CHAPTER 1
INTRODUCTION

Ageing brings about innumerable manifestations and challenges to approach towards them. Since times immemorial, humans are constantly striving to seek answers by conducting researches on the repercussions being brought through ageing process as a whole.

Population ageing is proceeding apace in all world regions, but the populations of many low, and particularly middle-income countries are ageing more rapidly than any country in the past; two-thirds of the world's older people live in low and middle-income countries (LMICs), rising to 80% by 2050 (United Nations 2009).

There are almost 900 million people aged 60 years and over living worldwide. Between 2015 and 2050, the number of older people living in high income countries is forecast to increase by 56%, compared with 138% in upper middle income countries, 185% in lower middle income countries, and by 239% low income countries (Alzheimer's Disease International 2015).

While morbidities mediate the relationship between population ageing and societal costs, the relationships with chronological age are variable, and potentially amenable to influence from public health, health, and social care interventions (Lloyd-Sherlock et al 2012).

Globally, there is stupendous rise in the incidences of neurodegenerative disorders being taking the toll of the human lives. Neurological disorders are diseases of the central and peripheral nervous system. In other words, the brain, spinal cord, cranial nerves, peripheral nerves, nerve roots, autonomic nervous system, neuromuscular junction, and muscles. These disorders include epilepsy, Alzheimer disease and other dementias, cerebrovascular diseases including stroke, migraine and other headache disorders, multiple sclerosis, Parkinson's disease, neuroinfections, brain tumours, traumatic disorders of the nervous system such as brain trauma, and neurological disorders as a result of malnutrition (World Health Organization 2014).

The global burden of neurodegenerative diseases is supposed to be the highest in almost all of the developed nations. Amongst them, the Alzheimer's disease and dementia are of a critical concern. Rising life expectancy is contributing to rapid increases in numbers, and is associated with increased prevalence of chronic diseases like dementia (Alzheimer's Disease International 2015).

Worldwide, 47.5 million people have dementia, with just over half (58%) living in low and middle income countries. Every year, there are 7.7 million new cases. The estimated proportion of the general population aged 60 and over with dementia at a given time is between 5 to 8 per 100 people. The total number of people with dementia is projected to 75.6 million in 2030 and almost triple by 2050 to 135.5 million. Much of this increase is attributable to the rising numbers of people with dementia living in low and middle income countries (WHO 2015).

Around the world, there will be 9.9 million new cases of dementia in 2015, one every 3 seconds. There is an estimate that 46.8 million people worldwide are living with dementia in 2015. This number will almost double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050. According to revised estimates in 2015, East Asia is the world region with the most people living with dementia (9.8 million), followed by Western Europe (7.4 million). At the country level, ten countries are home to over a million people with dementia in 2015: China (9.5 million), USA (4.2 million), India (4.1 million), Japan (3.1 million), Brazil (1.6 million), Germany (1.6 million), Russia (1.3 million), Italy (1.2 million), Indonesia (1.2 million) and France (1.2 million) (Alzheimer's Disease International 2015).

In the year 2000, India had 3.5 million patients with Alzheimer's disease/dementia as compared with 4.5 million in the United States of America (Upadhyay et al 2014). The most common form of dementia is Alzheimer's disease, accounting for 60–80% of dementia cases. Vascular dementia, which occurs after a stroke, is the second most common form, accounting for about 10% of cases (Alzheimer's Association 2014). The Forbes 2015 ranking estimated total worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to US$ 2 trillion by 2030 (Alzheimer's Disease International 2015).

Alzheimer's disease (AD) has increased from a few cases in a country at the beginning of the 20th century to an incidence of recording a case every 7 seconds in the world. From a rare disease it has reached the top 8 of major health problems in the world (Cornutiu 2015).

Alzheimer disease (AD) is a growing global health and economic issue as elderly populations increase dramatically across the world. Despite the many clinical trials conducted, currently no approved disease-modifying treatment exists (Sugino et al 2015).

Emerging data in clinically normal older individuals suggest that biomarker evidence of amyloid beta (A) accumulation is associated with functional and structural brain alterations, consistent with the patterns of abnormality seen in patients with mild cognitive impairment (MCI) and AD dementia (Sperling et al 2011).

It has been hypothesized that cognitively normal older individuals are at increased risk for developing cognitive decline over time, and that at some point during this 'preclinical' phase of disease, cognitive changes become evident (Sperling et al 2011), even though clinical symptoms have not yet been reported by the individual or his/her collateral source.

Several definitions have attempted to describe the transition between normal cognitive aging and the earliest manifestations of dementing disorders, particularly Alzheimer's disease (AD), such as benign forgetfulness of senescence (BFS), age associated memory impairment (AAMI), age-associated cognitive decline (AACD), cognitive impairment but no dementia (CIND) and mild cognitive impairment (MCI) (Kral 1958, Crook et al 1988, Levy 1994, Ebly et al 1995 and Petersen et al 1999). The latter has been the most widely employed definition both in clinical and research settings (Petersen et al 2006).

The current diagnostic framework for MCI was first used approximately 13 years ago by Mayo Clinic researchers (Petersen et al 1999). MCI describes the cognitive state of non-demented individuals who report memory deficits, which should preferably be corroborated by an informant and the measurable limits achieved through objective

testing; these deficits should not impair global cognitive function nor the ability to perform activities of daily living (ADLs) (Forlenza et al 2013).

Dementia prevalence is increasing with rapid aging in the population, and MCI as an intervention stage to prevent dementia has become a research hotspot (Lim et al 2015 and Davey 2014).

Mild cognitive impairment (MCI) refers to cognitive decline from a previous level of functioning, both subjectively and by objective evidence. The condition was first conceptualized in the 1980s, at which time it focused on memory impairment and was thought to be a transitional stage between normal cognitive ageing and Alzheimer's disease (AD) (Petersen et al 2014).

The MCI concept was developed to identify the earliest stages of cognitive impairment. MCI and, more specifically, amnestic MCI were initially proposed as transitional states that ultimately progress to full blown Alzheimer's disease (AD). However, MCI subjects do not uniformly progress to dementia (either AD or another) and may revert back to normal cognitive state. The MCI as concept has been borrowed from AD to other neurodegenerative diseases, particularly Parkinson's disease (PD). However the operational definition of MCI may not adequately convey the intended concept. Additional modifications to the concept and its operationalization are needed in order to better identify patients with incipient cognitive impairment and to guide clinical and research practices (Korczyn 2016).

The MCI conversion rate to AD is high (Younes et al 2014). Identifying MCI from normal aging has become a priority area of research. Neuropsychological assessment could help to identify these high risk individuals (Tripathi et al 2015).

An evidence based study on the individuals with MCI has shown that those who have memory impairment as a prominent feature in their cognitive profile (i.e. amnestic MCI) have the highest probability of developing Alzheimer's disease in the future (Fields et al 2011).

Little is currently known about the evolution of cognitive decline in preclinical MCI. While future MCI patients' cognitive performance in the preclinical MCI stage is still within normal limits according to diagnostic criteria, at some point in time, their neuropsychological functioning necessarily begins to decline, diverging from the performance of individuals who remain cognitively healthy (Mistridis et al 2015).

Estimating the population prevalence of MCI in low and middle income countries (LAMICs) is a public health priority as rapid demographic ageing is predicted to result in a large majority of people residing in these regions being at risk of dementia and cognitive decline. If so, this will have significant implications with regard to social support and future health care costs, especially as systems are not in place to cope with increased neurodegenerative disease and health resources at present are already extremely limited (Sosa et al 2012a).

MCI apart from imposing a massive health burden also increases the risk of dementia. It is imperative to reliably estimate the prevalence of MCI throughout the globe. Prevalence of MCI varies widely across international studies, from around 3% to 42% (Ward et al 2012). This high level of variability in reported MCI prevalence poses problems for public health policy and planning. Some of the variation may be associated with regional and/or ethnic differences. For example, the prevalence of aMCI in India is reportedly more than five times higher than in China, despite standardization for age, sex and education (Sosa et al 2012 b).

MCI is hence emerging as a major health problem in India as the people with MCI are three to four times more likely to develop Alzheimer's disease (6% to 25% annually). Various studies have shown that the prevalence of MCI lies between 0.5% and 36% depending upon the diagnostic criteria used and nature of the study population (Singh 2014). Moreover, very few studies have determined the putative cause of MCI in their sample. MCI and early stages of dementia particularly impact memory, attention, learning, and language (Blennow et al 2006). The episodic, semantic and working memory decline early in the disease progression (Spaan et al 2005 and Kalbe et al 2004). Among persons with incident MCI, patterns of neuropsychiatric symptoms may increase the likelihood of progression to dementia (Forrester et al 2015).

Regarding MCI/AD ratio, only about 1 in 2 people get AD (raising issues about the pathogenic disease relatedness) (Cornutiu 2015).

Cognitive performance declines several years before the MCI diagnosis, similar to findings with pre-AD patients, with varying profiles of longitudinal cognitive declines reported (Howieson et al 2008, Storandt et al 2006 and Wilson et al 2011). Such studies highlight the importance of determining the subsequent dementia diagnosis when investigating the evolution of cognitive decline in preclinical MCI (Mistridis et al 2015). The disease-modifying drugs are not available (Cummings 2004) and symptomatic medications have been found to have only modest benefit (Kaduszkiewicz et al 2005). Primary prevention of dementia is therefore of great importance (Wilcock 2004).

Identification of MCI is thought to be crucial to early intervention. MCI is associated with an increased risk of dementia (Petersen et al 2001), as well as with future disability (Purser et al 2005) and mortality (Hunderfund et al 2006).

There are a number of possible tests being recommended though the Mini-Mental State Examination (MMSE) (Folstein et al 1975) is the most widely used cognitive screening test used by physicians for general cognitive evaluation. The MMSE is also commonly used as a proxy for staging of Alzheimer's disease (AD) (Vertesi et al 2001).

With research based evidences, MMSE has been shown to be relatively sensitive to overt dementia (Harvan et al 2006), although its utility decreases when assessing patients with psychiatric conditions and mild cognitive decline (Nys et al 2005 and Benedict et al 1992). MMSE is also unable to differentiate between major types of dementia if applied alone (Santacruz et al 2001).

As research increasingly focuses on milder stages of AD, options other than the MMSE are needed for clinicians for earlier diagnosis and management (Imtiaz et al 2014). The MMSE should therefore be used in conjunction with a clinical examination, comprehensive assessment including neuropsychological testing, and not as the sole basis for diagnosis (O'Bryant et al 2008).

On the contrary, the other tests used to determine general cognitive status (ADAScog, Addenbrooke's Cognitive Examination) have been reported as good predictors, independently (Rozzini et al 2007) or associated with other neuropsychological measures (Fleisher et al 2007, Mitchell et al 2009).

Addenbrooke's Cognitive Examination (ACE) (Mathuranath et al 2000) and its revised version (ACE-R) (Mioshi et al 2006) were developed as a brief test of cognitive functions sensitive to the early stage of dementia. In addition to detection of dementia, the ACE and ACE-R are reported to be useful for detecting MCI (Mioshi et al 2006 and Alexopoulos et al 2010) and predicting conversion of MCI to dementia (Mitchell et al 2009).

Similarly, the case of Japanese ACE version when used in the patient series, the sensitivity for diagnosing dementia with an ACE score of ≤74 was 0.889 with a specificity of 0.987, and the sensitivity of an ACE score of ≤80 was 0.984 with a specificity of 0.867. The ACE-R is a very accurate instrument for the detection of early dementia and should be widely used in clinical practice (Yoshida et al 2011).

The problem with the establishment of diagnosis is the lack of appropriate clinical screening testing. An ideal screening test should be brief, fast, and appropriately sensitive and specific for detecting subjects possessing characteristics of cognitive impairment (Kaszás et al 2012).

Furthermore, it is assumed that the hand-gesture imitation test is useful to predict the conversion from MCI to AD. This hand-gesture imitation test, the YFPIT, is an effective 1-min test of dementia/AD, showing good sensitivity/ specificity, even though it is quite easy, rapid, and low in psychological burden (Yamaguchi et al 2010).

No treatments are available to cure or slow down cognitive decline, which makes prevention a critical strategy to address age-related cognitive disorders (de la Torre 2010). Nutritional factors, being modifiable, elicit due interest in the prevention of age-related cognitive decline, and solid understanding of their potential influence

could help to identify targets for intervention (Middleton et al 2009, Daviglus et al 2011, Coley et al 2008 and Plassman et al 2010).

Malnutrition is a widespread problem in elderly people and is associated with cognitive decline. Micronutrient supplementation improved serum micronutrient status with improved metabolic markers for B vitamins (von Arnim et al 2013).

A proactive epigenetics diet and nutraceuticals program holds promise as potential buffer against the negative impact of aging and stress responses on cognition, and can optimize vascular, metabolic, and brain health in the community (Chiu et al 2014).

Nutrients can protect against oxidative damage to mitochondria and lipids in the neuronal circuits associated with cognitive and affective behaviours. These nutrients include ω3 fatty acids, antioxidants (vitamin C and zinc), members of the vitamin B family (Vitamin B12 and folic acid) and magnesium. Accumulating data have shown that these nutrients can enhance neurocognitive function (Du et al 2014).

Epidemiological data is suggestive that a Mediterranean diet, physical activity, and moderate alcohol consumption protect against MCI, while cigarette smoking promotes it and should be stopped. Modifiable risk factors for MCI should be sought (at the very latest) in persons who already have MCI, as their optimal treatment may improve these patients' cognitive performance or keep the existing deficits from progressing (Etgen et al 2011).

A degree of cognitive impairment can be influenced by modifiable health behaviour, including diet and nutrition (Ogawa 2014). B vitamins of folate, vitamin B2, vitamin B6 and vitamin B12 are involved in one-carbon transfer reactions such as methylation, which is necessary for the production of monoamine neurotransmitters, phospholipids and nucleotides (Ueland et al 2001) in the brain.

Vitamin B12 is vital for the synthesis of myelin, the protective sheath surrounding many nerves in the periphery, spinal cord and brain (Zimmermann 2010). Foods from animals, but not plants, naturally have vitamin B12. These include fish, meat, poultry, eggs, milk, and other dairy products (National Institutes of Health 2011).

Low levels of B vitamins have been associated with increased homocysteine (Hcy) (Hutto, 1997), known to have a direct neurotoxic effect (Ho et al 2001). Low levels of vitamin B12 have been associated with neurocognitive disorders. This evidence-based analysis assessed the usefulness of serum vitamin B12 testing as it relates to brain function (Health Quality Ontario 2013).

The pathophysiological process of Alzheimer's disease (AD) is thought to begin many years before the diagnosis of AD dementia. This long "preclinical" phase of AD would provide a critical opportunity for therapeutic intervention (Sperlig et al 2011).

Polyunsaturated fatty acids (PUFAs), especially the (omega-3 fatty acids) n-3 series, are known for their protective effects (Baierle et al 2014). Docosahexaenoic acid (DHA) is also a product of the metabolism of the parent omega-3 compound known as alpha-linolenic acid (ALA). ALA can be found in small amounts in walnuts, soybeans, and some vegetable oils (primarily flaxseed, soy, and canola) (Carriere et al 2007). EPA (Eicosapentaenoic Acid) and DHA are found in fish, seafood and fish oils (Dietitians of Canada 2013).

The protective role of omega-3 fatty acids has also been shown in mild cognitive impairment, dementia, and the risk and progression of Alzheimer's disease in the elderly (Waitzberg and Garla 2014).

The usage of therapeutic interventions with the incorporation of functional foods as a therapy module for cognition has potential benefits. With the widespread disease incidences, the food industry has undergone a rapid makeover paving for economical, superior quality and novel ingredients. At this juncture, the flaxseed owing to the properties of functional food demonstrates as an excellent choice. In the Western countries too, the flax products are progressively used as functional foods and nutraceuticals (Herchi et al 2014 and Oomah 2001).

The flaxseed *(Linum usitatissimum L.)* is the seed from the flax plant, an annual herb which belongs to Linaceae family with more than 200 species. Currently, flaxseed has been the focus as associated with some of its biologically active components such as

dietary fiber (25–28 %) and α-linolenic acid (50–55 % of total fatty acids composition) (Bernacchia et al 2014).

Flax seed is a nutritional supplement containing dietary fiber, omega-3 fatty acids, and micronutrients such as magnesium, calcium, iron, and B vitamins (USDA Nutrient Data Laboratory 2011). Moreover, flaxseed is one of the richest plant sources of the ω-3 fatty acid i.e. α-linolenic acid (ALA) (Gebauer et al 2006 and Tonon et al 2011) and lignans (phytoestrogens) (Singh et al 2011).

Investigations into the health effects of whole flaxseed or flaxseed products (for example, defatted flaxseed meal, flaxseed extracts) in human clinical trials and animal models have shown beneficial changes in blood lipid profiles (Bloedon et al 2008 and Lucas et al 2002) and protection against some types of cancer (Demark-Wahnefried et al 2008 and Jenab et al 1996).

The ever increasing body of evidence on benefits of flaxseed consumption has led to the constant developments in the flaxseed based food approaches.

The food products namely, flaxseed chutney (Shakir et al 2007), flaxseed chutney powder (PrabhakaraRao et al 2013), peanut chikki incorporated with flaxseeds (Chetana et al 2011), flaxseed cookies (Rajiv et al 2012), flaxseed energy bar (Mridula et al 2013), flaxseed soup mix (Kaur et al 2015) and flaxseed yoghurt (Dal Bello et al 2015), have been prepared owing to increased ALA content, numerous health incentives and physiological wellness on flaxseed intakes.

Processes that underlie AD pathogenesis include: membrane/synaptic degeneration, abnormal protein processing (amyloid-beta, tau), vascular risk factors (hypertension, hypercholesterolemia), inflammation, and oxidative stress. Consideration of mechanistic evidence till date suggests that several nutritional components can effectively counteract these processes, e.g., by promoting membrane formation and synaptogenesis, enhancing memory/behavior, improving endothelial function, and cerebrovascular health. There is need for reinforcement of early intervention in AD and that multi-nutritional intervention, targeting multiple aspects of the

neurodegenerative process during the earliest possible phase in the development of the disease, is likely to have the greatest therapeutic potential (Kamphuis et al 2010).

Flaxseeds are commonly consumed in Gujarat at the household levels. But, there is massive paucity of literature specifically from the state of Gujarat with no studies being conducted on the role of flaxseed supplementation for the cognition status.

Omega-3 fatty acids have shown therapeutic potential with respect to hyperlipidemia, depression, attention-deficit hyperactivity disorder, and mild cognitive impairment (Bailes et al 2014). A double-blind randomized interventional study provides first-time evidence that LC-n3-FA exert positive effects on brain functions in healthy older adults, and elucidates underlying mechanisms (Witte et al 2014).

ALA can be acquired via regular dietary intake of foods that contain ALA or dietary supplementation of foods high in ALA, for example flaxseed. ALA has been reported to have cardiovascular-protective, anti-cancer, neuro-protective, anti-osteoporotic, anti-inflammatory, and antioxidative effects. Although there are limited toxicological data for ALA, no serious adverse effects have been reported (Kim et al 2014).

Nutritional interventions like flaxseed can beneficially disrupt oxylipins playing a key role in chronic disease progression being associated with inflammation and aging (Caligiuri et al 2014).

Plasma folate, vitamin B12, and Hcy are associated with cognitive function in cognitively impaired (AD and MCI) elderly, and the association was stronger in patients with AD (Kim et al 2013).

Folic acid and vitamin B12 intervention in people with elevated hcy levels in India could prove to be effective in lowering hcy levels and help maintain or improve cognitive function (Agrawal et al 2015).

Vitamin B12 deficiency due to malnutrition or malabsorption may lead to pernicious anemia and neurological disorders. It is still common practice to treat patients with neurological symptoms with intramuscular cyancobalamin injections (Wellmer et al 2006).

Evidence indicates that patients with vitamin B12 malabsorption (intrinsic factor deficiency) absorb only 1 to 2 percent of oral vitamin B12. High-dose oral treatment has been investigated as an alternative to intramuscular (IM) administration (Andrès et al 2007, Oh and Brown 2003, Butler et al 2006, Nyholm et al 2003, Eussen et al 2005).

The intramuscular route should be considered only when the delivery of a medication must be confirmed, such as when a patient cannot tolerate an oral medication, or when compliance is uncertain (Shatsky 2009).

With linkage to this, a wide gap seems to be prevalent in supplementation studies identifying the nascent prevalence of cognitive decline MCI with targeted approaches for management of this menace. Currently, the obscure Indian data crucially demands the regular measured usage of omega-3 fatty acid emerging as flaxseed and vitamin B12 supplementation for cognition improvements in elderly population. For this reason, an intervention trial primarily focussing these two treatment modalities seem to be of great relevance.

On account of modulate MCI prevalence with vitamin B12 and flaxseeds in the cognitive milieu, enlisted research objectives were framed:

1. To chalk out the prevalence of MCI in elderly attending out–patient departments in hospitals of urban Baroda through neuropsychological testing
2. To assess socio-demographic, activity,anthropometric ,biophyscial, dietary and bio-chemical pattern
3. To conduct proximate nutrient analysis of flaxseeds
4. To standardise and perform organoleptic evaluation for intervening flaxseed incorporated food product
5. To execute intervention and impact evaluation of the MCI elderly group with Omega -3 fatty acids and Vitamin B_{12} supplementation.