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Early Detection & Management of Alzheimer's Disease & Dementia in India: *A Policy Perspective*

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1. Introduction

Alzheimer's disease (AD) is a disorder of the brain. It is the most common form of dementia and constitutes ~75% of all dementia cases. AD associated dementia is amongst the chief causes of debilitation in the elderly (>65 years of age), however early onset forms of AD are also known and these comprise ~2-5% of all AD cases (Qiu et al, 2022). AD is a progressive disease that remains undiagnosed at its prodromal stages due to the absence of noticeable symptoms, but as the disease progresses further and symptoms first appear, the extent of neuronal damage becomes irremediable. In due course, neuronal cells that are required for conducting even simple bodily tasks such as swallowing and walking are affected, rendering the patient to become bedridden (Alzheimer's disease facts and figures, 2021). AD is a complex disease with pathological contributions from several factors. Researchers have thus far been unable to arrive at a definite conclusion regarding what initiates the chain of events that culminates in the atrophy of brain. The accumulation of amyloid beta ($A\beta$) peptide and tau protein into highly stable aggregates termed beta-amyloid plaques and tau tangles has long been held as the central feature of AD pathogenesis but has been challenged in recent times. Aggregated $A\beta$ and Tau get deposited in the neurons of the brain, extracellularly (in case of $A\beta$) and intracellularly (in case of tau), this is suggested to contribute to cellular and inflammatory stress from which cells are unable to recover and consequently they die. Furthermore, the brain's ability to metabolize glucose also gets impaired in AD. The disease remains incurable as of now and is a cause of anguish for millions around the globe. The multifactorial nature of AD is considered to be the reason behind failure in contriving adequate therapeutic and diagnostic measures against it (Fan et al, 2020). AD forms a major burden to the worldwide healthcare system, it is estimated that in the coming decades this burden will be vastly impacting developing countries like India that are currently lacking adequate awareness and infrastructural support to combat the rising disease caseload. ■

2. Epidemiology

Worldwide, the disease represents a major health burden with the latest estimates predicting more than 57.4 million people to be currently afflicted by it. Increased life span combined with reduced fertility rates is suggested to be the reason for the emerging age structure of population, where the number of elderly people is on the rise than what was the case originally. These demographic trends are anticipated to be maintained in future, leading to an increasingly elderly population and hence increased caseload of dementia and AD. According to the Global Burden of Disease Study (GBDS) 2019 within the span of 2019-2050 the number of dementia cases will undergo a whopping increase of 166%, impacting the lives of ~152.8 million individuals; these estimates are similar to those predicted by WHO. Furthermore, this elevation in the number of dementia cases is projected to be highest (up to 330%) for countries like India that scale low on the Socio-demographic index (SDI). SDI is a combined measure of average years of education in individuals aged >15 years, overall fertility rate, and lag-distributed per capita income (Nichols et al, 2022). In 2019, India was the 4th largest contributor to the global burden of dementia and by 2050 it is expected to surpass Japan and USA to become the country with the 2nd largest number of dementia cases (next only to China) (Figure 1).

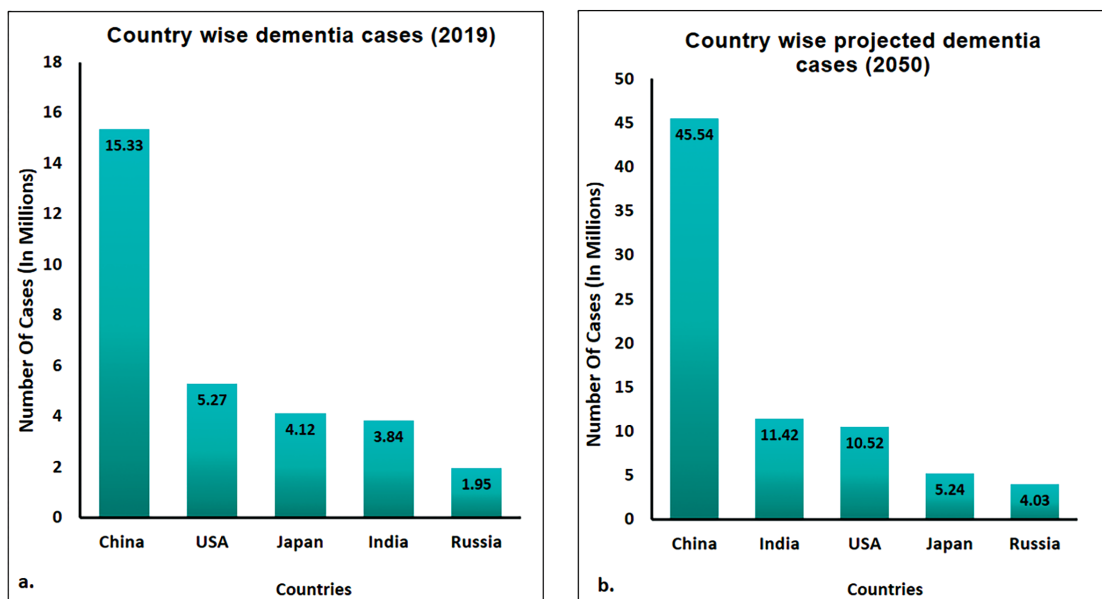


Figure 1: Top five Contributors to the worldwide Dementia caseload. (a) The number of individuals estimated to be suffering from dementia in the top five worldwide contributors of the disease in the year 2019. (b) The projected number of individuals that will be developing dementia by the year 2050 (source: Singh et al, 2021).

As a part of the GBDS 2019, a study that specifically dealt with the burden of different neurological disorders (including AD) in India was also conducted. This study is till date the only comprehensive account that is available to describe the likely prevalence and trend of different neurological disorders for every state of the country. It reports that in almost 3 decades (1990-2019) the contribution of non-communicable neurological disorders (including AD) and injury-related neurological disorders to the total neurological disease burden has more than doubled in India while the incidence of communicable neurological disorders has decreased by three quarters. In the year 2019, India was estimated to have ~3.69 million active cases of AD and other dementias. A prevalence rate of 4.3% for AD and other dementias in India was reported. However, the prevalence of AD varies markedly in different states of the country with Kerala, Goa, Andhra Pradesh, Tamil Nadu and Himachal Pradesh ranked as the top 5 contributors to the country's total AD caseload (Figure 2) and this positively correlates with proportion of elderly individuals in the total population of the states (Figure 3).

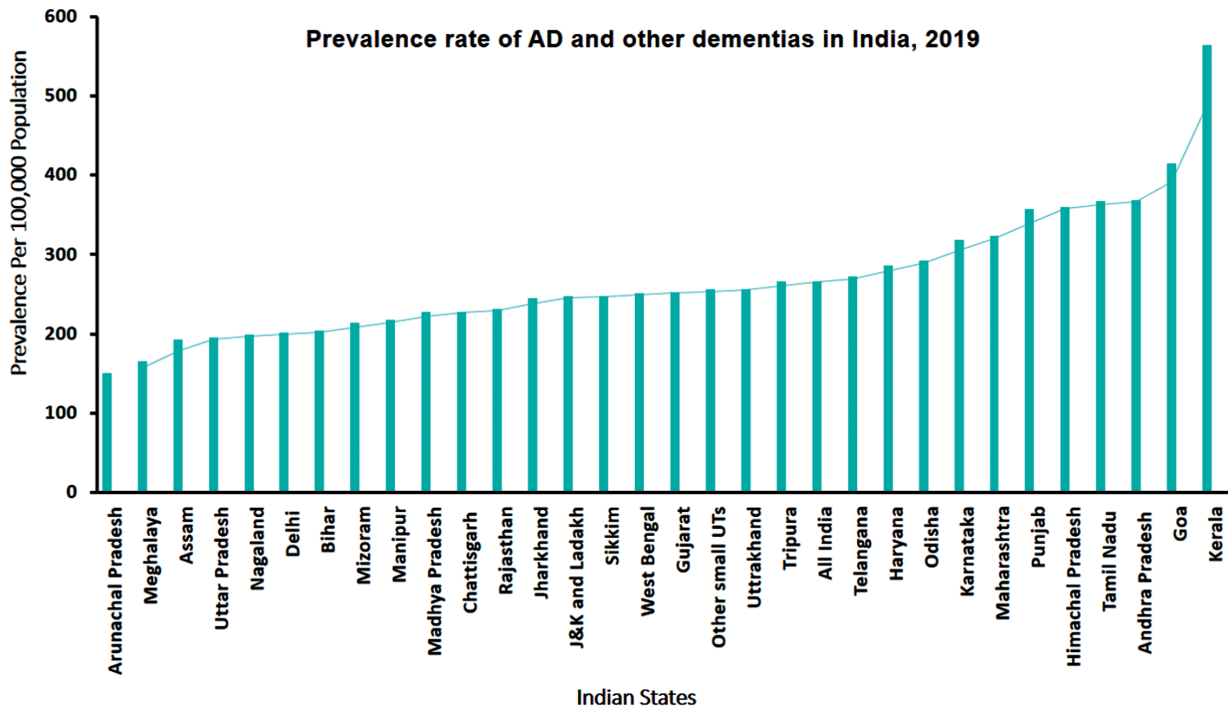


Figure 2: The prevalence of AD and other dementia cases in the different Indian states in the year 2019 (source: Nichols et al, 2022).

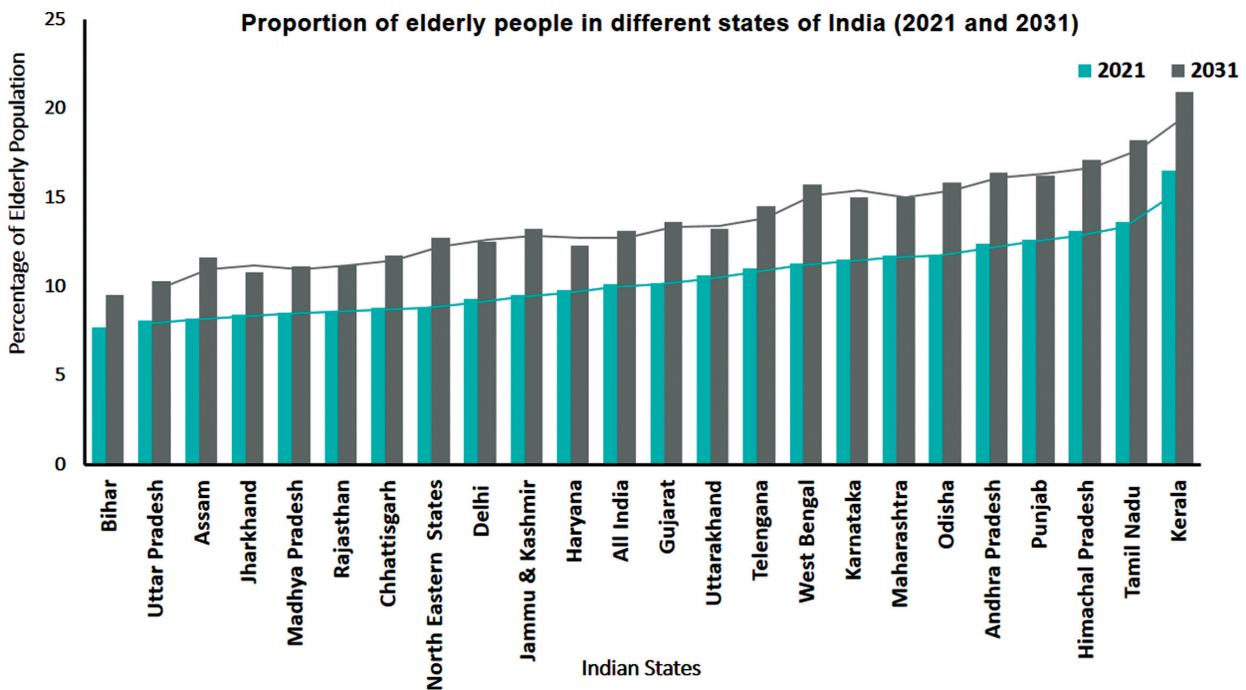


Figure 3: The estimated percentage of elderly people constituting the population of the different Indian states in the year 2021 and 2031 (source: Elderly in India, 2021-MOSPI).

Similar to global standards, the proportion of disease burden was observed to be higher in the female population. Figure 4 and Figure 5 illustrates the age and gender specific prevalence of AD in the Indian population. Additionally, AD and other dementias resulted in the death of ~0.13 million within the time frame of years 1990 to 2019 (Singh et al, 2021). However, it is worth mentioning that for India the above projections have been made via extrapolation of sparsely available data, since no detailed epidemiological studies on the prevalence of either AD or dementia have been undertaken clinically at a country wide level. Therefore, conducting accurate, large-scale epidemiological studies to inspect the prevalence of AD associated dementia in India is still very much warranted. Currently, a definite

conclusion about the proportional contribution of rural vs. urban population to the AD or dementia caseload in India cannot be drawn due to a dearth in availability of such comparative epidemiological studies. The Indian government does not maintain records of the number of dementia cases in the country. However, according to analysis conducted by Alzheimer's and Related Disorders Society of India (ARDSI), that is internationally affiliated to WHO backed Alzheimer's Disease International (ADI), in the year 2010 the prevalence of dementia in India ranged between 0.9%-4.8 % in urban areas vs. 0.6%-3.5% in rural areas (Shaji et al, 2010).

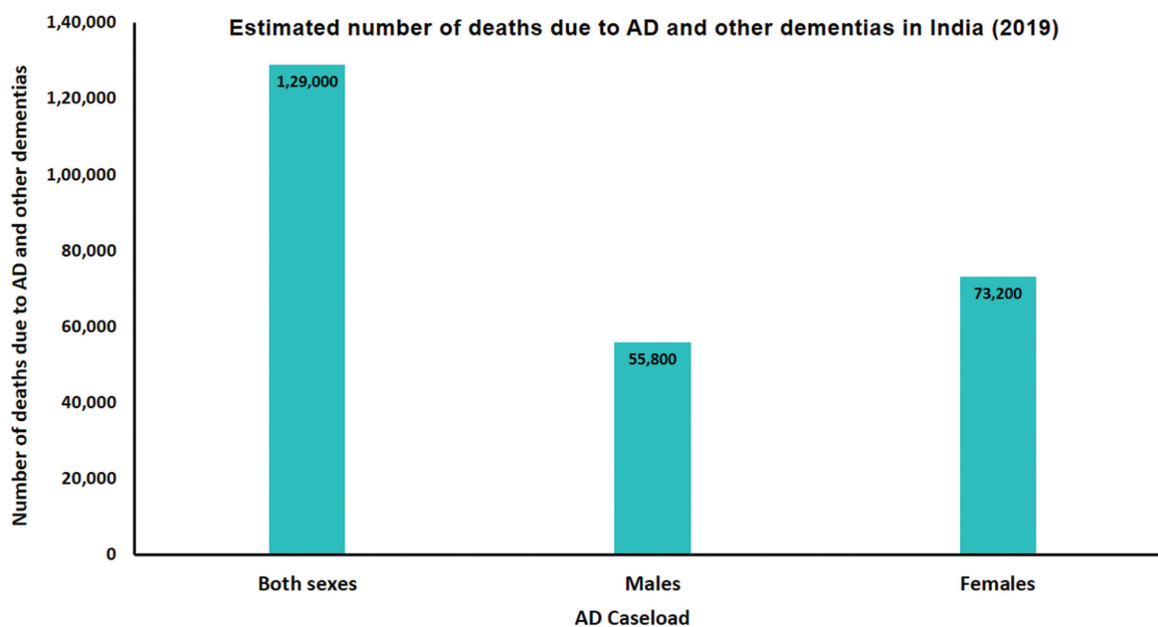


Figure 4: Gender specific comparison of the number of deaths arising due to AD and other dementias in the year 2019 (source: Singh et al, 2021).

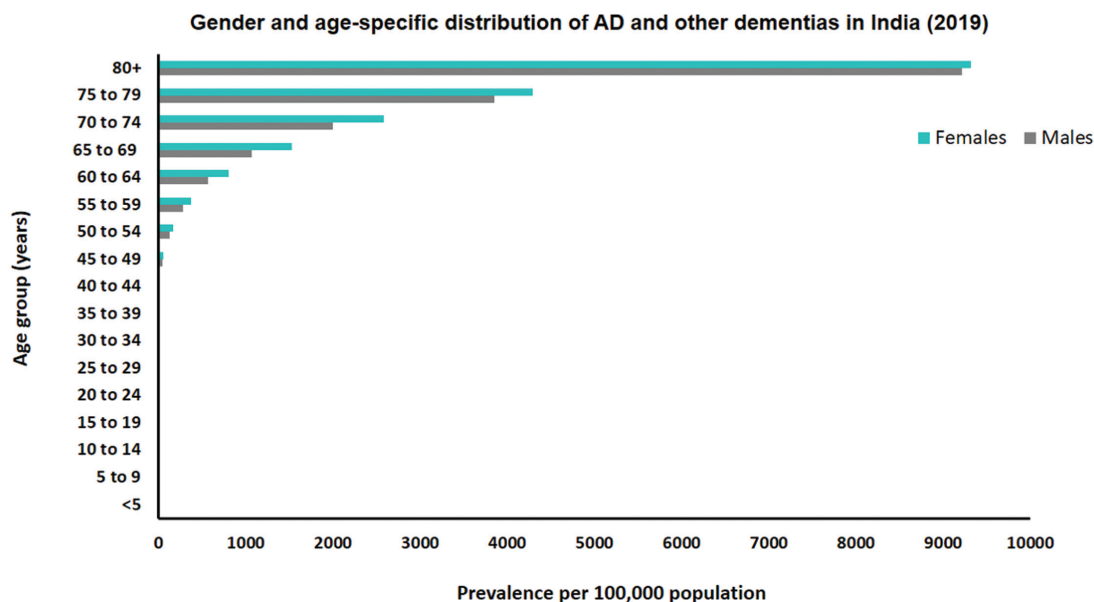


Figure 5: Distribution of the number of AD and other dementia cases on the basis of age and sex, in the year 2019 (source: Singh et al, 2021).

Likewise, a recent report published in Nature Reviews Neurology indicates that disparity exists in the reported prevalence rates for AD and related dementias in the limited number of studies that are currently available on this aspect (Ravindranath and Sundarakumar, 2021). It is suggested that demographic differences amongst the different states or regions and the choice of diagnostic tests/ sampling methods utilized to screen dementia cases are the principal factors behind the observed discrepancy as the screening tools are often adapted to the local socio-cultural settings. ■

3. Government Initiatives

In 2013 the annual domestic cost of dementia care in India was estimated to range between 20,300-66,025 INR in rural districts and 45,600-2,02,450 INR in urban districts; more than 50% of the cost was attributed to the expenditure meted towards informal care (Rao and Bharath, 2013). Compounded by the vast increase in the number of dementia patients, in the coming years a huge burden is anticipated to be inflicted on Indian families, society and healthcare system. The Indian government has come to this realization and over the years has rolled out different schemes that are likely to benefit patients with senile dementia and AD.

- i. District Mental Health Program (DMHP), 1996:** DMHP was initiated under 1982's National Mental Health Program to ensure that mental health services are made accessible along with the general healthcare structure at the community level. In recent times the government has proposed setting up facilities for the diagnosis as well as treatment of mental diseases across the 704 nationwide districts under the same program. Increased intake of practitioners specializing in mental health is proposed under NMHP through establishment of 25 Centres of Excellence and 47 PG Departments across the nation. Also, support is to be provided to different health institutions at the centre as well as the state level, in order to facilitate the early diagnosis and management of AD.
- ii. National Program for Health Care of the Elderly (NPHCE), 2011:** This scheme aims to address miscellaneous health associated problems in the elderly. Major initiatives under this scheme comprise setting up of geriatric departments, wards and units in regional geriatric centers and district headquarters; establishing rehabilitation units at all community health centers; weekly organization of geriatric clinics at primary health centers by trained medical officers and disseminating knowledge on healthy lifestyle. This scheme holds promise in setting a framework where screening and management of dementia patients can be performed.
- iii. Rights to Persons with Disabilities Act (RPWD), 2016:** The RPWD was incorporated in compliance with the convention on the rights of person with disabilities (UNCPRD) formulated by the United Nations. RPWD concerns itself with the resource limitations and socio-cultural issues facing the individuals with disabilities in India, it intends to preserve their self-esteem and prevent any form of discrimination. However, the act's provisions remain to be utilized by people with mental disabilities such as dementia due to its low engagement in defining, assessing and certification of dementia as a less physical sort of disability. It fails to consider the distinctive nature of diagnosing dementia as a disability due to its major association with the elderly cohort and its complex and progressive pathogenesis.
- iv. Mental Healthcare Act (MHA), 2017:** This act came into effect after the mental healthcare bill was passed in the year 2017. MHA aims to deliver affordable and geographically accessible healthcare to patients with mental illness; it provisions for such individuals to thrive and participate in societal activities with dignity and protection against any kind of ill-treatment. As the primary caregivers for majority of the patients with neurological ailments are their family members, this act also aims to assist the family of dementia patients in caring for them.
- v. Ayushman Bharat Scheme (ABS), 2018:** The national health protection scheme- ABS proposes to deliver affordable and accessible healthcare facilities across the country by catering to the medical requirements of over 100 million poor and susceptible families with a monetary package of up to 0.5 million INR/family. This is particularly relevant in case of dementia patients as currently dementia care is chiefly provided at private medical institutions with health specialists and the contribution of government health services or community care services is limited. Successful implementation of ABS can make dementia care services available and accessible to the most vulnerable dementia patients.

vi. Atal Vayo Abhyuday Yojna, 2020: In 2020 when this scheme was first proposed it was termed- National Action Plan for Welfare of Senior Citizens (NAPSrC), however it was later renamed as Atal Vayo Abhyuday Yojna. Amongst government's latest scheme for the elderly, AVYAY is targeted towards the welfare of senior citizens. Amongst the different plans of this scheme is the proposal of building and maintaining housing facilities for senior citizens that are suffering from severe AD and require round the clock care and/or those who are diagnosed with it.

Research has unveiled diabetes and hypertension to be amongst the chief predisposing factors for rising AD/dementia caseload. The government has therefore stepped up to the task of reducing the imminent AD associated health burden through modulation of these risk factors in population. To this end, execution of the National Program for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) that centers on growing the healthcare infrastructure for early diagnosis and treatment of frequently encountered non-communicable diseases (including hypertension and diabetes) can prove beneficial. Screening these diseases is additionally vital under the provisions of health and wellness centers proposed under ABS.

Currently, India allocates a mere 1% of its gross domestic product (GDP) in favor of healthcare infrastructure and a meager 1-2% of this health budget is directed towards mental health. This contribution is suggested to be insufficient in combating the rising health burden of dementia patients in the country (Nulkar et al, 2019). An increasing need for enhancing the investment towards health infrastructure is felt and the government has vowed to increase the share of GDP towards healthcare to 2.5% by the year 2025. The COVID-19 pandemic has drawn attention towards the deteriorating state of overall mental health in the vast sphere of Indian population. Consequently in the Union Budget 2022-2023, the government had proposed to set up a National Tele-Mental Health program (NTMHP) in the country to facilitate access to quality mental health counseling and care services. Under the aegis of the same, a Tele Mental Health Assistance and Networking Across States (Tele-MANAS) platform was launched in October 2022. Tele-MANAS is currently operational and provides 24X7, free tele-mental health services across India; chiefly it is liable to serve people residing in rural settings. At present, there are 5 regional coordination centres along with 51 State/UT Tele MANAS cells (www.pib.gov.in). The present budget (2023-2024) has proposed to increase the allocated funds for the NTMHP from Rs 121 crore to Rs 133.73 crore (economictimes.indiatimes.com).

Most of the schemes outlined above that specifically accommodate AD/dementia patients, are currently at an early stage of implementation. Therefore, predicting their success in managing the AD associated disease burden is not feasible at present. The schemes implemented/proposed by the government thus far, lack a proactive plan to increase the awareness about AD or dementia. This is important considering the fact that in India only 10% of the individuals affected with dementia get a definite medical diagnosis (Dias and Patel, 2009) and the vast majorities are misconstrued as mere instances of senile memory impairment. This can be attributed to the lack of knowledge about dementia, particularly amongst the rural community (which forms the major share in population). Cognizance of the disease is the first step towards its management; therefore there is an urgent need for government to educate the masses about AD through print, networking or media. This will further promote individuals with disease symptoms and/or their families to go for a clinical diagnosis and empower them to utilize the facilities provided by the government under the schemes outlined above and those formulated in future. ■

4. Major Risk Factors

AD is a complex disease with contributions from several factors. Worldwide, aging is considered as the strongest risk factor behind developing AD (Qiu et al, 2022; Livingston et al, 2020). Epidemiological studies have observed the incidence of AD to be higher in women as compared to men; however conclusive evidence regarding sex as a risk factor for AD has not been established and is an area of active research (Mielke, 2018). The other major risk factors for AD can be broadly classified under three categories- genetic, vascular, and psychosocial (Qiu et al, 2022).

- i. Genetic factors:** Most cases of AD are sporadic in form and display significant heterogeneity with pathological contributions from several risk factors. However, early onset or familial forms of AD representing ~2-5% of all AD cases are also known. Autosomal dominant mutations in certain genes, most widely established of which are- apolipoprotein E gene (APOE), amyloid precursor protein (APP), presenilin-1 (PS-1) and presenilin-2 (PS-2), predispose individuals towards developing AD before the age of 60 years. First-degree relatives of such patients are at an elevated risk of developing AD in their lifetimes than the common population. Particularly important is the E4 allelic variant of the apolipoprotein E gene (APOE), which forms the strongest genetic cause behind early as well as late onset AD (Qiu et al, 2022).
- ii. Vascular risk factors:** Features that augment a person's likelihood of developing cardiovascular diseases are categorized as vascular risk factors. Emerging evidence from several studies supports the role of vascular risk factors, including hypertension, diabetes, obesity, increased alcohol intake, smoking, and increased cholesterol levels in heightening the chances of developing AD or other forms of dementia (Qiu et al, 2022; Livingston et al, 2020).
- iii. Psychosocial factors:** Psychosocial factors comprise both psychological and social aspects and thereby influence an individual's overall mental health. Increasing evidence from recent studies has identified psychosocial factors such as- depression, social isolation, physical inactivity and low educational and socioeconomic status to be positively correlated with instances of AD.

While strong epidemiologic evidence is available for the positive correlation between genetic risk factors and AD; moderate to adequate evidence is presented for vascular and psychosocial factors. ■

5. Available Diagnostic Methods

As of now, both a clinical presentation of symptoms and a post-mortem histopathology of the brain are required to provide a definitive diagnosis of AD. Identification of the clinical features of AD is important for an accurate diagnosis. In order to diagnose AD, extensive testing is required to rule out any other potential forms of dementia. Clinical diagnosis of AD is typically done using patient's family history, medical records, neuroimaging, cognitive tests, biomarkers, and laboratory tests (in order to rule out thyroid problems, metabolic issues, kidney disorders, anemia and vitamin B12 deficiency etc.) (Zvěřová M, 2019).

Cognitive assessments are an essential component of clinical diagnosis of AD. It includes evaluations of one's orientation, attention, learning, memory, calculation, reading, and writing skills as well as the ability to copy or draw (McKhann et al, 1984). Before referring a patient to a dementia specialist, non-specialists can use cognitive tests like the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) to determine the degree of cognitive impairment in the patient. These tests can be completed quickly (in less than 10 minutes) (Porsteinsson et al, 2021). Although both these tests are widely used in clinical practice, their sensitivity to detect AD in early stages varies.

MMSE is reliable and sensitive enough for detecting general memory and language abnormalities but has limitations in detecting executive functioning problems. MoCA is more sensitive than the MMSE in evaluating memory, language, visuospatial, executive function, as well as time and place orientation (Porsteinsson et al, 2021). The CSF (cerebrospinal fluid) biomarkers are helpful in AD diagnostic testing because they can directly show the presence of amyloid and tau aggregation inside the brain. Imaging techniques like magnetic resonance imaging (MRI) and positron emission tomography (PET) unveil early structural and molecular changes in the brain, respectively. Numerous clinical studies have demonstrated that amyloid and tau biomarkers can provide diagnostically significant information in the early stages of the disease. Research is still ongoing to broaden the currently available tests that could be used as part of the multi-stage diagnostic procedure (Porsteinsson et al, 2021). Table 1 summarizes the advantages and limitations of the currently available diagnostic methods for AD.

Table 1: Available diagnostic techniques for Alzheimer's disease (AD) along with their advantages and limitations.

S.No.	Method	Advantages	Limitations
1.	MMSE (Mini-Mental State Examination)	<ul style="list-style-type: none"> As it is popular, a great number of testing results are available. It is concise and simple. Highly specific and accurate. Various cognitive functions can be assessed (Jin et al, 2020). 	<ul style="list-style-type: none"> Depends highly on language, with outcomes determined by the general language skills of the patient Doctors face financial challenges because of intellectual property problems. Since the MMSE is patented, clinicians are required to pay MiniMental, the current patent holders a fee for its utilization. Quite limited in assessing an individual's visuospatial reasoning ability. Low sensitivity. Unable to accurately predict the future course of disease or debilitation (Jin et al, 2020).
2.	MoCA (Montreal Cognitive Assessment)	<ul style="list-style-type: none"> Covers wide range of cognitive functions. Freely available and easy to use. Has various tests for visuospatial ability. Short time (Jin et al, 2020). 	<ul style="list-style-type: none"> Scores can be affected by sensory deficits (Jin et al, 2020).
3.	CT (Computed Tomography)	<ul style="list-style-type: none"> Low price. High accessibility (Ortiz-Terán et al, 2011). 	<ul style="list-style-type: none"> Exposure to radiation. Less sensitive than MRI (Turner et al, 2020). Resolution is relatively poor (Ortiz-Terán et al, 2011). Limited distinction between white and grey matter of the brain (Ortiz-Terán et al, 2011).

4.	CSF (Cerebrospinal fluid) biomarkers assessment	<ul style="list-style-type: none"> • Low cost in various countries. • Able to analyse the neurodegenerative, tau pathology and inflammatory markers (Hardy-Sosa et al, 2022). 	<ul style="list-style-type: none"> • Sample collection is invasive in nature (Lee et al, 2019). • Despite their sensitivity, CSF biomarkers are not able to distinguish AD from other types of dementia (Khoury and Ghossoub, 2019). • Regular or frequent CSF analysis is not feasible due to the limited availability of CSF samples and potential health risks associated with oversampling (Lee et al, 2019). • A normal CSF profile indicates the absence of AD; however an abnormal CSF profile may have significant false positives given its great sensitivity and limited specificity (Khoury and Ghossoub, 2019).
5.	PET (positron emission tomography)	<ul style="list-style-type: none"> • Metabolic changes are detected with PET in AD (Ortiz-Terán et al, 2011). • PET is suitable for patients who cannot undergo lumbar puncture or in cases where CSF amyloid beta (Aβ 42) measurement does not match the patient's clinical symptoms (Hardy-Sosa et al, 2022). 	<ul style="list-style-type: none"> • PET examinations are expensive and not easily available (Nangre and Patil, 2022). • Lacks spatial resolution (Nangre and Patil, 2022). • Radiation exposure is unavoidable for patients undergoing PET (Khoury and Ghossoub, 2019). • Although an amyloid PET scan can identify AD associated brain changes, it cannot distinguish between the various phases of disease or its severity (Khoury and Ghossoub, 2019). • There is no clear cut-off/threshold value for distinguishing between pathological and normal results (Porsteinsson et al, 2021).
6.	MRI (Magnetic Resonance Imaging)	<ul style="list-style-type: none"> • Its application is extensive. • The availability is high (Ortiz-Terán et al, 2011). 	<ul style="list-style-type: none"> • It's an expensive process with slow scanning speeds (Nangre and Patil, 2022). • Suffers from motion artifacts (Nangre and Patil, 2022). • It has no molecular specificity, which means it cannot be used to detect the histopathological signs of AD (amyloid and neurofibrillary tangles) (Johnson et al, 2012). • Some patients, such as those who have pacemaker or heart stent, cannot undergo this imaging procedure (Khoury and Ghossoub, 2019).
7.	SPECT (Single Photon Emission Computed Tomography)	<ul style="list-style-type: none"> • Affordable or less expensive than PET (Ortiz-Terán et al, 2011). 	<ul style="list-style-type: none"> • Exposure to radiation. • Inadequate resolution (Ortiz-Terán et al, 2011).

6. Treatments

Since there is presently no cure for AD, the goal of treatments is to delay or further slow cognitive and functional impairment and thus maintain a patient's quality of life for as long as possible. Many treatments are available including behavioral, psychological and pharmacological therapies. Although research efforts continue to develop and test novel drug treatments for the disease, therapeutic options for AD remain limited to two classes of drugs: acetyl cholinesterase inhibitors (AChEIs) and the N-methyl-D-aspartate (NMDA)-receptor antagonists.

The FDA has approved three cholinesterase inhibitors namely donepezil, rivastigmine, and galantamine for use as first-line treatments for AD (Khoury et al, 2018). These drugs improve neurotransmission in the brain by inhibiting acetylcholine breakdown. Acetylcholine, a cholinergic neurotransmitter integral to memory and cognition, is deficient in brain of AD patients. However, AChEIs can only produce modest cognitive improvements; further side effects like vomiting, nausea and diarrhea are often evidenced (Grossberg, 2003). Memantine is another FDA approved drug that is used to treat AD. It acts by inhibiting the NMDA receptor, thereby preventing neuron loss and improving symptoms by helping repair the damaged neurons (Briggs et al, 2016).

Memantine is commonly prescribed with a cholinesterase inhibitor, e.g., donepezil, for enhanced efficiency and lower adverse effects because of the combination of their doses. This combination therapy has a better effect than either therapy used alone, as their combined action can inhibit both NMDA receptors and acetylcholinesterase (Ehab et al, 2019). Table 2 summarizes the side effects of currently available anti-AD treatments.

Table 2: The available treatments for Alzheimer's disease with their respective advantages and limitations (Adapted from, Wollen, 2010).

S.No.	Therapeutic agents	Advantages	Limitations
1.	Cholinesterase inhibitors- donepezil, rivastigmine and galantamine	<ul style="list-style-type: none"> • Prolongs acetylcholine in brain. • FDA approved drugs. • Evidence of neuroprotective effects. 	<ul style="list-style-type: none"> • Effective for short period of time. • The side effects are adverse. • Expensive • The benefits are modest.
2.	NMDA-receptor antagonist (Memantine)	<ul style="list-style-type: none"> • It reduces glutamate excitotoxicity. • It is a neuroprotective agent that is well tolerated. • The drug is FDA-approved for moderate-to-severe AD, but also has been shown to alleviate mild-to-moderate AD symptoms. 	<ul style="list-style-type: none"> • It can cause neurotoxicity and severe side effects in some patients. • This drug is primarily suggested for moderate-to-severe AD patients. • It is expensive.

The major drawback of all the currently available medications against AD is that they cannot stop disease progression. These treatments can only help patients to feel better symptomatically, by improving their cognitive functionality over the medication period (Abeyasinghe et al, 2020). However, all the above described therapeutics only deal with the effects of AD and do not address the underlying disease cause, besides their effectiveness is partial and temporary. Also, the drug molecules have trouble crossing the

blood-brain barrier (BBB), which decreases their effectiveness. In fact, permeability problems at the BBB are a major factor in the failure of many drug trials for AD (Passeri et al, 2022).

FDA-approved medications are not available to treat the behavioral and psychiatric symptoms of AD. Antipsychotic medications are used to treat a variety of symptoms, including aggression, agitation, and hallucinations. Studies, however, have revealed that some antipsychotics are connected to an increased risk of stroke and death in dementia patients (Alzheimer's Disease Facts and Figures 2021).

Table 3: Typical side effects of currently available anti-AD treatments (Adapted from Abeysinghe et al, 2020).

S.No.	Anti-AD drugs	Common side effects
1.	Donepezil	Nausea, vomiting, diarrhea, fatigue, muscle cramps, decreased appetite, anorexia, sleep problems, headache, skin issues, hallucinations, and urinary incontinence.
2.	Galantamine	Headache, dizziness, drowsiness, hallucinations, decreased appetite, muscle spasms, arrhythmias and skin reactions.
3.	Rivastigmine	Skin reactions, drowsiness, anxiety, depression, nausea, vomiting, diarrhea, decreased appetite, anorexia, dyspepsia, asthenia and arrhythmias.
4.	Memantine	Headache, dizziness, drowsiness, confusion, poor balance, dyspnea, constipation and hypertension.

Approved AD treatments, such as acetylcholine inhibitors (Donepezil, Rivastigmine and Galantamine) and NMDA receptor antagonists (Memantine) are inefficient in slowing the disease's progression. Tremendous efforts have been made in attempting to discover new potential treatments that might halt AD progression (Vaz and Silvestre, 2020). The different clinical trials for AD therapeutics that have been focused in overcoming A β and tau pathology are listed in Table 3 along with their present status.

The advances in AD therapies that target amyloid beta (A β) have been ongoing for over two decades. For different forms of A β , including monomeric, oligomeric, and aggregated plaques, various drugs have been developed. Treatments are designed to improve A β clearance from the brain with approaches like inoculations with A β antigens (ABvac40, amilomotide), anti-A β monoclonal antibodies (solanezumab, bapineuzmab and crenezumab) and anti-A β monoclonal antibodies (immunoglobulins). Clinical trials to decrease A β synthesis and aggregation comprised of A β aggregation inhibitors (scyllo-inositol, tramiprosate), BACE1 (beta-site amyloid precursor protein cleaving enzyme) inhibitors (umibecestat, elenbecestat, verubecestat, lanabecestat and atabecestat), γ -secretase inhibitors (avagacestat and semagacestat), and γ -secretase modulators (tarenflurbil). However, none of these therapeutics demonstrated clinical efficacy. Furthermore, both BACE1 inhibitors were associated with further deterioration of cognitive function, and utilization of γ -secretase inhibitors exerted negative effects due to their role in Notch signalling pathways (Shi et al, 2020).

With a better understanding of the clinical importance of tau pathology compared to A β , tau protein targeting has gained interest among researchers. Investigations have been conducted into therapies targeting to reduce phosphorylated tau protein production. A methylene blue derivative called LMTM [Leuco-Methylthionium Bis (Hydromethanesulphonate)] that diminishes tau protein aggregation and tideglusib which prevents abnormal hyperphosphorylation of tau protein by inhibiting GSK-3 β (glycogen synthase kinase 3) were tested for their clinical efficacy but were found to be ineffective against AD (Shi et al, 2020).

The phase II clinical trials of immunotherapies targeting the tau protein (AADvac-1, ACI-35, ABBV-8E12 and BIIB092) are currently underway. Patients with progressive supranuclear palsy (PSP) have already been studied using ABBV-8E12. Since PSP has considerable contributions from tau pathology but none from amyloid pathology; therefore it is referred to as a 'pure' tauopathy. However, the PSP study was dismissed early due to futility (Shi et al, 2020).

Table 4: An overview of the clinical trials against the tau and amyloid pathologies in AD.

S.No.	Drug	Company	Mechanism of action	Subjects	Phase	Status
1.	Solanezumab	Eli Lilly	Anti-A β antibody	Mild to moderate AD; Mild AD	III	Lack of efficacy
2.	Bapineuzumab	Janssen/ Pfizer	Anti-A β antibody	Mild to moderate AD	III	Lack of efficacy
3.	Lecanemab (BAN2401)	Eisai, Biogen	Anti-A β antibody	Prodromal to mild AD	III	Ongoing trial
4.	Aducanumab	Biogen	Anti-A β antibody	Prodromal to mild AD	III	Terminated for futility
5.	Crenezumab	Roche/AC Immune	Anti-A β antibody	Prodromal to mild AD	III	Lack of efficacy
6.	ABvac40	Araclon Biotech	Anti-A β Vaccine (active immunotherapy)	Prodromal AD	II	Ongoing trial
7.	Amilomotide (CAD106)	Novartis/ Amgen	Anti-A β Vaccine (active immunotherapy)	Preclinical AD	II/III	Ongoing trial
8.	Scyllo-inositol	Elan Corporation	A β aggregation inhibitors	Mild to moderate AD	II	Lack of efficacy and toxicity at higher doses
9.	Tramiprosate	Bellus Health	A β aggregation inhibitors	Mild to moderate AD	III	Lack of efficacy
10.	Umibecestat	Amgen/ Novartis	BACE-1 Inhibitor (β -secretase inhibitor)	Preclinical AD (Normal cognitive function; increased A β ; ApoE4 carriers)	II/III	Lack of efficacy and adverse effects
11.	Elenbecestat	Eisai/Biogen	BACE-1 Inhibitor (β -secretase inhibitor)	Prodromal to mild AD	III	Lack of efficacy and adverse effects

12.	Verubecestat	Merck & Co.	BACE-1 Inhibitor (β -secretase inhibitor)	Mild to moderate AD Prodromal AD	II/III III	Lack of efficacy, more adverse effects
13.	Lanabecestat	AstraZeneca/ Eli Lilly	BACE-1 Inhibitor (β -secretase inhibitor)	Prodromal AD Mild AD	II/III III	Lack of efficacy and adverse effects
14.	Atabecestat	Janssen	BACE-1 Inhibitor (β -secretase inhibitor)	Preclinical AD (Normal cognitive function, increased A β levels)	II/III	Adverse cognitive effects, hepatotoxic nature
15.	Avagacestat	Bristol-Myers Squibb	γ -secretase inhibitor	Prodromal AD	II	Toxicity and no efficacy
16.	Semagacestat	Eli Lilly	γ -secretase inhibitor	Mild to moderate AD	III	Toxicity and no efficacy
17.	Tarenflurbil	Myrexis	γ -secretase modulator	Mild AD	III	Lack of efficacy, increased adverse reactions
18.	LMTM (TRx0237)	TauRx Therapeutics	Tau-aggregation inhibitor	Mild to moderate AD	III	Lack of efficacy
19.	Tideglusib	Noscira	GSK-3 β inhibitor	Mild to moderate AD	II	Lack of efficacy
20.	AADvac1	Axon Neuroscience	Anti-tau vaccine (active immunotherapy)	Mild AD	II	Favourable immunogenicity and statistically important biomarker changes
21.	ACI-35	Janssen/AC Immune	Anti-tau vaccine (active immunotherapy)	Mild to moderate AD	I	No published results
22.	Tilavonemab (ABBV-8E12)	AbbVie	Anti-tau antibody (passive immunotherapy)	Prodromal to mild AD	II	Lack of efficacy
23.	Gosuranemab (BIIB092)	Biogen	Anti-tau antibody (passive immunotherapy)	Prodromal to mild AD	II	Ongoing trial

7. Early Detection and Management

7.1 Early Detection

The perception about AD being a syndrome that impairs the cognitive and functional abilities in the elderly has been lost. Now it is increasingly recognized that AD pathogenesis develops silently for decades before its symptoms are first manifested. AD's succession from inconspicuous variations in the architecture of the brain to those impeding an individual's memory and cognition, and ultimately terminating in total physical disability and death is called the AD continuum. Preclinical AD, MCI by virtue of AD, and dementia by virtue of AD represent the three wide-ranging phases in the AD continuum.

During preclinical AD, quantifiable changes occur in the brain such as abnormal levels of β -amyloid and decreased glucose metabolism; these form the earliest indications (biomarkers) of AD pathogenesis, however the individual undergoing these changes does not display any loss in memory and cognitive abilities. It is evidenced that these changes begin as early as 20 years before the symptoms of memory impairment first appear. Nonetheless, it is observed that more often than not individuals with an underlying AD pathology do not acquire MCI or AD dementia. Individuals that go on to develop MCI begin displaying symptoms of short-term memory impairment and in due course degeneration in other cognitive domains ensues; however the patients can still perform their day to day activities independently. In the next 5-10 years ~30-50% of these MCI patients can progress to the AD dementia stage where the degree of cognitive decline severely impedes the patients' social functioning capacity, and assistance is required to perform the daily living activities.

The common, currently available therapeutics against AD are only efficacious in managing the symptoms of AD and do not halt its progression as they do not target the underlying cause of disease. Moreover, these treatments are prescribed only after the disease has progressed further from its pre-clinical stage and the loss of neuronal cells becomes essentially irreversible.

As the disease remains incurable as of now, an early and timely diagnosis of AD can offer several advantages to at risk individuals and by large to the society, these are outlined as follows-

- i. The timely prospect of setting up advanced support care plans with their family members or caregivers.
- ii. Can lower the overall state of ambiguity and anxiety that surrounds individuals with memory complaints and can increase the quality of their life.
- iii. Facilitates, availing early interventions against disease symptoms, incorporating lifestyle changes that can help preserve the overall quality of life, and also developing risk-reduction strategies to limit behavioral, functional, and cognitive deficits.
- iv. Reducing the healthcare system's burden; research conducted by the Alzheimer's Association has unveiled a timely diagnosis of AD in patients is likely to prevent the loss of ~7 trillion US dollars. These savings can be attributed towards the decline in clinical and long-term care costs for patients with managed MCI relative to those where MCI and dementia remains unmanaged (Mebane-Sims et al, 2018).
- v. Additionally, an early diagnosis will be extremely beneficial to patients in the event a therapy targeting the underlying AD pathology becomes accessible.

Within the prevailing medical settings, diagnosing AD at its preclinical stages is a formidable task that is compounded in its difficulty by numerous barriers, that are described below-

7.1.1 The changing scenario of AD diagnostic guidelines

The universal criteria for diagnosing AD were set forth in 1984 by the Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association

(ADRDA). These defined a classic clinical approach, recommended laboratory examinations to eliminate other co-morbidities, necessitated neuropathological evaluations for the diagnosis to be conclusive and if pathological verifications were not complete individuals were only classified as cases of probable AD. Thus in accordance with these criteria AD remained a plausible clinical-pathological syndrome for more than two decades.

Over time, as several biomarkers for AD pathology were identified, an International Working Group (IWG) formulated fresh diagnostic criteria that incorporated testing for the different biomarkers in the diagnostic procedures. Further, the term preclinical dementia was also coined by the IWG workgroup and the US National Institute on Aging-Alzheimer's Association (NIA-AA). This was specifically done to classify those individuals who evidenced the most primitive changes associated with developing AD and were most likely to benefit from the results of therapeutic trials against AD. In 2018, NIA-AA introduced a diagnostic framework for AD that solely relied on the biomarker status of the disease, specifically the pathological accumulation of A β and tau. The concept of preclinical AD was removed from the picture. Thus, even if a person displayed no clinical signs of cognitive impairment but tested positive for abnormal levels of A β and tau he/she would be categorized as having AD.

Transferal to a completely biological definition for AD has been criticized on account of serious shortcomings. Neuropathological examinations have revealed amyloid β plaques as well as tau tangles to frequently accompany other pathologies, therefore assigning the AD phenotype to a person testing positive for abnormal levels of amyloid beta and tau is likely to be inaccurate. The prospect of testing for the above biomarkers in individuals who are asymptomatic for AD is filled with problems like prognostic improbability and associated ethical concerns. After receiving backlash IWG has backed reverting to a clinical-biological definition for AD (especially under clinical settings), wherein biomarkers (abnormal A β and tau levels) as well as a characteristic clinical phenotype is necessary to identify individuals at risk of developing AD.

A definite and reliable diagnostic process for AD is still a work in progress. Novel biomarkers are being identified and along with those biomarkers that are already known, they are being assessed for their efficacy in longitudinal studies.

7.1.2 Stigma associated with dementia

Currently, there is a lot of public and self stigma associated with AD, which often deters those who display the early signs of disease from approaching experts for a definitive diagnosis. This stigma is also effectual in preventing individuals from approaching their family or caregivers for help. The reluctance of primary care physicians (PCP's) in meting out a diagnosis of AD on the basis of initial symptoms has also been reported. PCP's are of the opinion that since prognosis of AD is by and large a probabilistic event at its initial symptomatic stages, offering a likely AD diagnosis might negatively impact the general health of individuals. Certain studies report that physicians sense the requests for euthanasia or incidence of suicides to increase in patients when they are diagnosed with an incurable disease (Draper et al, 2010; Seyfried et al, 2011; Dubois et al, 2016).

7.1.3 Lack of awareness about the early signs of AD

In developing countries like India which have significantly lower literacy rates, awareness about Alzheimer's disease and dementia is deficient in the general public. A recent study conducted in the metropolitan cities of Delhi and Chennai identified poor awareness about the disease to be amongst the principal causes behind a delay in approaching diagnostic testing (Hurzuk et al, 2022). Locally in India, citizens are versed with the term "chinnan" that explains the condition of senile debilitation; but it is often thought to be a consequence of the usual course of ageing. Therefore people have a tendency to associate impairment in cognitive abilities as a part of the normal ageing process and often overlook the early symptomatic signs of AD. There is a need to raise awareness in public about this incurable disease and emphasis needs to be placed on improving general awareness to identify symptoms as part of an illness.

7.1.4 Lower number of trained PCP's and memory clinics

The mounting impact of dementia on health care resources concomitant with the rising number of AD cases is widely agreed to be abridged with the help of primary healthcare system as it is best positioned to identify and track suspected cases of dementia. However, the primary healthcare system often fails to provide a timely diagnosis of AD or completely misses it. PCP's form the backbone of the primary healthcare infrastructure, but a serious shortage of PCP's with appropriate training to detect the early signs of AD/dementia has been reported not just for developing countries like India (Ellajosyula et al, 2022) but also for high income countries like USA (de Levante et al, 2022). This is often attributed to lack of structured processes being available for diagnosing neurological disorders. PCP's often present low confidence in picking up the early signs of dementia and following up the symptoms in patients, due to their inadequate training.

Reports highlighting the crucial role of memory clinics in providing an early diagnosis of AD are available (Lam and Mattke, 2021). Memory clinics are hospital based facilities that offer a multidisciplinary approach towards managing dementia. Their role ranges from that of enabling an earlier diagnosis, to that of educating the family members of dementia patients about how to cope with its symptoms; additionally, memory clinics are also instrumental in creating general public awareness about dementia and its different forms. There is a dearth of government hospitals having an operable memory clinic. ADRSI in its Dementia India Report (Shaji et al, 2010) projects India to have just about 100 functional memory clinics, majorly in super specialty hospitals; this is equivalent to having a single clinic for 37,000 individuals. As of now, details are not available regarding the management and operation of these clinics.

In India, mental health is yet to transition from the purview of highly specialized, acute medical care towards the primary healthcare care system. This problem is further compounded by the fact that most of the elderly population in India resides in the rural areas of the country where such super speciality facilities are rarely known. Therefore it is important to constitute geriatric mental healthcare services across the different primary health centers in our country (Lodha and De Sousa, 2018). Figure 6 and Figure 7 provide an overview of the latest state wise tally of government run mental hospitals and number of trained psychiatrics in the country.

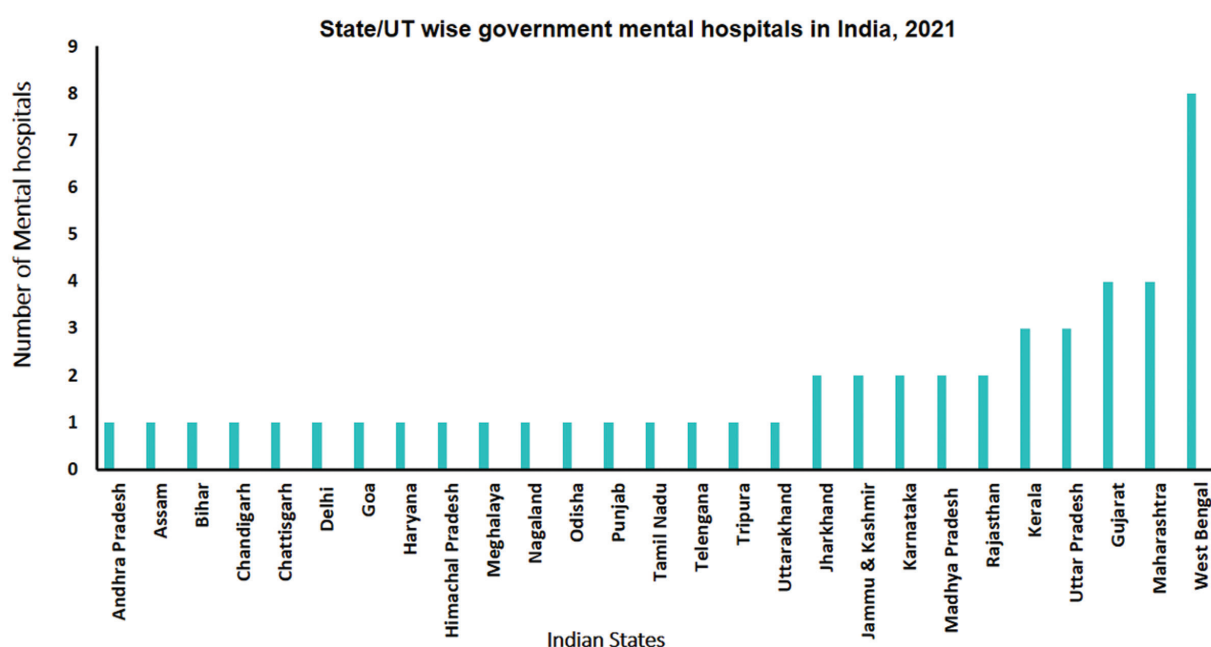


Figure 6: The number of government mental hospitals in the different states of the country (source: National Health Profile, 2021).

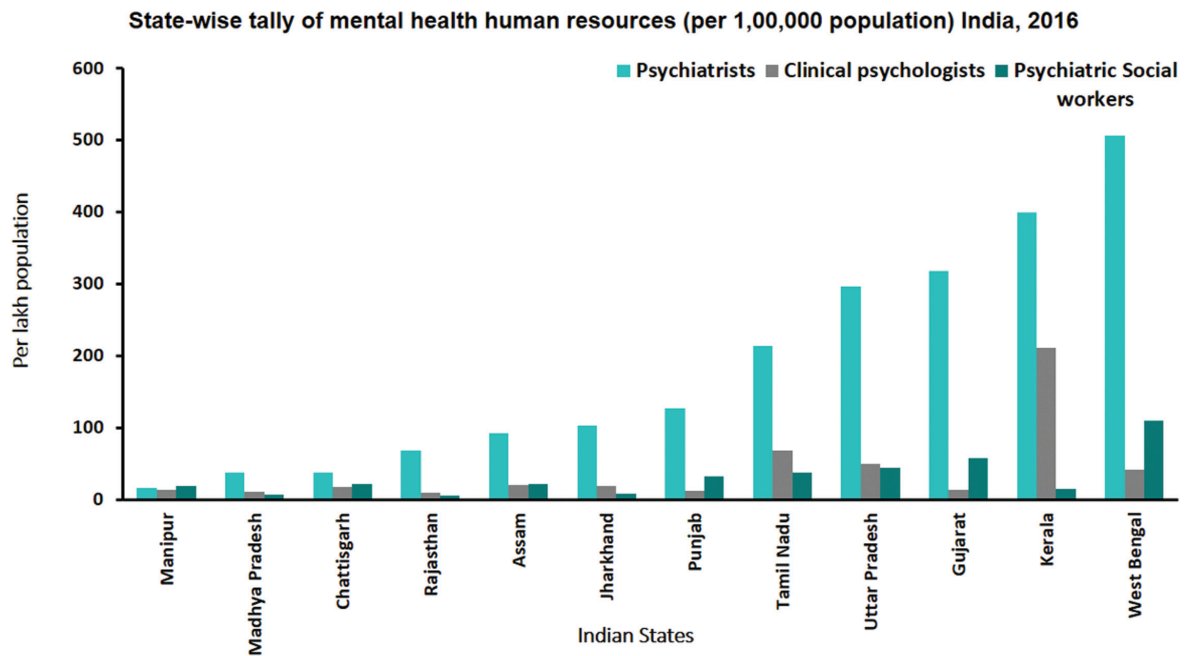


Figure 7: The number of trained psychiatrists, clinical psychologists and psychiatric social workers in the different Indian states (source: Gururaj et al, 2016).

The above mentioned points in combination with the vast multicultural and multilingual landscape of India provide further impediments to diagnosing MCI by means of neuropsychological tests. However, in recent times Indian Council of Medical Research (ICMR) has developed a Neurocognitive Tool Box (NCTB) to diagnose dementia, MCI, and their subtypes, in 5 Indian languages (Iyer et al, 2021). ICMR-NCTB shows promise in harmonizing the neuropsychological testing procedure both at the clinical as well as research capacities across the country (Menon et al, 2020).

7.2 Managing AD via non-pharmacologic means

Repeated failure in contriving a cure against AD and the rising economics associated with the currently available therapeutics has sparked interest in testing and designing non-pharmacologic therapies (NPTs) against AD. NPTs can help in managing the symptoms of AD in patients and improving their overall quality of living, especially at the early/mild stages of the disease. Although evidence in form of detailed laboratory examinations is not widely available at present, still such therapies have been revealed to be beneficial in managing disease associated symptoms like depression and in improving measures of functional independency in AD patients (Cammissuli et al, 2016; Zucchella et al; 2018).

There are several different forms of non-pharmacological interventions like- cognitive stimulation therapy (CST), reminiscence therapy, physical exercise, aromatherapy, and occupational activities amongst others. CST is the most well evidenced therapy amongst the current set of options available for the non-pharmacologic management of AD (Martha et al, 2020; Ballard et al, 2011); it has demonstrated effectiveness in slowing the progression of this disease (Matsuda et al, 2007). CST is a psychosocial intervention for patients at early stages of dementia; it is usually conducted over a brief period of time (14 sessions). By means of CST, the minds of patients are actively stimulated as they are motivated to participate in word association activities and share their opinions on issues such as current affairs. CST is mostly administered as a group activity by trained individuals at memory clinics, care homes or even residential facilities. UK's National Institute of Health and Clinical Excellence (NICE) has implemented the use of CST in individuals with mild to moderate dementia; further it is the only non-pharmacological intervention to be promoted at this level. Moreover, after the extensive success of CST in UK, an international surge in its cultural adaptation and utilization has also been observed in recent years (Gibbor et al, 2021). CST has been adapted

in over 29 countries for managing patients with mild dementia; however, there is only nominal evidence available to support its efficacy in countries with middle and lower levels of per capita income (Marinho et al, 2021).

The diversity of India's socio-cultural landscape and varying levels of education pose difficulty in developing a uniform cognitive stimulation therapy (CST) program for its population. The Alzheimer's Disease International's, World Alzheimer Report-2022 suggests incorporating culturally relevant activities such as Ayurveda, playing customary games, *rangoli* making, and *bhajan* recitals into India's CST program. In recent years, the Indian government's AYUSH program has gained momentum; additionally, WHO's Traditional Medicine Program also aims to expand the evidence base for utilizing traditional medicines for improving the overall quality of life for dementia patients (Gauthier et al, 2022). ■

8. A Possibility in Ayurveda

Inefficiency of contemporary system of medicine to thus far come up with an adequate remedial course against AD, coupled with the side-effects associated with the currently available therapeutics and low patient conformity is justification enough for exploring alternative pre-emptive and/or therapeutic interventions against AD. For chronic and complex ailments such as AD, a paradigm transition from a single-target approach to a multi-target intervention is being witnessed. Traditional medicinal systems are at the frontline of such measures because they offer a holistic approach in treating disease conditions.

The traditional medicinal systems of Ayurveda, Unani, Siddha, Homeopathy, Yoga and Naturopathy have originated in the Indian subcontinent; India is therefore replete with vast indigenous knowledge. Ayurveda originated over 5000 years back (2500-600 BC) and is widely considered as the most ancient form of traditional medicine (Mishra et al, 2001; Jaiswal et al, 2017). Nationally, it is the most extensively practiced form of traditional medicine (Shi et al, 2020). In recent times the popularity of ayurveda has increased on the global landscape and it is acknowledged amongst the leading forms of ancient medicinal systems (Rizvi et al, 2022). Ayurvedic plants are attractive sources for screening potential therapeutics as their formulations are well established in literature, have been tested over centuries and in contrast to allopathy demonstrate little or no side effects.

Even though dementia or AD is not directly mentioned in ayurvedic literature, indications of memory decline and loss are available. The Senior Triad of ayurveda- Charaka Samhita, Sushruta Samhita and Ashtanga Hridaya accounts certain plant extracts to possess mental vigour promoting effects and curative action against a range of neurological conditions. For centuries, plants with intellect/memory (medha) enhancing ability, termed as Medhya Rasayana's in the different texts of ayurveda, have been utilized in traditional medicine for their beneficial effects. Research suggests that robust knowledge of traditional medicinal systems such as ayurveda in conjunction with modern science can aid in identification of novel therapeutic leads against age-associated neurodegenerative diseases. In recent times, preventative and restorative efficacy of several ayurvedic plants has been validated in numerous pre-clinical studies and also in some clinical studies. Specifically, in context of AD, the neuroprotective and nootropic effects demonstrated by ayurvedic plants such as *Withania somnifera*, *Bacopa monnieri* and *Centella asiatica* have been most widely studied (Sharma et al, 2019). Research supports the extracts of these medicinal plants to contain bio-active molecules that are capable of negatively modulating AD pathogenesis through diverse mechanisms. Anti-inflammatory action, antioxidant effects, reducing amyloidogenic processing of amyloid precursor protein (APP), inhibition of amyloid aggregation, anti-apoptotic potency and inhibitory action on acetylcholinesterase and phosphodiesterase activity are amongst the principal beneficial effects delivered by the bio-active components present in these plants.

- i. *Withania somnifera*:** commonly known as Ashwagandha or winter cherry, *W. somnifera* a popular ayurvedic plant that has been inspected for therapeutic efficacy against AD (Zieneldien et al, 2022). *W. somnifera* is abundant with medically relevant bio-active compounds, principal amongst which are withanolides (A-Y), withanone, withanamides (A-I), withasomniferols (A-C), beta-sitosterol and sitoindosides (VII-X). A vast amount of pre-clinical evidence supports the therapeutic potential of *W. somnifera* against AD, as briefed below. In separate studies withanolides (A and B), withanosides (IV and V) and withanamides (A and C) were observed to impede the aggregation of A β into toxic amyloid aggregates and confer neuroprotective effects (Kumar et al, 2012; Dubey et al, 2021; Jayaprakasam et al, 2010). Additionally, Withanolide A was found to impede the processing of amyloid-beta precursor protein (APP) into the amyloidogenic A β 42 peptide and further up-regulate levels of insulin degrading enzyme that is involved in clearing aggregated A β (Patil et al, 2010). Another study observed levels of low-density lipoprotein receptor-related protein (LRP) to increase in APP/PS1 mice models of AD, when they were administered with *W. somnifera* root extract; further this treatment resulted in reversal of cognitive impairment observed in these mice. LRP mediates removal of aggregated A β (Sehgal et. al., 2012). Pandey et al found withanone to improve cognitive functions in streptozotocin induced mouse models of AD via the combinatorial effect of anti-inflammatory as well as anti-oxidant activities and a reduction in A β levels (Pandey et. al., 2018). Numerous studies have demonstrated that administering rats with extracts of *W. somnifera* enhances choline acetyl transferase activity, leading to increased levels of acetylcholine and improved cognitive and memory skills (Kuboyama et al, 2002; Schliebs et al, 1997; Konar et al, 2019). Sitoindosides (VII-X) and withaferin A have been found to reinstate acetylcholine levels and cognitive ability in rats previously impaired with ibotenic acid treatment (Bhattacharya et. al., 1995). Furthermore, several reports indicate withaferin A to inhibit acetyl cholinesterase and contribute to elevated levels of acetylcholine (Choudhary et al, 2004; Choudhary et al, 2005; Vinutha et al, 2007). *W. somnifera* extract has inhibitory effects on NF- κ B activation- a key player in inflammatory stress (Logie et al, 2020; Behl et al, 2020). *W. somnifera* extract is suggested to be effective in overcoming Streptozotocin induced memory loss in murine models on account of its antioxidant properties (Parihar et.al. 2004). Withaferin A promotes nuclear translocation of Nrf-2 transcription factor which promotes expression of anti-oxidant genes (Narayan et al, 2015; Sun and Grace, et al 2016). Administration of *W. somnifera* root extract in rats has been demonstrated to prevent stress induced degeneration in the brain hippocampus (Jain et. al., 2001). Withanolide A, and withanoside IV and VI are reported to possess neuroregenerative properties in in-vitro studies (Singh et al, 2010). However, under clinical settings the efficacy of *W. somnifera* against AD has not been investigated thoroughly. A single report is available wherein 50 individuals with MCI were examined in a pilot, randomized, double-blind and placebo-controlled study. The participants were either treated with root extract (300 mg, twice daily) from *W. somnifera* or placebo for a period of 56 days and the performance of the treated group was observed to be notably better, with greater attention span and cognitive function (Choudhary et al, 2017). Preliminary evidence therefore supports the memory and executive function enhancing role of *W. somnifera* in MCI patients; however larger clinical trials are required to establish *W. somnifera* and/or its components as therapeutic agents against AD.
- ii. *Bacopa monnieri*:** popularly known as water hyssop or Brahmi, *B. monnieri* is another ayurvedic plant that has been investigated for its potential efficacy in management of AD. Bacosides A and B, Bacosaponins A-E, bacopasides, betulic acid, monnierin, oroxindin, alkaloids (herpestine and brahmine), saponins (hersaponin and D-mannitol), sterols (beta-sitosterol, stigmaterol) and sulfhydryl compounds are the principal bio-active compounds present in *B. monnieri* extract. Numerous pre-clinical studies on animal models have pointed out to the potent anti-oxidant effects exerted by bacosides or *B. monnieri* extract against oxidative stress. Increased lipid peroxidation is one of the hallmarks of AD brain and studies on rat models have found treatment with *B. monnieri* extract to prevent the same in hippocampus, prefrontal cortex, and brain striatum (Simpson et

al, 2015). *B. monnieri* extract also has cholinergic action, brought about by an elevation in the expression levels of choline acetyl transferase (Le et al, 2013); additionally it has been reported that treatment with *B. monnieri* extract protects cholinergic neurons against degeneration in a rat model of AD (Uabundit et al, 2010). Additionally, amyloid inhibitory effects of the plant's extract are also documented in literature. *B. monnieri* extract is reported to dissociate pre-formed amyloid fibrils and prevent the assembly of monomeric A β peptide into amyloid aggregates (Mathew et al, 2012). Furthermore, treatment with Brahmi extract has been reported to reduce processing of APP into A β 40 and A β 42 in mouse models of AD (Holcomb et al, 2006). Constituents of *B. monnieri* extract also exhibit anti-inflammatory properties (Viji and Helen, 2011). Oral intake of bacosides in aged rats for a duration of three months resulted in reduced inflammatory and oxidative stress (Rastogi et al, 2012). Treating memory impaired rats with a combination of *B. monnieri* extract and melatonin was found to reinstate levels of Nrf2 and heme oxygenase-1. This treatment further helped in overcoming neuronal loss, oxidative stress and neuro-inflammation (Dwivedi et al, 2013). Under clinical settings, the efficacy of *B. monnieri* and/or its constituents has not been inspected in sufficient details. In one such study, efficacy of a standardized extract of *B. monnieri* in 35 memory impaired patients (>55 years in age) was examined, in a randomized, double-blind, placebo-controlled clinical trial. Participants were administered with either 125 mg of standardized *B. monnieri* extract or placebo, twice a day, over a time period of 3 months; this was followed by a month of placebo interval. An array of neuropsychological tests was utilized for evaluating the performance of the subjects and the treated cohort was observed to exhibit notable enhancement in paired learning, mental coordination and logical ability (Raghav et al, 2006). In another clinical study, administration of BacoMind (a standardized *B. monnieri* formulation) was found to significantly improve concentration and verbal memory retention ability in aged individuals with memory problems (Barbahiya et al, 2008).

iii. *Centella asiatica*: that is popularly recognized by the names Indian pennyworth, Gotu kola or Mandukaparni is another ayurvedic herb that has been well-studied for its nootropic properties. *C. asiatica* has been utilized for enhancing brain function and remedying several neurological disorders since ancient times; this has led to a renewed interest in inspecting its therapeutic efficacy in the management of AD. Asiaticosides, asiatic acid, asiaticin, brahmoside, brahminoside, centellicin, centelloside, madasiatic acid, madecassoside, scentellin, isothankuniside and thankuniside are the medicinally active constituents present in *C. asiatica* extract. *C. asiatica*'s role against AD has been evaluated in several pre-clinical studies that support its likely effectiveness; the most relevant amongst these are briefly described below. Mice models of AD when treated with *C. asiatica* extracts for a period of 8 months were observed to exhibit significantly lower levels of amyloid build-up and associated cytotoxicity as compared to controls (Dhanasekaran et al., 2009). Chronic treatment of rats with *C. asiatica* extract correlated with lowered AChE activity, oxidative damage and memory loss arising as a consequence of exposure to colchicines (Kumar et al, 2009). Furthermore, it was unveiled that administering *C. asiatica* extracts to mice who were simultaneously also treated with D-galactose protected the animals against the harmful effects of D-galactose- oxidative stress, mitochondrial dysfunction and impaired cognition (Kumar et al, 2011). Many other studies have highlighted the anti-oxidant efficacy of *C. asiatica* (Shinomol et al, 2008; Subathra et al, 2005; Hussin et al, 2007; Gray et al, 2017; Nataraj et al, 2017). In recent years it has come to light that the constituents of *C. asiatica* extract exert their anti-oxidative responses by up-regulating the expression of Nrf-2 transcription factor and its downstream targets, viz. the different antioxidant response element (AREs) genes (Matthews et al., 2019; Zweig et al., 2021). *C. asiatica* constituents are also likely to be efficacious against AD pathogenesis on account of their anti-inflammatory activity. In different reports, asiatic acid, madecassoside and asiaticoside were found to inhibit inflammatory stress in stroke models through downregulation of pro-inflammatory cytokines and microglial activation (Krishnamurthy et al, 2009; Luo et al, 2014; Chen et al, 2014). Treatment with asiaticoside protected rats against the ill effects of neuroinflammation ensuing from

intracerebroventricular administration of A β aggregates (Zhang et al., 2017). *C. asiatica* extract's bio-active components also exhibit neuroprotective properties, which are proposed to be relevant in managing AD pathogenesis. Asiaticoside and its derivatives have been observed to impede neuronal apoptosis (Song et al., 2018; Mook-Jung et al, 1999). Apart from the above beneficial effects, *C. asiatica* extract also possesses inhibitory activity against acetyl-choline esterase, contributing to increased levels of acetylcholine (Mukherjee et al, 2007; Orhan et al, 2013). Despite the vast amount of pre-clinical evidence, under clinical settings there are only limited reports where *C. asiatica*'s efficacy has been evaluated in memory impaired patients or those with a definite AD diagnosis. A double-blind, placebo controlled randomized trial inspected the effect of *C. asiatica* on cognitive function of healthy elderly individuals. Here subjects were treated with *C. asiatica* extract and the cognitive performance as well as mood of the treated groups was evaluated using a combination of tests; the treated cohort was observed to exhibit notably enhanced mood and working memory (Wattanathorn et al, 2008). Likewise, Dev et al have reported treatment with *C. asiatica* to enhance cognition in middle aged and healthy individuals (Dev et al, 2009). In another study 60 elderly individuals (aged >65) with a MCI diagnosis were treated daily with aqueous extracts of *C. asiatica* (two doses of 500 mg each) for a span of 6 months. Cognitive performance of the subjects and associated problems like hypertension, insomnia, etc. was evaluated using a combination of different tests and it was found that subjects receiving *C. asiatica* treatment performed better, however a serious limitation of this study was absence of a control group (Tiwari et al, 2008). In a latest clinical report pharmacokinetic and pharmacodynamic effect of treating cognitively impaired individuals with a standardized *C. asiatica* extract was evaluated. Although impact of the meted treatment on the overall cognitive function of the subjects was not evaluated in this report, the presented preliminary analysis indicated *C. asiatica* mediates enhanced expression of the anti-oxidant NRF2 gene; furthermore the study provides additional support for conducting larger and elaborate clinical trials with *C. asiatica* and MCI/AD patients (Wright et al, 2022). ■

9. Policy Recommendations

- i. A national plan for management of AD with funds allocated specifically towards this cause needs to be formulated.** Unlike other countries with large population of AD/dementia patients, India currently lacks an elaborate plan to tackle the disease associated burden. Further, for the plan to be successful a multidisciplinary approach involving collaborative efforts from the government, NGO's, researchers and families of patients, amongst others will be essential (Kumar et al, 2019).
- ii. More AD specific epidemiological data needs to be made available.** A need for establishing the state and district level burden of AD for two important reasons- identifying the region specific risk factors of the disease and controlling disease progression via their modulation; and framing customized policies that will be better suited to each individual state's population.
- iii. Need to examine the cost of dementia care in India.** There is a dearth of reports that have examined the cost of dementia care in the country. An accurate estimate of the same is imperative for developing appropriate dementia care plans for AD patients and their families or caregivers.
- iv. Awareness about AD and dementia needs to be increased.** In India, only 10% of the individuals suffering from AD are diagnosed; amongst the principal reasons behind the same is a serious lack of awareness in general public regarding AD/dementia. Disseminating information about the symptoms of the disease can encourage individuals to reach out to medical experts and get adequate diagnosis and care.

v. **Ayurveda is a promising, holistic approach that can be explored under clinical settings for management of AD.** Failure to arrive at a definite cure for AD through contemporary means, and ample amount of pre-clinical evidence available to support the therapeutic potency of plants such as- *W. somnifera*, *B. monnieri* and *C. asiatica* against the pathogenic processes involved in AD, warrants testing these plants for clinical efficacy against AD. In Figure 8 we depict a process flow that can aid in examining the therapeutic efficacy of the identified lead Medhya Rasayana herbs.

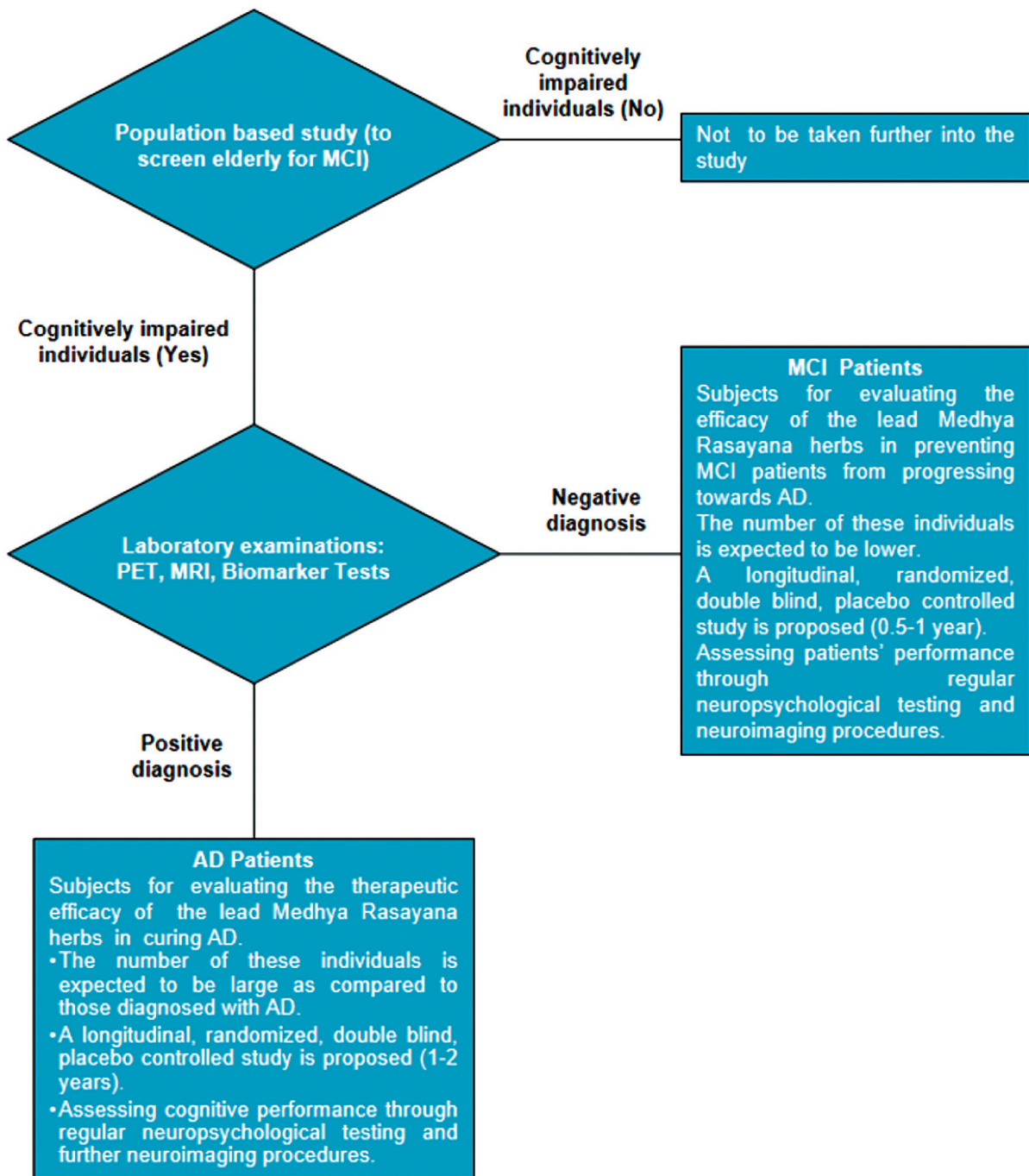


Figure 8: The proposed roadmap/framework for examining the therapeutic efficacy of Medhya rasayana plant formulations against MCI/AD: To begin with a large number of elderly individuals can be screened through a battery of neuropsychological tests to identify individuals with MCI. From this screen the individuals that are diagnosed to be cognitively impaired can be further examined in laboratory procedures such as APOE testing, brain MRI, PET and CSF biomarker analysis to discern individuals most likely to have AD. These subjects can be inspected to test the curative aspect of the Medhya Rasayana herbs, while those individuals that are only positive for MCI can be inspected to decipher the preventative aspect of Medhya Rasayana herbs against AD.

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