	β= -0.08	NR	0.04		
Gale (2003) Head circumference (cms)	Alice Heim Intelligence score			NR	NR	NR	0.38	Social class at birth, age, sex, education, history of cerebrovascular disease and Nottingham Health Profile emotion subscale	Medium
	Weschler Immediate Recall			NR	NR	NR	0.75		
	Weschler Delayed Recall			NR	NR	NR	0.74		
	Decline on Alice Heim Intelligence score			NR	NR	NR	0.94		
Shenkin (2009) Birth weight (gms)	Raven's Progressive Matrices	r=0.15	Ns	Ns	r= 0.08	Ns	ns	Gestational age and parity at birth, age, sex and social class	Low
	Moray House test	r=0.15	ns	ns	r= 0.10	Ns	ns		
	Test no 12	r= 0.08	ns	ns	r= 0.03	Ns	ns		
	Verbal Fluency	r= 0.09	ns	ns	r= 0.04	Ns	ns		
	g (General Intelligence)	r= 0.15	ns	ns	r= 0.12	0.27	0.27		
	National Adult Reading Test	r=0.10	ns	ns	r=0.15	0.19	0.19		
	g corrected for National Adult Reading Test	r= 0.10	ns	ns	r= 0.15 r= 0.05	0.19 0.63	0.19 0.63		

NR= Not reported ns=not significant but values not provided OR=Odds ratio ρ= correlation coefficient β=effect size from regression analyses r=rho SE: Standard error *** values for those with low education only

b) Hyvarinen et al 2009: investigated the associations of birth weight and diabetes with cognitive performance in 1243 randomly chosen members of the Helsinki Birth Cohort (mean age 64yrs) in Finland. Simple reaction time, choice reaction time, divided attention, working memory and associate memory were examined. After adjustments for age, sex and gestational age, reaction time in the divided attention task was faster by 3.8% for each kilogram increase in birth weight for gestational age [95% CI (−6.5,−1.1), p=0.005)]. Errors made in the associate learning task also decreased by 1.5% for each kilogram increase in birth weight for gestational age [95% CI (−0.1,−2.9), p=0.04]. These associations were independent of coronary heart disease, diabetes and depression. A lower birth weight enhanced the association between diabetes and poor performance in the working memory and episodic learning tasks in this cohort.

c) Erickson et al 2010: examined the association of self reported birth weight with cognitive function in 292 community dwelling older women in southern California. They were aged between 55 and 89 yrs (median=71 yrs). They were examined for verbal fluency, memory, attention and executive function. From six cognitive tests with 12 different measures, birth weight was significantly and positively associated with only one test, the Mini Mental State Examination (MMSE) subset of Serial 7's test score, independent of attained educational level (B=0.08 t=2.09 and p=0.04 for serial seven's score). When birth weight was categorised into tertiles (2-6.9 lbs, 7-8 lbs and 8.1-12.4 lbs), women in the lowest tertile for birth weight had significantly lower scores on tests for concentration and calculation ($p<0.05$). Analyses were adjusted for age and attained education, but not for indicators of socioeconomic position and cardiometabolic risk factors. The results of this study may be a false positive. Both the 'serial sevens' and 'world backwards' subtests from the MMSE are typically used interchangeably as components indicative of attention. The world backwards test was non-significant (β=−0.00, p=0.89). In addition, authors do not report unadjusted correlations.

d) Costa et al 2011: examined the relationship of self reported birth weight to cognitive performance in 3292 men and women aged 53 to 67 yrs [mean 59.8 SD (5.7) yrs] from the United States Atherosclerosis Risk in Communities Study (17.6% of the cohort). They were examined for verbal fluency, word recall and attention. After adjusting for adult factors (sociodemographics, BMI and cardiometabolic disorders) and childhood socioeconomic environment, there was a significant positive linear trend for the relationship of birth weight to verbal fluency scores (p for trend=0.04). An increment of

100 gms in birth weight was related to an average increase of 0.75 words [95% CI (0.17-1.33) p=0.004] .

e) Skogen et al 2013: examined the association of size at birth with cognitive function among 346 community dwelling men and women from Bergen in Norway. They were aged 72 to 74 yrs and matched to their birth records. Those with larger head circumference at birth had higher scores on Controlled Oral Word Association Test (COWAT) and trail making test [B=0.5, 95% CI (0.18-0.86), p<0.001]. Higher parental socioeconomic status (based on paternal occupation at birth) was associated with a higher composite cognitive score (by 0.25 SD, p=0.01). Both parental socioeconomic position and head circumference at birth predicted cognitive function in old age, independently of each other in this cohort. These regression models were adjusted only for age and sex.

f) Raikkonen et al 2013: investigated the effect of birth size on cognitive function and decline in 931 men from a longitudinal birth cohort in Helsinki, Finland. They were initially examined when aged 20 yrs (SD=1.4 yrs) for military conscription. They were tested for verbal, arithmetic and visuospatial reasoning. The assessments were repeated when they were 67.9 yrs (SD=2.5 yrs). Adjustments were made for birth parameters (gestational age and parity), history of breastfeeding, adult health status, education, and socioeconomic parameters at birth. After adjustments for gestational age, each standard deviation increase in birth weight was associated with an increase of 1.31 points on a general intelligence measure [95% CI (0.06, 2.55), p=0.04]. Lower weight, length and head circumference at birth were associated with lower cognitive ability at 68 yrs [1.04 to 1.55 points lower ability per each SD unit decrease in body size (95%CI: 0.05 to 2.72)] and with cognitive decline after 20.1 yrs [0.07 to 0.11 SD decline over time per each SD decrease in body size 95% CI (0.05 to 0.19)]

g) Muller et al 2014: In this study, within the Age Gene Environment Susceptibility Reykjavik population based cohort in Iceland, 1254 men and women underwent an examination that included a cognitive assessment and a brain MRI when aged between 69 and 81 yrs. Ponderal index was directly associated with volumes of total brain and white matter, processing speed and executive functioning, but only in those with low education [B (95% CI) were 21.0 (21.9 to 20.0) mL, 20.5 (21.0 to 20.0) mL, 20.14 (20.24 to 20.03) and 20.08 (20.15 to 20.0) for total brain volume, white matter, processing speed and executive functioning respectively, p<0.05 for all]. Authors

mention that birth weight and length at birth were not associated with cognitive outcomes (but the values were not reported). Unadjusted associations were not reported, and the association was not adjusted for gestational age.

3.5.2 Four studies that did not show an association of size at birth with cognitive function in late life

a) Gale et al 2003: assessed cognitive function in 215 men and women aged 66 to 75 years, whose size at birth was recorded in a maternity hospital in Sheffield (UK). Cognitive function was tested at baseline and at 3.5 yrs follow-up with the AH4 intelligence test and the Wechsler Logical Memory test. Birth weight, length at birth and head circumference at birth were not associated with score on the cognitive function tests or change in score over time. Authors report a trend of increase in AH4 score with increasing head circumference at birth, which was not significant (p for trend=0.38). There was no significant linear relation between change in score treated as a continuous variable with head circumference at birth (r=-0.09 p=0.20). Effect sizes of other birth size parameters with AH4 score at base line and follow-up were not reported.

b) Zhang et al 2009: conducted a retrospective birth cohort study of 2,062 individuals born during 1921–1954 in Beijing, China. Participants had standarised cognitive assessments (for intelligence, digit span and verbal fluency) and cardiometabolic health when aged between 50–82 years. A cumulative score below the 10th percentile was defined as lower cognition. Head circumference and ponderal index at birth were directly associated with lower cognition [OR=1.40 95%CI (1.09-1.78) p<0.001 for head circumference and OR=1.53 95% CI (1.13-2.06) p=0.02 for ponderal index]. The strength of these associations were attenuated and not significant after adjustment for indicators of socioeconomic position in early life and childhood [OR=1.06 (0.82-1.38) p<0.001 for head circumference and OR=1.12(0.82-1.54) p=0.02 for ponderal index]. The associations of birth weight and length at birth with cognitive function were not reported.

c) Shenkin et al 2009: investigated the relationship between birth parameters (birth weight, birth length, placental weight and social class) and cognitive ability among 128 community-dwelling volunteers (aged 75 to 81 yrs) who were born in one hospital in Edinburgh, UK between 1921 and 1926. Cognitive assessments included measurements for verbal and non-verbal reasoning, executive functioning and logical

memory. The National Adult Reading Test (NART) was used to estimate prior cognitive ability. NART score correlated positively with length at birth (r=0.25 p=0.02), but non-significantly with birth weight (r=0.15 p=0.19). Size at birth and social class at birth were not associated with cognitive ability in late life in this cohort [birth weight r=0.12 p=0.27; length at birth r=0.19 p=0.08; social class at birth: r=0.07 p=0.47].

d) de Rooij et al 2010: examined the association of birth size with cognitive function in 737 men and women aged between 56 and 59 yrs from the Dutch Famine Cohort. Birth weight and head circumference at birth were not associated with cognitive outcomes (intelligence, memory and selective attention). However, a subgroup of those exposed to famine during the early stage of gestation performed worse on a selective attention task. The median score for those exposed to famine in utero was 33.0 compared with 43.5 in the unexposed [B=-30 95% CI (-60 to 0) p=0.05]. The observed difference between the groups may not be due to prenatal under nutrition but prenatal stress, because mothers of individuals born before famine experienced stressful war circumstances during pregnancy, while mothers of those conceived after famine did not.

3.5.3 Important studies that were excluded

a) Araujo et al 2014 conducted cognitive assessments of 12,997 men and women aged 35 to 64 yrs from the Brazil Longitudinal Study of Ageing, nearly half of them were aged above 50 years. Birth weight (self-reported) was directly associated with cognitive abilities in this study. However, the authors were unable to provide data specific to those aged 50 yrs and above (Araujo et al.,2014).

b) Melrose et al 2013 examined the relationship between early life environment and cognitive abilities in 333 men and women from the UC Davis Diversity Ageing Cohort in the US. This study was excluded as authors did not specifically report the association of size at birth with cognitive abilities (Melrose et al.,2013).

c) Richards et al 2001 reported the relationship between birth weight and cognitive function in the British 1946 birth cohort. Participants were 43 yrs of age when examined and therefore excluded from this review (Richards et al.,2001).

d) Dawes et al 2015 examined the effect of prenatal and childhood development on hearing, vision and cognition in the UK Biobank Cohort. Participants were aged

between 40 to 66 yrs, and birth weight was self-reported. I have contacted the authors, and yet to receive data specific to those aged 50 yrs and above (Dawes et al.,2015).

3.6 Discussion

3.6.1 Key findings

Studying early determinants and predictors of cognitive ageing has been repeatedly identified as a research priority (Shah et al.,2016; World Alzheimer Report.,2016). The studies evaluated in this systematic review have contributed significantly to this research, and suggest that cognitive function in late life is influenced by nutrition and environment in early life. A majority of the studies (7 of the 11) included in this review indicate that intrauterine growth restriction, crudely reflected in size at birth is directly associated with lower cognitive ability in late life, at least in high income country settings. It was not possible to compare and appraise the effect sizes of studies with each other or conduct a meta-analysis to derive a pooled effect size. This was because the associations of different birth size parameters with multiple cognitive outcomes for different domains have been reported, and the strength of associations has been reported differently.

The association of birth size with late life cognition was independent of parental socioeconomic position at birth in most studies (Skogen et al.,2013; Costa et al.,2011; Raikkoken et al.,2013; de Rooij et al.,2010; Martyn et al.,1996), and was confounded by socioeconomic position at birth in one study (Zhang et al.,2009). Parental socioeconomic position at birth was not associated with cognitive function in late life in Shenkin et al, while this association was not examined in the remaining studies (Gale et al.,2003; Muller et al.,2014; Hyvairenen et al.,2009; Erickson et al.,2010).

Across all the studies, adjusting for education attenuated the strength of association of birth size with late life cognition. When reported separately, higher level of attained education was directly associated with higher scores for certain cognitive abilities. In a subgroup analysis by Muller et al, the direct association of ponderal index with processing speed and executive functioning was limited only to those with lower educational levels. In this study, those with smaller size at birth also had lower volumes of total brain and white matter (indicator of brain reserve) in late life. In summary, this review supports the universal finding that those with higher attained educational levels (an indicator of cognitive reserve) have higher cognitive ability in late life (Meng & D'Arcy.,2012). If there is a causal relationship between the prenatal environment and later cognitive ability, the data suggest that educational attainment

possibly lies on the same causal pathway, because educational achievement may be a proxy for cognitive ability.

A possible mediating or confounding effect of cardiometabolic disorders on the relationship between size at birth and late life cognition was evaluated in three studies included in this review: the direct association of size at birth with late life cognition was independent of stroke and coronary heart disease in Raikkonen et al, diabetes and hypertension in Costa et al and, diabetes and coronary heart disease in Hyvarinen et al. However, these studies did not examine if smaller size at birth was associated with an increased the risk of cardiometabolic disorders (as potential confounders).

The presence of a relationship between birth parameters and late life cognitive ability does not necessarily imply a direct causal relationship; birth parameters may merely reflect underlying influences. Residual confounding is a major possible reason for any false positive associations. The mechanism of any influence of birth parameters on cognitive aging has not yet been established, and this may be a direct or an indirect influence through cognitive reserve and cardiometabolic pathways respectively (Stern Y.,2002; Whalley et al.,2006). The studies in this review were not designed to examine the DOHaD pathways of cognitive aging. Such a study would have examined the association of size at birth with cognitive reserve and/or cardiometabolic risk factors in adult life, and in turn, association of these with cognitive function in late life.

Cognitive decline is thought to begin as early as forty years of age. In the Whitehall study, over the 10-year study period there was a 3.6% decline in mental reasoning in those aged 40-49 and a 9.6% decline in those aged 65-70 (Singh-Manoux et al.,2012). Most studies in this review conducted baseline cognitive assessments when participants were well above the age of 50, by which cognitive decline may already be evident, and observed associations (or a lack of) in these studies may be due to a horse racing effect (Peto.,1981). The horse-racing effect was originally advocated to explain findings from observational studies exploring the increase of clinical parameters (e.g., blood-pressure) with aging. It postulates the existence of a close correlation between the aging process and the health status as the speed of the horse is related to its position in the race (for example, the interpretation of results showing that blood-pressure increases with advancing age might meaningfully shift from “the higher they start, the faster they rise” to “the faster they rise, the higher they are”) (Peto.,1981).

While examining cognitive function in the studies included in this review, cognitive decline may have been measured, and mostly the papers were uninformative about this. However, cognitive decline was specifically measured in four studies in this review. Of those that examined the relationship between birth size and cognitive decline, no association was reported in three studies (Gale et al.,2003; Shenkin et al.,2007; Martyn et al.,1996), while in one study (Raikkonen et al.,2013) men with larger size at birth had slower rate of cognitive decline in late life. In Raikkonen et al, baseline cognitive performance was measured in adulthood (28 yrs) and in Shenkin et al at a much later age (63 to 72 yrs), with repeat cognitive assessments at 48 yrs and 3.5 yrs follow-up respectively. In Martyn et al cognitive decline was estimated by the difference between score on AH4 test and Mill Hill vocabulary tests, both administered at the same time to the participants when they were nearly 61 yrs. Such a methodology for measuring decline has not been replicated and therefore the results should be interpreted with caution. In Shenkin et al an estimate of peak cognitive ability was derived by conducting a National Adult Reading Test (NART) test in late life and decline was measured by computation. This test is exclusively based on reading ability, and validity of employing NART score as an index of prior intellectual ability has not been established beyond a single longitudinal study of a relatively small sample size (n=179) in Aberdeen, in the UK (Dykiert and Deary.,2013).

Findings from this review also suggest that the relationship of growth and development in early life is more likely with cognitive abilities that are associated with the fronto-temporal lobes of the brain such as verbal fluency, attention, trail making, calculation, executive functioning and working memory. Of these, verbal fluency is regarded as an index of crystallised intelligence, while others are generally considered as components of fluid intelligence. In fact, the verbal fluency test is particularly sensitive to linguistic impairment and early mental decline in older persons; it is also a sensitive indicator of damage to the left lateral lobe (Henry et al.,2004). Crystallised intelligence refers to the ability to retrieve and use information that has been acquired throughout a lifetime. In contrast, the fluid intelligence is the ability to store and manipulate new information. Fluid intelligence processes tend to be disrupted by healthy aging while crystallised intelligence, is thought to remain stable across the life span (Cattell.,1963).

3.6.2 Strengths and limitations of included studies

The studies which reported a positive association of size at birth with late life cognitive ability generally included relatively well educated, predominantly white and middle-class men and women from higher income settings, which limits the generalisability of the findings beyond

these settings. It is possible that the results are specific to the cohorts under study (cohort bias). These individuals have seen substantial changes in both prenatal and later health care.

None of the studies included in the review have information of the entire eligible population to assess the degree of potential bias. The studies used volunteers, who generally have higher cognitive ability and social class than non-volunteers (Morrow-Howell.,2010). As all analyses were performed within the study sample, unless the correlation between birth size and cognitive ability differs between the volunteers and non-volunteers, it is unlikely that significant bias would have been introduced. Birth weight in the UK, the US and Scandinavian countries, where these studies were conducted, is among the highest in the world, and they also have higher rates of literacy in comparison to LMIC settings (Shah et al.,2016). It is reasonable to postulate that the effect size would be different when studying the relationship between birth size and late life cognition in LMIC populations with proportionately lower birth size and literacy levels.

Attrition bias may have also affected results. Most studies do not provide details about losses to follow-up. When reported, those who were lost to follow-up had lower attained education level when compared to those who were re-examined; this bias may have influenced findings towards non-significant results.

As is common with longitudinal studies of older adults, participants who were lost to follow-up in Shenkin et al and Raikkoken et al, had lower mean cognitive scores at baseline than those who took part in the repeat testing. Such attrition may induce bias in the estimates of cognitive change. These two studies examined decline based on cognitive data only at two points in time. Random variation or regression to the mean may account for some of the observed changes in cognitive test scores and the results need to be treated with caution.

Participant exclusion is also known to introduce bias. Although most studies in this review excluded a minimal number of participants (table 3.1), one study (Costa et al.,2011) excluded 36.6% (n=3921) of participants examined at the initial visit and such an extensive exclusion may limit generalisability to the wider population. In two of the studies (Costa et al.,2011; and Erickson et al.,2010), both from the USA, birth weight was obtained by recall and non-hospital records like birth certificates and family diaries. A problem with this is a possible greater inaccuracy of birth weight recall in those with lower cognitive functioning. In fact, in Costa et al, poorer performance in cognitive tests was observed in those who recalled their birth weight when compared to those with available birth records. This was not

examined in Erickson et al, as only a small proportion of those recruited in this study had documented birth weight.

When birth size data were extracted from routinely recorded measurements from historic maternity records, it is possible that values were rounded off to the nearest unit by the midwives. The lack of association between cognitive performance and birth size measurements in some of the studies in this review may to due to this inaccuracy. This was specifically examined in Martyn et al and there was evidence of clumping of the data points suggesting rounding off values.

Studies were limited to participants who were given a cognitive test and whose birth weight was available. These participant samples may not be representative of the general population, particularly for those in this age group, where hospital births were less common. Very low birth weight babies who survived during the years in which men and women in these cohorts were born were probably healthier than those who did not survive, and only a small proportion of those who survived have been examined. Much lower birth weight babies survive today than survived 50 or more years ago when participants from the studies in this review were born. Though one may speculate that the association of low birth weight with low cognitive function may be magnified in cohorts with younger participants, in large representative birth cohort studies across three generations in the UK [the 1958 National Child Development Study (NCDS), the 1970 British Cohort Study (BCS), and the 2000-2002 Millennium Cohort Study (MCS)], the negative association between low birth weight and cognitive ability was large in the 1958 and 1970 birth cohorts [−0.37 SD, 95%CI (−0.46, −0.27) for NCDS cohort and −0.34, 95%CI (−0.43,−0.25) for BCS cohort], but had more than halved for the cohort born around the year 2001 [−0.14, 95%CI (−0.22,−0.06)] (Gosis et al 2017). This was despite a higher proportion of low birth weight babies in the MCS cohort, and adjustment for family characteristics did not explain the cross-cohort differences. Advances in obstetric and neonatal care in the UK in last 50 yrs may have attenuated the negative consequences associated with low birth weight. Similar data are not available from a LMIC setting to explore such a secular change in the association between birth weight and cognition.

Five studies (Costa et al.,2011; Erickson et al.,2010; Martyn et al.,1996; Muller et al.,2014; Skogen et al.,2013) did not adjust the analyses for gestational age, which reduces the specificity of birth weight as a measure of fetal growth. This may have resulted in the lack of associations in some of these studies. Most studies did not provide justifications for the majority of adjustments (table 3.2). Furthermore, one study (Costa et al.,2011) adjusted for a

total of 21 different measures (not including gestational age), which makes it difficult to assess how far participants represent the general population. Some studies also did not provide any unadjusted information, making it difficult to assess the role of covariates in the reported effect (table 3.2). Depression is related to both size at birth and cognitive function (Wojick et al.,2013, but the confounding effect of depression on the association of size at birth with cognitive ability was measured only in one study (Hyvarinent et al.,2009) in this review.

In this review, most studies report associations of multiple parameters of birth size with multiple cognitive tests, measuring different cognitive domains. While this allows for a comprehensive overview of a variety of cognitive assessments, some significant associations may have resulted from chance alone (risk of type I errors) and or due to multiple testing. For example, in Erickson et al, birth weight was associated with serial sevens test score (a single item from MMSE), though there were no significant associations with 12 cognitive function outcomes, including total MMSE score.

3.6.3 Strengths and limitations of the review process

This review strictly adhered to the study protocol which was developed prior to the formal search. The forward citation search and reference list search were conducted systematically. Several authors of potentially eligible study were contacted for additional information. All relevant studies appear to have been included in this review. There were no restrictions on publication language, and full-texts of all potentially relevant articles were evaluated against the inclusion criteria. However, the grey literature was not systematically searched and this may have resulted in non-identification of potentially relevant studies. Furthermore, it is possible that there are unpublished studies that were not available.

A limitation of this review was that only a small number of eligible studies were retrieved, and it was not possible to conduct meta-analyses for summary statistics due to heterogeneity. There was considerable heterogeneity across studies, and this is both a strength and a weakness. This was expected, given the range of different factors known to contribute to both birth size and late life cognition, the different cognitive tests with their own scoring systems, and the range of demographics across each study. Though most studies from this review indicate that small size at birth is a risk factor for reduced cognitive ability in late life, the clinical relevance of the findings is limited as they do not include outcomes like cognitive impairment and dementia. The generalisability of findings from this review is mostly limited to

higher income settings, and there is an urgent need for similar studies in LMIC settings where the burden of both low birth weight and dementia is highest (Shah et al.,2016).

3.6.4 Implications for future research

The lack of a substantial association between birth size and cognitive function in late life in some studies in this review may be a reflection of a diminished impact of early factors, as other factors that mitigated these initial differences, and reduced or eliminated their influence in later adult life come into play (Whalley et al.,2006; Zhang et al.,2009). These may include later nutrition, education and occupation status (Whalley et al.,2006; Stern.,2002). Both birth weight and socioeconomic position in early life are associated with cognitive function in childhood and adulthood, although postnatal growth and development is thought to be more important than prenatal factors (Shenkin et al.,2004; Grove et al.,2017). Cognition in late life is impacted by a cumulative effect of nutrition, education, social, and family environment in early and midlife (Whalley et al.,2006). Therefore, there is definitely a need for more research with a lifecourse approach while examining the relationship between birth size and late life cognitive ability. The mediating or confounding effect of childhood growth and development, education, cardiometabolic risk factors, depression and socioeconomic position should be explored to better understand the lifecourse pathways to cognitive ageing. Further, there is a need for studies examining the underlying mechanisms (for e.g. neuroimaging, genetic and epigenetic studies) linking early life nutrition to cognitive ageing.

3.7 Conclusions

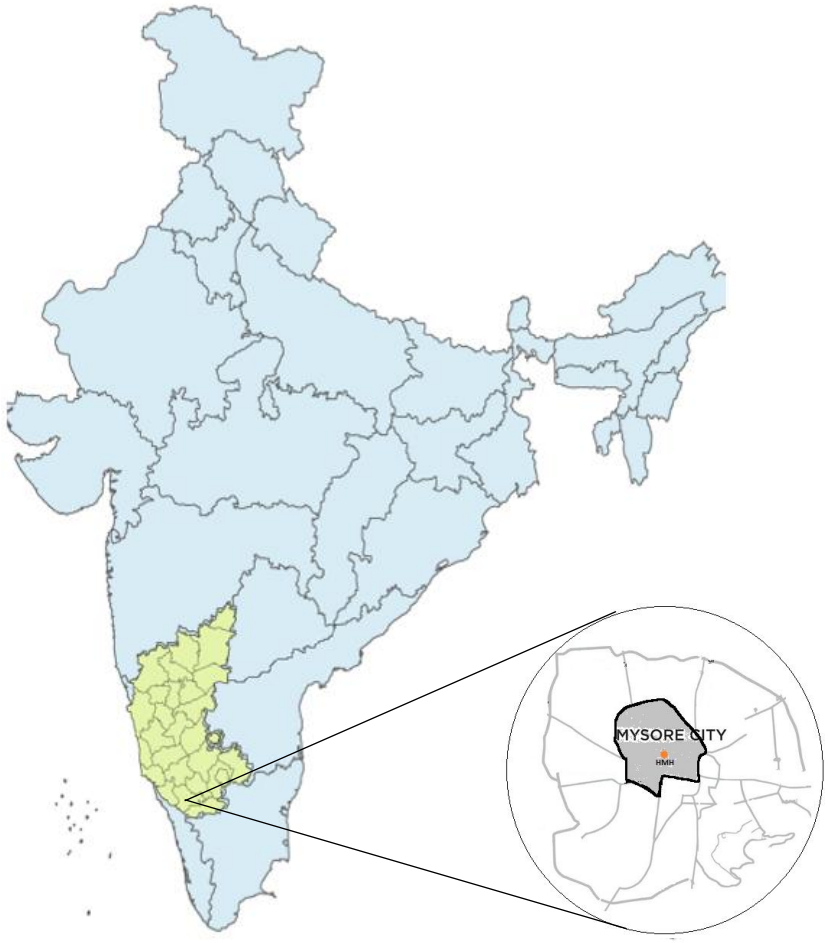
Most studies in this review indicate that smaller size at birth is a risk factor for lower cognitive function in late life, at least in higher income countries. It was not possible to conduct meta-analyses for summary statistics due to clinical heterogeneity. While the aim of assessing the association of birth size with cognitive ability in late life is to draw conclusions about the relationship between the prenatal environment and later cognitive outcomes, such definitive conclusions cannot be drawn from birth size data alone. Future research should take a considered approach to covariates across the lifecourse and explore pathways for cognitive ageing.

4. Methodology

4.1 Setting

This study was carried out at the Epidemiology Research Unit at CSI Holdsworth Memorial Hospital, Mysore, South India. Mysore, a city with a population of around 893,000, is in the southern Indian state of Karnataka (Figure 4.1). It has a large government hospital catering to the majority of the population of Mysore district, and 6 large, and numerous small private hospitals.

Fig 4.1 Mysore, South India; inset shows the area surveyed around the Holdsworth Memorial Hospital



Holdsworth Memorial Hospital (HMH) is a mission hospital, now governed by the Church of South India (CSI). It was built as a maternity hospital in 1905 in a poor, crowded area of the city. At that time, it was one of only two major maternity units in the city. Currently the hospital has 350 beds across all specialities with outpatient and inpatient services. The

hospital provides quality medical care at an affordable cost. About 25% of those receiving hospital care are from the surrounding villages and economically disadvantaged groups (Figure 4.2).

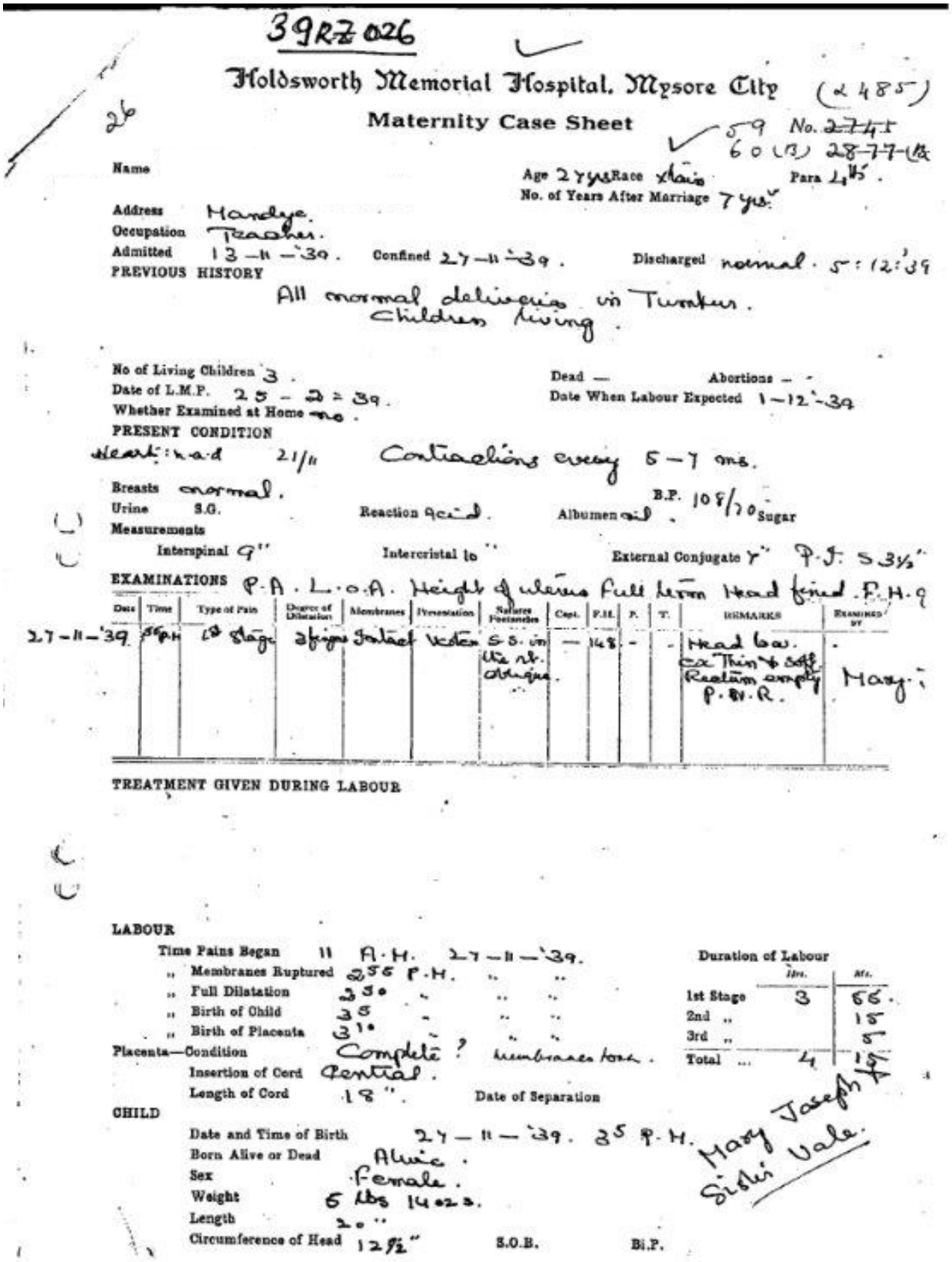
Fig 4.2 CSI Holdsworth Memorial Hospital, Mysore

4.2 Birth Records and Epidemiology Research Unit at CSI Holdsworth Memorial Hospital

4.2.1 Birth Records

Since 1934, CSI Holdsworth Memorial Hospital has preserved birth records in hard copy. These records include birth weight, length, and head circumference for all babies born in the hospital. Until the 1960's these measurements were made by one of three midwives, using an agreed protocol, although the details of how the measurements were made have been lost. The birth records also contain the parents' names, occupations, address, religion or caste, and the mother's obstetric history (Figure 4.3). Some of the mothers attended the antenatal clinic, and their records (approximately 40%) include their weight during pregnancy, whereas others came to the hospital for the first time only when they were in labour. In the latter case, maternal weight was generally missing, but approximately 55% of mothers had pelvic diameters measured on admission in labour. Data available from the birth records at CSI Holdsworth Memorial are provided in table 4.1.

Fig 4.3 Birth record at CSI Holdsworth Memorial Hospital, Mysore.



39R7026

Holdsworth Memorial Hospital, Mysore City (2485)

Maternity Case Sheet

59 No. 2741
60 (B) 2877

Name

Age 27 yrs Race Hindu Para 4+1.

No. of Years After Marriage 7 yrs.

Address Handya.
Occupation Teacher.
Admitted 13-11-'39. Confined 27-11-'39. Discharged normal. 5:12:'39

PREVIOUS HISTORY

All normal deliveries in Tumkur.
Children living.

No of Living Children 3.
Date of L.M.P. 25-2-39.
Whether Examined at Home no.
Dead — Abortions —
Date When Labour Expected 1-12-'39

PRESENT CONDITION

Heart: n.a.d 21/11 Contractions every 5-7 ms.

Breasts normal.
Urine S.G. Reaction acid. Albumen nil. B.P. 108/70 Sugar

Measurements

Interspinal 9" Intercristal 10" External Conjugate 7" P.J. 5 3½"

EXAMINATIONS P.A. L.o.A. Height of uterus Full term Head fixed. F.H.9

Date	Time	Type of Pain	Degree of Dilatation	Membranes	Presentation	Sutures Fontanelles	Cont.	F.H.	P.	T.	REMARKS	Examined by
27-11-'39	8 P.M	1st stage	2 fingers	Intact	Vertex	S.S. in the rt. oblique	—	148	-	-	Head low. ca Thin & soft. Realm empty P.R.V.R.	Mary.

TREATMENT GIVEN DURING LABOUR

LABOUR

Time Pains Began 11 A.M. 27-11-'39.
" Membranes Ruptured 2.55 P.M. " "
" Full Dilatation 3.30 " " "
" Birth of Child 3.35 " " "
" Birth of Placenta 3.40 " " "
Placenta—Condition Complete? membranes torn.
Insertion of Cord Central.
Length of Cord 18".

Duration of Labour

	Hrs.	Mts.
1st Stage	3	55.
2nd "		15
3rd "		5
Total ...	4	15

Date of Separation

CHILD

Date and Time of Birth 27-11-'39. 3.5 P.M.
Born Alive or Dead Alive.
Sex Female.
Weight 6 lbs 14 ozs.
Length 20"
Circumference of Head 12½" S.O.B. Bi.P.

Mary Joseph
Sister Vale.

Table 4.1 Data from the birth records	
	Contemporaneous data from birth records.
N=3427 Matched birth records for singletons born in HMH, Mysore between 1934 and 1966.	**Paternal**: occupation and religion **Maternal**: age, weight (40%), years of marriage, parity, religion and pelvic measurements-55% (interspinal, intercristal and external conjugate diameters) **Antenatal**: 40% of the records have date of last menstrual period, haemoglobin and blood pressure at antenatal visits. **Obstetric history** including birth order **Labour data**: Maternal pulse and BP, urine (specific gravity, sugar and albumin), course of labour, drugs administered and mode of delivery (normal, forceps or caesarean) **Child**: gender, birth weight, birth length and head circumference at birth **Placenta**: Insertion of cord, length of cord and cord condition **Postpartum**: Maternal haemoglobin the day after delivery

4.2.2 Epidemiology Research Unit (Figure 4.4)

Since 1991, in collaboration with the Medical Research Council Environmental Epidemiology Unit (now Lifecourse Epidemiology Unit- MRC LEU), University of Southampton, UK, these birth records have been used to trace people born at Holdsworth Memorial

Fig 4.4 Epidemiology Research Unit at Holdsworth Memorial Hospital

Hospital to examine the relationship between size at birth and cardiometabolic outcomes. These studies have helped set up birth cohorts across different age groups at the Holdsworth Memorial Hospital. These cohorts are regularly followed up at the purpose-built Epidemiology Research Unit at Holdsworth Memorial Hospital (Figure 4.4). This research unit was built in 2001 and is dedicated to studies examining Developmental Origins of Health and Disease (DOHaD). Studies from this unit were among the first in a LMIC setting to test the DOHaD concepts.

4.3 The Mysore Birth Records Cohort

4.3.1 Background

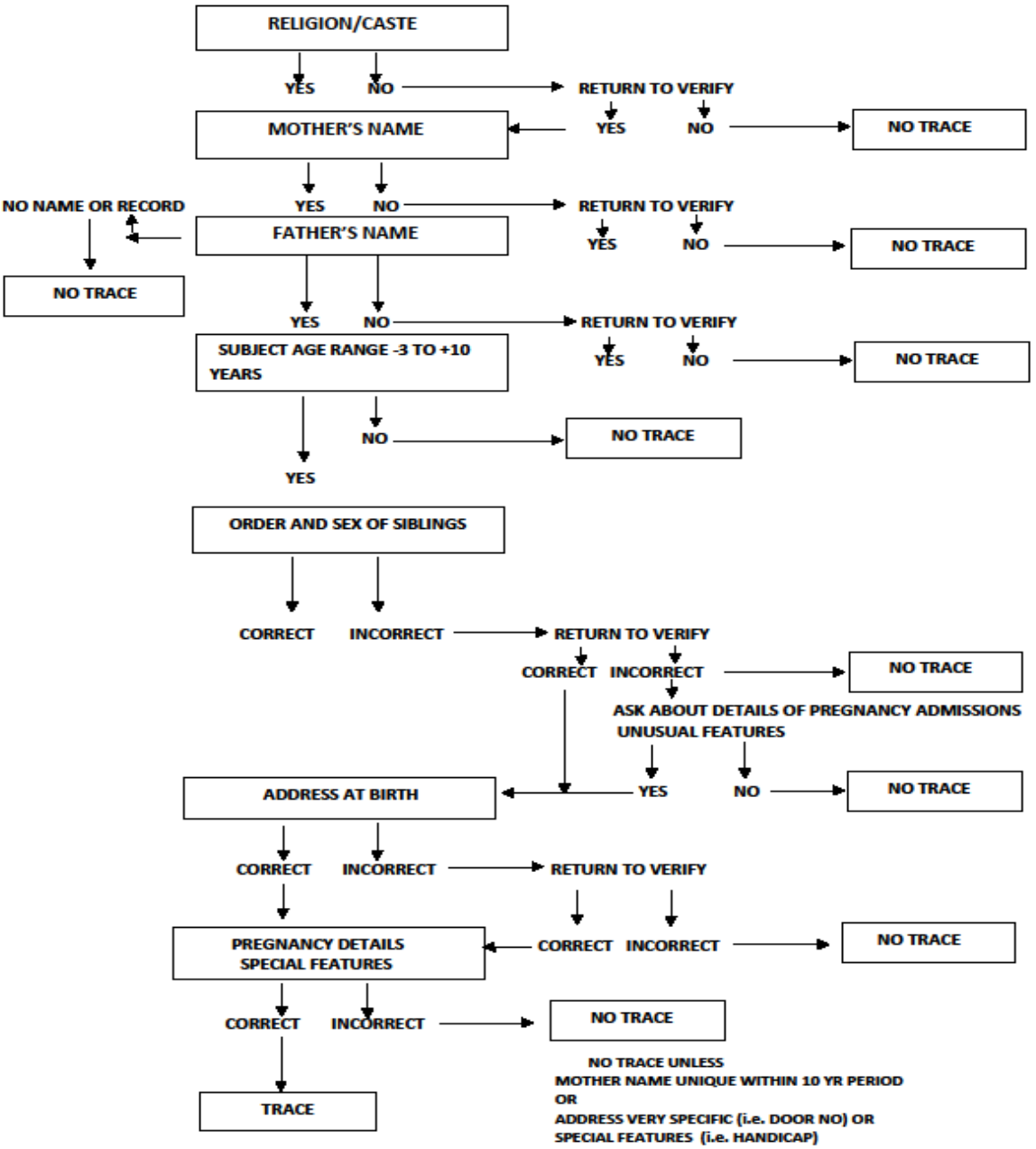
Coronary heart disease (CHD) and type 2 diabetes are common and a major cause of morbidity and mortality in LMICs, including India (Lozano R et al.,2012). In the early 1990s, small size at birth was shown to be associated with an increased risk of coronary heart disease and some of its risk factors like hypertension, type 2 diabetes and dyslipidaemia in the UK, European and US populations (Hales et al.,1991; Law et al.,1993; Barker et al.,1993). These associations were independent of adult lifestyle (including smoking, obesity and social class) and led to the Barker Hypothesis, which proposed that adult cardiometabolic disorders are 'programmed' in utero, and result from persisting changes in metabolism and organ structure that occurred in response to fetal and early post-natal under nutrition (Barker et al.,1993; Barker.,1995). Studies in the 1980s had recorded high rates of CHD in Indian populations living in the UK, which were largely unexplained by known risk factors (Chadha et al.,1990; McKeigue and Marmot.,1988). However, relationships between size at birth and adult cardiometabolic disorders had not been examined in India, where fetal growth restriction and small size at birth are common. India has a high incidence of low birth weight (nearly 30%) – one of the highest in the world (Black et al.,2013).

4.3.2 Setting up of the Mysore Birth Records Cohort

In 1991, Prof Caroline Fall from University of Southampton, my supervisor, wrote to over 300 long-established hospitals in India, to ask if any had preserved old birth records going back 25 years or more. She subsequently visited the twelve hospitals that replied affirmatively and welcomed collaboration, to assess the completeness and quality of the records, and the feasibility of tracing people born in the hospital many decades earlier. Holdsworth Memorial Hospital's records were in a good condition, and remarkably complete for birth measurements (weight, length and head circumference). Furthermore, the relative isolation

of Mysore has ensured stability of the population, and a tracing exercise showed that it was possible to locate people born in Holdsworth Memorial Hospital as far back as 1934 and match them accurately to their birth records.

Fig 4.5 Algorithm for matching participants with birth records



A total 24,824 singleton babies were born alive in Holdsworth Memorial Hospital between 1934 and 1966. In 1993-2001 a house-to-house survey of an 8-square mile section of the city surrounding Holdsworth Memorial Hospital identified 6059 people who said they had

been born as singletons in the hospital between 1934 and 1966, and of these 3427 were successfully matched to their birth records. The main difficulties in matching were that most adults were unaware of their date of birth and knew their age only vaguely, and that the birth records did not contain the infant's name because Indian babies are usually named several weeks after birth. Men and women were therefore matched to their birth record through their parents' names, addresses, and occupations, the number, sex, and order of older siblings, and the mother's obstetric history. All of these details had to match exactly. 3427 men and women were matched to birth records in this way using an algorithm (Figure 4.5). Of the 3427, 1069 (approximately 30%) participated in the initial study between 1993 and 2003 and constitute the Mysore Birth Records Cohort (Krishna M et al.,2015).

4.4 The first study of the Mysore Birth Records Cohort

4.4.1 Investigations

The first study between 1993-2003 examined associations of size at birth with adult cardiometabolic disorders (type 2 diabetes, CHD, hypertension, insulin resistance, and dyslipidaemia) and lung function (Stein et al.,1996; Fall et al.,1998; Ward et al.,2003; Stein et al.,1997). In this study, 1069 men and women aged 40-67 years underwent assessment for anthropometry, coronary heart disease, abnormal glucose tolerance, dyslipidaemia and lung function. A blood sample for DNA was collected from 551 participants. Data were also collected on socioeconomic status, education, occupation, and tobacco and alcohol consumption. Data available from the first study of the Mysore Birth Records Cohort are provided in table 4.2.

4.4.2 Key findings from the first Mysore Birth Records Cohort study

a. As in western populations, among adults aged 40-67 years, lower birth weight, smaller head circumference, and shorter body length at birth were associated with higher rates of adult coronary heart disease (Stein et al.,1996). In addition, lower maternal weight during pregnancy was associated with a higher risk of coronary heart disease. This study provided early evidence from India that fetal under-nutrition is associated with adult coronary heart disease. Coronary heart disease was associated with some conventional risk factors including older age, shorter stature, diabetes, hypertension, altered concentrations of serum lipids, and smoking, but not with raised plasma fibrinogen concentrations or obesity. Prevalence rates were similar in men and women.

There was a higher prevalence of the disease among men of lower social class, which was not explained by known risk factors (Stein et al.,1996).

Table 4.2 Data from the initial study of the Mysore Birth Records Cohort

N=1069 First study of the cohort between 1993 and 2003. The participants were then aged between 40-67 yrs.	1.**Blood tests** a. Biochemistry: Glucose tolerance test (WHO protocol, with blood taken fasting and 30 and 120 minutes after a 75g glucose load), plasma insulin (fasting, 30 and 120 minutes' post-glucose), fibrinogen, Factor 7, total cholesterol, triglycerides, LDL and HDL cholesterol, serum cortisol and cortisol binding globulin (n=509) b. Haematology: Full blood count, differential cell count and haemoglobin 2. **Anthropometry**: Height, weight, head circumference, hip and waist circumference and skin fold thicknesses (triceps, biceps, subscapular and supra-iliac). 3. **DNA** (n=551) 4.**Clinical evaluation**: Pulse rate, blood pressure, electrocardiographs Minnesota coded), Rose angina questionnaire and spirometry (n=518) 5.**Structured Interview** a. Marital status, family structure and living arrangements. b. Medication, medical history of stroke, angina, hypertension, diabetes, chronic bronchitis and emphysema, history of coronary artery bypass graft or angioplasty c. Family History of coronary heart disease and diabetes d. Physical activity at home and at work e. Alcohol and tobacco consumption f. Dietary history: vegetarian/nonvegetarian, dietary intake of meat, dairy products, fish, fruits, vegetables and oils per week. 6. **Kuppuswamy scale for socioeconomic indicators**: Locality in the town, household amenities (water, bathroom, toilet facilities), education level of subject and the spouse, income of the subject and the spouse, occupation of the subject and the spouse, number of members in the household and number per room, total family income and per capita income. 7. **Collected as a part of the tracing process**: birth order, family size, maternal and paternal occupation

b. The prevalence of type 2 diabetes was high (15%). Unlike studies in the west, however, it showed no association with lower birth weight. It was associated with shorter birth length, higher ponderal index at birth, higher maternal weight and larger pelvic diameters (Fall et al.,1998). These unexpected findings led to the hypothesis that maternal gestational diabetes, occurring among women who were stunted but

obese, may be an important factor in causing high rates of type 2 diabetes in Indian urban populations. This led to the setting up of the Mysore Parthenon Study, a prospective birth cohort study of gestational diabetes (Krishnaveni et al.,2015).

c. Associations between serum cortisol concentration and cardiovascular risk factors in this cohort were stronger than those previously shown in Caucasian populations, despite similar mean cortisol concentrations, and were amplified by adiposity. This suggested that increased glucocorticoid action may contribute to ethnic differences in the prevalence of the metabolic syndrome, particularly among men and women with a higher body mass index (BMI). Adult serum cortisol concentrations were not related to birth size (Ward et al.,2003).

d. Low birth weight and smaller head circumference at birth were associated with lower adult lung volumes, independent of gender and stature. The effects of low birth weight and smoking were additive, so that the lowest lung volumes were found in smoking men who were small at birth. The association between low birth weight and reduced lung volumes in adult life is consistent with the hypothesis that fetal under nutrition has permanent effects on lung structure (Stein et al.,1997).

4.5 Follow-up studies of the Mysore Birth Records Cohort

4.5.1 First follow-up study

A subset of those who participated in the first study between 1993-1995 (n=518) were invited to participate in a follow-up study 2-3 years later in 1996-1997. 435 returned for further cardiovascular investigations, when aged 43-70 years.

The first follow-up study examined whether smaller size at birth was associated with alterations in the cardiovascular system that increased the risk for coronary heart disease (increased left ventricular mass and reduced arterial compliance). Blood pressure was recorded, and left ventricular mass was measured by 2D and M-mode echocardiography. Pulse wave velocity was measured by a non-invasive optical method using the principle of photoplesythmography, to estimate arterial compliance. Data collected from this study are provided in table 4.3.

There were no associations between small size at birth and adult blood pressure, left ventricular mass, and arterial compliance (Kumaran et al.,2000; Kumaran et al.,2002; Kumaran and Fall.,2001). On the contrary, systolic blood pressure and left ventricular mass were higher in subjects who were longer at birth. Arterial compliance was higher in those whose mothers were lighter or had smaller pelvic diameters.

Table 4.3 Data from first follow-up study of the Mysore Birth Records Cohort

N= 435 Of the 1069, 435 examined between 1993-1995 participated in a follow-up study to examine cardiac dimensions and arterial compliance in 1996 - 1997. The participants were then aged between 43-70 yrs.	1. Blood pressure, weight and height, 2. Cardiac dimensions, pulse wave velocity, arterial compliance and left ventricular mass 3. Electrocardiograph 4. Hand X-ray and osteoarthritis questionnaire 5. Reproductive history for women only (age of menarche, parity, pregnancies and breast feeding) 6. Medications 7. Family history of diabetes and hypertension

4.5.2 Second follow-up study

A subset of those who participated in the first study between 1993 and1995 (n=518) were invited to participate in a 10 year follow-up study in 2003-2004 for incident diabetes and coronary heart disease. 383 of them aged 50-70yrs participated (Veena et al.,2009). They underwent repeat assessment for anthropometry, coronary heart disease, abnormal glucose tolerance and dyslipidaemia. Data were also collected on socioeconomic status, education, occupation, and tobacco and alcohol consumption. Data collected from this follow-up study are provided in table 4.4.

At the 10-year follow-up, shorter birth length remained a risk factor for incident type 2 diabetes, while higher maternal weight and larger maternal pelvic diameters showed no association with incident disease (Veena et al.,2009). Other parameters of birth size were unrelated to incident diabetes.

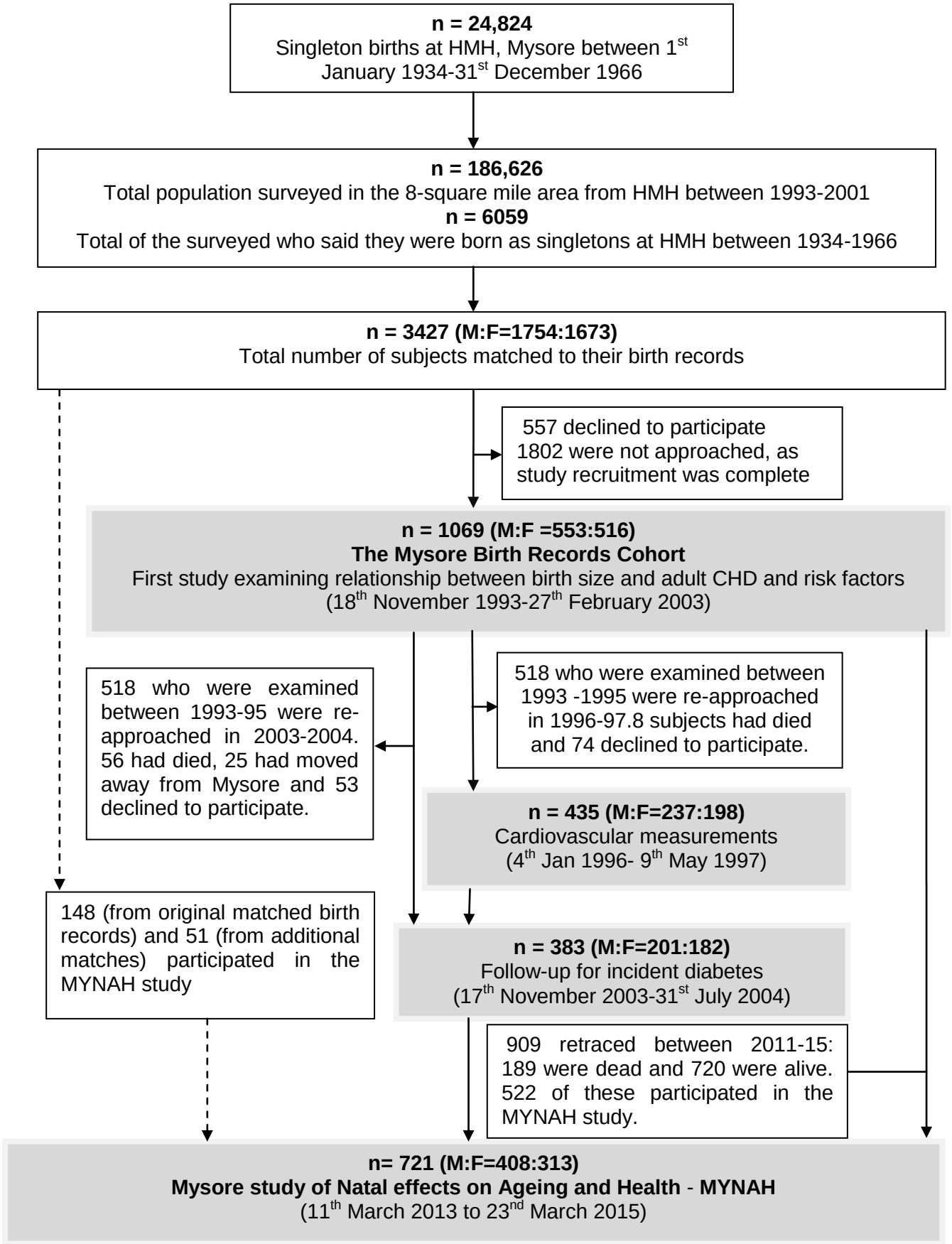
The 10-year follow-up study also suggested that men and women of higher birth size and socio-economic status were more likely to survive, be traceable and/or agree to continue taking part in the research. There was no contact with the cohort after this study.

Table 4.4 Data from second follow-up study of the Mysore Birth Records Cohort

N=383 Of the 1069, 383 examined between 1993-1995 were followed up 10 years later between 2003-2004 to study incident diabetes. The participants were then aged between 50-70.	1.**Blood tests** a. Biochemistry: glucose tolerance test, plasma insulin (fasting, 30 and 120 minutes' post-glucose), fibrinogen, factor 7, total cholesterol, triglycerides, LDL and HDL cholesterol b. Haematology: Full blood count, differential cell count, haemoglobin 2. **Anthropometry**: Height, weight, hip and waist circumference and skin fold thicknesses. 3.**Clinical evaluation**: Pulse rate, blood pressure, electrocardiography, spirometry and Rose angina questionnaire 4. **Structured Interview** a. Marital status, family structure and living arrangements. b. Medications, medical history for stroke, angina, hypertension, diabetes, chronic bronchitis and emphysema, history of coronary artery bypass graft or angioplasty c. Family History of CHD and diabetes d. Physical activity at home and at work e. Alcohol and tobacco consumption f. Diet and food frequency schedule: vegetarian/non-vegetarian, dietary intake of meat, dairy products, fish, fruits, vegetables and oils per week. g. Physical activities: walking, sports, exercises and manual labour h. Reproductive health from women: age of menarche and menopause, h/o breastfeeding, use of contraceptives and hormonal replacement therapy 5. **Kuppuswamy scale for socioeconomic indicators**: Locality in the town, household amenities (water, bathroom and toilet facilities), education level of subject and the spouse, income of the subject and the spouse, occupation of the subject and the spouse, number of members in the household and number per room, total family income and per capita income 6. **Bio impedance recordings**: total body fat weight, lean weight, body water and metabolic rate. 7. **Medical History** for peptic ulcer disease and H Pylori infection and any surgical procedures.

Figure 4.6 illustrates the setting up of the Mysore Birth Records Cohort and previous studies of this cohort (Krishna et al.,2015).

Figure 4.6 The Mysore Birth Records Cohort studies



4.6 Aims and objectives of the current study

4.6.1 Primary goal

The primary goal of this study was to test the hypothesis that lower birth weight and smaller head circumference at birth are associated with poorer scores in tests of cognitive function in 721 men and women aged 55 yrs and over from the matched birth records at Holdsworth Memorial Hospital in Mysore. The mediating effects of childhood growth (proxied by adult head circumference and leg length), education, cardiometabolic risk factors (in mid- and late life) and socioeconomic position (in mid- and late life) were examined to explore the two plausible pathways linking pre-natal growth and nutrition to cognitive function in late life:

a. *Programming* of metabolism by under nutrition in very early life, leading to reduced cognitive function in late life mediated through cardiometabolic disorders (David Barker or DOHaD hypothesis).

and /or

b A direct effect of reduced pre-natal growth and development on brain development leading to decreased peak cognitive capacity and hence reduced cognitive abilities in late life (cognitive reserve pathway) (Whalley et al.,2006)

4.6.2 Other key goals

Other key goals were to report the prevalence of dementia and depression, and their associations with

a. age, gender and education
b. socioeconomic position in mid- and late life
c. cardiometabolic risk factors in mid- and late life
d. nutritional factors (vitamin B12 and folate deficiency, and anaemia)
e. genetic (Apoε4 genotype), lifestyle and endocrine factors (thyroid function)
f. birth size and socioeconomic position in early life

4.7 The research team

I headed a team comprising two social workers, a clinical psychologist, a nurse, a laboratory technician, and a data manager (Figure 4.7). I trained the team members in anthropometry, blood pressure measurement and bio impedance techniques. I trained the clinical psychologist in conducting cognitive function tests. The data manager set up a computer

database for this study with the help of the computing department of the MRC LEU, Southampton.

I was trained in conducting the neurological examination and a structured diagnostic mental health assessment by Prof Martin Prince and Prof John Copeland. I ran day-to-day clinics, supervised clinical appointments, field visits, blood processing, storing of blood samples and computer data entry. I was responsible for the quality of data collection. I conducted inter observer variation studies (IOV) before, during and towards the end of the study (Appendix 3).

Fig 4.7 Research Team at Holdsworth Memorial Hospital

4.8 Recruitment to this study

4.8.1 Field work and retracing

There was no contact with the Mysore Birth Records cohort between 2005 and 2011. The field work to retrace the surviving members of the Mysore Birth Records Cohort and those above 55 yrs of age from the original matched birth records commenced in March 2011. To begin with, we used the most recent address available for the cohort members from the previous studies to establish contact with them. If this was not successful, we visited the address of the place where they were born and/or the address where they were first traced

for matching with their birth records. Well known members of the community (for e.g. councillors, local government leaders, heads of mosques and churches) and volunteers of the hospital helped us reach out to several cohort members. Cohort members from minority communities (Parsi, Anglo-Indian, Ursu etc) were contacted with the support from their respective welfare associations. Members of certain sub-castes in Mysore have characteristic jobs (e.g. Nayakas - Butchers; Bahushar Kshatriya - owners of liquor shops; Marathi - cloth merchants and tailoring) and this served as vital information to retrace cohort members through contacts with local businesses. As the study progressed, several cohort members learnt of this study by 'word of mouth' and voluntarily contacted the research unit for participation. Retracing the potentially eligible participants for this study stopped in March 2015.

4.8.2 Recruitment from the Mysore Birth Records Cohort

We attempted to retrace all 1069 members of the Mysore Birth Records Cohort. A total of 189 (18%) had died and 160 (15%) could not be contacted, leaving 720 (67%). Of these, 522 (73%) participated in this study and 33 (5%) declined to participate.

4.8.3 Recruitment from the original matched birth records

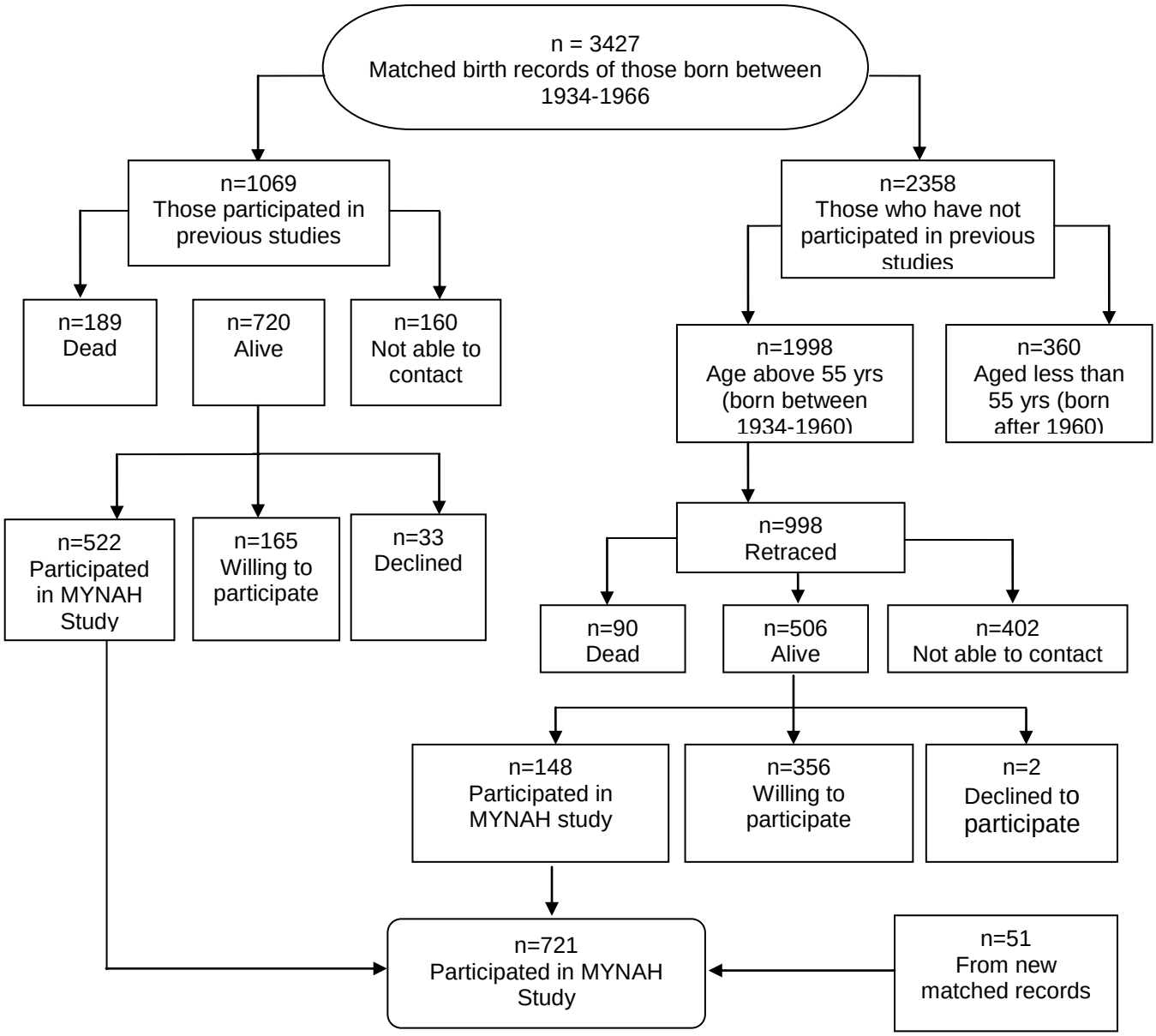
In order to maximise the sample size, we also went back to the rest of the 3427 matched to their records in 1993 -2003 and retraced 998 men and women aged 55 yrs and above (born before 1960). A total of 90 (9.0%) had died and 402 (40.2%) could not be contacted, leaving 506 (50.8%). Of these, 148 (29.2%) have participated in this study and 2 (0.3%) declined. The remaining 356 (70.5%) were willing to participate but could not be studied because the recruitment for this study stopped in March 2015.

4.8.4 Recruitment from additional matches

Once the study started 128 men and women, who had heard of the study by word of mouth, approached us stating that they were born at Holdsworth Memorial Hospital. They expressed a keen interest to participate. I tried to match them, their siblings and relatives with birth records held at Holdsworth Memorial hospital using the original protocol. 67 men and women from 89 families were successfully matched to their birth records, of whom 55 were born before 1960 and eligible to participate in this study. 51 of them participated. In total, I recruited 721 men and women to this study, hereafter called the MYNAH study (Mysore

studies of Natal effects on Ageing and Health). Figure 4.8 illustrates the recruitment for the MYNAH study.

Fig 4.8 Recruitment to the MYNAH study



4.8.5 Preparation of the MYNAH study participants and their families

Once the research assistants had established contact with eligible members of the cohort, I would talk to them or their family members personally over the phone and explain the purpose and the content of the study. I would also encourage them to visit the research unit to learn more about the study and what it entailed. Often this involved discussing about their

medical ailments, alleviating anxieties about blood collection and encouraging them to participate in the study. The fact that I speak local languages fluently was useful in establishing rapport with the participants and their families. Many said that participating in this study was a good and a timely opportunity for a 'body check-up', review of their medication and consultation with specialists in the hospital, if indicated.

The discussion over the phone was always followed up by a home visit by a research assistant, where there was a face to face meeting with the participants and their family members. An information leaflet (Appendix 4) in local languages was provided, and if they were illiterate information would be read to them and their family members. This gave them a second opportunity to discuss any issues related to the study and participation directly with the research team. They were provided with the contact details (phone numbers and address of the research unit) and were advised to inform us of their decision to participate in a week's time. They were told that participation was voluntary and that their travel expenses would be reimbursed. Only those willing to participate were recruited.

4.8.6 Reliable informant

The MYNAH study involved an interview with a reliable informant about participants' cognitive function, any evidence of decline and its impact on day to day functioning. Therefore, we encouraged all the willing participants to attend the research unit with a reliable informant. Individuals who were close to the subjects and had known them for most of their lives (spouse, relative or a friend) were considered as reliable informants.

4.8.7 Clinics

Participants were given an appointment at a time convenient to them. They were given clear instructions about overnight fasting, and advised to bring along their medication and medical records. Medical records in India are generally hand held and retained by the participants. They were advised not to attend if they were having fever, diarrhoea and any other acute medical illnesses. If the participants were unable to travel alone, a research assistant would accompany them to the clinic and return them home after the assessment. If the participant was unable to attend the clinic (e.g. following a stroke) assessments would be conducted at home. The investigations lasted 2 to 3 hours and if the participants were feeling tired they were encouraged to take a break. The informant interviews would take about 20 minutes. The informants were interviewed only with participants' consent. At the end of the clinic, I provided each participant with a detailed feedback and summary report of all assessments.

After the clinic, we reimbursed travel expenses, provided a small gift as a token of appreciation and a photograph was taken for the records. Participants would return the following day to collect their blood reports and I would inform them if there were any problems. If a specialist consultation was indicated, I would personally liaise with them, arrange for a free consultation and additional investigations at Holdsworth Memorial Hospital as advised.

4.8.8 Ethics and consent

This study was approved by the Ethics and Research Committee at CSI Holdsworth Memorial Hospital. Written consent to participate was obtained from all participants. If the participant was illiterate, verbal consent was obtained, which was witnessed and signed by a relative. If individuals were unable to consent (due to severe cognitive or communication problems resulting from stroke or dementia) assent was obtained from their nearest/authorised relative who was witnessed. A specific consent form was used to obtain consent for genetic tests, for storage of posterity samples and DNA material. A copy of the consent forms from this study is provided as an appendix (Appendix 5).

4.9 Investigations

This was a cross-sectional study with comprehensive assessment of cognition, mental health and cardiometabolic outcomes. All 721 men and women along with a reliable informant underwent one off assessments listed in table 4.5. Details of study procedures, investigations and assessments are provided below.

4.9.1 Sociodemographics and socioeconomic status

a) A structured interview for sociodemographics collected information on age, sex, marital status, level of education (none; some, but did not complete primary; completed primary; completed secondary; completed tertiary or further education), living circumstances (living with children, yes/no), family size and structure, religious affiliation and practice, community social activity, social support and social network, food insecurity and migration (rural or urban residence across the lifecourse and age when moved) (Prince et al.,2007).

b) A Standard of Living Index questionnaire was administered. The Government of India in the National Family Health Survey had used the Standard of Living Index (SLI) scale

which contains 11 items: house type, source of lighting, toilet facility, main fuel for cooking, source of drinking water, separate room for cooking, ownership of the house, ownership of agricultural land, ownership of irrigated land, ownership of livestock and ownership of durable goods for measuring the socioeconomic position both urban and rural areas for the entire country (National Family Health survey.,2006). The Kannada version of this questionnaire was used and it took approximately 5 minutes to complete.

Table 4.5. Instruments, assessments and investigations in the MYNAH study

Socioeconomic assessments	i) Structured interview for sociodemographics† ii) Standard of Living Index† iii) Kuppuswamy Scale
Battery of cognitive tests	i) The Community Screening Instrument for Dementia (CSI'D') COGSCORE incorporating the CERAD animal naming verbal fluency task. (CERAD-Consortium to Establish a register for Alzheimer's Disease) ii) The modified CERAD 10-word list learning task with delayed recall iii) Informant interview, for evidence of cognitive and functional decline*
Instruments for diagnosis of dementia	i) Battery of cognitive tests (listed above) ii) A structured clinical mental state interview, the Geriatric Mental State, which applies a computer algorithm iii) An extended informant interview, the History and Aetiology Schedule-Dementia Diagnosis and subtype***** iv) The NEUROEX, a brief fully structured neurological assessment, v) Behavioral and Psychological symptoms: assessed by Neuropsychiatric Inventory*****
Health status and physical health assessment	i) Self-reported global health, diagnoses and treatments for these conditions by a structured interview† ii) A self-reported list of 12 commonly occurring physical impairments† iii) Activity limitation and participation restriction measured by the WHO-Disability Assessment Schedule II† iv) Rose Angina questionnaire v) Direct physical assessments: pulse rate, systolic and diastolic resting blood pressure, weight, height, leg length, head circumference, waist circumference, waist/hip ratio, skin fold thickness (sub-scapular, triceps and abdominal), calf circumference, hand grip test, bio impedance measurements,12 lead ECG for Minnesota coding and 5 meters walking test vi) Reproductive status (for women) – menarche, menopause, reproductive period and number of children.
Blood tests and genetic assay.	**Blood tests**: Hemoglobin, glucose tolerance test, lipid profile, albumin, total protein, thyroid function tests, vitamin B12, folate, insulin and creatinine **Genetic assay**: Apoε lipoprotein

***** Instruments administered to informants only.
†Instruments administered to the informants ONLY if the participants had communication difficulties arising from cognitive problems, severe mental illness, deafness or mutism.

c) Kuppuswamy scale: The most widely used scale for urban populations was Kuppuswamy's socioeconomic scale, devised by Kuppuswamy in 1976. Kuppuswamy scale is a composite score of education and occupation of the head of the family along with monthly income of the family, which yields a score of 3-29. This scale classifies the study populations into high, middle, and low socioeconomic position (Kuppuswamy B.,1981). Though this is now an outdated instrument, I readministered the same scale to enable comparisons of change in socioeconomic position.

A copy of the structured interview of sociodemographics, Standard of Living Index and Kuppuswamy questionnaires is provided as an appendix (Appendix 6).

4.9.2 Cognitive function tests

Cognitive function as a continuous measure was obtained by administering a battery of cognitive tests developed and validated in India by the 10/66 Dementia Research group (Sosa et al.,2009; Prince et al.,2007; Prince et al.,2003). The 10/66 battery of cognitive function test comprises the Community Screening Instrument for Dementia (CSI'D'), Verbal Fluency, Word List Memory and Recall and a CSI'D' Informant Interview. Normative values of these tests for South Indian population, for men and women in urban areas were derived from the 10/66 pilot studies (Sosa et al.,2009).

This battery was translated into Kannada (local language) and the aim of the translation process was to achieve a Kannada version of the English 10/66 battery of cognitive tests that was conceptually equivalent to the study setting and would practically perform in the same way. The focus was cross-cultural and conceptual, rather than on linguistic or literal equivalence. This was achieved by using forward translation (carried out by me) and back translation (by a clinical psychologist and social worker) methods (Appendix 7).

Global Cognitive Function was measured by administering the Community Screening Instrument for Dementia (CSI 'D') to the participants (Hall et al.,2000). This is a 32-item cognitive test assessing orientation, comprehension, memory, naming and language expression, which generates a global cognitive score. The CSI 'D' was from the outset intended to be used across cultures with minimal adaptation. It was developed and first validated among Cree American Indians (Hendrie et al.,1995), further validated and used in population-based research among Nigerians in Ibadan, African-Americans in Indianapolis, white Canadians in Winnipeg and in Jamaica in conjunction with the CERAD battery (Consortium for Establishing Registry for Alzheimer's Disease battery) (Hendrie et al.,1995;

Hall et al.,2000; Unverzagt et al.,1999). The CSI 'D' test score distributions among those with dementia and controls, and the degree of discrimination provided was remarkably consistent across different cultural settings (Unverzagt et al.,1999).

a. For the purpose of this study, three items in the CSI'D' were modified. First, the phrase testing for verbal fluency “no ifs, ands, or buts” was replaced with a popular tongue twister in Kannada “ಅದು ಹೌದು ಆದರೆ ಇದು ಅಲ್ಲ”, translated as “that is, however this isn't”.

   The common knowledge question “what is the name of the mayor/village head?” was changed to “what is the name of the current prime minister?” Third, the long-term memory question was substituted with the local equivalent of: “Who was the freedom fighter that was assassinated after independence in 1948?” The modified CSI'D' was validated in a pilot study before administration to the participants.

b. Verbal fluency was measured by the animal naming verbal fluency task from the CERAD (Hall et al.,2000; Morris et al.,1989). After a brief practice, naming items from another category (clothing), participants were encouraged to name as many different animals as they could in the space of one minute. The instruction was read out to the participants: 'think of any kind of animal in the air, on land, in the water, in the forest, all the different animals'. If the participant stopped before the allotted time, they were encouraged to continue. The participants scored one point for each valid name.

c. Memory was measured by the modified Word List Memory and Recall (WLMR) test to evaluate immediate and delayed recall respectively. WLMR is taken from the adapted CERAD ten-word list learning task used in the Indo-US Ballabgarh dementia study (Ganguli et al.,1996). Six words- butter, arm, letter, queen, ticket and grass were taken from the original CERAD battery English language list (Guruje et al.,1995). Pole, shore, cabin, and engine were replaced with corner, stone, book and stick, which were deemed more cross-culturally applicable (Prince et al.,2003). In the learning phase, the list was read out to the participants from a green card, who then were asked to recall straight away the words that they remembered. This process was repeated three times, giving the subject a score out of 30. Approximately five minutes later, after a series of unrelated CSI'D' questions (name registration, object naming, object function and repetition) the participant was again asked to recall the 10 words, giving a delayed recall score out of 10 and a total WLMR score of 40. Word List Memory and Recall test has been reported to be of particular value in distinguishing early dementia from normal aging (Welsh et al.,1991).

d. The CSI'D' informant interview: In the informant section of the CSI'D', a reliable informant was asked about declining memory in general, and the frequency of six specific and characteristic memory lapses; '' forgetting where s/he has put things, where things are kept, names of friends, names of family, when s/he last saw informant, and what happened the day before'. If the subject was receiving care, the primary caregiver was considered as a reliable informant. The 26 items from this interview sought for evidence of cognitive and functional decline in the participants (Hendrie et al.,1995; Prince et al.,2003).

4.9.3 Assessments for diagnosis of dementia and depression

a. Battery of cognitive function tests (listed above).

b. Geriatric Mental State examination: I conducted a structured clinical mental state interview of the participants using the Geriatric Mental State Examination (Kannada version B3) which takes approximately 15 to 20 minutes (Appendix 8). The GMS is a clinical diagnostic interview which provides symptom scores in four diagnostic clusters (stage 1 diagnosis) from a computerised algorithm: organic brain syndrome (approximating to dementia), schizophrenia and related paranoid states, neurotic and psychotic depression, and anxiety neuroses. Stage 1 diagnoses are organised into final stage 2 diagnoses based on an algorithm that is hierarchically structured (Copeland et al.,1986). I was trained in conducting these assessments by Prof Copeland while working as a clinician in the UK.

c. History and Aetiology Schedule (HAS): This is an extended informant interview providing more detailed information on the onset and course of a possible dementia syndrome. (Dewey and Copeland.,2001; Prince et al.,2007; Prince et al.,2003). This was administered only to informants of those participants who were identified as requiring care from the CSI'D' informant interview (Appendix 9).

d. Neuropsychiatric Inventory. The Neuropsychiatric Inventory–Questionnaire (NPI-Q) was developed and validated to provide a brief assessment of neuropsychiatric symptomatology in those with dementia in routine clinical practice settings (Kaufer et al.,2000). The NPI-Q is a validated informant-based interview that assesses neuropsychiatric symptoms over the previous month. NPI-Q Includes 12 neuropsychiatric domains and the psychological impact of these symptoms on caregivers (Cummings et al.,1994). The domains include delusions, hallucinations,

agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/ lability, aberrant motor activity, night-time behavioral disturbances and appetite/eating abnormalities. Each of these domains contains a survey question that reflects cardinal symptoms of that domain. Initial responses to each domain question are "Yes" (present) or "No" (absent). If the response to the domain question is "No", the informant moves to the next item. If "Yes", the informant then rates both the severity of the symptoms present within the last month on a 3-point scale, and the associated impact of the symptom manifestations on them (i.e. caregiver distress) using a 5-point scale. The NPI-Q provides symptom severity and distress ratings for each symptom reported, and total severity and distress scores reflecting the sum of individual domain scores. Informants were able to complete the NPI-Q in 5 minutes or less in this study.

Fig 4.9 Neurological examination

e. Neurological examination: I conducted a brief and structured neurological assessment (the NEUROEX) for the participants lasting about 10 minutes (Figure 4.9). This assessment provides objectified quantifiable measures for lateralising signs, parkinsonism, ataxia, apraxia and primitive 'release' reflexes (Broe et al.,1976; Broe et al.,1998) (Appendix 10).

Fig 4.10a Measurement of height

Fig 4.10b Measurement of head circumference

Fig 4.10c Measurement of biceps skinfold

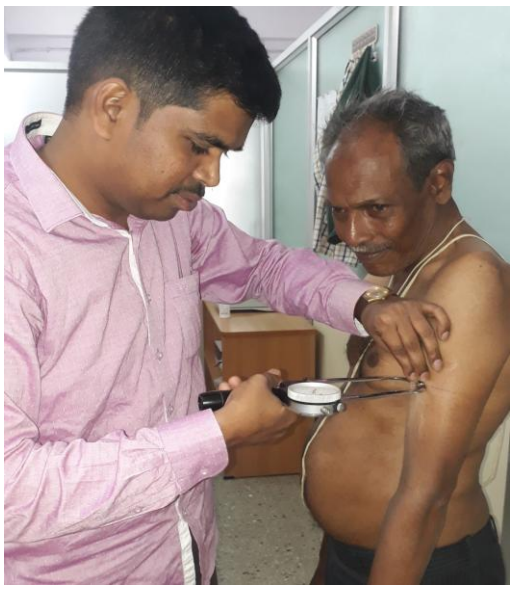
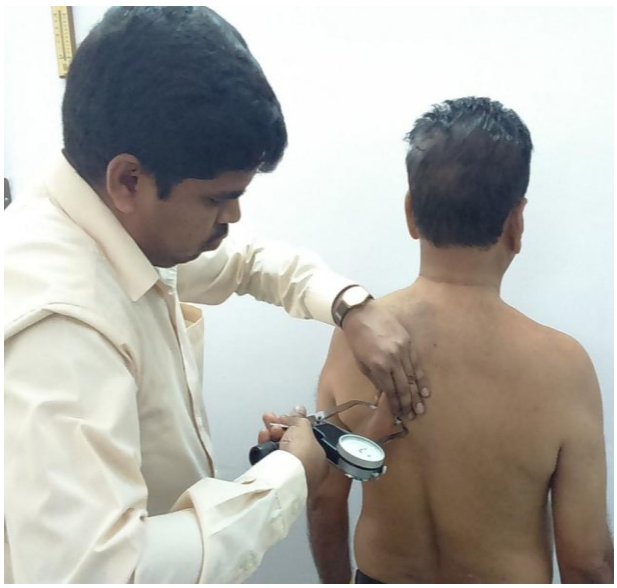


Fig 4.10d Measurement of subscapular skinfold



4.9.4 Health status and physical health assessments (Appendix 11)

a. Anthropometry: Anthropometric measurements were carried out by myself and two other male research assistants (for men) and two female research assistants (for women) (Figures 4.10 a-d). These assessments were not carried out if the participants were unable to stand (e.g. following stroke, severe arthritis, gross pedal oedema and general weakness). A list of anthropometric measurements conducted in this study along with the protocol for measuring them is provided in table 4.6.

Table 4.6 Anthropometry measurements with protocols used in this study

Measurements	Protocol
Weight (kg)	Measured using an electronic weighing scale (Seca, Germany) in minimal clothing, to the nearest 100g.
Height (cm)	Measured using Microtoise wall-mounted stadiometer, to the nearest 1 mm.
Leg length (cm)	Measured using anthropometric tape (Chasmors) to the nearest 1 mm as the distance from the iliac crest to the lateral malleoli of the ankle.
Head circumference (cm)	Measured using anthropometric tape (Chasmors) to nearest 1 mm at the level of maximum occipito-frontal diameter (farthest point of the occipital protuberance in the back and just above the eyebrows in front).
Mid upper arm circumference (cm)	Measured to the nearest 1 mm, at the mid-point between acromion and olecranon processes using an anthropometric tape (Chasmors).
Hip circumference (cm)	Measured using an anthropometric measuring tape (Chasmors) to the nearest 1 mm, as the maximum measurement around level of the greater trochanter.
Waist circumference (cm)	Measured using an anthropometric measuring tape to the nearest 1 mm at the level of umbilicus using anthropometric measuring tape (Chasmors) at the end of expiration.
Subscapular skinfold (mm)	Measured using Harpenden skinfold callipers just below the inferior angle of the scapula along the natural direction of the skin cleavage. Readings taken at the end of 5 seconds.
Biceps skinfold (mm)	Measured at the intersection of horizontal mid arm line and the vertical line at the most prominent point of the biceps using Harpenden skinfold callipers. Readings taken at the end of 5 seconds.
Triceps skinfold (mm)	Measured at the intersection of horizontal mid arm line and the vertical line at the most posterior point of the triceps using Harpenden skinfold callipers. Readings taken at the end of 5 seconds.

Blood pressure assessment: Systolic and diastolic blood pressures were measured using a fully automated device (CRITIKON, DINAMAP^{TM} model 8100). The measurements were done on the right hand following the 30-minute blood sample after allowing the subject to relax seated for 5 minutes. The measurement was repeated after 5 minutes. Team members

were trained in blood pressure measurements before the start of the study and methods were standardised (Figure 4.11).

Fig 4.11 Blood pressure measurement

b. Electrocardiogram (ECG): Each participant underwent a resting standard supine 12-lead electrocardiogram at least 1 hour after smoking or caffeine ingestion. Electrodes were positioned using a standardised protocol with Phillips C3i machine (Figure 4.12).

Fig 4.12 Electrocardiogram

Three ECG copies were obtained, one of which was given to the participants and the remaining two were coded by a trained physician using the Minnesota classification system (Macfarlane.,2000). This type of visual ECG coding helps to overcome the lack of standardisation and the poor repeatability of clinical ECG interpretation by providing a framework for reporting ECG findings in standardised and clearly defined terms. The Minnesota code combines three major elements: a set of measurement rules, a classification system for reporting ECG findings, and a set of exclusion rules (Macfarlane.,2000).

c. Bioelectrical Impedance Analysis (BIA): is a quick and easy method designed for measuring body composition. BIA for this study was carried out using the Bodystat 1500 machine (Bodystat, Isle of Mann, British Isles). Any jewellery and metal accessories were removed and participants were asked to lie supine for 5 minutes before starting the measurements. The measurement was done on the right side of the body. On the hand, one electrode was attached at the level of the ulnar head at the wrist and the other just behind the knuckles. On the foot, the two electrodes were attached at the level of the medial and lateral malleoli and just behind the toes, respectively (Figure 4.13).

Fig 4.13 Bioimpedance measurement

The principle of bioelectrical impedance analysis is based on the observation that the body's lean compartment (which includes muscle, bone and water), conducts electricity better than the body's non-aqueous fat compartment. This is because different components of the body have varying levels of resistance (impedance) in response to different frequencies of electrical signals. The bioelectrical impedance analysis is a 2-compartment model method, which measures total body water, and hence a measure of fat-free mass, by passing a low voltage alternating current through electrodes placed

on hand and feet. A measure of total body fat is derived by including the impedance value into sex-specific regression equations, along with weight and height. It is a relatively quick method and the equipment is easy to handle, and has been validated using different reference methods for several populations in the world (Dehghan & Merchant.,2008).

d. Grip strength: Grip strength was measured to the nearest 0.5 kg by one of the two trained research assistants using a Jamar dynamometer (Model J00105, Lafayette Instrument Company, Loughborough, UK).

Fig 4.14 Grip strength

Fig 4.15 Spirometry

The measurer demonstrated the technique to each participant who was seated with their forearm resting on the arms of the chair with the wrist free. The participant held the dynamometer with the research assistant supporting its weight.

Each participant was encouraged throughout the procedure, to squeeze as tightly and for as long as possible until the maximum reading was obtained. Two readings were made with each hand, alternation between right and left hand. Hand dominance was recorded. Average of the two measurements of the dominant hand was used for analysis (Figure 4.14).

e. Spirometry: Simple hand held microspirometers such as the PiKo-6 (nSpire Health Inc., Longmont, CO, USA) can be used to measure the FEV1/FEV6 ratio (Forced expiratory volume at 1 second / Forced expiratory volume at 6 seconds). PiKo-6 spirometry is effective and reliable for screening for Chronic Obstructive Pulmonary Disease (COPD) in primary care (Kaufmann et al.,2009; Frith et al.,2011). PiKo-6 spirometry testing was performed by me and a trained research assistant according to the manufacturer's instructions. PiKo-6 devices were checked for calibration errors before the start of the study. All participants were given a demonstration and were asked to practice blowing into the spirometer. The participants were required to inhale maximally, and exhale as hard and as fast as possible into the mouthpiece of the PiKo-6 until an end-of-test beep was heard after 6 secs. Each participant was encouraged to do this three times, and the highest FEV1 and FEV6 value of the three measurements was used to calculate the FEV1/FEV6 ratio. The PiKo-6 has an automatic test quality alert and indicates attempts that were invalid because of coughing or abnormal blow (Figure 4.15).

f. Rose angina questionnaire: This questionnaire (Figure 4.16) was administered by trained research assistant at the interview. 'Typical angina' was defined according to standard criteria as chest pain or discomfort (yes to question 1) that fulfilled all of the following criteria: (a) was brought on by exertion (yes to either question 3 or 4); (b) was situated in the central or left anterior chest (site 4, 5, or 8 on diagram in question 2); (c) forced the subject to slow down or stop (question 5); (d) was relieved if the subject did so (yes to question 6), and (e) was relieved within 10 minutes (question 7) (Rose.,1962; Cook et al.,1989).

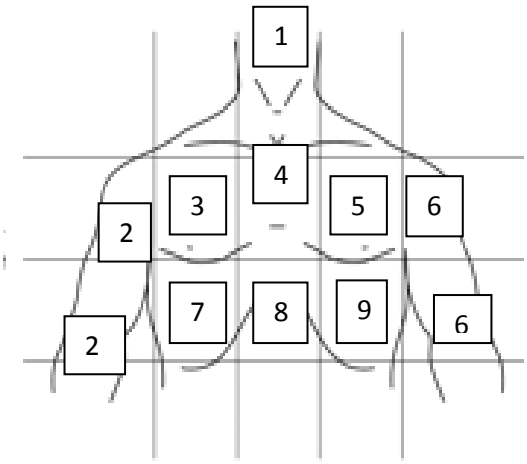
g. A structured interview for self-reported global health, self-reported diagnoses and treatments of common medical conditions (like diabetes, hypertension, heart disease, stroke, chronic obstructive airway disease, thyroid disorders, malaria, tuberculosis and epilepsy), lifestyle and cardiovascular risk factors (alcohol use-volume and frequency current and past; lifetime smoking-never, ever and current smokers and pack year calculation; dietary intake of fish, meat and fruit and vegetables; food insecurity; exercise and activity levels now and in earlier life) and reproductive health status of women (menarche, menopause, reproductive period and number of children) was administered. This assessment took approximately 10 minutes.

Fig 4.16 Rose angina questionnaire

1. Do you ever have any pain or discomfort in your chest? Yes/No.

2. Where do you get this pain or discomfort? Please mark X on the appropriate places

Your right side



Your left side

3. When you walk at an ordinary pace on the ground level does this produce the pain?

   Yes/No/Unable.

4. When you walk uphill or hurry does this produce the pain? Yes/No/Unable.

5. When you get any pain or discomfort in your chest on walking, what do you do?

   Stop Slow down Continue at same pace Not applicable.

6. Does the pain or discomfort in your chest go away if you stand still? Yes/No

7. How long does it take to go away? 10 minutes or less. More than 10 minutes

h. Physical Health Impairment Schedule: This is a self-reported list of twelve commonly occurring physical impairments, a measure of health impairment (Duke University.,1978). They include arthritis/rheumatism, eyesight problems, hearing difficulty or deafness, persistent cough, breathlessness/asthma, high blood pressure, heart trouble/angina, stomach problems, intestine problems, faints/blackouts, skin

disorders and paralysis/ weakness or loss of one leg or an arm. Impairments were rated as present if they interfered with activities “a little” or “a lot”, as opposed to “not at all”. This assessment took approximately 5 minutes.

i. WHO Disability Schedule-II: The degree of disability was measured by administering the WHO Disability Schedule-II (WHO DAS II) (Rehm et al.,2000). It was developed by the WHO as a culture-fair assessment tool for use in cross-cultural comparative epidemiological and health services research to measure activity limitation and participation restriction. The 12 items assess five activity limitation domains (communication, physical mobility, self-care, interpersonal interaction, life activities and social participation). Each domain is covered by two questions, with scores ranging from 0 (no difficulty) to 4 (extreme difficulty or cannot do), and yielding a total score between 0 and 48. This assessment took approximately 5 minutes.

4.9.5 Blood tests and assays

The following blood tests and assays were conducted as a part of this study

a. Haematology tests: Haemoglobin
b. Biochemistry tests: glucose tolerance test, lipid profile, total protein, albumin, thyroid function tests, vitamin B12, folate, homocysteine and creatinine
c. Genetic assay: DNA sample for Apoliprotein-ε genotyping

4.10 Blood collection and processing

4.10.1 Glucose tolerance test

Participants attended the clinic after overnight fasting. An oral glucose tolerance test was carried out if they were not known to be diabetic and blood samples were obtained at fasting, and at 30 minutes and 120 minutes after takings 75 gms of anhydrous glucose in 250 ml of water. If participants were known to have diabetes, fasting sample and postprandial sample (120 minutes after breakfast) were collected. The WHO protocol was followed for the glucose tolerance test (WHO.,1999) (Figure 4.17).

Fig 4.17 Blood collection

4.10.2 Blood processing

10ml of fasting blood sample was drawn in to an EDTA vacutainer, of which 2ml was separated for haematology tests. After separation, the rest was centrifuged immediately at 4000 revolutions per minute. Plasma was divided into 5 aliquots and fresh frozen at -80^{o}C for biochemistry and storage. EDTA vacutainers with packed cells were stored in a -80^{0}C freezer for DNA analysis. A 2 ml of the blood sample was drawn at 30 minutes and a 5ml blood sample at 120 minutes and processed similarly (Figure 4.18).

Fig 4.18 Blood processing

4.10.3 Blood transportation

Samples for haematology tests were analysed immediately at Holdsworth Memorial Hospital. Samples for biochemical analyses were sent to the Diabetes Unit at KEM Hospital, Pune which participates in the United Kingdom National External Quality Assessment Service (UKNEQAS) for insulin assays. One frozen packed cell sample for each participant was sent to the Centre for Cellular and Molecular Biology (CCMB), Hyderabad where DNA was extracted for APOε genotyping. CCMB is one of the constituent national laboratories of the Council of Scientific and Industrial research, Government of India. Samples sent to Pune and Hyderabad were packed in dry ice and transported in batches.

4.11 Outcomes

a. Cognitive function (primary outcome: scores on global cognition, verbal fluency and, immediate and delayed recall on the word list memory recall tests) as a continuous measure was obtained by administering the battery of cognitive tests described above.

b. A diagnosis of dementia was derived from the 10/66 algorithm. Dementia was defined as a score above a cut-off point of predicted probability of DSM IV Dementia Syndrome from the logistic regression equation of the 10/66 dementia diagnostic algorithm (American Psychiatric Association.,2000; Prince et al.,2003).

c. Diagnosis of Mild Cognitive Impairment (MCI) was derived from the 10/66 diagnostic algorithm which is based on the following criteria: objective memory impairment beyond that expected for age; subjective memory complaint; no (or only mild impairment) in core activities of daily living, and no dementia. MCI is an intermediate state between normal cognitive ageing and dementia (Prince et al.,2003).

d. Diagnosis of depression was derived from the Geriatric Mental State Examination with its computerised algorithm (GMS) (Copeland et al.,1986).

4.12 Definitions

a. By WHO standards a height less than 162 cms in men and 150 cms in women is defined as stunting (de Onis et al.,2007). Body mass index (BMI: kg/m^2) was used to define overweight (≥ 25 and < 30 kg/m^2) and obesity (≥ 30 kg/m^2) (WHO.,2012). A cut-

off point of total body fat ≥ 25% for males and ≥ 35% for females was used to define adiposity (WHO.,1995).

b. Hypercholesterolemia was defined as plasma total cholesterol ≥ 5.17 mmol/l using National Cholesterol Education Program criteria (NCEP 2002), hypertriglyceridaemia as triglycerides ≥ 1.7mmol/l and low HDL as HDL < 1.0 mmol/l for males and < 1.3 mmol/l for females (Alberti.,2006).

c. Glycaemic classification was done according to the WHO criteria (WHO.,2006):

- Impaired fasting glucose: fasting plasma glucose ≥ 6.1 and < 7.0 and 2-h plasma glucose < 7.8 mmol/l
- Impaired glucose tolerance: fasting plasma glucose < 7mmol/l and 2-h plasma glucose ≥7.8 and < 11.1 mmol/l *and*
- Diabetes mellitus: fasting plasma glucose ≥ 7 or 2 hr plasma glucose ≥ 11.1 mmol/l.

Those who were known to have diabetes and taking medication for diabetes were also classified as having diabetes.

Insulin resistance was estimated using the Homeostasis Model Assessment equation for insulin resistance (HOMA-IR) (Matthews et al.,1985)

Hypertension was defined as systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 85 mm Hg using International Diabetes Federation criteria (Alberti.,2006). Those who were known to have hypertension and taking antihypertensive medication were also classified as having hypertension. Orthostatic BP change was defined as the difference between the average standing and average supine blood pressure. Orthostatic hypotension (OH) was defined as a systolic blood pressure drop of ≥20 mm Hg or diastolic blood pressure of ≥10 mm Hg when changing position from supine to standing (Gibbons et al.,2017).

Metabolic syndrome was diagnosed using International Diabetes Federation criteria. (Alberti.,2006). According to these, for a person to be defined as having the metabolic syndrome they must have central obesity (defined as waist circumference ≥ 90 cms for South Asian men and ≥ 80 cms for South Asian women) plus any two of the following four factors:

- Raised triglycerides level: ≥ 1.7 mmol/l
- Reduced HDL cholesterol: <1.03 mmol/l in males and <1.29 mmol/l in females, or specific treatment for this lipid abnormality
- Raised blood pressure: systolic blood pressure ≥ 130 or diastolic blood pressure ≥ 85 mm Hg, or treatment of previously diagnosed hypertension
- Raised fasting plasma glucose 5.6 mmol/l, or previously diagnosed type-2 diabetes.

Diagnosis of coronary heart disease was derived from an algorithm, drawing information from the Rose chest pain questionnaire, Minnesota ECG coding and a clinical history of cardiac revascularisation procedures. Coronary heart disease was diagnosed if there was typical angina on Rose chest pain questionnaire, or a history of cardiac revascularisation procedures or the presence of Minnesota codes 1-1 or 1-2 (major Q waves) on the ECG.

Thyroid Stimulating Hormone (TSH) greater than 47 milli IU/l and Thyroxine (T4) lesser than 64.35 milliIU/l was defined as hypothyroidism according to the British Thyroid Association and British Thyroid Foundation guidelines (Okosieme et al.,2016)

Diagnosis of Anaemia: Haemoglobin less than 13 g/dl in men and 12 g/dl in women was defined as anaemia according to the Indian Guidelines for Control of Anaemia (Ministry of Family Health and Welfare, India.,2013)

Vitamin B12 and folate deficiency: Vitamin B12 lower than 150 pmol/l and folate lower than 7 nmol/l was considered as vitamin B12 and folate deficiency respectively. Homocysteine greater than 15 micromol/l was defined as hyperhomocysteinaemia (Aparicio-Ugarriza et al.,2015).

Stroke was diagnosed based on self-report (“have you ever been told by a doctor that you had a stroke?”), history of symptoms and findings from the neurological examination according to the 10/66 protocol. Stroke was coded only if there was a clear history of sudden onset of unilateral paralysis, loss of speech, or blindness lasting for more than 24 hours, hence excluding previous episodes of transient ischemic attack (Prince et al.,2007).

The 10/66 protocol and PiKo-6 spirometry were used for diagnosis of chronic obstructive airway disease. Chronic obstructive airway disease was diagnosed in people who responded “yes” to the question “do you usually cough up phlegm from your chest first thing in the morning?” and whose answer to the question “for how many months of the year does this usually happen?” was 3 months or more and FEV1/FEV6 ratio <0.7 (Prince et al.,2007).

4.13 Pilot study

A pilot study was carried out to examine the validity and feasibility of the modified 10/66 battery of cognitive function tests among community dwelling older adults in the city of Mysore. Key findings from this pilot are listed below and full details are provided as an appendix (Appendix 12).

a. Lower scores on individual domains of the 10/66 battery of cognitive tests were associated with higher levels of disability and functional impairment in community dwelling older adults in Mysore, South India. The inverse association between scores on all cognitive function tests cores and disability scores was strong and not attenuated after adjusting for self-reported chronic non-communicable disorders.

b. The 10/66 cognitive function tests were able to identify individuals with 'functional impairment' due to cognitive problems in this sample of community dwelling older adult population where nearly a third of them were illiterates. This reconfirmed the 'culture and education fair' properties of the 10/66 battery of cognitive tests, and that they were well suited for identification of older adults with cognitive and functional impairment at a population level in my study setting.

c. It was not feasible to administer the 10/66 instruments in participants' own homes in a standardised manner. Administering a battery of cognitive tests to an older adult and interviewing an informant in their own homes had its strengths and weaknesses. It was a challenge to administer cognitive tests in a standardised manner while strictly adhering to the test protocol. The reasons include: limited physical space, lack of privacy, poor lighting, noise levels and in some instances family members and friends attempting to prompt or answer for the subject despite clear instructions not to do so. However, being at the participants' own home provided an opportunity to observe them in familiar surroundings and it was easier to identify reliable informants. The informants were generally reluctant to report certain information like toileting needs, getting lost in

the neighbourhood and needing assistance with personal care out of respect to their elders. This may have potentially resulted in underreporting of cognitive and functional decline by the informants. Due to the above-mentioned reasons, it was decided to conduct both cognitive assessments and informant interviews in a clinical setting at the research unit for this study.

4.14 Power calculation

We estimated that 715 men and women will participate in this study. Using a test at the 5% significance level, a study with 715 men and women would have 80% power to detect an association of 0.105 standard deviations of a continuous outcome (cognitive score) per SD of a continuous exposure (e.g. birth weight). For a binary outcome (depression) with a prevalence of 19% and using a test at the 5% significance level the study would 80% power to detect an odds ratio of 1.35 for the outcome per standard deviation change in the predictor. I recruited a slightly more men and women to this study (n=721).

4.15 Data management

4.15.1 Data collection

Data were first collected on to paper. The data collected for the study were recorded directly, accurately, promptly, and legibly. I was responsible for the integrity of the data. After the clinic, I would personally review all the records of participants to ensure that the data were complete and document reasons for any missing or incomplete data.

4.15.2 Data storage

The manually collected data were stored in locked cabinets for the orderly storage and expedient retrieval of all study related material. An index has been prepared to identify the filed contents and their location. Access to the data is controlled and limited to authorised personnel only.

4.15.3 Data processing

All data were double entered into computerised databases driven by EpiData (version 3.1) software on different password protected computers. These databases, developed by the 10/66 Dementia Research Group incorporate conditional skips, and interactive checking of

data consistency (Dean et al.,1994). EpiData files developed at Mysore are identical to the 10/66 dementia archive at the Institute of Psychiatry, London. The data managers at the research unit and the MRC LEU have checked the data for consistency. Any discrepancy in the two datasets was checked against the hard copy entry, and the correct value was entered. Data were extracted into SPSS (Statistical Package for Social Sciences. version 21), and all processing (cleaning, processing of derived variables and running of the10/66 diagnostic algorithm) was carried out using SPSS batch files. The end result was a cleaned, processed and labelled data set that can be exported into other statistical programs for further analysis. Data archiving was also conducted in a standardised manner.

4.15.4 Confidentiality

Data encryption was done to protect the identity of all the participants. Special procedures are in place at the research unit to ensure that access to confidential information is limited and that the confidentiality of information about study subjects is protected.

4.16 Statistical analyses

4.16.1 Characteristics of the study participants

I examined the sociodemographics, anthropometry, cardiometabolic, cognitive and mental health characteristics of the study participants stratified by sex, and when indicated, by educational level and socioeconomic position. Differences in means and medians between the groups were examined by t-tests and Mann Whitney U tests respectively. Differences in proportions between the groups were examined by chi-square tests. These are reported in chapter 5.

4.16.2 Representativeness analyses of the MYNAH participants

I have carried out a series of analyses to examine the representativeness of the MYNAH participants. I examined how the originally matched 3427 men and women compare in birth size with all the births at HMH between 1934 and 1966. I have also compared birth size measurements between these 3427 individuals and the 1069 who participated in the earlier study, and the MYNAH participants. I examined the differences in birth size, sociodemographics and cardiometabolic risk factors between the 1069 men and women who had participated in the initial study and the MYNAH participants. Subgroup analyses of the 1069 individuals were carried out between those who were successfully retraced and lost to

follow-up, and between those who were alive and dead when retraced. The findings are reported in chapter 5 (section.5.2)

4.16.3 Associations of contemporaneous and lifecourse factors with cognitive outcomes in late life

The cognitive function test scores as continuous variables were derived from the 10/66 battery of cognitive tests. They include global cognition, verbal fluency and, immediate and delayed recall on the word list memory recall tests. The global cognitive function score was not normally distributed showing a skew towards left, therefore it was normalised employing Fisher Yates transformation. Verbal fluency, immediate and delayed word list recall scores were normally distributed.

I examined the associations of sociodemographics, cardiometabolic and other NCD risk factors (exposures) in mid- and late life with cognitive outcomes. I examined the associations of these exposures with individual cognitive function tests (continuous outcomes) by conducting simple linear regression analyses and with dementia by conduction logistic regression analyses. The analyses were adjusted for age and gender, and reported in chapter 6.

4.16.4 Associations of the size at birth and cognitive outcomes in late life

I examined the associations of measurements of size at birth with cognitive outcomes in late life by conducting mixed regression analyses. I examined for the evidence to support the DOHaD cardiometabolic pathway and DOHaD cognitive reserve pathway of cognitive ageing in this cohort. To explore the cardiometabolic pathway, I examined:

a. associations of birth weight with cardiometabolic risk factors in mid- and late life
b. associations of cardiometabolic risk factors in mid- and late life with cognitive function in late life
c. the effect of adjusting for cardiometabolic risk markers in regression models of birth weight as predictors of late life cognitive function

The following analyses were conducted to explore the DOHaD cognitive reserve pathway:

a. associations of size at birth with brain reserve and cognitive reserve
b. associations of brain reserve and cognitive reserve with cognitive function in late life

c. the effect of adjusting for brain reserve and cognitive reserve in regression models of birth size as predictors of late life cognitive function

Results and findings from the above analyses are reported in chapter 7.

4.16.5 Associations of contemporaneous and lifecourse factors with depression in late life

I have conducted mixed regression analyses to examine risk factors across the lifecourse for late life depression (binary outcome) in the MYNAH cohort. To achieve this, I examined the associations of:

a. sociodemographics factors in mid- and late life with depression in late life
b. cardiometabolic risk factors in mid- and late life with depression in late life and
c. other factors assessed in late life (genetic, nutritional/anthropometric, lifestyle and endocrine factors) with depression in late life
d. other factors assessed in midlife (nutritional/anthropometric and lifestyle) with depression in late life
e. size at birth, and socioeconomic position in early life with depression in late life.

The results from the above analyses are reported in chapter 8.

4.17 Discussion

4.17.1 Diagnosis of mental disorders

The 10/66 diagnostic criteria were used for diagnosis of mental disorders in late life in this study, instead of the more widely used DSM IV (Diagnostic and Statistical Manual of Mental Disorders) criteria in high income countries (American Psychiatric Association.,2000). Population based studies applying the DSM IV criteria have reported lower prevalence rates for dementia, particularly in low- and middle income countries (O'Connor et al.,1996). This is due to the fact that the DSM IV criteria, when strictly applied, allow only for a narrow diagnosis of dementia with moderate to severe impairment, and are less sensitive to mild but clinically relevant impairment (American Psychiatric Association.,1994; Baldereschi et al.,1994). This challenge was overcome by the 10/66 fully operationalised diagnostic criteria, which offer a broader category for the diagnosis of dementia, and are now recommended for population based studies of cognitive ageing and mental disorders in late

life, particularly in low- and middle income countries (Prince et al.,2008). In the 10/66 validation studies, there was better agreement of clinician diagnosis of dementia with a 10/66 diagnosis compared to the DSM IV diagnosis. The DSM IV algorithm missed less severe cases of dementia, and those with a 10/66 dementia diagnosis who did not meet the DSM IV criterion were less functionally and cognitively impaired compared with the DSM IV confirmed cases, but clinically impaired compared with those without dementia. Another major advantage of the 10/66 algorithm is its intrinsic ability to differentiate dementia from pseudo-dementia (cognitive impairment in those with depression) with remarkable accuracy (Prince et al.,2008). Therefore, I believe the mental health diagnoses derived from the 10/66 algorithm in this study to be reliable and of clinical relevance.

4.17.2 Adaptation of the study protocol

This study strictly adhered to the study protocol, but for a minor adaptation. It was planned to administer a Glucose Tolerance Test (GTT) to all consenting participants for diagnosis of hyperglycemia and diabetes. However, in the pilot study, participants who were already diagnosed with diabetes refused a GTT, as they were of the opinion that drinking glucose on an empty stomach was dangerous. Therefore the protocol was adapted, and only those without pre-existing diagnoses of diabetes were offered a GTT. For those with diabetes a fasting sample, and a 120 mins sample after breakfast, was obtained for estimation of blood glucose levels.

4.17.3 Issues related to the diagnosis of coronary heart disease

The diagnosis of coronary heart disease in this study was based on an algorithm (section 4.13) that included the Rose Angina Questionnaire, the most widely instrument for diagnosis of coronary heart disease in population based studies across the globe. Almost all previous validation studies of Rose Angina questionnaire have been conducted in North America or Europe, among predominantly white populations. However, there is evidence to suggest that the questionnaire is less reliable among South Asians. Findings from two studies in the UK (London and Newcastle), indicated that the Rose Angina questionnaire was less reliable and less accurate (in comparison with a gold standard clinician diagnosis) among South Asians (predominantly from India) when compared to the White Caucasian population for diagnosis of coronary heart disease (Fischbacher et al.,2001; Patel et al.,1997). In addition, ECGs were coded by only one independent but trained physician in this study, unlike in the previous studies of this cohort, where ECGs were coded by two independent investigators (Stein et al.1996). Those who were newly diagnosed with CHD in this study were not

confirmed by more conclusive cardiac investigations such as coronary angiography. Therefore, the prevalence of coronary heart disease and its associations with cognitive function and depression in late life in my study sample should be interpreted with caution.

4.17.4 Issues related to spirometry

The standard protocol for assessment of lung function is classical spirometry, after administration of a bronchodilator, as recommended by the GOLD (Global initiative for Chronic Obstructive Lung Disease) initiative (Vestbo et al.,2013). PIKO-6 spirometry, used in this study, has been reported as a reliable method for measuring lung function and screening for chronic obstructive pulmonary disease in primary care settings, in high income countries (Kauffmann et al.,2009; Frith et al.,2011). However, there have been no validation studies examining the reliability of PIKO-6 spirometry for lung assessment in late life in India or in other low- and middle income settings. During this study, I observed that many participants due to loss of teeth, use of dentures, general weakness and difficulty understanding instructions, were unable to blow optimally into the spirometer. It is possible that these issues might have resulted in slightly lower values on spirometry and consequently a slightly higher prevalence of chronic obstructive pulmonary disease.

The strengths and limitations of this study protocol have been discussed further in the context of key findings from this study in Chapter 9 (sections 9.4 and 9.5).

5. Results: Participant characteristics

5.1 Characteristics of the study participants

5.1.1 Demographic characteristics (table 5.1)

I studied 721 men and women (408 men and 313 women). The majority (75% of men and 70% of women) were aged under 65 yrs, while only 10% were aged 70 yrs and above. Almost all of the participants lived in the city of Mysore (99% of men and 97% women) while the rest lived in rural areas near the city of Mysore.

The study sample had a higher representation of Muslims and Christians than the overall population of Mysore. According to the 2011 census of Mysore, 74% of the population were Hindus, 22% were Muslims, 3% were Christians, and 1% were of other faiths (Registrar General India., 2011). In my sample, equivalent percentages were 41%, 43%, 15.5% and 0.5% among men, and 35%, 50%, 15% and 0.5% among women.

Only a very small proportion of the study participants had never married (3.2%) or were separated/divorced (2.2%). The majority were married and living with their spouse, but a higher proportion (34%) of the women were widowed, compared to men (4%).

The majority of the women had never used alcohol or smoked tobacco. More than half of the men (57%) had never used alcohol; a quarter (26%) were drinking alcohol at the time of the study. Nearly two thirds of the men in my study were either current smokers or had smoked previously. Life time smoking and alcohol status of the study participants was similar to those reported for community dwelling older adults in this region (31% current and 68% never for alcohol; 34% current and 29% never for smoking) by the WHO Study on Global Ageing and Adult Health (WHO SAGE India National Report.,2013).

Men and women from this study have higher levels of formal education compared to the general population of Mysore. Only 3% participants had not received any formal education compared to 13% of the general population of Mysore. A vast majority of men (86%) and women (81%) in this study had completed at least 10 yrs of schooling and had obtained Secondary School Leaving Certificate. Equivalent percentages for secondary schooling in urban India for this age group are 19% and 14% for men and women respectively (Registrar General India.,2011). More men were graduates and postgraduates than women in my study sample

Table 5.1 Demographic characteristics of participants by sex				
Demographic characteristics	**Men** n=408		**Women** n=313	
Age (yrs) mean(SD)	62.0	(5.2)	62.8	(5.4)
55-60 n(%)	164	(40)	110	(35)
60-65 n(%)	145	(36)	108	(35)
65-70 n(%)	63	(15)	60	(19)
70-75 n(%)	27	(7)	24	(8)
75-80 n(%)	9	(2)	11	(3)
Religion n(%)				
Hindu	167	(41)	109	(35)
Muslim	175	(43)	157	(50)
Christian	64	(15)	45	(14)
others	2	(1)	2	(1)
Lifetime alcohol status n(%)				
Never drinker	235	(57)	303	(96)
Ex drinker	68	(17)	8	(3)
Current drinker	105	(26)	2	(1)
Lifetime smoking status n(%)				
Never smoker	137	(33)	311	(98)
Ex smoker	137	(34)	1	(1)
Current smoker	134	(33)	1	(1)
Education (n%)				
Illiterate	7	(2)	15	(5)
Primary	49	(12)	46	(15)
Secondary	105	(26)	87	(28)
Preuniversity	78	(19)	67	(21)
Diploma	53	(13)	43	(14)
Graduate	65	(16)	18	(6)
Postgraduate	51	(12)	37	(11)
Marital status n(%)				
Never married	12	(3)	11	(3)
Married	370	(90)	189	(60)
Widowed	17	(4)	106	(34)
Divorced	9	(3)	7	(3)
Physical activity n(%)				
Sedentary	2	(1)	1	(1)
Mild	12	(3)	15	(5)
Moderate	319	(79	267	(85
Strenuous	73	(27)	30	(9)
Diet n(%)				
Vegetarian	53	(13)	49	(16)
Non vegetarian	355	(87)	264	(84)

Nearly 80% of men and women reported to have moderate levels of physical activitiy and around 15% of the participants were vegetarian.

5.1.2 Socioeconomic characteristics (tables 5.2 and 5.3)

Based on the Kuppuswamy classification system, the majority of the participants were in the middle socioeconomic classes, with very few from extreme lower and upper-class categories. Men had significantly higher monthly incomes than women, but their households had similar Standard of Living Index (SLI) score and per capita monthly income. Nearly half of women and a quarter of men from this study had no source of income (not even receiving state pension) and were financially dependent on their family.

Per capita monthly income of participants in my study was three to four times higher than the national average for urban older adults (1579 INR) (WHO SAGE India National Report., 2013).

Table 5.2 Socioeconomic characteristics of participants by sex

Socioeconomic indicators	**n**	**Men**		**n**	**Women**		**p**
Standard of Living Index (score) *	408	37.3	(7.4)	313	36.4	(8.0)	0.10
0-20 n(%)		8	(2)		6	(2)	
20-40 n(%)		248	(61)		202	(64)	
40-60 n(%)		152	(37)		105	(34)	
Kuppuswamy score *	407	15.5	(5.7)	313	14.7	(5.8)	0.05
Upper class n(%)		16	(4)		11	(3)	
Upper middle class n(%)		187	(45)		127	(41)	
Lower middle class n(%)		97	(24)		74	(24)	
Upper lower class n(%)		106	(26)		98	(31)	
Lower class n(%)		1	(1)		3	(1)	
Participant income per month(1000 INR) †	408	14	(7-25)	313	6.5	(2-5)	**<0.001**
Per capita income per month (1000 INR) †	407	4.5	(2.5-9.0)	313	4	(1.9-9.9)	0.07
People per room n (%)	408			312			
>4		64	(16)		50	(16)	
3-3.9		52	(13)		36	(11)	0.10
2-2.9		132	(32)		104	(34)	
1-1.9		160	(39)		122	(39)	

* mean (SD) † median (IQR). Difference between the groups was examined using t-test (for *) and Mann Whitney test (for †). Differences with categorical variables were examined using Chi-square test. Higher SLI and Kuppuswamy score indicate less deprivation

Almost all (98%) lived in houses with at least one bedroom. One participant was homeless and another lived in a care home. The median (IQR) number of adults and rooms per household of the study participants were 4 (3-5) and 2 (2-3) respectively.Two or more people per room is considered overcrowding in urban Indian settings (Park.,2015). According to this

criterion, just over 60% of both men and women from this study lived in overcrowded households.

The majority of men were in paid employment, while the majority of women were housewives. Among those employed, the majority of men were in skilled occupations (52%), while the majority of women were in professional jobs (58%) (table 5.3). The proportion of men (25%) and (6%) women employed beyond the age of retirement (60 yrs) was lower than the figures obtained from the WHO SAGE study (58% men and 28% women) (WHO SAGE India National Report.,2013).

Table 5.3 Occupation of participants by sex

Sociodemographics	n	**Men**		n	**Women**	
Current occupation n(%)	408			313		
Not in paid employment						
Unemployment		8	(2)		3	(1)
House wife		5	(1)		207	(66)
Retired		146	(36)		53	(17)
In paid employment						
Full time		228	(56)		45	(14)
Part time		21	(5)		5	(2)
Type of job n(%)	249			50		
Professional		54	(22)		29	(58)
Skilled		130	(52)		13	(10)
Semi-skilled		52	(21)		13	(26)
Unskilled		12	(5)		3	(6)

5.1.3 Current anthropometric characteristics (table 5.4)

Nearly a third of men and half of women in this study were stunted by WHO standards (de Onis et al.,2007). Age was directly associated with stunting [OR=1.06 95%CI (1.02-1.10) per year p=0.001], while socioeconomic status and education were inversely associated with stunting [OR=0.75 95%CI (0.68-0.83) per level education; OR=0.95 95%CI (0.93-0.97) per SLI score p<0.001].

Women had a higher mean BMI than men, and nearly three quarters were overweight or obese, compared with 48% in men. Only a few men (7%) and women (3%) were underweight. Compared to WHO SAGE averages for urban older adults (31% of men and 25% of women for underweight, 16% men and 28% of women for overweight or obese) the proportion of men and women who were underweight was lower, and of those overweight or obese was higher in my study sample (WHO SAGE India National Report.,2013).

Table 5.4 Anthropometric characteristics of participants by sex							
Current anthropometry	**n**	**Men**		**n**	**Women**		**p**
Weight (kgs)*	407	68.5	(6.6)	310	64.3	(13.3)	**<0.001**
Height (cms)*	407	164.1	(14.1)	311	150.3	(6.2)	**<0.001**
Stunting (n%)		127	(31)		149	(48)	**<0.001**
Leg length (cms)*	406	93.7	(4.9)	308	85.1	(4.5)	**<0.001**
Trunk length (cms)*	406	71.1	(3.5)	308	65.3	(3.6)	**<0.001**
BMI (kg/m^2)*	407	25.2	(4.6)	310	28.44	(5.5)	**<0.001**
Underweight n(%)		28	(7)		8	(3)	
Normal n(%)		184	(45)		76	(24)	**<0.001**
Overweight n(%)		136	(33)		120	(39)	
Obese n(%)		59	(15)		106	(34)	
Head circumference (cms)*	407	53.1	(1.1)	311	52.3	(1.4)	**<0.001**
Waist circumference (cms)*	406	96.5	(12.9)	305	88.7	(9.9)	**<0.001**
Central obesity n (%)		285	(70)		248	(79)	**0.005**
Hip circumference (cms)*	406	92.1	(9.4)	308	100.5	(11.6)	**<0.001**
Waist-hip ratio *	406	1.0	(0.1)	305	0.90	(0.1)	**<0.001**
Midarm circumference (cms)*	407	29.3	(3.8)	311	29.9	(4.2)	0.06
Calf circumference (cms)*	407	35.7	(4.9)	311	35.3	(4.4)	0.33
Skinfolds (mm) †							
Biceps	406	10	(7-14)	293	14	(12-17)	**<0.001**
Triceps		14	(10-19)		23	(20-27)	**< 0.001**
Subscapular		30	(22-36)		34	(28-40)	**< 0.001**
Suprailiac		14	(9-18)		13	(12-15)	0.87
Bio impedance	406			311			
Lean mass (kgs)*		48.8	(10.0)		34.1	(6.1)	**<0.001**
Fat mass (kgs)*		19.8	(5.4)		30.3	(8.4)	**< 0.001**
Body fat percentage*		28.9	(4.7)		46.6	(4.7)	**<0.001**
Adiposity n(%)		339	(83)		301	(99)	**<0.001**
Grip strength (kgs) *	402	30.3	(6.3)	301	21.6	(5.0)	**<0.001**

* mean (SD) † median (IQR). Difference between the groups were examined using t-test (for *) and Mann Whitney test (for †). Differences with categorical variables were examined using Chi-square test and Fisher exact test.

There were no significant differences in midarm and calf circumference between the sexes. Around 70% of men and 80% of women were classified as having central obesity; 78% of men and 69% of women had waist-hip ratio considered as high risk (>0.8) by WHO standards (Alberti.,2006). Adiposity (body fat percentage and fat mass) was higher in women than men. A high proportion of both men (84%) and women (99%) were classified as being adipose. Men had greater lean mass and grip strength than women. Mean grip strength for both men and women in my study was nearly 4 kgs greater than those reported in WHO SAGE study for urban older adults (30kgs vs 26kgs for men; 22kgs vs 17kgs for women) (WHO SAGE India National Report.,2013).

5.1.4 Anaemia and micronutrient status (tables 5.5 and 5.6)

Table 5.5 Nutritional status of participants by sex

Nutritional status	n	Men		n	Women		p
Hemoglobin (gms %) *	404	14.3	(1.8)	310	12.2	(1.5)	**<0.001**
Anaemia (Hb< 13g for men and <11 g for women) n (%)		76	(19)		56	(18)	0.80
Vitamin B12 (pmol/l) †	405	222	(153-388)	309	254	(164-459)	**0.007**
Vitamin B12 deficiency (< 150 pmol/) n (%)		96	(24)		65	(21)	0.40
Folate (nmol/l) †	406	12	(8-19)	310	14.5	(10-26)	**<0.001**
Folate deficiency (<7 nmol/l) n (%)		58	(14)		30	(10)	0.06
Homocysteine (micromol**/**l) †	406	19.8	(15-27)	310	14.2	(10-19)	**<0.001**
Hyperhomosysteinaemia (>15 micromol/l) (n%)		299	(74)		141	(46)	**<0.001**

*mean (SD) † median (IQR). Difference between the groups was examined using t-test (for *) and Mann Whitney test (for †). Differences with categorical variables n(%) were examined using Chi-square test.

Table 5.6 Anemia and micronutrient status of participants by age, SLI and education

Predictor	n	Anemia n (%) n=132	B12 deficiency n (%) n=161	Folate deficiency n(%) n=88
Age (yrs)				
55-60	274	33 (12)	62 (23)	34 (12)
60-65	253	50 (20)	51 (20)	26 (10)
65-70	123	28 (23)	34 (28)	22 (18)
70-75	51	13 (25)	10 (20)	4 (8)
75-80	20	8 (40)	4 (20)	2 (10)
B (95%CI)*		-0.50 (-0.81,-0.20)	2.61 (0.93,4.30)	0.09 (-0.26,0.44)
p		**0.005**	**0.03**	0.62
SLI (score)				
0-20	13	2 (15)	2 (15)	3 (23)
20-40	447	82 (18)	118 (26)	70 (16)
40-60	254	48 (19)	41 (16)	15 (6)
B (95%CI)*		0.01 (-0.01,0.03)	4.58 (0.43,8.72)	0.54 (0.34,0.74)
p		0.51	**0.03**	**<0.001**
Education				
Illiterate	22	6 (27)	4 (19)	2 (9)
Primary	93	24 (26)	21 (22)	22 (23)
Secondary	190	35 (18)	47 (24)	30 (16)
College	144	21 (15)	31 (21)	10 (7)
Diploma	94	15 (16)	20 (21)	9 (9)
Graduate	83	12 (14)	21 (25)	7 (8)
Post graduate	88	19 (21)	17 (19)	8 (9)
B (95%CI)*		0.09 (0.04,0.18)	-9.05 (-28.2,10.1)	2.02 (2.10,2.93)
p		**0.04**	0.35	**<0.001**

SLI: Standard of Living Index, * Regression analyses with both exposures and outcomes (Haemoglobin, B12 and Folate) as continuous variables.

Women had a lower mean haemoglobin concentration than men, and nearly 18% of both men and women were anaemic. Though women had significantly higher median levels of B12 and folate, there were no differences in the prevalence of vitamin B12 and folate deficiency between the sexes. Men had higher median levels of homocysteine and prevalence of hyperhomocysteinaemia compared to women (table 5.5).

Age was inversely associated with anaemia, but directly with B12 deficiency (table 5.6). There was a positive association of socioeconomic status with both B12 and folate. Education was directly associated with anaemia and folate deficiency. Hyperhomocysteinaemia was more common in those with B12 and folate deficiency [139 (86%) vs 22(14%) p<0.001 for B12 deficiency; 66 (75%) vs 22 (25%) p=0.006 for folate deficiency].

The prevalence of anaemia in my study is comparable to that reported in India for this age group (mean 17%, range 5%-69%) but higher than that reported in high income countries (10% -12%) (Tilak and Tilak.,2012; Gaskell et al.,2008; Guralnik et al.,2004), There are no data on prevalence of vitamin B12 and folate deficiency in community dwelling older adults in India.

5.1.5 Cardiometabolic outcomes and other physical health measures (tables 5.7 and 5.8)

Nearly 70% of the study participants had hyperglycaemia: 6.8% had impaired fasting glucose, 14.8% had impaired glucose tolerance and 47.3% had type-2 diabetes mellitus. Of those with diabetes, 257 (75%) of them where known to have diabetes and 84 (25%) were newly diagnosed in my study (50 men and 34 women). There was no difference in the prevalence of diabetes between men and women. Fasting glucose and glucose at 120 minutes were positively and significantly associated with socioeconomic status, but not with age or education [B=0.01 95%CI (0.0, 0.01) p=0.002 for fasting glucose and B=0.01 95%CI (0.0,0.01) p=0.009 for glucose at 120 mins]. There are limited data on prevalence of diabetes in older adults in India. Prevalence of diabetes (47%) in my study is higher than those reported from community studies of older adults in urban settings in India (17%-35%), other low and middle-income countries (20%-25%) and high income countries (22%- 33%) (Goswami et al.,2016; Jain and Parnjape.,2013; Tiwari et al.,2012; Salas et al.,2016; Yang et al.,2010; Aguilar-Salinas et al.,20013; Cowie et al.,2006). The higher prevalence of diabetes in this study may be due to classification of glycaemic status based on an oral glucose

tolerance test. Studies reporting prevalence of diabetes in India and other LMIC settings have diagnosed diabetes based on fasting and post prandial blood glucose levels.

Table 5.7 NCD characteristics of participants by sex

NCD characteristics	n	Men		n	Women		p
Glucose							
Fasting glucose (mmol/l) †	403	5.8	(5.3-6.5)	310	5.9	(5.4-6.3)	0.18
Glucose 120 mins (mmol/l) †	256	7.2	(5.7-9.5)	192	7.3	(6.1-9.2)	0.40
Glycaemic status n(%)	408			313			
Unknown		4	(1)		2	(1)	
Normal		125	(31)		93	(29)	
Impaired fasting glucose		24	(6)		25	(8)	0.79
Impaired glucose tolerance		63	(15)		44	(14)	
Diabetes		192	(47)		149	(48)	
Fasting insulin (pmol/l) †	406	63	(38-91)	310	67	(44-96)	**0.007**
Lipids (mmol/l)	406			310			
Total cholesterol*		4.51	(1.1)		4.9	(1.1)	**<0.001**
HDL cholesterol*		1.1	(0.3)		1.2	(0.3)	**<0.001**
LDL cholesterol*		2.7	(0.9)		2.9	(0.8)	**<0.001**
Triglycerides†		1.4	(1.0-1.9)		1.3	(1.1-1.8)	0.65
Hypercholesterolaemia n(%)		94	(23.2)		116	(37)	**<0.001**
Hypertriglyceridaemia n(%)		141	(34.6)		111	(35)	0.80
Low HDL cholesterol n(%)		161	(39.5)		189	(60)	**<0.001**
Blood pressure (mm of Hg)	407			311			
Systolic blood pressure *		136.7	(18)		135.8	(18)	0.49
Diastolic blood pressure *		76.6	(11)		70.8	(12)	**<0.001**
Hypertension n(%)		231	(57)		214	(69)	**0.001**
Metabolic syndrome n(%)	408	243	(60)	313	215	(69)	**0.01**
Coronary heart disease n(%)	408	104	(25)	313	95	(30)	0.15
Stroke n(%)	408	19	(5)	313	2	(1)	**0.001**
Lung function	406			311			
FEV in 1 second (lts) *		1.7	(0.5)		1.15	(0.32)	0.07
FEV in 6 seconds (lts)*		1.8	(0.5)		1.19	(0.34)	**<0.001**
FEV1/FEV6 ratio †		0.98	(0.91-1.0)		0.99	(0.94-1.0)	**0.04**
COPD n(%)		10	(3)		2	(1)	0.05
Hypothyroidism n(%)	406	4	(1)	310	26	(8)	**<0.001**

*mean (SD); † median (IQR); FEV Forced Expiratory Volume; COPD Chronic Obstructive Pulmonary Disease. Difference between the groups were examined using t-tests for * and Mann Whitney test for†. Differences with categorical variables n (%) were examined using Chi-square test and Fisher exact test.

Nearly 60% of the study participants were diagnosed with hypertension, with a higher prevalence among women than men. Of those with hypertension, 334 (75%) were known to have hypertension and 111 (25%) were newly diagnosed (72 men and 39 women). A third of the study participants had both diabetes and hypertension (n=244). Age was positively associated with systolic blood pressure [B=0.43 95%CI (0.14 to 0.73) p<0.004 per year], while SLI was inversely associated with diastolic blood pressure [B=-0.23 95%CI (-0.23, -0.01) p=0.04 per year]. Age, but not SLI or education, was directly associated with hypertension (table 5.8). There are limited data on prevalence of hypertension in older adults in India. Prevalence of hypertension in men (57%) and women (69%) in my study is twofold

higher than that reported in the WHO SAGE India study (30% in men and 35% in women), but similar to that reported for older adults from several LMIC settings (78% in South Africa, 60% in China and Mexico) and high income countries (53-72%) (Guerra et al.,2016; Llyod Sherlock et al.,2014; Sarki et al.,2015; Rigaud and Fourette.,2000; Babitskaou and Zavitsanou., 2010).

Table 5.8 Cardiometabolic outcomes for participants by age, SLI and education

Predictor	**n**	**Hypertension** n (%)	**Diabetes** n (%)	**CHD** n (%)
Age (yrs)				
55-60	274	148 (54)	133 (49)	59 (21)
60-65	253	151 (60)	121 (48)	71 (28)
65-70	123	90 (73)	54 (44)	40 (32)
70-75	51	38 (76)	24 (47)	20 (39)
75-80	20	18 (90)	9 (45)	9 (45)
OR (95%CI)*		1.08 (1.05,1.13)	0.99 (0.96,1.03)	1.07 (1.03,1.11)
p		**<0.001**	0.71	**0.001**
SLI (score)				
0-20	13	8 (57)	4 (31)	4 (31)
20-40	447	278 (62)	196 (44)	124 (28)
40-60	254	159 (62)	141 (55)	71 (28)
OR (95%CI)*		1.01 (0.99,1.03)	1.04 (1.01,1.06)	1.01 (0.98,1.03)
P		0.56	**<0.001**	0.59
Education				
Illiterate	22	14 (63)	12 (57)	7 (32)
Primary	93	67 (70)	42 (45)	26 (27)
Secondary	190	119 (62)	92 (48)	52 (27)
Preuniversity	144	82 (56)	76 (52)	48 (33)
Diploma	94	64 (67)	47 (49)	24 (25)
Graduate	83	49 (59)	34 (41)	24 (19)
Postgraduate	88	50 (57)	38 (43)	18 (21)
OR (95%CI)*		0.93 (0.85,1.02)	0.95 (0.87,1.04)	0.95 (0.86,1.05)
p		0.13	0.31	0.30

CHD: Coronary Heart Disease, SLI: Standard of Living Index. Odds ratio obtained by logistic regression analyses with exposures as continuous variables adjusted for age and gender

Hypercholesterolemia and low HDL cholesterol were more common among women than men. Approximately 35% of men and women had hypertriglyceridaemia, while 60% of women and 40% of men had low HDL cholesterol. The prevalence of metabolic syndrome was high (63.5%), and significantly higher in women than men. There are no data on prevalence of metabolic syndrome in community dwelling older adults in India. Nearly a third of participants were diagnosed with coronary heart disease (CHD) and the prevalence was similar in men and women. Age, but not socioeconomic status or education was directly associated with CHD. There are limited data on the prevalence of CHD in older adult population in India for any meaningful comparison. A systematic review of 14 population based studies from urban setting in India reports a CHD prevalence of 4 to 13% in those

aged 20 to 70 yrs (Gupta et al.,2016). Men had higher levels of Forced Expiratory Volume at 1 second (FEV1) and 6 seconds (FEV6), but lower median FEV1/FEV6 ratio compared to women. Very few had chronic obstructive pulmonary disease (1.5%); it was more common in men than in women. The prevalence of chronic obstructive pulmonary disease in my study is like the 2% reported from a population based study of older adults in the city of Mysore using the same diagnostic criteria (McKay et al.,2012). Diagnosis of COPD was based on PiKO- 6 spirometry readings in my study, while in McKay et al clinical spirometers were used.

The prevalence of clinician diagnosed stroke in this study was low (3%) and more common in men than women, but similar to that reported in the WHO SAGE study (3%) (WHO SAGE India National Report.,2013). Hypothyroidism was diagnosed in 8% of the participants and was more common in women than men. There no prevalence studies of thyroid disorders in this age group in India.

5.1.6 Cognitive and mental health outcomes (tables 5.9 - 5.12)

Table 5.9 Cognitive function of participants by sex, age and education

Predictor	**Global cognition** median (IQR)	**Verbal fluency** mean (SD)	**Immediate recall** mean (SD)	**Delayed recall** mean (SD)
Sex				
Men	28.7 (27.2-30.1)	13.4 (3.1)	15.6 (3.8)	5.1 (1.9)
Women	28.9 (27.1-30.1)	13.5 (4.1)	17.1 (4.1)	5.9 (2.1)
B (95%CI)*	0.02 (-0.13,0.17)	0.06 (-0.53,0.66)	1.52 (0.93,2.10)	0.80 (0.50,1.09)
P	0.81	0.84	**<0.001**	**<0.001**
Age (yrs)				
55-60	28.8 (27.3-30.2)	13.1 (4.2)	17.1 (3.9)	5.7 (2.0)
60-65	28.8 (27.0-30.0)	13.2 (3.9)	15.1 (4.0)	5.3 (1.1)
65-70	28.9 (27.2-30.3)	13.5 (4.1)	15.9 (4.0)	5.1 (2.0)
70-75	28.8 (27.4-29.8)	12.0 (4.0)	15.4 (4.1)	5.0 (1.9)
75-80	28.4 (27.1-29.9)	12.4 (3.3)	14.2 (3.4)	4.6 (1.8)
B (95%CI)*	-0.20 (-0.37,-0.00)	-0.12 (-0.19,-0.06)	-0.17 (-0.24,-0.10)	-0.07 (-0.11,-0.03)
p	**0.02**	**<0.001**	**<0.001**	**<0.001**
Education in years				
Illiterate	25.6 (23.7-26.9)	9.9 (4.0)	13.2 (4.1)	4.0 (2.2)
Primary	26.6 (25.1-28.5)	11.0 (3.9)	14.5 (3.9)	4.8 (1.8)
Secondary	27.9 (26.6-29.1)	12.4 (3.4)	15.2 (3.8)	4.9 (1.9)
Preuniversity	28.9 (27.9-30.0)	13.7 (3.5)	16.5 (3.6)	5.7(1.8)
Diploma	29.6 (28.6-30.36)	14.6 (3.6)	17.0 (3.2)	5.8 (1.9)
Graduate	29.1 (28.8-30.6)	15.3 (3.8)	17.5 (4.)	5.5 (2.1)
Postgraduate	30.4 (29.3-31.2)	15.9 (4.2)	18.4 (4.0)	6.4 (2.1)
B (95%CI)*	0.30 (0.26, 0.35)	0.86 (0.67, 1.05)	0.76 (0.58, 0.94)	0.28 (0.18, 0.37)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**

SLI: Standard of Living Index. * Regression analyses with both exposures and outcomes as continuous variables. Analyses of education with outcomes was adjusted for age and gender.

Compared to men, women scored higher across all four domains of cognitive function tests: global cognitive function, verbal fluency and, immediate and delayed word recall (table 5.9). The difference was significant for immediate and delayed recall components of the Word list Memory and Recall (WLMR test). In general, scores on all cognitive function tests decreased with age and increased with levels of education, socioeconomic status and occupation (tables 5.9 and 5.10).

Women had significantly higher scores on the depression inventory and disability assessment schedule, and a higher prevalence of depression than men. Of the 37 (5%) participants classified as having cognitive impairment, 12 (1.6%) were diagnosed with Mild Cognitive Impairment and 22 (3.1%) with dementia. There were no significant differences in the prevalence of dementia and Mild Cognitive Impairment between the sexes (table 5.11).

Age was directly associated with Mild Cognitive Impairment, but not with dementia. Current socioeconomic position was not associated with dementia and Mild Cognitive Impairment (table 5.12). There was a significant inverse association between education and dementia.

Table 5.10 Cognitive function of participants by socioeconomic position and education

Predictor	**Global cognition** median (IQR)	**Verbal fluency** mean (SD)	**Immediate recall** mean (SD)	**Delayed recall** mean (SD)
SLI (score)				
0-20	25.7 (22.7-27.4)	9.3 (4.1)	11.9 (4.0)	3.8 (1.2)
20-30	27.9 (25.7-29.4)	12.4 (3.9)	15.2 (4.0)	5.1 (1.9)
30-40	28.6 (27.3-30.0)	13.2 (3.8)	16.2 (3.8)	5.4 (1.9)
40-50	29.3 (28.1-30.4)	14.5 (4.1)	17.0 (4.0)	5.6 (2.1)
50-60	29.7 (27.2-31.1)	14.2 (4.2)	17.5 (5.2)	6.3 (1.7)
B(95%CI)*	0.04 (0.03,0.05)	0.09 (0.05,0.13)	0.10 (0.06,0.14)	0.04 (0.02,0.06)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Level of occupation				
Professional	29.9 (28.7-30.7)	15.3 (4.0)	17.4 (3.9)	5.8 (2.2)
Skilled	28.5 (27.2-30.0)	113.1 (3.9)	15.7 (3.9)	5.1 (1.8)
Semi-skilled	28.1 (26.3-29.4)	12.4 (3.7)	14.8 (3.7)	5.0 (1.8)
Unskilled	28.1 (26.4-29.7)	12.7 (3.8)	16.8 (4.1)	5.5 (2.0)
B(95%CI)*	-0.27 (-0.33,-0.21)	-0.84 (-1.08,-0.60)	-0.34 (-0.59,-0.09)	-0.09 (-0.22,0.04)
p	**<0.001**	**<0.001**	**0.007**	0.17

SLI: Standard of Living Index. * Regression analyses with both exposures and outcomes as continuous variables adjusted for age and gender.

Table 5.11 Mental health characteristics of participants by sex

Mental health characteristics	Men n=408		Women n=313		p
EURO-D depression (score)†	0	(0-1)	1	(0-6)	**<0.001**
Depression n(%)	54	(13)	84	(27)	**<0.001**
Mild cognitive impairment n(%)	10	(3)	5	(2)	0.43
Dementia n(%)	12	(3)	10	(3)	0.84
WHO Disability Assessment Schedule II (score)†	0	(0-0)	0	(0-3)	**<0.001**

† median (IQR). Difference between the groups were examined using Mann Whitney U test (for †). Differences with categorical variables n (%) were examined using Chi-square test. Mental health characteristics of the study participants were derived from the 10/66 mental health diagnostic algorithm.

Rates of depression increased significantly with age, but decreased with increasing level of socioeconomic status and education. Among those with depression, 53% were diagnosed with severe depression requiring treatment.

Table 5.12 Mental health outcomes of participants by age, SLI and education

Predictor	n	Depression n (%)	Dementia n (%)	MCI n (%)
Age (yrs)				
55-60	274	46 (17)	4 (1)	0 (0)
60-65	253	47 (18)	11 (4)	2 (1)
65-70	123	24 (19)	3 (2)	9 (7)
70-75	51	13 (25)	3 (6)	3 (6)
75-80	20	8 (4)	1 (5)	1 (5)
OR (95%CI)*		1.06 (1.02,1.10)	1.07 (0.98,1.17)	1.19 (1.08,1.30)
P		0.06	0.11	**<0.001**
Standard of Living Index (score)				
0-20	14	7 (50)	2 (14)	0 (0)
20-40	450	105 (23)	15 (3)	11 (2)
40-60	257	26 (10)	5 (2)	4 (2)
OR (95%CI)*		0.94 (0.91,0.96)	0.96 (0.91,1.01)	0.98 (0.92,1.05)
P		**<0.001**	0.10	0.58
Education				
Illiterate	22	10 (45)	2 (9)	1 (4)
Primary	95	29 (30)	9 (10)	1 (1)
Secondary	192	37 (19)	5 (3)	6 (3)
College	145	33 (22)	2 (2)	4 (3)
Diploma	96	12 (13)	1 (1)	1 (1)
Graduate	83	10 (12)	2 (2)	1 (1)
Postgraduate	88	7 (8)	1 (1)	1 (1)
OR (95%CI)*		0.73 (0.65,0.83)	0.65 (0.45,0.85)	0.84 (0.60,1.17)
P		**<0.001**	**0.003**	0.30

MCI: Mild Cognitive Impairment, SLI: Standard of Living Index. * Odds ratio obtained by logistic regression analyses with exposures as continuous variables, adjusted for age and gender.

Dementia of Alzheimer's type was the most common type of dementia. Of the 22 diagnosed with dementia, 16 (72%) had Alzheimer's disease (including mixed type), 4 (18%) had vascular dementia, 1 (5%) had frontotemporal dementia and 1 (5%) had dementia in Parkinson's disease.

The prevalence of dementia in my study is within the range (0.9% to 4.8 %) reported from population based studies in urban settings in India (The National Dementia Report India.,2010). The prevalence of dementia in Chennai (a city in South India), using similar criteria as in my study, was nearly two times higher (7.5%, n=1033), but nearly half of them were above 80 yrs of age (Prince et al.,2009; The National Dementia Report India.,2010).

The prevalence of depression in my study was slightly lower for men and higher for women than those reported by the WHO SAGE study (13% vs 17% for men and 28% vs 21% for women), but comparable to that reported from a recent meta analysis of depression rates among older adults (>60 years) in India [median (IQR) 21.9% (11.6%–31.1%)] (Barua et al., 2011). These studies also report higher rates of depression in women than men (SAGE India National Report.,2013; Barua et al., 2011). The prevalence of depression was higher compared to high income settings [median (IQR) 10.3% (4.6%-16.0%), n=487,275] but within the range (15% to 48%) reported for LMIC settings by the 10/66 dementia research group (Barua et al.,2011; Prince M et al.,2009**).**

The relationship of contemporaneous and midlife exposures with mental health outcomes are examined in greater detail in chapters 6-8.

5.1.7 Genetic factors

Apolipoprotein is known to play an important role in the metabolism of triglycerides and cholesterol. It acts as a receptor binding ligand and mediates the clearance of very low density lipoprotein and chylomicrons from plasma (Dallongeville et al.,2002). Three different alleles of Apoε (ε4, ε3, and ε2) on chromosome number 19 encode three different Apoε isoforms: Apoε2, Apoε3, and Apoε4 respectively, providing six different genotypes (ε2/2, ε3/3, ε4/4, ε2/3, ε2/4, and ε3/4) (Das et al.,2008; Das et al.,1985; Paik et al.,1985).

In this study, Apoε4 genotyping was carried out for 710 men and women. The proportion of individuals carrying Apoε2, Apoε3 and Apoε4 allele in this study sample was 6 (10%), 610 (86%) and 94 (14%) respectively. Globally, substantial variations have been observed with

Apoε allelic variants with ranges from 0-20% for ε2, 60-90% for ε3 and 10-20% for ε4 alleles (Singh et al.,2006; Corbo and Scacchi.,2009).

Allele frequencies for Apoε2, Apoε3 and Apoε4 allele in this study were 0.005, 0.435 and 0.067 respectively, and comparable to findings from other studies in India. There is a huge variation in the Apoε allele frequencies reported from studies in India, all of which are from north India: 0.003-0.094 for ε2; 0.423-0.968 for ε3 and 0.000-0.133 for ε4 (Ganguli et al., 2000; Thelma et al.,2001; Das et al.,2008; Mastana et al.,1998; Hallman et al.,1991; Gounden et al.,1995; Singh et al.,2001; Singh et al.,2002).

5.1.8 Size at birth (table 5.13)

Table 5.13 Size at birth for participants by sex

Size at birth	n	Men		n	Women		p
Birth weight (kgs)*	406	2.8	(0.4)	312	2.7	(0.4)	**0.003**
<2.5 kgs n(%)		101	(25)		98	(31)	
2.5-3.0 kgs n(%)		170	(42)		147	(47)	
3.0-3.5 kgs n(%)		114	(28)		52	(17)	
>3.5 kgs n(%)		21	(5)		15	(5)	
Head circumference (cms)*	358	33.7	(1.7)	280	33.3	(1.5)	**0.005**
<32 cms n(%)		41	(11)		50	(18)	
32-34 cms n(%)		166	(46)		135	(48)	
34-36 cms n(%)		135	(38)		87	(31)	
>36 cms n(%)		16	(5)		8	(3)	
Length at birth (cms)*	358	48.2	(2.1)	283	47.7	(2.9)	**0.03**
<46 cms n(%)		113	(32)		109	(38)	
46-49 cms n(%)		130	(36)		101	(36)	
49-52 cms n(%)		76	(21)		53	(19)	
>52 cms n(%)		39	(11)		20	(7)	
Ponderal Index (kg/m^3)*	357	25.4	(4.6)	281	25.4	(5.1)	0.88
<20		33	(9)		33	(12)	
20-30		274	(77)		205	(73)	
>30		50	(14)		43	(15)	

* mean (SD). Difference between the groups were examined using t-test.

Just over a quarter of the participants weighed less than 2.5 kgs at birth (low birth weight), only 5% weighed 3.5 kgs and above. Weight, length and head circumference at birth were significantly higher in men compared to women, but ponderal index at birth was similar. There are no birth cohort studies with participants in this age group in India to compare measurements of size at birth.

5.2 Representativeness of the MYNAH cohort (tables 5.14-5.16)

The 3427 men and women who were re-traced and matched to their birth records in 1993-2001 were a small percentage (14%) of all the births at CSI Holdsworth Memorial Hospital during 1934-1966. Compared to those who were not traced, these 3427 individuals were 48 gms heavier (95% CI 28, 68, p<0.001), 0.25 cms longer (95% CI 0.08, 0.42, p=0.005) but had similar head circumference (difference 0.09 cm; 95% CI -0.00, 0.19) at birth. Of those traced, approximately 30% (n=1069) took part in the initial study (1993-1999). Participants had similar birth size measurements compared to non-participants [birth weight -36 g (95% CI -74, 2.0); birth length -0.26 cm (95% CI -0.55, 0.03); head circumference 0.07 cm (95% CI -0.09, 0.23)]. The participants in the current MYNAH study (n=721) were also similar in birth size measurements to those originally traced (table 5.14).

Table 5.14 Comparison of birth size of the MYNAH participants with the 3427 matched records

Size at birth	**n**	**Participated in MYNAH** mean (SD)		**n**	**Not participated in MYNAH** mean (SD)		**p***
Birth weight (kgs)	670	2.8	(0.4)	2757	2.8	(0.4)	0.62
Length at birth (cms)	597	47.1	(3.2)	1897	47.1	(3.2)	0.92
Head circumference (cms)	594	33.6	(1.7)	1866	33.4	(2.2)	0.07

*Difference between the groups was examined by t-tests

For the current MYNAH study, we attempted to retrace all of the 1069 cohort members who had participated previously. We successfully retraced 909 men and women (85%); 21% (189) had died and 79% (720) were alive. Of the traced cohort members who had died, the cause of death was usually unknown. Compared to those who had died (n=189), those alive (n=720) were younger and, had higher educational attainment and socioeconomic position at the time of the initial study (table 5.15). They also had higher body mass index and skinfolds, lower glucose, insulin and total cholesterol concentrations, lower blood pressure and better lung function. Prevalence of hypertension, diabetes and coronary heart disease were lower in those alive than dead. However, the groups were similar in size at birth.

Of these 720, 73% (522) participated in the current study, 5% (33) declined to participate, and the remaining 22% (154) were willing to participate if the study had continued beyond March 2015. These 522 participants were heavier, but similar in length and head circumference at birth when compared with the remaining 547 non-participants (table 5.16). At the time of the earlier study, they were younger and had higher educational attainment

Table 5.15 Birth size, cardiometabolic and other NCD risk factors among those alive and dead when retraced for this study

Characteristics	Alive n=720		Dead n=189		p
Size at birth					
Birth weight (kgs)*	2.7	(0.4)	2.7	(0.4)	0.61
Length (cms)*	47.8	(3.1)	47.8	(3.6)	0.99
Head circumference (cms)*	33.5	(1.7)	33.4	(1.7)	0.26
Sociodemographics (20 yrs ago)					
Age (yrs)*	46.2	(4.8)	49.1	(5.7)	**<0.001**
Education n(%)					
Illiterate	16	(2)	11	(6)	
Primary	113	(16)	48	(25)	
Secondary	162	(22)	45	(24)	
Preuniversity	172	(24)	30	(16)	**<0.001**
College	89	(12)	19	(10)	
Graduate	107	(15)	21	(11)	
Postgraduate	61	(9)	15	(8)	
Smoking (cig/week)†	15	(6-26)	15	(10-32)	0.10
Alcohol (units/week)†	0	(0-9.5)	2	(0-42)	**<0.001**
Other NCD risk factors (20 yrs ago)					
BMI (kg/m^2)*	24.6	(5.0)	23.7	(5.7)	**0.02**
Sum of skinfolds (mms)†	17	(12-23)	14	(9-20)	**<0.001**
Fasting glucose (mmol/l)†	4.9	(4.4-5.4)	4.9	(4.3-5.4)	**0.009**
120 mins glucose (mmol/l)†	6.2	(5.2-7.5)	6.4	(5.3-8.1)	0.09
Diabetes n(%)	94	(13)	50	(26)	**<0.001**
Fasting insulin (pmol/l)†	22	(11-43)	30	(15-74)	**<0.001**
120 mins insulin (pmol/l)†	169	(73-359)	245	(125-500)	**<0.001**
Systolic BP (mm of Hg)*	127.7	(16.1)	135.4	(22.1)	**<0.001**
Diastolic BP (mm of Hg)*	75.3	(10.8)	80.1	(12.9)	**<0.001**
Hypertension n(%)	134	(19)	64	(34)	**<0.001**
Total cholesterol (mmol/l)*	4.9	(1.1)	5.16	(1.1)	**0.01**
Hypercholesterolaemia n(%)	274	(38)	95	(50)	**0.002**
Coronary Heart Disease n(%)	14	(2)	12	(6)	**0.001**
Haemoglobin (gms%)*	12.4	(1.8)	12.1	(1.8)	0.06
Lung function					
Forced Expiratory Volume (ltr)*	2.2	(0.5)	1.9	(0.7)	**0.002**
Peak Expiratory Flow (ltr/min)*	389	(105)	346	(124)	**0.006**
Forced Vital Capacity (ltr)*	2.8	(0.6)	2.5	(0.7)	**0.02**

*mean (SD) † median (IQR).
Difference between the groups were examined using t-test (for *) and Mann Whitney test (for †).
Differences with categorical variables were examined using Chi-square test.
Association of education (as continues exposure) with outcomes was examined by logistic regression analyses.

and socioeconomic status. They also had lower rates of hypertension, diabetes and coronary heart disease and, higher haemoglobin levels and better lung function. However, the groups were similar in body mass index, skin folds, and glucose and total cholesterol concentrations.

Some would have moved out of the study area, and this is likely to have removed better educated 'upwardly mobile' families, which may explain why the studied group was slightly smaller at birth than the non-studied group. Some individuals would have remained in the study area but could not be matched to their birth records due to incomplete information, and some adults would have been unaware that they were born in HMH.

Table 5.16 Size at birth, sociodemographics and NCD risk factors of the 1069 cohort members by participation in this study

Characteristics	Participated in MYNAH n=522		Not participated in MYNAH n=547		p
Size at birth					
Birth weight (kgs)*	2.8	(0.4)	2.7	(0.4)	0.05
Length (cms)*	47.8	(3.1)	47.8	(3.2)	0.94
Head circumference (cms)*	33.5	(1.7)	33.4	(1.7)	0.31
Sociodemographics (20 yrs ago)					
Age (yrs)*	46.1	(4.7)	47.5	(5.5)	**<0.001**
Gender M:F n(%)	299:223	(54:43)	254:293	(46:57)	**<0.001**
Education n(%)					
lliterate	11	(2)	25	(5)	
Primary	81	(15)	121	(22)	
Secondary	113	(22)	135	(25)	
Preuniversity	123	(24)	107	(20)	**<0.001**
College	66	(13)	59	(11)	
Graduate	82	(15)	63	(11)	
Postgraduate	46	(9)	35	(6)	
Kuppuswamy score*	36.0	(5.5)	33.0	(4.5)	**<0.001**
Smoking (cig/week)†	13	(6-25)	20	(10-30)	**0.02**
Alcohol (units/week)†	0	(0-12)	0	(0-15)	0.90
Cardiometabolic risk factors (20 yrs ago)					
BMI (kg/m^2)*	24.3	(4.3)	24.3	(4.5)	0.94
Sum of skinfolds (mms)†	16.3	(11-22)	16	(11-23)	0.95
Fasting glucose (mmol/l)†	4.9	(4.4-5.4)	4.9	(4.3-5.4)	0.22
120 mins glucose (mmol/l)†	6.2	(5.2-7.5)	6.3	(5.2-7.8)	0.25
Diabetes n(%)	64	(12.3)	111	(20)	0.14
Systolic BP (mm of Hg)*	127.0	(15.3)	131.4	(19.7)	**<0.001**
Diastolic BP (mm of Hg)*	75.3	(10.6)	77.4	(12.1)	**0.002**
Hypertension n(%)	94	(18)	140	(25)	**0.003**
Total cholesterol (mmol/l)*	4.9	(1.1)	5.0	(1.1)	0.13
Coronary Heart Disease n(%)	9	(2)	27	(5)	**0.004**
Haemoglobin (gms%)*	12.5	(1.8)	12.2	(0.7)	**0.02**
Lung function					
Forced Expiratory Volume (ltr)*	2.3	(0.6)	2.1	(0.6)	**0.01**
Peak Expiratory Flow (ltr/min)*	393	(106)	366	(118)	**0.04**
Forced Vital Capacity (ltr)*	2.8	(0.1)	2.6	(0.7)	**0.04**

* mean (SD) † median (IQR). Difference between the groups were examined using t-test (for *) and Mann Whitney test (for †). Differences with categorical variables were examined using Chi-square test. Association of education (as continues outcome) with outcomes was examined by logistic regression analyses.

It is difficult to say how these various factors have influenced the representativeness of the traced cohort sample. Losses to follow-up due to the reasons mentioned above, could attenuate associations between newborn size and adult health outcomes among survivors but are unlikely to create spurious associations. In a within-cohort analysis, such bias would be introduced only if the associations between fetal growth and adult outcomes differed between those born in and outside the hospital.

6. Results: Relationship between current and midlife sociodemographics, cardiometabolic and other NCD risk factors and cognitive outcomes in late life

Approximately 20 yrs ago, a subset of the MYNAH participants (299 men and 223 women) had participated in a study examining the relationship between size at birth and cardiometabolic outcomes when they were aged between 40 and 67 yrs [mean 46.7 yrs SD (4.7)]. From now on, I will use the term 'midlife' for measurements obtained from the previous study and 'late life' for measurements from this study.

In this chapter, I examined the relationship between sociodemographics, cardiometabolic and other NCD risk factors (exposures in mid- and late life) with cognitive outcomes of interest in my study: cognitive function and cognitive impairment. I examined the associations of these exposures with scores from individual cognitive function tests (continuous outcomes) and cognitive impairment (categorical outcomes) by conducting simple linear regression analyses and logistic regression analyses respectively. The analyses were adjusted for age and gender. The objectives of conducting these analyses were to:

a. examine for similarities and differences in the associations between exposures in late life and midlife with cognitive outcomes, and if these associations change over the lifecourse. For example, the association between blood pressure and late life cognition is complex, non-linear and age dependent (Qiu et al.,2004; Qiu et al.,2005). Raised blood pressure in midlife is associated with lower cognitive function 10 to 20 yrs later. However, by the time cognitive impairment is manifest, blood pressure levels are relatively low, although this has not been a universal finding (Qiu et al.,2005). The complex relationship of cardiometabolic disorders across the lifecourse with cognitive ageing in the MYNAH cohort was examined.

b. identify exposures in late life and midlife that were potentially confounding or mediating the relationship between birth size and cognitive outcomes in late life.

Of the 721 examined in this study, 12 (1.6%) had Mild Cognitive Impairment (MCI) and 22 (3%) had dementia. There was insufficient power in the study sample to examine the associations of mid- and late life exposures with MCI and dementia, and the findings related to these outcomes should be interpreted with caution. Findings related to dementia are provided in this chapter and those for MCI are provided as an appendix (Appendix 13)

6.1 Sociodemographics and cognitive function (tables 6.1- 6.3)

Table 6.1 Associations of sociodemographics in late life with cognitive outcomes in late life

Predictor (late life)	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) □ (95%CI)* p	**Immediate recall** (score) □ (95%CI) * p	**Delayed recall** (score) □ (95%CI) * p	**Dementia** (no/yes) OR (95%CI) † p
Age (yrs)	-0.02 (-0.04,-0.01) **0.009**	-0.12 (-0.19,-0.06) **<0.001**	-0.17 (-0.24,-0.10) **<0.001**	-0.07 (-0.01, -0.03) **<0.001**	1.07 (0.98,1.17) 0.11
Sex (0=M, 1=F)	0.02 (-0.13,0.17) 0.81	0.06 (-0.53,0.66) 0.84	1.52 (0.93,2.10) **<0.001**	0.80 (0.50,1.09) **<0.001**	1.09 (0.46,2.55) 0.84
Marital status (0=married, 1=others)	-0.50 (-0.71, -0.29) **<0.001**	-1.20 (-2.07, -0.32) **0.007**	-1.24 (-2.08, -0.40) **0.004**	-0.46 (-0.87, -0.04) **0.03**	4.32 (1.37,13.60) **0.01**
Education**	0.30 (0.26,0.35) **<0.001**	0.86 (0.67,1.05) **<0.001**	0.76 (0.58,0.94) **<0.001**	0.28 (0.18,0.37) **<0.001**	0.63 (0.43,0.92) **0.02**
Employment (0=paid, 1=unpaid)	-0.12 (-0.33,0.09) 0.26	-1.02 (-1.86, -0.18) **0.02**	0.34 (-0.48,1.14) 0.42	0.13 (-0.27,0.54) 0.52	1.08 (0.30,3.85) 0.91
Type of occupation***	0.31 (0.23,0.39) **<0.001**	1.03 (0.72,1.35) **<0.001**	0.66 (0.35,0.97) **<0.001**	0.22 (0.07,0.38) **0.005**	0.53 (0.28,1.00) 0.05
Income (INR/month)	0.04 (0.03,0.05) **<0.001**	0.09 (0.05,0.13) **<0.001**	0.10 (0.06,0.14) **<0.001**	0.04 (0.02,0.06) **<0.001**	0.95 (0.89,1.01) 0.08
Percapita income (1000 INR/month)	0.10 (0.05,0.15) **<0.001**	0.04 (0.02,0.06) **<0.001**	0.05 (0.03,0.07) **<0.001**	0.02 (0.01,0.03) **<0.001**	0.80 (0.65,0.99) 0.05
People per room	0.53 (0.34,0.71) **<0.001**	1.72 (0.98,2.46) **<0.001**	1.44 (0.72,2.16) **<0.001**	0.74 (0.38,3.44) **<0.001**	0.17 (0.03,0.98) **0.04**
Kuppuswamy score	0.07 (0.05,0.08) **<0.001**	0.18 (0.12,0.24) **<0.001**	0.07 (0.04,0.10) **<0.001**	0.18 (0.13,0.24) **<0.001**	0.87 (0.77,0.97) **0.02**
Standard of Living Index (score)	0.04 (0.03,0.05) **<0.001**	0.09 (0.05,0.13) **<0.001**	0.10 (0.06,0.14) **<0.001**	0.04 (0.02,0.06) **<0.001**	0.95 (0.89,1.01) 0.08

***** Simple linear regression analyses and † logistic regression analyses adjusted for age and gender.
**Education: 0=illiterate, 1=primary, 2=secondary, 3=preuniversity, 4=diploma, 5=graduate, 6=postgraduate.
***Type of occupation: 0=unskilled, 1=semiskilled, 2=skilled, 3=professional.

Age was inversely associated with scores across all cognitive function tests, but was unrelated to dementia. Women had higher immediate and delayed recall scores than men,

but there were no differences in rates of dementia between the sexes. Participants who were married at the time of the study scored significantly higher on all cognitive function tests and were less likely to have dementia than others (widowed, single or divorced).

Table 6.2 Associations of sociodemographics in late life with verbal fluency and dementia

Predictor	**n**	**Verbal fluency** (score) mean (SD)	**p***	**Dementia** n (%)	**p†**
Age (yrs)					
55-60	274	14.0 (4.2)		4 (1)	
60-65	253	13.2 (3.9)		11 (4)	
65-70	123	13.5 (4.1)	**<0.001**	3 (2)	0.11
70-75	51	12.0 (4.0)		3 (6)	
75-80	20	12.4 (3.3)		1 (5)	
Marital status					
Married	559	13.7 (4.0)		12 (2)	
Single/widowed/divorced	162	12.7 (4.2)	**0.007**	10 (6)	**0.01**
Education					
Illiterate	22	9.91 (4.0)		2 (9)	
Primary	95	11.0 (3.9)		9 (9)	
Secondary	192	12.4 (3.4)		5 (3)	
Preuniversity	145	13.7 (3.5)	**<0.001**	2 (1)	**0.02**
Diploma	96	14.6 (3.6)		1 (1)	
Graduate	83	15.3 (3.8)		2 (2)	
Postgraduate	88	16.0 (4.2)		1 (1)	
Occupation level					
Unskilled	215	12.7 (3.8)		10 (5)	
Semiskilled	120	12.4 (3.7)	**<0.001**	7 (6)	0.05
Skilled	213	13.2 (3.9)		2 (1)	
Professional	172	15.5 (4.0)		3 (2)	
Standard of Living Index (score)					
0-20	14	9.3 (4.1)		2 (14)	
20-30	133	12.4 (3.9)	**<0.001**	5 (4)	0.08
30-40	317	13.2 (3.8)		10 (3)	
40-50	241	14.5 (4.1)		5 (2)	
50-60	16	14.2 (4.2)		0 (0)	
Current family size					
<3	269	14.4 (4.1)		8 (3)	
3-6	354	13.0 (3.9)	0.64	11 (3)	0.10
6-9	66	12.2 (3.8)		2 (3)	
>9	32	12.5 (3.8)		1 (3)	

p derived from ***** simple linear and † logistic regression analyses adjusted for age and gender.

Educational attainment and occupational level in late life were directly associated with scores across all cognitive function tests, and inversely with dementia. Those in paid

employment had higher verbal fluency scores than those who were not in paid employment, but there were no differences in rates of dementia between them.

Monthly income of the participants and percapita monthly household income were directly associated with scores across all cognitive function tests. There were inverse associations of borderline significance between monthly income and percapita income with dementia in late life. Number of people per room in the household was directly associated with scores across all cognitive function tests and inversely with dementia. Men and women of lower socioeconomic position in late life (indicated by Kuppuswamy score and Standard of Living Index score) had lower scores across all cognitive function tests and higher rates of dementia in late life, though the inverse associations of SLI scores with dementia was of was of borderline significance.

Table 6.3 Associations of sociodemographics in midlife with cognitive outcomes in late life

Predictor	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** yes/no OR (95%CI)† p
Marital status	0.29	-0.62	-1.18	-0.55	1.43
(0=married	(0.60,0.02)	(-1.85,0.62)	(-2.36,0.01)	(-1.14,0.04)	(0.29,6.96)
1=others)	0.07	0.33	0.05	0.07	0.66
Education**	0.30	0.92	0.84	0.31	0.60
	(0.25,0.35)	(0.72,1.12)	(0.65,1.03)	(0.21,0.41)	(0.41,0.88)
	<0.001	**<0.001**	**<0.001**	**<0.001**	**0.01**
Percapita income	0.00	-0.01	0.87	0.02	1.00
	(-0.02,0.02)	(-0.09,0.06)	(0.41,1.33)	(-0.02,0.05)	(1.00,1.00)
(1000 INR/mth)	0.84	0.69	0.12	0.37	0.25
People per room***	-0.21	-0.85	-0.78	-0.32	1.76
	(-0.29,-0.13)	(-1.18,-0.52)	(-1.10,-0.46)	(-0.48,-0.16)	(1.09,2.81)
	<0.001	**<0.001**	**<0.001**	**<0.001**	**0.02**
Area of residence****	0.66	2.12	2.34	1.02	0.17
	(0.40,0.92)	(1.08,3.16)	(1.35,3.34)	(0.52,1.52)	(0.06,0.45)
	<0.001	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Kuppuswamy score	0.05	0.17	0.15	0.06	0.91
	(0.04,0.06)	(0.13,0.21)	(0.11,0.19)	(0.04,0.08)	(0.85,0.97)
	<0.001	**<0.001**	**<0.001**	**<0.001**	**0.005**

*****Simple linear and †logistic regression analyses adjusted for age and gender
**Education: 0=illiterate, 1=primary, 2=secondary, 3=preuniversity, 4=diploma, 5=graduate, 6=postgraduate.
*** People per room: 0=1-1.9, 1=2-2.9, 2=3-3.9, 3=4 or more.
****Area of residence: 0=slum, 1=low class, 2=middle class, 3=high class.

Those who were widowed, when examined in midlife had higher global cognition scores and lower scores on immediate and delayed recall tests in late life. However, these associations were of borderline significance (table 6.3). Participants of higher socioeconomic position in midlife (indicated by Kuppuswamy score, area of residence and number of adults per room) had higher scores across all cognitive function tests and lower rates of dementia in late life. Percapita income of the participants in midlife was unrelated to cognitive outcomes in late life. Information related to occupation and income of the participants in midlife was unavailable.

6.2 Anthropometry, body composition and cognition (tables 6.4-6.7)

Height in late life was directly associated with scores across all cognitive function tests and inversely with dementia. Of the height components, leg length was directly associated with cognitive function scores across all domains, while trunk height was inversely associated with dementia. Those with larger head circumference had significantly higher scores on global cognition and verbal fluency tests, but head circumference was unrelated to dementia. The inverse associations of stunting and leg length in late life with dementia were of borderline significance.

Those with higher BMI in late life had higher verbal fluency and immediate recall scores. The association of BMI with verbal fluency was of borderline significance. Waist circumference was positively associated with scores on global cognitive function, verbal fluency and immediate recall tests, while central obesity was directly associated with scores on verbal fluency and immediate recall tests. Those with greater skinfolds in late life had higher global cognition and immediate recall scores. Those with higher BMI, larger waist circumference, central obesity and greater skinfolds in late life had lower rates of dementia.

Those with higher body fat percentage in late life had lower scores on global cognition and verbal fluency tests in late life. Fat mass in late life was directly associated with scores on verbal fluency and recall tests, and inversely with dementia in late life.

Adiposity was not related to scores on cognitive function tests. However, adiposity in late life was directly associated with dementia in late life, though this was of borderline significance.

Table 6.4 Associations of anthropometric measurements in late life with cognitive outcomes in late life

Predictor (late life)	**Global cognition** (SD) β(95%CI)* p	**Verbal fluency** (score) β(95%CI)* p	**Immediate recall** (score) β(95%CI)* p	**Delayed recall** (score) β(95%CI)* p	**Dementia** no/yes OR(95%CI)† p
Skeletal measurements					
Height (cms)	0.03 (0.02,0.05) **<0.001**	0.10 (0.05,0.15) **<0.001**	0.11 (0.06,0.16) **<0.001**	0.04 (0.01,0.06) **0.006**	0.90 (0.83,0.98) **0.01**
Stunting (0=no 1=yes)	-0.27 (-0.45,-0.10) **0.002**	-1.13 (-1.83,-0.43) **0.002**	-1.09 (-1.76,-0.42) **0.002**	-0.38 (-0.72,-0.04) **0.03**	2.94 (0.96,8.95) 0.06
Trunk height (cms)	0.03 (0.01,0.06) **0.006**	0.09 (-0.01,0.18) 0.08	0.08 (-0.01,0.17) 0.09	0.03 (-0.01,0.08) 0.14	0.87 (0.76,0.99) **0.03**
Leg length (cms)	0.04 (0.02,0.06) **<0.001**	0.14 (0.06,0.21) **<0.001**	0.14 (0.08,0.21) **<0.001**	0.04 (0.01,0.08) **0.02**	0.90 (0.81,1.00) 0.07
Head circumference (cms)	0.11 (0.05,0.16) **<0.001**	0.30 (0.04,0.48) **0.02**	0.11 (-0.10,0.32) 0.31	-0.04 (-0.14,0.07) 0.50	0.81 (0.58,1.14) 0.23
Weight (kgs)	0.01 (0.00,0.01) **0.001**	0.04 (0.01,0.06) **0.001**	0.04 (0.02,0.07) **<0.001**	0.01 (0.00,0.03) **0.03**	0.91 (0.87,0.96) **<0.001**
Body composition					
BMI (kgs/m^2)	0.01 (-0.00,0.03) 0.21	0.06 (-0.00,0.13) 0.06	0.07 (0.00,0.14) **0.04**	0.02 (-0.01,0.06) 0.16	0.81 (0.71,0.92) **0.001**
Waist circumference (cms)	0.01 (0.00,0.02) **0.009**	0.04 (0.01,0.07) **0.01**	0.03 (0.01,0.06) **0.02**	0.01 (-0.01,0.02) 0.29	0.91 (0.87,0.96) **<0.001**
Sum of skinfolds (mms)	0.01 (0.00,0.01) **0.04**	0.01 (-0.00,0.03) 0.17	0.02 (0.01,0.04) **0.005**	0.01 (-0.00,0.02) 0.09	0.96 (0.93,0.99) **0.01**
Body fat percentage	-0.03 (-0.05,-0.02) **<0.001**	-0.10 (-0.17,-0.03) **0.006**	-0.04 (-0.11,0.03) 0.23	-0.03 (-0.07,0.00) 0.07	1.03 (0.92,1.14) 0.60
Lean mass (kgs)	0.02 (0.01,0.03) **<0.001**	0.09 (0.05,0.13) **<0.001**	0.08 (0.05,0.12) **<0.001**	0.03 (0.01,0.04) **0.01**	0.90 (0.84,0.95) **<0.001**
Fat mass (kgs)	0.05 (-0.01,0.01) 0.08	0.07 (0.02,0.12) **0.007**	0.07 (0.02,0.12) **0.01**	0.02 (-0.01,0.04) **0.02**	0.81 (0.70,0.93) **0.003**
Central obesity (0=no,1=yes)	0.14 (-0.06,0.33) 0.16	1.08 (0.30,1.85) **0.007**	1.23 (0.49,1.97) **0.001**	0.34 (-0.04,0.71) 0.08	0.34 (0.14,0.80) **0.01**
Adiposity (0=no,1=yes)	-0.16 (-0.42,0.10) 0.24	0.66 (-0.38,1.71) 0.21	0.63 (-0.37,1.63) 0.21	-0.30 (-0.80,20) 0.24	1.07 (1.00,1.16) 0.06

***** Simple linear and † logistic regression analyses adjusted for age and gender.

Table 6.5 Associations of anthropometry in late life with verbal fluency and dementia in late life

Predictor (late life)	**n**	**Verbal fluency** (score) mean (SD)	**p***	**Dementia** n (%)	**p†**
Leg length (cms)					
< 80	31	11.5 (4.7)		1 (3)	
80-85	143	13.3 (4.2)		6 (4)	
85-90	169	13.5 (3.8)	**<0.001**	5 (3)	0.07
90-95	209	13.1 (3.8)		6 (3)	
95-100	125	14.7 (4.2)		2 (2)	
>100	37	14.0 (3.4)		1 (3)	
Head circumference (cms)					
< 50	15	12.5 (4.2)		0 (0)	
50-52	165	13.0 (4.2)		5 (3)	
52-54	299	13.5 (4.0)	**0.02**	12 (4)	0.23
54-56	202	13.7 (3.9)		4 (2)	
>56	37	14.7 (3.9)		0 (0)	
Midarm circumference (cms)					
<22	17	9.8 (4.9)		4 (23)	
22-27	174	12.8 (4.0)		6 (3)	
27-32	349	13.8 (3.9)	**0.01**	11 (3)	**<0.001**
32-37	151	13.7 (3.9)		0 (0)	
>37	27	14.9 (4.4)		0 (0)	
Skinfolds (mms)					
<25	24	11.8 (4.0)		1 (4)	
25-40	75	12.3 (4.0)		4 (5)	
40-55	139	13.6 (3.9)		7 (5)	
55-70	199	13.8 (3.8)	0.17	4 (2)	**0.01**
70-85	186	13.6 (4.3)		4 (2)	
85-100	59	13.6 (3.5)		1 (2)	
>100	32	13.9 (4.2)		0 (0)	
Fat mass (kgs)					
< 15	56	12.3 (3.1)		3 (5)	
15-25	387	13.3 (4.1)		15 (4)	
25-35	208	13.9 (4.0)		3 (1)	
35-45	47	14.3 (3.9)	**0.007**	1 (2)	**0.003**
45-55	20	12.8 (3.5)		0 (0)	
> 55	3	21.0 (2.6)		0 (0)	
BMI (kgs/m^2)					
<18.5	36	11.2 (4.6)		4 (11)	
18.5-20	26	12.0 (3.9)	0.06	1 (4)	**0.001**
20- 23	108	13.3 (3.9)		4 (4)	
23-25	126	13.6 (4.0)		5 (4)	
25-30	256	13.7 (4.0)		5 (2)	
>30	165	13.9 (3.9)		2 (1)	

p derived from ***** simple linear and † logistic regression analyses adjusted for age and gender.

Measures of muscle mass (mid arm circumference, calf circumference and lean mass) and strength (hand grip strength) in late life were directly associated with scores on cognitive function tests. Measures of muscle mass, but not grip strength were inversely associated with dementia (table 6.6). None of the current anthropometric measurements were associated with Mild Cognitive Impairment (Appendix 13).

Table 6.6 Associations of muscle mass and strength in late life with cognitive outcomes in late life

Predictor (late life)	**Global cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Midarm circumference (cms)	0.02 (0.00,0.04) **0.03**	0.11 (0.02,0.20) **0.01**	0.12 (0.04,0.20) **0.004**	0.05 (0.01,0.09) **0.01**	0.75 (0.65,0.88) **<0.001**
Calf circumference (cms)	0.02 (0.00,0.04) **0.02**	0.09 (0.02,0.16) **0.008**	0.08 (0.02,0.15) **0.01**	0.03 (0.01,0.06) 0.11	0.76 (0.66,0.88) **<0.001**
Grip strength (kgs)	0.03 (0.01,0.05) **<0.001**	0.14 (0.08,0.21) **<0.001**	0.13 (0.07,0.19) **<0.001**	0.06 (0.03,0.09) **<0.001**	0.94 (0.84,1.04) 0.20

***** Simple linear and † logistic regression analyses adjusted for age and gender.

In general, the associations of BMI and other indicators of body composition in mid- and late life with cognitive outcomes in late life were in the same direction. BMI in midlife was directly associated with verbal fluency and immediate recall scores, and inversely with dementia in late life. However, the overweight/obese and normal / underweight groups in midlife were similar in cognitive function in late life (table 6.7)**.**

Participants with greater waist and hip circumferences in midlife had higher global cognition, verbal fluency and immediate recall scores, and lower rates of dementia in late life. Those with central obesity midlife had higher scores across all the cognitive function tests, though the associations of central obesity with global cognition and delayed recall were of border line significance. Central obesity in midlife was unrelated to dementia in late life.

Those with greater skinfolds in midlife had higher scores across all cognitive function tests and lower rates of dementia in late life. But the associations of skinfolds in midlife with global cognition and verbal fluency scores, and with dementia were of borderline significance.

None of the anthropometric measurements in late life and midlife were related to Mild Cognitive Impairment in late life (Appendix 13).

Table 6.7 Associations of anthropometry in midlife with cognitive outcomes in late life

Predictor (midlife)	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR(95%CI)† p
Height	0.03	0.10	0.11	0.03	0.91
(cms)	(0.02,0.05)	(0.05,0.16)	(0.06,0.16)	(0.01,0.06)	(0.84,0.99)
	<0.001	**<0.001**	**<0.001**	**0.007**	**0.03**
BMI	0.01	0.08	0.10	0.03	0.87
(kg/m^2)	(-0.01,0.03)	(0.01,0.16)	(0.02,0.18)	(-0.00,0.07)	(0.77,0.99)
	0.17	**0.04**	**0.01**	0.08	**0.04**
Obesity/ overweight	0.06	0.23	0.55	0.23	0.43
	(-0.12,0.23)	(-0.47,0.93)	(-0.12,1.22)	(-0.10,0.56)	(0.13,1.39)
(0=no, 1=yes)	0.53	0.52	0.11	0.18	0.12
Waist circumference	0.01	0.04	0.04	0.01	0.95
	(0.00,0.02)	(0.01,0.07)	(0.02,0.07)	(0.00,0.03)	(0.91,0.99)
(cms)	**0.02**	**0.003**	**0.002**	0.09	**0.04**
Hip circumference	0.01	0.06	0.07	0.02	0.92
	(0.00,0.02)	(0.02,0.10)	(0.04,0.11)	(0.00,0.04)	(0.87,0.98)
(cms)	**0.008**	**0.001**	**<0.001**	**0.02**	**0.007**
Central obesity	0.17	0.75	0.91	0.32	0.54
(0=no, 1=yes)	(-0.01,0.34)	(0.05,1.45)	(0.24,1.58)	(-0.02,0.65)	(0.19,1.53)
	0.06	**0.04**	**0.008**	0.06	0.25
Sum of skin folds	0.00	0.00	0.01	0.01	0.99
	(0.00,0.00)	(0.00,0.01)	(0.00,0.01)	(0.00,0.01)	(0.98,1.00)
(mms)	0.05	0.05	**0.001**	**0.008**	0.08

***** Simple linear and † logistic regression analyses adjusted for age and gender

6.3 Nutrition and cognition (tables 6.8 and 6.9)

Vitamin B12 concentrations and deficiency in late life were not related to cognitive outcomes in late life. Folate levels were directly associated with global cognition scores, while folate deficiency was inversely associated with scores on global cognition, verbal fluency and delayed recall tests. Participants with folate deficiency had higher rates of dementia in late life.

Those with higher homocysteine levels in late life had lower global cognition and delayed recall scores, homocysteine was unrelated to dementia. Hyperhomocysteinaemia in late life was unrelated to cognitive outcomes in late life.

Haemoglobin levels in late life were directly related to scores across all cognitive function tests, but the associations of haemoglobin in late life with global cognition and delayed recall were of borderline significance. Anaemia in late life was not associated with cognitive outcomes.

Table 6.8 Associations of nutritional status with cognitive outcomes in late life

Predictor**	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
B12 (pmol/l)	0.00	0.00	0.00	0.00	1.00
	(0.00,0.00)	(-0.00,0.00)	(-0.00,0.00)	(0.00,0.00)	(1.00,1.00)
	0.41	0.35	0.57	0.80	0.15
B12 deficiency	0.03	-0.11	0.10	0.22	0.23
	(-0.17,0.23)	(-0.93,0.71)	(-0.68,0.88)	(-0.17,0.61)	(0.03,1.75)
(0=no, 1=yes)	0.78	0.79	0.80	0.27	0.16
Folate	0.05	0.01	0.00	0.01	0.93
(nmol/l)	(0.00,0.01)	(-0.01,0.02)	(-0.00,0.00)	(-0.00,0.01)	(0.85,1.01)
	0.01	0.42	0.29	0.16	0.07
Folate deficiency	-0.41	-1.68	-0.63	-0.48	4.27
	(-0.66,-0.16)	(-2.66,-0.69)	(-1.58,0.33)	(-0.96,-0.01)	(1.48,12.32)
(0=no, 1=yes)	**<0.001**	**<0.001**	0.11	**0.04**	**0.007**
Homocysteine	-0.01	-0.00	-0.01	-0.01	1.02
(micromol/l)	(-0.01,-0.00)	(-0.03,0.02)	(-0.03,0.01)	(-0.02,-0.00)	(0.10,1.04)
	<0.001	0.69	0.36	**0.02**	0.18
Hyperhomocysteinaemia	-0.08	-0.07	-0.29	-0.14	0.85
	(-0.26,0.10)	(-0.81,0.66)	(-0.99,0.42)	(-0.49,0.21)	(0.29,2.48)
(0=no, 1=yes)	0.39	0.85	0.42	0.44	0.77
Hemoglobin	0.57	0.25	0.20	0.09	0.80
(gms%)	(0.01,0.10)	(0.05,0.44)	(0.02,0.40)	(-0.00,0.18)	(0.62,1.05)
	0.06	**0.01**	**0.03**	0.06	0.10
Anemia	-0.16	-0.75	-0.67	-0.30	1.60
(0= no, 1=yes)	(0.38,0.05)	(-1.60,0.10)	(-1.49,0.14)	(-0.71,0.11)	(0.53,4.80)
	0.13	0.08	0.10	0.15	0.40
	0.07	0.40	0.11	0.03	0.70
Hb (gms%)	(0.01,0.13)	(0.15,0.64)	(-0.13,0.35)	(-0.09,0.15)	(0.50,0.99)
(midlife)	**0.02**	**0.002**	0.36	0.66	**0.04**
	-0.18	-1.07	-0.08	0.02	2.70
Anaemia	(-0.35,0.00)	(-1.78,-0.36)	(-0.77,0.61)	(-0.33,0.36)	(0.95,7.66)
(midlife)	0.53	**0.003**	0.81	0.93	0.06

* Simple linear and † logistic regression analyses adjusted for age and gender
**Exposures are from late life unless stated

Those with higher haemoglobin levels in midlife had higher scores on global cognition and verbal fluency tests, and lower rates of dementia in late life. Those with anaemia in midlife had lower verbal fluency scores, and there was a direct association of borderline significance between anaemia in midlife and dementia in late life.

Table 6.9 Associations of vitamin B12, folate and haemoglobin with verbal fluency and dementia

Predictor	**n**	**Verbal fluency** (score) mean (SD)	**p***	**Dementia** n (%)	**p**†
Vitamin B12 (pmol/l) (late life)					
<200	280	13.6 (3.9)		7 (2)	
200-400	246	13.6 (4.1)	0.35	4 (2)	0.15
400-600	94	13.2 (4.3)		3 (3)	
>600	94	13.1 (4.2)		8 (8)	
Folate (mmo/l) (late life)					
<10	227	13.0 (4.0)		8 (3)	
10-20	286	13.6 (4.1)	0.42	10 (3)	0.07
20-30	68	14.0 (4.7)		3 (4)	
>30	135	13.6 (3.8)		1 (1)	
Haemoglobin (gm%) (late life)					
<10	42	13.4 (4.3)		3 (7)	
10-15	536	13.3 (3.9)	**0.01**	17 (3)	0.10
>10	136	14.1 (4.3)		2 (1)	
Anemia (midlife)					
No	331	13.9 (4.0)	**0.003**	6 (2)	0.06
Yes	190	12.7 (3.8)		10 (5)	

p derived from ***** simple linear and † logistic regression analyses adjusted for age and gender.

6.4 Cardiometabolic disorders and cognition

6.4.1 Glucose and insulin (tables 6.10 and 6.11)

Neither fasting nor 120 minutes' blood glucose levels in late life were associated with cognitive outcomes. To explore the relationship between glycaemic status (exposure) and cognitive outcomes, glycaemic status was examined as continuous (normal through impaired fasting glucose and glucose intolerance to diabetes) and binary variables [normal vs hyperglycaemia (impaired fasting glucose, impaired glucose tolerance and diabetes); diabetes vs others]. Glycaemic status, hyperglycaemia, diabetes and duration of diabetes in late life were unrelated to cognitive outcomes.

Though fasting insulin levels in late life were unrelated to scores on cognitive function tests, there was an inverse borderline significant association of fasting insulin levels in late life with dementia. Those with insulin resistance in late life had lower rates of dementia.

Table 6.10 Associations of blood glucose and insulin in late life with cognitive outcomes in late life

Predictor (late life)	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Fasting glucose (mmol/l)	0.00 (-0.02,0.03) 0.80	-0.05 (-0.16,0.06) 0.38	0.06 (-0.05,0.17) 0.28	0.01 (-0.04,0.06) 0.66	0.71 (0.48,1.07) 0.10
120 mins glucose (mmol/l)	-0.01 (-0.03,0.02) 0.62	-0.00 (-0.11,0.10) 0.96	0.03 (-0.08,0.13) 0.61	0.01 (-0.04,0.06) 0.69	0.94 (0.79,1.13) 0.51
Glycemic status**	0.02 (-0.05,0.81) 0.58	-0.01 (-0.27,0.24) 0.91	0.01 (-0.23,0.25) 0.92	0.04 (-0.08,0.16) 0.56	0.75 (0.52,1.09) 0.13
Hyperglycaemia***	0.06 (-0.1 3,0.23) 0.55	-0.0 (-0.74,0.73) 0.99	0.15 (-0.55,0.85) 0.66	0.15 (-0.20,0.50) 0.39	0.44 (0.16,1.21) 0.11
Diabetes (0=no, 1=yes)	0.01 (-0.16,0.18) 0.92	-0.16 (-0.84,0.52) 0.65	-0.23 (-0.88,0.42) 0.49	-0.06 (-0.38,0.27) 0.74	0.51 (0.17,1.50) 0.22
Duration of diabetes (yrs)	-0.01 (-0.03,0.01) 0.44	0.03 (-0.06,0.11) 0.52	0.00 (-0.07,0.08) 0.95	-0.01 (-0.05,0.03) 0.66	0.95 (0.77,1.18) 0.67
Fasting insulin (pmol/l)	0.00 (-0.00,0.01) 0.22	0.01 (-0.01,0.03) 0.23	0.01 (-0.01,0.03) 0.33	0.00 (-0.00,0.01) 0.34	0.87 (0.79,0.96) 0.06
Insulin Resistance	0.01 (-0.01,0.03) 025	-0.04 (-0.10,0.05) 0.38	0.07 (-0.01,0.16) 0.08	0.02 (-0.02,0.06) 0.29	0.68 (0.48,0.96) **0.03**

***** Simple linear regression analyses and † logistic regression analyses adjusted for age and gender.
**Glycaemic status 1= normal, 2= impaired fasting glucose, 3=impaired glucose tolerance, 4=diabetes.
***Hyperglycaemia: 0=Normal, 1=Impaired fasting glucose, Impaired glucose tolerance and diabetes.

Similar to the associations observed in late life, glucose levels, glycaemic status and hyperglycaemia in midlife were unrelated to cognitive outcomes in late life. There was a direct association of borderline significance between hyperglycaemia in midlife and global cognition scores in late life. Though diabetes in late life was unrelated to cognitive outcomes, those with diabetes in midlife had lower verbal fluency scores in late life. There were inverse associations of borderline significance between diabetes in midlife with scores on immediate and delayed recall tests in late life. Diabetes in midlife was unrelated to dementia.

Fasting insulin levels and insulin resistance in midlife were unrelated to cognitive outcomes in late life.

Table 6.11 Associations of blood glucose and insulin in midlife with cognitive outcomes in late life

Predictor (midlife)	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Fasting glucose (mmol/l)	0.00 (-0.04,0.04) 0.93	-0.11 (-0.28,0.07) 0.23	-0.11 (-0.28,0.06) 0.19	-0.05 (-0.14,0.03) 0.21	0.75 (0.45,1.24) 0.27
30 mins glucose (mmol/l)	0.01 (-0.02,0.04) 0.67	0.01 (-0.11,0.13) 0.89	0.05 (-0.06,0.16) 0.38	0.01 (-0.05,0.06) 0.82	0.84 (0.70,1.02) 0.16
120 mins glucose (mmol/l)	0.01 (-0.01,0.04) 0.36	0.00 (-0.09,0.10) 0.94	0.04 (-0.05,0.13) 0.42	0.00 (-0.04,0.05) 0.94	0.85 (0.69,1.05) 0.13
Glycaemic status**	0.05 (-0.02,0.13) 0.18	-0.10 (-0.40,0.20) 0.52	-0.13 (-0.42,0.15) 0.36	-0.02 (-0.16,0.12) 0.80	- 0.89 (0.56,1.43) 0.63
Hyperglycemia***	0.17 (-0.01,0.36) 0.07	0.03 (-0.71,0.78) 0.93	-0.15 (0.87,0.56) 0.67	0.10 (-0.25,0.46) 0.56	0.76 (0.24,2.40) 0.64
Diabetes (0=no, 1=yes)	-0.05 (-0.31,0.21) 0.72	-1.33 (-2.36,-0.30) **0.01**	-0.86 (-1.84,0.13) 0.09	-0.42 (-0.91,0.07) 0.09	0.44 (0.06,3.41) 0.43
Fasting insulin (pmol/l)	3.488*10^-6 (0.00,0.00) 0.62	1.284*10^-5 (0.00,0.00) 0.64	-1683*10^-5 (0.00,0.00) 0.53	-9.341*10^-6 (0.00,0.00) 0.49	1.00 (099,1.00) 0.52
30 mins insulin (pmol/l)	1268*10^-5 (0.00,0.00) 0.60	7.916*10^-5 (0.00,0.00) 0.40	0.00 (0.00,0.00) 0.15	9.737*10^-6 (0.00,0.00) 0.83	1.00 (1.00,1.00) 0.72
Insulin Resistance	0.0 (0.0,0.0) 0.51	0.0 (-0.0,0.0) 0.68	0.00 (-0.0,0.0) 0.60	0.00 (-0.0,0.0) 0.52	1.23 (0.42,3.58) 0.70

***** Simple linear and † logistic regression analyses adjusted for age and gender.
**Glycaemic status: 0=Normal, 1=Impaired fasting glucose, 2=Impaired tolerance, 3=Diabetes.
***Hyperglycemia: 0=Normal, 1=Impaired fasting glucose, Impaired glucose tolerance and diabetes

6.4.2 Blood pressure (table 6.12)

Systolic blood pressure in late life was not associated with cognitive outcomes, while diastolic blood pressure was inversely associated with global cognition score. Though systolic and diastolic blood pressure in late life was unrelated to dementia, those with hypertension in late life had lower rates of dementia in late life. Those with longer duration of hypertension had higher immediate recall scores in late life, and there was an inverse association of borderline significance between the duration of hypertension and dementia.

Orthostatic change (difference between the average standing and average supine BP) in systolic blood pressure in late life was directly associated with scores on global cognition, verbal fluency and immediate recall tests, while orthostatic change in diastolic blood pressure in late life was directly associated with verbal fluency and immediate recall scores. However, orthostatic change in systolic and diastolic blood pressure was not related to dementia. Orthostatic hypotension in late life was not associated with cognitive outcomes.

Table 6.12 Associations of blood pressure with cognitive outcomes in late life

Predictor**	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Systolic BP	-0.00	0.00	-0.00	-0.00	1.00
(mm of Hg)	(-0.01,0.001)	(-0.02,0.02)	(-0.02,0.01)	(-0.01,0.01)	(0.97,1.03)
	0.15	0.84	0.57	0.61	0.90
Diastolic BP	-0.01	-0.01	-0.02	-0.01	1.03
(mm of Hg)	(-0.02,-0.00)	(-0.04,0.02)	(-0.05,0.01)	(-0.02,0.01)	(0.98,1.07)
	0.008	0.44	0.16	0.30	0.22
Hypertension	-0.00	0.43	0.19	0.25	0.23
(0=no, 1=yes)	(-0.18,0.18)	(-0.29,1.14)	(-0.50,0.88)	(-0.09,0.59)	(0.07,0.70)
	0.99	0.24	0.58	0.15	**0.01**
Duration of	0.36	0.03	0.59	0.20	0.27
hypertension	(-0.09,0.16)	(-0.50,0.56)	(0.10,1.08)	(-0.05,0.46)	(0.07,1.08)
(yrs)	0.57	0.90	**0.02**	0.11	0.06
Orthostatic					
change in	0.01	0.03	0.03	0.01	0.99
systolic BP	(0.00,0.01)	(0.01,0.06)	(0.00,0.05)	(0.00,0.02)	(0.95,1.02)
(mm of Hg)	**0.008**	**0.005**	**0.02**	0.06	0.38
Orthostatic					
change in	0.01	0.44	0.03	0.01	0.99
diastolic BP	(-0.00,0.02)	(0.01,0.08)	(0.00,0.07)	(-0.00,0.03)	(0.94,1.04)
(mm of Hg)	0.15	**0.01**	**0.04**	0.20	0.73
Orthostatic	0.17	1.13	0.07	0.55	1.05
hypotension	(-0.19,0.54)	(-0.33,2.60)	(-1.34,1.50)	(-0.15,1.25)	(0.13,8.52)
(0=no, 1=yes)	0.36	0.13	0.92	0.13	0.96
Systolic BP	0.00	0.01	0.01	0.00	0.97
(midlife)	(-0.00,0.01)	(-0.01,0.04)	(-0.01,0.04)	(-0.01,0.01)	(0.93,1.01)
(mm of Hg)	0.55	0.27	0.19	0.70	0.15
Diastolic BP	0.00	0.01	0.01	0.01	0.95
(midlife)	(-0.00,0.01)	(-0.02,0.05)	(-0.02,0.04)	(-0.01,0.02)	(0.90,1.01)
(mm of Hg)	0.24	0.40	0.66	0.45	0.09
Hypertension	0.06	0.11	0.14	0.10	0.86
(midlife)	(-0.17,0.28)	(-0.79,1.00)	(-0.72,1.00)	(-0.33,0.53)	(0.23,3.17)
(mm of Hg)	0.61	0.81	0.75	0.65	0.82

***** Simple linear and † logistic regression analyses adjusted for age and gender.
**Exposures are from late life unless stated.

Systolic blood pressure, diastolic blood pressure and hypertension in midlife were unrelated to cognitive outcomes in later life.

6.4.3 Lipids (tables 6.13 and 6.14)

Total cholesterol levels in late life were unrelated to cognitive outcomes in late life, while hypercholesterolemia was inversely associated with scores on delayed recall test (table 6.13).

HDL cholesterol levels in late life were directly, and low HDL cholesterol in late life was inversely associated with verbal fluency scores in late life. Levels of triglycerides and LDL cholesterol in late life were unrelated to cognitive outcomes.

Table 6.13 Associations of lipids in late life with cognitive outcomes in late life

Predictor (late life)	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR(95%CI)† p
Total cholesterol (mmol/l)	-0.04 (-0.12,0.04) 0.37	0.21 (-0.11,0.54) 0.11	-0.01 (-0.32,0.21) 0.94	-0.11 (-0.26,0.05) 0.18	0.90 (0.55,1.45) 0.65
Hypercholesterolaemia (0=no, 1=yes)	-0.10 (-0.28,0.10) 0.34	-0.00 (-0.75,0.74) 0.99	-0.25 (-0.96,0.47) 0.50	-0.40 (-0.75,-0.04) **0.03**	1.44 (0.51,4.07) 0.49
HDL cholesterol (mmol/l)	0.16 (-0.16,0.48) 0.32	1.60 (0.33,2.87) **0.01**	0.52 (-0.70,1.74) 0.41	0.01 (-0.60,0.62) 0.98	0.82 (0.12,5.53) 0.84
Low HDL cholesterol (0=no, 1=yes)	-0.15 (-0.33,0.02) 0.08	-0.99 (-1.68,-0.30) **0.005**	-0.43 (-1.09,0.24) 0.21	-0.03 (-0.36,0.31) 0.87	1.56 (0.55,2.40) 0.40
LDL cholesterol (mmol/l)	-0.09 (-0.19,0.02) 0.09	0.15 (-0.26,0.56) 0.47	-0.16 (-0.55,0.24) 0.43	-0.14 (-0.33,0.06) 0.17	1.04 (0.58,1.88) 0.90
Raised LDL cholesterol (0=no, 1=yes)	-0.08 (-0.28,0.12) 0.41	0.30 (-0.50,1.11) 0.46	-0.02 (-0.80,0.75) 0.95	-0.20 (-0.58,0.18) 0.30	1.08 (0.34,3.44) 0.90
Triglycerides (mmol/l)	-0.04 (-0.09,0.01) 0.94	0.13 (-0.05,0.31) 0.73	0.17 (-0.19,0.53) 0.35	-0.05 (-0.23,0.13) 0.61	0.52 (0.21,1.25) 0.14
Hypertriglyceridaemia (0=no, 1=yes)	-0.03 (-0.20,0.15) 0.76	-0.20 (-0.90,0.50) 0.57	0.03 (-0.64,0.71) 0.92	0.11 (-0.23,0.44) 0.52	0.60 (0.19,1.90) 0.39

OR: Odds ratio ***** Simple linear regression analyses
† Logistic regression analyses.
All analyses adjusted for age and gender.

Cholesterol (total, HDL and LDL) and triglycerides levels in late life were not related to dementia in late life.

Those with higher total cholesterol and LDL cholesterol levels in midlife had higher global cognition and verbal fluency scores, and lower rates of dementia in late life (table 6.14).

Table 6.14 Associations of lipids in midlife with cognitive outcomes in late life

Predictor (midlife)	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Total cholesterol (mmol/l)	0.10 (0.03,0.18) **0.01**	0.50 (0.19,0.81) **0.002**	0.13 (-0.16,0.43) 0.38	0.06 (-0.09,0.21) 0.42	0.59 (0.36,0.99) **0.04**
Hypercholesterolaemia (0=no, 1=yes)	0.09 (-0.08,0.26) 0.31	0.32 (-0.38,1.02) 0.37	0.24 (-0.43,0.92) 0.47	0.06 (-0.27,0.40) 0.72	0.87 (0.31,2.48) 0.80
LDL cholesterol (mmol/l)	0.12 (0.04,0.20) **0.004**	0.54 (0.22,0.86) **0.001**	0.14 (-0.16,0.45) 0.36	0.07 (-0.08,0.22) 0.38	0.57 (0.33,0.96) **0.04**
Raised LDL cholesterol (0=no, 1=yes)	0.16 (-0.01,0.33) 0.07	0.59 (-0.10,1.28) 0.09	0.24 (-0.42,0.91) 0.48	-0.04 (-0.37,0.29) 0.81	0.55 (0.20,1.52) 0.25
HDL cholesterol (mmol/l)	-0.05 (-0.39,0.29) 0.78	0.41 (-0.94,1.77) 0.55	0.15 (-1.15,1.45) 0.82	0.01 (-0.63,0.66) 0.96	1.22 (0.16,9.37) 0.85
Low HDL cholesterol (0=no, 1=yes)	-0.04 (-0.24,0.16) 0.72	-0.35 (-1.15,0.45) 0.39	0.10 (-0.67,0.87) 0.80	0.00 (-0.38,0.39) 0.99	0.66 (0.20,2.19) 0.50
Triglycerides (mmol/l)	-0.02 (-0.11,0.08) 0.74	-0.27 (-0.66,0.12) 0.18	-0.07 (-0.45,0.30) 0.71	-0.04 (-0.22,0.15) 0.69	0.97 (0.52,1.80) 0.91
Hypertriglyceridaemia (0=no, 1=yes)	-0.05 (-0.22,0.12) 0.55	-0.53 (-1.22,0.16) 0.13	-0.03 (-0.69,0.63) 0.93	0.15 (-0.18,0.48) 0.38	0.69 (0.24,1.98) 0.49

* Simple linear regression analyses
† Logistic regression analyses adjusted
All analyses adjusted for age and gender

Levels of HDL cholesterol and triglycerides in midlife were unrelated to cognitive outcomes in late life.

There were direct associations of borderline significance between raised LDL cholesterol in midlife and scores on global cognition and verbal fluency in late life. Hypercholesterolaemia, low HDL cholesterol and hypertriglyceridaemia in midlife were unrelated to cognitive outcomes in late life.

6.4.4 Metabolic syndrome (table 6.15)

Though metabolic syndrome in late life was unrelated to performance on cognitive function tests, those with metabolic syndrome in late life had lower rates of dementia in late life. There was a direct association of borderline significance between metabolic syndrome in midlife and delayed recall scores in late life. Metabolic syndrome in midlife was unrelated to dementia.

Table 6.15 Associations of metabolic syndrome with cognitive outcomes in late life

Predictor	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Metabolic** **syndrome** (late life)	0.03 (-0.15,0.20) 0.76	0.43 (-0.27,1.14) 0.22	0.72 (0.05,1.14) 0.22	0.22 (-0.12,0.56) 0.11	0.32 (0.11,0.90) **0.03**
Metabolic** **syndrome** (midlife)	0.01 (-0.17,0.20) 0.87	-0.55 (-1.31,0.20) 0.15	0.26 (-0.47,0.98) 0.49	0.31 (-0.05,0.67) 0.09	0.49 (0.13,1.79) 0.28

***** Simple linear and †logistic regression analyses adjusted for age and gender.
** Metabolic syndrome: 0=no, 1=yes)

6.4.5 Coronary heart disease (table 6.16)

Coronary heart disease in mid- and late life was unrelated to cognitive outcomes in late life. However, there was an inverse association of borderline significance between coronary heart disease in midlife and scores on immediate recall tests in late life.

Table 6.16 Associations of coronary heart disease with cognitive outcomes in late life

Predictor	**Global Cognition** (SD) B (95%CI)* p	**Verbal fluency** (score) B (95%CI)* p	**Immediate recall** (score) B (95%CI)* p	**Delayed recall** (score) B (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
CHD (late life) (0=no 1=yes)	-0.04 (-0.23,0.15) 0.69	-0.62 (-1.38,0.14) 0.11	0.18 (-0.55,0.91) 0.63	-0.01 (-0.37,0.36) 0.96	1.06 (0.36,3.15) 0.92
CHD (midlife) (0=no 1=yes)	-0.37 (-1.02,0.28) 0.26	-0.11 (-2.72,2.51) 0.26	-2.41 (-4.91,0.09) 0.06	-0.52 (-1.77,0.73) 0.41	0.85 (0.32,2.24) 0.74

CHD: Coronary Heart Disease
***** Simple linear and † logistic regression analyses adjusted for age and gender.

6.4.6 Stroke (table 6.17)

Those who were diagnosed as having stroke in this study had lower scores on global cognition and verbal fluency tests. There were inverse associations of borderline significance between stroke and scores on immediate and delayed recall test in late life. Stroke in late life was unrelated to dementia. The cohort members were not examined for stroke in midlife.

Table 6.17 Associations of stroke with cognitive outcomes in late life

Predictor	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Stroke (0=no, 1=yes)	-0.81 (-1.25,-0.36) **<0.001**	-2.70 (-4.49,-0.91) **0.003**	-1.72 (-3.44,0.08) 0.05	-0.78 (-1.64,0.08) 0.08	3.21 (0.60,17.3) 0.17

***** Simple linear and † logistic regression analyses adjusted for age and gender.

6. 5 Lifestyle factors and cognition

6.5.1 Alcohol and smoking (tables 6.19 and 6.20)

In this study sample very few women smoked tobacco or drank alcohol. Therefore, the analyses examining the associations of smoking and alcohol with cognitive outcomes were restricted to men only. There were no differences in cognitive outcomes between those using alcohol at the time of the study (current drinkers) and others (previously drinking and lifelong abstainers). However, among those drinking at the time of the study, the amount of weekly consumption of alcohol was inversely associated with performance on global cognition test. Those drinking in moderation (1-5 units per week) had significantly higher verbal fluency when compared those drinking more than 5 units per week [mean score 14.45 (3.75) vs 13.34 (4.06) p=0.02 for the difference]. When compared to ex-smokers and non-smokers, those smoking at the time of the study had significantly lower scores on immediate recall test. Current amount of smoking was inversely associated with immediate recall scores while smoking pack years was inversely associated with global cognition.

Amount of alcohol consumption (units/week) in midlife was unrelated to cognitive outcomes in late life, while amount of smoking (cigarettes/week) in midlife was inversely associated immediate recall scores in late life. Amount of alcohol intake and smoking in midlife were unrelated to dementia in late life.

Exposures related to smoking and alcohol in mid- and late life were unrelated to dementia.

Table 6.18 Associations of smoking and alcohol with cognitive outcomes in late life

Predictor	Global Cognition (SD) β (95%CI)* p	Verbal fluency (score) β (95%CI)* p	Immediate recall (score) β (95%CI)* p	Delayed recall (score) β (95%CI)* p	Dementia no/yes OR (95%CI)† p
Current alcohol intake (units per week)	-0.00 (-0.01,0.01) **0.001**	0.01 (-0.04,0.06) 0.70	0.01 (-0.04,0.06) 0.81	0.01 (-0.01,0.04) 0.38	0.91 (0.70,1.20) 0.47
Current alcohol drinking (0=others, 1=current)	-0.10 (-0.34,0.13) 0.40	-0.73 (-1.68,0.21) 0.13	-0.54 (-1.44,0.37) 0.24	-0.32 (-0.77,0.13) 0.16	1.36 (0.28,6.56) 0.70
Current smoking (No of cigarettes/day)	-0.01 (-0.01,0.00) 0.08	-0.03 (-0.05,0.00) 0.08	-0.04 (-0.07,-0.01) **0.007**	-0.01 (-0.02,0.01) 0.38	0.99 (0.93,1.05) 0.71
Current smoking (0=others, 1=current)	-0.18 (-0.42,0.05) 0.13	-0.82 (-1.78,0.13) 0.09	-1.12 (-2.03,-0.21) **0.02**	-0.11 (-0.56,0.35) 0.65	1.22 (0.29,5.14) 0.78
Smoking pack years	-0.01 (-0.01,-0.00) **0.01**	-0.02 (-0.03,0.00) 0.09	-0.02 (-0.03,0.00) 0.09	0.00 (-0.00,0.01) 0.82	0.99 (0.95,1.03) 0.53
Alcohol intake in mid life (units/week)	-0.00 (-0.01,0.00) 0.45	0.011 (-0.03,0.04) 0.64	-0.00 (-0.03,0.03) 0.64	0.01 (-0.01,0.02) 0.48	0.99 (0.92,1.06) 0.74
Smoking in midlife (No of cigarettes/day)	-0.00 (-0.01,0.06) 0.64	-0.01 (-0.05,0.02) 0.54	-0.04 (-0.07,-0.00) **0.03**	-0.01 (-0.03,0.01) 0.21	0.98 (0.92,1.06) 0.73

***** simple linear and † logistic regression analyses adjusted for age.

Table 6.19 Associations of smoking and alcohol in with verbal fluency and dementia

Predictor	n	Verbal fluency (score) mean(SD)	p*	Dementia n (%)	p†
Smoking (pack/yrs)					
0	451	13.6 (4.2)		14 (3)	
1-10	128	13.7 (3.7)	0.09	2 (2)	0.53
10-20	33	12.9 (4.3)		0 (0)	
>20	104	12.9 (3.8)		4 (4)	
Alcohol (units/week) (late life)					
0	587	13.3 (4.1)		19 (3)	
1-5	82	14.4 (3.7)	0.70	3 (4)	0.47
5-10	14	13.4 (3.2)		0 (0)	
>10	38	13.6 (4.1)		0 (0)	

p derived from ***** simple linear & † logistic regression analyses adjusted for age.

6.5.2 **Physical activity** (tables 6.20- 6.23)

Higher levels of physical activity in late life were associated with higher scores on tests for global cognition and immediate recall, though the latter association was of borderline significance. Similarly, the frequency of physical exercise in the month preceding the examination was directly associated with global cognition, verbal fluency and immediate recall scores.

Table 6.20 Associations of physical activity in late life and midlife with cognitive outcomes in late life

Predictor	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Physical activity	0.22	0.53	0.73	0.09	0.54
(late life)**	(0.04,0.41)	(-0.23,1.28)	(0.01,1.46)	(-0.27,0.45)	(0.20,1.46)
	0.02	0.17	0.05	0.64	0.22
Exercises	0.00	0.20	0.01	-0.10	0.99
(late life)	(0.00,0.01)	(0.10,0.30)	(0.00,0.02)	(-0.34,0.13)	(0.97,1.01)
(times/month)	**0.001**	**<0.001**	**0.03**	0.40	0.46
Physical activity	0.03	0.20	0.08	0.05	1.40
(midlife) **	(-0.06,0.13)	(-0.16,0.57)	(-0.27,0.43)	(-0.12,0.22)	(0.85,2.32)
	0.45	0.27	0.66	0.58	0.19
Walking	-0.16	-0.65	-0.34	-0.14	1.94
(midlife)***	(-0.35,0.02)	(-1.45,0.14)	(-1.07,0.40)	(-0.50,0.22)	(0.88,4.30)
	0.09	0.11	0.37	0.45	0.99
Cycling	-1.13	-0.08	0.06	0.03	1.50
(midlife)***	(-0.34,0.07)	(-0.91,0.75)	(-0.68,0.81)	(-0.36,0.42)	(0.67,3.33)
	0.19	0.84	0.87	0.88	0.32
Sports	0.09	0.39	0.23	0.11	1.07
(midlife)	(0.02,0.15)	(0.14,0.65)	(0.01,0.46)	(-0.01,0.23)	(0.84,1.36)
(hrs/week)	**0.007**	**0.003**	**0.04**	0.08	0.58
Labour work	-0.02	-0.03	-0.03	0.00	1.05
(midlife)	(-0.03,-0.00)	(-0.07,0.01)	(-0.07,0.01)	(-0.02,0.03)	(1.01,1.09)
(hrs/week)	**0.004**	0.24	0.20	0.65	**0.03**

***** Simple linear and † logistic regression analyses adjusted for age and gender.
**Physical activity: 0= sedentary, 1=mild, 2=moderate, 3=strenuous
***kms/day : 0= <1km, 1=1-4km, 2=4-8km, 3= >8km

Levels of physical activity, amount of walking and cycling in midlife were unrelated to cognitive outcomes. The amount of time spent on sports (hrs/week) in midlife was directly associated with scores on global cognition, verbal fluency and immediate recall tests in late life. The amount of manual labour work (hours/week) in midlife was inversely associated with global cognition scores in late life, and directly with dementia in late life.

Table 6.21 Associations of physical activity with verbal fluency and dementia

Predictor	n	Verbal fluency (score) mean (SD)	p*	Dementia n (%)	p†
Level of physical activity (late life)					
Sedentary	3	9.3 (3.8)		3(1)	
Mild	30	12.0 (5.0)		2 (7)	
Moderate	586	13.4 (3.9)	0.17	16 (3)	0.22
Strenuous	103	14.0 (4.2)		3 (3)	
Exercises (times/mth) (late life)					
0-15	235	12.6 (3.9)		7 (3)	
15-30	342	13.7 (4.1)	**<0.001**	12 (3)	0.40
>30	143	14.1 (3.9)		3 (2)	
Level of physical activity (midlife)					
Sedentary	246	13.6 (4.0)		5 (2)	
Mild	151	13.5 (3.7)	0.27	5 (5)	0.19
Moderate	76	12.0 (3.9)		3 (4)	
Strenuous	49	14.9 (4.0)		3 (6)	

p derived from ***** simple linear and † logistic regression analyses adjusted for age and gender.

6.5.3 Dietary factors (tables 6.22 and 6.23)

Non-vegetarians had significantly lower scores on global cognition and verbal fluency tests in late life, when compared to vegetarians. However, within the non-vegetarian group, frequency of meat and fish intake in late life was inversely associated with global cognition and verbal fluency scores. Number of servings of fresh fruits and vegetables (in the week preceding the assessment) was directly associated with both immediate and delayed word list recall scores. There were direct associations of borderline significance between the number of serving of fresh fruits and vegetables with global cognition and verbal fluency. In this study, there were no associations between type of diet, frequency of meat and fish consumption, and amount of consumption of fruits and vegetables in late life with dementia.

Frequency of meat consumption in midlife was inversely associated with verbal fluency and immediate recall scores, while frequency of fish consumption in midlife was unrelated to cognitive outcomes in late life. Frequency of consumption of fresh fruits and vegetables in midlife was directly associated with global cognition, verbal fluency and immediate recall

Table 6.22 Associations of dietary factors with cognitive outcomes in late life

Predictor	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
Type of diet	-0.30	-1.50	-0.14	0.14	0.70
(0=veg, 1=nonveg)	(-0.54,-0.06)	(-2.41,-0.52)	(-1.06,0.78)	(-0.31,0.60)	(0.19,2.53)
	0.01	**0.003**	0.76	0.53	0.58
Meat consumption***	-0.10	-0.78	-0.03	0.14	1.12
(late life)	(-0.19,-0.01)	(-1.15,-0.42)	(-0.39,0.33)	(-0.03,0.32)	(0.64,1.95)
	0.03	**<0.001**	0.87	0.11	0.69
Fish consumption***	-0.18	-1.35	-0.24	0.03	1.08
(late life)	(-0.29,-0.07)	(-1.80,-0.92)	(-0.67,0.11)	(-0.19,0.24)	(0.56,2.08)
	0.001	**<0.001**	0.29	0.80	0.82
Fruit and veg**** **consumption**	0.02	0.06	0.06	0.05	0.95
(late life)	(0.00,0.04)	(-0.01,0.13)	(-0.01,0.12)	(0.02,0.08)	(0.86,1.04)
	0.05	0.06	**0.002**	**0.002**	0.28
Meat consumption	-0.01	-0.16	-0.02	0.03	1.02
(times/week)	(-0.04,-0.02)	(-0.26,-0.06)	(-0.11,0.08)	(-0.02,0.08)	(0.88,1.17)
	0.31	**0.002**	**0.02**	0.20	0.82
Fish consumption	-0.07	-0.36	-0.27	-0.11	0.54
(times/week)	(-0.17,0.02)	(-0.76,0.04)	(-0.65,0.10)	(-0.29,0.08)	(0.16,1.75)
	0.13	0.08	0.16	0.27	0.30
Fresh veg consumption	0.01	0.09	0.06	0.02	0.99
(times/week)	(0.00,0.03)	(0.03,0.14)	(0.00,0.11)	(-0.00,0.05)	(0.91,1.08)
	0.04	**0.002**	**0.04**	0.08	0.90
Dairy product consumption	0.01	0.03	0.03	0.04	0.99
(times/week)	(-0.00,0.02)	(-0.02,0.08)	(-0.02,0.08)	(0.02,0.06)	(0.93,1.07)
	0.07	0.25	0.21	**0.001**	0.94

Exposures from midlife unless stated

* Simple linear and † logistic regression analyses adjusted for age and gender

**Physical activity: 0= sedentary 1= not very active 2= fairly active 3= very active.

***Consumption frequency: 0= never 1= some days 2=most days 3= every day

**** Fruit and vegetable consumption was total number of servings over a three day period prior to the day of assessment.

scores, while frequency of consumption of dairy products was directly associated with scores on delayed recall test. Frequency of fish consumption in midlife was unrelated to scores on cognitive function tests. There were direct associations of borderline significance between frequency of consumption of dairy products in midlife and global cognition in late life, and between frequency of consumption of fresh vegetables in midlife and delayed recall test scores in late life.

None of the dietary exposures in midlife were related to dementia in late life.

Table 6.23 Associations of dietary factors in late life with verbal fluency and dementia					
Predictor	**n**	**Verbal fluency** (score) mean (SD)	**p***	**Dementia** n (%)	**p†**
Frequency of eating meat					
Never	102	14.6 (3.9)		5 (5)	
Some days	274	13.9 (4.0)	**<0.001**	6 (2)	0.69
Most days	262	12.8 (4.0)		6 (3)	
Every day	93	12.6 (4.0)		3 (3)	
Frequency of eating fish					
Never	149	14.8 (3.8)		6 (4)	
Some days	406	13.5 (4.0)	**<0.001**	11 (3)	0.82
Most days	130	12.3 (3.8)		4 (3)	
Every day	36	11.2 (4.7)		1 (3)	
Fruit and veg consumption (servings in last 3 days)					
<10	157	13.5 (4.2)		5 (3)	
10-15	159	12.8 (4.4)	0.06	10 (6)	0.28
>15	405	13.7 (3.8)		7 (2)	

p derived from ***** simple linear and † logistic regression analyses adjusted for age and gender.

6.6 Other NCD factors and cognition

6.6.1 Thyroid function (table 6.24)

T4 levels in late life were inversely associated with verbal fluency while, T3, TSH (Thyroid Stimulating Hormone) and hypothyroidism were unrelated to cognitive outcomes.

Table 6.24 Associations of thyroid function with cognitive outcomes in late life					
Predictor	**Global Cognition** (SD) β (95%CI)* P	**Verbal fluency** (score) β (95%CI)* P	**Immediate recall** (score) β (95%CI)* P	**Delayed recall** (score) β (95%CI)* p	**Dementia** no/yes OR (95%CI)† p
T3 (nmol/l)	-0.02 (-0.13,0.01) 0.77	-0.12 (-0.59,0.34) 0.60	-0.15 (-0.60,0.29) 0.51	-0.01 (-0.23,0.22) 0.95	0.50 (0.21,1.18) 0.56
T4 (nmol/l)	-0.00 (-0.01,0.01) 0.12	-0.02 (-0.03,-0.01) **0.01**	0.00 (-0.01,0.01) 0.97	-0.00 (-0.01,0.00) 0.36	1.00 (0.98,1.02) 0.78
TSH (milliIU/l)	-0.00 (-0.01,0.00) 0.43	-0.01 (-0.04,0.03) 0.71	-0.01 (-0.05,0.02) 0.40	0.00 (-0.01,0.02) 0.80	0.76 (0.54,1.06) 0.10
Hypothyroidism (0=no, 1=yes)	-0.10 (-2.91,0.92) 0.31	-0.98 (-8.76,6.81) 0.80	-5.24 (-12.61,2.14) 0.16	-1.22 (-4.92,2.48) 0.52	0.00 (0.00,0.00) 1.00

* Simple linear and † logistic regression analyses adjusted for age and gender. Analyses excluded those on thyroxine supplement. TSH: Thyroid stimulating hormone.

6.6.2 Depression (tables 6.25 and 6.26)

Those with higher scores of depression and depression had lower scores across all cognitive function tests. Neither of these were associated with dementia.

Table 6.25 Associations of depression with cognitive outcomes in late life

Predictor	Global Cognition (SD) β (95%CI)* p	Verbal fluency (score) β (95%CI)* p	Immediate recall (score) β (95%CI)* p	Delayed recall (score) β (95%CI)* p	Dementia no/yes OR (95%CI)† p
Depression (EURO-D Score)	-0.05 (-0.08,-0.03) **<0.001**	-0.18 (-0.28,-0.08) **0.001**	-0.14 (-0.24,-0.04) **0.005**	-0.06 (-0.11,-0.00) **0.02**	0.47 (0.09,2.40) 0.37
Depression (0=no, 1=yes)	-0.44 (-0.66,-0.23) **<0.001**	-1.52 (-2.38,-0.67) **0.001**	-1.20 (-2.02,-0.38) **0.004**	-0.52 (-0.93,-0.11) **0.01**	2.31 (0.79,6.81) 0.13

***** Simple linear and † logistic regression analyses adjusted for age and gender
EURO-D: EURO Depression Inventory

Table 6.26 Associations of depression with verbal fluency and dementia in late life

Predictor	n	Verbal fluency (score) mean (SD)	p*	Dementia n (%)	p†
EURO-Depression (score)					
0-4	564	13.7 (4.0)		12 (2)	
4-8	88	12.8 (4.4)	**0.001**	7 (8)	0.37
>12	69	12.1 (4.0)		3 (4)	
Depression					
no	583	13.8 (4.0)	**0.001**	12 (2)	0.13
yes	138	12.0 (4.0)		10 (7)	

p derived from ***** simple linear and † logistic regression analyses adjusted for age and gender

6.7 Genetic factors and cognition (table 6.27)

In this study there were no differences in scores across cognitive function tests in those carrying the Apoε4 allele when compared to others (Apoε2 and Apoε3 allele). Of the 94 participants carrying the Apoε4 allele only one was diagnosed with dementia in this study. Therefore, there was insufficient power to examine the relationship of Apoε allelic variants with dementia in this cohort.

Table 6.27 Associations of Apoε4 allelic variants with cognitive outcomes in late life				
Predictor	**Global Cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* p	**Delayed recall** (score) β (95%CI)* p
Apoε4 (0=no, 1=yes)	-0.04 (-0.26, 0.18) 0.72	0.44 (-0.44,1.32) 0.33	0.38 (-0.47,1.22) 0.38	0.07 (-0.35,0.50) 0.74
***** Simple linear regression analyses adjusted for age and gender.				

6.8 Discussion

To the best of my knowledge, there are no longitudinal studies in India that have examined the relationship between sociodemographics and cardiometabolic risk factors in mid- and late life with cognitive outcomes in late life. Key findings from this chapter are discussed below.

6.8.1 Potential confounders

Analyses in this chapter helped me identify exposures from late life and midlife that were potentially confounding or mediating the associations of birth size with late life cognition. They included:

a. late life factors: BMI, socioeconomic position, metabolic syndrome, stroke, HDL cholesterol, homocysteine, haemoglobin, physical activity and diet.
b. midlife factors: BMI, socioeconomic position, diabetes, CHD, total and LDL cholesterol, and haemoglobin.
c. childhood factors: education and indicators of childhood growth (leg length and head circumference measured in this study)

The mediating or confounding effect of the above factors on the relationship of birth weight and late life cognition was explored in chapter 7.

6.8.2 Sociodemographics and cognitive function

As expected, those who were older, men and the widowed at the time of the study had lower cognitive function. Aging is a globally recognised risk factor for cognitive decline and dementia (World Alzheimer Report.,2014). However, in this study, advancing age was not associated with dementia. The most likely explanation is that the majority of men (75%) and

women (70%) in this study were less than 65 yrs of age, and very few were diagnosed with dementia. Consistent with findings from studies in both high income countries and India, those who were widowed had lower cognitive function and higher rates of dementia than who were married. (The Dementia India Report.,2010; Sundstrom et al.,2014; Helmer et al.,1999).

Those with higher levels socioeconomic position (both in mid- and late life) had higher cognition and lower rates of dementia in late life. These findings are compatible with findings from both high and LMIC settings (World Alzheimer's Report.,2014).

In a recent systematic review of 133 studies with 437,477 participants, the prevalence of dementia was higher in those with lower education [pooled OR = 2.61 95%CI (2.21,3.07)] (Meng and Darcy.,2012). Similarly, occupational complexity is directly associated with cognitive performance in later life, independent of prior cognitive abilities (Smart et al.,2014; Then et al.,2014; Finkel et al.,2009). Consistent with these findings, among the MYNAH participants, education and occupational levels were directly associated with cognitive function and inversely with dementia. If educational attainment and occupational levels are considered as proxy markers of 'Cognitive Reserve', their associations with cognitive function and dementia in this study indicates that cognitive reserve hypothesis of cognitive ageing may be of relevance in this cohort. The cognitive reserve pathway of cognitive ageing in the MYNAH cohort was explored further in chapter 7 (section 7.6)

A hypothetical construct of ‘cognitive reserve’ or ‘brain reserve’ is widely used to explain how, in the face of neurodegenerative changes that are similar in nature and extent, individuals vary considerably in terms of their cognitive decline and clinical manifestation of cognitive impairment (Whalley and Deary.,2004). Cognitive reserve refers to the ability to tolerate the age-related changes and disease related pathology in the brain without developing clinical symptoms or signs of disease (Fratiglioni and Wang.,2007).

Cognitive reserve also explains the relationship between education and occupational complexity and cognitive ageing. This reserve is believed to result from changes in brain structure and processing (Katzman.,1993). Cognitive reserve can take two forms: (1) neural reserve in which existing brain networks are more efficient, or have greater capacity, may be less susceptible to disruption; and, (2) neural compensation in which alternate networks may compensate for the pathological disruption of pre-existing networks.

6.8.3 Adult skeletal measurements and cognition

Adult skeletal size is considered a marker of early life development and nutritional status in childhood (Wadsworth et al.,2002; Gunnell.,2002). In this study, skeletal measurements in mid and late life were directly associated with cognitive function in late life. Contemporaneous associations of skeletal measurements with cognitive function in late life should be viewed cautiously as intervening osteodegenerative changes in this age group are known to affect the skeletal measurements. Nevertheless, several studies from both high and LMIC settings, have found similar associations between contemporaneous measurements of skeletal size and cognitive outcomes in late life. Head circumference (Borenstein Grave et al.,2001; Schofield et al.,1997; Mortimer et al.,2003), height, (Huang at al.,2008: Abbott et al.,1998; Kim et al.,2003), trunk height (Stewart et al.,2015) and leg length, (Kim et al.,2003; Mak et al.,2006; Kim et al.,2008; Huang et al.,2008) were inversely associated with cognitive function and cognitive impairment or dementia in late life.

6.8.4 Nutritional factors and cognition

In this study lower haemoglobin levels in mid- and late life were associated with lower cognitive function in late life. These findings are comparable to findings from a systematic review of five observational studies and six prospective cohort studies that reported direct associations of haemoglobin levels with cognitive function in late life (Andro et al.,2013).

Folate and vitamin B12 have been proposed to have protective effects on cognitive ageing. When they are deficient, homocysteine levels rise, which predisposes to cardiovascular disease, cognitive impairment and dementia. Deficiencies in B12 and in folate are known increase with age (Ho et al.,2011).

The direct association of folate with global cognitive function in this study is compatible with findings from two systematic reviews which report lower cognitive abilities in those with lower folate levels and higher rates of dementia in those with folate deficiency (Araujo et al.,2015; Raman et al.,2007).

In my study, vitamin B12 concentrations were not associated with cognitive outcomes. This is not entirely surprising as the association between B12 and cognition in late life has been a subject of controversy and findings from several systematic reviews are equivocal (Moore et al.,2012; O'Leary et al.,2012; Raman et al.,2007). Systematic review of thirty five cohort studies (n=14,325 subjects) by O'Leary and colleagues reported no associations between

serum vitamin B12 concentrations and cognitive decline or dementia. However, a systematic review of forty three studies by Moore and colleagues concluded that low serum vitamin B12 concentrations were associated with cognitive impairment (Moore et al.,2012). There is insufficient evidence, despite a large number of cohort studies, for an association between vitamin B12 and cognitive function or dementia in late life

The inverse associations of homocysteine with certain cognitive abilities, and a lack of association with dementia in my study sample is similar to results from several epidemiological studies that are inconsistent (Wald et al.,2011; Ho et al.,2011). While some longitudinal studies report higher prevalence of cognitive impairment and dementia in those with hyperhomocysteinaemia, other studies have reported inverse or no associations (Ariogul et al.,2005; Gunstad et al.,2006; Reitz et al.,2009).

6.8.5 Cardiometabolic factors and cognition

The direct associations of BMI in mid- and late life with cognitive function in late life in this study is partly consistent with findings from several epidemiological studies that have reported midlife BMI as a negative predictor and late life BMI as a positive predictor of higher cognitive function and lower risk of dementia in late life (Dahl and Hassing.,2013; Buchman et al.,2005; Fitzpatrick et al., 2009). The associations of BMI with cognitive function and dementia in late life have not been examined in India. The BMI-cognition relatonship was examined further and results discussed with potential mechanisms in the next chapter (section 7.9.8)

Though midlife diabetes was inversely associated with certain cognitive abilities in late life, diabetes in late life was unrelated to cognitive outcomes in this study. This is paradoxical to the findings from several systematic reviews which have consistently reported lower cognitive performance and increased risk for dementia in those with diabetes (Cheng et al.,2012; Gudala et al.,2013; Roberts et al.,2014; World Alzheimer Report.,2014). The lack of contemporaneous associations between diabetes and cognitive outcomes in this study may be due to the potential confounding structure of BMI, education and socioeconomic position in this cohort. Higher socioeconomic position in late life was directly related to diabetes (section 5.1.5); socioeconomic position was positively correlated with BMI (correlation coefficient = 0.3 $p < 0.001$) and attained educational level (correlation coefficient=0.4 $p<0.001$) in this study sample. All of these: socioeconomic position, BMI and education were directly related to cognitive function in late life (sections 6.1and 6.2). Alternate explanations for the diabetes-cognition relationship in this study for example, insufficient information about

the control of diabetes and its complications, and psychometric properties of the 10/66 battery are discussed in greater detail in chapter 7 (section 7.9.8).

There are limited data on diabetes and cognitive outcomes in late life from India. Similar to the findings in this study, a population based study of 900 older adults in the city of Lucknow (north India) reported that those with diabetes were 1.3 times more likely to have dementia. However, the 95% CI for the OR in this study was wide and included one suggesting that the association was not significant [OR=1.3 95% CI (0.65 to 2.57)] (Tiwari et al.,2012). Diabetes was not associated with cognitive function and dementia in another population based study of 500 men and women from tribal, rural and urban areas in the north west of India (Raina et al.,2015). Among 745 community dwelling older adults in the city of Kolkata, those with diabetes had lower cognitive function when compared those without (Das et al.,2007).

Hypertension in late life, but not in midlife was inversely associated with dementia in this study. There is no consensus of the blood pressure-cognition relationship, though several studies that have examined this relationship taking a lifecourse approach. While raised blood pressure in midlife has been associated with an increased risk of cognitive impairment and dementia 10 to 20 years later (Peila et al.,2001; Launer et al.,2000), by the time cognitive impairment is manifest, blood pressure levels are relatively low (Guo et al.,1996; Ruitenberg et al.,2001) or normal (Qiu et al.,2003). Orthostatic change in blood pressure was directly related to cognitive function in late life in this cohort, a similar finding was reported from another study (Wulmuter et al.,2012). There are limited data on blood pressure and late life cognitive function in India. In contrast to the findings in my study, two population based studies in India have reported an increased risk of Mild Cognitive Impairment and dementia in those with hypertension (Riana et al.,2015; Das et al.,2007).

Older adults with lower cognitive function and dementia are known have normal (Notkola et al.,1998; Reitz et al.,2004) or relatively lower levels of total cholesterol (Mielke et al.,2010; Stewart et al.,2007). Similar to findings from these studies, total cholesterol was not associated with cognitive function or cognitive impairment in late life among the MYNAH participants.

Metabolic syndrome in late life, but not from midlife was inversely associated with dementia in this study. The relationship between metabolic syndrome and cognition in late life has been controversial. Though metabolic syndrome has been found to be a risk factor for lower cognition and dementia in late life, a definitive conclusion cannot be drawn from the available data. Discrepancies between the results are due to several factors, e.g., study design,

heterogeneity of the population enrolled, reliability and sensitivity of detection tools for cognitive changes, cut-offs and criteria used to diagnose metabolic syndrome, the outcome measures considered, duration of metabolic syndrome before the onset of cognitive decline, and also the analytical approach performed (Frisardi.,2014). A systematic review and meta-analysis including 19,522 subjects aged 59-85 years from 13 longitudinal population-based studies showed a marginal significant association with cognitive functioning and impairment in late life only in the younger old group (<70 years), and not the in older group (>70 years). It is not yet clear how age can influence this relationship (Hao et al.,2011).

CHD in mid- and late life was not related to cognitive function and dementia in this study. This finding must be interpreted with caution as only two participants with CHD in midlife were diagnosed with dementia in this study. There is no consensus on the relationship between CHD and cognitive function in late life, mainly due to the survivor effect. Though several studies have shown that CHD is associated with increased risk of cognitive impairment, decline and dementia in late life (Newman et al.,2005; Roberts et al.,2010), other studies have found no such associations (Knopman et al.,2005; Petrovitch et al.,1998). There no studies that report the association of CHD with cognitive outcomes in late life in India.

The finding that those with stroke in my study had lower cognition is a universal observation including population based studies from India (Mijajlović et al.,2017; Das et al.,2012). There was insufficient power to examine stroke-cognition relationship in this study: of the 21 participants who were diagnosed with stroke, only two were diagnosed with dementia in this study.

6.8.6 Lifestyle factors and cognition

Smoking pack years was inversely associated with global cognition in late life in my study. This finding is consistent with those reported in systematic reviews examining the relationship between smoking and late life cognition (World Alzheimer Report.,2014; Plassman et al.,2010; Lee et al.,2010; Anstey et al.,2007; Cataldo et al.,2010; Peters et al.,2008; Beydoun et al.,2014; McKenzie et al.,2014; Zhong et al.,2015)

In a recent systematic review of 43 cohort studies, drinking alcohol was not associated with dementia (Cao et al.,2016). In my study, amount of alcohol intake (units/week) was inversely associated with global cognition, but was unrelated to dementia; those who were drinking moderate amounts of alcohol had higher cognitive function. These observations are

consistent with findings from a recent systematic review by Ilomaki and colleagues that cognitive function was better among those drinking moderately compared to heavy drinkers (Ilomaki et al.,2015). Caregivers are more likely to restrict access to alcohol in those with cognitive impairment and dementia, and this (reverse causality) may explain the absence of associations between current drinking and dementia in my study.

The direct association of physical activity with global cognition in late life is consistent with reports from several systematic reviews and meta-analyses that have shown that higher level of physical activity is associated with higher cognitive function in later life (Lee et al.,2010; Beydoun et al.,2014; Blondell et al.,2014; Ahlskog et al.,2011; Smith et al.,2010; Bherer et al.,2013).

In this study, though non-vegetarians had lower scores on certain cognitive function tests compared to vegetarians, there was no difference in the rates of dementia between the groups. This observation is consistent with findings from a recent systematic review of 43 cohort studies by Cao and colleagues. There were no significant differences in cognitive function and prevalence of dementia between the vegetarians and non-vegetarians (Cao et al.,2016). This systematic review also found no associations between amount of intake of fish and, fruits and vegetables with cognitive function or dementia [fish RR: 0.79, (95 % CI:90.59-1.06) p = 0.11), vegetables and fruits (RR: 0.46, 95 % CI (0.16-1.32), p = 0.15]. However, in this study, there were inverse associations between frequency of meat and fish consumption with global cognition verbal fluency, while amount of fruits and vegetable consumption was directly related to scores across all cognitive function tests.

An important limitation in examining the association between meat and fish consumption with cognitive outcomes in this study was that only data on frequency of consumption was available, but not the total amount of consumption. There are several cultural factors that are known to influence the pattern of meat and fish consumption in the study setting. Muslims are known to eat meat more frequently while even non-vegetarian Hindus tend to eat meat only once or twice in a week. Both Hindus and Muslims do not eat pork, while Hindus also do not eat beef. Sea fish is 3 to 4 times more expensive than lamb and 7- 8 times more expensive than beef or pork. In general, only those with higher incomes would be eating fish in Mysore. Influence of religion, socioeconomic position and other cultural factors on diet and dietary intake were not obtained in this or the previous study. The differences in levels of attained education, socioeconomic position and, concentrations of vitamin B12, folate and homocysteine between the vegetarians and non-vegetarians was examined further in chapter 8 (section 8.3.3).

6.8.7 Thyroid function and cognition

In the MYNAH, T4 levels were inversely associated with verbal fluency in late life. Several studies have investigated the association of thyroid function with cognitive function and impairment in late life, but the findings are inconsistent (Annerbo and Lokk.,2013; van Osch et al.,2004; Kalmijn et al.,2000; Volpato et al.,2002; Prinz et al.,1999; de Jong.,2006; van der Cammer et al.,2003). Low serum TSH concentrations as well as high thyroxine levels were associated with cognitive impairment and dementia in some studies (de Jong et al.,2007; van Osch et al.,2004; Kalmijn et al.,2000) but not in others (Lopez et al.,1989; Small et al.,1985). This inconsistency may be partly explained due to changes associated in thyroid production and metabolism with normal ageing, and the heterogeneity of study populations (Begin et al.,2008). Secretion of T4 and T3 is reduced in the healthy elderly, but serum concentrations of total and free T4 remain relatively unchanged because T4 degradation is also reduced in the elderly. Circulating total and free T3 concentrations demonstrate a clear, age-dependent decline because of both reduced secretion and reduced peripheral conversion from T4. TSH secretion may actually be slightly decreased in healthy elderly individuals (Begin et al.,2008).

6.8.8 Depression and cognition

The relationship between late life depression and dementia is complex, bidirectional and not well understood. The inverse association of depression with cognition in this study is consistent with findings several studies that report a range of cognitive problems and higher rates of dementia in those with depression (Kessing.,2012; Morimoto and Alexopoulos.,2013; Bennett and Thomas.,2014). Similarly, depressive symptoms and depression are more common in those with dementia (Kessing.,2012; Morimoto and Alexopoulos.,2013; Bennett and Thomas.,2014). This relationship between depression and cognition among participants was explored further in multivariate regression models (Chapter 7 section 7.8)

Half of those with dementia in this study had comorbid depression. In this study, though participants with higher depression scores and those with clinical depression scored lower on all cognitive function tests, depression was unrelated to dementia. This may partly be due to the hierarchical nature of the 10/66 diagnostic algorithm, and a relatively smaller number of cases with dementia. Those with major depression and severe cognitive impairment would be classified as dementia and not depression. This may have resulted in slightly higher number of cases with dementia, but unlikely to have created spurious associations.

6.8.9 Apoε4 and cognition

Insufficient power is a likely explanation for the lack of association of Apoε4 allele with cognitive outcomes in this study. In other studies, the Apoε4 allele has been identified as a major risk factor for lower cognition and cognitive impairment, cognitive decline and dementias in late life (Wisdom et al.,2011; Small et al.,2004; Haan et al.,1999; Ganguli et al.,2000, Farrer et al.,1997). The average risk for developing Alzheimer's disease at the age of >65 years is about 15%. However, studies have shown that in carriers of an Apoε4 allele, this increases to 30% compared with 9% in individuals without an Apoε4 allele in Caucasian populations (Seshadri et al.,1995; Small et al.,2004). The adjusted odds of age-related cognitive decline, Mild Cognitive Impairment, and Alzheimer's in Apoε4 carriers were 3.0 (1.2-7.3), 3.7 (2.3-6.0) and 5.6 (3.6-8.9) respectively when compared to non-carriers (Rosich-Estragó et al.,2004).

6.8.10 Causality

Age was inversely associated with Mild Cognitive Impairment [OR=1.2 95%CI (1.1,1.3)] and folate levels in late life were directly associated with cognitive impairment in late life [OR=1.02 95%CI (1.00,1.05)]. None of the sociodemographics, anthropometric measurements, nutrition and life style factors, cardiometabolic risk factors, endocrine and genetic factors were related to Mild Cognitive Impairment (Appendix 13). There was insufficient power to examine the relationships of mid- and late life exposures with Mild Cognitive Impairment and dementia in the MYNAH study. Therefore, the findings related to these outcomes should be interpreted with caution and causality should not be assumed.

Reverse causality is a potential explanation for several contemporaneous associations with cognitive function that were observed in this chapter. For example, nutrition and lifestyle factors- cognition, depression-cognition and physical activity-cognition associations do not provide any temporal relationship or offer directionality.
In this chapter, univariate analyses were conducted to examine the relationship between exposures in mid- and late life with cognitive outcomes in this study. These relationships were further explored in multivariate regression analyses adjusting for potential confounders, and by construction of lifecourse models with key exposures from early, mid-and late life as predictors of late life cognitive function in chapter 7.

7. Results: Size at birth and cognitive function in late life in the MYNAH cohort

In this chapter, I examined the relationship between size at birth and cognitive function in late life in the MYNAH cohort.

7.1 Exposures

Measurements of size at birth were extracted for all the MYNAH participants from their birth records (chapter 5 section 5.1.6). Birth weight was available for all the 721 men and women who had participated in this study. However, length and head circumference at birth were available for 638 and 641 participants respectively. It was possible to compute ponderal index for 638 of them.

7.2 Cognitive outcomes (table 7.1)

The 10/66 battery of cognitive tests provided four cognitive measurements: global cognition, verbal fluency, immediate recall and delayed recall (chapter 5 section 5.1.7). These were available for all the MYNAH participants. From these four cognitive measures, a composite measure of cognitive function was derived by principal component analysis. Highest proportion of variance (61%) was explained by the first principal component (table 7.1).

Table 7.1 Total variance explained by principal components

Principal Component	Initial Eigen values		
	Total	% of Variance	Cumulative %
First	2.45	61.39	61.39
Second	0.81	20.41	81.80
Third	0.44	10.97	92.77
Fourth	0.29	7.23	100.0

As expected these measures of cognitive function were positively correlated with each other (table 7.2). Furthermore, strong positive correlations were observed between these four measures of cognitive function and the first principal component on (Pearson correlation coefficient ≥ 0.7 and $p < 0.001$ for all). This confirmed that the first principal component was a reliable indicator of cognitive function in this cohort.

Only a small proportion of the participants were diagnosed with dementia (n=22, 3%) in this study, and therefore it was not meaningful to retain dementia as a cognitive outcome of interest in this chapter. Instead, the composite cognitive score was identified as the best summary measure of cognitive function in this study.

Table 7.2 Correlations between cognitive outcomes in late life					
Cognitive outcomes in late life	**Global cognition score** (SD) n=721	**Verbal fluency** (score) n=721	**Immediate recall** (score) n=721	**Delayed recall** (score) n=721	**Composite cognitive score** (SD) n=721
Global cognition score (SD) correlation*	1	0.52	0.49	0.45	0.76
Verbal fluency (score) correlation*		1	0.39	0.32	0.70
Immediate recall (score) correlation*			1	0.71	0.80
Delayed recall (score) correlation*				1	0.80
Composite cognitive score (SD) correlation*					1
All values in the table are Pearson correlation coefficients. * p<0.001 for all					

7.3. Size at birth and cognitive outcomes in late life (tables 7.3 and 7.4)

The 721 men and women were the offspring of 421 marriages. Siblings were more similar in their standardised cognitive function score than those who were unrelated. The between-sibship variance of 0.203 was 3.5 times larger than its standard error (0.058, p=0.0005). The intra-class correlation was 0.20. So, to account for the influence of sibship, I have used mixed linear regression models to examine the association between possible predictors and cognitive function. Fixed effects models with random intercepts were chosen, taking into account the influence of sibship.

Birth weight was directly associated with scores across all cognitive function tests, while length at birth was directly associated with scores on the delayed recall test only (table 7.3). Those who were heavier and longer at birth had higher composite cognitive scores in late life. A 418g (1 SD) higher birth weight and a 3 cm (1 SD) longer length at birth were associated with a 0.1 SD higher composite cognitive score in late life. A 418g (1 SD) higher birth weight was associated with higher verbal fluency by 0.4 words, higher immediate recall by 0.3 words and a higher delayed recall by 0.2 words in late life. The effect size of length at birth with delayed word recall was similar to birth weight, a 3 cm (1 SD) longer length at birth was associated with a greater immediate word recall by 0.2.

Head circumference at birth and ponderal index at birth were unrelated to cognitive outcomes in late life.

Table 7.3 Associations of size at birth with cognitive outcomes in late life

Predictor Birth size	**Global cognition** (SD) β (95%CI)* p	**Verbal fluency** (score) β (95%CI)* p	**Immediate recall** (score) β (95%CI)* P	**Delayed recall** (score) β (95%CI)* p	**Composite cognitive score** (SD)* β (95%CI) p
Birth weight (kgs)	0.28 (0.11,0.46) **0.002**	0.95 (0.24,1.60) **0.008**	0.82 (0.14,1.50) **0.02**	0.37 (0.58,1.15) **0.03**	0.29 (0.12,0.46) **0.001**
Birth weight (SD)	0.12 (0.04,0.19) **0.002**	0.40 (0.10,0.69) **0.008**	0.34 (0.06,0.63) **0.02**	0.16 (0.01,0.11) **0.03**	0.12 (0.05,0.19) **0.001**
Length at birth (cms)	0.02 (0.00,0.04) 0.11	0.05 (-0.05,0.15) 0.34	0.07 (-0.03,0.17) 0.18	0.06 (0.01,0.11) **0.03**	0.03 (0.00,0.05) **0.04**
Length at birth (SD)	0.06 (-0.01,0.13) 0.11	0.15 (-0.15,0.44) 0.34	0.20 (-0.09,0.50) 0.18	0.17 (0.02,0.32) **0.03**	0.07 (0.00, 0.15) **0.04**
Head circumference (cms)	0.01 (-0.04,0.06) 0.78	0.05 (-0.14, 0.25) 0.60	0.09 (-0.10, 0.28) 0.34	0.05 (-0.04,0.15) 0.26	0.02 (-0.02,0.07) 0.34
Head circumference (SD)	0.01 (-0.06,0.09) 0.78	0.08 (-0.22, 0.39) 0.60	0.14 (-0.15, 0.45) 0.34	0.09 (-0.06, 0.24) 0.26	0.04 (-0.04, 0.11) 0.34
Ponderal index (kgs/m^3)	0.00 (-0.01,0.01) 0.96	0.01 (-0.05,0.06) 0.83	-0.01 (-0.07,0.06) 0.86	-0.01 (-0.04,0.02) 0.37	-0.01 (-0.09,0.06) 0.70
Ponderal index (SD)	0.00 (-0.07,0.07) 0.96	0.03 (-0.27,0.33) 0.83	-0.03 (-0.33,0.27) 0.86	-0.07 (-0.22,0.08) 0.37	-0.01 (-0.09,0.06) 0.70

***** Mixed linear regression analyses adjusted for age, sex and sibship in which all exposures were treated as continuous variables.

Table 7.4 Interactions between birth weight and sex for cognitive outcomes

Cognitive outcomes	**Birth weight (**SD) **Men**			**Birth weight (**SD) **Women**			**Interaction**
	β	**(95% CI)**	**p**	**β**	**95% CI**	**p**	**p**
Global Cognition (SD)	0.12	(0.03, 0.21)	**0.01**	0.17	(0.05, 0.28)	**0.005**	0.52
Verbal fluency (score)	0.48	(0.10, 0.86)	**0.01**	0.53	(0.06, 1.01)	**0.03**	0.85
Immediate Recall (score)	0.26	(-0.10, 0.63)	0.15	0.40	(-0.08, 0.87)	0.10	0.67
Delayed recall (score)	0.12	(-0.07, 0.30)	0.21	0.19	(0.04, 4.30)	0.10	0.61
Composite Cognitive Score (SD)	0.11	(0.02, 0.20)	**0.01**	0.16	(0.04, 0.28)	**0.01**	0.57

In general, coefficients for the effect of birth weight on cognitive outcomes were slightly larger in women than men. For example, a 1 SD higher birth weight was associated with an 0.11 SD and 0.16 SD higher composite cognitive score in men and women respectively. However, there were no statistically significant interactions between sex and birth weight for cognitive outcomes, indicating that associations of birth weight with cognitive outcomes were similar for men and women (table 7.4)

7.4 DOHaD pathways to cognitive ageing (Figure 7.1)

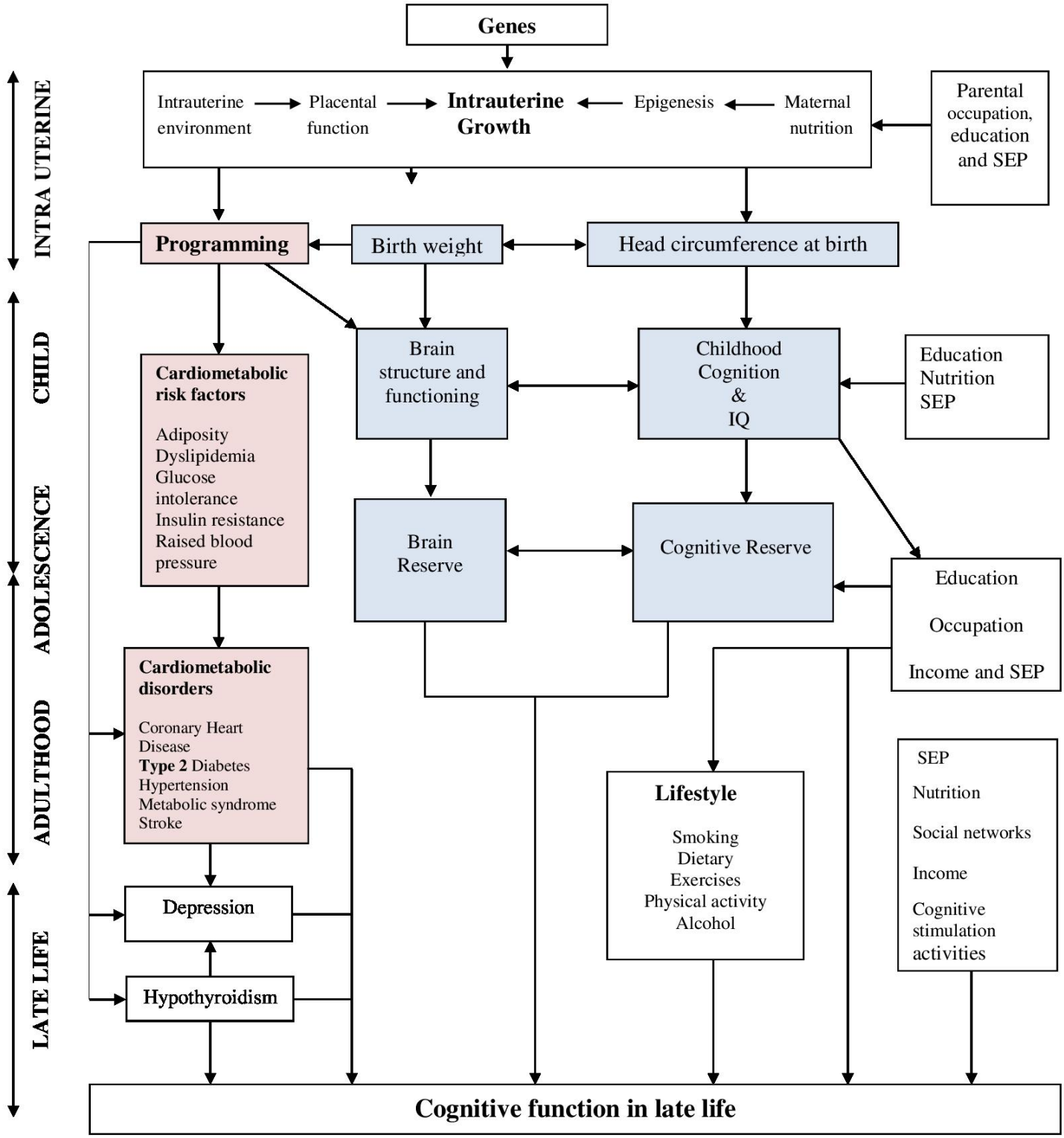
There are two plausible pathways linking pre-natal growth and nutrition to late life cognitive function (Whalley et al.,2006):

1. Programming of metabolism by under nutrition in very early life, exacerbated by relative over nutrition in later life, leading to reduced cognitive function in late life mediated through cardiometabolic disorders (David Barker or DOHaD hypothesis). I call this the **'programmed cardiometabolic pathway'** (indicated by red boxes in Figure 7.1). Small size at birth has been linked to cardiometabolic disorders: type-2 diabetes, coronary heart disease, hypertension and metabolic syndrome in adult life (Barker.,1995; Huxley et al.,2002; Huxley et al.,2007; Whincup et al.,2008), and these cardiometabolic disorders are independently associated with lower cognitive abilities in late life (Whalley et al.,2006; Craft S., 2009). To explore this pathway of cognitive ageing, I examined if size at birth was associated with cardiometabolic disorders in mid- and late life, and if these cardiometabolic disorders were inversely associated with cognitive ability in late life.

and /or

2. A direct effect of reduced pre-natal growth and development on brain development leading to decreased peak cognitive capacity and hence reduced cognitive abilities in late life (Whalley et al., 2006). This **'cognitive reserve pathway'** was explored by examining if those with better pre-natal growth and development (indicated by birth size in this cohort) had gained higher brain and cognitive capacity in adult life (indicated by adult head circumference and attained education respectively), and had higher cognitive ability in late life.

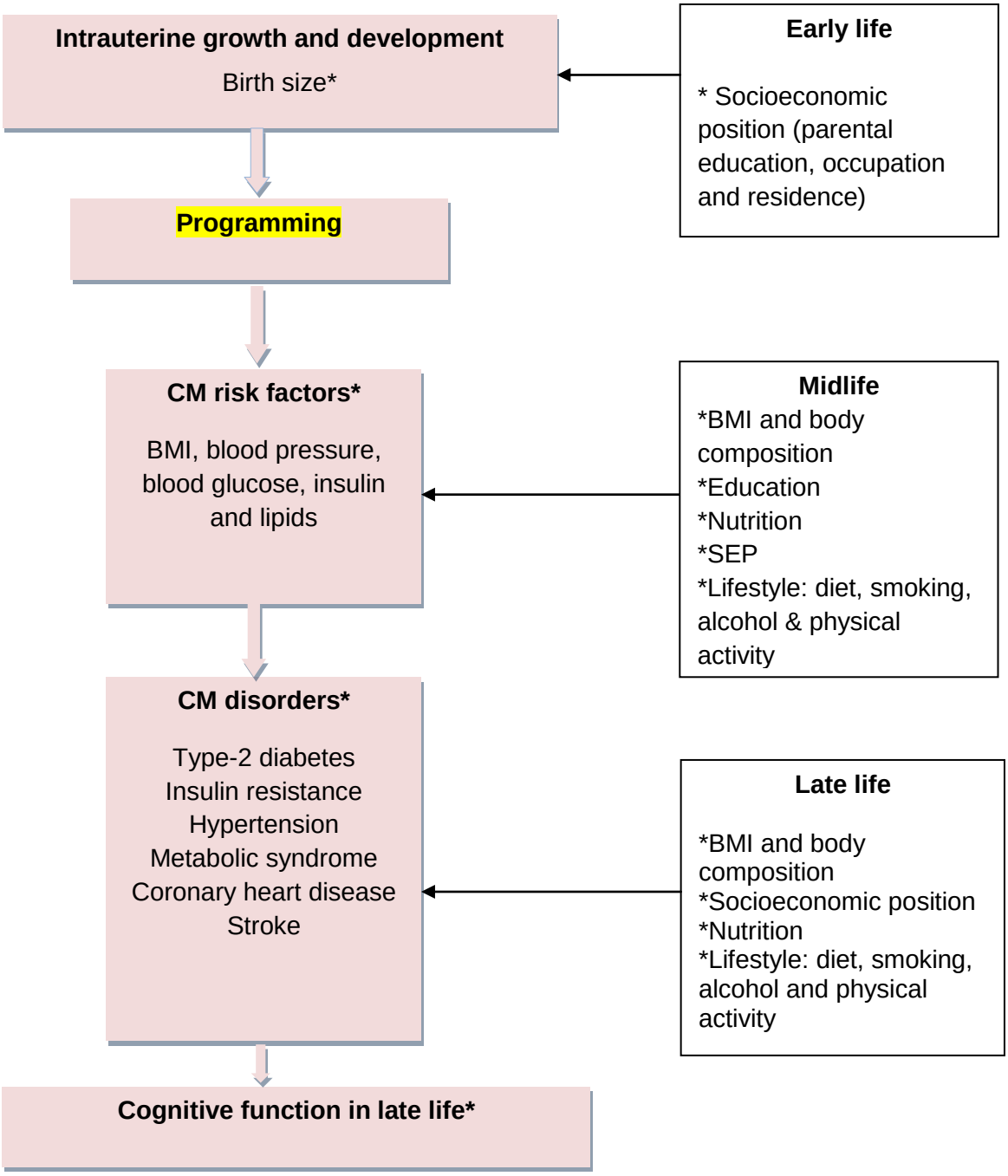
Fig 7.1 Illustration of the DOHaD cardiometabolic (in pink) and cognitive reserve (in blue) pathways to cognitive ageing SEP: socioeconomic position



7.5. Exploring the DOHaD cardiometabolic pathway of cognitive ageing in the MYNAH cohort (figure 7.2)

If the programmed cardiometabolic pathway of cognitive ageing in an explanation for the association between birth weight and late life cognitive function in the MYNAH cohort, a) men

Figure 7.2 The DOHaD cardiometabolic pathway of cognitive ageing
CM: cardiometabolic * variables available in the MYNAH cohort.



and women with lower birth weight would be expected to have higher cardiometabolic risk markers in mid- or late life and b) those with higher cardiometabolic risk makers would have lower cognitive scores in late life. Furthermore, any associations between size at birth and late life cognitive function would be attenuated by adjusting for mid- or late life cardiometabolic risk markers.

Figure 7.2 illustrates the DOHaD cardiometabolic pathway of cognitive ageing and provides an indication of the domains with a list of variables available in the MYNAH cohort to explore this pathway.

To seek evidence in support of this pathway, I examined:

a. associations of birth weight with cardiometabolic risk factors in mid- and late life
b. associations of cardiometabolic risk factors in mid- and late life with cognitive function in late life
c. the effect of adjusting for cardiometabolic risk markers in regression models of birth weight as predictors of late life cognitive function

Size at birth is generally positively related to measures of adult size, like BMI, while adult BMI tends to be positively related to cardiometabolic risk markers, BMI can therefore mask an effect of fetal programming on later cardiometabolic outcomes. This is a controversial issue, and has been hotly debated in the DOHaD literature (Tu et al.,2005). However, I will carry out the above analyses both unadjusted and adjusted for adult BMI, and test for interactions between birth measures and adult BMI. Depending on my findings, I will return to this issue in the Discussion (section 7.9).

7.5.1 Size at birth and cardiometabolic factors in mid- and late life (tables 7.5 and 7.6)

As expected, those who where were heavier at birth had greater BMI and waist circumference in midlife (table 7.5). While birth weight was unrelated to blood glucose levels and diabetes, those who were heavier at birth had higher insulin resistance and systolic blood pressure, and higher rates of metabolic syndrome in midlife. There were positive associations of borderline statistical significance between birth weight and midlife skinfolds, fasting insulin concentration and systolic blood pressure. These associations were in a direction opposite to those expected, lost statistical significance after adjusting for BMI, and did not support the fetal cardiometabolic programming pathway of cognitive ageing.

Table 7.5 Associations of birth weight (kgs) with cardiometabolic factors in midlife

Outcomes	**β* or OR† (95%CI)** Adjusted for age sex and sibship **p**	**β* or OR† (95%CI)** Adjusted for age, sex, sibship and BMI **p**	BWT-BMI interaction **p**
Body Mass Index (kg/m^2)*	1.59 (0.71, 2.47) **<0.001**	_	_
Waist circumference (cms)*	4.49 (2.10, 2.47) **<0.001**	_	_
Sum of skin folds (mms)*	14.65 (-1.27, 30.56) 0.07	_	_
Fasting glucose (mmol/l)*	0.03 (-0.02, 0.09) 0.26	0.01 (-0.04, 0.08) 0.72	0.82
120 mins glucose (mmol/l)*	-0.05 (-0.15, 0.05) 0.33	-0.01 (-0.19, 0.01) 0.10	0.25
Diabetes (0=no, 1=yes) †	1.40 (0.80, 2.47) 0.24	1.12 (0.67, 2.12) 0.54	0.54
Fasting insulin (pmol/l)*	0.21 (0.00, 0.43) 0.05	0.07 (-0.12, 0.29) 0.08	0.80
Insulin resistance (pmol/l)*	4.63 (0.62, 8.64) **0.03**	3.16 (-0.81, 7.03) 0.12	0.25
Systolic BP (mm of Hg)*	3.12 (-0.05, 6.28) 0.05	1.93 (-1.21, 3.23) 0.23	0.95
Diastolic BP (mm of Hg)*	0.75 (-1.44, 2.94) 0.50	0.21 (-2.00, 2.00) 0.85	0.74
Hypertension (0=no,1=yes)†	1.25 (0.74, 2.70) 0.40	1.15 (0.67, 1.95) 0.61	0.73
Total cholesterol (mmol/l)*	0.08 (-0.15, 0.31) 0.50	0.01 (-0.22, 0.24) 0.44	0.40
LDL cholesterol (mmol/l)*	0.02 (-0.20, 0.25) 0.85	-0.04 (-0.27, 0.18) 0.71	0.24
HDL cholesterol (mmol/l)*	0.05 (-0.10, 0.10) 0.08	0.05 (-0.00, 0.10) 0.06	0.26
Triglycerides (mmol/l)*	0.05 (-0.05, 0.15) 034	-0.00 (-0.10, 0.10) 0.99	0.46
Coronary heart disease† (0=no, 1=yes)	0.73 (0.19, 2.86) 0.65	0.75 (0.18, 3.14) 0.69	0.93
Metabolic syndrome† (0=no, 1=yes)	1.85 (1.16, 2.97) **0.01**	1.35 (0.79, 2.32) 0.27	0.62

Effect sizes * B for continuous outcomes and † OR for binary outcomes derived from mixed regression analyses adjusted for age, sex and sibship . BWT: birth weight BMI: Body Mass Index LDL: Low density lipoprotein HDL: High density lipoprotein

Similar to the associations of birth weight with adult body measurements in midlife, men and women who were heavier at birth also had higher BMI, larger waist circumference, and greater skin folds in late life (table 7.6).

Table 7.6 Associations of birth weight (kgs) with cardiometabolic factors in late life

Outcomes	β* or OR† (95%CI) Adjusted for age, sex and sibship **p**	β* or OR† (95%CI) Adjusted for age, sex, sibship and BMI **p**	BWT-BMI interaction **p**
Body Mass Index (kg/m^2)*	1.25 (0.38, 2.13) **0.005**	–	–
Waist circumference (cms)*	3.66 (1.59, 5.73) **0.001**	–	–
Sum of skin folds (mms)*	5.29 (1.92, 8.65) **0.002**	–	–
Fasting glucose (mmol/l)*	-0.01 (-0.07, 0.05) 0.71	-0.03 (-0.08, 0.03) 0.36	0.52
120 mins glucose (mmol/l)*	-0.07 (-0.15, 0.02) 0.13	-0.09 (-0.17, -0.00) **0.05**	1.00
Diabetes (0=no, 1=yes)†	0.91 (065, 1.29)** 0.61	0.82 (0.57, 1.12) 0.29	0.73
Fasting insulin (pmol/l)*	0.08 (-0.04, 0.19) 0.18	-0.01 (-0.10, 0.09) 0.88	0.24
Insulin resistance (pmol/l)*	0.03 (-0.67, 0.73) 0.93	-0.25 (-0.98, 0.42) 0.47	0.71
Systolic BP (mm of Hg)*	-1.30 (-4.56, 1.89) 0.42	-1.38 (-4.68, 1.88) 0.41	0.35
Diastolic BP (mm of Hg)*	-0.21 (-2.21, 1.79) 0.84	0.08 (-1.93, 2.09) 0.93	0.06
Hypertension† (0=no,1=yes)	1.02 (0.69, 1.50)** 0.91	0.88 (0.58, 1.34) 0.55	0.33
Total cholesterol (mmol/l)*	0.02 (-0.17, 0.21) 0.84	0.01 (-0.18, 0.20) 0.90	0.99
LDL cholesterol (mmol/l)*	0.06 (-0.09, 0.22) 0.42	0.06 (-0.09, 0.21) 0.44	0.91
HDL cholesterol (mmol/l)*	0.01 (-0.04, 0.05) **0.02**	0.02 (-0.03, 0.06) 0.49	0.82
Triglycerides (mmol/l)*	-0.04 (-0.12, 0.04) 0.31	-0.07 (-0.15, 0.01) 0.10	0.50
CHD† (0=no, 1=yes)	1.03 (0.68, 1.55)** 0.89	0.92 (0.62, 1.38) 0.92	0.32
Metabolic syndrome† (0=no, 1=yes)	1.33 (0.68, 1.94)** 0.13	0.90 (0.57, 1.43) 0.66	0.93
Stroke† (0=no, 1=yes)	0.37 (0.13, 1.01) 0.06	0.35 (0.13, 0.93) **0.05**	0.19

Effect sizes * B for continuous outcomes and † OR for binary outcomes derived from mixed regression analyses adjusted for age, sex and sibship. BWT: birth weight BMI: Body Mass Index LDL: Low density lipoprotein. HDL: High density lipoprotein CHD: Coronary heart disease

Participants with lower birth weight had higher levels of blood glucose (120 mins) in late life and this association gained borderline statistical significance after adjusting for BMI. Birth weight was directly associated with HDL cholesterol levels in late life (not significant after

adjusting for BMI) and inversely associated with stroke in late life (borderline significant after adjusting for BMI).

Other parameters of birth size: length at birth, head circumference and ponderal index were unrelated to cardiometabolic factors in mid- and late life (data not shown). There were no significant interactions between birth weight and BMI for cardiometabolic risk factors in mid- and late life (tables 7.5 and 7.6).

7.5.2 Cardiometabolic factors in mid- and late life, and cognitive function in late life

(tables 7.7 and 7.8)

Men and women with greater BMI, waist circumference and skin folds in mid- and late life had higher composite cognitive scores in late life.

Table 7.7 Associations of cardiometabolic factors in midlife with composite cognitive score in late life

Midlife predictors	Composite cognitive score (SD) in late life	
	β (95%CI)*	p
BMI (kg/m^2)	0.02 (0.00, 0.04)	**0.02**
Waist circumference (cm)	0.01 (0.00, 0.02)	**0.005**
Sum of skin folds (mm)	0.00 (0.00, 0.00)	**0.002**
Fasting glucose (mmol/l)	-0.13 (-0.43, 0.17)	0.40
120 mins glucose (mmol/l)	0.23 (0.00, 0.47)	0.05
Diabetes (0=no, 1=yes)	-0.26 (-0.50, -0.02)	**0.03**
Fasting insulin (pmol/l)	0.10 (0.02, 0.18)	**0.02**
Insulin resistance (pmol/l)	0.00 (-0.00, 0.00)	0.98
Systolic BP (mm Hg)	0.00 (-0.00, 0.01)	0.26
Diastolic BP (mm Hg)	0.00 (-0.00, 0.01)	0.38
Hypertension (0=no, 1=yes)	0.05 (-0.16, 0.27)	0.61
Total cholesterol (mmol/l)	0.08 (0.01, 0.16)	**0.02**
LDL cholesterol (mmol/l)	0.09 (0.02, 0.17)	**0.02**
HDL cholesterol (mmol/l)	0.03 (-0.29, 0.34)	0.87
Triglycerides (mmol/l)	-0.04 (-0.13, 0.05)	0.43
CHD (0=no, 1=yes)	-0.23 (-0.84, 0.38)	0.46
Metabolic syndrome (0=no, 1=yes)	0.02 (-0.15, 0.20)	0.78

*Mixed regression analyses adjusted for age, sex and sibship.
LDL: Low density lipoprotein. HDL: High density lipoprotein. CHD: Coronary heart disease

Blood glucose level (at 120 mins) in midlife was directly associated with composite cognitive score in late life, though this of borderline significance. Participants with diabetes in midlife had lower composite cognitive scores in late life, while those with higher levels of fasting

insulin, total cholesterol and LDL cholesterol had higher composite cognitive scores in late life.

Blood pressure, coronary heart disease and metabolic syndrome in midlife were unrelated to cognitive function in late life.

Table 7.8 Associations of cardiometabolic factors in late life with composite cognitive score in late life

Late life predictors	**Composite cognitive score** (SD)	
	β (95%CI)*	p
Body Mass Index (kg/m^2)	0.03 (0.01,0.04)	**<0.001**
Sum of skinfolds (mm)	0.00 (0.00,0.01)	**0.002**
Waist circumference (cm)	0.01 (0.00,0.02)	**<0.001**
Fasting glucose (mmol/l)	0.20 (-0.02,0.42)	0.07
120 mins glucose (mmol/l)	0.23 (0.00,0.47)	0.05
Diabetes (0=no, 1=yes)	-0.00 (-0.15,0.14)	0.94
Fasting insulin (pmol/l)	0.19 (0.08,0.30)	**0.01**
Insulin resistance	0.02 (-0.00,0.04)	0.06
Systolic BP (mm Hg)	-0.00 (-0.01,0.00)	0.13
Diastolic BP (mm Hg)	-0.01 (-0.01,-0.00)	**0.02**
Hypertension (0=no, 1=yes)	0.03 (-0.12, 0.18)	0.68
Total cholesterol (mmol/l)	0.03 (-0.03, 0.10)	0.33
LDL cholesterol (mmol/l)	0.02 (-0.06, 0.11)	0.62
HDL cholesterol (mmol/l)	0.18 (-0.08, 0.45)	0.18
Triglycerides (mmol/l)	0.08 (0.08, 0.23)	0.33
Coronary heart disease (0=no, 1=yes)	-0.03 (-0.18,0.13)	0.73
Metabolic syndrome (0=no, 1=yes)	0.13 (-0.01,0.28)	0.08
Stroke (0=no, 1=yes)	-0.64 (-1.07,-0.22)	**0.003**

Mixed regression analyses adjusted for age, sex and sibship in which all exposures were treated as continuous variables. LDL: Low density lipoprotein
HDL: High density lipoprotein CHD: Coronary heart disease

Men and women with higher levels of fasting glucose and glucose at 120 mins in late life had higher composite cognitive score in late life, but these associations were of borderline significance. Diabetes in late life was not related to composite cognitive score in late life.

Fasting insulin, insulin resistance and metabolic syndrome in late life were directly associated with composite cognitive score in late life, though the associations of insulin resistance and metabolic syndrome with composite cognitive score was of borderline significance. These associations were clearly in an opposite direction to what was expected.

As expected, diastolic blood pressure and stroke in late life were inversely associated with composite cognitive score in late life.

7.5.3 Regression model examining the effect of adjusting for cardiometabolic factors on the associations of birth weight with cognition in late life (table 7.9)

Table 7.9 Relationship between birth weight, cardiometabolic factors and cognition in late life

Predictor	Composite Cognitive Score (SD)			
	Adjusted for	β*	(95%CI)	p
Birth weight (kgs)	Age, sex and sibship	0.29	(0.12, 0.46)	**0.001**
	Age, sex, and BMI in midlife	0.22	(0.02, 0.42)	**0.04**
	Age, sex, and BMI in late life	0.24	(0.06, 0.41)	**0.006**
	Age, sex, and fasting glucose in midlife	0.25	(0.06, 0.46)	**0.001**
	Age, sex, and fasting glucose in late life	0.28	(0.11, 0.46)	**0.001**
	Age, sex, and 120 mins glucose in midlife	0.26	(0.06, 0.47)	**0.01**
	Age, sex, and 120 mins glucose in late life	0.29	(0.06, 0.51)	**0.01**
	Age, sex, and fasting insulin in midlife	0.27	(0.06, 0.48)	**0.01**
	Age, sex, and fasting insulin in late life	0.28	(0.11, 0.46)	**0.002**
	Age, sex, and insulin resistance in midlife	0.28	(0.07, 0.49)	**0.009**
	Age, sex, and insulin resistance in late life	0.29	(0.11, 0.46)	**0.001**
	Age, sex, and systolic BP in midlife	0.25	(0.05, 0.45)	**0.02**
	Age, sex, and systolic BP in late life	0.27	(0.10, 0.44)	**0.002**
	Age, sex, and diastolic BP in midlife	0.25	(0.05, 0.45)	**0.01**
	Age, sex, and diastolic BP in late life	0.27	(0.10, 0.44)	**0.002**
	Age, sex, and total cholesterol in midlife	0.25	(0.05, 0.45)	**0.01**
	Age, sex, and total cholesterol in late life	0.28	(0.11, 0.45)	**0.002**
	Age, sex, and HDL cholesterol in midlife	0.26	(0.06, 0.46)	**0.01**
	Age, sex, and HDL cholesterol in late life	0.28	(0.11,0.45)	**0.001**
	Age, sex, and metabolic syndrome in midlife	0.25	(0.05, 0.46)	**0.01**
	Age, sex, and metabolic syndrome in late life	0.29	(0.11, 0.46)	**0.001**
	Age, sex, and CHD in midlife	0.26	(0.06, 0.46)	**0.09**
	Age, sex, and CHD in late life	0.29	(0.11, 0.46)	**0.001**
	Age, sex, and stroke in late life	0.28	(0.11, 0.45)	**0.01**

* Mixed regression analyses adjusted for age, sex and sibship.
CHD: Coronary heart disease BMI: Body Mass Index BP: Blood pressure.
Adjustments for waist circumference, sum of skinfolds hypertension, triglycerides, LDL and HDL cholesterol in mid- and late life did not change the effect size and the association of birth weight with composite cognitive score remained significant (not shown in the table)

Birth weight was directly associated with composite cognitive score in late life, in a mixed effects model adjusted for age, sex and sibship (table 7.9). This model was separately adjusted for each of the cardiometabolic factors from mid- and late life. None of these adjustments attenuated the association of birth weight with composite cognitive score in late life, which remained significant. These models indicated that the association of birth weight with cognitive function in late life was independent of, and not mediated by cardiometabolic risk factors in mid- and late life.

7.5.4 Size at birth, cardiometabolic factors and cognition in late life

In summary, cardiometabolic factors in mid- and late life that were related to birth weight were unrelated to cognitive function in late life. Cardiometabolic factors in mid- and late life that were related to cognitive function in late life were unrelated to birth weight. The association of birth weight with cognitive function in late life was independent of, and not mediated by BMI and cardiometabolic risk factors in mid- and late life. There was no interaction of birth weight with BMI for cardiometabolic outcomes. These findings were not consistent with the programmed cardiometabolic pathway of cognitive ageing in the MYNAH cohort.

7.6 Exploring the DOHaD cognitive reserve hypothesis of cognitive ageing in the MYNAH cohort (Figure 7.3)

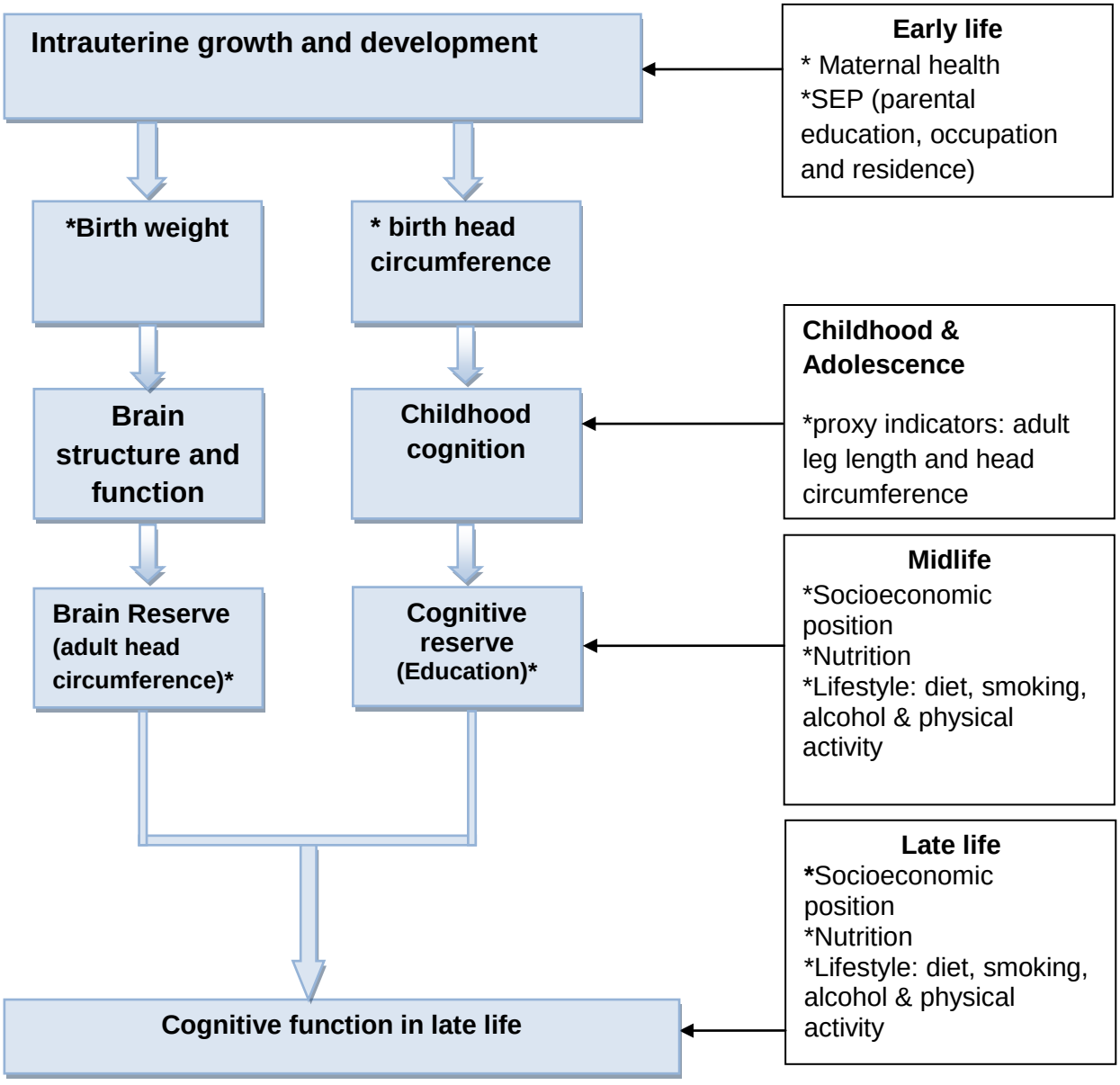
If the DOHaD cognitive reserve pathway is an explanation for the association of birth weight with late life cognitive function in the MYNAH cohort,

a. men and women with larger size at birth would be expected to have higher brain reserve and/or cognitive reserve;
b. those with higher brain and/or cognitive reserve would have a higher composite cognitive score in late life and
c. any associations between size at birth and cognitive function would be attenuated by adjusting for brain reserve and or cognitive reserve.

It is important to note that direct measures of peak cognitive reserve or brain reserve in adult life were unavailable in this cohort. Therefore, adult head circumference (measured in this study) and attained education levels were considered as proxy indicators for brain reserve and cognitive reserve respectively, on the cognitive reserve pathway.

Figure 7.3 illustrates the DOHaD cognitive reserve pathway with a list of variables available under different domains in the MYNAH cohort to explore this pathway.

Figure 7.3 The DOHaD cognitive reserve pathway of cognitive ageing.
* variables available in the MYNAH cohort



The following analyses were conducted to explore the DOHaD cognitive reserve pathway in this cohort:

a. associations of size at birth with brain reserve and cognitive reserve
b. associations of brain reserve and cognitive reserve with cognitive function in late life
c. the effect of adjusting for brain reserve and cognitive reserve in regression models of birth size as predictors of late life cognitive function.

7.6.1 Associations of size at birth with indicators of brain reserve and cognitive reserve (table 7.10)

There was a positive correlation between brain reserve (adult head circumference) and cognitive reserve (attained educational level of the participants): correlation coefficient=0.2, p<0.001. As expected, men and women with larger size at birth had higher brain reserve as adults, though the association of length at birth with adult head circumference was of borderline significance.

Table 7.10 Associations of size at birth with adult head circumference and education

Predictor (Size at birth)	**Head circumference** (current) (cms) β (95%CI)*	**p**	**Education** (per level)** β (95%CI)*	**p**
Birth weight (kgs)	0.87 (0.62, 1.12)	**<0.001**	0.29 (0.01, 0.56)	**0.04**
Length at birth (cms)	0.03 (-0.00, 0.07)	0.07	0.02 (-0.01, 0.06)	0.24
Head circumference (cms)	0.08 (0.01, 0.15)	**0.02**	-0.00 (-0.08, 0.07)	0.92
Ponderal index (kgs/m^3)	0.03 (0.01, 0.05)	**0.01**	0.00 (-0.02, 0.03)	0.63

* Mixed regression analyses adjusted for age, sex and sibship in which all exposures were treated as continuous variables.
**Educational level 0=illiterate, 1=primary, 2=secondary, 3=preuniversity, 4=college, 5=graduate, 6=postgraduate.

In addition, those who were heavier at birth also had higher attained educational levels, a proxy for cognitive reserve. However, other measurements of size at birth were unrelated to cognitive reserve.

7.6.2 Associations of brain reserve and cognitive reserve with cognitive function in late life (table 7.11)

As expected, men and women with larger head circumference as adults (brain reserve) and attained educational level (cognitive reserve) had higher composite cognitive scores in late life.

The above analyses (in section 7.6.1 and 7.6.2) indicated that brain reserve and cognitive reserve were related to both birth weight and composite cognitive score in late life, potentially mediating the association of birth weight with late life cognitive function. The

mediating effect of brain reserve and cognitive reserve on the associations of birth size with cognitive function was further explored in a regression model in section 7.6.4

Table 7.11 Associations of brain reserve and cognitive reserve with cognition in late life

Predictor	**Composite cognitive measure in late life** (SD)		
	β*	95% CI	p
Current head circumference (cms)	0.06	(0.01, 0.10)	**0.02**
Education (per level) **	0.30	(0.26, 0.33)	**<0.001**

* Mixed regression analyses adjusted for age, sex and siblingship in which exposures were treated as continuous variables
** Education level 0=illiterate, 1=primary, 2=secondary, 3=pre university, 4=college, 5=graduate, 6=postgraduate.

7.6.3 Interaction between birth weight and cognitive reserve (education) for cognitive outcomes (table 7.12)

I examined for potential interaction between birth weight and cognitive reserve (education) for cognitive outcomes, testing the hypothesis that the negative impact of birth weight on composite cognitive score in late life would be greater in those with lower attained education. There were no significant interactions between birth weight and education for cognitive outcomes.

Table 7.12 Interaction between birth weight and education for cognitive outcomes in late life

Cognitive Outcomes	**Birth weight** (SD) Education ≤ 10 years			**Birth weight** (SD) Education >10 years			**Interaction**
	β*	95% CI	p	β*	95% CI	p	p
Global cognition (SD)	0.12	(-0.06, 0.29)	0.18	0.11	(0.03, 0.18)	**0.004**	0.91
Verbal Fluency (score)	1.09	(0.32, 1.86)	**0.006**	0.29	(-0.01, 0.60)	**0.06**	0.06
Immediate recall (score)	0.37	(-0.43, 1.17)	0.36	0.13	(-0.18, 0.44)	0.41	0.58
Delayed recall (score)	-0.04	(-0.41, 0.34)	0.85	0.10	(-0.06, 0.26)	0.23	0.54
Composite cognitive score (SD)	0.14	(-0.04, 0.33)	0.14	0.08	(0.01, 0.16)	**0.03**	0.57

***Regression analysis

Similarly, there was no interaction between birth weight and brain reserve (adult head circumference) for cognitive outcomes (data not shown).

7.6.4 Regression model examining the effect of adjusting for brain reserve and cognitive reserve on the associations of birth size with cognition in late life (table 7.13)

Adjusting for brain reserve or cognitive reserve separately or together resulted in a marginal attenuation of the association between birth weight and composite cognitive score in late life, which remained significant. The association of length at birth with late life composite cognitive score was attenuated, and not significant after adjusting for brain reserve or cognitive reserve or both together. The effect size of the association of birth weight with composite cognitive score in late life almost reduced by a third after adjustment for participants' brain development in early life and childhood (head circumference) and cognitive capacity (attained level of education). This analysis indicated that the association of birth weight with cognitive function may have been partly mediated by brain reserve and cognitive reserve in this cohort. In summary, analyses in section 7.6, support the DOHaD cognitive reserve hypothesis of cognitive ageing in the MYNAH cohort.

Table 7.13 Mixed regression models examining the associations of size at birth with cognition in late life

	Composite cognitive score in late life (SD)			
Predictor	**Model 1**	**Model 2**	**Model 3**	**Model 4**
Size at birth	β (95%CI) p	β (95%CI) p	β (95%CI) p	β (95%CI) p
Birth weight	0.29	0.24	0.21	0.20
(kgs)	(0.12,0.46)	(0.06,0.42)	(0.06,0.36)	(0.05,0.36)
	0.001	**0.008**	**0.005**	**0.009**
Length	0.02	0.02	0.01	0.01
(cms)	(0.00,0.05)	(-0.00, 0.04)	(-0.00, 0.03)	(-0.0,0.03)
	0.04	0.11	0.17	0.27
Head circumference	0.02	0.02	0.02	0.02
(cms)	(-0.02,0.07)	(-0.03,0.07)	(-0.02,0.07)	(-0.01,0.07)
	0.34	0.42	0.24	0.20
Ponderal index	-0.01	-0.01	-0.00	-0.00
(kgs/m^3)	(-0.0,0.01)	(-0.02,0.01)	(-0.01,0.01)	(-0.01,0.01)
	0.70	0.72	0.86	0.97

Model 1: Adjusted for age, sex and sibship.
Model 2: Adjusted for age, sex, sibship and adult head circumference.
Model 3: Adjusted for age, sex, sibship and attained educational level of the participants.
Model 4: Adjusted for age, sex, sibship, adult head circumference and attained educational level of the participants.

7.7 Childhood factors and cognitive function in late life

The cohort members were not examined in childhood. Therefore, adult leg length measured in this study and maternal educational level at the time of birth of the participants were considered as proxy indicators of childhood growth and environment respectively. In this

section, I examined the associations of these exposures in childhood with cognitive function in late life.

7.7.1. Associations of childhood factors with composite cognitive function in late life

Better environment and growth in childhood (indicated by maternal educational level and adult leg length) were directly related to higher brain and cognitive function in this cohort. A one category higher in maternal education level was associated with a 0.25 SD higher composite cognitive sore. Similarly, participants with greater leg length as adults had higher composite cognitive score in late life; a 10 cm longer adult leg length was associated with a 0.4 SD higher composite cognitive score. These findings suggest that a better environment and better growth during childhood were related to higher cognitive function in late life.

Table 7.14 Associations of growth and environment in childhood with cognitive function in late life

Predictor	**Composite Cognitive Score** (SD)		
	β*	95% CI	p
Maternal education at the time of participants' birth**	0.25	(0.19, 0.30)	**< 0.001**
Adult leg length (cms)	0.04	(0.02, 0.05)	**< 0.001**

* Mixed effect analyses adjusted for age, sex and sibship
**Education per level: 0=illiterate, 1=primary, 2=secondary, 3=pre-university, 4=college, 5=graduate, 6=postgraduate

7.7.2 Associations of childhood factors with brain reserve and cognitive reserve (table 7.15)

Indicators of better growth and development in childhood were directly related to indicators of higher cognitive and brain reserve in this cohort. I have already identified cognitive reserve as an important associate of late life cognitive function in this cohort (section 7.6.2).

Table 7.15 Associations of growth and environment in childhood with brain and cognitive reserve

Predictor	**Participants' education*** β (95% CI)* p	**Adult head circumference** (cms) β (95% CI)* p
Maternal education at the time of participants' birth ***	0.61 (0.52, 0.70) **< 0.001**	0.07 (-0.02, 0.16) 0.13
Adult leg length (cms)	0.06 (0.04, 0.08) **< 0.001**	0.05 (0.03, 0.08) **< 0.001**

*Mixed effect analyses adjusted for age, sex and sibship
** Education per level: 0=illiterate, 1=primary, 2=secondary, 3=pre-university, 4=diploma, 5=graduate, 6=postgraduate. *

7.7.3 Regression model examining the effect of adjusting for brain reserve, cognitive reserve on the associations of childhood factors with cognition in late life (table 7.16)

Adjustment for brain reserve did not change the effect size or statistical significance of these associations of maternal educational level and adult leg length with late life composite cognitive score (model two). However, there were substantial reductions in the effect size of these associations upon adjustment for cognitive reserve: the effect size of the association of maternal educational level with composite cognitive score reduced by two thirds, while that of leg length with composite cognitive score was halved in model three. There was little further attenuation when both brain reserve and cognitive reserve were adjusted for, in model four. The attenuation of effect size was therefore primarily from attained educational level of the participants and not from adult head circumference.

Table 7.16 Mixed effect models examining the associations of childhood environment with cognitive function in late life

	Composite Cognitive Score (SD)			
Predictors	**Model 1** β (95% CI) p	**Model 2** β (95% CI) p	**Model 3** β (95% CI) p	**Model 4** β (95% CI) p
Maternal education*	0.25 (0.19,0.30) **<0.001**	0.24 (0.19,0.30) **<0.001**	0.08 (0.03,0.14) **0.004**	0.08 (0.03,0.14) **0.003**
Adult leg length (cms)	0.04 (0.02,0.05) **<0.001**	0.04 (0.02,0.05) **<0.001**	0.02 (0.01,0.03) **0.004**	0.02 (0.01,0.03) **0.005**

*Education per level: 0=illiterate, 1=primary, 2=secondary, 3=pre-university, 4=college, 5=graduate, 6=postgraduate
Model 1: Adjusted for age, sex, sibship
Model 2: Adjusted for age, sex, sibship and adult head circumference
Model 3: Adjusted for age, sex, sibship and attained educational level of the participants.
Model 4: Adjusted for age, sex, sibship, adult head circumference and attained educational level of the participants.

This model suggested that the direct associations of growth and environment in childhood with cognitive function in late life may be mediated by cognitive reserve in this cohort.

7.7.4 Regression model examining the effect of adjusting for growth and environment in childhood, brain reserve and cognitive reserve on the associations of birth weight with cognitive function in late life (tables 7.17 and 7.18)

The relationship between birth weight and cognitive function in late life was explored further in a regression model by serially adjusting for the indicators of growth and environment in childhood, cognitive reserve and brain reserve. Adjustment for maternal educational level

produced a marginal reduction in effect size and the association remained significant in model one. However, further adjustment for adult leg length in model two not only reduced the effect size considerably, but also rendered the association non-significant. Additional adjustment for educational level did not change the effect size in model three, though the association of birth weight with late life cognition reached borderline significance. Further adjustment for head circumference in model four halved the effect size further, and the association of birth weight with cognition function remained insignificant.

Table 7.17 Mixed effect models examining the associations of birth weight with cognitive function in late life

	Composite Cognitive Score (SD)			
Predictors	**Model 1**	**Model 2**	**Model 3**	**Model 4**
	β (95% CI) p	β (95% CI) p	β (95% CI) p	β (95% CI) p
Birth weight (SD)	0.10 (0.02, 0.16) **0.008**	0.06 (-0.01, 0.13) 0.11	0.06 (-0.00, 0.12) 0.06	0.03 (-0.04, 0.10) 0.48

Model 1: Adjusted for age, sex, sibship and maternal educational level at the time of birth of the participants.
Model 2: Adjusted for age, sex, sibship, maternal educational level and adult leg length.
Model 3: Adjusted for age, sex, sibship maternal educational level, adult leg length, and attained educational level of the participants.
Model 4: Adjusted for age, sex, sibship maternal educational level, adult leg length, attained educational level of the participants and adult head circumference of the participants.

Estimates of variance in cognitive function that could be attributed to birth weight and other predictors examined in the analyses in table 7.17 are provided in table 7.18.

Table 7.18 Variance in cognitive function in a sequence of regression models

Model Predictors	**Estimates of Variance Components**			
	Explained by Predictors	Within Sibship	Between Sibship	Total
None	0.000	0.799	0.203	1.002
+ age and sex	0.052	0.743	0.207	1.002
+ birth weight	0.068	0.750	0.184	1.002
+ mother's education	0.162	0.743	0.097	1.002
+ leg length	0.181	0.747	0.074	1.002
+ subject's education	0.308	0.694	0.000*	1.002
+ subject's head circumference	0.307	0.695	0.000*	1.002

* Because there is so little suggestion of between sibship variation, the mixed model becomes equivalent to a multiple linear regression model.

The between sibship variance in cognitive function was reduced a little by allowing for birth weight, as siblings were more similar than non-siblings in their birth weight. This variance was greatly reduced by allowing for maternal educational level, a constant for all siblings.

The between sibship variance was eliminated by allowing for the attained educational level of the participants which again was more similar for siblings than non-siblings examined in this study. Finally, the full set of predicators: growth and environment in early life and childhood, cognitive reserve and brain reserve accounted for about 31% (0.307/1.002) of variance in cognitive function in late life in this cohort.

7.8 A lifecourse approach to cognitive ageing in the MYNAH cohort (tables 7.19 and 7.20)

In this section, I examined the associations of factors across the lifecourse with cognitive ageing in the MYNAH cohort, and how much variance in composite cognitive score is explained by including variables from each stage of the lifecourse. A mixed effects regression model was constructed with predictors across the lifecourse to better understand the contributions and salience of each of these to cognitive function in late life in this cohort (table 7.19).

Effect sizes from unadjusted univariate regression analyses for each of the predictors are provided in the second column for comparison with effect sizes from mixed models that were serially adjusted for factors from early life, childhood, adult life and late life. Estimates of variance in cognitive function attributable to the set of predictors examined in each of the model are provided at the bottom of the table.

As expected, there was an attenuation of effect size of birth weight with cognitive function upon adjustments for environment and growth in childhood. However, the borderline significant p values for birth weight right across the table suggest a possible small but consistent effect of birth weight on cognitive function independent of attained education and socioeconomic position in midlife, cardiometabolic factors, stroke and depression in late life, and nutrition and lifestyle factors across the lifespan.

Participants who were younger and women (compared to men) had higher composite cognitive scores in late life, independent of growth and environment in childhood, attained educational level and socioeconomic position in midlife, cardiometabolic factors, stroke and depression in late life, and nutrition and lifestyle factors across the lifespan.

Table 7.19 A mixed effects lifecourse model for cognitive ageing in the MYNAH cohort

	Composite cognitive Score (SD)				
Predictor	**Unadjusted (univariate analyses) β (95%CI) p**	**Model 1 β (95%CI) p**	**Model 2 β (95%CI) p**	**Model 3 β (95%CI) p**	**Model 4 β (95%CI) p**
Birth weight (SD)	0.10 (0.03, 0.18) **0.008**	0.12 (0.05, 0.19) **0.001**	0.06 (-0.01, 0.12) 0.11	0.05 (-0.01, 0.12) 0.10	0.08 (-0.01, 0.18) 0.07
Age (yrs)	-0.03 (-0.04, -0.02) **<0.001**	-0.04 (-0.05, -0.03) **0.001**	-0.03 (-0.04,-0.01) **<0.001**	-0.03 (-0.04, -0.02) **<0.001**	-0.02 (-0.04, -0.00) **0.04**
Sex (0=M, 1=F)	0.28 (0.14, 0.42) **<0.001**	0.33 (0.19, 0.47) **<0.001**	0.57 (0.39, 0.75) **<0.001**	0.54 (0.38, 0.71) **<0.001**	0.65 (0.37, 0.93) **<0.001**
Maternal education*	0.26 (0.20, 0.32) **<0.001**		0.23 (0.17, 0.28) **<0.001**	0.07 (0.02, 0.13) **0.008**	0.08 (0.00, 0.16) **0.04**
Adult leg length (cms)	0.01 (-0.01, 0.02) 0.36		0.03 (0.01, 0.04) **<0.001**	0.01 (0.00, 0.03) **0.03**	0.01 (-0.01, 0.03) **0.01**
Education*	0.29 (0.25, 0.33) **<0.001**			0.22 (0.17, 0.27) **0.02**	0.21 (0.15, 0.28) **<0.001**
SLI (score)	0.04 (0.03, 0.05) **<0.001**			0.02 (0.01, 0.03) **<0.001**	0.01 (0.01, 0.02) **0.006**
Metabolic syndrome (0=no, 1=yes)	0.15 (0.00, 0.30) **0.04**				-0.11 (-0.30,0.08) 0.23
Stroke (0=no, 1=yes)	-0.92 (-1.35, -0.50) **<0.001**				-0.68 (-1.21, 0.16) **0.01**
Depression (0=no, 1=yes)	-0.47 (-0.65, -0.29) **<0.001**				-0.04 (-0.28, 0.19) 0.69
Haemoglobin (gms %)	-0.00 (-0.04, 0.04) 0.96				0.06 (0.01, 0.09) 0.09
Smoking (pack years)	-0.01 (-0.01, 0.00) **<0.001**				0.00 (-0.00, 0.00) 0.26
Alcohol (units/week)	-0.00 (-0.00, 0.00) 0.59				-0.00 (-0.00, 0.01) 0.35
Physical activity**	-0.21 (-0.37, -0.04) **0.01**				-0.10 (-0.31, 0.10) 0.33
Marital status (0=married 1= others)	-0.25 (-0.37,-0.13) **0.003**				-0.17 (-0.41, 0.06) 0.15
Estimate of the variance explained by the predictors in each model		**0.08**	**0.19**	**0.33**	**0.41**

Model 1: Adjusted for factors from early life (birth weight), age, sex and sibship.
Model 2: Adjusted for factory from early life (birth weight) and childhood (maternal education, adult leg length) age, sex and sibship.
Model 3: Adjusted for factors from early life), childhood and adult life (SLI and education), age, sex and sibship
Model 4: Adjusted for factors from early life, childhood, adult life and late life factors (metabolic syndrome, stroke, depression, marital status), nutritional and life style factors across the life (haemoglobin, smoking, alcohol and physical activity).
* Education per level: 0=illiterate, 1=primary, 2=secondary, 3=pre-university, 4=college, 5=graduate, 6=postgraduate
** Physical activity: 0=sedentary, 1=mild, 2=moderate, 3=strenuous SLI: Standard of Living Index

In general, the effect size of the association of educational level of the participants with their cognition in late life remained unchanged despite adjusting for factors across the lifecourse. In contrast, the effect size of the association of maternal education at the time of birth of the participants with offspring cognition in late life reduced by two thirds when adjusted for offspring's growth in early life and childhood, and their attained levels of education and socioeconomic position in adult life (model three), with no further reduction after additional adjustment for late life factors (model four).

The direct effect of socioeconomic position on cognition in late life reduced by half in model three, when adjusted for growth and environment in early life and childhood and attained educational level in adult life. There was a further marginal reduction in this effect size in model four (after adjustments for cardiometabolic factors, stroke and depression in late life and nutrition and lifestyle factors across the lifespan), and but the direct association remained significant.

Smoking pack years, haemoglobin and levels of physical activity were inversely and significantly associated with cognition in late life in univariate analyses, but these were unrelated to cognition in mixed models after adjusting for lifecourse factors.

The full set of predictors in this lifecourse model (model four): growth and environment in early life and childhood, attained education and socioeconomic position in adult life and, cardiometabolic factors, stroke and depression in late life, and nutrition - lifestyle factors across the lifespan accounted for about 41% of variance in cognitive function in late life in this cohort.

This lifecourse model indicated that growth and environment in childhood (indicated by maternal educational level and adult leg length), cognitive reserve (indicated by attained educational level), adult socioeconomic position and stroke were independent determinants of cognitive function in late life in this cohort. There was some indication that pre-natal growth (birth weight) had a small independent effect.

After allowing for age and sex, as expected, the highest proportion of variance in composite cognitive score was attributable to attained education (29%), followed by adult socioeconomic position (16%), maternal educational level at the time of their birth (10%), their growth in childhood (10%) and birth weight (8%).

7.9 Discussion

7.9.1 Key conclusions

a. Birth weight and length, crude indicators of growth in fetal life, were positively associated with cognitive function in late life in this cohort, possibly mediated by growth and environment in childhood, and cognitive reserve.

b. Head circumference and ponderal Index at birth were unrelated to cognitive function in late life in this cohort.

c. The association of birth weight with cognitive ability in late life was independent of and not mediated by adult cardiometabolic disorders. There was no evidence to support the DOHaD hypothesis that ***programming*** for cardiometabolic disorders due to reduced pre-natal growth and development had resulted in lower cognitive function in late life in the MYNAH cohort.

d. Birth weight was directly associated with cognitive reserve, and those with higher cognitive reserve had higher cognitive function in late life. The direct association of birth weight with cognitive function in late life was partly attenuated by cognitive reserve, a finding consistent with the DOHaD cognitive reserve hypothesis of cognitive ageing.

e. Growth and environment in childhood (as indicated by maternal educational level and adult leg length), cognitive reserve (indicated by the participants' attained educational level), and adult socioeconomic position were significantly independently positively associated with cognitive function in late life in this cohort. Older age and a history of stroke were associated with lower cognitive function.

7.9.2 Birth size and cognition

Findings from this study are consistent with some previous studies that have tested associations of growth in early life with cognitive ability in childhood, adolescent and young adult populations (Shenkin et al.,2004; Grove et al.,2017). The previous studies that have tested if body size at birth is associated with cognitive ability in older age have, however, produced contradictory findings (Grove et al.,2017; Chapter 3 section 3.5). Lower birth weight was associated was associated with lower cognitive ability in three studies (Erickson

et al 2010; Costa et al.,2011; Raikkonen et al.,2013). In one other study lower bi-parietal head diameter at birth, but not weight, length, ponderal index, head circumference or occipitofrontal head diameter at birth was associated with lower cognitive function in late life (Martyn et al.,1996). Birth weight or length at birth in one study (Shenkin et al.,2009), head diameter at birth in another study (Gale et al.,2003), and head circumference and ponderal index at birth in a study from LMIC -China (Zhang et al.,2009) were unrelated to cognitive abilities in late life. The study by Zhang and colleagues did not report how other measurements at birth: weight or length at birth was related to cognition in late life. Direct comparisons of findings from my study with the above mentioned studies in older populations are, however, complicated by differences in the populations examined, methodology, study design and measurements of cognitive function, as discussed in chapter 3 (section 3.6.3)

7.9.3 Measurements of size at birth and gestational age

It is unclear why only certain measurements of birth size, but not others were related to cognitive abilities in late life in this and other similar studies. Lack of accuracy in measurements of birth size and not adjusting for gestational age are two plausible explanations. Gestational age, as an estimate from the date of last menstrual period was available only for a third of the participants in this cohort, was most commonly reported by mothers whilst in labour, and this was not fully reliable. Therefore, birth weight was not adjusted for gestational age, which may have reduced the specificity of the birth weight as a measure of fetal growth. It was impossible to differentiate the influence of smaller birth size due to intrauterine growth restriction (small for gestational age) or prematurity on cardiometabolic and cognitive outcomes in this study. This, along with lack of accuracy in measurements of head circumference and length at birth, due to the greater technical difficulty of these measurements, the absence of a standard protocol when the measurements were made and rounding off of these measurements by midwives at birth may partly explain the absence of associations of these birth size measures with cardiometabolic and cognitive outcomes in this study. (Nearly 50% of the cohort members had their head circumference measuments rounded off to 13 inches and nearly 30% of them had their measurements of length at birth rounded off to 21 inches). It is also plausible that birth weight may have been more affected by intra-uterine growth restriction than leg length and head circumference in this cohort. The lack of associations of head circumference with cognition may also be due to the fetal brain sparing adaptation effect, relatively little restriction of fetal brain development is known to occur as result intra-uterine growth

restriction, when compared to other organ systems like musculoskeletal growth (Miller et al.,2016).

7.9.4 Measurements of cognitive function

Cognitive decline is thought to begin as early as forty years of age (Singh-Manouex et al., 2012). In this study, the participants were well above the age of 55 yrs, by which cognitive decline may already be evident, and observed associations (or a lack of them) in this study may be due to a horse racing effect (described in chapter 3 section 3.6.1). Therefore, it is possible that in this study, I may have measured cognitive decline than peak cognitive ability of the participants.

The 10/66 battery of cognitive tests, despite its culture and education fair properties, was developed to make an accurate diagnosis of dementia by non-specialists in LMIC settings including south India. Therefore, this was not sophisticated enough to examine several domains of cognitive function in greater detail, such as higher executive function, frontal lobe function and non-verbal memory which have been related to size at birth in several studies (Skogen et al 2013; Raikkonnen et al.,2013; Muller et al.,2014)

7.9.5 Sibship and cognition

Studies from higher income settings have consistently shown that siblings are more similar in cognitive function scores than those who are unrelated (Holmgren et al.,2006). A similar pattern was observed in this cohort, indicating that family configuration and shared environment pre-natally and in childhood had long lasting effect on cognitive function in this cohort. Siblings who were examined in this study were more similar in birth weight and attained educational levels when compared to non-siblings, while educational level of their parents was a constant. This is the first time that influence of sibship on cognitive function has been examined in India. Various theoretical models have offered possible explanations for the effect of sibship on the cognition of an individual in higher income settings. Parental attention, teaching function and intellectual interaction are shared by siblings, but this is known to decrease with birth of each child particularly with shorter birth spacing (Confluence model of Markus & Zajonc, 1977). Similarly, financial and non-financial resources (e.g. education and neighbourhoods) of parents are shared by siblings, the availability of which decreases with increase in family size (Resource Dilution theory of Guo & Van Wey.,1999). The amount, extent and impact of social contact of an individual is dependent on the family size (Social Contact model of Steelman.,1985). Shared genetic factors (Genetic Legacy

model of Grotevant, Scarr, and Weinberg.,1977) are an alternative explanation offered. The above mentioned factors may be relevant to this cohort, but the validity of these theories to my study setting, which is structurally and culturally different to higher income countries, is yet to be established.

7.9.6 Gender and cogntion in late life

Studies have suggested that the cognitive health of women in high income settings is at least as good as that of men or better (Langa et al., 2008; Langa et al.,2009). By contrast, studies of cognitive function in LMIC settings (e.g., China, Latin America and the Caribbean, and Egypt) find that cognitive functioning of women is worse than men, even after adjusting for social, economic, and clinical risk factors (Lei et al 2011; Maurer., 2011; Yount., 2008; Zunzunegui et al.,2009). A few studies of cognitive functioning in India among older adults have shown mixed results regarding gender disparity. One study found that women in the northern state of Haryana did worse than men (Ganguli et al.,1995). Other studies in southern India have not found gender differences in cognitive functioning (Mathuranath et al., 2003, Mathuranath et al.,2007). Gender differences in educational attainment may contribute to disparities in cognitive functioning in developing settings. In my study, women had higher cognitive scores than men and this may be partly explained by higher levels of attained education among women than men in Mysore. (These analyses were done separately by sex, rather than just adjusting for sex in the analyses). It is also hypothesised that women in later life have higher cognitive abilities due to greater amount of exposure to endogenous estrogen. Estrogen exerts potentially helpful effects on brain synapse structure and function in regions such as the prefrontal cortex and hippocampus (Harada et al.,1995). In women, endogenous estrogen exposure occurs mainly during the reproductive phase. Estrogen levels rise during pregnancy, but fall postnatally, particularly with breastfeeding, and are lower after a first pregnancy than in nulliparous women. Earlier menarche and later menopause (hence longer reproductive period), nulliparity or lower parity, older age at birth of first child, and less breastfeeding are therefore proxy indicators of lifetime (Smith et al., 1999).

The hypothesis that estrogen is neuroprotective for women is supported by inverse associations between indicators of lifetime estrogen exposure and late-life cognitive function (Lebrun et al., 2005; Ryan et al.,2009 ; Heys et al., 2011; Hesson.,2012; McLay et al.,2003), and prospective and historic cohort studies indicating adverse cognitive outcomes associated with premature surgically-induced menopause, and premature ovarian failure (Ryan et al.,2014); However, the evidence remains inconclusive. Only three studies of

endogenous estrogen exposure were population-based and effects on cognition were small (Low et al., 2005; Rocca et al.,2014; Ryan et al.,2009); associations with dementia were not replicated in a large Finland registry linkage study (Imtiaz et al.,2014).

Few studies have examined the effects of endogenous estrogen exposure on cognitive decline, incident dementia or Alzheimer's disease). In the population-based Esprit study in France, endogenous estrogen exposure indicators were directly associated baseline cognitive function, but unrelated to cognitive decline at 4 yrs follow up (Ryan et al.,2009). In case-control studies, childlessness was inversely associated with Alzheimer's disease among women but not men (Ptok.,2002) and increasing numbers of pregnancies were associated with Alzheimer's disease, and age of onset among the cases (Colucci.,2006). In a nested case-control study, Alzheimer's Disease risk increased with increasing age at menarche (Paganini-Hili.,1994). The largest and most definitive study to date was carried out in the population-based Rotterdam cohort; 3601 postmenopausal women aged 55 years or older were followed up for a median of 6.3 years (21,046 person years) (Geerlings et al.,2001). Counter to the hypothesis, women with natural menopause and more reproductive years had an increased risk of dementia (adjusted RR for highest versus lowest quarter 1.78, 95% CI confidence interval [CI] 1.12–2.84). The association was modified by Apo e genotype, with a stronger association among Apo e4 carriers, while among non-carriers no association with dementia or Alzheimer's disease was observed (Geerlings et al.,2001). More recently the 10/66 dementia research group found no evidence to support the theory that natural variation in cumulative exposure to endogenous oestrogens across the reproductive period influences dementia incidence in late life in women from China and Latin American countries (n=9428 women mean age 72 yrs) (Prince et al.,2018).

7.9.7 Growth in childhood and cognition in late life

Adult skull circumference and leg length are indicators of brain development (Gale et al.,2004; Werner and Bodin.,2006) and the nutritional environment in early life (Gunnell.,2002; Wadsworth et al.,2002; Bogin and Varela-Silva.,2010) respectively. Skull circumference can be considered a long-term stable marker of early brain development (Gale et al.,2004; Werner and Bodin.,2006). In MYNAH, contemporaneous measurements of head circumference and leg length were directly associated with late life cognition and this is consistent with other studies from higher and lower income countries including India (Kim et al.,2008; Mortimer et al.,2003; Borenstein et al.,2005; Prince et al.,2011).

Of the 12 birth cohort studies examining the birth size-cognition relationship in to late life, only one had direct measurements of growth in the postnatal period and childhood. In this study, among the 931 men from the Helsinki birth cohort, slower growth between birth and two years in weight, height and BMI was associated with lower cognitive ability at 68 years (Raikkonen et al.,2013). Similar to my study, in a small birth cohort study in the UK (n =215), adult head circumference (as an indicator of brain development in childhood) was directly associated with scores on intelligence test in older men and women aged 66-75 yrs (Gale et al.,2003). However, these studies (Raikkonen et al.,2013; Gale et al.,2003) do not report the effect of adjustment for indicators childhood development on the associations of birth size with cognitive function in late life.

7.9.8 DOHaD cardiometabolic pathway of cognitive ageing

There was no evidence to support the DOHaD *programmed* cardiometabolic pathway of cognitive ageing in the MYNAH cohort. Of the twelve birth cohort studies reporting associations of birth size with late life cognition, only three explored confounding effect of a selected cardiometabolic risk factors on this relationship. The direct effect of birth size measures with late life cognition were independent of stroke and coronary heart disease (in Raikkonen et al.,2013), diabetes and hypertension (in Costa et al.,2011) and, diabetes and coronary heart disease (in Hyvarinen et al.,2009). However, these studies were uninformative about the relationship between birth size and the above mentioned cardiometabolic disorders, and were limited to reporting the birth size-cognition associations Unlike this study, none of these twelve birth cohort studies were set up to explore the pathways of cognitive ageing in a manner described in this chapter. Furthermore, this is the only birth cohort study in which midlife cardiometabolic factors were explored as pathway variables.

Those with lower birth weight had higher rates of stroke in late life, and those who were diagnosed with stroke (n=21) had lower cognitive function in late life, independent of socioeconomic position and attained education in this study. Though this provided an indication that negative impact of lower birth weight on late life cognition may have been mediated by stroke in this cohort, there was insufficient power to explore this relationship further. Two previous birth cohort studies, both from higher income settings (the US and Finland) have shown that the direct effect of birth weight on cognition in late life was independent of self-reported stroke (Costa et al.,2011; Raikkonen et al.,2013). These studies were reviewed in detail in chapter 3.

7.9.9 Fetal programming for cardiometabolic disorders

There is consistent evidence for fetal *programming* by under nutrition for adult cardiometabolic disorders from both higher and lower income countries (WHO.,2002). In fact, in a subset of the MYNAH cohort who were examined in adult life (approximately 20 yrs ago), smaller size at birth was related to higher rates of coronary heart disease (Stein et al.,1996). While, shorter length at birth (but not birth weight) was related to diabetes (Fall et al.,1998), size at birth was unrelated to hypertension (Kumaran et al.,2000). In this study, though birth weight was directly associated this higher levels of blood glucose and HDL cholesterol in late life, and inversely with stroke in late life, these associations, even after adjustments for BMI, were only of borderline significance. There was no evidence of fetal programming for cardiometabolic disorders in late life in this cohort.

When a subset of the members of this cohort were first examined between 1991-1993, lower birth weight was related to higher rates of coronary heart disease (52 of the 518 were diagnosed with CHD), independent of BMI and socioeconomic position (Stein et al.,1996). Unlike the previous finding, in a proportion of them (232 of the 518; 9 out of 52 who were diagnosed with CHD in midlife) who were recruited to this study, birth weight was unrelated to coronary heart disease in midlife. Of the 52 who were diagnosed with CHD in midlife, 38 had died and 14 of them were alive when retraced for this study. Of those 14, 9 participated in this study. Insufficient power, mainly losses due to death may have resulted in the lack of association of birth weight with CHD in midlife.

Of the 1069 original cohort members, 189 had died before commencing this study. Those who had died, had higher rates of cardiometabolic disorders, lower levels of education and socioeconomic position, but they were similar in birth weight, when compared to those who were alive (n=720). Of these 720, 522 men and women who participated in this study were heavier at birth, had higher levels of attained education as adults, higher in socioeconomic position in mid- and late life, and had lower rates of cardiometabolic disorders in mid- and late life, compared to those who did not participate (Chapter 5- tables 5.14 and 5.15). These findings indicated that those who had survived since the original study and followed-up in this study were not only heavier at birth, but also had better cardiometabolic health, education and socioeconomic position in mid- and late life. These factors and insufficient power partly explain the lack of associations of birth weight with cardiometabolic disorders in late life in this study.

7.9.10 Cardiometabolic disorders and cognition

BMI, both in mid- and late life was directly associated with cognitive function in late life in the MYNAH cohort. This is in contrast to the findings from a systematic review by Albanese and colleagues (19 studies, n=589,649 participants followed up for up to 42 yrs) that concluded that higher BMI in midlife (age 35 to 65 years) was associated with lower cognitive function in late life (Albanese et al.,2015). Two of the studies in this review were from LMIC settings (Israel and Taiwan), with inconsistent findings. Among the1189 men from the Israel Ischemic Heart Disease Cohort, who were initially examined between 40 to 70 yrs of age, midlife BMI was unrelated to cognitive function measured 35 yrs later (Ravona-Springer et al.,2013).

While, in a retrospective case control study from Taiwan, midlife BMI was directly related to dementia in late life (157 cases vs 628 controls) (Chiang et al.,2007). Similar to the finding in the MYNAH study, and since the publication of the systematic review by Albanese and colleagues, in a large retrospective cohort study of 1,958,191 individuals from the UK Clinical Practice Research Data linkage (45-66 yrs at baseline and a median follow-up of 9.1 yrs), midlife BMI was directly associated with cognitive function and inversely with dementia (Qizilbash et al.,2015). Midlife BMI was not related to cognitive function in late life in several studies (Gustafson et al.,2009; Albanese et al.,2015; Kivipelto et al.,2005).

These conflicting findings appear to be accounted for by: reverse causality, duration of follow-up and confounding effect of accelerated late-life weight loss in the years preceding the clinical onset of dementia, education and socioeconomic position). These studies examining the BMI-cognition relationship have not fully explored the confounding effect of education and socioeconomic position (or changes in socioeconomic position in longitudinal studies) on this relationship. Higher BMI and attained educational levels may be a reflection of higher socioeconomic position as evident in the MYNAH cohort. There are no comparable lifecourse studies examining the associations of BMI and cognition in late life from India.
As expected, diabetes in midlife was inversely associated with cognitive function in late life in this study, consistent with findings from several longitudinal population-based studies from higher income countries (Cheng et al.,2012; Gudala et al.,2013; Roberts et al.,2014; World Alzheimer Report.,2014). However, contrast to a huge body of evidence, diabetes in late life was unrelated to cognitive function in late life in my study. This could be partly attributed to higher levels of BMI, attained education and socioeconomic position in those with diabetes when compared to those without diabetes in this cohort. Similar to findings in this study, diabetes in late life was unrelated to global cognitive function among community dwelling older adults in two studies from India (Tiwari et al.,2012; Raina et al.,2015) and a few studies from higher income countries (Scott et al.,1998; Bourdel-Marchasson et al., 1997; Wu et al.,2003).

In addition to verbal memory, among those with diabetes, non-verbal memory (semantic, declarative and visual memory), executive function, attention and processing speed are the most adversely affected cognitive functions in late life. (Saczynski et al.,2008; Yeung et al., 2009; Gregg et al.,2000; Fontbonne et al 2001; Kanaya et al.,2004). Of the different types of memory, only verbal memory was examined in this study, executive function, attention and processing speed were not measured by the 10/66 battery of cognitive tests.

The negative effect of diabetes on cognition in known to be higher among those with longer duration of diabetes, poor glycaemic control (as indicated by HBA1C levels), frequent episodes of hypoglycaemia, and in those with white matter changes in the brain (Bourden-Marchasson et al.,2010). The duration of diabetes was self-reported and was not reliable (of those with diabetes in this cohort, 25% (84) were newly diagnosed in this study). Information about these additional risk factors for lower cognition in those with diabetes: glycaemic control, hypoglycaemia or cerebrovascular brain changes were not collected in the MYNAH study. These are the possible reasons for lack of contemporaneous associations of diabetes with cognitive function in my study.

Insulin levels and insulin resistance in midlife were unrelated to cognitive function in late life. However, both were directly related to composite cognitive scores in late life, though the latter associations were of borderline significance. A meta-analysis of 36 studies involving 8931 participants showed that higher contemporaneous insulin levels were associated with lower cognitive function, but there was significant heterogeneity between studies (Pan et al.,2017). More importantly, in 16 of the 36 studies included in this review, insulin levels were directly related to (as in the MYNAH study) or unrelated to cognitive function in late life.

Only two studies have examined the relationship of insulin resistance in midlife with cognitive function in late life: the Atherosclerosis Risk In the Communities cohort in the US (Young et al.,2006) and a longitudinal population-based study in Finland (Ekblad et al.,2017). Findings were similar in both studies, higher fasting insulin levels and insulin resistance in midlife were associated with lower cognitive function tests in late life. In contrast, in the MYNAH cohort, insulin levels and insulin resistance in midlife were unrelated to cognitive function in late life. This is the first study from a LMIC setting to report the lifecourse associations of insulin and insulin resistance with late life cognition.

Diastolic blood pressure in midlife was inversely associated with late life cognition in this study. However, blood pressure in late life and hypertension in both in mid- and late life were

unrelated to cognitive function in late life. Meta-analyses of cross-sectional studies, longitudinal studies and clinical trials including a Cochrane review, have reported inconsistent relationship between hypertension across the lifecourse and cognitive function in later life (Power et al 2011; McGuiness et al.,2009; Shah et al.,2009; Guan et al.,2011; Sharp et al.,2011). Conflicting results from these systematic reviews may be result of heterogeneity across the study designs, patient populations, exposures, outcomes and duration of the follow-up.

Metabolic syndrome in midlife was unrelated to cognition in late life, while metabolic syndrome in late life was inversely related to cognitive function in late life (borderline significance). The relationship between metabolic syndrome and late life cognition has been heavily debated and the findings have been inconsistent and controversial (Bourdel-Marchasson et al.,2010; World Dementia Report.,2014).

In a systematic review of 13 longitudinal follow-up studies (n=19,522), metabolic syndrome in midlife and late life were directly related to cognitive function only in those under 60-70 yrs of age, but these associations were of borderline significance (Hao et al.,2011). In a small case-control study (n=100) in Calcutta, those with metabolic syndrome in late life had lower global cognition scores (Ghosh et al.,2015).

Cholesterol levels in midlife (total and LDL cholesterol) were directly related to cognitive function in late life, while cholesterol levels in late life were unrelated to cognitive function in late life. Systematic reviews of prospective studies have found mixed results for the associations of both mid- and late-life cholesterol levels with late life cognition, including no association between cholesterol levels and late life cognition (Anstey et al.,2008; Kivipelto and Solomon.,2006). Similar to the findings in this study, across several studies examining contemporaneous associations of cholesterol and cognition in late life, cholesterol levels were unrelated to cognition in late life (Notkola et al.,1998; Reitz etal.,2004; Mielke et al.,2010; Stewart et al.,2007).

7.9.11 The DOHaD cognitive reserve pathway in the MYNAH cohort

The direct relationship between birth weight and cognitive function in late life in the MYNAH cohort can in part be explained by the cognitive reserve hypothesis. The term *cognitive reserve* refers to a universal finding that those with greater levels of experiential resources (like education, knowledge) in early life and adulthood have higher levels of cognitive function in later life. This may be due to a protective effect of these resources against age

associated changes in cognitive function or merely the persistence differences in individual cognitive abilities since early adulthood (Stern.,2002).

This study provides partial support to the DOHaD cognitive reserve hypothesis in the MYNAH cohort, as only proxy measures of brain and cognitive reserve were explored as pathway variables. In addition, in the absence of measurements of peak cognitive reserve and brain volumes in adult life, and brain pathology in late life, it was not possible to explore the processes that would have contributed cognitive reserve and cognitive ability in late life.

A better test of the DOHaD cognitive reserve hypothesis would have been models that included: direct measurements of growth and development in childhood (e.g. anthropometry, cognitive function and brain volume), of peak cognitive capacity and brain reserve in adult life (cognitive function, brain volume and brain function) and indicators of brain pathology in late life (e.g. brain volume and vascular changes by neuroimaging). None of these were available in this cohort.

Three independent systematic reviews provide robust evidence for the cognitive reserve hypothesis by concluding that attained education level, a proxy for cognitive reserve, was directly associated with cognitive function and inversely with rates of cognitive impairment and dementia in late life, independent of measurements of brain volumes and pathology (Meng and Darcy.,2012; Chapko et al.,2018; Opdebeeck et al.,2014).

7.9.12 Interaction between birth weight and education for cognitive outcomes

In this study, there was no interaction between birth weight and education for cognitive outcomes. This is a rather unusual finding, in the context of widely held conviction that higher educational achievement can compensate for adversities in early life resulting in smaller birth size, by enhancing cognitive reserve, and offering protection from age related brain changes and pathology. However, there is insufficient objective evidence from the literature to support this argument (Chapko et al.,2018). Of the 12 birth cohort studies examining the association of birth size with late life cognition (reviewed in chapter 3), only one study from Finland has demonstrated that the negative impact of lower newborn ponderal index on cognition and brain volume in late life was evident *only* in individuals with lower attained education (Muller et al.,2014).

7.9.13 Causality

Body size at birth and in early childhood are crude proxies of prenatal developmental milieu and early living conditions that are affected by multiple factors with potential long-term neurodevelopmental consequences. An association between birth weight and cognition in late life does not prove causality, and it can be argued that these associations may be a result of several other factors from early life that were not examined in this study like genetic factors, maternal stress and adversities other than under nutrition.

Poor maternal nutrition is a predominant cause for impaired fetal growth in LMIC settings including India (Black et al.,2013). This study specifically examined the effect of fetal programming by under nutrition (crudely indicated by small size at birth), which is just one of the several mechanisms of fetal programming that it known to influence brain and cognitive development in the offspring. They include fetal programming through alterations in the maternal Hypothalamic Pituitary Adrenal (HPA) system, maternal stress and levels of maternal glucose, micronutrients and leptins (Sandman et al.,2011). None of these were explored in this study. However, Fall et al. have proposed that the absence of an inverse association between birth weight and type-2 diabetes (among those who were examined midlife from this cohort), along with a positive association between maternal weight or pelvic size and type-2 diabetes, could indicate that gestational diabetes was an important problem in Mysore even when this cohort was in utero (Fall et al.,1998). Gestational diabetes increases birth weight (‘macrosomia’) and is a strong programming factor for later diabetes. In a population with two common pathologies that both lead to later type 2 diabetes (intra-uterine growth restriction and gestational diabetes) and which have opposite effects on birth weight, the relationship between birth weight and later diabetes would tend to disappear. Alternative explanations for the observed associations (or lack of them) of birth weight with cardiometabolic and cognitive outcomes, for example due to the 'selection' of the participants and ‘measurements' in this study were discussed in earlier sections of this chapter (7.9.2, 7.9.3 and 7.9.7)**.**

Reverse causality is a potential explanation for several contemporaneous associations with cognitive function in this cohort. For example, depression-cognition and physical activity-cognition relationships do not provide any temporal relationship or directionality to these associations.

8. Results: Contemporaneous and lifecourse factors associated with depression in late life

Population based studies with longitudinal follow-up indicate that adversities across life have a cumulative effect on depression in later life (Cole and Dendukuri.,2003). Studies have consistently reported that lower socioeconomic position across the lifecourse is associated with higher rates of depression in late life (Colman and Ataullahjan.,2010). Studies examining the associations of BMI and cardiometabolic disorders with depression have reported inconsistent findings: while some studies have reported direct associations of these with depression, in several studies these were unrelated to depression (Valkanova and Embierer.,2013). Universally, lower educational level is a well established risk factor for depression across all age groups (Chang-Quan et al.,2010). A small number of studies have shown that depression in late life may have origins in early life (Thompson et al., 2001; Osler et al., 2005: Raikkonen et al.,2007). However, birth cohort studies have presented mixed results: currently there is no consensus whether poorer growth in early life, indicated by lower birth weight is associated with depression in later life (Wojcik et al.,2013).

I have explored risk factors across the lifecourse for late life depression in the MYNAH cohort. To achieve this, I examined the associations of:

a. sociodemographics factors in mid- and late life with depression in late life
b. cardiometabolic risk factors in mid- and late life with depression in late life and
c. other factors assessed in late life (genetic, nutritional, anthropometric, lifestyle and endocrine factors) with depression in late life
d. other factors assessed in midlife (nutritional, anthropometric and lifestyle) with depression in late life
e. size at birth, and socioeconomic position in early life with depression in late life.

8.1 Associations of sociodemographics in late life and midlife with depression in late life (tables 8.1-8.3)

As expected, rates of depression increased with increasing age and depression was more common in women than men: 13% of men and 27% of women examined in this study were diagnosed with depression (table 8.1). Those who were widowed or single had higher rates of depression than who were married at the time of the study, independent of educational attainment and socioeconomic position [OR=1.8, 95% CI (1.1, 3.1) p=0.02 for widowed vs married adjusted for attained educational level and Standard of Living Index score].

Educational attainment was inversely associated with depression: 55% of those with less than ten years of schooling had depression in late life: Those with lower socioeconomic position in late life had higher rates of depression in late life: nearly 80% of those with Standard of Living Index scores of less than 40 had depression. Confirming this association participants living in overcrowded (more than 2 people per room) households had higher rates of depression.

Table 8.1 Associations of late life sociodemographic characteristics with depression in late life

Demographic characteristics	**n**	**Depression** yes	**Depression** no	**OR** * (95% CI)	**p**	**p2**
Age (yrs)**	721	63.4 (6.0)	62.1 (5.1)	1.06	**0.001**	**0.01**
55-60 n(%)	274	46 (17)	228 (83)	(1.01, 1.11)		
60-65 n(%)	253	47 (18)	206 (82)			
65-70 n(%)	123	24 (19)	99 (81)			
70-75 n(%)	51	13 (26)	38 (74)			
75-80 n(%)	20	8 (40)	12 (60)			
Male: Female (0=M, 1=F)	721	54:84 13%:27%	354:229 87%:73%	2.30 (1.61,3.39)	**<0.001**	**<0.001**
Marital status n(%)	721					
0= Married	559	85 (15)	474 (85)	1.99	**0.001**	**0.02**
1= Others (widowed, separated or single)	162	53 (33)	109 (67)	(1.31, 3.02)		
Education n(%)	721					
0= Illiterate	22	10 (45)	12 (55)			
1= Primary	95	29 (31)	66 (69)			
2=Secondary	192	37 (19)	155 (81)	0.76	**<0.001**	**0.01**
3=Pre-university	145	33 (23)	112 (77)	(0.67, 0.86)		
4=Diploma	96	12 (12)	84 (88)			
5=Graduate	83	10 (12)	73 (88)			
6=Postgraduate	88	7 (8)	81 (92)			
SLI (score)**	721	33.6 (8.2)	37.7 (7.4)			
0-20 n(%)	14	7 (50)	7 (50)	0.94	**<0.001**	**--**
20-40 n(%)	450	105 (23)	345 (77)	(0.91, 0.96)		
40-60 n(%)	257	26 (10)	231 (90)			
People per room†	702	2 (1, 3)	1.5 (1, 2)			
<1 n(%)	214	33 (15)	181 (84)			
1-2 n(%)	302	55 (18)	247 (82)	1.28	**<0.001**	0.18
2-3 n(%)	112	20 (18)	92 (82)	(1.11, 1.47)		
>3 n(%)	74	23 (31)	51 (68)			

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
** mean (SD) † median (IQR) P2= p values for Odds ratios derived from mixed effects model adjusted for age, sex, sibship and Standard of Living Index (SLI) score.

The per capita income of the households of participants with and without depression was similar. Monthly income of the participants with depression was almost half of those without depression, though this was not statistically significant after adjusting for socioeconomic position. Those who were in paid employment in late life had lower rates of depression. Among those in paid employment, occupational level was inversely associated with depression (table 8.2), but this was not significant after adjusting for socioeconomic position.

Table 8.2 Associations of income and occupation in late life with depression in late life

	n	**Depression** yes		**Depression** no		**OR*** (95% CI)	**p**	**p2**
Per capita income† (1000 INR/mth)	719	3.0	(1.7, 6.5)	5.0	(2.5, 1.0)	1.00 (1.00, 1.00)	0.18	0.40
Income† (lakhs INR/mth)	719	0.06	(0.2, 0.1)	0.12	(0.06, 0.23)	0.56 (0.01, 0.51)	**0.01**	0.06
In paid employment (0=yes, 1=no) n (%)	721					2.07 (1.23, 3.48)	**0.006**	**0.006**
Unemployed	422	107	(25)	315	(75)			
In paid employment	299	31	(10)	268	(90)			
0=Unskilled n		0	(0)	15	(100)	0.66**	**0.03**	0.39
1=Semiskilled		15	(23)	50	(77)	(0.45, 0.97)		
2=Skilled		11	(7)	137	(93)			
3=Professional		5	(7)	65	(93)			

* OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship in which exposures were treated as continuous variables. † median (IQR)
* * OR for occupational level in those who were employed.
p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score. One Lakh = 100,000 INR

Marital status in midlife was unrelated to depression in late life. Similar to socioeconomic position in late life, socioeconomic position in midlife (as indicated by Kuppuswamy score) was inversely associated with depression in late life (table 8.3).

Information related to occupation and income of the participants was not obtained in the initial study, instead the occupation of the main bread winner of the family and total income of the household were recorded. Per capita income in midlife derived from this information, was unrelated to depression in late life.

Table 8.3 Associations of sociodemographic characteristics in midlife with depression in late life

Predictor	n	Depression yes		Depression no		OR (95% CI)*	p	p2
Marital status								
0=Married n (%)	478	89	(19)	389	(81)	1.50	0.27	0.65
1=Others n (%)	44	14	(33)	30	(67)	(0.73, 3.04)		
People per room†	521	2	(1, 3)	2	(1, 2)			
< 1.9 n (%)	184	34	(18)	150	(82)	1.14	0.24	0.16
2-2.9 n (%)	205	36	(17)	170	(83)	(0.91, 1.4)		
3-3.9 n (%)	65	15	(13)	50	(77)			
> 4 n (%)	67	18	(27)	49	(73)			
Kuppuswamy score**	522	34.0	(8.4)	36.7	(7.7)	0.96 (0.93, 0.99)	**0.004**	0.94
< 20 n (%)	14	8	(57)	6	(43)			
20-40 n (%)	237	70	(21)	267	(79)			
> 40 n (%)	171	25	(15)	146	(85)			
Percapita income† (1000 INR/month)	522	0.5	(0.4,1.0)	0.7	(4.3,1.0)	1.0 (0.99, 1.00)	0.10	0.24
< 0.4 n (%)	124	32	(26)	92	(74)			
0.4-0.8 n (%)	205	37	(18)	168	(82)			
0.8-1.2 n (%)	92	20	(22)	72	(78)			
> 1.2 n (%)	101	14	(14)	87	(86)			

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
** mean (SD) † Median (IQR)
p2 = p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

8.2 Associations of cardiometabolic risk factors in late life and midlife with depression in late life (tables 8.4 and 8.5)

Participants with higher levels of blood glucose (at 120 mins) had lower rates of depression in late life, though this was of borderline significance. This was not significant after adjustment for socioeconomic position.

Those with metabolic syndrome in late life had lower rates of depression in late life, while those with higher levels of triglycerides and those who were diagnosed with stroke in this study had higher rates of depression. These associations were independent of socioeconomic position of the participants.

Table 8.4 Associations of cardiometabolic factors in late life with depression in late life								
Predictor	**n**	**Depression** yes		**Depression** no		**OR*** (95% CI)	**p**	**p2**
Fasting glucose (mmol/l) †	713	5.7	(5.3, 6.2)	5.8	(5.4, 6.5)	0.99 (0.93, 1.07)	0.90	0.66
120 mins glucose (mmol/l) †	442	6.9	(5.8, 8.2)	7.4	(5.9, 9.6)	0.91 (0.82,1.01)	0.09	0.12
Diabetes								
0 =no n(%)	374	72	(19)	302	(81)	0.98	0.92	0.48
1= yes n(%)	341	64	(19)	277	(81)	(0.67, 1.43)		
Fasting insulin (pmol/l) †	705	60	(38, 92)	66	(41, 91)	1.00 (1.0,1.0)	0.51	0.09
Insulin resistance†	705	2.9	(1.6, 4.9)	3.1	(1.8, 5.0)	1.02 (0.98, 1.07)	0.30	0.07
Systolic BP (mm of Hg) **	718	135.8	(17.0)	136.4	(18.4)	1.00 (0.99, 1.10)	0.58	0.45
Diastolic BP (mm of Hg)**	718	74.0	(11.8)	74.0	(11.5)	1.01 (1.00, 1.03)	0.21	0.44
Hypertension								
0=no n (%)	274	48	(18)	226	(88)	0.97	0.88	0.99
1=yes n (%)	445	89	(20)	356	(80)	(0.66, 1.40)		
Total cholesterol (mmol/l)**	716	4.6	(1.1)	4.7	(1.1)	0.87 (0.72, 1.05)	0.87	0.12
HDL cholesterol (mmol/l)**	716	1.1	(0.29)	1.1	(0.27)	0.60 (0.26, 1.38)	0.23	0.18
Triglycerides (mmol/l) †	716	1.5	(1.1, 2.1)	1.4	(1.1,1.9)	1.21 (0.98, 1.48)	0.07	**0.03**
LDL cholesterol (mmol/l)*	702	2.7	(0.85)	2.8	(0.86)	0.82 (0.64, 1.04)	0.10	0.07
Metabolic syndrome								
0= no n(%)	263	62	(24)	201	(76)	0.56	**0.003**	**0.04**
1= yes n(%)	458	76	(17)	382	(83)	(0.39,0.82)		
Coronary heart disease								
0= no n(%)	522	92	(18)	430	(82)	1.27	0.26	0.21
1= yes n(%)	199	46	(23)	153	(77)	(0.84,1.92)		

* OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship.
† median (IQR) ** mean(SD) p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

Those with higher levels of fasting blood glucose in midlife had lower rates of depression in late life. However, this association was of borderline significance and was not statistically significant after adjusting for the socioeconomic position of the participants.

Diabetes, insulin levels, insulin resistance, blood pressure and coronary heart disease in both late life and midlife were unrelated to depression in late life.

Table 8.5 Associations of cardiometabolic factors in midlife with depression in late life

Predictor	n	Depression yes		Depression no		OR (95%CI)*	p	p2
Fasting glucose (mmol/l) †	521	4.7	(4.3, 5.4)	4.9	(4.4, 5.5)	0.88 (0.77, 1.01)	0.09	0.15
120 min glucose (mmol/l) †	521	6.2	(5.1, 7.8)	6.3	(5.2, 7.2)	0.99 (0.92, 1.07)	0.86	0.75
Diabetes								
0=no n(%)	457	91	(20)	366	(80)	0.87	0.70	0.99
1=yes n(%)	64	12	(19)	52	(81)	(0.44, 1.74)		
Fasting insulin (pmol/l) †	521	121	(62, 251)	138	(65, 252)	1.00 (1.00, 1.00)	0.66	0.44
Insulin 120 mins (pmol/l) †	521	924	(420, 2184)	1014	(420, 2184)	1.00 (1.00, 1.00)	0.32	0.70
Insulin resistance†	521	49.0	(2.1, 10.9)	5.2	(2.3, 9.4)	1.00 (0.99, 1.01)	0.78	0.26
Systolic BP (mm of Hg)**	522	12.6	(16.6)	127.2	(15)	0.99 (0.97, 1.00)	0.22	0.30
Diastolic BP (mm of Hg)**	522	74.1	(10.9)	75.5	(10.5)	0.99 (0.96, 1.00)	0.27	0.90
Hypertension								
0=no n(%)	428	82	(19)	346	(81)	1.04	0.88	0.29
1=yes n(%)	94	21	(22)	73	(78)	(0.58, 1.87)		
Total cholesterol (mmol/l)**	521	4.8	(1.0)	5.0	(1.1)	0.86 (0.71, 1.08)	0.14	0.29
LDL cholesterol (mmol/l) **	521	3.5	(1.0)	3.6	(1.1)	0.87 (0.71, 1.07)	0.20	0.44
HDL cholesterol (mmol/l)**	521	1.0	(0.25)	1.0	(0.25)	0.76 (0.31, 1.89)	0.76	0.61
Triglycerides (mmol/l) †	521	1.5	(1.1, 2.1)	1.6	(1.1,2.2)	0.93 (0.72, 1.22)	0.93	0.73
Metabolic syndrome								
0=no n(%)	369	72	(20)	297	(80)	0.83	0.47	0.83
1=yes n(%)	152	31	(20)	121	(80)	(0.50, 1.38)		
Coronary Heart Disease								
0=no n(%)	514	100	(20)	414	(80)	1.42	0.64	0.87
1=yes n(%)	9	3	(33)	6	(67)	(0.33,6.06)		

* OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
** mean (SD) † median (IQR)
p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score
LDL: Low density lipoprotein HDL: High density lipoprotein.

8.3 Other factors assessed in late life (genetic, nutritional/anthropometric, lifestyle, endocrine factors and cognitive function) with depression in late life

8.3.1 Genetic factors (table 8.6)

Nearly a quarter of those with Apoε 4 allelic variant were diagnosed with depression in this study. Those with Apoε4 allelic variant had higher rates of depression compared to those with Apoε2 and Apoε3 allelic variants, independent of socioeconomic position and attained education level [OR=1.7 95%CI (1.03, 2.75) p=0.04 after adjusting for both socioeconomic position and education].

Table 8.6 Associations of Apoε allelic variant with depression in late life

Apoε allelic variant	**Depression**			**OR*** (95% CI)	**p**	**p2**
	n	yes	no			
Apoε 4 n(%)	94	26 (28)	68 (72)	1.7	**0.03**	**0.04**
Apoε 2 and 3 n(%)	616	111 (13)	505 (87)	(1.05, 2.75)		

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship Exposure Apoε4 (0=no, 1=yes)
p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

8.3.2 Nutritional and anthropometric factors (tables 8.7 and 8.8)

Anthropometric indicators of childhood growth and development: height and leg length measured in this study, were inversely associated with depression in late life. However, adult head circumference was unrelated to depression (table 8.7). In both men and women, BMI was unrelated to depression, and there was no difference in rates of depression between underweight/normal and overweight/obese groups [20% vs 18% OR=0.7 95% CI (0.4,1.0), p=0.08]. Depression was more common in those who were underweight or obese compared to those who were normal and overweight (table 8.7), but there was no U shaped relationship between BMI and depression in either men or women [OR=1.0 95% CI (1.0,1.0) p=0.37 for the quadratic association of BMI with depression].

Those with greater skinfolds, larger waist circumference and central obesity had lower levels of depression. However, these were not significant after adjusting for socioeconomic position in late life. Fat mass was unrelated to depression, while body fat percentage was directly associated with depression and this was independent of socioeconomic position.

Men and women with greater muscle mass (midarm circumference and lean mass) and hand grip strength in late life had lower rates of depression in late life. While the association of midarm circumference with depression was not significant after adjusting for socioeconomic position, associations of lean mass and grip strength with depression were independent of socioeconomic position.

Table 8.7 Associations of anthropometric measurements in late life with depression in late life

Predictor***	**Depression** yes (n=138)	**Depression** no (n=583)	**OR (95% CI)*** p	**OR (95% CI)**** p
Height (cms)	154.2 (9.1)	159.5 (9.5)	0.95 (0.96, 0.99) **<0.001**	0.96 (0.93, 0.99) **0.01**
Stunting (0=no, 1=yes)	68 (25%)	208 (75%)	1.46 (0.98, 2.19) 0.07	1.24 (0.81, 1.89) 0.31
Trunk length (cms)	67.1 (4.5)	68.9 (4.5)	0.97 (0.93, 1.01) 0.21	1.00 (0.94,1.05) 0.94
Head circumference (cms)	52.7 (1.7)	53.3 (1.7)	0.90 (0.79,1.02) 0.11	0.95 (0.83, 1.08) 0.40
Leg length (cms)	87.3 (6.0)	90.6 (6.3)	0.94 (0.91, 0.99) **<0.001**	0.94 (0.90, 0.98) **0.004**
Weight (kgs)	62.8 (14.3)	67.6 (13.6)	0.95 (0.92, 0.98) **<0.001**	0.99 (0.99, 1.01) 0.94
BMI (kg/m^2)	26.5 (5.9)	26.6 (5.1)	0.97 (0.93,1.01) 0.21	1.00 (0.96, 1.05) 0.92
Waist circumference (cms)	89.6 (13.0)	94.0 (12.0)	0.98 (0.96, 0.99) **0.03**	0.99 (0.97,1.01) 0.40
Central obesity (0=no, 1=yes)	0.90 (17%)	443 (83%)	0.51 (0.34, 0.77) **0.001**	0.65 (0.42, 1.00) 0.05
Sum of skin folds (mms) †	65 (48,77)	64 (49, 77)	0.98(0.96,0.99) 0.01	0.99 (0.98, 1.00) 0.16
Body fat percentage	41.0 (9.7)	35.6 (9.8)	1.06 (1.02, 1.10) **0.003**	1.05 (1.01, 1.10) **0.01**
Fat mass (kgs)	25.8 (9.1)	24.0 (8.4)	0.99 (0.96, 1.02) 0.56	1.01 (0.98, 1.04) 0.51
Adiposity (0=no, 1=yes)	132 (20%)	516 (80%)	2.0 (0.75, 5.26) 0.16	1.81 (0.67, 4.86) 0.24
Lean mass (kgs)	37.1 (10.3)	43.6 (11.1)	0.95 (0.93, 0.97) **0.001**	0.97 (0.94, 0.99) **0.03**
Mid arm circumference (cms)	28.9 (4.4)	29.7 (3.8)	0.95 (0.90, 0.99) 0.05	0.98 (0.93,1.04) 0.53
Grip strength (kgs)	21.9 (6.2)	27.0 (6.9)	0.88 (0.85, 0.92) **0.001**	0.90 (0.86, 0.93) **<0.001**

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
** adjusted for age, sex, sibship and Standard of Living Index. median (IQR)
*** Exposures are in mean (SD) unless stated

Those with lower levels of haemoglobin in late life had higher rates of depression (table 8.8). Though vitamin B12 and folate levels were unrelated to depression, homocysteine levels and hyperhomocysteinaemia were directly related to depression in late life. The direct association of homocysteine levels with depression was independent of socioeconomic position.

Table 8.8 Associations of nutritional status in late life with depression in late life

Predictor	**n**	**Depression** yes		**Depression** no		**OR** (95% CI)*	**p**	**p2**
Hemoglobin** (gms%)	714	12.7	(2.0)	13.5	(2.0)	0.88 (0.78, 0.99)	**0.03**	**0.03**
Anaemia n(%)								
0=no	582	106	(18)	476	(82)	1.25	0.35	0.32
1=yes	132	30	(23)	102	(77)	(0.78, 2.01)		
Vitamin B12 † (pmol/l)	714	248	(145,425)	239	(158,403)	1.00 (1.00, 1.00)	0.89	0.55
B12 deficiency n(%)								
0=no	553	102	(18)	451	(82)	1.28	0.25	0.38
1=yes	161	35	(22)	126	(78)	(0.83, 1.99)		
Folate † (pmol/l)	716	13	(8, 20)	13	(9, 22)	0.99 (0.98, 1.0)	0.12	0.48
Folate deficiency n(%)								
0=no	628	118	(19)	510	(81)	1.32	0.32	0.76
1=yes	88	19	(22)	69	(78)	(0.76,2.28)		
Homocysteine† (micromol/l)	715	17	(13, 23)	17	(13,24)	1.01 (1.01, 1.02)	**0.01**	**0.03**
Hyperhomocysteinaemia								
0=no	275	49	(18)	226	(82)	1.49	0.05	0.17
1=yes	440	88	(20)	352	(80)	(0.99,2.23)		

* OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship in which exposures were treated as continuous variables.
** mean (SD) † median (IQR)
p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

8.3.3 Lifestyle factors (tables 8.9-8.11)

Very few women smoked or drank alcohol, and so the analyses examining their associations with depression in late life were performed only for men (table 8.8).

The amount of consumption of alcohol (units/week) among men was unrelated to depression. Rates of depression were similar between those drinking alcohol at the time of the study and those who were not.

Depression was more common among men who were smoking at the time of this study than non-smokers, independent of socioeconomic position.

Amount of smoking across the lifecourse is best indicated by smoking pack years. There was a borderline significant direct relationship between smoking pack years and depression in late life, but statistical significance was lost after adjusting for socioeconomic position.

Table 8.9 Associations of alcohol and smoking with depression in late life

Predictor (men only)	**n**	**Depression** yes		**n**	**Depression** no		**OR** (95% CI)*	**p**	**p2**
Current alcohol intake status n(%)	54			354			0.79 (0.41,1.50)	0.47	0.38
0= yes		18	(14)		106	(86)			
1= no		36	(13)		248	(87)			
Current alcohol drinking † (units/week)	53	0	(0,2)	350	0	(0,2)	1.02 (0.99,1.05)	0.17	0.15
Current smoking n(%)	54			354			2.34	**0.005**	0.01
0= no		29	(11)		245	(89)	(1.20,4.24)		
1= yes		25	(19)		109	(81)			
Smoking pack years†	53	8.6	(2,33)	350	2.5	(0,20)	1.01 (1.00,1.02)	0.06	0.13

* OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
p2=p values for odds ratios derived from mixed effect model adjusted for age, sibship and Standard of Living Index score. † median (IQR)

Higher levels of physical activity and frequency of physical exercises in late life were associated with lower rates of depression, independent of socioeconomic position (table 8.10).

Those who consumed more fruits and vegetables had lower rates of depression, but this association was not significant after adjusting for socioeconomic position.

Non-vegetarians had higher rates of depression in late life compared to vegetarians, independent of socioeconomic position. Nearly a fifth of non-vegetarians were diagnosed with depression. The relationship of diet with depression should be to be interpreted with caution, a very small proportion of the vegetarians (10/102) were diagnosed with depression in this study. Among the non-vegetarians, frequency of fish or meat consumption was unrelated to depression.

Table 8.10 Associations of physical activity and dietary factors in late life with depression in late life

Predictor	n	Depression yes		Depression no		OR (95% CI)*	p	p2
Physical activity n(%)								
0=Sedentary	3	2	(67)	1	(33)	0.48	**0.008**	**0.01**
1=Mild	27	13	(48)	14	(52)	(0.27, 0.82)		
2=Moderate	586	109	(19)	477	(81)			
3=Strenuous	103	13	(13)	90	(87)			
Physical exercises (times/month) †	721	0	(0,30)	30	(0,30)	0.98 (0.97, 0.99)	**0.001**	**<0.001**
Fruits & veg consumption (servings / 3days) †	721	13	(12,16)	16	(12,16)	0.95 (0.91,0.99)	**0.009**	0.31
Type of diet n (%)								
0=vegetarian	102	10	(10)	92	(90)	2.66	**0.003**	**0.01**
1=non-vegetarian	619	128	(21)	491	(79)	(1.38, 5.1)		
Meat consumption n(%)								
0=Some days	272	58	(21)	216	(79)	0.93	0.64	0.86
1=Most days	252	54	(21)	198	(79)	(0.71,1.02)		
2=Every day	93	16	(17)	77	(83)			
Fish consumption n(%)								
0=Never	48	11	(23)	37	(77)	1.13		
1=Some days	405	79	(19)	326	(81)	(0.85,1.51)	0.39	0.14
2=Most days	130	30	(23)	100	(77)			
3=Every day	36	8	(22)	28	(78)			

* OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship.
†Median (IQR)
p2=p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

In this study sample, compared to vegetarians, the non-vegetarians had lower levels of attained education, socioeconomic position, folate and homocysteine, and higher levels of vitamin B12 (table 8.11). However, the difference in vitamin B12 levels between the groups was not significant after adjusting for socioeconomic position. Haemoglobin levels were similar between vegetarians and non-vegetarians.

Higher rates of depression among non-vegetarians in this cohort may be partly explained by the differences in attained educational levels and socioeconomic position between the groups.

Table 8.11 Education, socioeconomic position and nutritional status of participants by diet

Predictor	n	Vegetarian	Non-vegetarian	p	p2
Education*					
<10 yrs n(%)	117	8 (7)	109 (93)	**0.01**	**0.02**
> 10 yrs n(%)	604	94 (16)	510 (94)		
SLI (score)**	721	39.3 (7.2)	36.5 (7.7)	**0.01**	**--**
Vitamin B12 (pmol/l) †	714	204 (131, 381)	244 (162, 415)	**0.02**	0.12
Folate (nmol/l) †	716	16.5 (12.0, 38.1)	12.2 (8.4, 21.1)	**<0.001**	**0.03**
Homocysteine (nmol/lt) †	715	19.3 (13.6, 25.6)	17.0 (12.6, 23.6)	**0.03**	**0.002**
Haemoglobin (gms%) **	714	13.2 (1.8)	13.4 (2.0)	0.29	0.54

* Chi square test for differences in proportions. ** t-tests for differences in mean
† Mann Whitney U test for differences in median.
p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index (SLI) score

8.3.4 Endocrine factors (table 8.12)

T4 levels were directly associated with depression in late life, independent of socioeconomic position. Levels of T3 and TSH, and hypothyroidism were unrelated to depression in late life in this cohort.

Table 8.12 Associations of thyroid function with depression in late life

Predictor	n	Depression yes		Depression no		OR (95% CI)*	p	p2
T3 nmol/l **	686	1.8	(0.79)	1.8	(0.79)	0.93 (0.71, 1.20)	0.57	0.55
T4 nmol/l **	686	94.0	(29.60)	85.7	(23.87)	1.01 (1.01, 1.02)	**0.002**	**<0.001**
TSH (milliIU/l)†	686	2.1	(1.4, 3.4)	1.8	(1.1, 3.1)	1.03 (0.96, 1.11)	0.34	0.36
Hypothyroidism								
0=no n (%)	686	130	(19)	556	(81)	0.85	0.75	0.78
1=yes n (%)	30	7	(23)	23	(77)	(0.33, 2.23)		

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship.
** mean (SD) †median (IQR)
p2= p values for the odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score
Associations of T3, T4 and TSH with depression excluded those receiving thyroxin supplements.
TSH: Thyroid Stimulating Hormone

8.3.5 Cognitive function (table 8.13)

Participants who were diagnosed with dementia were excluded from the analyses examining the relationship between cognitive function and depression in late life. As expected, those with higher scores across all the cognitive function tests and composite cognitive scores had lower rates of depression in late life. However, the association of immediate recall with depression in late life was not significant after adjusting for socioeconomic position in late life.

Table 8.13 Associations of cognitive scores with depression in late life

Predictor	Depression yes (n=128)		Depression no (n=571)		OR (95% CI)*	p	p2
Global cognition (score)†	28	(26, 29)	29	(28, 30)	0.62 (0.49, 0.77)	**<0.001**	**0.01**
Verbal fluency (score)**	12.5	(3.6)	13.9	(3.9)	0.91 (0.87, 0.96)	**<0.001**	**0.02**
Immediate recall (score)**	15.8	(3.7)	16.6	(3.8)	0.93 (0.88, 0.98)	**0.004**	0.13
Delayed recall (score)**	5.2	(1.9)	5.6	(1.9)	0.84 (0.76, 0.93)	**0.001**	**0.03**
Composite cognitive score (SD)	-0.22		0.13		0.60 (0.48, 0.74)	**<0.001**	**0.004**

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
†median (IQR) ** mean (SD)
p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score
These analyses excluded persons with dementia.

8.4 Associations of other factors assessed in midlife (anthropometry, nutritional and lifestyle factors) with depression in late life

8.4.1 Anthropometry and nutrition in midlife (table 8.14)

As with height in late life, there was a significant inverse relationship between height in midlife and depression in late life. However, this was not significant after adjusting for socioeconomic position.

Other anthropometric measurements (BMI, skinfolds, and waist and hip circumferences) and levels of haemoglobin in midlife were unrelated to depression in late life.

Table 8.14 Associations of anthropometry and haemoglobin in midlife with depression in late life

Predictor	n	Depression yes		Depression no		OR (95%CI)*	p	p2
Height (cms)**	522	156.2	(8.2)	160.4	(9.2)	0.97 (0.94, 1.0)	0.05	0.30
Weight (kgs)**	522	59.6	(12.3)	62.3	(11.8)	0.99 (0.97, 1.0)	0.35	0.70
BMI (kg/m^2)**	522	24.5	(5.0)	24.2	(4.1)	0.99	0.82	0.38
Underweight n (%)	47	14	(30)	33	(70)	(0.93,1.0)		
Normal n (%)	251	40	(16)	211	(84)			
Overweight n (%)	271	33	(19)	138	(81)			
Obese n (%)	53	16	(30)	37	(70)			
Waist circumference (cms)**	522	85.9	(73.6)	87.2	(10.9)	0.99 (0.97, 1.02)	0.65	0.54
Hip circumference (cms)**	522	98.5	(10.9)	97.7	(9.0)	0.99 (0.97, 1.02)	0.66	0.38
Central obesity								
0= no n (%)	224	43	(19)	181	(81)	0.84	0.44	0.84
1= yes n (%)	298	60	(20)	238	(80)	(0.54,1.31)		
Sum of skin folds (mms) †	521	178	(106, 253)	165	(120, 218)	1.00 (0.99, 1.00)	0.88	0.26
Haemoglobin (gms %)**	521	12.1	(1.9)	12.5	(1.7)	1.05 (0.89, 1.25)	0.54	0.43
Anaemia								
0=no n(%)	331	66	(20%)	265	(81%)	0.84	0.44	0.44
1=yes n(%)	190	37	(19%)	153	(80%)	(0.54, 1.31)		

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
** mean (SD) †median(IQR)
p2=p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

8.4.2 Lifestyle factors in midlife (tables 8.15 and 8.16)

A greater amount of time spent playing sports in midlife was associated with lower levels of depression in late life, and this was not significant after adjusting for socioeconomic position of the participants. Amount of time spent walking, cycling and doing labouring work in midlife was unrelated to depression in late life (table 8.15).

Those with a greater frequency of consumption of fresh vegetables in midlife had lower rates of depression in late life, but this was of borderline significance and lost significance after adjusting for socioeconomic position (table 8.16). Other dietary factors (frequency of consumption of meat, fish and dairy products) and, amount of smoking and drinking alcohol in midlife were unrelated to depression in late life. Analyses examining the associations of smoking and alcohol with depression were restricted to men only.

Table 8.15 Associations of physical activities in midlife with depression in late life									
Predictor	**n**	**Depression** yes		**Depression** no		**OR** (95% CI)*	**p**	**p2**
Physical activity n(%)	522					0.92 (0.72, 1.18)	0.52	0.39
0=Sedentary	246	50	(20)	196	(80)			
1=Mild	151	32	(21)	119	(79)			
2=Moderate	76	13	(17)	63	(83)			
3=Strenuous	49	8	(16)	41	(84)			
Walking (kms /day) n(%)	522					0.97 (0.72, 1.30)	0.97	0.67
0=<1 km	192	44	(23)	148	(77)			
1=1-4 kms	242	44	(18)	198	(82)			
2=4-8 kms	84	11	(17)	53	(83)			
3= >8 kms	24	4	(17)	20	(23)			
Cycling (kms /day) n(%)	322					1.23 (0.91, 1.61)	0.14	0.31
0= None	263	52	(20)	211	(80)			
1= <1 km	5	1	(20)	4	(80)			
2=1-4 kms	24	4	(17)	20	(83)			
3= 4-8 kms	18	3	(17)	15	(83)			
4= >8 kms	12	5	(42)	7	(58)			
Sports (hrs/week) †	294	0.0	(0,0)	0.0	(0,0)	1.03 (1.01, 1.05)	**0.03**	0.14
Labour work (hrs/week) †	294	7.5	(0.0,14)	1.0	(0.0,7.0)	0.85 (0.64, 1.1)	0.31	0.31

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
† median (IQR) p2 = p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

Table 8.16 Associations of dietary factors, alcohol and smoking in midlife with depression in late life								
Predictor	**n**	**Depression** yes		**Depression** no		**OR** * (95% CI)	**p**	**p2**
Meat consumption (times/week) †	506	3	(2, 6)	3	(2, 6)	0.98 (0.92, 1.04)	0.52	0.67
Fresh veg consumption (times/week) †	522	14	(13, 23)	15	(10, 21)	0.96 (0.92, 1.00)	0.05	0.24
Dairy products consumption (times/week)†	522	20	(9, 24)	15	(10, 20)	1.0 (0.96, 1.03)	0.91	0.67
Fish consumption (times/week) †	503	0	(0, 0)	0	(0, 1)	0.86 (0.60, 1.24)	0.42	0.54
Alcohol consumption (units/week) †	318	0	(0, 12)	0	(0, 12)	1.01 (0.99, 1.04)	0.24	0.25
Amount of smoking (cigarettes/day) †	318	24	(11, 30)	10	(5, 25)	1.0 (1.00, 1.00)	0.12	0.23

† median (IQR) *OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and SLI. Associations of smoking and alcohol with depression were for men only.

8.5. Associations of size at birth and socioeconomic position in early life with depression in late life

8.5.1 Size at birth (table 8.17)

Birth weight was inversely associated with depression in late life, though this was of borderline statistical significance and not significant after adjusting for socioeconomic position in late life. Other birth measurements were unrelated to depression.

Table 8.17 Associations of parameters of size at birth with depression in late life

Predictor	n	Depression yes		Depression no		OR (95% CI)*	p	p2
Birth weight (kgs) **	721	2.7	(0.4)	2.8	(0.4)	0.67 (0.42, 1.07)	0.09	0.27
Head circumference (cms) **	638	33.4	(1.35)	33.6	(1.7)	0.98 (0.87, 1.10)	0.72	0.99
Length at birth (cms)**	641	47.6	(2.8)	48.1	(3.0)	0.96 (0.90, 1.03)	0.25	0.43
Ponderal index ** (kg/m3)	638	25.4	(4.7)	25.4	(4.9)	1.0 (0.96, 1.04)	0.87	0.95
Low birth weight (<2.5 kgs)								
0=no n (%)	199	41	(21)	158	(79)	0.94 (0.62, 1.42)	0.76	0.89
1=yes n (%)	519	97	(19)	422	(81)			

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
** mean (SD) p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

8.5.2 Maternal age, parity and maternal pelvic measurements (table 8.18)

Maternal age at the time of birth of the participants was inversely associated with depression in the offspring, though this was of borderline significance.

Maternal parity and pelvic measurements at the time of participants' birth were unrelated to depression in the offspring, in late life. Neither linear nor non-linear associations of these exposures with depression were significant (data on quadratic analyses not shown). The lack of associations of maternal pelvic measurements with offspring depression should be interpreted with caution, these measurements were available only for 16% (n=116) of the participants.

Table 8.18 Associations of maternal age, parity and pelvic measurements at the time of participants' birth with depression in late life

Predictor	N	Depression yes		Depression no		OR (95% CI)*	p	p2
Maternal age (yrs)**	721	23.7	(5.8)	25.1	(7.1)	0.97 (0.93, 1.00)	0.06	0.06
Parity†	721	3	(0, 4)	0	(0, 3)	1.12 (0.97, 1.32)	0.12	0.13
Maternal pelvic measurements**								
Intercristal diameter (cms)	116	24.4	(1.4)	22.1	(1.3)	0.95 (0.72, 1.25)	0.71	0.57
Interspinous diameter (cms)	116	21.9	(1.4)	22.1	(1.3)	0.93 (0.66, 1.30)	0.66	0.58
External conjugate (cms)	114	17.9	(1.2)	18.1	(1.3)	1.04 (0.71, 1.50)	0.83	0.60

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
** mean (SD), † median (IQR)
p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score.

8.5.3 Socioeconomic position in early life (table 8.19)

The affluence of the area of residence of parents at the time of participants' birth was unrelated to depression in late life. The educational level of both parents, but only the occupational level of the mothers at the time of participants' birth (indicators of socioeconomic position in early life) were inversely related to depression of the participants, in late life. After adjusting for the socioeconomic position (of the offspring in late life), the associations of: maternal education with depression was not significant, and that of paternal education with depression was of borderline significance, and that of maternal occupation with depression remained significant.

However, it is important to note that, while the associations of parental education with depression were confounded by the attained educational level of the participants [OR=0.9 per level 95% CI (0.8,1.0), p=0.2 for per level of paternal education; OR=1.0 per level 95% CI(0.8,1.2), p=0.7 for per level of maternal education after adjusting for educational level of the participants], the association of maternal occupation with depression was independent of attained educational level of the participants [OR=0.7 per level 95% CI (0.6,0.9), p=0.01 for per level of maternal occupation after adjusting for educational level of the participants].

Table 8.19 Associations of indicators of socioeconomic position at birth with depression in late life

Predictor	N	Depression yes n (%)		Depression no n (%)		OR* (95% CI)	p	p2
Area of residence at birth								
0=Low class	649	119	(18)	530	(82)	1.51		
1=Middle class	72	19	(26)	53	(74)	(0.86, 2.6)	0.15	0.17
Maternal occupation								
0=Unemployed	653	131	(20)	522	(80)			
1=Unskilled	19	3	(16)	16	(84)	0.74		
2=Semiskilled	3	2	(67)	1	(33)	(0.58, 0.95)	**0.02**	**0.01**
3=Skilled	0	0	(0)	9	(100)			
4=Semiprofessional	37	2	(5)	35	(95)			
Maternal education								
0=Illiterate	248	56	(23)	192	(77)			
1=Primary education	172	38	(22)	134	(78)			
2=Middle class	180	31	(17)	14.9	(83)	0.81		
3=High school	82	8	(10)	74	(90)	(0.68, 0.97)	**0.02**	0.23
4=Preuniversity	26	2	(8)	24	(92)			
5=Graduate	11	3	(27)	8	(73)			
6=Postgraduate	2	0	(0)	2	(100)			
Paternal occupation								
0=Unemployed	-	-	-	-	-			
1=Unskilled	66	13	(20)	153	(80)			
2=Semiskilled	80	17	(21)	63	(79)	1.02		
3=Skilled	493	89	(18)	404	(82)	(0.85, 1.23)	0.78	0.53
4=Semiprofessional	71	15	(21)	56	(79)			
5=Professional	11	4	(36)	7	(64)			
Paternal education								
0=Illiterate	137	28	(20)	109	(80)			
1=Primary education	153	42	(27)	111	(73)			
2=Middle class	165	33	(20)	132	(80)	0.81		
3=High school	152	27	(18)	125	(82)	(0.72, 0.91)	**<0.001**	0.06
4=Preuniversity	52	3	(6)	49	(94)			
5=Graduate	38	4	(10)	34	(90)			
6=Post graduate	24	1	(4)	23	(96)			

*OR=Odds ratio derived from mixed effects model adjusted for age, sex and sibship
p2= p values for odds ratios derived from mixed effect model adjusted for age, sex, sibship and Standard of Living Index score

8.6 Summary

8.6.1 Early life

Higher birth weight and maternal age at the time birth of participants were associated with lower rates of depression in late life, but these were of borderline significance. Higher levels of parental education and maternal occupation at the time of birth of participants were associated with lower levels of depression.

8.6.2 Childhood

Those with better growth in childhood, indicated by adult height and leg length had lower rates of depression in late life.

8.6.3 Midlife

Those with higher attained levels of educational and socioeconomic position in adult life had lower rates of depression in late life. BMI and cardiometabolic disorders (insulin resistance, diabetes, hypertension, metabolic syndrome and coronary heart disease) were unrelated to depression in late life. Levels of haemoglobin and, amount of smoking, alcohol intake and physical activity in midlife were unrelated to depression.

8.6.4 Late life

Participants who were married, employed, and of higher socioeconomic position had lower rates of depression in late life. Those who were vegetarians and those with higher levels of haemoglobin had lower levels of depression. Those with higher levels of physical activity had lower levels of depression in late life, while smoking pack years and amount of alcohol intake were unrelated to depression in late life.

BMI, insulin resistance, diabetes, hypertension and coronary heart disease were unrelated to depression in late life. Those with central obesity, metabolic syndrome, lower levels of triglycerides and homocysteine had lower levels of depression in late life in late life. Those without a diagnosis of stroke and those with higher cognitive function and had lower rates of depression.

Those with Apoε 2-3 allelic variant had lower levels of depression compared to those with Apoε4 allelic variant. These findings indicate that factors from early life, through midlife into late life were associated with depression in this cohort, and this was explored further by employing a lifecourse approach in the next section (9.7)

8.7 A lifecourse approach to late life depression in the MYNAH cohort.

In this cohort, prenatal development was best indicated by birth weight, childhood environment by maternal education and adult leg length, and adult life by attained educational level and socioeconomic position. Associations of these, along with key

contemporaneous factors: marital status, metabolic syndrome, homocysteine and haemoglobin with depression in late life were further explored in a mixed model by conducting multivariate regression analyses (section 8.6.3.) Prior to this, I examined for:

a. correlations between these lifecourse predictors for depression in late life and

b. potential interactions between these predictors for depression in late life.

8.7.1 Correlations (table 8.20)

There was a weak positive correlation between indicators of prenatal development (birth weight) and childhood environment (maternal education, leg length and education). Further, these indicators from early life and childhood were positively correlated with attained educational level of the participants and their socioeconomic position in late life.

An interesting observation was that adult leg length, showed a weak but positive correlation with both haemoglobin and homocysteine levels in late life.

There was a modest positive correlation between attained educational level of the participants and their socioeconomic position in late life. Socioeconomic position in late life was weakly and negatively correlated with homocysteine levels, but not with haemoglobin.

There was a weak and positive correlation between education and haemoglobin, but education was not correlated with homocysteine levels and metabolic syndrome in late life. Haemoglobin and homocysteine levels in late life were positively correlated, but this was of borderline significance.

Metabolic syndrome in late life was not correlated with prenatal growth, childhood environment and attained education. It was weakly positively correlated with socioeconomic position in late life.

Marital status was negatively and weakly correlated with leg length, education, socioeconomic position and haemoglobin.

Table 8.20 Correlations between factors from early life, midlife and late life that are known to be related to depression in late life

	Maternal education* coefficient p	Birth weight coefficient p	Adult leg length coefficient p	Education level* coefficient p	SLI coefficient p	Haemoglobin coefficient p	**Homocysteine** coefficient p	**Metabolic syndrome** coefficient p	**Marital status** coefficient p
Maternal education at the time of birth*	1	0.10 **0.004**	0.10 **0.007**	0.49 **<0.001**	0.24 **<0.001**	0.02 0.57	-0.06 0.11	-0.01 0.72	-0.08 **0.03**
Birth weight (kgs)		1	0.24 **<0.001**	0.11 **0.002**	0.12 **<0.001**	0.03 0.33	0.02 0.50	0.04 0.21	-0.03 0.41
Adult leg length (cms)			1	0.24 **<0.001**	0.14 **<0.001**	0.33 **<0.001**	0.14 **<0.001**	-0.03 0.34	-0.32 **<0.001**
Education level of subject*				1	0.44 **<0.001**	0.07 **0.04**	-0.02 0.53	0.01 0.62	-0.15 **<0.001**
Standard of Living Index (score)					1	0.02 0.51	-0.08 **0.02**	0.17 **<0.001**	-0.15 **<.001**
Haemoglobin in late life (gms%)						1	0.07 0.05	-0.02 0.46	-0.15 **<0.001**
Homocysteine (micromol/l)							1	-0.03 0.35	-0.02 0.51
Metabolic syndrome (0=no, 1=yes)								1	-0.02 0.47
Marital status (0=married, 1=others)									1

*Education level: 0-illiterate, 1=primary, 2=secondary, 3=pre-university, 4=college, 5=graduate, 6=postgraduate SLI : Standard of Living Index

8.7.2 Interactions

There were no significant interactions between sex and the following exposures: marital status, education, socioeconomic position, BMI and cardiometabolic factors in mid- and late life for depression in late life. These interactions were examined to test the hypotheses that the associations of the above mentioned exposures with depression would be different between the sexes.

There were no significant interactions between

a. education and following exposures: socioeconomic position, BMI, cardiometabolic disorders in mid- and late life for late life depression.

b. socioeconomic position and following exposures: BMI, cardiometabolic disorders in mid- and late life for late life depression.

The above analyses were conducted to test that hypotheses that the associations of the above mentioned exposures with depression would be different between those with lower and higher attained education, and between those with higher and lower socioeconomic position respectively.

8.7.3 Predictors across the lifecourse and depression in late life (table 8.21)

A mixed effects regression model was constructed with predictors across the lifecourse to better understand the contributions and salience of each of these to depression in late life (table 9.22), and how much variance in rates of depression is explained by including variables from each stage of the lifecourse in this cohort.

Age was directly associated with depression in late life, independent of growth and environment in early life and childhood, attained education and socioeconomic position (model three). The effect size of this association remained unchanged, but lost statistical significance in model four after adjusting for other contemporaneous predictors of late life depression.

Women had higher rates of depression compared to men, independent of growth in early life (model one). This difference between the sexes was not significant after adjusting for growth in childhood (model two), which led the attenuation of the effect size of this association.

Table 8.21 A lifecourse model for depression in late life in the MYNAH cohort

Predictor	**Depression** (0=no 1=yes)				
	Unadjusted/Univariate OR (95%CI) p	**Model 1** OR (95%CI)* p	**Model 2** OR (95%CI)* p	**Model 3** OR (95%CI) * p	**Model 4** OR (95%CI)* p
Age (yrs)	1.05 (1.01,1.08) **0.009**	1.04 (1.01,1.08) **0.02**	1.04 (1.00,1.08) **0.03**	1.04 (1.01,1.08) **0.03**	1.02 (0.97,1.06) 0.38
Sex (0=M, 1=F)	2.34 (1.65,3.47) **<0.001**	2.26 (1.56,3.27) **<0.001**	1.42 (0.88,2.29) 0.15	1.45 (0.88,2.37) 0.14	1.37 (0.60,2.05) 0.35
Birth weight (SD)	0.82 (0.68,1.00) **0.05**	0.85 (0.70, 1.03) 0.09	0.93 (0.76, 1.15) 0.51	0.96 (0.78,1.18) 0.71	1.02 (0.81,128) 0.88
Maternal education (per level) **	0.81 (0.68,0.96) **0.02**		0.85 (0.70,1.02) 0.09	0.99 (0.81,1.22) 0.44	0.93 (0.76,1.14) 0.51
Adult leg length (cms)	0.92 (0.89,0.95) **<0.001**		0.94 (0.90,0.98) **0.004**	0.95 (0.91,0.99) **0.02**	0.95 (0.91,0.99) **0.04**
Education (per level) **	0.73 (0.65,0.83) **<0.001**			0.88 (0.75,1.03) 0.10	0.97 (0.75,1.07) 0.24
SLI (score)	0.94 (0.91,0.96) **<0.001**			0.95 (0.93,0.98) **<0.001**	0.97 (0.94,0.99) **0.03**
Marital status (0=married, 1=others)	2.91 (1.86,4.02) **<0.001**				1.81 (1.12,2.92) **0.01**
Hb (gms%)	0.81 (0.73,0.89) **<0.001**				0.87 (0.76,0.99) **0.03**
Homocysteine (nmol/l)	1.01 (1.00,1.02) **0.01**				1.01 (1.01,1.02) **0.03**
Metabolic syndrome (0=no, 1=yes)	0.64 (0.45,0.92) **0.02**				0.63 (0.42,0.98) **0.04**
Physical activity** (per level)	0.42 (0.24,0.71) **0.001**				0.60 (0.35,1.01) **0.05**
Diet (0=veg, 1=non-veg)	2.40 (1.26,4.57) **0.007**				2.48 (1.31,4.67) **0.005**
Stroke (0=no 1=yes)	6.06 (2.35,15.63) **<0.001**				8.72 (2.69,28.2) **<0.001**
Apoε4 allele (0=no 1=yes)	1.74(1.07,2.84) **0.03**				1.74 (1.03,3.09) **0.04**

* OR=Odds ratios derived from mixed regression analyses

** Education:0=illiterate 1=primary 2=secondary 3=preuniversity 4=college 5=graduate 6=postgraduate.

*** Physical activity: 0=sedentary 1=mild 2=moderate 3=strenuous.

SLI: Standard of Living Index Hb: Haemoglobin

Model 1: Adjusted for age, sex and sibship, and pre-natal factors (birth weight),

Model 2: Adjusted for age, sex and sibship, pre-natal factors and childhood factors (mother education and leg length)

Model 3: Adjusted for age, sex and sibship, pre-natal, childhood, and adult factors (education, SLI),

Model 4: Adjusted for adjusted for age, sex and sibship, pre-natal, childhood, adult life and late life factors (metabolic syndrome, physical activity, diet, homocysteine, stroke and Apoε allelic variants),

There was a negative association of borderline significance of birth weight with depression in model one. However, this was attenuated after adjustment for growth and environment in childhood in model two, and the association was not significant. It is important to note that the effect size did not attenuate further after serial adjustments for factors in adult life and late life. This indicated that the modest effect of birth weight on depression was possibly mediated by growth and environment in childhood.

The inverse associations of maternal education level at the time of birth of the participants, with depression in the offspring was independent of growth in early life (model one) and childhood (model two), though the latter association was of borderline significance, The effect size attenuated with further adjustment for education and socioeconomic position in adult life (model three), and the association of maternal education with depression was not significant. This indicated that the effect of childhood environment on depression in late life may be mediated through attained education and socioeconomic position in adult life in this cohort.

The inverse associations of adult leg length, an indicator of growth in childhood with depression in late life remained significant despite serial adjustment for factors across the lifecourse. Furthermore, the effect size of this relationship remained constant right across the table, indicating that the childhood growth was an independent predictor of depression in late life in this cohort.

Participants with higher attained educational level had lower rates of depression, independent of growth and environment in early life and childhood (model two). The effect size of this association reduced with further adjustment for socioeconomic association in model three, and the relationship was not significant. This indicated that educational level of the participants may be acting through socioeconomic position resulting in lower rates of depression in late life, in this cohort. The inverse associations of socioeconomic position with depression in late life remained significant, with no change in the effect sizes after serial adjustment for factors across the lifecourse.

Contemporaneous predictors were either directly or inversely associated with depression in late life: Participants who were married (compared to those who were widowed) at the time of the study, vegetarians (when compared to non-vegetarians), those with higher levels of physical activity and those with higher haemoglobin concentration had lower rates of depression.

Stroke and homocysteine were directly, while metabolic syndrome was inversely related to depression. Participants with Apoε4 allelic variant, when compared to those with Apoε2 or 3, had lower rates of depression. Furthermore, these associations remained significant without any attenuation in effect sizes, despite adjustments for growth and environment in early life (model one) and childhood (model two), attained education and socioeconomic position in adult life (model three), other contemporaneous factors in late life (lifestyle, nutritional, cardiometabolic factors and stroke) and Apoε4 genotype (model four).

This lifecourse model indicated that growth in childhood, socioeconomic position, marital status, diet, physical activity, haemoglobin, homocysteine, metabolic syndrome, stroke and Apoε allelic variant were independent predictors of depression in late life in the MYNAH cohort.

8.8 Discussion

8.8.1 Key conclusions

a. There was an inverse association of borderline significance between birth weight, a crude indicator of fetal growth, with depression in late life. The association of birth weight with depression was possibly mediated by growth and environment in childhood in this cohort. There was therefore only weak evidence of fetal *programming* by under nutrition for late life depression in the MYNAH cohort.

b. The inverse association of childhood environment (indicated by maternal educational level) with depression in late life was possibly mediated through attained levels education and socioeconomic position of the participants in adult life.

c. Participants with higher levels of attained education had lower rates of depression in late life, independent of growth and environment in early life and childhood. This association was possibly mediated by adult socioeconomic position.

d. Growth in childhood, socioeconomic position in adult life, and marital status, haemoglobin, homocysteine, metabolic syndrome, stroke, physical activity in late life were independent predictors of depression in late life in the MYNAH cohort.

e. Vegetarians had lower rates of depression in late life. However, micronutrients (vitamin B12 and folate) were unrelated to depression in late life.

f. BMI, diabetes, hypertension, insulin resistance and coronary heart disease in mid- and late life were unrelated to depression in late life.

g. The direct association of smoking pack years with depression was confounded by socioeconomic position in late life, while the amount of alcohol intake in mid- and late life was unrelated to depression.

8.8.2 Age, gender and depression

Depression is the most common psychiatric disorder in late life, the prevalence of which is known to increase with age (World Alzheimer's Report.,2014; Grover and Malhotra.,2016). In this study, rates of depression increased with increasing age, independent of attained education and socioeconomic position. As expected, women in this study had higher rates of depression compared to men. A consistent universal finding, including studies from India, is that depression is more common among women and this gender difference in rates of depression persists in to old age (Cole and Dendukuri.,2003; Djernes JK.,2006; Grover and Malhotra.,2015). In general, older women are more vulnerable to depression than men, possibly because they are exposed to multiple physical, economic and social adversities associated with late life depression: longer survival, greater likelihood of widowhood, malnutrition, lower attained education and personal income, less skilled occupations, higher social isolation and greater physical morbidities with resulting functional limitations (Rajkumar et al.,2009; Barefoot et al.,2001; Sonnenberg et al., 2000; Van Grootheestet al.,1999). In the MYNAH study, most women were unemployed, in less skilled occupations when employed, had lower income and lower haemoglobin when compared to men (chapter 5), which may partly explain the gender differences in depression observed in this study. However, men and women were comparable in age, attained educational levels and socioeconomic position, despite which women had higher rates of depression in this study.

8.8.3 Marital status and depression

In the MYNAH study, widowhood in late life was an independent predictor of depression. Universally, marriage is known to provide a range of mental and physical health benefits, longevity and functionality (Perkins et al.,2016; Carr and Springer.,2010; Manzoli et al.,2007; Goldman et al.,1995). Some of the reported mechanisms include: access to resources and support within marriage, strain from widowhood leading to negative impacts and dependence on others, and assortive mating based on health (Koball et al.,2010). Regardless of these mechanisms, several studies, mostly from higher income settings, but

also from India, have reported that those who were widowed had poor physical and mental health related outcomes in late life (including depression), when compared to those who were married, independent of education and socioeconomic position (Carr et al.,2010; Perkins et al.,2016)

In India, with a long tradition of kinship systems, widowhood is a dreaded stage of life, particularly by women. A widowed woman is frequently viewed as a burden. Widowhood for women in India is characterised by financial strain, reduced social support, social isolation and inability to remarry (Sengupta and Agree.,2002; Lamb.,1999). Widowhood for elderly women in India can be a highly stigmatizing experience, for example, it is customary for them to dress in only white or plain clothes, have fewer meals per day, and be excluded from social and family gatherings. Such strict norms, practices and attitudes towards widows often leads to perceived or experienced discrimination, stigma, restricted economic resources, and these may lead to higher rates of depression in later life (Williams et al.,2008; Perkins et al.,2016)

8.8.4 Education and depression

Lower levels of education were associated with higher levels of depression in late life in this study. This is consistent with the findings from several studies in India and from across the world (Grover and Malhotra et al.,2015; Cole and Dendukuri.,2003). In a systematic review of 36 prospective longitudinal studies (n=50,988), those with less education had a higher risk of depression in late life [OR=1.58, 95% CI (1.38-1.82); Relative risk=1.49, 95% CI (1.16-1.91)] (Chang-Quan et al.,2010).

School is the first and the most important socialising institution outside the family. Education itself can augment cognitive skills independently of prior cognitive ability. Schooling not only imparts specific knowledge but also teaches practical skills necessary for employment, refines other cognitive skills, increases opportunities for socialising, and is known to increase levels of self regulation, confidence and motivation (Ross and Mirowsky.,2010). Educational achievement is a readily identifiable credential that promotes selection of an individual into the workforce and determines socioeconomic position as an adult, with significant consequences for health and social outcomes across life. Higher levels of education are known to be protective, particularly in those exposed to adverse environments in early life and childhood, through “resource substitution.” According to this theory, education can compensate for preexisting vulnerabilities to depression by providing the means to access

more health, social, and economic resources (Ross and Mirowsky.,2010). When compared to those from similarly deprived and disadvantaged conditions in early life and childhood, those who attain higher education are more likely to have higher cognitive ability, achieve good employment, financial stability, maintain healthy lifestyle, and have improved access to health facilities and social resources. (Zimmerman and Woolf.,2014). Supporting these theories, in the MYNAH cohort those with higher educational levels had more skilled employment in adult life, and higher cognitive function and socioeconomic position in late life (chapter 5) that may have protected them from depression.

8.8.5 Socioeconomic position and depression

Indicators of lower socioeconomic position across the lifecourse were associated with higher rates of depression in late life, independent of attained educational level of the participants in the MYNAH cohort. These findings are similar to a well-established body of research that has demonstrated inverse and independent effect of contemporaneous socioeconomic position with depression in late life (Cole and Dendukuri.,2003; Lorant et al.,2013). The observations that lower socioeconomic position in early and mid-life were associated with higher rates of depression in late life in this study, support the emerging evidence that socioeconomic adversity experienced in early life and adulthood may contribute to depressive symptoms in late life (Gilman et al.,2003; Chiao and Weng.,2016; Luo and Waite.,2005; Tiffin.,2005; Kahn and Pearlin.,2006)

The association of socioeconomic position across life with depression in late life has been controversial and studies mainly from higher-income settings have been inconsistent in their findings (Cole and Dendukuri.,2003; Lorant et al.,2013). Socioeconomic inequalities in depression are heterogeneous and vary according to the populations examined, diagnostic criteria for depression, indicators chosen to measure socioeconomic position and, contextual and sociocultural features of the study, setting and time of the study (Lorant et al.,2013)

The associations of indicators of lower socioeconomic position in early life with depression in late life in this cohort should be interpreted with caution. Higher parental educational levels at the time of birth of the participants were related to lower rates of depression in late life, but this was possibly mediated by educational level of the participants. Maternal occupational level at the time of birth of birth of the participants was inversely associated with the late life depression in the offspring, independent of the offspring educational level. However, the majority of mothers were not in paid employment at the time of birth of the participants and most of the employed mothers were in low skilled jobs. Above all, the indicators of early life

socioeconomic position in this cohort were obtained either by extraction from the obstetric records and or by recall during the initial household surveys. It is impossible to ascertain how the above mentioned indicators correlate with socioeconomic position of the households in Mysore when participants were born, 55 to 80 yrs ago.

The lifecourse hypothesis of depression proposes that the accumulation of socioeconomic adversities across the life span synergistically leads to social and health inequalities in late life (Colman and Ataullahjan.,2010; Gilman et al.,2003). But, very limited research has examined the how these social factors interact with other factors (most importantly with education, cognition, and life style factors) leading to depression in late life. Reverse causality is a potential explanation of the contemporaneous socioeconomic position with depression in late life. The MYNAH study reports only cross-sectional associations of these exposures with depression, and does not confirm any causality or provide mechanistic explanations for late life depression.

8.8.6 Genetic factors and depression

The aetiology of depression in late life is multi-factorial and involves complex interaction of environmental and genetic factors. Results of genetic studies in relation to late life depression have been inconsistent for several reasons, such as methodological differences in sampling strategies, diagnosis and measurement of depression, and relatively small sample sizes with insufficient power (Levinson.,2006). A systematic review by Tsang and colleagues (Tsang et al.,2017) included 16 studies that examined the associations of Apoε allelic variants with depression in late life. However, when these studies were subject to metanalysis, the between-study heterogeneity was significant, and there were no differences in the rates of depression between the Apoε allelic variants groups. A majority of the studies in this review were among community dwelling Caucasian older adults from higher income settings. This review included a relatively small case-control study in a clinical population from India (the only study from a LMIC setting), that reported higher rates of depression among older adults with Apoε4 allele when compared to others [OR=4.7, 95% CI(1.12-19.79) P=0.04] (Sureshkumar et al.,2012) These associations were not adjusted for potential confounders such as education and socioeconomic position. The authors of this systematic review explored the relationship further, and in the metanalysis of a subgroup of the four studies that provided complete genotype frequencies (366 cases vs 610 controls): the pooled effect size (OR) for the Apoε4 allele compared to the Apoε3 allele was 1.49 (95% CI 1.03–2.17), without significant heterogeneity, and none of the other comparisons (Apoε4 vs Apoε2; Apoε2 vs Apoε3) were statistically significant. To my knowledge, my study is the

largest genetic study of late life depression in India to report significantly higher rates among Apoε4 carriers compared to others, independent of socioeconomic position.

Apoε 4, a susceptibility gene for both depression and dementia, plays an important role in the regulation of synaptic plasticity of hippocampus (Liu et al.,2015). Studies examining genetic risk factors for late life depression are underpowered and or lack replication. Currently there is insufficient evidence to draw any meaningful conclusions on the role of Apoε 4 genotype in the aetiology of depression in late life.

8.8.7 Birth weight, growth in childhood and depression

In this study there was an inverse association of borderline significance of birth weight with depression in late life. Birth cohort studies examining this association have presented mixed results and there is currently no consensus as to whether lower birth weight is associated with higher rates of depression in later life (Wojick et al.,2013). A systematic review by Wojcik and colleagues in 2013 examined the relationship between birth weight and depression in those above 18 yrs of age (Wojcik et al.,2013). All 18 studies included in this review were from higher income settings. The odds of depression were greater for those of low birth weight (<2500 g) compared to those of normal birth weight (>2500 g) or greater [OR=1.15, 95%CI (1.00–1.32)]. However, this association became non-significant after trim-and-fill correction for publication bias [OR=1.08, 95% CI (0.92–1.27)]. No differences in effect size were observed by gender or outcome measure of depression. Of the18 studies in this review, three of these were in adults above 50 yrs of age (Thompson et al.,2001; Raikkonen et al.,2007; Osler et al.,2005).

Men, but not women, exposed in utero to the Dutch famine of 1944–45 during the first trimester were at significantly increased risk of psychoses [OR= 1.54, 95% CI (1.12–2.13)], but not for depression in late life (60-63 yrs), when compared to those who were exposed in second and third trimester (Brown et al.,2000). Famine no doubt represents a complex cluster of exposures, which in the perinatal period could include extreme material deprivation, maternal ill health and severe stress. However, the interpretation of this finding is complex and difficult to generalise to less extreme conditions, and therefore was not included in the systematic review by Wojcik et al (Wojick et al.,2013).

Thompson and colleagues examined the associations of birth weight and growth in childhood (weight at one year) with depression at 68 yrs of age, among 882 men and women from the Hertfordshire cohort in the UK (Thompson et al.,2005). Depression was determined

either by administering the Geriatric Depression scale or the Geriatric Mental State Examination. Current social class, social class at birth, recent bereavement, social isolation and physical illness increased the risk of depression. After adjusting for these and weight at 1 year, the odds ratios for depression among men, but not women, rose incrementally with decreasing birth weight [OR=3.5 95%I CI (1.0,12.8) P=0.007]. There was also a positive association of borderline significance between weight at 1 yr of life and depression in late life (OR=1.18 p=0.05), but this was not significant after adjusting for birth weight. The authors concluded that fetal under nutrition predisposed men of this cohort to depression in late life.

The relationship between size at birth and discharge diagnosis of depression from a psychiatric ward was examined in a cohort of 10,753 male singletons born in Copenhagen, Denmark in 1953 with record linkage (Osler et al 2005). A total of 190 men, corresponding to 1.8% of the cohort, had a discharge diagnosis of depression between 55-58 yrs of age. Birth weight and ponderal index were unrelated to depression, before or after adjustment for social indicators at birth.

Susceptibility to depressive symptoms in late life may relate to shorter length of gestation and not only to fetal growth rate. This was specifically examined among 1371 members of a birth cohort born between 1934 and 1944 at term in Helsinki. Depression was determined by administration of the Beck Depression Inventory and the Center for Epidemiological Studies Depression scale when participants were between 61.5 and 63.4 years (Raikonnen et al., 2007). Weight, length and head circumference at birth were unrelated to depressive symptoms. The results did not change when adjusted for age, gender, gestational age, socioeconomic characteristics (at birth and in adulthood) and BMI in adulthood. Gestational length predicted depressive symptoms linearly and independently of gender and birth weight: per day decrease in gestational length, depressive symptoms scores increased by 0.8-0.9% [95% CI (0.2-1.4) P<0.009). Information about gestational age was available only for less than a third of the MYNAH participants, and therefore the associations of gestational age and of birth weight adjusted for gestational age with depression in late life were not carried out in this chapter.

In this study, adult leg length, a proxy indicator of childhood growth was inversely and independently associated with depression in late life. Weight at 1 yr of age was unrelated to depression in late life, after adjusting for birth weight in the Hertfordshire Cohort in the UK (described above- Thompson et al.,2001). Measurements of growth in childhood: height and weight at 2, 5 and 7 yrs of age were available for the members of the Helsinki Birth Cohort (described above-Raikonnen et al.,2007), but the relationship of these with depression in

late life was not examined. Similarly, two birth cohort studies had measurements of depression in late life: one from Helsinki in Finland with scores on the Becks Depression Inventory (Hyvarinen et al.,2009) when participants were 60-66 yrs, and another from Sheffield in the UK with depression scores derived from the Nottingham Health Profile emotion subscale between 60 to 72 yrs (Gale et al.,2003). However, these studies do not report the associations of size at birth with depression in late life.

None of the birth cohort studies (described in this section and others reviewed in chapter 3) have reported associations of adult leg length as an indicator of childhood growth with later depression. It is difficult to directly compare the findings from the MYNAH study with findings from the other birth cohort studies due to heterogeneity in populations, settings and methodology,particularly relating to measurement of depression. Furthermore, the participants from Dutch Famine Cohort, were exposed to extreme conditions whilst in utero, making it impossible to make any meaningful comparisons.

8.8.8 BMI, Cardiometabolic disorders and depression

In this study, though BMI was unrelated to depression in late life, central obesity was inversely associated with depression. Epidemiological studies of depression and obesity have measured obesity indirectly using BMI instead of assessing true adiposity. Cross-sectional studies have yielded conflicting results, generally along Eastern–Western paradox. Two studies in Asia found that BMI was negatively associated with depression. Obese older adults in China (n = 56,167) were found to be 20% less likely to suffer from depression (Li et al.,2004). A higher BMI was also found to be associated with fewer depressive symptoms in the Singapore Longitudinal Aging Study (n=2604) (Ho et al.,2008). By contrast, large epidemiological studies performed in western societies have found a direct association between BMI and depression among older adults. They include: the Health Plan Study of Women and the National Health and Nutrition Examination Survey in the US, the Antidepressant Response Signature Study in Germany and the Stirling County Study from Canada (Simon et al.,2008; Ma et al.,2010; Klobier et al.,2007; Murphy et al.,2009; Ma and Xiao.,2010).

A number of factors may explain the conflicting findings of cross-sectional studies, including differences in age and sex across the studies, genetic differences, cultural factors, differential effects of elevated BMI and moderating effect of education and socioeconomic position. Older individuals in western societies may be under greater pressure to remain thin when compared to eastern societies like India. Studies from Asian populations, support the

'jolly fat hypotheses - lower depression in those who are obese (Crisp and McGuiness.,1976), while from the Western countries often show the opposite effect. In the MYNAH study, the BMI-depression relationship reflects the confounding effect of socioeconomic position in this setting. Participants from higher socioeconomic position were more adipose, and those who were adipose had lower rates of depression. This is the likely explanation for the opposite effect in high income settings where the confounding structure is different (poorer people are more adipose).

Cardiometabolic disorders and depression are known to have a bidirectional relationship. Those with cardiometabolic disorders are known to have higher levels of physical impairment, limitation of daily activities, reduction in quality of life; higher levels of systematic inflammation, higher levels of homocysteine, endothelial dysfunction, cerebral hypoperfusion and cerebrovascular changes which increase the risk of depression in late life (Lippi et al.,2009; Do et al.,2010). In the opposite direction, depression is associated with: poor health behaviours (i.e., smoking, physical inactivity, caloric intake and poor sleep patterns), central obesity, impaired glucose tolerance and physiological abnormalities, such as activation of the hypothalamic-pituitary-adrenal axis, sympathoadrenal system, and proinflammatory cytokines. These are possible mechanisms leading to higher risk of cardiometabolic disorders among those with depression (Pan et al.,2012; Alzoubi et al.,2018 Nemeroff and Goldschmidt-Clermont., 2012) .

In this study, diabetes (in mid- and late life) was unrelated to depression in late life. Several metanalyses have previously examined the relationship between diabetes and depression (Ali et al.,2006; Gavarad et al.,1993; Anderson et al 2001; Nouwen et al 2010). The earliest of these reviews by Gavarad et al. included 20 studies and was limited to reporting the range of prevalence of depression in those with and without diabetes. The range of the prevalence of depression in those with diabetes was 8 to 27% and in those without diabetes was 5-20%. The effect sizes were not pooled for a summary statistic in this review. The systematic review by Ali et al included 51,331 men and women from ten studies and reported a higher prevalence of depression in those with diabetes compared to those without [17.6 vs. 9.8%, OR=1.6, 95%CI (1.2-2.0)]. The review by Anderson et al included 42 studies, in which the odds of depression in those with diabetes were twice that of the comparison group without diabetes [OR=2.0, 95%CI (1.8-2.2)]. The systematic review by Nouwen et al included 48,808 men and women from 11 studies. Again, depression was more common in those with diabetes [RR=1.24 (95% CI 1.09-1.40)]. In general, these reviews reported an increased risk of depression among those with diabetes, but failed to clarify the temporal relationship of diabetes with depression. Across these reviews, the prevalence of depression in those with

diabetes was significantly higher among women than men, in uncontrolled than in controlled studies, in clinical than in community samples, and when assessed by self-report questionnaires than by standardised diagnostic interviews.

A systematic review by Mezuk and colleagues included studies with a longitudinal follow up design only, to clarify the bidirectional relationship of diabetes and depression (Mezuk et al.,2008). Of 42 potentially eligible studies, 13 met eligibility criteria for depression predicting onset of diabetes, representing 6,916 incident cases. Seven met criteria for diabetes predicting onset of depression, representing 6,414 incident cases. The pooled relative risk for incident depression associated with baseline diabetes was 1.15 (95%CI 1.02–1.30). The pooled relative risk for incident diabetes associated with baseline depression was 1.60 (95% CI1.37–1.88). There was a strong and robust association between depression and incidence of type 2 diabetes, but only a weak relation between diabetes and risk of depression in this review.

All of the above systematic reviews included participants across the age groups, while a systematic review by Valkanova and Embierer included 26 studies from late life only. This study reported a positive association of diabetes with depression in late life [OR=1.51 95% CI(1.30-1.76)]. While there was evidence of publication bias, there was no significant heterogeneity across the studies included in this review (Valkanova and Embierer.,2013).

Studies from these reviews, mostly from higher income setting, identified higher BMI, central obesity, lower education and lower socioeconomic position as important risk factors for depression in those with diabetes. However, in the MYNAH cohort: attained educational level and socioeconomic position were directly related to diabetes inversely with depression, BMI was unrelated to depression and those with central obesity had lower rates of depression. These observations, paradoxical to those observed in higher income settings, may partly explain the lack of associations of diabetes with depression in this cohort. Studies examining the relationship of diabetes and depression in India are limited to reporting rates of prevalence (range 25%-56%) in clinical settings (Madhu et al.,2013; Raval et al.,2010; Siddiqui et al.,2014; Joseph et al.,2013; Thour et al.,2015). There are no community studies examining the relationship of diabetes in mid- and late life with depression in late life India, including the population based 10/66 and WHO SAGE studies of ageing.

In MYNAH, insulin resistance in mid- and late life was unrelated to depression in late life. This finding is supported by a systematic review of case-control, observational and longitudinal studies examining the association of insulin resistance and depression (Kan et al.,2013). Of

the 21 studies reviewed in this study, 18 had appropriate data for the meta-analysis (n= 25,847). The pooled estimate of the mean standardised effect size was 0.19 (95%CI 0.11–0.27) with marked heterogeneity due to differences in methods of assessments in depression and insulin resistance. There was evidence of publication bias, correction of which attenuated the effect size to 0.07 (-0.02 to 0.16) and rendered the association non-significant (P=0.117). Majority of the studies included in this metanalysis (12 out of 18) had participants aged above 50 yrs of age (50-80 yrs). Only one study was from a LMIC setting (China- Pan et al.,2012) and the rest were from higher income countries. Among 3285 men and women from this population-based cross-sectional study (the Nutrition and Health of Aging Population in China Study) those with insulin resistance had higher levels of depression after adjusting for education, socioeconomic position and life style factors: physical activity, smoking and alcohol intake [OR=1.54, 95%CI (1.17-2.04)]. None of the studies included in this systematic review (and since publication of this review) have examined the relationship of midlife insulin resistance and depression in late life.

In my study, metabolic syndrome in late life was associated with lower rates of depression in late life, while metabolic syndrome in midlife was unrelated to depression. Currently, there is no consensus on the relationship between metabolic syndrome and depression. A systematic review by Pan and colleagues included 29 cross-sectional studies (n=155,333): 27 studies reported unadjusted ORs with a pooled estimate of 1.42 [95%CI (1.28–1.57)]; 11 studies reported an adjusted OR with depression as the outcome [OR=1.27 95%CI (1.07–1.57)] and 12 studies reported an adjusted OR with metabolic syndrome as an outcome [OR=1.34 95%CI (1.18–1.51)]. Eleven cohort studies were found (2 studies reported both directions): 9 studies (n=26,936 with 2,316 cases of incident depression) reported an adjusted OR with depression as the outcome [OR=1.49 95%CI (1.19–1.87)]; 4 studies (n=3,834 with 350 cases of metabolic syndrome reported an adjusted OR with metabolic syndrome as an outcome [OR=1.52 95% CI (1.20–1.91)] (Pan et al.,2012). Though the authors concluded that these findings supported a bidirectional relationship between metabolic syndrome and depression, this has to be regarded with caution. Of the 29 cross-sectional studies included in this review: 3 showed an inverse (similar to the MYNAH study), 16 a neutral and the rest a direct association of metabolic syndrome with depression. In the forest plot illustrating the associations of metabolic syndrome with depression in longitudinal studies, the confidence intervals in 9 out of 14 studies crossed the line indicating no effect.

There are limited data examining the relationship of metabolic syndrome to depression in India and other LMICs. In a case control study of a clinical population in Lucknow, India, metabolic syndrome was unrelated to depression (Agarwal et al.,2016). Similar findings were

observed in two cross-sectional studies, one from Turkey (Demicri et al.,2011) and another from Brazil (Vargas et al.,2014).

In MYNAH, hypertension (in mid- and late life) was unrelated to depression in later life, consistent with findings from a systematic review by Valkanova and Embierer. In systematic review of 14 studies (n=20,197) hypertension was not significantly associated with prevalent or incident depression in late life [OR: 1.14 95% CI (0.94–1.40) p = 0.19] (Valkanova and Ebmeieir.,2013). There are no population based studies reporting associations of hypertension with depression in late life in India.

Epidemiological studies of late life depression have consistently reported 2-3 fold higher rates of depression in those with CHD (Rudisch and Nemeroff.,2003; Carney and Freedland., 2008). It was unexpected to find that CHD (both in mid and late life) were unrelated to depression in late life in this cohort. There are no studies in India or from other LMICs examining the relationship between CHD and depression among community dwelling older adults. It is difficult to explain this in the MYNAH cohort. Probable reasons might include: of those with CHD, the ones with severe disease, comorbid depression and higher disabilities may have been lost to follow-up, particularly due to premature death. Among those diagnosed with CHD in midlife, approximately 20 yrs ago, survival up to this follow-up, would suggest that they had recovered well from CHD. The diagnosis of CHD in this study was on based on history, ECG findings and a clinical evaluation. The diagnosis of CHD was not confirmed by more accurate investigations such as stress tests or angiography, resulting in possible under diagnosis of CHD in this study.

As expected, those with stroke had higher rates of depression in this study. This is a universal finding (Robinson and Jorge.,2016) including studies from India (Paul et al.,2013; Bannerjee et al.,2001; Ghosal et al.,2014; Banerjee and Das.,2016: Kaul et al.,2009). Studies from India examining this relationship were limited to clinical settings.

8.8.9 Thyroid function and depression

In this study, participants with higher levels of T4 had lower rates of depression. Elevated T4 levels are likely to be a result of depression (reverse causality). Serum T4 levels in the upper range of normal or slightly higher have been reported in depressed patients as compared to healthy controls (Hage and Azar.,2012). One mechanism explaining the increase in T4 seen in depression is the activation of hypothalamic TRH producing neurons and subsequent increase in thyroid function secondary to the rise in cortisol in those with depression. In addition, it has been shown that elevated serum T4 levels decrease after successful

treatment of depression (Hage and Azar 2012). There have been no studies in India examining the relationship of thyroid function with depression among older adults, for any comparisons.

8.8.10 Lifestyle factors and depression

Lower physical activity was an independent predictor of depression in late life in this cohort. This is consistent with findings from World Health Organization's Study on Global Ageing and Adult Health from 6 LMIC countries including India (Lee et al.,2015; Vancampfort et al., 2018; Koyanagi et al.,2017). A total of 42,469 individuals were examined, and those who were sedentary had higher rates of depression compared to those who were physically active [OR=1.94 95%CI (1.31–2.85)]. The largest proportion of variance in physical activity-depression relationship was explained by mobility limitations, followed by impairments in sleep/energy, pain/discomfort, anxiety, disability, cognition, and problems with vision. Other health behaviors (alcohol consumption, smoking), body mass index, and social cohesion did not influence the physical activity-depression relationship in late life (Vancampfort et al., 2018; Koyanagi et al.,2017).

Smoking pack years was directly related to depression in late life, but this association was probably confounded by socioeconomic position in this cohort. Similar findings were reported in several studies from India (Barua et al.,2010), other LMICs (Lin et al.,2017) and higher income countries (Almeida and Pfaff., 2005; Luger et al.,2014). Among 41,785 men and women from six LMIC settings, including India, tobacco smoking (smoking status, frequency, duration and amount) was directly and significantly associated with depression (Lin et al.,2017).

Amount of alcohol consumption (in mid- and late life) was unrelated to depression in late life in MYNAH. Few studies have examined the relationship between drinking alcohol and depression in late life. While some have shown direct associations of alcohol with depression in late life (Boden and Fergusson., 2011; Kim et al.,2015) others have shown an inverse association (particularly among those with moderate alcohol intake and wine consumption), while in some studies alcohol and depression were unrelated) (Wilson et al., 2018; García-Esquinas.,2018; Graham et al.,2007; Power et al.,1998; Sareen et al.,2004; Skogen et al., 2009; Rodgers et al.,2000). Such controversial and inconsistent findings are due to a wide range of alcohol related exposures (alcohol status, frequency, duration and amount) and ways of ascertainment of depression, duration of follow-up, a possible bidirectional relationship, different confounding structures in different populations in relation

to alcohol consumption and socioeconomic position (Hartka et al.,1991; Brennan et al.,2016; Gea et al.,2012). There is no consensus on the relationship of alcohol intake and depression in later life.

In this study vegetarians had lower rates of depression than non-vegetarians. There are no other studies examining the differences in rates of depression among vegetarians and non-vegetarians in late life in India. There are limited data examining the diet-depression relationship among adults from higher income setting: vegetarians had higher rates of depression compared to non-vegetarians in a large survey of Australian women, Norwegian students and among men from Britain and Germany (Baines et al.,2007; Jacka et al., 2012; Larsson et al., 2002.; Michalak et al.,2012; Hibbeln et al.,2018). In contrast, a small survey of Seventh Day Adventists found no increased risk of depression among vegetarians (Beezhold et al.,2010). Not all diets identified in higher income settings as vegetarian are homogeneous, with some including fish, and some meat, and others excluding eggs and dairy products. It is plausible that differences in socioeconomic position, educational level, economic disadvantage and occupational status, between the vegetarians and non-vegetarians may partly explain the diet-depression relationship. It has been suggested that low levels of omega fatty acids (found in fish) and vitamin B12 (found in red meat) may prevent depression (Grosso et al.,2014; Hallahan et al.,2016; Stanger et al.,2009)

There was no assessments of quality of diet or detailed information about food intake (e.g food frequencies) in the MYNAH cohort: frequency of meat, fish, and dairy consumption in mid- and late life were unrelated to depression, white the direct association of frequency of consumption of fresh fruits and vegetables in late life with depression was probably confounded by socioeconomic position. Two prospective population based studies examined the relationship of dietary patterns and depression in later life: the Nurses Health Study (NHS) in the US (women only n=50,675, age 50-77) and Personality and Total Health Through Life study (PATH) in Australia (n=1437, age 60-64). In both the studies, those with the highest scores on western diet had higher levels of depression compared to those with the lowest scores on western diet, but these association were not significant after adjustment for socioeconomic position (Chocano-Bedoya et al.,2013; Jacka et al.,2014).

Folate is required for the synthesis and release of serotonin and other neurotransmitters, and Vitamin B12 is essential for folate metabolism, serotonin synthesis and myelin sheath formation. Homocysteine is believed to be both cardio- and neuro-toxic, and may be elevated in the absence of adequate B2, B6, B12 or folate (Payne.,2009). In this study, though levels of vitamin B12 and folate were unrelated to depression in late life, higher levels

of homocysteine were directly related to depression. No studies in India have examined this relationship, while studies from higher income settings have reported conflicting results due to differences in assessment methodology of micronutrients, diagnostic criteria used to define their deficiencies and depression, and extent of adjustment of other potential confounders like diet, education, cardiometabolic disorders and socioeconomic position (Payne et al.,2009).

In three population based studies folate levels were inversely related to depression in late life (Sachdev et al.,2005; Ramos et al.,2004; Dimopolos et al.,2007), while five found no significant association between folate levels and depression (Eussen et al.,2002; Lindeman et al.,2000; Penninx et al.,2000; Bjelland et al.,2003 Tiemeier et al.,2002). These studies varied significantly in size (n=66–5984), location (Europe, Australia and North America), depression assessment and age, although no specific factors appeared to differentiate the significant and non-significant findings. Two studies have reported inverse associations of vitamin B12 with depression in late life, independent of cardiovascular disorders and socioeconomic position (Penninx et al.,2000; Bjelland et al.,2003). In contrast, vitamin B12 levels and depression were unrelated in large cross-sectional epidemiological studies in Europe and Australia (Sachdev et al.,2005; Eussen et al.,2002; Bjelland et al.,2003). Higher levels of homocysteine were associated with depression in late life in some studies (Sachdev et al.,2005; de Koning et al.,2016; while they were unrelated in others (Beydoun et al.,2010; Seppala et al.,2013). A small number of randomised trials in younger men and women with depression have shown that folate (Alpert and Mischoulon.,2002) and B12 (Syed et al.,2013) supplementation can effectively reduce depressive symptom severity, while others have not (Bedson et al.,2014).

The contemporaneous associations of lifestyle and nutritional factors with depression can be due to reverse causality. For example, depression in late life is associated with poor dietary intakes, lower physical activity, and an increase in amount of smoking and alcohol intake (Pan.,2010.)

8.8.11 Causality and reverse causality

The majority of the contemporaneous associations of BMI, cardiometabolic disorders, lifestyle factors and nutrition, and cognition with depression in late life in this study should be interpreted with caution, as reverse causality is a possible explanation. In this study, I examined the cross-sectional associations of various lifecourse factors with depression in late life, this does not determine any causality. Different risk factors across the lifecourse are

thought to exert an additive and or an interactive effect in the aetiology of late life depression, In this study, I have not explored any pathways of late life depression and future follow-up studies with repeat assessments for depression will help ascertain the temporal relationship and directionality of these exposures with depression in late life.

9. Discussion

9.1. Summary and key conclusions

9.1.1 Summary

Birth weight, a crude indicator of growth in fetal life, was positively associated with cognitive function in late life in this cohort. This relationship was: independent of cardiometabolic disorders, possibly mediated by growth and environment in childhood and attained educational level of the participants (cognitive reserve).

Participants who were heavier at birth had lower rates of depression in late life. This inverse association was of borderline significance and possibly mediated by growth and environment in childhood.

Growth in childhood (adult leg length) was an independent positive predictor of cognition and negative predictor of depression in late life. Direct associations of the childhood environment (maternal educational level and adult leg length) with cognition were independent of attained educational levels and socioeconomic position of the participants. In contrast, the inverse associations of childhood environment with depression were possibly mediated by the educational level and socioeconomic position of the participants.

Those with higher attained educational levels had higher cognitive function and lower rates of depression in late life, independent of growth and environment in early life and childhood. This relationship of education with cognition was independent of socioeconomic position, while the relationship of education with depression was possibly mediated by socioeconomic position. Those with higher socioeconomic position had higher cognition and lower levels of depression in late life independent of growth and environment in early life and childhood, attained educational level and cardiometabolic disorders

Similar to birth weight, most exposures across the lifecourse that were directly related to cognition were inversely related to depression in late life. They include: maternal education, growth in childhood (adult leg length), attained education and socioeconomic position. Likewise, those with metabolic syndrome in late life and those without a history of stroke had higher cognitive function and lower rates of depression. However, this was not true of BMI and diabetes: while higher BMI was associated with higher cognition in late life, possibly mediated by socioeconomic position, it was unrelated to depression. Though diabetes in

midlife was inversely related to cognition in late life, diabetes (in mid- and late life) was unrelated to depression. Insulin resistance, hypertension and CHD in mid- and late life were unrelated to both cognition and depression in late life.

Cognition and depression in late life in this study were inversely and significantly related to each other. The similarities and differences in the nature of relationship between lifecourse exposures with these mental health outcomes in late life, may partly be due to the confounding structure of BMI, education and socioeconomic position across different stages of the life and, partly due to the complex relationship between depression and cognition in late life. The latter is often termed the depression-dementia paradigm and discussed further in section 9.3.

9.1.2 Key conclusions

This birth cohort study was set out to examine the evidence for fetal programming of cognitive ageing in a South Indian population. Birth weight was positively associated with cognitive function in late life, independent of cardiometabolic disorders and possibly mediated by nutrition and education in childhood. Findings from this study do not support the DOHaD *programmed* cardiometabolic pathway of cognitive ageing, but provide partial support for the DOHaD cognitive reserve hypothesis of cognitive ageing. There was little evidence of fetal programming of late life depression; an inverse association between birth weight and depression was only of borderline significance, with evidence of possible mediation by childhood indicators. Growth and environment in childhood, educational level of the participants and socioeconomic position were independent predictors of cognitive function in late life in this cohort. Body size at birth and in early childhood are indicators of the prenatal developmental milieu and early living conditions that are affected by multiple factors with potential long-term neurodevelopment consequences. Therefore, associations between these pre-natal and childhood indicators and cognition in late life in this study do not prove causality.

9.2 Lifecourse approach to brain ageing

The aim of this study was to examine the relationship between exposures across the lifecourse: early life through midlife into late life with cognitive function and depression in late life. My study was a longitudinal follow-up of a well-established birth records cohort, and the study framework, hypotheses and statistical methods were driven by a lifecourse approach. Lifecourse epidemiology is defined as the study of long term effects on later health or

disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life (Kuh et al.,2003). Application of such a lifecourse framework for examining cognitive ageing and depression in this cohort presented many challenges beyond the study design. A major difficulty was the absence of data from childhood and early adult life, and availability of midlife data only for a subset of the cohort members. Others included analytical problems associated with multiple exposures and outcomes, latent exposures (e.g. proxies for cognitive reserve), missing data (e.g. gestational age), insufficient power in relation to certain important exposures (e.g. stroke) and outcomes (e.g. dementia), and potential for residual confounding.

Reverse causality was a strong possible explanation for many of the cross-sectional contemporary associations of cardiometabolic, life style and nutritional exposures with cognition and depression in late life. This limited my ability to assume causality or define directionality of relationships. While these problems are common to any cohort study, they were particularly relevant for testing lifecourse models of cognitive ageing and late life depression in this study.

9.3 The Depression and Dementia Paradigm

Depression and dementia in late life were two important mental health outcomes examined in this study. The relationship between these is complex, bidirectional, non-linear and age dependent. Late life depression is a well established risk factor for incident dementia (Geerlings et al.,2008; Speck et al.,1995; Green.,2003). Life time or past history of depression is also known to increase the risk of developing dementia in later life, this risk is known to persist even after 10 yrs of remission from depression (Speck et al.,1995). History of depression increases the risk of incident dementia two to three fold, as estimated by a meta-analysis of prospective and case-control studies (Jorm.,2011). It has been suggested that, rather than a prodrome to dementia, depression in late life may be an independent risk factor for Alzheimer's disease (Ownby et al.,2006). This hypothesis is supported by several neuropathological studies demonstrating more amyloid plaques in the hippocampus and tangle formation among patients with Alzheimer's disease who have a lifetime history of depression (Rapp et al.,2006). Prolonged hypercortisolaemina due to hypothalamo-pituitary-adrenal (HPA) axis dysfunction in those with depression may result in hippocampal damage and contribute to white matter changes in the cerebrum that lead to cognitive problems (Ganguli.,2009).

The other way this relationship has been construed is that late life depression may serve as

a prodrome of cognitive decline or represent a pre-dementia syndrome (Brommelhoff et al.,2009). Comorbid cognitive impairment in those with late life depression is a predictor of incident dementia within a few years of diagnosis of depression. Therefore, it is argued that depression in late life may be an early manifestation of the underlying neurodegenerative pathology of dementia. The commonly observed coexistence of dementia and depression in late life may also be due to shared risk factors such as genetic, cardiometabolic, vascular, or environmental determinants (Ganguli.,2009; Panza at al.,2010).

Depression may be a reactive response to the cognitive impairment, particularly in those with insight, and in early stages of dementia (Ganguli.,2009). Comorbid depression is likely to unmask cognitive impairment, and compromise cognitive reserve, resulting in earlier manifestation of dementia (Panza et al.,2010).

Lower cognitive impairment among those with depression can also be due to the anticholinergic property of several antidepressants such as tricyclic antidepressants and selective noradrenaline reuptake inhibitors. Of the 138 men and women diagnosed with depression in my study, only 4 of them were receiving selective serotonin reuptake inhibitors (SSRIs) as antidepressants. SSRIs lack anticholinergic properties and this is an unlikely explanation of the inverse association of cognitive function with depression in this cohort. All of the hypotheses mentioned above are not mutually exclusive and multiple types of interaction may be involved.

9.4 Strengths of this study

9.4.1 Availability of data across the lifecourse

In addition to measurements of size at birth, indicators of socioeconomic position in early life and in midlife were available for the MYNAH participants, which is unusual for cohorts of this age. Detailed data on cardiometabolic risk factors in midlife were available for nearly three quarters (73%) of the study participants. This allowed me to explore the mediating effect of cardiometabolic disorders and socioeconomic position in mid- and late life in regression models examining the associations of birth weight with cognition and depression. Such analyses for mediation/confounding in previous studies were limited to a few contemporaneous cardiometabolic disorders and socioeconomic position indicators, and rarely included exposures from midlife (Chapter 3 table 3.2).

Furthermore, unlike previous studies (reviewed in detail in Chapter 3) which were mostly limited to reporting associations of birth size with cognitive function, this study was specifically designed to explore the different DOHaD pathways of cognitive ageing.

9.4.2 Quality assurance of the study

Findings from the pilot study informed the protocol for conducting cognitive assessments. Physical assessments were conducted according to standarised protocols. I trained and supervised the research assistants in study procedures. I carried out IOV (inter-observer variability) evaluation of research assistants conducting anthropometry, cognitive and physical assessments before, during and towards the end of the study. All equipment was regularly calibrated. Blood tests were conducted at a UKNEQAS accredited laboratory. ECG coding for evidence of coronary heart disease was carried out by an independent trained physician. Data were double entered and cleaned before processing.

9.4.3 Completeness of the data

Another strength of my study was the completeness of the data available for analyses. Birth weight (exposure) and cognition and depression (outcomes) were available for all the 721 MYNAH participants. Almost all participants had agreed for physical health assessments (n=718), blood tests (n=716), genetic tests (n=716) and for an interview of a reliable informant about their cognitive function and mental health (n=720). When the participant was receiving care (any assistance with activities of daily living), a primary caregiver was always interviewed (n=21).

9.4.4 Quality of cognitive and mental health data

In this study, all assessments for cognitive function and mental health were conducted using validated and culturally adapted instruments. Depression was ascertained by a structured mental state examination by administering a standardised diagnostic interview schedule by a trained psychiatrist. The diagnostic schedule utilised a hierarchical algorithm and depression secondary to dementia and other psychotic disorders was not classified as primary depression. The 10/66 diagnostic algorithms for cognitive measures, dementia and depression were run independently by me and a senior data manager from the MRC Lifecourse Epidemiology Unit.

This is the first birth cohort study of ageing in which all participants were examined for concurrent clinical diagnoses of dementia and depression. All previous birth cohort studies of cognitive ageing (reviewed in Chapter three) have reported continuous measures of cognitive function, while some have reported categorical cognitive outcomes like lower cognitive function or cognitive impairment based on cohort specific cut-offs. Unlike this study, none of the previous studies have ascertained if cognitive problems were of the nature or severity warranting a diagnosis of dementia.

9.5 Limitations

9.5.1 Representativeness and generalisability

This cohort was not a true 'population' sample. It was based on all births within a single major hospital during selected years, who were still alive, lived locally and provided sufficient information to be able to match them to their birth records with certainty. Most deliveries at that time took place either at home or at the government hospital in the city. It is not clear what factors influenced these families to choose the Holdsworth Memorial Hospital for delivery. The reputation of the hospital was such that in addition to serving the poor, many wealthy people chose to deliver there. Many babies, especially those with low birth weight would have died in infancy. Those who were matched to their birth records were heavier and longer at birth when compared to all births at the hospital (section 5.2). The sample is therefore unrepresentative of all births in Mysore during this period.

As described in section 4.8, there have been large losses to follow-up since birth, especially between birth and the first adult follow-up, and further since the initial study. Furthermore, the representativeness analyses in section 5.2 indicated that men and women who were heavier at birth, and those with higher levels of education (an indication of cognitive reserve) and socioeconomic status, and with lower rates of cardiometabolic disorders in mid life were more likely to survive, be traceable and take part in the research in late life. Nearly a fifth of the original cohort members, when traced for this study, had died and the cause of death was usually unknown. While it is possible that these losses could have attenuated associations of size at birth with cardiometabolic and cognitive outcomes among the survivors who were examined in this study, they are unlikely to have created spurious associations.

The majority of cohort members who were examined in this study were from lower and upper middle socioeconomic classes. This is explained by the fact that the initial survey was

carried out in relatively poor and middle class areas of the city. The study sample also had a higher percentage of Muslims compared to the rest of the Mysore population. This is due to the fact that the hospital is situated in a predominantly Muslim area. Men and women who participated in this study had higher levels of education and income compared to the general population of Mysore in this age group (Registrar General India.,2011). My study sample is therefore unrepresentative of older adults currently living in the city of Mysore.

9.5.2 Insufficient information from birth records

The early life information available in the birth records was sub-optimal in many ways. Gestational age estimated from the mothers' last menstrual period (LMP) was available only for a third of the MYNAH participants. Therefore, it was not possible to distinguish if low birth weight was due to prematurity or intra-uterine growth restriction in this cohort.

Maternal weight and pelvic diameters at the time of birth of participants, the only direct indices of maternal nutrition for this cohort, were available for only a few (16%). In the initial study, these were directly associated with diabetes in the offspring during adult life (Fall et al.,1998). Measurements of maternal pelvic size were unrelated to cognitive function or depression in the offspring in late life in this study, while greater mean of intercristal, interspinous and external conjugate diameters of maternal pelvis was associated with significantly higher scores on Mini Mental State Examination scores in a birth cohort study of 346 older men and women from Bergen, Norway (Skogen et al.,2013).

The Mysore birth records did not have information about placental size or weight. Placental weight is thought to be related to childhood neurocognitive development (Sferruzzi-Perri and Camm.,2016), though it was unrelated to cognitive function in late life in a small birth cohort study (n=128, aged 75-81yrs) in Edinburgh, UK (Shenkin et al.,2007).

9.5.3 Lack of information about childhood

There were no direct measures of growth in the post-natal period or in childhood for the MYNAH participants. These are known to be related to cognitive function in late life (Raikkonen et al.,2013; Gale et al.,2003). Better nutrition in childhood is thought to mitigate the adverse effect of fetal under nutrition on neurocognitive disorders in late life (Prince et al.,2018)

Leg length and head circumference measured in late life, as proxy indicators of childhood growth and development, were directly associated with cognitive function and inversely with

depression in this study, similar to findings from other lower and middle income countries like Mexico, Brazil, Peru and China (Prince et al.,2011; Prince et al.,2018). Age related muscle wasting and osteoporotic changes in late life can result in reduction of head circumference and shortening of leg length (Prince et al.,2018). The reliability and stability of these proxy indicators of childhood growth, measured for the first time in late life is unclear even in high income countries.

9.5.4 Insufficient information from adult life

The cohort members were middle aged (40 to 67 yrs) when examined in the initial study, and this did not include measurements of cognitive function or depression. If measurements of cognitive function were available in mid life, these would have served as a better indicator of peak cognitive ability to explore the DOHaD pathways of cognitive ageing. Instead, I have used attained educational level and head circumference of the participants (recorded or measured in this study) as proxy indicators of cognitive reserve and brain reserve respectively, to explore the DOHaD cognitive reserve pathway.

Levels of attained education, occupational complexity and social functioning are considered reliable indicators of cognitive reserve in high income countries (Meng and Darcy.,2012; Chapko et al.,2017). Education is the most widely available and researched measure of cognitive reserve. Most women from this cohort were homemakers. Information about occupation of the subjects was not obtained in the initial study. Measurements of occupational complexity or social functioning were not available from the current study.

Like all residents of Mysore, the cohort members had access to free schooling and higher education. However, this would not have been availed uniformly, particularly by women, even though the Maharajas of Mysore had built several educational institutions that were for 'women only'. In general, women would be asked to stop schooling after class 10 and be given away in arranged marriages at an early age. Women very rarely pursued higher education after marriage. Due to poverty many, particularly men from this cohort, would have discontinued education and taken up jobs to support their families. These socio-cultural factors would have influenced the amount of time spent in formal education by cohort members. Therefore, use of attained educational level as a proxy for cognitive reserve in this cohort was far from ideal, particularly when most participants (85%) of this cohort were bilingual. A greater number of languages spoken is known to be associated with greater neural and cognitive reserve, independent of educational levels (Gold.,2015).

The implications of the above limitations have to be thought through in interpreting the results of this study and generalising the findings beyond the study setting. Despite these limitations, this was a large sample of community dwelling healthy older men and women. Very few (5%) of the surviving cohort members declined to participate. None of the cohort members were excluded from this study. Those examined in this study were similar in height but greater in weight compared to other urban Indian populations (details in Chapter 5 section 5.1.3) (WHO SAGE India National Report.,2013). The prevalence of diabetes was much higher in the study sample than in the general population, while the prevalence of other cardiometabolic disorders, dementia and depression were similar to rates obtained in other populations in urban India (details in Chapter 5 sections 5.1.5 and 5.1.6).

9.5.5 Robustness of the 10/66 battery of cognitive tests

The 10/66 battery of cognitive tests were developed for diagnosis of dementia in lower and middle income countries by non specialists- it was not designed for neuropscyhological assessments particularly for healthy community dwelling older adults. As it was culturally adapted for use in settings with low literacy levels several cognitive domains are not evaluated by the 10/66 battery. They include non-verbal memory (semantic, declarative and visual memory), executive function, attention and processing speed. These cognitive domains are known to affected in normal ageing and also in early stages in cognitve impairment.(Saczynski et al.,2008; Yeung et al., 2009; Gregg et al.,2000; Fontbonne et al 2001; Kanaya et al.,2004). Of the different types of memory, only verbal memory was examined in this study, executive function, attention and processing speed were not measured by the 10/66 battery of cognitive tests. Use of a more robust battery of cognitive tests like the Weschler Inventory would have helped overcome these limitations of the 10/66 battery of cognitive tests.

The Wechsler Inventory is a battery of neuropsychological tests designed to measure memory and other cognitive domains: verbal comprehension, perceptual reasoning and processing speed (Wisdom et al.,2012). The Weschler Memory Scale comprises of tests for: Spatial Addition, Symbol Span, Design Memory, General Cognitive Screener, Logical Memory, Verbal Paired Associates, and Visual Reproduction, and an individual's performance is reported as five Index Scores: Auditory Memory, Visual Memory, Visual Working Memory, Immediate Memory, and Delayed Memory. The Weschler Memory Scale also incorporates an optional cognitive exam (Brief Cognitive Status Exam) that helps to assess global cognitive functioning in people with suspected memory deficits or those who have been diagnosed with a various neural, psychiatric and/or developmental disorders. This

may include conditions such as dementias or mild learning difficulties. Weschler inventory is validated for use in older adults in India and normative values for each of the domains are available for meaningful comparisons (Wisdom et al.,2012) .

9.6 Issues related to statistical analyses

9.6.1 Power of the study

It was estimated that I would recruit 715 men and women in this study. For this sample size, using a test at the 5% significance level, the study would have had 80% power to detect an association of 0.105 standard deviations of a continuous measure of cognitive function per SD of weight at birth as a continuous exposure. For depression (a binary outcome) with a prevalence of 19% and using a test at the 5% significance level, the study would have had 80% power to detect an odds ratio 0.65 for the outcome per standard deviation increase in birth weight (details of power calculation in Chapter 4 section 4.14)

I recruited slightly more men and women (n=721). My estimates of the prevalence of depression and cognitive outcomes were remarkably accurate. In my study, a SD deviation increase in birth weight was associated with a 0.12 SD increase in composite cognitive score [95% CI (0.05, 0.19) p<0.001], a slightly larger effect size than predicted. Similarly, a SD increase in birth weight was associated with an odds ratio of 0.85 for depression [95%CI (0.68,1.00) p=0.05], a slightly lower effect size than estimated. The confidence interval for the odds of depression included 1.00 and the relationship was of borderline significance.

My study had insufficient power to examine the relationship of birth weight with dementia, as only a small proportion (n=22) were diagnosed with dementia. Associations (or lack of them) for certain exposures like Apoε4 allelic variant and stroke with cognition and depression in my study may also be due to insufficient power, and these results should be interpreted with caution.

9.6.2. Multiple analyses

I examined the associations of multiple exposures from early, mid- and late life with multiple cognitive outcomes in late life (in Chapters 6, 7 and 8). This was unavoidable, and multiple analyses may have resulted in some false positive findings. The following steps were taken to minimise type 1 error.

a. Of several indicators of birth size (birth weight, length, head circumference at birth and ponderal index), birth weight was available for all of them and there was no evidence of rounding off of weight measurements at birth. Therefore birth weight was considered as the single most reliable indicator of pre-natal growth.

b. Several measurements of cognitive function (outcomes) - verbal fluency, global cognition, immediate recall, delayed recall, mild cognitive impairment and dementia were available for all the participants. Only a few (n=22) participants were diagnosed with dementia and due to insufficient power to examine this binary outcome, dentia was excluded as an outcome of interest in chapter 7 and 8. Scores from the four cognitive function tests were reduced into one composite cognitive score using principal component analysis, and this was considered as a single reliable indicator of cognitive function in this cohort.

c. Finally, in the lifecourse models examining for the evidence of associations of growth in early life with cognition in late life, the analyses were carried out with one exposure (birth weight) and one outcome (composite cognitive score) of interest. This grossly minimised the need for multiple testing.

d. Potential confounders or mediating variables from early life, midlife and late life, for the relationship between birth weight and cognition in late life were examined in detail in section 7.7. Only carefully considered variables that were thought to best represent different phases of the life course (for e.g. maternal education as the best available indicator of early life environment and adult leg length as best available indicator of childhood growth and development) were adjusted for in the lifecourse models examining the associations of growth in early life and cognition in late life (in section 7.8).

9.6.3. Principal component analysis

Principal component analysis, a dimensionality reduction technique was used to convert four sets of correlated cognitive outcomes into a set of four linearly uncorrelated principal components (Chapter 8, table 8.1) (Abidi and Williams.,2010). Further to this orthogonal

transformation, and as expected the highest proportion of variance was explained by the first principal component, resulting in minimal data redundancy. In addition, the cognitive data reduction substantially minimised the number of analyses. This method was qualitatively superior to other commonly employed types of data reduction in birth cohort studies of cognitive ageing: sum of z scores (Skogen et al.,2013; Zhang et al.,2009; Raikkonen et al., 2013) or average of z scores (Muller et al.,2014) as the principal component explains a greater amount of the variance across the individual variables than these techniques.

9.6.4 Residual confounding

The lifecourse models of cognitive function and depression were adjusted for a number of potential confounding factors, including socioeconomic position. In a country like India, which has a wide and diverse range of socioeconomic positions, scores from standard instruments cannot perfectly capture all the effects and influence of socioeconomic position on health and ageing.

9.6.5 Advanced lifecourse analyses

I explored DOHaD pathways of cognitive ageing, and conducted lifecourse models for cognitive ageing and depression, by carrying out a series of multivariate regression models that were adjusted for carefully considered potential mediators and confounders from different stages of life. There were direct data from only three points across the lifecourse, with limited opportunity to identify critical periods for cognitive ageing or depression in this cohort. There is a clear need to extend these analyses using path analysis and structural equation modelling to explore lifecourse pathways and mediating effects in more detail, allowing for the assumed causal ordering of latent (e.g cognitive reserve) and observed variables across the lifecourse (Gamborg et al.,2011; De Stavola et al.,2006). I need additional training to conduct these analyses and I have identified this as a key learning objective.

9.7 Importance of this study

Data spanning the lifecourse are rare in a LMIC setting. This is the first lifecourse birth cohort study in a LMIC setting with cognitive and mental health outcomes in older adults. The study adds to the scientific understanding of the early life origins of cognitive ageing and depression in late life in an Indian population. The study has uniquely brought together two

major public health research programmes: the DOHaD and the 10/66 Dementia Research in India.

9.8 Implications for future research

This cohort provides a unique opportunity to begin to chart the epidemiologic transition and its impact upon older persons in India. In addition to rich data from midlife, this study has provided baseline measurements of cognitive function and depression in late life. This will enable an exploration of pathways of cognitive decline and incident depression in future follow-up studies of this cohort.

Further, there is a need for studies examining the underlying mechanisms (for e.g. neuroimaging, genetic and epigenetic studies) linking early life nutrition to cognitive ageing. Currently, a pilot study is underway for validation of more sophisticated neuropsychological assessments and MRI neuroimaging for the cohort members in collaboration with University of Aberdeen, UK. This pilot study aims to compare the similarities and differences in cognitive and brain reserve between participants from the MYNAH cohort and the Aberdeen Children of the 1950s cohort (Leon et al.,2006). A Genome Wide Association Study (GWAS) for cognitive ageing is also planned.

The MYNAH cohort is a constituent member of an international consortium, COSMIC (Cohort Studies of Memory in an International Consortium) constituted with an aim to harmonise data from international cohort studies of cognitive ageing, in order to better understand the determinants of cognitive ageing and neurocognitive disorders in late life (Sachdev et al.,2013). A large number of longitudinal studies of population-based ageing cohorts are in progress internationally, but the insights from these studies into the risk and protective factors for cognitive ageing, depression and dementia have been inconsistent. Some of the challenges of this research can be reduced by harmonising and pooling data across studies with different confounding structures. I plan to conduct comparative analyses within the COSMIC examining the relationship of socioeconomic position and social mobility across the lifecourse on cognitive ageing.

9.9 Policy implications

Numbers of older people are growing rapidly in India and the extent to which nutrition in early life and cardiometabolic risk factors across the lifespan are related to late life cognition is of substantial public health relevance. This study was aimed at understanding the nature

of this relationship. Indicators of growth in childhood, maternal educational level and attained educational level of the participants were independently and directly associated with higher cognitive function in late life in this cohort. Studies from both higher and LMIC settings provide support for improving growth in early life and childhood, and educational levels to promote healthy cognitive ageing. A summary of this is provided in sections 9.9.1 and 9.9.2

9.9.1 Maternal and child health

Recent studies from high income countries have indicated a decline in the incidence of dementia in late life (Grasset et al.,2015; Satizabal et al.,2015; Prince et al.,2016). This was not fully explained by improvements in cardiometabolic risk profile or in education, and has been attributed to improvements in nutrition and development in early life and childhood, as indicated by increased mean adult height by 5-9 cms (since the 1920s) in these populations (Baten and Blum.,2010). Recent findings from large 10/66 population based longitudinal studies in 10 LMIC countries, including India, provides support for an inverse association between growth in childhood and dementia in late life. This was attributed to better nutrition and environment in early life and childhood (Prince et al., 2012; Prince et al.,2018). The 10/66 study predicted that a 5 cm increment in adult height would result in nearly a 7% reduction in incident dementia in LMIC settings (Prince et al.,2018).

9.9.2 Education and cognitive reserve

Most studies reporting the direct association of attained education with cognitive reserve are from high income countries and relatively little is known about this in LMIC settings. The WHO SAGE study investigated whether higher cognitive reserve (higher education) is associated with enhanced cognitive functioning even under the constraint of poverty (low income) among 45,000 men and women from low- and middle-income countries including India (Then et al.,2017). Analyses adjusted for age, sex, childhood socioeconomic indicators, health status and country identified that both higher education and income were significantly and directly related to better cognitive functioning – with similar effects in midlife and late life. More importantly, the WHO SAGE study indicated that cognitive reserve obtained from only six years of formal education was associated with substantially greater cognitive health of individuals living in poverty in LMICs. Therefore, efforts to achieve universal education should be expanded to try to mitigate the negative impact of poverty and early life adversities for promoting better cognitive health across the lifecourse.

9.9.3 Relevance of this study to public health policies in India

The above findings (sections 9.9.1 and 9.9.2) and finding from this study strengthen the rationale for existing policies aimed at improving maternal health, childhood nutrition and development and education in India. They include: the Integrated Child Development Service-1975, Sarva Shiksha Abhiyan-2001 (Education for All) and the more recent Beti Bachao Beti Padao-2015 (Save a girl child; educate a girl child).

The Integrated Child Development Service (ICDS-1975) is aimed at improving maternal nutrition, and the health and development of children in India (Ministry of Human Resource Development.,1995) This programme provides nutritional supplementation and health education to pregnant and lactating women, and preschool education and growth monitoring for children (up to 5 yrs). These services are delivered by Anganwadi (courtyard of a house) centres and integrated with Primary Health Centres. Primary education in India has been made free and compulsory under the "Sarva Shiksha Abhiyan-2001" (Department of School Education and Literacy.,2001). This has resulted in an increase in literacy rates by around 9% in the last decade, more among girls than boys (12% in girls vs 7% in boys) (Registrar General India.,2011). The Beti Bachao Beti Padhao scheme was started in 2015 to address the decline in the girl child sex ratio in several parts of India and to promote the empowerment of women through education (wcd.nic.in/BBBPScheme/main.htm).

9.9.4 Mental health programme for older adults

In 2008, WHO provided a set of coherent and clear programmes and activities for member countries for scaling up care for mental disorders through the Mental Health Gap Action Programme (mhGAP), with an aim to improve access to mental health services in the community to reduce 'the treatment gap', particularly in LMICs (WHO.,2008). A vast majority of those who were diagnosed with dementia and depression in my study were undiagnosed and were not receiving any treatment for these conditions, indicating an unacceptable treatment gap for mental disorders in this cohort (98%), a finding similar to other population based urban studies in India and other LMICs (Patel et al.,2009; Prince et al.,2009). Both dementia and depression are considered priority mental health conditions in LMIC settings resulting in a high burden of economic costs and mortality.

There has been very little effort from the Government of India for the scaling up of mental health services for older adults. WHO has updated the mhGAP programme and has called for an urgent implementation and scaling up of the WHO 'packages of care' for depression and dementia among older adults in India and other LMICs (WHO.,2015)

9.10. Impact

The MYNAH study is now recognised as a major study of older adults in India, and I have been asked to contribute to the second National Dementia Report for India by the Alzheimer's and Related Disorders Society of India (ARDSI), and to the National Framework for Improving Mental Health of Older Adults in India by Help Age India and the Ministry of Family Health and Welfare India. This study has put Mysore at the focus of dementia research in India. I have been nominated as one of the scientific advisors for ARDSI India. I have trained several clinicians and non-clinicians in administering the battery of cognitive tests used in the study to recognise older adults with cognitive problems. The protocol of this study has heavily influenced ongoing population based surveys for diagnosis of risk factors for dementia in India, jointly conducted by the Centre for Brain Research at Indian Institute of Sciences and the National Institute of Mental Health and Neurosciences, Bangalore India.

Findings from this study will be effectively disseminated through scientific journals, and at national and international scientific meetings. I will continue to engage with key stake holders and relevant organisations to influence policies related to healthy ageing and care of the elders in India.

9.11 Conclusions

In India, recent improvements in the nutrition and education of both mothers and children is likely to produce younger generations with better cognitive health, compared to the generation of older adults examined in this study. There is evidence of such an improvement in cognitive function and IQ scores across the generations, mainly from high income countries. This is termed the Flynn effect (Flynn.,1987). A comparison of scores from identical cognitive tests administered to adults 10 to 30 years apart has shown an increase of about 5 to 9 IQ points per decade, and an increase of about 5 to 25 IQ points over a generation (Flynn.,1987). Further, a rise in intelligence scores of about 12 IQ points over a period of 50 years or 2 IQ points per decade has also been observed in the UK cohorts (Lynn et al.,1987). The reasons for such improvements in cognition and IQ across the generations are not well understood. Possible mechanisms include improvements in nutrition in early life and childhood, improvements in educational standards and schooling, improvements in technology leading to easier access to information, and perhaps increased complexity of the environment. Thus, the existence of a Flynn effect, though not fully proven, suggests that intelligence is not a fixed genetic attribute, but is modifiable by the environment.

Appendices

Sl. No	Particulars
1	Search strategy for systematic review
2	Data extraction sheet for the systematic review
3	STROBE checklist
4	Inter observer variability study
5	Information leaflet for the MYNAH study
6	Consent forms for the MYNAH study
7	Sociodemographic assessments
8	Battery of cognitive assessments
9	Geriatric Mental State Examination
10	History and Aetiology Schedule -Dementia Diagnosis and subtype
11	Physical Health
12	Neurological examination
13	Pilot validation study
14	Associations of current and midlife exposures with MCI

Appendix 1

Search strategy from Medline

1. MEDLINE; exp BIRTH WEIGHT/; 34390 results.
2. MEDLINE; (birth adj5 length).ti,ab; 3033 results.
3. MEDLINE; (birth adj5 circumference).ti,ab; 1149 results.
4. MEDLINE; "ponderal index".ti,ab; 938 results.
5. MEDLINE; exp INFANT, SMALL FOR GESTATIONAL AGE/; 5360 results.
6. MEDLINE; "small for gestational age".ti,ab; 6414 results.
7. MEDLINE; "foetal origins hypothesis".ti,ab; 15 results.
8. MEDLINE; "fetal origins hypothesis".ti,ab; 103 results.
9. MEDLINE; "growth in utero".ti,ab; 178 results.
10. MEDLINE; exp FETAL DEVELOPMENT/; 75682 results.
11. MEDLINE; "fetal growth".ti,ab; 10233 results.
12. MEDLINE; "foetal growth".ti,ab; 592 results.
13. MEDLINE; exp FETAL GROWTH RETARDATION/; 13101 results.
14. MEDLINE; "intrauterine growth".ti,ab; 10002 results.
15. MEDLINE; (prenatal adj5 undernutrition).ti,ab; 134 results.
16. MEDLINE; (birth adj5 size).ti,ab; 2958 results.
17. MEDLINE; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16;
121676 results.
18. MEDLINE; exp COGNITION/; 112890 results.
19. MEDLINE; exp MEMORY/; 102877 results.
20. MEDLINE; exp MENTAL RECALL/; 27549 results.
21. MEDLINE; exp ATTENTION/; 61050 results.
22. MEDLINE; cognition.ti,ab; 35514 results.
23. MEDLINE; memory.ti,ab; 163113 results.
24. MEDLINE; recall.ti,ab; 37487 results.
25. MEDLINE; attention.ti,ab; 251466 results.
26. MEDLINE; 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25; 576383 results.
27. MEDLINE; 17 AND 26; 2300 results.
28. MEDLINE; 27 [Limit to: (Age Groups Middle Aged 45 plus years or All Aged 65 and Over or Aged 80 and Over)]; 99 results

Appendix 2
Data Extraction sheet for systematic review

First Author:		**Journal:**	
Year:		**Country:**	
Population:		**Setting:**	
Study design:		**Sample Size:**	
Sample Characteristics:		**Early Life Exposures:**	
Age:			
M/F:			
Occupation:			
Life Style:			
Exclusion Criteria:		**Cognitive Outcomes:**	
Confounders examined:			

Report of Effect Sizes		
Exposure	**Outcome**	**Effect Size**

Comments:

Appendix 3

Strengthening the Reporting of OBservational Studies in Epidemiology (STROBE)

	Item No	Recommendation	Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	
Objectives	3	State specific objectives, including any prespecified hypotheses	
Methods			
Study design	4	Present key elements of study design early in the paper	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix- 4

Inter-observer variation

12 male subjects, 3 male observers, each subject measured 2 times

Table 1 Inter-observer variation for male measurers in the MYNAH study

	Height (cms)	**Weight** (kgs)	**Leg length** (cms)	**Midarm*** (cms)	**Head*** (cms)	**Waist*** (cms)	**Hip*** (cms)	**Calf*** (cms)	**Biceps**** (mms)	**Triceps**** (mms)	**Subscapular** (mms)**
Mean	165.2	70.7	93.0	30.2	53.3	94.2	92.5	36.6	12.5	18.1	28.9
Subject range	-9.5, 15.5	-22.0,23.4	-6.6, 8.8	-5.2, 4.7	-1.8, 1.6	-18.6, 14.1	-16.5, 13.0	-6.1, 9.9	-8.4, 9.8	-10.3 12.7	-12.6, 8.8
Observer range	-0.3 ,0.4	-0.02, 0.02	-0.5, 0.8	-0.1, 0.2	-0.01,0.01	-0.6, 0.4	-0.2, 0.1	-0.02, 0.04	-0.03,0.07	-0.04,0.03	-0.27, 0.32
Observer sum of squares	1.24	0.01	6.10	0.43	0.00	3.60	0.34	0.02	0.04	0.02	1.07
Subject sum of squares	1188.60	3607.51	616.50	225.43	23.08	2168.43	1597.41	386.14	742.01	1253.04	973.72
% Variation due to observer	0.097	0.000	0.933	0.192	0.003	0.163	0.021	0.004	0.005	0.001	0.108
P value (observer)	0.28	0.91	0.08	0.06	0.99	**0.005**	0.47	0.70	0.81	0.93	0.34

* circumferences ** skinfolds

Inter observer variation

12 female subjects, 3 female measurers, each subject measured 2 times

Table 2 Inter-observer variation for female measurers in the MYNAH study

	Height (cms)	**Weight** (kgs)	**Leg length** (cms)	**Midarm** (cms)	**Head** (cms)	**Waist** (cms)	**Hip** (cms)	**Calf** (cms)	**Biceps** (mms)	**Triceps** (mms)	**Subscapular** (mms)
Mean	152.8	63.4	89.0	29.2	51.9	89.3	90.3	40.3	15.3	26.1	30.8
Subject range	-9.4, 11.8	-22.2, 24.9	-8.7, 7.2	-6.1, 6.2	-3.1, 2.3	-23.5, 16.1	-30.7, 20.8	-10.5, 55.3	-10.3, 7.6	-10.4, 16.4	-15.8, 14.8
Observer range	-0.01,0.16	-0.07, 0.09	-0.57, 0.65	-0.16, 0.18	-0.15, 0.08	-0.52, 0.47	-4.26, 5.09	-0.21, 0.38	-0.53, 0.37	-0.35, 0.37	-1.26 ,0.76
Observer sum of squares	0.23	0.08	4.55	0.33	0.20	2.92	268.51	1.27	2.61	1.58	14.45
Subject sum of squares	944.90	4990.76	451.41	416.63	51.77	4178.41	4256.27	6844.89	728.80	1552.06	2502.67
% variation due to observer	0.023	0.001	0.980	0.078	0.308	0.067	4.720	0.017	0.335	0.099	0.562
P value (observer)	0.32	0.16	0.08	0.38	0.14	0.50	0.36	0.08	0.70	0.73	0.15

* circumferences ** skinfolds

Inter observer variability study

Order	name	Interviewer	Height (cms)	Weight (cms)	Leg length (cms)	MUAC (cms)	Head (cms)	Waist (cms)
Subject 1	A	Murali	169	94.3	99.5	34.8	55.1	108.3
order AB	B	Santhosh	169	94	99.8	34.9	54.8	108.3
Subject 2	A	Murali	166.5	77.8	90.8	33	52.5	96.8
order AC	C	Somshekar	166.6	77.9	90.9	33.2	52.6	96.7
Subject 3	B	Santhosh	161.6	75.7	91.2	33.6	52	99.2
order BC	C	Somshekar	161.2	75.6	88	33.6	51.2	98.7
Subject 4	C	Somshekar	159.1	59.4	86	29.1	52.2	90.6
order CA	A	Murali	159	58.8	86	28.8	52	88.4
Subject 5	C	Somshekar	159.6	66.1	88.6	29.3	52.1	94.4
order CB	B	Santhosh	160.1	66.1	92.4	29.6	52	94.5
Subject 6	B	Santhosh	157.4	48.8	91	25.5	53.9	77.5
order BA	A	Murali	154.2	48.7	90.4	25.4	54	76.1
Subject 7	B	Santhosh	159.9	77	91.8	33.7	53.8	103
order BA	A	Murali	159.8	77	90.9	33.5	53.8	101.6
Subject 8	C	Somshekar	160.3	59	86.7	28.1	54.3	91.1
order CB	B	Santhosh	160.1	59	86.5	27.4	54.1	90.9
Subject 9	C	Somshekar	180.4	87.8	101.9	32.1	53.1	105.6
order CA	A	Murali	180.8	87.7	101	31.5	53.1	103.3
Subject 10	A	Murali	168.2	70.2	96.4	30.6	54.2	95.8
order AB	B	Santhosh	168.4	69.9	96.3	30.5	54.1	95.6
Subject 11	A	Murali	177.3	61.7	101.2	25	54	75.2
order AC	C	Somshekar	177.4	61.7	101.7	25.3	54.2	75.7
Subject 12	B	Santhosh	165.2	72.4	92.5	28.8	54	98.6
order BC	C	Somshekar	165.2	71.8	91.3	29.6	54.1	96.8

Order	name	Interviewer	Hip (cms)	Calf (cms)	Biceps (mms)	Triceps (mms)	Subscapular (mms)	Suprailiac (mms)
Subject 1	A	Murali	105	46.6	22.5	31	36.2	23.5
order AB	B	Santhosh	106	46.4	22.2	30.6	36.4	24.6
Subject 2	A	Murali	97.5	37.8	13	26	38	37.8
order AC	C	Somshekar	97.6	37.9	13.2	26.2	37.9	37.9
Subject 3	B	Santhosh	98.5	39.2	16.5	22.4	31.1	23
order BC	C	Somshekar	98.7	39.2	16.3	22.4	32.8	18.2
Subject 4	C	Somshekar	84.8	33.4	8.2	11.9	28.8	10.9
order CA	A	Murali	85	33.3	8.7	11.4	28.5	10.8
Subject 5	C	Somshekar	91.2	35.6	9.5	10.8	23.2	11.1
order CB	B	Santhosh	90.8	35.5	10	11.2	24.7	10.4
Subject 6	B	Santhosh	75.7	30.6	4.2	9.5	20.2	7.8
order BA	A	Murali	76.3	30.5	4.2	9.2	20.2	6.8
Subject 7	B	Santhosh	98.3	37.7	19.8	26.6	32.3	19.8
order BA	A	Murali	99.5	37.5	20	26	32.4	19.4
Subject 8	C	Somshekar	85.1	31.2	7.9	13.7	22.6	11.4
order CB	B	Santhosh	84.9	31.3	7.6	13.6	22.6	12.2
Subject 9	C	Somshekar	102	38.8	19	22.9	33	18.8
order CA	A	Murali	101	38.7	19	23.8	33.2	19.8
Subject 10	A	Murali	91.5	35.5	11.2	16.5	31.8	9.2
order AB	B	Santhosh	90.9	35.8	11.6	16.4	30.9	9.2
Subject 11	A	Murali	85.7	35.3	5	7.6	15.8	6.8
order AC	C	Somshekar	85.4	34.8	5.8	7.9	17.1	7.1
Subject 12	B	Santhosh	95	38.2	13.2	18	31.2	10.2
order BC	C	Somshekar	95.1	38.1	12.7	18.6	33.5	10.8

Order	Interviewer	Height (cms)	Weight (cms)	Leg length (cms)	MUAC (cms)	Head (cms)	Waist (cms)
Subject 1 order AB	Malathi	151.4	72.5	90.3	34.6	51.4	101.3
	Pavithra	152	72.1	89.5	33.8	51.6	99.2
Subject 2 order AC	Malathi	154.6	57.9	92.3	25.3	51.5	86.6
	Saroja	154.5	57.5	90.4	24.6	51.7	88
Subject 3 order BC	Pavithra	145.4	49.5	83.7	27.2	53.4	72.1
	Saroja	145.7	49.5	83.2	26.9	53.2	71.4
Subject 4 order CA	Saroja	155.6	41.5	88.4	23	51	65.4
	Malathi	155.5	41.2	89.5	23.3	50.9	65.8
Subject 5 order CB	Saroja	158.7	80.4	92.8	35.2	53.2	102
	Pavithra	159.1	80.3	93.2	35.6	53.5	102.4
Subject 6 order BA	Pavithra	152.3	75.3	90.8	31.2	50.1	106
	Malathi	151.9	75.3	89.7	31.5	50.2	105.5
Subject 7 order BA	Pavithra	146.4	46.9	86.7	23.6	49	75.3
	Malathi	146.9	46.9	87.4	23.4	48.6	73.4
Subject 8 order CB	Saroja	154.4	51.6	89.4	27	53.8	79.6
	Pavithra	155	51.7	89.3	26.4	54	79.7
Subject 9 order CA	Saroja	145.4	54.2	84.7	28.2	50.2	83.2
	Malathi	145.1	53.9	84.3	28.9	50.3	87.3
Subject 10 order AB	Malathi	143.6	75.8	81	33.8	51.5	102.6
	Pavithra	143.5	75.4	80.3	33.6	51.8	103.4
Subject 11 order AC	Malathi	164.6	88.7	96.5	33.9	52.9	102.6
	Saroja	164.6	88.2	92.4	34.6	53.7	104
Subject 12 order BC	Pavithra	161.8	68.7	95.6	28.6	54	95.6
	Saroja	161	68.7	96.2	27.8	54.6	92.3

Order	Interviewer	Hip (cms)	Calf (cms)	Biceps (mms)	Triceps (mms)	Subscapular (mms)	Suprailiac (mms)
Subject 1	Malathi	97.8	37.4	24.1	36	38.4	18.1
order AB	Pavithra	94.3	38.3	20.1	33.1	36.4	20.5
Subject 2	Malathi	87.4	31.5	7.5	18.3	38.7	13.8
order AC	Saroja	89.4	31.5	11.4	16.8	44.2	15.1
Subject 3	Pavithra	84.3	33.6	14.6	21.6	15.3	17.4
order BC	Saroja	84.1	33.2	15.2	21.2	16	17
Subject 4	Saroja	78	29.6	7.7	17.3	16.8	8.3
order CA	Malathi	74.4	29.6	6.9	16.4	14.8	6.6
Subject 5	Saroja	103	42.4	25.1	44.6	47.8	22
order CB	Pavithra	98.2	43.2	20.6	40.5	44.8	28.6
Subject 6	Pavithra	98.2	37	20.4	32.7	32.2	24.8
order BA	Malathi	101.3	36.7	20.9	35.2	30	19.2
Subject 7	Pavithra	83.4	33.7	5.8	16.7	20.9	12.2
order BA	Malathi	84	33.3	4	14.5	18.3	10.4
Subject 8	Saroja	83.2	30.6	15.1	24.2	22.3	18.2
order CB	Pavithra	84.6	30.2	16.1	24.2	23.1	18.6
Subject 9	Saroja	87.2	94.8	14.2	28.1	33.8	20.6
order CA	Malathi	32.9	96	13.4	26.2	30.6	19.3
Subject 10	Malathi	109.3	38.7	16.1	25.2	26.2	22.4
order AB	Pavithra	107.9	40.5	15.9	24.8	27.3	24.1
Subject 11	Malathi	106.2	41.9	22.8	32.5	41.6	22.6
order AC	Saroja	106	42.2	18.3	35.1	42.1	18.2
Subject 12	Pavithra	97.3	30.8	16.5	23.1	42.1	21.2
order BC	Saroja	95.5	30.5	15.8	20	37.1	24.3

APPENDIX – 5

Information leaflet for the MYNAH Study

What is this research study about?

Previous research has shown that small size at birth is associated with diabetes, heart disease, hypertension and high cholesterol in adult life. Similarly, small size at birth may be associated with decreased mental abilities in old age. This study is aimed at understanding if reduced mental ability in old age is associated with small size at birth. We will also examine the effect of diabetes, high blood pressure, heart disease and cholesterol on mental health in old age.

Why have I been chosen?

You were born in CSI Holdsworth Memorial Hospital (Mission Hospital). You have been chosen as we know your size at birth from the hospital birth records. You may have participated in previous studies at our research unit. You are now above 60 yrs of age and eligible to participate in this study.

What does the study involve?

The study will be conducted at the Research Unit at CSI Holdsworth Hospital. We will interview you and a family member to collect information about your household, living conditions, life style (physical activity, alcohol use, smoking and diet), social functioning and general health. We will administer tests to assess your mental wellbeing. We will carry out a physical examination and you will receive blood tests (for diabetes, cholesterol and anaemia), an ECG and measurement of body fat. We will examine for any genetic factors for decreased mental abilities in old age.

What are the benefits by participating in this study?

By participating you will have the opportunity of a detailed assessment of your physical health and mental health. You will have all the investigations and assessments free of cost. We will provide you with a report of tests and assessments we conduct.

Is my participation voluntary? What if I do not want to participate?

Your participation is voluntary. You do not have to participate if you do not wish to do so. Your treatment at the Mission Hospital or future participation will not be affected if do not participate.

Who should I contact if I need more information about this study?

You are advised to contact ***Dr Murali Krishna****,* the head of this project if you need more information. You can contact him at the research unit on phone number ***0821-2521651***

APPENDIX - 6

CONSENT FORMS

I _____ have been informed about the "The **MYNAH Study"** conducted by **CSI, HMH, Mysore**. I have been explained that that participation in the study will include assessments and investigations listed below. My participation is voluntary. I am willing to take part in this study and will undergo the assessment and tests specified. I am aware that I can withdraw my consent at any time during the study without having to provide any explanation without any impact on my clinical care and future participation. I give permission for taking photos and using the same for training and scientific purposes.

Check list

1. Cognitive function test and Mental state examination
2. Physical examination including Neurological examination
3. Socio-Demographic and Household inventories
4. ECG (Electrocardiogram)
5. Blood tests (Glucose tolerance test, Blood Cell counts, Thyroid function test, Vitamin B12 and Folate, Urea, Creatinine, Lipid Profile, Total Protein and Albumin)
6. Bio-impedance
7. Muscle grip strength
8. Blood pressure
9. Risks / complications if any

Subject Name _____ Signature _____

Date_____

Informant Name _____ Signature _____

Date_____

Staff Name Name _____ Signature _____

Date _____

Informed consent for genetic tests and storage of blood sample for future genetic studies

- In this study we will obtain your blood sample for examining genetic factors known to increase the risk of memory problems in old age. We will use the same sample that you have provided for tests. Therefore resampling is not required.
- The genetic studies are mainly for research only and do not have any commercial value. There may be no immediate therapeutic implications.
- In most cases the families will not be getting any results. The results are mainly useful for future generations and not to subjects themselves.
- The results are strictly confidential.
- The genetic studies will be done in reputed laboratories within India.

I / we have been explained about the objectives of the Wellcome DBT funded *Mysore Birth Records Mental Health Study***. I / we hereby agree to participate in the above mentioned study on a purely voluntary basis. I / we have been informed that the study is intended only for research purpose and not for any commercial use. I / we have been also informed that there may be no immediate therapeutic implications of the study and the results are handled confidentially.**

1) Signature:_____ 2) Signature:_____

Name: _____ Name: _____

Date: _____ Date: _____

Relationship to subject:
Self/Mother/Father/Husband/Wife/Brother/
Sister/Son/Daughter/Other

Relationship to subject:
Self/Mother/Father/Husband/Wife/Brother
Sister/Son/Daughter/Other

APPENDIX - 7

Sociodemographic Assessment

1. EARLY LIFE

1.1 How long have you lived in this city?

1.2 Where were you born?

City	0	
Town	1	
Country	2	{pborn}

1.3 What about between the ages of 20 and 55, where did you live most of the time?

City	0	
Town	1	
Country	2	{pmidlife}

1.4 Since you turned 55, where have you lived most of the time?

City	0	
Town	1	
Country	2	{platlife}

1.5 How much schooling have you had?

None	1	
Some, but did not complete primary	2	
Completed Primary	3	
Completed Secondary (metric)	4	
Completed Tertiary (college) /further education	5	{peduc}

1.6 Can you read a newspaper?

No 0 Yes 1 {pread}

1.7 Could you write a letter, if you needed to?

No 0 Yes 1 {pwrite}

1.8 Are your parents consanguineous?

No	0
Yes	2
Don't Know	3

IF "NO" SKIP TO 1.10 {parcons}

1.9 If consanguineous marriage describe the type (Mother married to)

a. Her mother's brother
b. Her mother's brothers son
c. Her mother's sister's son
d. Her father's sister's son
e. Other {constype}

1.10 Were you drinking milk daily during the childhood?

No	0
Yes	1
Don't Know	2

{milkch}

1.11 How many languages do you speak well? {langspeak}

1.12 How many languages do you write well? {langwrite}

2. CURRENT CIRCUMSTANCES

2.1 Are you the head of household?

No 0 Yes 1 {pheadhse}

IF "YES" SKIP TO 2.3

2.2 Is the head of household your

Spouse	1	
Son/Daughter	2	
Son/Daughter-in-law	3	
Brother or sister	4	
Other relative	5	
Friend	6	{prel}

2.3 Are you currently married?

Never married	1	
Married/Co-habiting	2	
Widowed	3	
Divorced/Separated	4	{pmarry}

2.4 Are you a member of any religious group?

Agnostic/ Atheist	0	
Roman Catholic	1	
Anglican/Protestant	2	
Other Christian	3	
Jewish	4	
Muslim	5	
Buddhist	6	
Hindu	7	
Other	8	{prelig}

2.5 Do you attend religious meetings?

No	0	
Yes, regularly	1	
Yes, occasionally	2	{pgochch}

2.6 Do you attend meetings of any community or social groups, such as clubs, lectures or anything like that?

No	0	
Yes, regularly	1	
Yes, occasionally	2	{pclubs}

3. SOCIAL NETWORK

3.1 How far away does your nearest (in terms of distance) relative live?

Within one Km/same home	1		
1-5	Kms	2	
6-15	Kms	3	
16-50	Kms	4	
50+	Kms	5	{preldist}

3.2 Where does your nearest sister or brother live?

No siblings		0
Within one Km/same home		1
1-5	Kms	2
6-15	Kms	3
16-50	Kms	4
50+	Kms	5 {psibdist}

3.3 Do you have any children?

No 0 Yes 1 {pch}

IF NONE SKIP TO 3.6

3.4 Where does your nearest child live?

No children		0
Within one Km/same home		1
1-5	Kms	2
6-15	Kms	3
16-50	Kms	4
50+	Kms	5 {pchdist}

3.5 How often do you see any of your children or other relatives to speak to?

Never	0
Daily	1
2-3 times a week	2
At least weekly	3
At least monthly	4
Less often	5 {prelfrq}

3.6 Do you have friends in this community?

No 0 Yes 1 {pfrd}

IF NONE SKIP TO 3.10

3.7 How often do you have a chat or do something with one of your friends?

No friends/ Never	0
Daily	1
2-3 times a week	2
At least weekly	3
At least monthly	4
Less often	5 {pfrdfrq}

3.8 Which close friends do you meet or contact regularly (at least once a month)?
What are their names (Code number of friends positively identified)
…….{pfrdnum}

3.9 All in all are you satisfied or dissatisfied with the help and support you can get from your close friends?

Dissatisfied 0
Satisfied 1 {pfrdsat}

3.10 How often do you see any of your neighbors to have a chat or do something with?

No contact	0
Daily	1
2-3 times a week	2
At least weekly	3

At least monthly	4	
Less often	5	{pneifrq}

3.11 How many good neighbors do you have whom you meet or talk to regularly (at least once a month)? What are their names? Code number of neighbors identified.
…… {pneinum}

4. SOCIO-ECONOMIC STATUS

4.1 Do you have a job?

1 Paid full-time work
2 Paid part-time work
3 Unemployed (looking for work)
4 Student
5 Housewife/husband (full-time)
6 Retired {pjob}

4.2 What is the best (highest level) job you have ever had? What kind of work did you do in this job?

1 Manager/administrator
2 Professional (eg health, teaching, legal, financial)
3 Associate professional (eg technical, nursing, artistic)
4 Clerical worker /secretary
5 Shop keeper
6 Skilled labourer (e.g building, electrical etc.)
7 Semi-skilled labourer (e.g helper of skilled labourer)
8 Unskilled labourer
9 Agricultural worker
99 Missing Value {pjobcat}

4.3 What is the best (highest level) job your husband/ wife ever had? What kind of work did they do in this job?

1 Manager/administrator
2 Professional (eg health, teaching, legal, financial)
3 Associate professional (eg technical, nursing, artistic)
4 Clerical worker /secretary
5 Shop keeper
6 Skilled labourer (e.g building, electrical etc.)
7 Semi-skilled labourer (e.g helper of skilled labourer)
8 Unskilled labourer
9 Agricultural worker
99 Missing Value {pcjobcat}

4.4 Do you receive any income, benefits, pensions or allowances?

No 0 Yes 1 {pincome}

IF NO SKIP TO SECTION 5

Please list any benefits or allowances with the approximate monthly income from each
Benefit type

Government pension	1
Occupational pension	2
Disability pension or benefit	3
Money from family	4
Income from rented land or property	5
Income from paid work	6
Other	7
No further benefits to enter	9

Type of benefit	**Monthly income**
4.5 {bentype1}	4.6 {ben1}
4.7 {bentype2}	4.8 {ben2}
4.9 {bentype3}	4.10 {ben3}
4.11 {bentype4}	4.12 {ben4}

5 REPRODUCTIVE HEALTH

The following four questions are for women only.

5.1 Enter the participant's gender here

Female	1	
Male	2	{psexre}

IF PARTICIPANT IS Male SKIP TO SECTION 12

5.2 How old were you when your periods began? {pmenarc}

5.3 How many children did you have? {pchino}

5.4 How old were you when your first child was born? {pchiage}

5.5 How old were you when you had the first symptoms of the menopause? {pmenpaus}

6. BEHAVIOUR AND LIFESTYLES

6.1 SMOKING

6.1.1 Has there ever been a period when you smoked cigarettes, cigars, or a pipe, chewing tobacco or snuff nearly every day?

No	0	Yes	1	{psmoke}

IF NO SKIP TO Q 6.2.2

6.1.2 What did you smoke?

Non-smoker	0	
Cigarettes/Beedies	1	
Cigars	2	
Pipe	3	
Chewing tobacco	4	
Snuff	5	{psmoke2}

6.1.3 How old were you when you started using tobacco regularly? {pstart}

6.1.4 Do you still use tobacco regularly?
No 0 Yes 1 {psmknow}

IF YES, SKIP TO 6.1.6

6.1.5 How old were you when you stopped? {pstop}

6.1.6 How many did you/do you have each day? {pcigdose}

Type of Tobacco {typtobac}	**0-No 1-Yes** **{yesno}**	**Frequency** * {freq}	**Quantity** **{quan}**	**Age of start (yrs)** **{agestar}**	**Age of stop (yrs) {agestop}**
1 Cigarette/Cigar/Chutta					
2 Beedies					
3 Tobacco chewing (No. of pieces)					
4 Snuff					

* 1- Occasionally 2- Daily 3- Weekly

Comments:

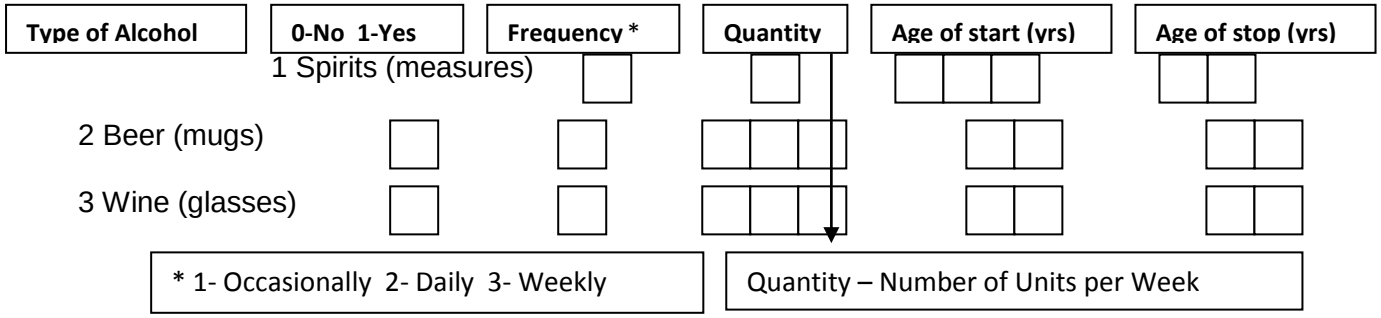
7 ALCOHOL

7.1 Before you reached the age of 55, what was the most you would drink in an average week?
(Record maximum regular consumption in UNITS of alcohol per week)

1 unit = a small glass of beer
a single measure of spirits
1 glass of wine or sherry
32 units = 1 bottle of spirits
999 = Don't know {palcpast}

7.2 What about after the age of 55?
(Record total consumption in units of alcohol) {palcnow}

IF NEVER A DRINKER SKIP TO 7.3



Comments: _____

7.2.3 Has there ever been a period of several years when you would have said that you were a heavy drinker?

No 0 Yes 1 {pheavy}

7.2.4 Have you ever had treatment or help for drinking from a doctor or some other agency? No 0 Yes 1 {palctrt}

8.0 Standard of Living Index

8.1) Family type:
1) Nuclear 2) Joint 3) Other {famtype}

8.2) Number of persons (specify): _____

8.3) What is the main source of drinking water for members of your household?
1) Piped water
2) Hand pump
3) Well
4) Public tap/p, hand pump/p, well
5) River/stream
6) Tanker
7) Other
{water}

8.4) What kind of toilet facility does your household have? {toilet}
1) Own flush toilet
2) Shared flush toilet
3) Public flush toilet
4) Own pit toilet/Latrine
5) Shared pit toilet/Latrine
6) Public pit toilet/Latrine
7) No facility/Bush/Field
8) Others

8.5) What is the main source of lighting for your household? {elec}

1) Electricity 2) Kerosene
3) Oil 4) Gas
5) Other (specify): _____

8.6) How many rooms are there in your household?

Rooms No: _____ {rooms}

8.7) Do you have a separate room that is used as a kitchen? {kitchen}

1) Yes 2) No

8.8) What type of fuel does your household mainly use for cooking? {fuel}

1) Electricity 2) Wood
3) Crop residues 4) Liquid petroleum gas
5) Biogas 6) Coal/Charcoal/Coke
7) Kerosene 8) Other (specify):

_____

8.9) Does this household own this house or any other house? {ownhouse}

1) Yes 2) No

8.10) Type of house (record observation)

Roof _____ 1) Pucca {housetype}
Walls _____ 2) Semi-pucca
Floor _____ 3) Kachha

8.11) Does this household own any agriculture land? {agriland}

1) Yes (specify): _____ acres
2) No

8.12) Out of this how much is irrigated land? {irrland}

1) _____ acres 2) None

8.13) Does this household own any livestock?

1) Yes (specify): { lsstock} ☐ Number: {lstockno}
2) No

8.14) Does this household own any of the following?

1)	Mattress	1. Yes	0. No	{mattress}
2)	Pressure cooker	1. Yes	0. No	{cooker}
3)	Chair	1. Yes	0. No	{chair}
4)	Cot/Bed	1. Yes	0. No	{bed}
5)	Table	1. Yes	0. No	{table}
6)	Clock/Watch	1. Yes	0. No	{clock}
7)	Electric fan	1. Yes	0. No	{elefan}

8)	Bicycle	1. Yes	0. No	{bicycle}
9)	Radio/Transistor	1. Yes	0. No	{radtras}
10)	Television (B&W)	1. Yes	0. No	{TV}
11)	Television (colour)	1. Yes	0. No	{TVcolr}
12)	Moped/Scooter/M'cycle	1. Yes	0. No	{scooter}
13)	Car/Jeep	1. Yes	0. No	{car}
14)	Water pump	1. Yes	0. No	{waterpump}
15)	Bullock cart	1. Yes	0. No	{bullcart}
16)	Thresher	1. Yes	0. No	{thresher}
17)	Tractor	1. Yes	0. No	{tractor}
18)	Refrigerator	1. Yes	0. No	{fridge}
19)	Telephone	1. Yes	0. No	{phone}
20)	Sewing machine	1. Yes	0. No	{sewmachne}

8.15 **Total SLI Score** **{sli}**

9. Kuppuswamy Score

9.1) Education Level of Mother: ..... {mothered}

9.2) Education Level of Father: ..... {fathered}

9.3) Education level of Subject :..... {subedu}

9.4) Education level of Partner (**Wife / Husband**) : ..... {eduhswf}

9.5) Occupation of Subject or Main breadwinner:..... {headoccup}

10.1 Locality in the Town
1. Slum 2. Low Class 3. Middle Class 4. High Class {locltwn}

10.2 People per Room {peprom}
1. 4 or More 2. 3 to 3.9 3. 2 to 2.9 4. 1 to 1.9

10.3 Water 3. Separate 2. Common 1. Not Avail {water}

10.4 Bathroom 3. Separate 2. Common 1. Not Avail {bathroom}

10.5 Toilet 3. Separate 2. Common 1. Not Avail {toilet}

10.6 Income of Main Breadwinner of the family {famin}

10.7 Total income into the household {income}

10.8 Number of members of household {numem}
10.9 Per Capita Income {percap}
(Total income from all the member of the Household divided by the Total number in the household/month)

APPENDIX - 8

The 10/66 battery of cognitive Tests

The Community Screening Instrument for Dementia (CSI-D)

WORD LIST LEARNING

I am now going to read out a list of words. Please listen carefully, as I will ask you to repeat them back to me when I have finished. The words are on this green card

Read out the ten words, pausing for one second between each. Score correct words on the grid below

	1ST	2ND	3RD	
BUTTER				BUTTER
ARM				ARM
LETTER				LETTER
QUEEN				QUEEN
TICKET				TICKET
GRASS				GRASS
CORNER				CORNER
STONE				STONE
BOOK				BOOK
STICK				STICK
TOTAL SCORE				

1st trial

1. {LEARN1} ##

Now please tell me all the words you can remember

Interviewer - Score total number of words correctly recalled

2nd trial

Thank you. Now I will read out the words to you one more time. Again, please listen carefully, as I will ask you to repeat the words when I have finished.

Interviewer - Read out the ten words, pausing for one second between each.

2. {LEARN2} ##

Now please tell me all the words you can remember

Interviewer – Score total number of words correctly recalled

3rd trial

Thank you. Now I will read out the words to you one last time. Again, please listen carefully, as I will ask you to repeat the words when I have finished.

Interviewer - Read out the ten words, pausing for one second between each.

3. {LEARN3} ##

Now please tell me all the words you can remember

Interviewer - Score total number of words correctly recalled.

4. {NAME} #

I'd like you to remember my name.

My last name is xxxxxxxxx. Can you repeat that please?

Cannot repeat name	0
Successfully repeats name	1

WE WILL BEGIN WITH NAMING THINGS. I WILL POINT TO SOMETHING AND I WOULD LIKE YOU TO TELL ME THE NAME OF THE OBJECT. FOR EXAMPLE

5. {PENCIL} #

(Interviewer shows a pencil)

What is this called?

Incorrect	0
Correct	1

6. {WATCH} #

(Interviewer points to their watch)

What is this?

Incorrect	0
Correct	1

7. {CHAIR} #

(Interviewer pats chair)

What about this?

Incorrect	0
Correct	1

8. {SHOES} #

(Interviewer points to shoes [or socks or stockings if they have left shoes outside])

And these?

Incorrect	0
Correct	1

9. {KNUCKLE} #

(Interviewer shows their knuckles)

What do we call these?

Incorrect	0
Correct	1

10. {ELBOW} #

(Interviewer points to their elbow)

What do we call this?

Incorrect	0
Correct	1

11. {SHOULD} #

(Interviewer points to their shoulder)

What do we call this?

Incorrect	0
Correct	1

I WAS JUST SHOWING YOU THINGS AND YOU TOLD ME WHAT WE CALL THEM. NOW I WILL TELL YOU THE NAME OF SOMETHING AND I WANT YOU TO DESCRIBE WHAT IT IS. FOR EXAMPLE

12. {BRIDGE} #

What is a bridge?

Incorrect	0
Correct*	1

*Correct answers: to walk across water, to climb up etc.

13. {HAMMER} #

What do you do with a hammer?

Incorrect	0
Correct*	1

*Correct answers: to drive a nail into something

14. {PRAY} #

What do people do in a church/ temple/ mosque(as appropriate)

Incorrect	0
Correct*	1

*Correct answers: to pray, to wed

15. {CHEMIST} #

Where do we go to buy medicine

Incorrect	0
Correct*	1

*Correct answers: chemist, pharmacy etc (accept locally appropriate answers)

16. {REPEAT} #

Now I would like you to repeat what I say

(Only one presentation is allowed, so the interviewer must read the phrase clearly and slowly enunciating carefully)

'No ifs, ands or buts'

Incorrect	0
Correct	1 (exact phrase only)

WORD LIST LEARNING - delayed recall

Do you remember that I readout to you a list of words on a green card? How many of those words do you remember now? Could you please tell me all the words you can remember.

Interviewer - Score correct words in the grid below

BUTTER	
ARM	
LETTER	
QUEEN	
TICKET	
GRASS	
CORNER	
STONE	
BOOK	
STICK	
TOTAL SCORE	

17. {RECALL} ##

Total number of words correctly recalled

18. {NRECALL} #

Do you remember my name? What is it?

Incorrect	0
Correct	1

(allow minor errors)

19. Now we are going to do something a little different, I am going to give you a category, and I want you to name, as fast as you can, all of the things that belong in that category. For example, if I say 'articles of clothing' you could say shirt, tie or hat. Can you think of other articles of clothing?

Wait for the subject to give two words. If the subject succeeds, indicate that the responses were correct and proceed to the test itself. If the subject gives an inappropriate word or reply, correct the response and repeat the instructions. If it becomes clear that the subject still does not understand the instruction, terminate this task and explain why this is so. After

you are satisfied that the subject understands the task, and has given two words naming articles of clothing, say:

That's fine. I want you to name things that belong to another category, 'animals'. I want you to think about all the many different kinds of animal you know. Think of any kinds of animal in the air, on land, in the water, in the forest, all the different animals. Now I would like for you to tell the names for as many different animals as you can. You will have a minute to do this. Are you ready? Let's begin.

Allow one minute precisely. If the subject stops before the end of the time, encourage them to try to find more words. If they are silent for 15 seconds repeat the basic instruction ('I want you to tell me all the animals you can think of'). No extension on the time limit is made in the event that the instruction has to be repeated.

(The score is the sum of acceptable animals. Any member of the animal kingdom, real or mythical is scored correct, except repetitions and proper nouns. Specifically, each of the following gets credit: a species name and any accompanying breeds within the species; male, female and infant names within the species)

19. {ANIMALS} ##

Number of animals in one minute

20. Now I am going to tell you three words and I would like you to repeat them after me

Boat

House

Fish

Interviewer - Score one point for each correct word on first attempt

20.1 {WORDIMM} #

First trial score

No words remembered	0
1 word remembered	1
2 words remembered	2
3 words remembered	3

Then go on to repeat the three words, up to a total of six times until the subject has remembered them all correctly

20.2 {TRIALNO} #

Record number of trials until repeated successfully

Very good, now try to remember these words because I will be asking you later

21. {TOWN} #

What is the name of this city/ town/ village(as appropriate)

Incorrect	0
Correct	1

22. {CHIEF} #

What is the name of the mayor/ village head (as appropriate)

Incorrect	0
Correct	1

23. {STREET} #

What are the names of two main streets near here?
Or (if inappropriate)
What is the name of a river near here?

Incorrect	0
Correct	1

24. {STORE} #

Where is the local market/ local store?

Incorrect	0
Correct	1

25. {ADDRESS} #

What is your address?
Or (if inappropriate)
Who lives next door?

Incorrect	0
Correct	1

26. {WORDDEL} #

Do you remember the three words I told you a few minutes ago?

No words remembered	0
1 word remembered	1
2 words remembered	2
3 words remembered	3

27. {LONGMEM} #

Long term memory
Construct a locally appropriate equivalent of
USA: What is the name of the civil rights leader who was assassinated in Memphis in 1968
Nigeria: Who was the military leader of the Ibos during the Nigerian Civil war fought between 1967-1970

Incorrect	0
Correct	1

The key to this is to give the participant the date and the event and ask them for the identity of the famous person who was involved. The event should be so well known that practically no non-demented person should get it wrong!

Now I would like to ask some questions about time

28. {MONTH} #
What month is it?

Incorrect	0
Correct	1

29. {DAY} #
What day of the week?

Incorrect	0
Correct	1

30. {YEAR} #
What year is it?

Incorrect	0
Correct	1
(within one year)	

31. {SEASON} #
What season is it?

Incorrect	0
Correct	1

(Wet or dry were the appropriate alternatives in Nigeria)

I am going to ask you to carry out some actions so please listen carefully, because I will only tell you one time
(Interviewer -, give complete instructions at one time, do not give step by step)

32. {NOD} #
Please nod your head

Incorrect	0
Correct	1

33. {POINT} #
Please point first to the window and then to the door

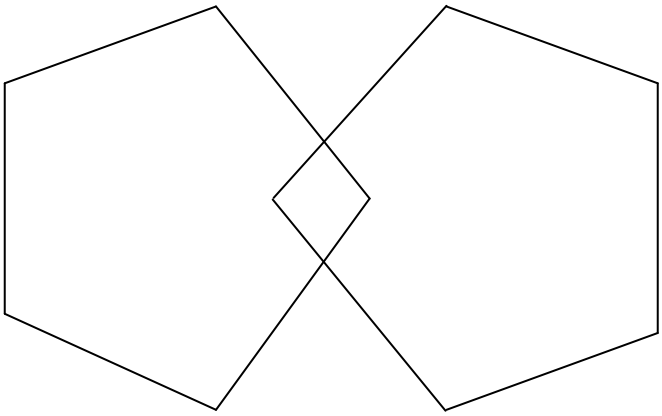
Incorrect	0
Correct	1

34. {PAPER} #
I'm going to give you a piece of paper. When I do, take the paper in your right hand, fold the paper in half with both hands, and put the paper down on your lap.

Score one point for each component carried out correctly

Completely incorrect	0
Uses right hand	1
Folds in two	1
Places in lap	1
(maximum score = 3)	

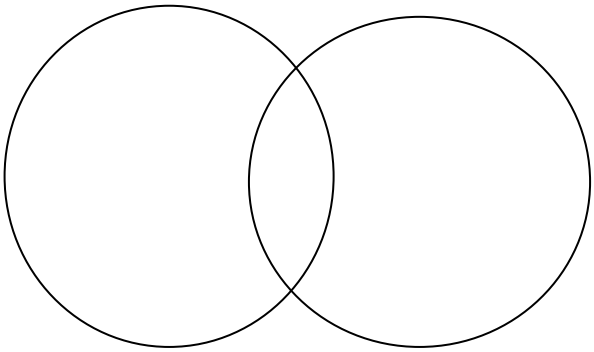
35. Now I would like you to take my pencil and copy these figures in the space given below them on the sheet
See figures on next two sheets



35.1 {CIRCLE} #
Score for circles

Incorrect	0
Correct	1

Score one if two vaguely circular objects intersect to form a meniscus



35.2 {PENTAG} #

Score for pentagons

Incorrect	0
Correct	1

Score one if two five sided objects intersect to form a diamond shape

36. Now I will tell a short story, then I will ask you to repeat as much of the story as you can remember. I want you to listen very carefully because I want you to try to tell me the whole story with as many details as you can remember.

Three children were alone at home and the house caught on fire. A brave man managed to climb in a back window and carry them to safety. Aside from minor cuts and bruises, all were well.

Now I would like you tell me the story in as much detail as possible

36. {STORY} #

Story recall – total items recalled

Interviewer - score one point for each component correctly recalled

3 children		1
house on fire		1
brave man climbed		1
children rescued		1
minor injuries		1
everyone well	1	
(maximum score = 6)		

APPENDIX - 9

Geriartic Mental State examination

GMS (B) 3rd Edition

Study Number .....

Follow-up Number .....

Name of the Subject .....

Date of Interview .....

Time of Interview .....

Investigator Name .....

Investigator Code .....

1. I would like you to remember my name.
   My name is xxxxx can you repeat that?

1.1 Cannot repeat rater's name correctly

2. Can you spell your last name, and your first name?

2.1 Cannot spell both names correctly

3. What year were you born?

3.1 States or indicates by gestures does not know

3.2 Incomplete, irrelevant or no reply

4. How old are you?

4.1 States or indicates by gestures does not know

4.2 Incomplete, irrelevant or no reply

Interviewer Rating

Was there any discrepancy between stated birthdate and stated age?

No 0 Yes 1

If no discrepancy between birth date and age, skip to question 6

5. That doesn't seem to come out right when I add it up.
   Can you help me?

5.1 Shows marked uncertainty about age and birth date 0 1 8 9

5.2 Discrepancy between stated birth date and age which is not corrected by subject 0 1 8 9

5.3 Error of 2 or 3 years. 0 1 8 9

5.4 Error of more than 3 years 0 1 8 9

6. Some people when they are unwell or upset lose track of time;
   So, we always ask- what is the date today?
   Can you tell me what day of the week it is? (What month? What year?)
7. Rate errors in date etc.

7.1 Error in day of week

7.2 Error in month

7.3 States or indicates by gestures does not know month

7.4 Some of the response is incomplete, irrelevant or no reply

7.5 Error in year

7.6 States or indicates by gesture does not know year

Interviewer rating

Is the interview conducted in the participant's own home?

No 0 Yes 2

If interviewed in a place other than own home, skip to question 9

8. What is the (correct) postal address of this place?

8.1 Gives incorrect or incomplete address

8.2 States or indicates by gesture does not know

8.3 Incomplete, irrelevant or no reply

If interviewed at home skip to question 10

9. What is the name of this place, where is it located?

9.1 States or indicates by gestures does not know either name or address

9.2 Incomplete, irrelevant or no reply

9.3 Error in name (partial name accepted)

10. Have you ever seen me before? If yes... When? Where? What was I doing?

10.1 Gives a positive answer and a simple explanation within the bounds of possibility

10.2 Confabulation. An elaborate description of events which clearly could not have occurred. If positive, rate 1 for previous item

OBSERVATION

10.3 Talks in an aimless fashion. Object in view at the beginning is not reached

S3. WORRY

11. What kind of things do you worry about?
11.1 Any kind of worries mentioned

12. What about money or family problems, your own health or someone else's health? (Anything else?)
If no worries mentioned, skip to question 17

16. Content of worries, if any

16.1 Own health

16.2 Other's health

16.3 Own finances

16.4 Family problem

14. How much do you worry?

14.1 Worries a lot (i.e about one or two things)

14.2 Is a worrier or worriers about almost everything

15. Does this worrying bother you a lot? Is it unpleasant? Do the thoughts keep coming back? (Can you stop yourself worrying?)

15.1 Unpleasant worrying which keeps coming back or cannot be stopped

17. Do you have any children?

No 0 Yes 1

If NO, skip to question 19

18. Is there anything about your relationship with your children that upsets or bothers you?

18.1 Upset or bothered by relationship with children

S4. GENERAL ANXIETY

19. Do you get frightened? (Very anxious?) (Has that happened lately?) (What made you feel that way?)

19.1 Subjective fear or anxiety, out of proportion to the event, if any, that provoked the feeling

20. Have you had attacks of fear or panic, when you had to do something to end it?

20.1 Episode of anxiety which subject tries to terminate

S5. DEPRESSION

21. Have you been sad (depressed, miserable, in low spirits) recently?

21.1 Depressed mood

22. Have you cried at all? (How often)

22.1 Has cried

If has cried, skip to question 24

23. Have you felt like crying, without actually weeping? (How often?)

23.1 Has felt like crying

If interviewee does not admit to depression,* crying*, or feeling like crying, skip to question 28

24. Is the depression/crying/ feeling like crying three most of the time?

How long does it last? (Just a few hours at a time or longer than that?)

24.1 Depression, crying or feeling like crying lasts Longer than just the occasional few hours
24.2 Depression, crying or feeling like crying is present most of the time

24.3 Present for at least two continuous weeks in the last month

25. Are there times when you feel back to your normal self?

25.1 Fluctuating mood

26. What time of day do you feel the worst?

If none- rate 0 for all

If all – rate 1 for all

26.1 Morning predominantly

26.2 Afternoon predominantly

26.3 Evening predominantly

27. What relatives the depression? For how long?

27.1 Nothing relieves

27.2 Depression not relieved for several hours at a time by having visitors, entertainment, etc.

28. Have you felt that life was not worth living?

28.1 Has felt life was not worth living

29. How do you see your future? (What are your hopes for the future?) (How do you feel things will work out for you in the future?)

29.1 Not pessimistic, but has empty expectations

If pessimistic- why is that? Have you ever felt really hopeless?

Is there something about the future that you do not like to think about?

29.2 Is pessimistic or future seems bleak or can see

No future at all or future seems unbearable

29.3 A general feeling of hopelessness, despair

29.4 Pessimism obviously warranted by circumstances

30. Have you ever felt that you'd rather be dead? Have you ever felt you wanted to end it all? (Have you ever thought about doing something about it yourself?) (Killing yourself?)

30.1 Has ever felt suicidal or wished to be dead

If NOT (0) skip to item 33

31. When was that? Have you felt like that recently? (In the last month?)

31.1 In last month

31.2 In last year

31.3 Has felt a wish to be dead for at least two weeks in the last month

If NOT in last month, skip to item 33

32. Did you actually try anything? When was that? What did you do? Why do you think you felt that way?

32.1 Has done something or planned to do something about killing self

32.2 Has rejected suicide but has wished to be dead because life is a burden

33. Observation

33.1 Looks or sounds tense, worried, depressed or fearful

If does NOT, skip to question 34

33.2 Looks or sounds tense or worried

33.3 Looks or sounds sad, gloomy, mournful or depressed

33.4 Looks or sounds apprehensive or fearful

33.5 Eyes moist: tearful or crying

S6. MEMORY

34. Have you had any difficulty with your memory? If yes.... (Is that a problem for you?)

34.1 Subjective difficulty, i.e implies memory impairment is a problem for him/her

35. Have you tended to forget things recently? (What kind things?) (Name of your family or close friends?) (Where you have put things?)

35.1 Forgets names of family or friends, misnames them

35.2 Forgets where he/she has placed things

36. Do you have to make more effort to remember things than you used to? What sort of things? When did you notice this beginning?

36.1 Has to make a greater effort to remember things than used to ***If no, skip to question 37***

36a. When did you notice this beginning?

36.2 During the last 1-2 years

36.3 During the last 3-4 years

36.4 During the last 5-10 years

36.5 Over 10 years ago

37. Do you remember my name? What is it?

37.1 Does not recall rater's name correctly

38. What is the name of the prime minister?

38.1 Does not recall name of Prime minister

39. Who was the last Prime minister?

39.1 Does not recall name of previous prime minister

40. Observation

40.1 In rater's opinion subject has difficulty with memory

45. OBSERVATION

45.1 Subject looks emaciated, frail, physically ill or handicapped

45.2 One or more limbs, or one side of face appears to be wholly or partially paralysed.

If NO paralysis skip to question 48

47. What did the doctor say was wrong with your ...was the possibility of a stroke mentioned?

47.1 Interview indicates he/she had, or probably had a stroke.

S8 TENSION

48. Do you get worn out (exhausted)? What about towards the evening?

48.1 Gets worn out or exhausted during daytime or evening

49. Do you have difficulty in relaxing (resting)?

49.1 Difficulty in relaxing

50. Do you have headaches? Where? What are they like?

50.1 Describe headaches

50.2 Describes tension headaches

S9. SOMATIC DYSFUNCTION

51. What has your appetite been like? Do you enjoy your food? Have you been eating more or less than usual?

51.1 Diminution in the desire for food

51.2 Increase in the desire for food

If no diminution or increase, skip to question 53

52. Why is that? Has it been like that most days in the last month?

52.1 Poor appetite in the absence of known medical condition and without nausea

52.3 Increased appetite present most days for at least two weeks in the last month

53. Have you lost any weight during the past three months? (Have you gained weight?) How much in the last month?

53.1 Lost 10 lbs (4.5kg) or more over the past 3 months

53.2 Lost 10 lbs (4.5kg) or more within the past 1 month

53.3 Lost 10 lbs (4.5kg) or more within the past 1month

54. Have you had trouble sleeping recently? (Have you taken anything to help you sleep?)

How long has it been going on for? What used to happen?

54.1 Trouble with sleep or recent change in pattern

If none, skip to question 61

54.2 Trouble falling or staying asleep, or taking medication or alcohol for sleep

54.3 Has insomnia for most of the night and sleeps mainly during the daytime

54.4 Marked insomnia most nights for at least two weeks in the last month

54.5 Marked excessive sleep most nights for at least two weeks in the last month

55. Have you had any difficulty falling asleep? (Getting off to sleep)?

Do you lie awake for long periods of time (waiting for sleep?)

55.1 Difficulty in falling asleep. If tablets take, rate what interviewee thinks would have happened without them

56. Is your sleep interrupted during the night?

56.1 Sleep interrupted during the night

If tablets take, rate what interviewee thinks would have happened without them

If no sleep interruption, skip to question 61

57. Have you recently been waking up early in the morning and found it impossible to get back to sleep? What time would that be?

Is that your usual time? How often has it happened?

57.1 Awakens about two hours or more before normal time of awakening and cannot get back to sleep, most nights for at least two weeks in the last month.

58. What wakes you up? (What is the difficulty?) Is it a physical problem like having to pass urine, or pain? Does noise bother you?

58.1 Difficulty is due to altered moods or thoughts, or tension

58.2 Mainly due to or arising from a physical cause in the body, or noise, etc

S11. AUTONOMIC SYMPTOMS

61. Have you felt your heart pound or felt yourself trembling in the last month? (When this was not due to exercise?) What was happening at the time?

61.1 palpitations

61.2 Trembling or tremulous feeling due to anxiety

61.3 Other bodily features due to anxiety

S12. THINKING DIFFICULTIES

62. Do you seem to be very slowed down in your thinking recently?

62.1 Subjective slowing in thinking

63. Do your thoughts get mixed up(muddled)?

(Can you think clearly (straight)?) (How long has that bothered you? How often?)

63.1 Feeling of being muddled

64. Do you find it difficult to make up your mind (to make decisions)? (How long has that bothered you? How often?)

64.1 Feels indecisive

64.2 A feeling of muddled thinking or indecisiveness has been present most days, for at least two weeks

64a. How are you coping with the things you have to do every day?

64.3 Feeling of not coping properly with everyday routine

64b. How confident would you say you felt (In yourself)?

64.4 Loss of confidence in self

65. Observation

65.1 Sounds (seems) muddled

65.2 Appears indecisive

S13. SLOWING

71. Do you seem slowed down in your (Physical) movements at all?

71.1 Subjectively slowed in movements

72. Have you had too little energy (to do the things you want to do)? How long have you had that for? Are you like that most days?

72.1 Listlessness or subjective restriction of energy

72.2 Present most days for at least two weeks

73. Have you been doing more, less, or about the same as usual?

73.1 Doing less than usual?

If no slowing, anergia or reduced activity, skip to observation item 78

74. Did this (SLOWING/LOSS OF ENERGY/REDUCTION IN ACTIVITES)

Start or perhaps get worse in the last three months?

74.1Started or became worse in the last three month

75. Is there any time of the day when this is at its worst?

Is it present most days?

75.1 Slowness or anergia is worst in the morning

75.2 Slowness or anergia is worst in the evening.

75.3 Slowness is present most days for at least two week

76. What about when someone visits you or you have to go out? Does that make any difference?

76.1 Does not lift with usually pleasant activities

77. Have you actually been sitting around a lot (or spending more time in bed than usual) because of lack of energy.

77.1 Sites or lies around because of lack of energy

78. OBSERVATION

78.1 Very slow in all movements

S15 LONLINESS

87. Do you feel lonely?

87.1 Admits to feeling lonely

If does not feel lonely, skip to question 90

88. Does it bother you very much? Can you get out of it?

88.1 Feels lonely and cannot turn away from it

88.2 Bothered or depressed by current loneliness

89. Does the possibility of being alone in the future worry you?

89.1 Worries about being alone in the future

S16. PERSECUTION

90. How do you get on with people generally? Do they make you feel ill at ease?

90.1 Feels ill at ease

91. Do you something get the feeling people are laughing at you or talking about you?

91.1 Does have that feeling

If previous question negative, skip to question 93

92. Do you think it really is true, or is it perhaps just the way you feel about it? (Are you sure?)

92.1 Probably not true

92.2 Considers it is true

92.3 Convinced it is true

93. We can't be expected to get on with everybody. Is there anyone (you don't need to tell me who) that you have particular difficulty with?

93.1 There is such a person/persons

If there is person or persons, skip to question 95

94. Is anyone trying deliberately to annoy you or harm you?

94.1 Unrealistic belief that someone is trying to annoy or harm him

If no unrealistic belief... skip to observation item 103

95. Well, I expect you are generally a reasonable person MR/MRS/MS so is it probably their fault?

95.1 Says it is their fault but subject has doubts95.2 Says it is their fault and subject has no doubt

96. Of course some people can be really unpleasant; and that can be upsetting. Do you suppose that they are doing it on purpose to annoy you?

96.1 Subject believes they are?

97. What do they do?

97.1 Subject unrealistically believes people are deliberately trying to annoy or harm him/her

98. Why do they do that do you suppose? Do you believe you've done anything to deserve it. Do you really feel strongly about it?

98.1 Indicates he/she feels strongly about it

98.2 Indicates he/she deserves to be persecuted

99. Do you think you could be mistaken?

99.1 Subject does not believe he/she is mistaken.

If interviewee believes he or she is mistaken, skip to item 102

100. Could they be trying to do you real harm? (In what way?)

100.1 Subject believes person/persons are trying to do him/ her serious physical harm or kill him/her

100A. Do they resort to any tricks? (What do they do?)

100.3 No = 0 Yes = 1

101. You don't need to tell me who it is of course, but I would be interested to know?

101.1 Subject claims it is an official body/person or organisation, (police M.I.5, K.G.B., etc)

101.2 Subject claims it is a private person, known or unknown

102. Judgement – The subject's beliefs are:

102.1 Unlikely to be true, but possible

102.2 Absurd, or almost certainly not true

103. Observation

103.1 Subject looks or sounds unduly suspicious

S17. GUILT

104. Do you tend to blame yourself or feel guilty about anything? What? (Do you mean you actually feel worthless?) (How long have you felt like this?) Is it reasonable?

104.1 Obvious guilt or self blame over past and present peccadilloes (Do not include justifiable or minor self blame)

104.2 Mentions regrets about past which may or may not be justifiable

104.3 Feeling worthless or severe guilt most days for at least 2 weeks

104.4 Worthlessness or guilt of delusional intensity, most days

S18. IRRITABILITY

105. Have you been more irritable (angry) lately? (For how long?)

105.1 Admits to irritability (anger)

105.2 Irritable most days for at least two weeks in the last month

106. Do you get angry with yourself?

106.1 Gets angry with self

S20. INTEREST

113. How is your interest in things? (Do you keep up your interests?)

113.1 Has less interest in things in the last month than used to have

114. What have you enjoyed doing recently? (Has been any change?)

114.1 Almost nothing enjoyed

If no decrease in interest or enjoyment, skip to question 117

115. When did you notice this loss of interest/ enjoyment? When did it start? Has it been present recently? For how long? Is it there most days?

115.1 Gradual over several years

115.2 Only within the last 3 months

115.3 Loss of interest or enjoyment most days for at least two weeks in the last month

116. Is it that you're too depressed or nervous?

116.1 Too depressed or nervous

S21. CONCENTRATION

117. How is your concentration? Can you concentrate on a television (Radio, film) programme? Can you watch it (Listen to it) All the way through?(How long has that bothered you? how long has that bothered you? How often?)

117.1 Difficulty in concentrating on entertainment

118. Do you read? Can you concentrate on something you read?(can you read it right through?) (How long has that bothered you? How often?)

118.1 Difficulty in concentrating on reading

118.2 Difficulty with some form of concentration most days, for at least two weeks

119. Observation

119.1 Obvious difficulty in concentrating on interview

S22. PERCEPTUAL

120. Does your imagination ever play tricks on you?

120.1 Describes abnormal perceptual experience

121. Is something odd (strange) going on which you cannot explain?

121.1 Puzzled by something odd going on

122. Do you get strange sensations in your body?

122.1 Somatic hallucinations

122.2 Delusions involving sexual sensations

123. Do you smell strange odours (SMELLS) that others do not notice?

123.1 Olfactory hallucinations

123.2 Delusions involving smell, e.g subject or other person gives off smell, gas pumped into rooms etc.

123.3 Subject claims that he/she gives off a bad smell

(If 123.2 of 123.3 are positive, rate 1 or 2 for previous two items.)

124. Do you notice an unusual taste in your food or drink?

What is it like? What is it due to?

124.1 unpleasant taste not necessarily hallucinations e.g. bitter taste

124.2 Gustatory hallucinations

125. Do you hear things other people cannot hear? If yes – (what do you hear?)

(What about voices?) (When there is no one about?) (What do they say?)

125.1 Indicates he/she hear voices in the absence of identifiable external stimulation.

127. Do you have visions or see things that are invisible to other people?

127.1 Indicates he/she experiences visual perceptions in the absence of identifiable external stimulation

If no visual hallucinations, skip to question 130

128. Was it when you were wide awake?

128.1 Visions while wide awake

129. Did you think it was real?

129.1 Thought it was real

INTERVIEWER RATING

Have you made any positive rating for delusions (fixed false beliefs) or hallucinations (sensory perceptions in the absence of external stimulation?)

NO 0 YES 1

If no delusions or hallucinations, skip to question 136

130. What do you feel about these experiences? (Do you get angry or sad or frightened?) (Do you deserve it?) (How do you show it?) (Do you even enjoy it?)

130.1 Marked affective response
130.2 Indignantly feels the experiences are not deserved

130.3 Feels the experiences are deserved punishment

130.4 Subject seems indifferent and apathetic or does not report much emotional reaction

130 a. AFFECTIVE RESPONSE TO DELUSIONS OR HALLUCINATIONS

130.5 Content of delusions/ hallucinations are unpleasant or persecutory, but not resented and consistent with depression

130.6 Content of delusions/ hallucinations are pleasant, appreciative or grandiose and consistent with elation

130.7 TIMING OF DELUSIONS OR HALLUCINATIONS IN RELATION TO MOOD

At no time have there been delusions or hallucinations for as long as 2 weeks in the absence of prominent mood symptoms (i.e before the mood symptoms developed or after they have remitted)

135. OBSERVATION

135.1 Subject is taking drug prescribed by doctor for mental problem

S24. DRUG ABUSE

136. Do you take any medications you can't do without? To help you cope or feel better or calm you down?

136.1 Opium, heroin, morphine- like analgesics, cocaine

136.2 Hallucinogens

136.3 Cannabis

136.4 Other psycho stimulants (e.g. amphetamines)

136.5 Barbiturates

136.6 Other Hypnotics and sedatives

136.7 Tranquillizers (Valium, Librium etc.)

136.8 Other

S25. ALCOHOL INTAKE

137. May I ask you about your drinking habits- for alcohol? Do you have a drink more or less every day?

137.1 Does

138. Do you sometimes go without for a while and then drink for several days at a time?

138.1 Does

139. Is alcohol in any way a problem for you?

139.1 Subject admits that it is a problem

IF ABOVE 3 QUESTIONS RATED 0 SKIP TO QUESTION 144

140. How much do you drink when you are by yourself?

140.1 Indicates that, while alone, he/she often has 3 or more alcoholic drinks in succession.

141. How many times a day do you usually have a drink?

141.1 Indicates he/she usually drinks alcohol on 4 or more occasions spaced out throughout the day

141.2 Indicates he/she usually drinks alcohol for sustained periods of time (over 3 hours) each day

IF ALL PARTS OF Q 140 AND Q141 RATED 0 SKIP TO QUESTIONS 144

142. Have you in the last 3 months suffered falls or unsteadiness, forgotten what happened for part of the day, had shaking of the hands, vomiting, or anything else which has occurred because of drinking too much, or not being able to get a drink?

142.1 Has suffered such effects of excessive drinking or withdrawal

143. Do you need a drink in the morning before you start the day?

143.1 Needs such a drink

144. OBSERVATION

144.1 Rater believes the subject has a drinking problem

S26. ERROR BEHAVIOUR

INTERVIEWER RATING

Were there any errors or 8's in the orientation or memory sections, or numerous 8's elsewhere in the interview?

No 0 Yes 1

IF NO, SKIP TO S29, FINALE

145. OBSERVATION

145.1 Errors made in clear consciousness due to agitation, depression elation, etc.

145.2 Errors made in clear consciousness due to memory defect

145.3 Errors made in clouded consciousness

145.4 Subject's reaction to errors was characteristically bland, indifferent ceuphoric

S29. FINALE

155. How would you describe your satisfaction with life..?

155.1 Good = 0, Fair = 1, or poor = 2?

156. In general, how happy would you say you are...?

156.1 Very happy= 0, fairly happy=1, not very happy =2, not happy at all=3

Is there anything else at all that I have not covered?

Well, thank you very much MR/MRS/MISS x – that completes this part of the interview.

INTRERVIEWER RATING

Is the interview complete?

No 0 Yes 1

IF YES SKIP TO S31

S30. BEHAVIOURAL RATINGS –GENERAL

(Rate this page only if interview is incomplete)

158. DEPRESSION

158.1 Looks or sounds sad or mournful or depressed

158.2 Eyes moist: tearful or crying

159. Slow

159.1 Very slow in all movements

160. THINKING DIFFICULTIES

160.1 Sounds muddled

160.2 Appears indecisive

161. SOCIAL DISCOMFORT

161.1 Looks or sounds unduly suspicious

162. CONCENTRATION

162.1 Obvious difficulty in concentrating on interview

S31. AFFECT

163. DIMINISHED EMOTIONAL EXPRESSION

163.1 Expressionless FACE.

163.2 Monotonous VIOCE.

163.3 No gesture accompanying speech

163.4 No appropriate emotion shown when delusional or normal material is discussed which would usually bring out emotion

163.5 Uniforms blunting of mood, whatever the tone of conversation

164. EXCESSIVE EMOTIONAL EXPRESSION

164.1 Uncontrollable short bouts of crying

164.2 Uncontrollable short bouts of laughing

165. LAUGHING

165.1 Elated, euphoric, even though perhaps changing to irritability or depression

165.2 Inectious gaiety

166. OTHER AFFECT

166.1 Facetious: silly jokes, flippant remarks

167. UNCO-OPERATIVE, ETC.

167.1 Tries to start an argument

170. SPECIAL MOVEMENTS

170.1 Choreiform movements

170.2 Athetoid movements

170.3 Parkinsonian movements

170.4 Gait – obvious abnormality of walking

170.5 Gait – obvious evidence of paralysis or stroke

170.6 Gait-obvious evidence of physical abnormality of the legs

170.7 Gait normal, just unsteady

170.8 Staggers as if drunk

170.9 Takes slow shuffling steps

174. INCOHERENCE

174.1 Vague quality to speech

174.2 Patient talks fairly freely but vaguely and ambiguously

174.3 Irrelevance:

174.4 Circumstantial:

174.5 Rambling:

175. RATE OF SPEECH

175.1 Extremely rapid speech but can be interrupted

175.2 Pressure of speech:

175.3 Flight of ideas

175.4 Speech very slow. Distinct pauses between words

175.5 Long pauses before replying

177. PERSEVERATION

177.1 Repeats answers in appropriately

178. JUDGEMENT

178.1 Problem with memory are more prominent than problems with thinking

S35. COMMUNICATION DIFFICULTIES

179. NON- PATHOLOGICAL COMMUNICATION DIFFICULTIES

179.1 Foreign language

179.2 Unclear English dialect or accent

179a. PHYSICAL DEFECTS.

179.3 Dysphasia (due to brain damage)

179.4 Dysarthria (due to brain damage)

179.5 Dysarthria (due to speech organs)

179.6 Deafness- severe

179.7 Blindness- nearly total

179.8 Stuttering

179.9 Mutism specified as due to physical defect

179.10 Weakness –severe

179.11 Other

179.12 LOW INTELLIGENCE

179b. NON SPECIFIC BEHAVIOUR

179.18 Slurring not specified as due to physical defect or drugs

179.19 Other

179.20 Interview conditions unfavourable

179.21 Patient repeatedly falls asleep

179.22 Patient appears generally sleepy

180. PATHOLOGICAL COMMUNICATION DIFFICULTIES

180.1 Memory defect (clear-cut)

180.2 Memory defect (dubious)

180.3 Incoherent in clear consciousness

180a. VIVIDLY PATHOLOGICAL BEHAVIOUR

180.4 Keeps referring to delusion or hallucinations

180.5 Incorporates rater's in delusions

180.6 Posturing

180.7 speaks coherently to self; speaks to voice

180.8 Cries uncontrollably

180.9 Pressure of speech

180.10 Gross Suspiciousness

180.11 Other

180b. AMBIGUOUS PATHOLOGICAL BEHAVIOUR

180.12 Mutism not specified as due to physical defect

180.13 Suspicious. Negativistic

180.14 Withdrawal or apparent apathy

180.15 Over- talkative but not pressure of speech

180.16 Lack of insight. Total denial of symptoms or illness

180.17 Excited or agitated or obviously elated

180.18 Pre-occupied with inner experiences

180.19 Distractibility

180.20 Other

181. CONFIDENCE AND CASENESS

181.1 Rater's confidence in data

0 = Reasonable 1 = A few doubts 2 = Moderate doubts 3 = Grave doubts 4 = Worthless

182. _____ Rater doubts reliability due to:

182.1 Exaggeration or tendency to say yes, indiscriminately

182.2 Minimization or tendency to say no, indiscriminately

183 MENTAL HEALTH

183.1 Primary Psychiatric Clinical Diagnosis

183.2 Secondary Psychiatric Clinical Diagnosis

APPENDIX – 10

HISTORY AND AETIOLOGY SCHEDULE – DEMENTIA DIAGNOSIS AND SUBTYPE (HAS-DDS)

A. ONSET

HAS 1. Thinking back, could you give an approximate date when you or anyone else first noticed she was having difficulties with .....
(List cognitive and functional impairmentsidentified above)
Code time since onset in months {TIMEONS}

HAS 2. Did this begin rapidly or gradually?
(If rapid onset)- When was that?
1 Rapid onset of organic features over 1-3 days
2 Rapid onset over more than 3 days but less than 3 weeks
3 Gradual onset over a longer period {TYPEONS}

HAS3 I am going to ask you now about some problems that she may have had right at the beginning of her illness. Please tell me if any of these were a problem in the first few months of her illness.

HAS3.1 Did she have difficulties in remembering things?
0 No 1 Yes {ONS1}

I.HAS.3.2 was she confused about the time, or what day it was, or where she was?
0 No 1 Yes {ONS2}

I.HAS.3.3 Was she drowsy?
0 No 1 Yes {ONS3}

I.HAS.3.4 Did she feel sad, or cry?
0 No 1 Yes {ONS4}

I.HAS.3.5 Did she lose energy or show a lack of interest?
0 No 1 Yes {ONS5}

I.HAS.3.6 Was she unusually elated?
0 No 1 Yes {ONS6}

I.HAS.3.7 Did she become excited or overactive?
0 No 1 Yes {ONS7}

I.HAS.3.8 Did she complain of physical disease or illness?
0 No 1 Yes {ONS8}

I.HAS.3.9 Did she have difficulty sleeping?
0 No 1 Yes {ONS9}

I.HAS.3.10 Was she losing or gaining weight?
0 No 1 Yes {ONS10}

I.HAS.3.11 Did she see things that other people did not see?
0 No 1 Yes {ONS11}

I.HAS.3.12 What about hearing things that other people did not hear?
0 No 1 Yes {ONS12}

I.HAS.3.13 might it have started with some kind of stroke?
prompt - a stroke is a paralysis (weakness) of the face or Limbs on one side of the body, lasting at least 24 hours
if yes - can you describe what happened?
NB - Must be a clear history of stroke
0 No 1 Yes {ONS13}

I.HAS.3.14 Did she have problems finding the right word?
If yes - Can you give some examples
NB - Code only gross and persistent word finding difficulty and exclude delirium
0 No 1 Yes {ONS14}

I.HAS.3.15 Did she forget how to do familiar things like dressing?
NB - Exclude difficulties related to delirium or to physical disorder
0 No 1 Yes {ONS15}

I.HAS.3.16 Might it have started with some kind of epileptic fit?
If yes - was this diagnosed by a doctor?
NB- Code only epileptic fits diagnosed by a doctor
0 No 1 Yes {ONS16}

I.HAS.3.17 did she suffer from any sudden blackouts in which she actually lost consciousness?
0 No 1 Yes {ONS17}

I.HAS.3.18 Was she unsteady or slow on her feet?
0 No 1 Yes {ONS18}

I.HAS.3.19 Was she tending to fall for no apparent reason?
0 No 1 Yes {ONS19}

I.HAS.3.20 Did she have difficulty in controlling her emotions, for Example, laughing or crying uncontrollably
0 No 1 Yes {ONS20}

I.HAS.3.21 Did she wet herself?
0 No 1 Yes {ONS21}

I.HAS.3.22 How are things now compared with when the illness came on? Has it become worse, got better, or remained about the same?
1 Overall deterioration described
2 Overall improvement described
3 None or very little change in condition {ONS221}

3. COURSE OF ILLNESS

I.HAS.4 Has the present illness tended to vary a lot, day to day, week to week, becoming worse, then perhaps improving for a while - up and down?
(If yes- - How much did it vary? How long did these periods last?)
1 A fluctuating course with several days or weeks of improvement
0 No such pattern
IF "0" No such pattern' then skip to I.HAS.6 {FLUCT}

I.HAS.5.1 During the periods of improvement did thinking, memory and Concentration become normal again or almost normal?

1 Condition described as returning to normal or almost normal
0 No such pattern
IF "0" No such pattern' Then skip to I.HAS.6 {FLUCTCOG}

I.HAS.5.2 How often has this happened?"

1 Once
2 Twice
3 Three times
4 Four times or more {FLUCTOFT}

I.HAS.6 Would you say there has been a gradual deterioration of memory or .... (list current cognitive impairments) Over a period of more than 2 years?

0 No 1 Yes {GRADDEC}

I.HAS.7.1 Has the present illness suddenly got worse at anytime,within three days and then stayed like that?

0 No 1 Yes
If ' NO' then skip to I.HAS.10 {STEPWISE}

I.HAS.7.2 When was that?
(Code time in months since each of up to four episodes - code 99 if no nth episode)

First episode {STEP1}
Second episode {STEP2}
Third episode {STEP3}
Fourth episode {STEP4}

I.HAS.8 Were any of these episodes preceded by;

1 Blackouts or loss of consciousness?
2 An epileptic fit?
3 Difficulties in speaking?
4 Weakness of the arm and/ or leg or face on one side of the body?
0 None of these

(Code highest applicable number - code 9 if no nth episode)

First episode {STEPPRE1}
Second episode {STEPPRE2}
Third episode {STEPPRE3}
Fourth episode {STEPPRE4}

I.HAS.9 Was this sudden worsening followed by almost complete recovery? More or less back to her normal self?

0 No 1 Yes
(Code 9 if no nth episode)

First episode {STEPREC1}
Second episode {STEPREC2}
Third episode {STEPREC3}
Fourth episode {STEPREC4}

B. Other mental phenomena

B1) Delirium

I.HAS.10 Are there periods over 24 hours when she seems very changeable; Alert at one time, drowsy and confused the next?
0 No 1 Yes {CLOUDING}

I.HAS.11 Does she get confused at night, wander about, talk nonsense?
0 No 1 Yes {CONFNITE}

I.HAS.12 What about during the day?
0 No 1 Yes {CONFDAY}
IF NO FOR THE 3 ITEMS ABOVE SKIP TO I.HAS.14

I.HAS.13 Is the confusion worse towards the dusk or evening?
0 No 1 Yes {NOCTURN}

B2) Behavioural and Perceptual disturbance

I.HAS.14 How does she treat you (her relatives, friends) now compared with before the onset of the illness – for example

I.HAS.14.1 Does she show a lack of interest, concern or affection now Compared with before?
0 No 1 Yes {BCHANGE}

I.HAS.14.2 Does she tend to be too suspicious or mistrusting?
0 No 1 Yes {BSUSPIC}

.HAS.15 Has she been more irritable lately?
0 No 1 Yes {BIRRIT}

I.HAS.16 Does she ever wrongly accuse you of things?
0 No 1 Yes {BACCUSE}

I.HAS.17 Has there been a change in behaviour, perhaps doing embarassing things, or tending to upset people?
0 No 1 Yes
IF "NO" THEN SKIP TO I.HAS.19 {BUPSET}

I.HAS.18 Were these one of the first things that you noticed or has this come on only recently?
0 Come on only recently
1 One of the first things noticed {BFIRST}

I.HAS.19 Has she ever seemed to be responding to things – for example

I.HAS.19.1 Did she see things that other people did not see?
0 No 1 Yes {BVIS}

I.HAS.19.2 What about hearing things that other people did not hear?
0 No 1 Yes {BAUD}

I.HAS.20 Does she have any odd or strange beliefs which you have good evidence to beleive are unfounded?
0 No 1 Yes {BDELUDE}

B3) DEPRESSION

I.HAS.21.1 Were there times in the last year when she felt or appeared depressed, low, sad or miserable
0 No 1 Yes {DEPRESS}

I.HAS.21.2 How long did it last?
1 Less than a day
2 One day to two weeks
3 Lasted longer than 2 weeks {DEPDUR}

I.HAS.22.1 Has she cried or complained of feeling like crying over the Last year?
0 No 1 Yes
IF '0 NO' SKIP TO I.HAS.23 {CRY}

I.HAS.22.2 How long did it last?
0 Only for a few hours
1 Lasted longer than a few hours {CRYDUR}

I.HAS.23 Has she sometimes felt or said that life was not worth living
0 No 1 Yes {WISHDIE}

I.HAS.24 Were there times over the last year when she seemed to lose interest in life generally?
0 No 1 Yes {INTEREST}

I.HAS.25 Were there times over the past year when she stopped enjoying life?
0 No 1 Yes {ANHED}

I.HAS.26 Has she had particular difficulty sleeping?
If yes - Why was that?
Was it because of noise?
Was it because she needed to go to the bathroom?
(rate only if primary sleep difficulty, not due to pain, passing urine,noise etc.)
0 No primary sleep difficulty
1 Primary sleep difficulty {SLEEP}

I.HAS.27 Has she stopped enjoying food over the last year?
If yes - Why was that?
Was she ill?
Did she complain of feeling sick?
(Rate only if primary loss of appetite, not explained by medical condition or nausea
0 No unexplained loss of appetite
1 Unexplained loss of appetite {EAT}

I.HAS.28.1 May i ask if somebody close to her has died recently?
0 No 1 Yes
IF '0 NO' SKIP TO I.HAS.29 {BEREAVE}

I.HAS.28.2 Was this -

1 A first degree relative in the last six weeks?
2 A first degree relative, more than six weeks but less than 2 years ago?
3 Another close person in the past six weeks?
4 Another close person, more than six weeks but less than two years ago?

{BERWHEN}

I.HAS.29 Interviewer judgement
0 No episode of depression
1 Probable episode of depression
2 Definite episode of depression
9 Insufficient information {DEPIMP}

C. PHYSICAL HEALTH

C1) Vascular disease

I.HAS.30 Has a doctor ever told her that she had raised blood pressure?
0 No 1 Yes {TOLDBP}
IF NO SKIP TO I.HAS.32.1

I.HAS.31 Has this ever been treated?
0 Never treated
1 Treated in the past
2 Treated now {TREATBP}

I.HAS.32.1 Has she ever experienced a sudden weakness in one arm or leg, or an arm and leg on the same side of the body?
0 No 1 Yes
IF '0 NO' THEN SKIP TO I.HAS.33 {CVEVENT}

I.HAS.32.2 When did it happen? How long did it last?
Was a doctor consulted? What did they say had happened?
Record up to four clear cut cerebrovascular events giving -

a) Type	b) Time
1 Less than 24 hours (TIA)	in months since event
2 24 hours or more (CVA)	
9 No nth event	

a) {CVTYPE1}	b) {CVDATE1}
a) {CVTYPE2}	b) {CVDATE2}
a) {CVTYPE3}	b) {CVDATE3}
a) {CVTYPE4}	b) {CVDATE4}

I.HAS.33 If something happens to make her laugh or feel sad or cry, is it sometimes difficult for her to control?
1 Appropriate but uncontrolled prolonged laughter and/or tears described
0 no uncontrolled laughter or tears

{AFFINCON}

I.HAS.34 Has there ever been pain or discomfort in the chest or legs that comes on with walking and goes away after a few minutes rest?
Clear history of angina pectoralis?
0 No 1 Yes {ANGINA}

Clear history of intermittent claudication?
0 No 1 Yes {INTCLAUD}

I.HAS.35 Has a heart attack ever been diagnosed by a doctor?
0 No 1 Yes {MIDIAG}

C2) PARKINSONISM

I.HAS.36 Has she ever been diagnosed as having parkinson's disease?
0 No
1 Probable
2 Certain
(If rated '2 Certain', Skip to I.HAS.41) {PARK}

I.HAS.37 Does she have any tremor or shakiness in her hands? If yes - when is that most noticeable?7
0 No
1 Yes - when she tries to do something
2 Yes - when resting {TREMOR}

I.HAS.38 Does she have difficulty in starting to move?
0 No
1 Yes - probably due to Parkinson's Disease
2 Yes - probably due to another problem {INITIATE}

I.HAS.39 Has her walking become slower recently?
0 No
1 Yes - probably due to Parkinson's Disease
2 Yes - probably due to another problem {SLOW}

I.HAS.40 Has her handwriting changed recently?
If yes- in what way?
0 No change
1 Yes - become smaller
2 Yes - some other change {MICROG}

I.HAS.41 How many times has she fallen for no apparent reason over the past year?
Code number of falls {FALLSNO}

C3 ALCOHOL

I.HAS.42 Before she reached the age of 55, what was the most she Would drink in an average week ?
(Record maximum regular consumption in UNITS of alcohol per week)
1 unit = a small glass of beer
a single measure of spirits
1 glass of wine or sherry
32 units= 1 bottle of spirits
99 = Don't know {ALCPAST}

I.HAS.43 What about after the age of 55?
(Record total consumption in units of alcohol) {ALCNOW}
IF NEVER A DRINKER SKIP TO I.HAS.47

I.HAS.44 Has there ever been a period of several years, when you would have said that she was a heavy drinker?
0 No 1 Yes {HEAVYALC}

I.HAS.45 Has she ever had treatment or help for drinking from a doctor or some other agency?
0 No 1 Yes {ALCTREAT}

INTERVIEWER JUDGEMENT

I.HAS.46 She has a current drinking problem
0 No 1 Yes {ALCPROB}

C4) OTHER FACTORS FOR SECONDARY DEMENTIA

I.HAS.47 Does she have an overactive or underactive thyroid gland?
If yes - How did that start? How was it diagnosed?
Who diagnosed it? How is it treated?

CODE - Subject known to suffer from underactive thyroid?
0 No 1 Yes {HYPOTHY}

CODE - Subject known to suffer from overactive thyroid?
0 No 1 Yes {HYPERTHY}

I.HAS.48 Did she ever have an accident resulting in a serious injury to her head or brain?
0 No
1 Yes, probably
2 Yes, definitely {HI}

I.HAS.49 Did she ever have an illness or infection resulting in a serious injury to her head or brain?
0 No
1 Yes, probably
2 Yes, definitely
IF 'NO' SKIP TO I.HAS.52.1 {HILL}

I.HAS.50 Was there a period of unconsciousness following the illness (accident)?

0 No
1 A few minutes to an hour
2 Longer than an hour {LOC}

I.HAS.51 Did her behaviour become changed in some way?
(If yes - Describe in what way she changed,was that permanent?)

1 Serious condition affecting the head causing permanent personality/intellectual change
0 No such condition and/ or behaviour change
{BEHCHANG}

I.HAS.52.1 Has she ever suffered from epilepsy (fits)?

0 No 1 Yes
IF '0 NO' SKIP TO I.HAS.53 {FITSEVER}

I.HAS.52.2 Has that been a problem for a long time?

0 No 1 Yes {LONGFITS}

I.HAS.53 Interviewer observation

Participant's present intellectual state dates from birth or from occurrence of pathology earlier in life,it is not due to mental illness in recent years

0 No 1 Yes {EARLYCHG}

APPENDIX – 11

Neurological Examination

Study Number: ..... Follow-Up Number: .....

Subject's Name: ..... Date of Interview: .....

Investigator Name : .....Code : .....

1. GAIT

1.1 NUMBER OF STEPS {neo12a}

1.2 TIME (SECONDS) {neo12b}

1.3.1 ARM SWING, RIGHT

0 normal arm swing
1 reduced arm swing
2 no arm swing {neo12c}

1.3.2 ARM SWING, LEFT

0 normal arm swing
1 reduced arm swing
2 no arm swing {neo13d}

1.4 ATAXIA

0 normal gait
1 unsteady, broad-based gait
2 very unsteady broad-based gait {neo14e}

1.5 BRADYKINESIA

0 all movements normal speed
1 somewhat slow movements
2 very slow movements {neo14g}

EYE SIGNS

2. VERTICAL GAZE

0 Normal upgaze
1 Limited upgaze
2 No upgaze, or almost no upgaze {noe1}

3. VISUAL FIELD DEFECT

0 No diminution of visual fields
1 Left-sided diminution or hemianopia
2 Right-sided diminution or hemianopia
3 Bilateral (concentric) diminution {noe3b}

4. PRIMITIVE REFLEXES

4.1 GLABELLAR TAP

1 1-4 TAPS
2 5 TAPS
3 6-9 TAPS
4 10+ TAPS {noe2a}

4.2 POUT REFLEX

0 No pout
1 Pout reflex present {noe2b}

4.3 PALMO-MENTAL REFLEX

0 No facial twitch
1 Facial twitch reflex present {noe2c}

5 USE AND QUALITY OF DENTURES

5.1 Do you have dentures?

0 No 1 Yes {denture}

5.2 OBSERVATION: Are the dentures worn at the time of examination?

0 No 1 Yes {dentex}

IF "NO" SKIP TO 5.3

If yes, ask participant to remove dentures, before counting number of teeth

5.3 NUMBER OF TEETH (OWN TEETH)

5.3.1 UPPER JAW {teeth1}

5.3.2 LOWER JAW {teeth2}

5.4 Do you have problems with chewing?

0 No problems
1 Some problems
2 Many problems {chewing}

6. TREMOR

0 NO TREMOR 1 SLOW 2 MEDIUM 3 FAST

6.1 HEAD {neo4b}

6.2 RIGHT UPPER LIMB {neo4e}

6.3 LEFT UPPER LIMB {neo4f}

7. DRIFT

7.1 DRIFT PRESENT

0 No drift 1 Drift present {neo5a}

IF NO DRIFT, GO TO QUESTION 8

7.2 DRIFT SIDE

1 Right 2 Left {neo5b}

8. TONE

Code as follows

0 Normal tone
1 Slightly increased tone
2 Much increased tone

	UPPER LIMB	LOWER LIMB
8.1 RIGIDITY		
RIGHT	{neo6au}	{neo6al}
LEFT	{neo6bu}	{neo6bl}
8.2 COGWHEELING		
RIGHT	{neo6cu}	{neo6cl}
LEFT	{neo6du}	{neo6dl}

9. COORDINATION

9.1 DOMINANCE

1 Right 2 Left {domhand}

9.2 FINE FINGER MOVEMENT

RIGHT

0 No limitation
1 Limitation (slow, and/or clumsy) {neo7a}

LEFT

0 No limitation
1 Limitation (slow, and/or clumsy) {neo7b}

9.3 DYSDIADOCHOKINESIS

9.3.1 SPEED

0 Normal rate 1 Slow

ALTERNATING MOVEMENT RATE RIGHT {neo7c}
ALTERNATING MOVEMENT RATE LEFT {neo7d}

9.3.2 COORDINATION

0 Normal coordination
1 Clumsy, uncoordinated

ALTERNATING MOVEMENT COORDINATION RIGHT {neo7e}
ALTERNATING MOVEMENT COORDINATION LEFT {neo7f}

10. LURIA'S TESTS FOR FRONTAL LOBE FUNCTION

10.1 WHICH HAND USED FOR PALM-FIST-SIDE?

1 dominant
2 non-dominant {hand}

10.2 FIST-PALM-SIDE

10.2.1 LEARNING - FIST-PALM-SIDE {neo8a}

0 Requires only one demonstration
1 Requires 2-3 demonstrations
2 Requires 4-5 demonstrations
3 Unable to learn correctly within 5 demonstrations
(if so, do not attempt sequencing [below] and score 3 for neo8b)

10.2.2 SEQUENCING - FIST-PALM-SIDE {neo8b}

0 5 sequences correct
1 5 sequences performed with one mistake
2 5 sequences after one re-demonstration
3 Unable to complete 5 sequences correctly (include those who scored 3 on learning above)

10.3 RECIPROCAL CO-ORDINATION (BOTH HANDS)

10.3.1 LEARNING - RECIPROCAL CO-ORDINATION {neo8c}

0 Requires only one demonstration
1 Requires 2-3 demonstrations
2 Requires 4-5 demonstrations
3 Unable to learn correctly within 5 demonstrations
(if so, do Not attempt sequencing [below] and score 3 for neo8d)

10.3.2 SEQUENCING - RECIPROCAL CO-ORDINATION {neo8d}

0 5 sequences correct
1 5 sequences performed with one mistake
2 5 sequences after one re-demonstration
3 Unable to complete 5 sequences correctly (include those who scored 3 on learning above)

11. TENDON REFLEXES

0 Absent
1 Normal (+)
2 Brisk normal (2+)
3 Pathological brisk (3+)

11.1	Biceps jerk, right	{neo11a}
11.2	Biceps jerk, left	{neo11b}
11.3	Jaw jerk	{neo11c}
11.4	Knee jerk, right	{neo11d}
11.5	Knee jerk, left	{neo11e}

12. PARTICIPANT'S INDEPENDENT LEVEL OF MOBILITY

1. Bed bound
2. Chair bound (can transfer from bed to chair only)
3. House bound (limited mobility around the house, but cannot go outside on their own)
4. Limited mobility outside of the home
5. Freely mobile outside of the home, no significant restrictions

APPENDIX - 12

Physical Examination

Module 1

Study Number: .....

Follow-Up Number: .....

Subject's Name: .....

Date of Interview: .....

Investigator Name: ..... Code: .....

1. Height (cms)	{height1}	{height2}
2. Weight (Kgs)	{weight1}	{weight2}
3. Leg Length (cms)	{lglength1}	{lglength2}

Comments _____

CIRCUMFERENCES	Test 1	Test 2
4. MUAC (cms)	{armcirc1}	{armcirc2}
5. Head (cms)	{skcirc1}	{skcirc2}
6. Waist (cms)	{wstcirc1}	{wstcirc2}
7. Hip (cms)	{hipcirc1}	{hipcirc2}
8. Calf (cms)	{calfcirc1}	{calfcirc1}

Comments _____

SKIN FOLDS	Test 1	Test 2
9. Biceps (cms)	{biceps1}	{biceps2}
10. Triceps (cms)	{triceps1}	{triceps2}
11. Subscapular (cms)	{subscap1}	{subscap2}
12. Suprailiac (cms)	{supiliac1}	{supiliac2}

Comments

_____

13.0 BIO-IMPEDANCE

13.1 Investigator's Name **13.2** Code

13.3 Test {bino} **13.4** Time {bitime} AM/PM

13.5 Activity level Selected {biactlevel} **Medium**

13.6 Bio-impedance Complete 0. No 1. Yes, If No, Code

13.7 Fat {bifatper} % **13.8** Fat weight {bifatkg} kg

13.9 Lean {bileanper} % **13.10** Lean weight {bileankg} kg

13.11 TBW {bitbwper} % 13.12 TBW Ltr.

13.13 Est. metabolic rate at rest {bimrest} kcal

13.14 Energy required {bienergy} kcal

13.15 Impedence 50 Khz { bikhz} Hz

Comments _____

STRENGTH:

14 GRIP STRENGTH ***(Record to nearest 0.5 kg)***

14.1 Investigator Name Code

	Test 1		**Test 2**	
14.2 Right Side	{griprt1}	kg	{griprt2}	kg
14.3 Left Side	{griplt1}	kg	{griplt2}	kg

14.4 Which hand do you mostly use to write or hold a pencil? {handuse}

1.Left 2. Right 3. Both (Ambidextrous)

Comments:

_____

LOWER LIMB STRENGTH

14.5 Chair Stand Test
14.5.1 Use of hands required? 0. No 1. Yes {hanreq}

14.5.2 Number of repetitions completed in 30 seconds……..… {norep}

UPPER LIMB STRENGTH

14.6 Water bottle lifting
14.6.1 Able to lift in the right hand : 0. No 1. Yes {alrthan}

14.6.1 Able to lift in the left hand : 0. No 1. Yes {allthan}

15 PULSE AND BLOOD PRESSURE

Investigator Name: ..... Code: .....

15.1 Time AM/PM {bptime}

15.2 Room Temperature {roomtemp}

15.3 Side: 1. Left 2. Right {bpside}

15.4 Cuff Size: 1. Small Adult 2. Adult 3. Large Adult {bpcuff}

LYING SYSTOLIC, DIASTOLIC & PULSE

Investigator Name: ..... Code: .....

	Test 1	**Test 2**
15.5 Lying Systolic (mm Hg)	{lybpsys1}	{lybpsys2}
15.6 Lying Diastolic (mm Hg)	{lybpdias1}	{lybpdias2}
15.7 Lying Pulse (beats / min)	{lypulse1}	{lypulse2}

STANDING SYSTOLIC, DIASTOLIC & PULSE

	Test 1	**Test 2**
15.8 Standing Systolic (mm Hg)	{stbpsys1}	{stbpsys2}
15.6 Standing Diastolic (mm Hg)	{stbpdias1}	{stbpdias2}
15.7 Standing Pulse (beats / min)	{stpulse1}	{stpulse2}

16.0 ELECTROCARDIOGRAM (ECG)

Investigator Name: ..... Code: .....

16.1 HR : {ecghr} bpm

16.2 Rhythm : {ecgrhythm}

16.3 PR Int : {ecgprint} ms

16.4 QRS Dur : {ecgqrsdur} ms

16.5 QT / QTC Interval: {ecgqtqtc} ms

17 Minnesota Code

17.1 1. :{mincode1}

17.2 2. :{mincode2}

17.3 3. :{mincode3}

18.0 SPIROMETERY

Investigator Name: ..... Code: .....

18.1 Time {spitime} Hrs

	Test 1	**Test 2**
18.2 FEV 1	{spifev11}	{spifev21}
18.3 FEV 6	{spifev16}	{spifev26}
18.4 FVC1/FEV6	{spifvc1}	{spifvc2}

Comments

19.0 CORONARY HEART DISEASE (CHD)

1. Does the subject fulfill the criteria for Coronary Heart Disease (CHD) 0. No 1. Yes

Comments

_____

_____

19.0 BLOOD REPORT AND ASSAYS

19.1	Hb (Haemoglobin)	{hb}	gm %
19.2	Blood Insulin (30 Minutes)	{insu30}	microU/ml

19.3	Blood Glucose Fasting		{fbs}	mg/dl
19.4	Blood Glucose 2 Hours		{ppbs}	mg/dl
19.5	Blood Insulin Fasting		{insulin1}	microU/ml
19.6	Blood Insulin 2 Hours		{insulin2}	microU/ml
19.7	Total Cholesterol		{tchol}	mg/dl
19.8	HDL Cholesterol		{hdl}	mg/dl
19.9	LDL Cholesterol		{ldl}	mg/dl
19.10	Triglycerides		{tgl}	mg/dl
19.11	Vitamin B12		{vb12}	pc/ml
19.12	Folate		{folate}	ng/ml
19.13	Urea		{urea}	mg/dl
19.14	Creatinine		{creati}	mg/dl
19.15	Total Protein		{topro}	gm/dl
19.16	Albumin		{album}	gm/dl
19.17	Thyroid T3		{thyt3}	ng/ml
19.18	Thyroid T4		{thyt4}	microg/ml
19.19	Thyroid TSH		{thytsh}	mIU/ml
19.20	Homocysteine		{homocyst}	µmol/L
19.21	Oral Glucose Tolerance Test			
	19.20.1 Normal	0.	{gtt}	
	19.20.2 Diabetic	1.	{diabe}	
	19.20.3 Not done	9.	{notd}	
19.22	Genetic Assay			
	APOE4 Genotype		{Apoε4}	0. No 1. Yes

Comments _____

Appendix-13

Pilot validation study

Cognitive function and disability in late life: An ecological validation of the 10/66 battery of cognitive tests among community dwelling older adults in south India

Key Points

- 10/66 cognitive tests are well suited for identification of older adults with cognitive and functional impairment at a population level in LMIC setting.
- Lower scores on individual domains of the 10/66 battery of cognitive tests are associated with higher levels of disability and functional impairment.
- It is feasible to administer 10/66 cognitive assessments in participant's own homes in India.
- 10/66 cognitive tests are education and culture fair, suitable for use in population based research in India.

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Background

Neurocognitive disorders are a major cause of disability and mortality in late life and are associated with high costs for health systems and society (Mathers & Matilde 2000; WHO 2004; Dementia India Report 2010; WHO Report 2001). Population based studies in India report 7.5% and 10.6% prevalence for dementia in those aged above 60 yrs in urban and rural areas respectively (Dementia India Report 2005; Prince 2005**).** The proportion of persons with dementia is expected to increase two-fold by 2030 because of the steady growth in the older population and stable increments in life expectancy (Dementia India Report 2010; World Alzheimer Report 2009; Ferri et al., 2006). Although neurocognitive disorders are the second highest source of burden after tropical diseases, research in India remains minimal (Murray & Lopez1996).

The Global Burden of Disease report identifies cognitive impairment as one of the main causes of disability and this has a disproportionate impact on capacity for independent living in later life. Comorbidity with cardiometabolic disorders is common and interacts in complex ways to create disability, and dependence (Lozano et al.,2012). Therefore, it is important to understand the contribution of cognitive disorders, relative to that of other chronic diseases, to disability and dependence.

The population based studies by 10/66 Dementia Research Group have assessed the impact of dementia and Mild Cognitive Impairment on disability and dependency in late life in low and middle income countries (LMIC) including India (Sousa et al.,2009; Sosa et al.,2012). Those with greater disability and need for care were characterised by co-morbidity between cognitive impairment and physical and mental disorders. Dementia emerged as the leading independent cause of both disability and dependency, followed by limb weakness, stroke, depression, eyesight problems and arthritis. Neither ischaemic heart disease nor hypertension, or even chronic obstructive pulmonary disease was associated with disability or dependency. (Sousa et al., 2009; Sosa et al., 2012).

A culture and education fair battery of cognitive tests was developed, validated and normed for use in LMICs (including south India) by the 10/66 Dementia Research Group. This is suitable for use in people with little or no education (Prince et al., 2003). 10/66 battery of cognitive tests comprises: the Community Screening Instrument for Dementia (CSID) incorporating the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) animal naming verbal fluency task, the modified CERAD 10 word list learning task with delayed recall and an informant interview for evidence of cognitive and functional decline

(Prince et al., 2003; Prince et al., 2007). In the 10/66 pilot studies, the CSID, informant interview and the modified CERAD 10 word list-learning task were independently able to predict the diagnosis of dementia (Prince et al., 2003).

The ecological validity and relationship between the individual domains of the 10/66 battery of cognitive tests and disability has not been examined in community dwelling older adults in India**.** *Ecological validity* refers to the extent to which the findings of a research study are able to be generalised to real-life settings.

This study examined the association between individual domains of the 10/66 battery of cognitive tests [word list memory and recall (WLMR), verbal fluency (VF) and a global cognitive function score derived from the Community Screening Instrument for Dementia (CSI'D' COGSCORE)] and 'disability' and 'functional impairment' in community dwelling older adults in the city of Mysore, South India. The mediating effect of self reported chronic non-communicable diseases is examined. In addition, we explored the feasibility of administering the 10/66 battery cognitive tests to an older person and a reliable informant in their own homes.

Methods

Design and Setting

This single phase cross sectional validation study was carried out at the Epidemiology Research Unit, Holdsworth Memorial Hospital, Mysore, south India. The study was approved by the Ethics and Research Committee at Holdsworth Memorial Hospital.

Adults aged 60 yrs and above and residing at Karunapura (colony number 1), a mainly Christian community in the inner city of Mysore were eligible to participate. All households in the study area (n=186) were approached by a door to door survey and study information was provided. 151 individuals aged 60 yrs and above were identified from 138 households. 129 of them agreed to participate and were recruited along with a reliable informant after obtaining written consent. Individuals who were close to the subjects and knew them for most of their lives (spouse, relative or a friend) were considered reliable informants. If the participant was illiterate, verbal consent was obtained, which was witnessed and signed by a relative. If individuals were unable to consent (due to severe cognitive problems) assent was obtained from their nearest/authorised relative who was witnessed.

Instruments

a. Cognitive function tests: Cognitive functioning as a continuous measure was obtained by administering the Kannada (local language) version of the 10/66 cognitive assessment battery. This is drawn principally from the Community Screening Instrument for Dementia (CSID) developed by the Ibadan-Indianapolis study group (Hall et al., 2000) specifically for use in cross-cultural research, and in low education settings, and from the CERAD (Morris et al., 1989). The aim of the translation process was to achieve a Kannada version of the English 10/66 battery of cognitive tests that was conceptually equivalent to the study setting and practically perform in the same way. The focus was cross-cultural and conceptual, rather than on linguistic or literal equivalence. This was achieved by using forward translation (by author MK) and back translation (by authors EB and SA) methods. This battery comprises:

i) Global Cognitive Function measured by administering the Community Screening Instrument for Dementia (CSI 'D') to the subjects (Hall et al., 2000). This includes a 32 item cognitive test assessing orientation, comprehension, memory, naming and language expression, which generates a global cognitive score (CSID COGSCORE).

The CSI 'D' was from the outset intended to be used across cultures with the minimal adaptation. It was developed and first validated among Cree American Indians (Nath et al., 1993; Hendrie et al., 1995), further validated and used in population-based research among Nigerians in Ibadan, African-Americans in Indianapolis, white Canadians in Winnipeg and in Jamaica in conjunction with the CERAD battery (Hendrie et al.,1995; Hall et al., 2000; Unverzagt et al., 1999). The CSI 'D' test score distributions among those with dementia and controls, and the degree of discrimination provided was remarkably consistent across the aforementioned cultural settings (Unverzagt et al., 1999).

ii) Verbal fluency (VF) measured by the animal naming verbal fluency task from the CERAD [Hall et al., 2000; Morris et al., 1989]. After a brief practice, naming items from another category (clothing), participants are encouraged to name as many different animals as they can in the space of one minute. The instructions read out to the participant stipulate: 'think of any kinds of animal in the air, on land, in the water, in the forest, all the different animals'. If the participant stops before the allotted time has elapsed they are encouraged to continue. The score is one point for each valid name.

iii) Memory is measured by the modified Word List Memory and Recall (WLMR) test to evaluate immediate and delayed recall respectively. WLMR has been reported to be of particular value in distinguishing early dementia from normal aging (Welsh et al., 1991). WLMR is taken from the adapted CERAD ten word list learning task used in the Indo-US Ballabgarh dementia study (Ganguli et al., 1996). Six words- butter, arm, letter, queen, ticket and grass were taken from the original CERAD battery English language list (Guruje et al., 1995). Pole, shore, cabin, and engine were replaced with corner, stone, book and stick, which were deemed more cross-culturally applicable (Prince et al., 2003). In the learning phase, the list is read out to the participant from a green card, who is then asked to recall straight away the words that they remember. This process is repeated three times, giving the subject a score out of 30. Approximately five minutes later, after a series of unrelated CSI'D' questions (name registration, object naming, object function and repetition) the participant is again asked to recall the 10 words with prompting that they were read from a green card, giving a recall score out of 10. This makes the total WLMR score of 40.

iv) The CSI'D' informant interview: In the informant section of the CSI'D', a reliable informant is asked about declining memory in general, and the frequency of six specific and characteristic memory lapses; forgetting where s/he has put things, where things are kept, names of friends, names of family, when s/he last saw informant, and what happened the day before. If the subject was receiving care, the primary caregiver was considered as a reliable informant. The 26 items from the interview seek for evidence of cognitive and functional decline (Nath et al., 1993; Hendrie et al., 1995; Prince et al., 2003). The response to each item is weighted and for the purpose of this study, a summative score (CSI'D" RELSCORE) of more than 2 was considered as indicative of cognitive decline resulting in 'functional impairment'. The 10/66 battery of cognitive tests in English is provided as an appendix (appendix one) and the Kannada version will be shared upon request by interested readers.

The following instruments were administered to the participant and if they were unable to provide accurate information (for example due to cognitive problems or following a stroke), they were administered to the reliable informant.

a. Socio-demographic questionnaire collecting information on age, sex, marital status, level of education (none; some, but did not complete primary; completed primary; completed secondary; completed tertiary or further education) and living circumstances (living with children, yes/no) (Prince et al., 2007).

b. Medical history questionnaire: Hypertension and diabetes were ascertained by a positive answer to the question “have you ever been told you had diabetes or hypertension?” The ascertainment of previous episodes of stroke or ischaemic heart disease (IHD) was based on self-report (“have you ever been told by a doctor that you had a stroke/angina/heart attack?”). Stroke was coded only if there was a clear history of sudden onset of unilateral paralysis, loss of speech, or blindness lasting for more than 24 hours, hence excluding previous episodes of transient ischemic attack. Chronic obstructive airway disease (COAD) was diagnosed in people who responded “yes” to the question “do you usually cough up phlegm from your chest first thing in the morning?” and whose answer to the question “for how many months of the year does this usually happen?” was 3 months or more. (Prince et al., 2007)

c. Physical Health Impairment Schedule: This is a self-reported list of twelve commonly occurring physical impairments, a measure of health impairment (Duke University 1978). They include arthritis/rheumatism, eyesight problems, hearing difficulty or deafness, persistent cough, breathlessness/asthma, high blood pressure, heart trouble/angina, stomach problems, intestine problems, faints/blackouts, skin disorders and paralysis/ weakness or loss of one leg or an arm. Impairments were rated as present if they interfered with activities “a little” or “a lot”, as opposed to “not at all”.

d. WHO Disability Schedule-II: The degree of disability was measured by administering the WHO Disability Schedule-II (WHO DAS II) (Rehm et al., 2000). It was developed by the WHO as a culture-fair assessment tool for use in cross-cultural comparative epidemiological and health services research to measure activity limitation and participation restriction. The 12-items assess five activity limitation domains (communication, physical mobility, self-care, interpersonal interaction, life activities and social participation). Each domain is covered by two questions, with scores ranging from 0 (no difficulty) to 4 (extreme difficulty or cannot do) and yielding a total score between 0 to 48.

Data collection

A clinical psychologist (EB) was trained by MK, a member of the 10/66 Dementia Research Group to administer the instruments in subjects' own homes. The interviews for participants and a key informant were carried out separately, but this was not always feasible. The data were manually collected on paper and then entered into the Epidata (version 3) driven database developed by the 10/66 Dementia Research Group. These files have in built

checks to minimise errors and thereby assist in cleaning of the data. The data were double entered, cleaned and directly exported to SPSS version 19 for analysis.

Statistics

a. A power calculation was not carried out before commencing the study, as no study had previously examined the association between individual domains of the 10/66 cognitive battery and disability in an older adult population from this region. A post hoc power calculation indicated that our sample size had more than 90% power to detect a correlation of at least 0.20 between disability and exposure variables (WLMR, VF and CSI'D' COGSOCRE) significance at the 5% level (table 1).

Table 1. Post hoc power calculation

Dependent Variable	Independent	R-Square	Effect Size	Number of Predictors	Alpha	Sample Size	Power
Disability	Word list memory recall WLMR)	0.245	0.32450	8	0.05	129	0.9987834
	Verbal fluency (VF)	0.292	0.41243	8	0.05	129	0.9999228
	CSI'D' COGSCORE	0.281	0.39082	8	0.05	129	0.9998448

b. Descriptive statistics were done to calculate mean, standard deviation and proportions. Independent samples t-tests were used to test for differences in socio-demographics, cognitive function, health impairment and disability scores between men and women. Multiple linear regression was used to examine the association between the dependent variables (WHO DAS II score) and independent variables/predictors (WLMR, VF and CSI'D' COGSCORE).

The cognitive scores were adjusted for age, education and gender. The regression analyses were adjusted to examine the mediating effect of self-reported chronic non communicable disorders (diabetes, hypertension, stroke, COAD and IHD).

Results

The 129 participants included 42 men and 87 women aged between 60 and 90 yrs of age. Table 2 shows their characteristics. The women had significantly lower levels of literacy and

were more likely to be widowed when compared to men (p=<0.001). Table 2 provides mean scores on individual cognitive tests, health impairment and disability for men and women.

Table 2. General characteristics of the study participants.

Characteristics	Male (N=42)	Female (N=87)	p value
Age mean (SD)	67.81 (6.64)	69.46 (7.30)	0.22
Education			
None	1 (2.4%)	28 (32.2%)	<=0.001
Some, but did not complete primary	5 (11.9%)	5 (5.7%)	
Completed primary	5 (11.9%)	18 (20.7%)	
Completed secondary (metric)	15 (35.7%)	24 (27.6%)	
Completed tertiary (college)	16 (38.1%)	12 (13.8%)	
Marital Status			
Never married	-	4 (4.6%)	<=0.001
Married/Co-habiting	31 (73.8%)	27 (31.0%)	
Widowed	11 (26.2%)	56 (64.4%)	
Religion			
Roman Catholic	3 (7.1%)	2 (2.3%)	
Anglican / Protestant	23 (54.8%)	39 (44.8%)	0.304
Muslim	2 (4.8%)	6 (6.9%)	
Hindu	14 (33.3%)	40 (46.0%)	
Job			
Paid full-time work	3 (7.1%)	3 (3.4%)	<=0.001
Paid part-time work	4 (9.5%)	0 (0%)	
Housewife/husband	4 (9.5%)	45 (51.7%)	
Retired	30 (71.4%)	35 (40.2%)	
Hypertension	6 (14.3%)	11 (12.6%)	0.834
Ischemic heart disease	6 (14.3%)	11 (12.6%)	0.834
Stroke	2 (4.8%)	1 (1.1%)	0.197
Diabetes	16 (38.1%)	27 (31.0%)	0.478
Chronic obstructive airway disease (COAD)	4 (9.5%)	6 (6.9%)	0.641
Smoking (ever)	7 (16.7%)	2 (2.3%)	0.007
Alcohol (ever)	5 (11.9%)	0 (0%)	
Alcohol (Present)	5 (11.9%)	0 (0%)	
Cognitive Function			
CSI'D' COGSCORE	37.46 (4.27)	34.61 (5.10)	0.002
Verbal fluency (VF)	13.76 (4.0)	12.03 (4.85)	0.047
Word list memory recall (WLMR)	19.43 (7.23)	17.56 (6.70)	0.150
Physical health impairment schedule score	12.48 (1.90)	13.18 (1.90)	0.05
WHO Disability II score	1.76 (5.09)	2 .29 (3.01)	0.464

CSI'D' : Community Screening Instrument for Dementia

The CSI'D informant interview identified 33 of the 129 subjects as having cognitive decline severe enough to cause 'functional impairment' (i.e. CSI'D' RELSCORE of 2 or more). The associations of functional impairment and cognitive function score are provided in table 3.

Table 3. Association between cognition and functional impairment

Cognitive Function	Functional impairment n=23	No functional impairment n=106	P
CSI'D ' COGSCORE	32.82 (5.61)	36.47 (4.44)	<0.01
Verbal fluency (VF)	11.0 (4.52),	13.40 (4.52),	0.03
Word list memory recall (WLMR)	15.94 (6.38)	18.94 (6.94)	0.03

The association between cognitive function and disability score (WHO DAS II) was examined in regression analyses (see table 4). The analyses were adjusted for age, education and gender. There was a significant inverse association between WHO DAS II score and WLMR (p=0.004), VF (0.006) and CSI'D' COGSCORE scores (P<=0.001) even after adjusting for self-reported IHD, stroke, COAD, hypertension and diabetes.

Table 4. Association between cognition and disability

Dependent Variable	Predictors	B	95% CI value	p values
WHO DAS II score	CSI'D ' COGSCORE	-0.282	-0.408, -0.155	<=0.001
	Verbal fluency (VF)	-0.215	-0.366, -0.064	0.006
	Word list memory and recall (WLMR)	-0.150	-0.25, -0.05	0.004

Predictors are adjusted for age, education and gender. The regression analyses were adjusted for IHD, stroke, COAD, hypertension and diabetes. CSI'D': Community Screening Instrument for Dementia

Discussion

Lower scores on individual domains of the 10/66 battery of cognitive tests are associated with higher levels of disability and functional impairment in community dwelling older adults in Mysore, South India. This is the first population-based ecological validation study of the 10/66 instruments in India to examine these associations. The association between CSI'D' COGSCORE, VF, WLMR scores and disability were strong and independent of self-reported chronic non-communicable disorders. The associations between lower cognitive function scores and disability in late life were not attenuated after adjusting for chronic non-communicable disorders. Our finding is similar to the observation by the 10/66 Dementia Research Group that dementia and amnesic Mild Cognitive Impairment independently predict disability in late life (Sosa et al., 2012). Unlike the previous 10/66 research reports

from India that examined the impact of diagnostic categories of cognitive impairment (amnesic Mild Cognitive Impairment and dementia) on disability, this study examined cognitive function as a continuous variable.

Independently, all three cognitive function tests were able to identify individuals with 'functional impairment' due to cognitive problems in this sample of community dwelling older adult population where nearly a third of them were illiterates. This reconfirms 'culture and education fair' properties of the 10/66 cognitive tests and that these are well suited for identification of older adults with cognitive and functional impairment at a population level in LMIC setting.

In this study, women had significantly lower global cognitive function score (CSI'D'COGSCORE) than men. This may be due to lower education levels attained by the women in the study. Interestingly, despite lower attained educational levels and lower CSI'D'COGSCORE, there were no significant gender differences in disability. This may be partly explained by the fact that health impairment between men and women were the same, but this needs to be examined further.

It was feasible to administer the 10/66 instruments in participants' own homes and all assessments were completed. Administering a battery of cognitive tests to an older adult and interviewing an informant in their own homes has its strengths and weaknesses. It was a challenge to administer cognitive tests in a standardised manner while strictly adhering to the test protocol. The reasons include: limited physical space, lack of privacy, poor lighting, noise levels and in some instances family members and friends attempting to prompt or answer for the subject despite clear instructions not to do so. However, being at the participants' own home provided an opportunity to observe them in familiar surroundings and it was easier to identify reliable informants. The informants were generally reluctant to report certain information like toileting needs, getting lost in the neighbourhood and needing assistance with personal care out of respect to their elders. This may have potentially resulted in underreporting of cognitive and functional decline by the informants.

Strengths: This study was carried out in an inner city area of the district with even distribution of families across various socioeconomic classes. Therefore, the sample is likely to represent normal community dwelling older adults in Mysore. A reliable informant was interviewed for all the participants. In those who were receiving care, the main 'hands on' caregiver was interviewed. The few refusals to participate were mainly due to social inconvenience (e.g. visitors at home, festivities and ceremonies) and not genuine

unwillingness to participate. The clinical psychologist was supervised to ensure that tests were administered in a standardised manner. There were no missing data and all analyses are complete.

Limitations: The major limitation of this validation study is that no diagnostic interview schedule was administered to determine if the participants had a diagnosable mental disorder particularly depression and dementia. Depression is a common comorbidity with cognitive disorders and enhances the resulting impairment and disability in late life. This limitation was partly overcome by administering a CSID informant interview that generated a final score indicating if the subjects' cognitive problems were severe enough to impair the subject's activities of daily life and any other functional impact. All chronic diseases were self-reported with a negligible few having any medical records to verify.

Appendix 14

Table 1. Associations of sociodemographics and NCD factors in late life with Mild Cognitive Impairment (MCI) in late life				
Predictor	**MCI** (0=no, 1=yes) OR(95%CI)* p		Predictor	**MCI** (0=n0,1=yes) OR(95%CI) * p
Marital status	2.40 (0.61,9.46)		**Stroke**	0.00 (0.00, 0.00)
(0=married,1=others)	0.21		(0=no, 1=yes)	0.10
Education**	0.89 (0.62,1.27)		**Total cholesterol**	0.61 (0.34,1.10)
(per level)	0.53		(mmol/l)	0.10
Percapita income	1.0 (1.0-1.0)		**LDL cholesterol**	0.55 (0.27,1.12)
(INR/mth)	0.71		(mmol/l)	0.10
People per room	0.63 (0.15,2.70)		**HDL cholesterol**	0.55 (0.05,5.65)
	0.63		(mmol/l)	0.61
SLI (score)	0.98(0.91,1.05)		**Triglycerides**	0.79 (0.32,1.94)
	0.56			0.79
BMI (kg/m^2)	0.99 (0.87,1.14)		**Metabolic syndrome**	0.67 (0.21,2.01)
	0.92		(0=no, 1=yes)	0.49
Waist circumference	0.99 (0.94,1.04)		**Hb** (gms %)	1.04 (0.74,1.45)
(cms)	0.76			0.83
Sum of skin folds	1.00 (0.97,1.03)		**Vitamin B12** (pmol/l)	1.00 (1.0,1.00)
	0.94			0.37
Fasting glucose	1.12 (0.95,1.33)		**Folate** (nmol/l)	1.02 (1.00,1.05)
(mmol/l)	0.16			**0.03**
120 mins glucose	1.06 (0.91,1.24)		**T3** (nmol/l)	0.88 (0.34,2.26)
(mmol/l)	0.42			0.79
Diabetes	3.80 (0.98,14.6)		**TSH** (milliIU/l)	1.00 (0.95,1.06)
(0=no, 1=yes)	0.53			0.83
Fasting insulin	0.99 (0.93,1.05)		**FEV1** (lts)	0.36 (0.08,1.47)
(pmol/l)	0.72			0.15
Systolic BP	1.00 (0.97,1.03)		**FEV1/FEV6**	0.70 (0.00,1.70)
(mm of Hg)	0.85			0.70
Diastolic BP	1.00 (0.96,1.06)		**Alcohol intake**	0.56 (0.13,2.39)
(mm of Hg)	0.77		(units/week)	0.44
Hypertension	0.94 (-0.27,3.30)		**Amount of smoking**	0.89 (0.74,1.08)
(0=no, 1=yes)	0.93		(No of cigarettes/day)	0.25
CHD	0.88 (0.26,3.00)		**Physical activity****	2.48 (0.80,7.7)
(0=no, 1=yes)	0.84		(0-3)	0.12

* Logistic regression analyses adjusted for age and gender.
Education** : 0=illiterate, 1=primary, 2=secondary, 3=Preuniversity, 4=diploma, 5=graduate, 6=postgraduate. People per room: 0=1-1.9, 1=2-2.9, 2=3-3.9, 3=4 or more.
Physical activity** : 0= sedentary, 1=mild, 2=moderate, 3=strenuous.
CHD: Coronary Heart Disease SLI: Standard of Living Index
FEV1 and FEV6: Forced Expiratory Volumes at 1 and 6 seconds.

Table 2. Associations of sociodemographics and NCD factors in midlife with Mild Cognitive Impairment (MCI) in late life.				
Predictor	**MCI** (0=no,1=yes) OR(95%CI)* P		Predictor	**MCI** (o=no, 1=yes) OR(95%CI)* p
Marital status	0.0 (0.0,0.0)		**Hypertension**	0.46 (0.09,2.28)
(0=married,1=others)	0.99		(0=no, 1=yes)	0.34
Education**	0.89 (0.61,1.28)		**Total cholesterol**	0.78 (0.44,1.38)
(per level)	0.52		(mmol/l)	0.39
Percapita income	1.00 (1.00,1.00)		**LDL cholesterol**	0.85 (0.48,1.52)
(INR/mth)	0.94		(mmol/l)	0.59
People per room	0.38 (0.38,1.44)		**HDL cholesterol**	0.36 (0.03,4.89)
	0.74		(mmol/l)	0.45
Kuppuswamy score	1.02 (0.95,1.10)		**Triglycerides**	0.63 (0.26,1.55)
	0.58		(mmol/l)	0.32
BMI (kg/m^2)	1.01 (0.88,1.17)		**Metabolic syndrome**	0.65 (0.16,2.54)
	0.83		(0=no, 1=yes)	0.53
Waist circumference	0.99 (0.94,1.04)		**Hb** (gms %)	0.84 (0.54,1.31)
(cms)	0.65			0.44
Hip circumference	0.99 (0.92,1.06)		**CHD (0=no,1=yes)**	0.88(0.26,3.00)
(cms)	0.73			0.84
Waist-hip ratio	0.15 (0.00,1415)		**FEV1** (lts)	0.93 (0.35,2.50)
	0.68			0.89
Central obesity	0.97 (0.30,3.11)		**PEF** (lts)	0.10 (0.99,1.01)
(0=no, 1=yes)	0.96			0.88
Sum of skin folds	1.00 (1.00,1.01)		**FVC** (lts)	0.64 (0.14,2.91)
	0.58			0.57
Fasting glucose	1.01 (0.88,1.17)		**Alcohol intake**	0.99 (0.91,1.08)
(mmol/l)	0.83		(units/week)	0.82
120 mins glucose	0.99 (0.94,1.04)		**Amount of smoking**	1.03 (0.98,1.09)
(mmol/l)	0.65		(No of cigarettes/day)	0.21
Diabetes	0.97 (0.30,3.11)		**Physical activity*****	1.04 (0.58,1.89)
(0=no, 1=yes)	0.96		(0-3)	0.88
Fasting insulin	1.00 (1.00,1.01)		**Walking******	1.13 (0.35,3.65)
(pmol/l)	0.58		(0-3)	0.84
120 mins insulin	0.67 (0.20,2.31)		**Cycling********	1.35 (0.50,3.65)
(pmol/l)	0.53		(0-3)	0.56
Systolic BP	0.98 (0.94,1.02)		**Sports** (hrs/week)	0.83 (0.44,1.57)
(mm of Hg)	0.40			0.57
Diastolic BP	0.99 (0.94,1.05)		**Labor work** (hrs/week)	1.00 (0.92,1.08)
(mm of Hg)	0.77			0.98

* Logistic Regression Analyses adjusted for age and gender.
**Education : 0=illiterate, 1=primary, 2=secondary, 3=Preuniversity, 4=diploma, 5=graduate, 6=postgraduate. **Physical activity : 0= sedentary, 1=mild, 2=moderate, 3=strenuous.
****kms/day : 0= <1km, 1=1-4km, 2=4-8km, 3= >8km
CHD: Coronary Heart Disease
FVC: Forced expiratory volume at 1 secs PEF: Peak expiratory flow FEV: Forced vital capacity

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