Putative ante-mortem indicators of Alzheimer's dementia: Analysis of fluid biomarker and neuroimaging studies

by

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Abstract

Dementia is a clinical state, characterized by symptoms indicative of deterioration of memory and cognitive functions that interferes with social or occupational functioning. According to 2018 statistics, around 50 million people are living with dementia, and this number will increase to 131.5 million by the year 2050. Furthermore, the financial burden of dementia in the global economy was around 1 trillion US$ in the year 2018. Among different forms of neurodegenerative dementia, Alzheimer's disease (AD) is the most common, accounting for up to 60-80% among all dementias. AD proceeds through a precursor stage, known as Mild Cognitive Impairment (MCI), between healthy ageing and full dementia. Subjects with MCI, however, may or may not progress to AD or related dementia. Contemporary diagnosis of AD is based on clinical examinations and cognitive grading, but definitive diagnosis is currently possible only following autopsy or, rarely, biopsy. Despite massive investment in the search for therapies of AD, all clinical trials of AD indicate a current lack of effective drug therapies for AD dementia. This may be due to excessive damage to brain prior to clinical symptom onset, or to insufficient understanding with respect to diagnosis and disease progression. In addition, evidence in the literature has been inconsistent with the classification of AD patients from normal ageing, and the relationship between body fluid metabolite concentrations and severity of AD dementia.

This PhD investigation sought to synthesize evidence from the existing literature by using systematic review and meta-analysis procedures for additional knowledge contributing to improved diagnosis, prognosis, and prediction of AD dementia. The investigation addressed three questions (i) Is differential diagnosis of Alzheimer's disease versus healthy ageing possible based on body fluid metabolites? (ii) Do concentrations of ante-mortem body fluid metabolites correlate with severity of Alzheimer's disease dementia? (iii) Can we predict age at onset of Alzheimer's

disease dementia from concentrations of body fluid metabolites? In addition, a systematic investigation of neuroimaging studies was carried out to assess the evidence for possible neuroimaging-based differential diagnosis and prediction of AD dementia from healthy ageing and other related dementia.

In conclusion, this doctoral investigation found that the cerebrospinal fluid CSF amyloid beta (Aβ) (1-42), hyperphosphorylated tau (P-tau) and total tau (T-tau) protein concentrations were significantly different in AD patients' than healthy controls. In addition, there are some other biofluid metabolites that are being extensively investigated as potential biomarkers for AD research. Furthermore, none of these biofluid metabolites have been found to be predictive for both the severity of dementia and age at onset for AD. Some of the CSF biomarkers such as Aβ oligomers, norepinephrine, and pyruvate concentrations demonstrate a significant predictive information about AD dementia severity, but based on the small number of studies with relatively small patient sample size, these findings may not be generalizable to the broader AD patient population and further research is needed. In addition, this systematic investigation also indicates a large variation of methodology across studies, which needs to be considered in future clinical research.

Preface

This thesis is an original work by Manoj Malik, the Ph.D. candidate. Because this thesis follows a paper-based format, there is occasional repetition of some information in different chapters.

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Each chapter contains a reference list specific to the references cited in that Chapter. The thesis also contains a comprehensive bibliography at the end of the document, which are the references from the entire thesis.

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Chapter 1: Dementia and Alzheimer's disease

1.1 The History of Dementia and Alzheimer's disease

In ancient history, from as early as 2000 BC, Egyptians believed that the heart and the diaphragm were the major physical components of mental life. They also thought that a major memory disorder could occur in older age (Boller and Forbes, 1998). Around 630–560 BC, Solon, an Athenian statesman, wrote that judgement may be "impaired by physical pain, violence, drugs, old age or the persuasion of a woman'" (Boller and Forbes, 1998). Furthermore, many ancient scholars [including Plato, Horatius, Aulus Cornelius Celsus, Aretheus, Hippocrates and Galen] considered concepts related to dementia, ageing, neurological and mental disorders [for a review, see (Boller and Forbes, 1998)]. This evidence and many other historical reports have suggested that dementia-related concepts had their origins in prehistoric time and terms like "amentia, imbecility, morosis, fatuitas, anoea, foolishness, stupidity, simplicity, carus, idiocy, dotage and senility [but not dementia] were used to name, in varying degree, states of cognitive and behavioural deterioration leading to psychosocial incompetence" (Berrios, 1994). The word 'dementia', arising from the Latin *demens* [relating to the concept of madness or insanity], was first reported in "the vernacular in Blancard's popular Physical Dictionary (1726) as an equivalent of 'anoea' or' extinction of the imagination and judgement" and its adjective form "demented" is reported by the Oxford English Dictionary as used in this sense since 1644 (Berrios, 1994). Of note, the Oxford English dictionary reports earlier uses of the words dementia and demented in the more general context of reference to unspecified madness [e.g. "*Dementia 1598 J. MOSAN tr. C. Wirsung Praxis Med. Vniuersalis I. xii. 130 (heading) Of Melancholia or Dementia, a woonderfull madnesse"; and "Demented 1545 G.*

Joye Expos. Daniel (v.) f. 90^{v} He was thus demented and bewitched with these pestilent perswasions." From U of A libraries OED database].

However, the early modern description of dementia was first written by a French psychiatrist Dr. Philippe Pinel (1745–1826) as "démence" in the year 1797 (Boller and Forbes, 1998). Since then, many reports suggested the evolutionary concept of dementia until nineteenth century (see reviews (Berrios, 1994; Boller and Forbes, 1998).The dementia of Alzheimer's disease (AD) was first described by the great neurologist Dr. Alois Alzheimer in the year 1906 (Hippius and Neundörfer, 2003). Dr. Alzheimer investigated a female patient named Auguste Deter (~ 50 years), who was suffering from "sleep disorders, disturbances of memory, aggressiveness, crying, and progressive confusion" (Hippius and Neundörfer, 2003). After the death of Auguste Deter in 1906, the post-mortem analysis of her brain suggested many amyloid plaques and neurofibrillary tangles in the cerebral cortex, which are now considered as pathological hallmarks of AD (Hippius and Neundörfer, 2003). Extracellular deposition of amyloid plaques in the brain is produced from the misfolded protein amyloid beta (Aβ), while the intracellular deposition neurofibrillary tangles (NFT) is due to hyperphosphorylated tau proteins, which may impede or prevent communication and signalling between neurons, eventually leading to death [see reviews (Lane et al., 2018; Querfurth and LaFerla, 2010)]. Although, these abnormal protein depositions in the brain are not the only causes for AD pathogenesis, they currently identify AD as a distinct neurodegenerative disorder among different forms of cognitive disorders, which may later lead to dementia (Jack et al., 2018).

There are several risk factors for development of AD (Reitz et al., 2011), among them increased age is considered as the greatest risk factor (Guerreiro and Bras, 2015). Furthermore, many studies suggested that the neurotransmitters like acetylcholine (ACh), serotonin, noradrenaline,

Glutamate, Dopamine, and γ-aminobutyric acid (GABA) including their respective transporters and receptors play a crucial role in AD, based on the postulate that their imbalance, in whole or part, may contribute to cognitive impairment and determine the severity of symptoms in AD (for recent review: Strac et al., 2015).

Neurotransmitters are endogenous chemicals that enable communication between neurons by transmitting signals across synapses (Sudhof, 2014). All neurotransmitter-related clinical trials in the domain of AD suggest the involvement of different neurotransmitters in the pathophysiology and clinical symptoms of AD (Cummings et al., 2017; Francis, 2005; Reddy, 2017; Strac et al., 2015). For example, the neurotransmitter acetylcholine plays an important role in learning and memory (Hasselmo, 2006) and the cholinergic hypothesis states that the dysfunction of cholinergic neurons in the brain contributes to cognitive deficits as observed in AD patients (Craig et al., 2011; Francis et al., 1999).

There are several other distinct forms of dementia such as vascular dementia, dementia with Lewy bodies (DLB), mixed dementia, fronto-temporal lobar degeneration (FTLD), Parkinson's disease (PD), Creutzfeldt-Jakob disease, and normal pressure hydrocephalus, that have their own proposed underlying pathogenic causes and characteristics (see Alzheimer's Association, 2018; Camicioli, 2004).

1.2 Alzheimer's disease (AD) and scope of the problem

AD dementia is symptomatically characterized by progressive impairment of memory and other cognitive functions such as disorientation, confusion, communication, judgement, and disturbances in motor functions like speaking, swallowing and walking (Alzheimer's Association, 2018; McKhann et al., 1984). However, the symptoms vary from individual to

individual, and sometimes it is very challenging to distinguish between normal ageing associated cognitive changes and early stages of AD (Alzheimer's Association, 2018; Fjell et al., 2014). Most incidence of AD occurs sporadically in old age and hence, old age is believed to be the greatest risk factor of AD (Guerreiro and Bras, 2015) among other risk factors (Crous-Bou et al., 2017). Sporadic AD occurs after age of 65 years, known as later age of onset (LOAD), and accounts more than 90% of clinical cases (Bertram and Tanzi, 2004; Prince et al., 2013). The age of 65 years as a cut-off point has no particular biological significance rather a sociological partition with regard to employment and retirement age (Rossor et al., 2010).

Only around 1-6% cases of AD developing through genetic mutation are identified as the familial form of AD (FAD), and the symptoms in FAD cases appear between 30 to 65 years, and hence, it is called early onset of AD (EOAD) (Cruts and Van Broeckhoven, 1998; Piaceri et al., 2013; Shea et al., 2016). FAD is generally attributed to the expression consequences of autosomal dominant mutation of three genes, including amyloid precursor protein (APP) gene on chromosome 21, presenilin-1 (PS1) gene on chromosome 14, and presenilin-2 (PS2) gene on chromosome 1 (Bateman et al., 2011; Brouwers et al., 2008; Piaceri et al., 2013). Furthermore, the apolipoprotein E (APoE) gene on chromosome 19 is also associated with LOAD in both familial and sporadic forms of AD (Holtzman et al., 2012; Verghese et al., 2011). The APoE gene has three alleles including APoE Ɛ2, APoE Ɛ3 and APoE Ɛ4, and the inheritance of APoE Ɛ4 allele yields a three-times higher risk of developing AD than other forms (Holtzman et al., 2012). Likewise, subjects' carrying two copies of APoE Ɛ4 gene have an 8-12-fold increased risk of AD development (Holtzman et al., 2012; Loy et al., 2014). In addition, an increased number of copies of APoE Ɛ4 genes may also decrease the mean age of onset of dementia symptoms from 84 years to 68 years, and individuals with the homozygous condition of ApoE Ɛ4 are at risk of

expressing AD by the age of 80 years (Corder et al., 1993). It is of great interest that Down's syndrome (DS) patients (Asim et al., 2015) are also at a high risk of EOAD due to the presence of three copies of chromosome 21 with AAP gene (Goedert, 2015). In fact, AD patients typically survive with a mean duration of only 8.5 years after the diagnosis with dementia symptoms (Francis et al., 1999).

According to the World Alzheimer Report (2018), It has been estimated that around 50 million people were living with dementia globally in the year 2017, and this number will exceed 75 million and then 131.5 million by the years 2030 and 2050 respectively (International, 2018). However, the prevalence of AD accounts for only up to 60-80% among all dementia cases (Alzheimer's Association, 2018). Currently, around 5.7 million Americans are living with AD as per recent US statistics (Alzheimer's Association, 2018). According to the Alzheimer's society of Canada, (http://alzheimer.ca/en/Home/About-dementia/What-is-dementia/Dementia-numbers) around 564,000 Canadians are currently living with dementia. The globally financial burden of dementia was around 818 billion United States Dollar (USD) in 2015 and this amount will exceed 1 trillion USD by 2018 (Wimo et al., 2017).In the year 2018, the total financial burden for the US dementia population, who are greater than the age of 65 years is reported as around $ 277 billion USD (Alzheimer's Association, 2018). Similarly, the total annual cost of the Canadians living with dementia was around $10.4 billion Canadian in 2016 (http://alzheimer.ca/en/Home/About-dementia/What-is-dementia/Dementia-numbers). Clearly, if AD dementia is neither diagnosed nor treated properly with new strategies to halt or delay the onset of disease, it will impose an increasingly severe burden on the global economy, both from a human suffering and a fiscal perspective.

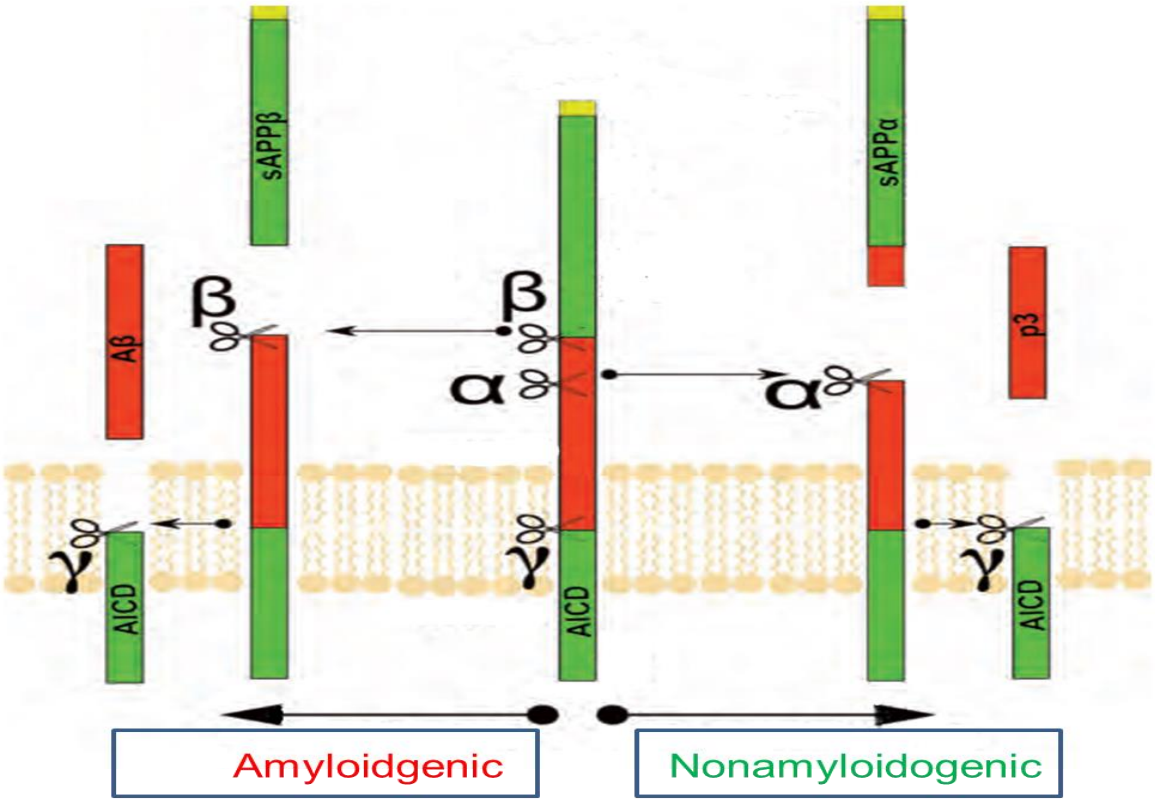

Figure 1.1 Amyloid precursor protein processing. Aβ = Amyloid beta, α = Alpha secretase enzyme, β = Beta secretase enzyme, γ = Gama secretase enzyme, sAPPα = secreted amyloid precursor protein α, P3 = P3 peptide, AICD = amyloid precursor protein intracellular domain. Adapted from: Arbor et al. (2016).

The exact cause of AD remains elusive, however, abnormal accumulation of the Aβ plaques and NFTs is the most well-characterized pathological feature of AD, among different neurodegenerative diseases leading to dementia (Jack et al., 2018). The Aβ plaques are produced from the amyloid precursor protein (APP) and deposited extracellularly, while the NFTs are made up of hyperphosphorylated tau proteins and deposited inside the neurons (Jack et al., 2018). Evidence suggests that the APP metabolism occurs in two alternative pathways in different pathological condition and normal physiological process (Arbor et al., 2016). As

illustrated by the Arbor et al., (2016), APP is processed through the amyloidogenic and nonamyloidogenic pathways by the actions of α, β, and γ-secretases enzymes. In AD, the APP processes through the amyloidogenic pathway by the actions of β-secretase and γ-secretase (see **Figure 1.1**) leading to the formation of Aβ plaques, while in the nonamyloidogenic pathway the APP is cleaved by the α-secretase and followed by the γ-secretase enzymes, which prevent the formation of Aβ peptides [see details in review (Arbor et al., 2016)]. Similarly, Tau protein is a soluble microtubule-associated protein that stabilizes microtubules in neurons and other cells (Johnson, 2004)]. In AD pathology, these axonal proteins become highly phosphorylated [see **Figure 1.2**) by the actions of different kinases leading to the formation phosphorylated tau, and finally, it accumulates intracellularly in the form of NFTs [see detail in review (Johnson, 2004)].

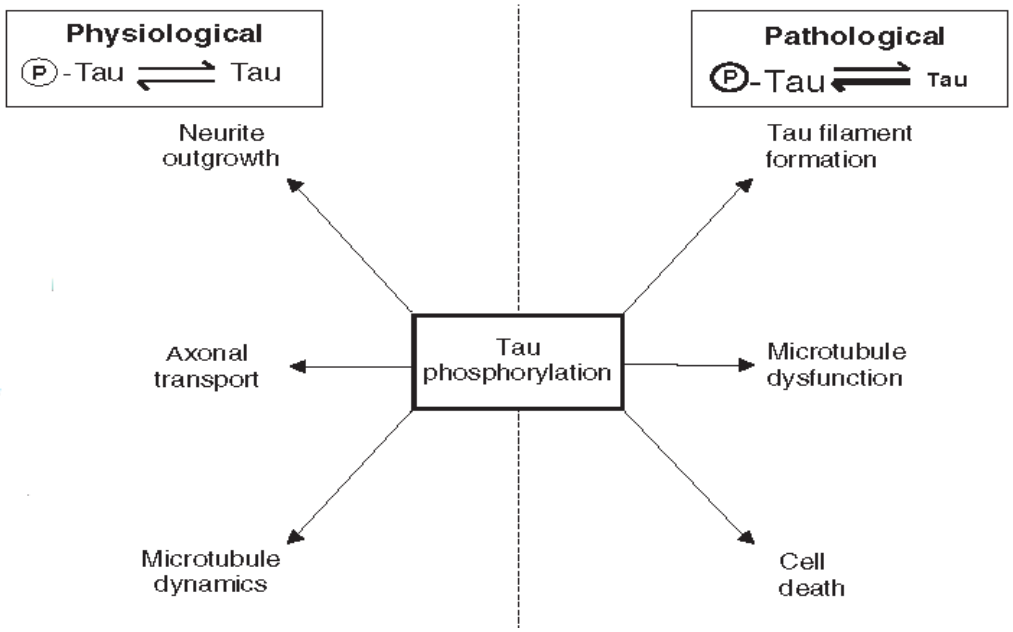

Figure 1.2 Tau phosphorylation in both physiological and pathological condition. Figure adapted from the review by Johnson (2004).

1.3 Mild Cognitive Impairment (MCI)

Mild cognitive impairment (MCI) is a precursor stage of AD and of other related dementias (Petersen, 2011). MCI is a clinical condition in which individuals with MCI show mild changes in memory and other cognitive functions like "thinking" abilities, that can be noticed by the family members and friends, but they are able to carry out daily life activities with a reasonable degree of competence (Alzheimer's Association, 2018; Petersen et al., 2014). People with the MCI condition are classified into two subtypes based on neuropsychological test performance, those are amnestic MCI (aMCI) and non-amnestic MCI (naMCI) (Petersen et al., 2014). The aMCI patients perform poorly on neuropsychological tests of episodic memory (Tulving, 2002), while patients with naMCI perform poorly on other cognitive domains of neuropsychological tests than memory, such as executive functions, language or visuo-spatial abilities (Petersen et al., 2014). In addition, MCI patients have impairments in single to multiple cognitive domains and therefore, the above MCI groups may be further classified into four possible subtypes, such as (i) aMCI-single domain, (ii) aMCI-multiple domain, (iii) naMCI-single domain and (iv) naMCI-multiple domain (Petersen et al., 2014). People with MCI conditions are at a higher risk of developing AD or other forms of dementia than normal ageing individuals without MCI (Alzheimer's Association, 2018). For example, a meta-analysis on 41 longitudinal studies of MCI subjects found that an average of 38% progressed to AD or other dementias after more than 5 years (Alzheimer's Association, 2018; Mitchell and Shiri-Feshki, 2009). The authors also reported that most people with MCI conditions remain stable after 10 years on follow-up from the initial diagnosis (Mitchell and Shiri-Feshki, 2009). Similarly, a recent systematic review suggested that around 32% of subjects with unspecified MCI or aMCI conditions progressed to AD dementia within 5 years (Alzheimer's Association, 2018; Ward et al., 2013). Therefore, early

diagnosis of people with MCI condition, who are greater risk of developing AD or other dementia is a key target of current research (Alzheimer's Association, 2018).

1.4 Diagnostic Guidelines for AD

The traditional diagnostic criteria of AD were reported by the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) in 1984 (McKhann et al., 1984). According to these 1984 guidelines, based on the level of evidence, AD dementia was divided into three separate nosological entities: probable AD, possible AD and definitive AD (McKhann et al., 1984). Of these, the most accurate clinical diagnosis of AD in living patients was considered as probable AD, based mainly on the clinical judgement of a doctor's investigation of a patient's symptoms [see diagnostic guidelines (Cummings, 2012; McKhann et al., 1984)]. However, the definitive diagnosis of AD was, and is, based on autopsy or biopsy evidence of Aβ plaques and NFTs with probable AD causes (McKhann et al., 1984). Interestingly, a study with 208 possible AD and 432 probable AD patients found no group differences in clinical outcomes for dementia (Villareal et al., 2003). The 1984 diagnostic guidelines of AD were revised in 2011(Jack et al., 2011; McKhann et al., 1984, 2011). The revised guidelines described AD in three stages: an early preclinical stage, an intermediate stage called MCI, and the final stage of AD dementia [see (McKhann et al., 2011)].

As with many clinical disorders, there are alternate guidelines for diagnosis of AD, including the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the 10th revision of the International Classification of Diseases (ICD-10) International Work Group criteria (IWG) that have been reported to define AD [see review (Cummings, 2012)]. Of these, the NINCDS-

ADRDA diagnostic guidelines of AD have become the most extensively used guidelines for AD dementia research because of their very high sensitivity and specificity (Zhu et al., 2010) based on post-mortem confirmation of AD diagnosis than other sets of diagnostic criteria [see (Cummings, 2012; Husain and Garrett, 2005)]. Most recently, the National Institute on Ageing-Alzheimer's Association (NIA-AA) updated the 2011 guidelines of AD, and now defines AD as a continuum starting with underlying brain pathological processes (Jack et al., 2018). According to these 2018 guidelines, AD is defined by its pathological process, that can be characterized by post-mortem analysis, diagnosis for living AD patients using biomarkers (Biomarkers Definitions Working Group, 2001; Jack et al., 2018). AD biomarkers are categorized in three general groups known as AT(N), which were based on the kind of pathological processes that each group contributes (Jack et al., 2018). The biomarker category "A" stands for aggregated Aβ plaques or associated pathologic state, that can be observed in low concentrations in CSF Aβ42, Aβ42/ Aβ40 ratio; or cortical amyloid Positron Emission Tomography (PET) ligand binding (Catafau and Bullich, 2015; Jack et al., 2018). Likewise, the "T" category biomarker is for aggregated hyperphosphorylated tau (P-tau) proteins such as NFTs or associated pathologic indicators, that are elevated in CSF or cortical tau PET ligand binding (Jack et al., 2018; Okamura et al., 2014). Finally, the "(N)" category of biomarker stands for measures associated with is neurodegeneration or neuronal injury of the brain, and the reason for putting parenthesis in this category because neurodegeneration or neuronal injury may not be specifically related to AD (Jack et al., 2018). Furthermore, neurodegeneration or neuronal injury can be assessed with increased CSF total tau protein (T-tau) (Ferreira et al., 2014), fluorodeoxyglucose (FDG)PET hypometabolism (Shivamurthy et al., 2015), and atrophy on magnetic resonance imaging (MRI) (Frisoni et al., 2010; Jack et al., 2018). However, these guidelines were intended only for

research purposes to generate and test new hypotheses focusing on the interactions among different pathologic states, rather than the clinics (Jack et al., 2018).

1.5 Treatment of AD

Six drugs were approved by the United States Food and Drug Administration (FDA) to treat for a symptomatic relief of AD dementia (Alzheimer's Association, 2018). These medications fall into two categories, cholinesterase inhibitors and a N-methyl D-aspartate (NMDA) antagonist (Casey et al., 2010), including rivastigmine, galantamine, donepezil, tacrine, memantine, and donepezil combined with memantine (Alzheimer's Association, 2018). While memantine is a NMDA antagonist, the other drugs are all cholinesterase inhibitors, (Casey et al., 2010).

Cholinesterase inhibitors increase cholinergic transmission by cleaving the enzyme acetylcholinesterase (AChE), that hydrolyses the neurotransmitter acetylcholine (Ach) [see review (Anand and Singh, 2013)]. Similarly, the NMDA receptors are a kind of glutamate receptor (Traynelis et al., 2010), which is believed to be involved in Ca^{2+} toxicity in AD, that may lead to the death of brain cells [see review (Olivares et al., 2012)]. Therefore, memantine is used to block the NMDA receptors to regulate the glutamatergic system in an attempt to enhance cognitive and memory impairments (Olivares et al., 2012). However, all these drugs are used for partial symptomatic relief rather than as disease modifying therapies for AD, and the efficacy of these drugs varies from patient to patient to a limited period (Alzheimer's Association, 2018). In addition, although more than 244 drugs were clinically tested in between 2002-2012 for the treatment of AD dementia, none of them was approved by the US FDA except memantine (Alzheimer's Association, 2018; Cummings et al., 2014). Furthermore, some evidence also suggested that non-pharmacologic therapies like physical exercise and cognitive stimulation (Aguirre et al., 2013; Farina et al., 2014; Groot et al., 2016) may be effective for the

enhancement of memory and cognitive functions in some AD patients. However, currently, none of these pharmacologic and non-pharmacologic therapies proved to be effective for AD dementia treatment (Alzheimer's Association, 2018). This may be because of excessive damage in to brain prior to the appearance of the clinical symptoms (Sperling et al., 2014), or to insufficient understanding with respect to AD diagnosis and disease progression. Therefore, the main objective of this present investigation is to synthesize evidence from the existing literature, which will provide useful additional knowledge contributing to improved diagnosis and prognosis, prediction of AD dementia by using systematic review and meta-analysis procedures.

Meta-analysis is a statistical method for combining results of an investigated research question(s) from the different studies to synthesize more precise estimates of true effect size (Button et al., 2013; Rosenthal and DiMatteo, 2001a). It is widely used in clinical and applied research of medicine, education, psychology, criminal justice and in the basic sciences for evaluation of research evidence across studies (Borenstein et al., 2009).

An effect size is a measure of strength and association between variables (Button et al., 2013). For example, a standardized mean difference (SMD) between two variables is an effect siz; a few other forms of effect sizes are also investigated in meta-analytic procedures [see (Rosenthal and DiMatteo, 2001a)].

Similarly, a systematic review is a qualitative synthesis of evidence on an investigated question from the literature in a systematic way (Dijkers, 2015; Haidich, 2010; Rosenthal and DiMatteo, 2001b).

Unlike meta-analysis and systematic review, a scoping review is a review of literature to address the key concepts or phenomena by qualitative integration of relevant evidence without a systematic process (Dijkers, 2015).

1.6 The present PhD Investigation

As mentioned in an earlier section, meta-analysis is a statistical method for integrating existing evidence from multiple studies in the form of effect size (Button et al., 2013; Rosenthal and DiMatteo, 2001a). The findings of AD research evidence are inconsistent across the body of published data, and significantly vary from study to study. The main goal of this meta-analytic investigation of AD literature is to estimate the true effect size across the body of data as accurately as possible, and to quantify the existence of variability (Borenstein et al., 2009). Research in the field of AD is very wide and it includes many advanced investigations in areas like neuroimaging, genetics, immunology, biofluids, and other forms of data such as text data and speech data etc. It was not possible to incorporate all areas of investigation in this PhD investigation. Therefore, the scope of this thesis was defined as classical biofluid metabolites in AD. In addition, we also performed a systematic investigation of neuroimaging studies that used machine learning algorithms to attempt classification of AD from healthy controls and MCI at group levels and the individual level. All other areas of AD research are beyond the scope of this PhD investigation. Therefore, in addition to the question of classification of AD from controls in neuroimaging studies mentioned above, additional research questions were restricted to the following for biofluid metabolites: (i) Is differential diagnosis of Alzheimer's disease and normal ageing possible based on the body fluid metabolites? (ii) Do the antemortem body fluid metabolites correlate with the severity of Alzheimer's disease dementia? (iii) Can we predict age at onset of Alzheimer's disease dementia from body fluid metabolites?

Therefore, this PhD dissertation comprises:

(i) A systematic review and meta-analysis on differential diagnosis of AD dementia from normal healthy controls using the antemortem levels of biofluid such as cerebrospinal fluid, blood, serum, plasma, urine, etc.

(ii) A systematic review and meta-analysis on prediction of AD dementia from the biofluid metabolites concentration.

(iii) A systematic review of predicting the age at onset of AD dementia from biofluid metabolite levels.

(iv) A systematic review for differential diagnosis and prediction of AD dementia using systematic review of neuroimaging literature.

Hopefully, this work will offer valuable knowledge for better diagnosis, prognosis and prediction of AD dementia, and may open new windows for future research.

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Chapter 2: Ante-mortem biofluid biomarkers of Alzheimer's disease: A systematic review and meta-analysis on differential diagnosis of Alzheimer's disease from healthy ageing.

2.1 Introduction

Dementia comprises a group of neurodegenerative disorders that are characterized by decline in memory, disturbances in language use, changes in behaviour and other cognitive functions, which interferes with social or occupational functioning of peoples' daily life activities (Chertkow et al., 2013; Qiu et al., 2009a). The prevalence of dementia in 2010 was about 36.5 million globally, and this prevalence will exceed 115.4 million by 2050 (Prince et al., 2013). However, in western countries the incidence of dementia in the male population may be decreasing (Lane et al., 2018). Although, the exact cause of this decline is yet not fully understood, it may be due to better management of vascular risks (Lane et al., 2018). In forthcoming years, the prevalence of dementia in low- and middle-income countries is expected to increase most, because of increased prevalence of cardiovascular disease, hypertension and diabetes (Lane et al., 2018). The global financial burden of dementia was around 818 billion US$ in 2015, which was an increase of 35% over the 2010 cost of 604 billion US$, these costs may have crossed the threshold of US$ 1 trillion by the year 2018 (Wimo et al., 2017).

Among the different forms of dementia (Camicioli, 2004; Shaik and Varma, 2012), Alzheimer's disease or Alzheimer's dementia (AD) is the most common, accounting for up to 50-75% of all dementia cases (Fiest et al., 2016; Qiu et al., 2009b; Reitz and Mayeux, 2014). The vast majority of AD cases appears sporadically, and it's prevalence nearly doubles after the age of 65, every 5 years (http://www.alzheimers.net/resources/alzheimers-statistics/).Therefore, old age is generally considered as the greatest of risk factors in this context (Crous-Bou et al., 2017). Sporadic AD symptoms, which develop after age of 65 years known as later age of onset (LOAD), accounts

for more than 90% of cases (Bertram and Tanzi, 2004; Prince et al., 2013). By contrast, around 1-6% cases of AD develop due to gene mutations and constitute the familial form of AD (FAD) The symptoms usually appear earlier than sporadic AD, typically between 30 to 65 years and are referred to as early onset of AD (EOAD) (Cruts and Van Broeckhoven, 1998; Piaceri et al., 2013; Shea et al., 2016). The FAD cases are mainly caused by the autosomal dominant mutation of three genes: amyloid precursor protein (APP) gene on chromosome 21, Presenilin-1(PS1) gene on chromosome 14, and Presenilin-2(PS2) gene on chromosome 1 (Brouwers et al., 2008; Piaceri et al., 2013). In addition, another gene called apolipoprotein E (APoE) gene on chromosome 19, is also associated with the LOAD in both familial and sporadic forms of AD (Holtzman et al., 2012; Verghese et al., 2011). The APoE gene has three alleles such, APoE Ɛ2, APoE Ɛ3 and APoE Ɛ4, and the individuals who inherit a single copy of APoE Ɛ4 allele have a three-fold high risk of developing AD than those who inherit other forms of the APoE gene (Holtzman et al., 2012). Similarly, individuals carrying two copies of APoE Ɛ4 gene have a further increased risk (up to 8-12 fold risk) of developing AD (Holtzman et al., 2012; Loy et al., 2014). Furthermore, increased copy number of APoE Ɛ4 genes also decreases the mean age at onset of dementia symptoms from 84 years to 68 years (Corder et al., 1993). Interestingly, Down's syndrome (DS) patients also manifest a high risk of EOAD due to the presence of three copies of chromosome 21 with the AAP gene (Goedert, 2015). Typically, AD patients may survive with a mean duration of 8.5 years after appearance of dementia symptoms (Francis et al., 1999).

Generally, AD precedes through a transition stage called the mild cognitive impairment (MCI) stage, that is an intermediate stage between normal healthy ageing and advanced forms of dementia symptoms (Petersen, 2011). Patients with MCI are classified as amnestic MCI (aMCI) and non-amnestic MCI (naMCI) according to their performance on neuropsychological tests

(Petersen et al., 2014). Patients with aMCI perform poorly in the episodic memory domain (Tulving, 2002), whereas naMCI patients perform poorly on other cognitive domains, such as executive functions, language or visuo-spatial abilities rather than memory (Petersen et al., 2014). Based on the impairments in single to multiple cognitive domains, MCI patients may be categorized into four possible subtypes, such as (i) aMCI-single domain, (ii) aMCI-multiple domain, (iii) naMCI-single domain and (iv) naMCI-multiple domain (Petersen et al., 2014). Patients with aMCI condition are conventionally believed to be at the prodromal stage of AD, however, it may progress to other dementia types like logopenic aphasia, posterior cortical atrophy, frontal lobe-dysexecutive presentation of AD (Mitchell and Shiri-Feshki, 2009; Petersen, 2016; Souza et al., 2013). Interestingly, a meta-analysis (Mitchell and Shiri-Feshki, 2009) on progression of MCI patients to AD, vascular dementia (VaD) and other dementia types (Camicioli, 2004; Shaik and Varma, 2012) suggests that the MCI condition remains stable after 10 years of follow-up from the initial diagnosis. As noted above, some MCI patients progress to AD, VaD and other forms of dementia, and some remain stable. Currently, we can't accurately predict who will progress to AD and related dementias from the MCI stage, and we still don't fully understand why some MCI patients remain stable for long time periods. Therefore, predicting AD from MCI, and understanding their relative disease causes and symptoms would allow, in future, the targeting of disease-modifying therapies, risk-modifying strategies and psychosocial management (Ritchie et al., 2014).

2.2 Neuropathology of AD

Although, the exact cause of AD is not fully understood yet, the abnormal accumulation of β-amyloid (Aβ) plaques and neurofibrillary tangles (NFTs) defines AD as a unique neurodegenerative disease among different disorders (Jack et al., 2018). Extracellular depositions

of Aβ plaques and intracellular NFTs in the brain are well established characteristics of AD pathology (Ballard et al., 2011), and these pathological processes begin around 15-20 years before the onset of clinical symptoms (Villemagne et al., 2011). NFTs are the aggregates of hyperphosphorylation of a microtubule-associated protein known as tau proteins (Noble et al., 2013), that contribute to the second major pathological hallmark of AD. However, many neurological disorders and other forms of dementia also show similar kinds of pathological conditions known as tauopathies (Irwin, 2016). There are many hypotheses that have been proposed for mechanisms of AD pathogenesis, such as (i) Aβ-amyloid hypothesis, (ii) tau hypothesis (iii) Aβ-amyloid oligomers hypothesis, (iv) Presenilin hypothesis, (v) Ca^{2+} dysregulation hypothesis (vi) Lysosome hypothesis, and (vii) Inflammation hypothesis (see recent reviews (Du et al., 2018; Kocahan and Doğan, 2017)). Although all these hypotheses offer an explanation for the underlying mechanism of AD pathology, however, the failure of all clinical trials to date (Anderson et al., 2017; Cummings et al., 2017) and the identification of similar kinds of disease pathological processes in other neurological disorders and related dementia undermine their potential explanatory power to some extent. For example, a recent review suggests that approximately 20-40% of normal ageing individuals show AD-like pathological conditions with normal cognition (Fjell et al., 2014). In addition, many studies have also suggested the lack of or very weak correlation between the Aβ deposition and cognitive impairment and cerebral atrophy (Kocahan and Doğan, 2017).

2.3 Biomarkers of AD

A biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (Biomarkers Definitions Working Group, 2001). However, there is a constant

evolution of the biomarker definition in clinical sciences, that is particularly used in disease diagnosis in terms of medical signs and symptoms, surrogate endpoints, clinical endpoints and validation (Strimbu and Tavel, 2010). Biomarker(s) for disease diagnosis will be very useful for the clinics if they offer very high accuracy or sensitivity and specificity (Zhu et al., 2010). According to the 2018 National Institute on Ageing—Alzheimer's Association (NIA-AA) research framework definition of AD (Jack et al., 2018), the putative AD biomarkers are labelled in three general groups known as AT(N), which are based on the kind of pathological processes that each group relates to. The biomarker category "A" stands for aggregated Aβ plaques or associated pathologic state, that are low in CSF Aβ42, Aβ42/ Aβ40 ratio or cortical amyloid Positron Emission Tomography (PET) ligand binding (Catafau and Bullich, 2015; Jack et al., 2018). Similarly, the "T" category stands for aggregated hyperphosphorylated tau (P-tau) proteins as NFTs or associated pathologic state, that are elevated in CSF or cortical tau PET ligand binding (Jack et al., 2018; Okamura et al., 2014). Likewise, the "(N)" category of biomarker stands for neurodegeneration or neuronal injury of the brain, and the reason for putting parenthesis around the N in this category is because such neurodegeneration or neuronal injury need not be specifically due to AD (Jack et al., 2018). Furthermore, the neurodegeneration or neuronal injury can be assessed with increased CSF total tau protein (T-tau) (Ferreira et al., 2014),fluorodeoxyglucose (FDG) PET hypometabolism (Shivamurthy et al., 2015), and atrophy on magnetic resonance imaging (MRI) (Frisoni et al., 2010; Jack et al., 2018). However, each of these biomarkers of AD has its own strengths and weaknesses in terms of disease diagnosis, progression and prediction (Johnson et al., 2012; Stefani et al., 2013). A recent review (Gaugler et al., 2013) of systematic reviews and meta-analyses in this area suggested that the CSF tau has a sensitivity of 73.3 -100% and specificity 70.0 - 92.4% for diagnosis of AD, when compared

with the neuropathological clinical criteria for AD, while various PET imaging modalities showed similar range of sensitivity (80-100%) and specificity (62-90%). In addition, numerous studies have been published on differential diagnosis of AD from other forms of dementia with very high sensitivity and specificity [see (Chen et al., 2017; Ferreira et al., 2014; Kandimalla et al., 2013; Mo et al., 2015; Paterson et al., 2018; Van Harten et al., 2011)]. Although, a plethora of publications reported on the biofluid biomarkers for differential diagnosis of AD, due to inter laboratory variability in biomarkers measurement (Mattsson et al., 2013; Watt et al., 2012), it is quite challenging to set up a cut-off point of biomarker levels for discriminatory diagnosis. In the present investigation, we performed meta-analysis of studies reporting biofluid metabolite concentrations in AD and healthy control subjects in attempts to provide a biomarker-based differential diagnosis AD dementia from healthy ageing subjects. We analyzed reports for different types of biofluids including CSF, blood, plasma, serum, urine and saliva.

2.4 Methodology

2.4.1 Literature search strategy

We conducted this systematic review and meta-analysis as per the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). We searched the PubMed data base (https://www.ncbi.nlm.nih.gov/pubmed/) from July 1, 2012, to September 5, 2018 [within the last 6 years] of recent novel biomarkers, that have been investigated in the AD dementia literature. In addition, numerous recent systematic reviews and meta-analyses have been reported on body fluid biomarkers of AD targeting differential diagnosis (please see: Chen et al., 2017; Ferreira et al., 2014; Lai et al., 2017; Mo et al., 2015; Olsson et al., 2016; Ritchie et al., 2017, 2014; Van Harten et al., 2011). Therefore, we focused only recent [last 6 years] of studies for our systematic review and meta-analysis.

Our search keywords were ("biomarkers" OR "diagnosis" OR "prognosis" OR "prediction" OR "classifier") AND ("CSF" OR "cerebrospinal fluid" OR "blood" OR "serum" OR "protein" OR "amyloid beta" OR "tau") AND ("accuracy" OR "sensitivity" OR "specificity" OR "ROC" OR "receiver operator characteristic") AND ("Alzheimer's" OR "mild cognitive impairment" OR "normal ageing"). We limited our search to human species studies written in English. We included only summary estimates of metabolite concentrations from those peer reviewed articles. However, no grey literature sources were assessed. The PubMed data base search retrieved a total of 476 articles, those were screened by two independent reviewers (M.M & A.G). We included a total of 51 articles for our systematic review and meta-analysis based on our study inclusion and exclusion criteria (see details below as well as the study selection Flowchart 2.1). Final inclusion and exclusion of studies were decided independently by the two reviewers. However, if any discrepancies appeared between the reviewers in study selection, these cases were discussed between the two authors until full agreement was reached. In those cases, where the disagreement was not resolved between the two reviewers, we discussed with a third independent reviewer.

2.4.2 Inclusion Criteria

- Original peer-reviewed studies published between July 1, 2012, and September 5, 2018.
- Only human species English language studies were included.
- Studies performing differential diagnosis of Alzheimer's disease dementia from healthy ageing using antemortem cerebrospinal fluid (CSF) or peripheral body fluid metabolites.
- Use of clinical diagnosis criteria for AD, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) by McKhann et al. (1984).

- AD patient group must be compared with a healthy control group (HC).

2.4.3 Exclusion Criteria

- All animal studies, meta-analyses, review articles, letters, comments, case reports, and unpublished articles.
- Studies did not mention the sample size of each subject group or included fewer than ten individuals or reported data in a format other than the mean metabolite's concentration with standard deviation (SD) or standard error of mean (SEM) (Altman and Bland, 2005; Olsson et al., 2016).
- Studies only presenting post-mortem or autopsy or neuroimaging data.
- When a healthy control group (HC) included participants with other neurological diseases or psychiatric disorders.

2.4.4 Data extraction

From each of the included studies, we recorded the following information:

(i) The first author and the year of publication.

(ii) Study design/setting (i.e. longitudinal or cross-sectional).

(iii) Sample size

(iv) Mean/median age

(v) Mean/median MMSE score

(vi) Classification or diagnostic accuracy or sensitivity and specificity or receiver operating characteristic (ROC) area under curve (Zhu et al., 2010).

(vii) Types of assays used for measuring biomarkers.

(viii) The mean ± SD or SEM of metabolite(s) concentration and the sample size (n) of AD, healthy control (HC) groups.

In those cases, where a study provided more than one cohort of data and for machine learning studies which presented results for training and testing data sets separately (Falahati et al., 2014), we considered each cohort or set as a single study and coded that study by study first author's name and year of publication with cohort 1 as C-1, cohort 2 as C-2, and cohort 3 as C-3, depending on the number of cohorts or sets. For example, in our analyses, a study (Molinuevo et al., 2013) provides data in both AD and controls on three cohorts. So, we coded each cohort from that study as Molinuevo et al., 2013 (C-1), Molinuevo et al., 2013 (C-2), and Molinuevo et al., 2013 (C-3). In addition, when a study reported metabolite concentrations that were analyzed with more than one assay, we chose a commercial assay in preference to an in-house assay for selection of only one assay (Olsson et al., 2016). The metabolite data from the CSF and peripheral blood of were meta-analyzed separately. However, the plasma and serum same metabolite data were meta-analyzed together (Olsson et al., 2016). Most of our included studies were cross-sectional, whereas very few studies included longitudinal measurements with clinical follow up. In longitudinal studies, we took only baseline measurement data to meta-analyze with cross-sectional data (Olsson et al., 2016). Some studies reported metabolite concentrations using different units than those used in the majority, Such units were converted into one unit format in each category of analyses (Ritchie et al., 2014). Finally, we conducted meta-analysis if there were at least two studies available in each category of metabolite (Olsson et al., 2016; Valentine et al., 2010).

2.4.5 Statistical analyses

Standardized mean difference (SMD) or Cohen's d (Faraone, 2008; Rosenthal and DiMatteo, 2001a) with 95% Confidence interval (CI) and P-value (Cumming and Maillardet, 2006) were

calculated for each analysis. We employed the random effects model to our analysis because of variability in inter laboratory estimation of biomarker concentrations (Mattsson et al., 2013; Noble et al., 2008; Watt et al., 2012) and participant demographics across the world (Borenstein et al., 2010; Diener et al., 2009; Hedges and Vevea, 1998). The random effects model is more conservative and fit to the real world data for generalization of findings to a targeted population (Diener et al., 2009). The evidence of publication bias was assessed qualitatively by the Egger's test to create a Funnel plot by plotting standard error and SMD of means (Egger et al., 1997). We decided to create the funnel plots if at least three studies were available in each category of analysis. Graphical visualization of the Funnel plots showing symmetrical distribution of studies is indicative of no publication bias. Furthermore, we also assessed the fail-safe number (Duval and Tweedie, 2000; Rosenthal and DiMatteo, 2001b) for only statistically significant results to estimate the number of studies with negative or null effects that are potentially missing in the literature, which would have been contributed to non-significant results. Finally, we quantified the heterogeneity across the sampling studies by using the I-squared (I^2) test, that suggests "the percentage of total variation across the studies that is due to heterogeneity rather than chance" (Higgins, 2003). I^2 values vary from 0% to 100%., A value of 0% suggests no observed heterogeneity, while increasing values ($I^2 > 50\%$ as large and $I^2 > 75\%$ as very large) indicate increasing heterogeneity (Higgins, 2003; Lai et al., 2017). A P-value less than 5% ($P < 0.05$) was indicative of significant heterogeneity across the studies (Lai et al., 2017). We used the Cohen's d criterion for interpreting our results as small (SMD = 0.2), moderate (SMD = 0.5) and large (SMD $\geq$ 0.8) effect sizes (Cohen, 1988; Faraone, 2008). A negative value of effect sizes in all of our analyses indicates higher biomarker concentration in the control group, while positive values suggest higher concentration in the AD group (Lai et al., 2017).

All the statistical analyses were performed by the comprehensive Meta-Analysis Version 3.0 software package (https://www.meta-analysis.com/) (Bax et al., 2007; Borenstein et al., 2009).

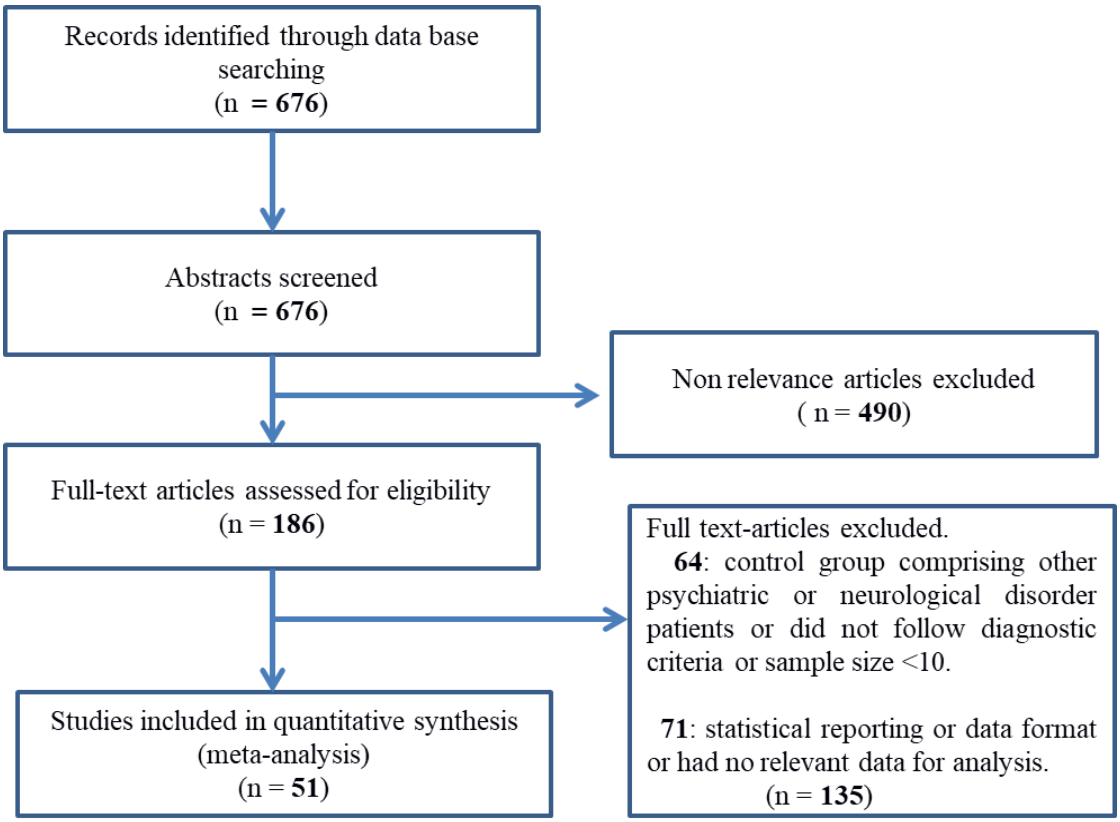
2.5 Results

A PubMed search identified 676 initial studies, and the abstracts were screened for eligibility. Of these, the full text of 186 articles was assessed for eligibility, and 490 non-relevant studies were excluded, (See Flowchart 2.1 for study selection.). 135 of the 186 studies were excluded because (i) the control group included other psychiatric or neurological disorder patients or did not follow diagnostic criteria or had a sample size <10 (total n = 64), and (ii) statistical reporting or data format or had no relevant data for analysis (n = 71). Finally, only 51 studies (Total; AD patients = 4509, and HC = 4202 subjects) met our stringent study inclusion and exclusion criteria (See table 2.1 for all included studies). As mentioned earlier, we conducted meta-analyses of studies if the metabolite concentration of AD and HC groups was reported in at least two studies (see table 2.2 for summary of meta-analyses studies and results). We first meta-analyzed, the CSF studies of $A\beta_{1\text{-}42}$ concentration in pg/ml (total studies; n =25), P-tau_{181} concentration in pg/ml (total studies; n = 22), T-tau concentration in pg/ml (total studies; n =19), and the heart type fatty acid binding protein (hFABP) concentration in pg/ml (total studies; n = 2). The majority of CSF studies reported the concentration of $A\beta_{1\text{-}42,}$ P-$tau_{181,}$ T-tau metabolites level together. Therefore, the same CSF studies included in each category of biomarker analysis repeatedly, and hence, the total number of studies are more than the included studies.

A total of 41 studies met our inclusion and exclusion criteria in plasma, serum and urine categories of metabolites. Likewise, the CSF studies, the majority of peripheral plasma and serum biomarkers studies also provided data on Plasma $A\beta_{1\text{-}42}$ (total studies; n =9), plasma $A\beta_{1\text{-}40}$ (total studies; n = 8) and plasma T-tau (total studies; n = 3). In addition, we also meta-analyzed

the plasma and serum biomarkers together for each category (details are discussed in later sections).

All our meta-analyses results are shown in forest plots (Lewis, 2001) by computing the overall effect sizes (i.e. standardized mean difference or Cohen's d) across the sampling studies with 95% CI, and p-values (Cumming and Maillardet, 2006; Faraone, 2008). A P-value less than 0.05 ($P < 0.05$) was considered statistically significant for all of our examined hypotheses.



Flowchart 2.1 Study selection process.

Table 2.1 Characteristics of studies (total; n = 51) that met our inclusion criteria

Study 1st Author and year of publication	CSF/blood/ Plasma/Serum/ Urine	Sample size(n) in each group	Assay type	Reported maximum classification/ prediction accuracy(ACC) /SN & SP/ROC in AUC (in %)
(Lin et al., 2018)	Plasma	HC = 32 AD = 32	ELISA	SN 81.25% SP 61.62%
(Zhu et al., 2018)	Serum	HC = 51 MCI = 139 AD = 51	ELISA	SN 92.1% SP 74.5%
(Wang et al., 2017)	CSF and Plasma	HC = 24 AD = 24	ELISA	AUC = 0.97
(Kouzuki et al., 2018)	CSF	HC =40 MCI=34 AD = 40	ELISA	AUC = 0.656
(An et al., 2017)	CSF	HC= 29 AD =24	ELISA	AUC =0.896
(Jiang et al., 2016)	Plasma	HC=128 AD=110	ELISA	SN 69.1% SP 74.2%
(Niemantsverdriet et al., 2016)	CSF	HC=100 sMCI=38 pMCI=47 AD = 72	ELISA	SN 87.5% SP 87%
(Siotto et al., 2016)	Serum	HC=58 AD=84	Immunoturbidi-metric method	AUC= 0.88
(Spiegel et al., 2015)	CSF	HC=87 AD=28	ELISA	SN 85% SP 92%
(Kim et al., 2015)	Plasma	HC=46 AD=100	ELISA	AUC=0.76
(Jiao et al., 2015)	CSF and Plasma	HC=129 AD=156 PD=79 Stroke=83	ELISA	SN 72.5% SP 75.3%

Study 1st Author and year of publication	CSF/blood/ Plasma/Serum/ Urine	Sample size(n) in each group	Assay type	Reported maximum classification/ prediction accuracy(ACC) /SN & SP/ROC in AUC (in %)
(Li et al., 2015)	CSF	HC=120 MCI=21 AD=16	ELISA	SN 93% SP 93%
(Khan et al., 2015)	CSF	HC=88 MCI=142 AD=65	Multiplex assay ELISA	ACC=77.1%
(Ma et al., 2016)	Urine	HC=118 AD=121	ELISA	AUC=0.926
(Madeira et al., 2015)	CSF	HC=10 AD=21 DP=9 HP=9	ELISA	SN 92.9% SP 85.7%
(Coart et al., 2015)	CSF	HC=109 AD=96	ELISA	AUC=0.975
(Peng et al., 2015)	Plasma	HC=113 AD=113	ELISA	ACC=76.1%
(Haris et al., 2015)	CSF	HC=17 MCI=17 AD=27	Multiplex assay ELISA	AUC=0.83
(T. Wang et al., 2015)	Plasma	HC=81 aMCI=116 AD=97	ELISA	ACC=83.7%
(Spellman et al., 2015)	CSF	HC=85 MCI=134 AD=66	Spectrometry assay, bicinchoninic acid assay	AUC=0.79
(C. Wang et al., 2015)	Serum and Urine	HC=90 MCI-ST=68 AD=64	ELISA	SN 96% SP 95%
(Laske et al., 2015)	CSF and Serum	HC=54 AD=64	ELISA, Chemiluminesc-ence assay.	ACC=91.4%

Study 1st Author and year of publication	CSF/blood/ Plasma/Serum/ Urine	Sample size(n) in each group	Assay type	Reported maximum classification/ prediction accuracy(ACC) /SN & SP/ROC in AUC (in %)
(Nazeri et al., 2014)	Plasma	HC=49 MCI=300 AD=85	Multiplex immunoassay	SN 93% SP 92%
(Lautner et al., 2014)	CSF	HC=251 sMCI=399 MCI-AD=287 AD=309 OD=99	ELISA	AUC=0.91
(Edwards et al., 2014)	Serum	HC=137 AD = 129	Electrochmilum -inescence assay	ACC=92%
(Schmidt et al., 2014)	CSF	HC=32 AD=32	ELISA	AUC=0.977
(Krishnan and Rani, 2014)	Blood	HC=40 VaD=35 AD=30	ELISA	AUC=0.911
(Jinbiao Zhang et al., 2014)	Plasma	HC= 120 aMCI=32 AD=90	ELISA	AUC =0.90
(Apostolova et al., 2014)	CSF	HC=111 MCI=182 AD=95	Multiplex immunoassay	ACC=87%
(Marksteiner et al., 2013)	Plasma	HC=63 MCI=51 YC=15 AD=76	ELISA	AUC=0.732 AUC=0.777
(Wang et al., 2014)	Plasma	HC=122 aMCI=54 AD=97	ELISA	SN 80% SP 69.6%
(Hu et al., 2014)	Blood	HC=116 AD=116	ELISA	SN 68% SP 72%

Study 1st Author and year of publication	CSF/blood/ Plasma/Serum/ Urine	Sample size(n) in each group	Assay type	Reported maximum classification/ prediction accuracy(ACC) /SN & SP/ROC in AUC (in %)
(Maftei et al., 2013)	CSF and Serum	Serum donors: HC=42 AD=45 CSF donors: HC=29 AD=39	ELISA	AUC=0.97
(Abraham et al., 2013)	CSF	HC=21 MCI=23 AD=23	Multiplex immunoassay	AUC=0.89
(Korff et al., 2013)	CSF	HC=110 MCI=187 AD=92	ELISA	AUC=0.719
(L.-H. Guo et al., 2013)	CSF	HC=92 sMCI=76 pMCI=73 AD=69	Multiplex immunoassay	ACC=67%
(Molinuevo et al., 2013)	CSF	HC = 103 AD = 238	ELISA	SN 88.6% SP 85%
(Zhang et al., 2013)	Plasma	HC=120 aMCI=98 AD=153 VaD=53	ELISA	AUC=0.92
(Mangialasche et al., 2013)	Plasma	HC=86 MCI=86 AD=81	HPLC	ACC=98.2%
(Guo et al., 2013)	CSF and Plasma	HC=58 AD=109	Multiplex immunoassay	SN 89.36% SP 79.17%
(Olsson et al., 2013)	CSF	HC=65 AD=96 sMCI=81 MCI-AD=61 MCI-VaD=19 MCI-others=9	ELISA	AUC = 0.89

Study 1st Author and year of publication	CSF/blood/ Plasma/Serum/ Urine	Sample size(n) in each group	Assay type	Reported maximum classification/ prediction accuracy(ACC) /SN & SP/ROC in AUC (in %)
(Alsadany et al., 2012)	Blood	HC=25 AD=25	ELISA	AUC=0.966
(Laske et al., 2013)	Serum	HC=82 AD=82	ELISA	ACC=90%
(Öztürk et al., 2013)	Blood	HC=133 AD=197	Automated analyzer	AUC=0.720
(López et al., 2013)	Blood	HC=33 MCI=18 AD=36	HPLC, Immunoturbidi-metric assay	AUC=0.803
(Llano et al., 2013)	Plasma	HC=58 MCI=360 AD=109	Multiplex immunoassay, Luminex assay	AUC=85.3%
(Chiu et al., 2012)	Plasma	HC=26 MCI=16 AD=18	Immunomagnet-ic reduction method	SN 85.3% SP 88.5%
(Kuyumcu et al., 2012)	Blood	HC=175 AD=241	Automated analyzer	AUC=0.787
(Soares et al., 2012)	CSF and Blood	HC=58 MCI=396 AD=112	Multiplex Immunoassay,	AUC= 0.80
(Han et al., 2012)	Plasma	HC=116 AD=112 VaD=85 OND=30	ELISA	AUC=0.94
(Wolz et al., 2012)	CSF	HC = 116 AD = 103	Multiplex immunoassay	ACC=87%

Table legends: AD = Alzheimer's disease, VaD = Vascular dementia, OD= Other dementia, OND= Other neurological disorder, PD=Parkinson's disease, DP=Depression, BC=Breast cancer, FTD= Frontotemporal dementia, HC=Healthy control, YC = young control, HP= Hydrocephalus,

SN= Sensitivity, SP= Specificity, MCI=Mild cognitive impairment, aMCI = amnestic MCI, sMCI=Stable MCI, pMCI=Progressive MCI, nMCI= non-progressive MCI, MCI-ST= Maintaining an MCI status after 2 years, ROC= Receiver operating characteristic, AUC= Area under curve, ACC= Accuracy, ELISA = enzyme-linked immunoabsorbent assay, HPLC= high-performance liquid chromatography.

Table 2.2: **Meta-analyses of studies measuring biofluid metabolites concentration in AD versus HC subjects**

Name of metabolite	Number of studies	N (AD/HC)	SMD (95% CI)	P-value	I-squared (%)	P-value for heterogeneity
CSF $A\beta_{1-42}$	25	1686/1684	-1.659 (-1.849 to -1.470)	<0.001	79.818	<0.001
CSF P-tau_{181p}	22	1422/1469	1.084 (0.959 to 1.028)	<0.001	28.712	0.003
CSF T-tau	19	1313/1279	1.251 (1.152 to 1.351)	<0.001	16.133	0.257
CSF hFABP	2	165/157	0.819 (0.589 to 1.050)	<0.001	0	0.518
Plasma $A\beta_{1-42}$	9	869/832	-0.009 (-0.388 to 0.371)	0.964	92.964	<0.001
Plasma $A\beta_{1-40}$	8	839/792	0.192 (-0.051 to 0.434)	0.121	82.313	<0.001
Plasma T-tau	3	283/291	-0.235 (-0.992 to 0.522)	0.543	94.313	<0.001
Plasma Albumin	4	551/419	-0.402 (-0.719 to -0.086)	0.013	80.199	0.002
Plasma IL-6	2	194/107	-0.652(-0.893 to -0.410)	<0.001	0	0.587

Name of metabolite	Number of studies	N (AD/HC)	SMD (95% CI)	P-value	I-squared (%)	P-value for heterogeneity
Plasma creatinine	4	570/386	-0.179(-0.686 to 0.328)	0.490	92.035	<0.001
Serum copper	3	145/116	1.186(0.192 to 2.186)	0.019	91.614	<0.001
Plasma sTNF-α receptor-1	4	325/322	1.472(0.798 to 2.145)	<0.001	92.526	<0.001
Plasma sTNF-α receptor-2	2	243/240	0.583 (0.400 to 0.767)	<0.001	0	0.487
Urine AD7c-NTP	2	185/208	2.271 (-1.778 to 6.321)	0.272	99.386	<0.001

Table legends: AD = Alzheimer's disease, Aβ = Amyloid beta protein, T-tau = total tau, P-tau = phosphorylated tau, CSF = cerebrospinal fluid, IL= Interleukin, CI = confidence Interval, HC = healthy controls, hFABP = heart type fatty acid binding protein, N = sample size, SMD = standardized mean difference, sTNF = Soluble tumour necrosis factor, AD7c-NTP = Alzheimer-associated neuronal thread protein.

2.5.1 CSF $A\beta_{1-42}$ concentration in AD and HC subjects

In this category of analysis, a total of 25 studies met our study inclusion criteria. Of these, one study (Molinuevo et al., 2013) reported data of AD and HC groups in three cohorts. So, this study appears three times on the forest plot (See **Fig 2.1**) with three different cohorts as C-1, C-2 and C-3. A total of 1686 AD patients and 1684 healthy control subjects' data were meta-analyzed by the random effects model. We found a statistically significant average large effect size of SMD = -1.659 (CI: -1.849 to -1.470; $P < 0.001$), suggesting the CSF $A\beta_{1-42}$ concentration (pg/ml) significantly reduced in AD patients than HC subjects (see **Fig 2.1**). We examined the evidence

of publication bias by creating a funnel plot (see **Fig 2.2**) and it shows a minimal publication bias. In addition, we also examined that the study heterogeneity by I^2 test. The I^2 value is around 79.81% with $P < 0.001$, which indicates a large percentage of variation across the included CSF $A\beta_{1-42}$ studies are due to study heterogeneity.

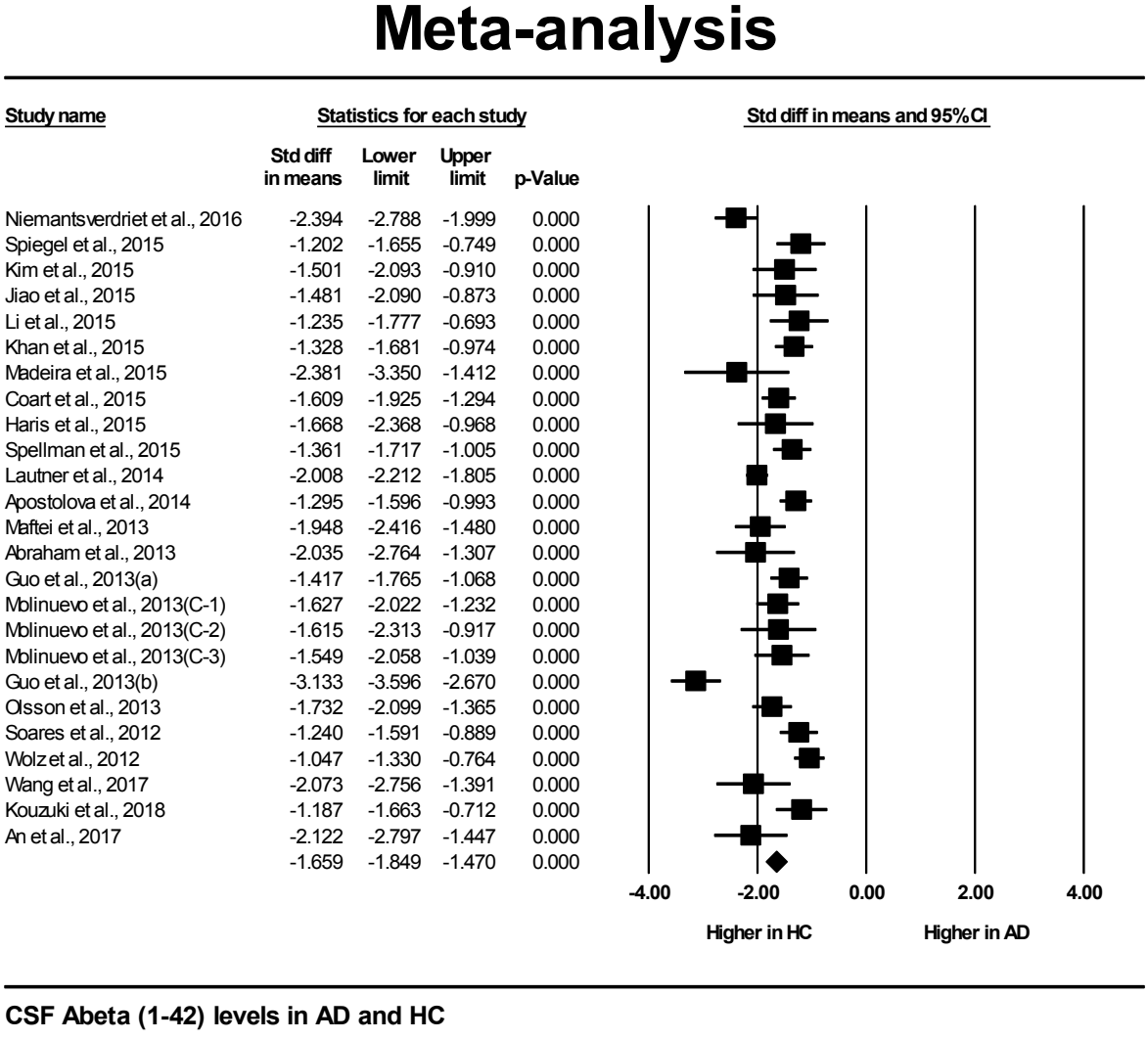


Figure 2.1: Meta-analysis of CSF $A\beta_{1-42}$ concentration in AD and HC subjects. Calculated effect sizes are expressed in standardized mean difference (SMD) with 95% confidence interval (CI). Negative value indicates higher concentration in HC subjects, C = cohort.

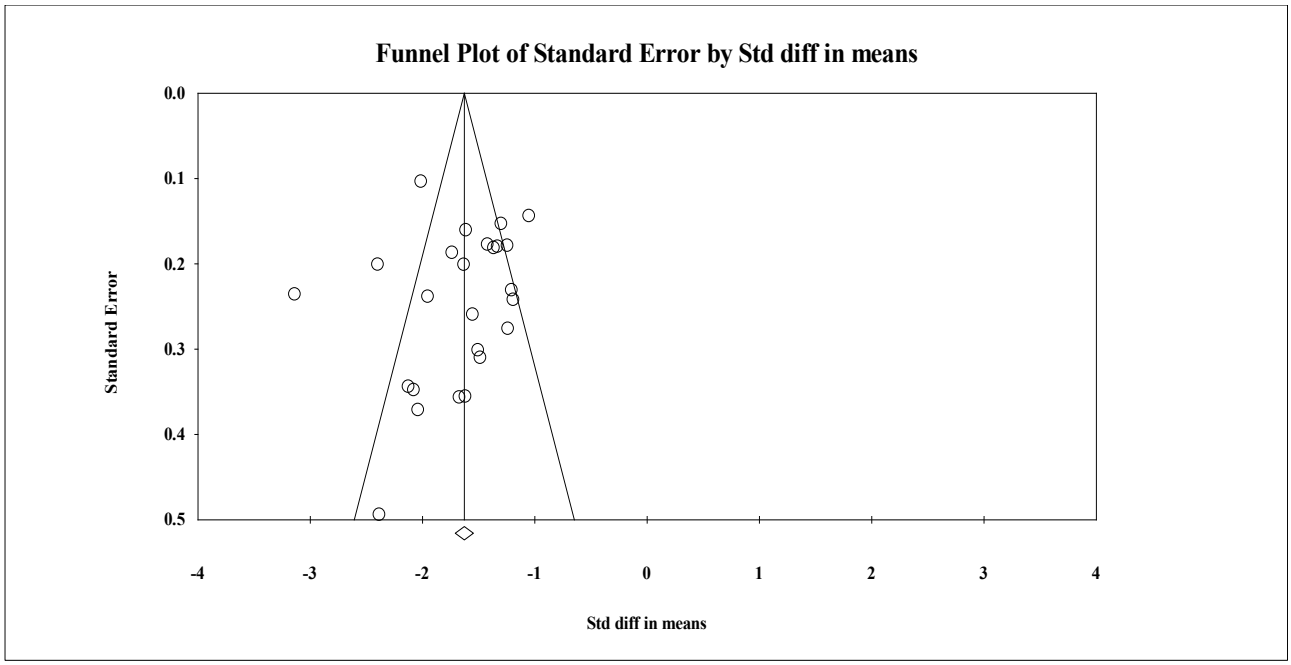


Figure 2.2: Funnel plot depicts the publication bias of CSF Aβ $_{1\text{-}42}$ concentration in AD and HC studies.

Finally, we assessed the Rosenthal's fail-safe N to determine the number of studies with a null effect that would be required to provide a non-significant result ($P > 0.05$). We found that N = 9109 studies with null results that would be required to indicate no statistically significant difference between CSF Aβ $_{1\text{-}42}$ concentration in AD patients and HC subjects.

2.5.2 CSF P-tau$_{181p}$ concentration in AD and HC subjects

To examine the difference of CSF P-tau$_{181p}$ concentration (pg/ml) in AD and HC subjects, we meta-analyzed the data from a total of 22 studies (which met our study criteria) comprising of 1422 AD patients and 1469 HC subjects by using the random effects model. We found a statistically significant overall large effect size of SMD = 1.084 (CI: 0.959 to 1.208; $P < 0.001$), which indicates increased levels of CSF P-tau $_{181p}$ in AD patients than HC subjects (See **Fig 2.3**).

The evidence of publication bias was assessed by creating a funnel plot (see **Fig 2.4**), that suggests no publication bias in this category of analysis. Furthermore, we examined the study heterogeneity across the studies by I-squared test and found that I^2 = 50.86 % with P = 0.003, which indicates a very minimal study heterogeneity across the sampled studies. In addition, we calculated the Fail safe N, and found that N = 3403 studies with a null effect would be required to indicate no statistically significant difference between CSF P-tau$_{181p}$ concentration in AD patients and HC subjects.

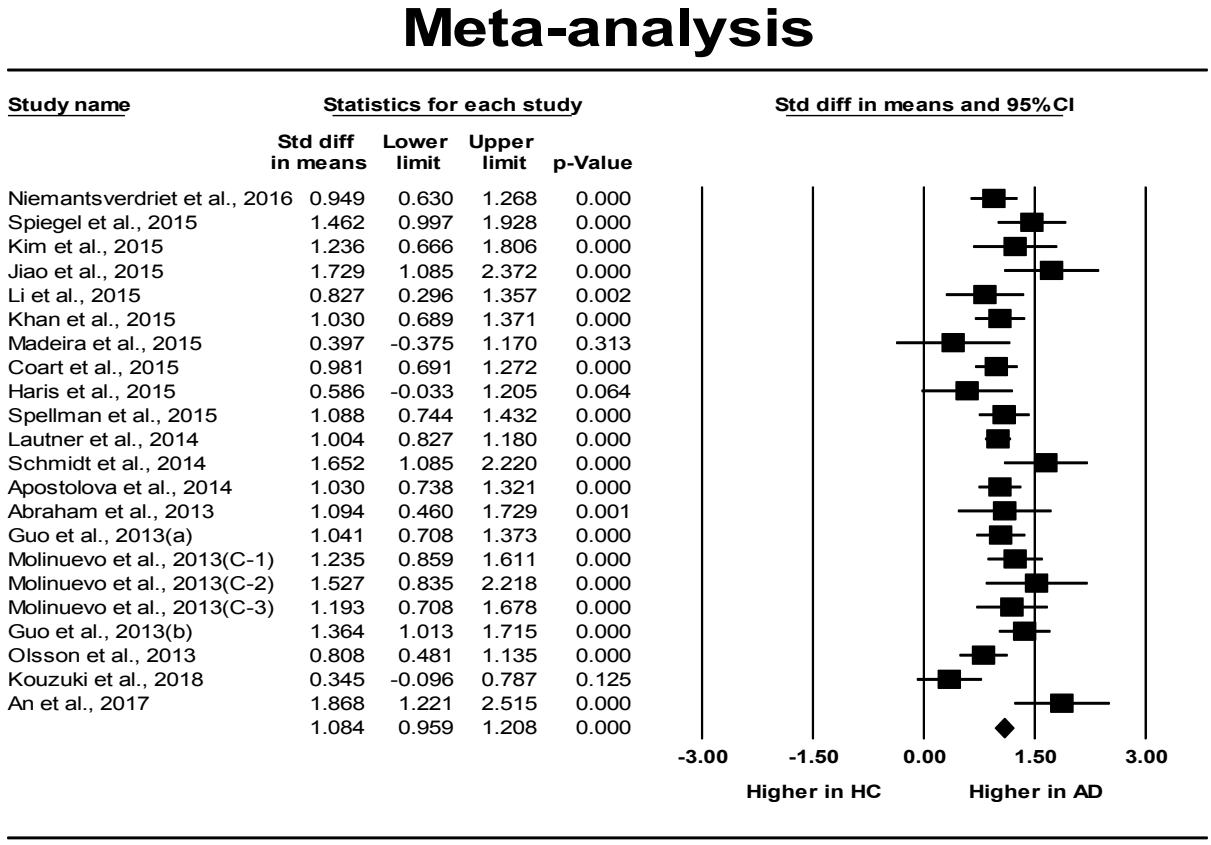


Figure 2.3: Meta-analysis of CSF P-tau$_{181p}$ concentration in AD and HC subjects. Positive value indicates higher concentration in AD patients, C = cohort.

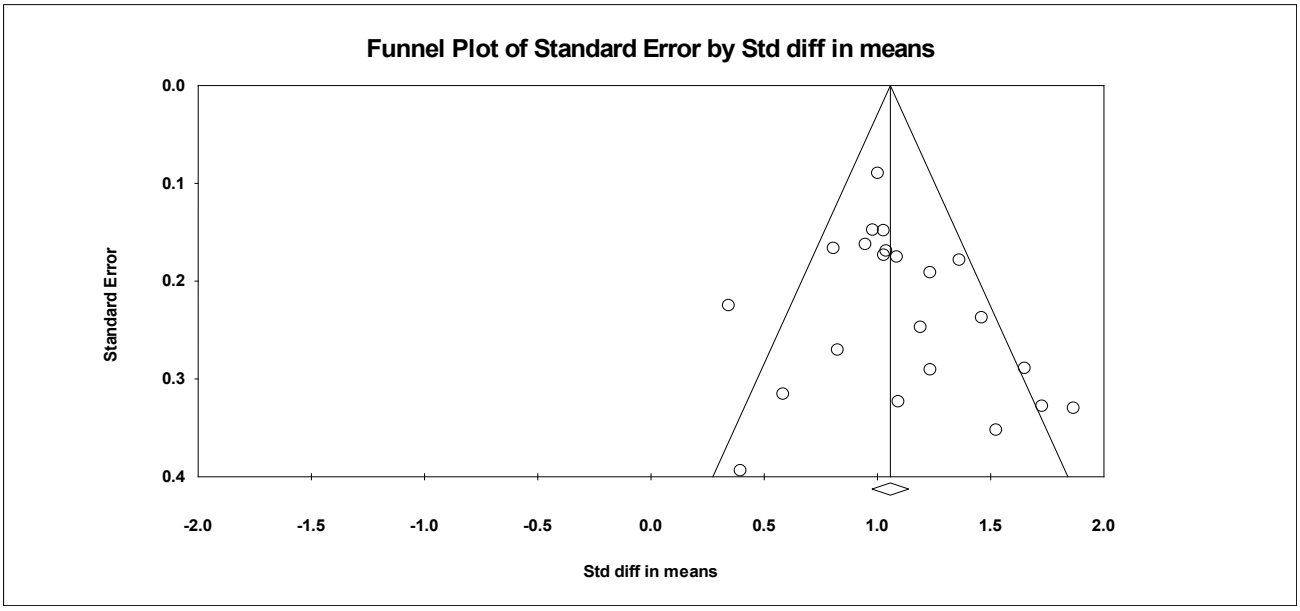


Figure 2.4: Funnel plot depicts the publication bias of CSF P-tau $_{181p}$ concentration in AD and HC studies.

2.5.3 CSF T-tau concentration in AD and HC subjects

To calculate the overall standardized mean difference of CSF T-tau concentration (pg/ml) in AD and HC groups, we meta-analyzed data from 19 studies (which met our study criteria) comprising 1313 AD patients and 1279 subjects by using the random effects model. We found a strong statistically significant effect size of SMD = 1.251 (CI: 1.152 to 1.351; P < 0.001), suggesting a higher concentration of CSF T-tau levels in AD than HC subjects (See **Fig 2.5**).

As shown on the forest plot (**Fig 2.5**), all the included studies favour one direction of effect with P-values less than 0.001 (P < 0.001). Therefore, the CSF T-tau protein is a strong biomarker that is used appropriately in routine clinical practice. Publication bias was assessed by creating a funnel plot across the sampling studies in this category (See **Fig 2.6**), and which suggests a very

minimal publication bias. Furthermore, the I-squared test revealed that I^2 = 16.133% with P = 0.257, suggesting a very small study heterogeneity.

Similarly, the fail-safe number test indicated that N = 3448 studies with a null effect would be required indicate no statistically significant difference between CSF T-tau concentration in AD patients and HC subjects.

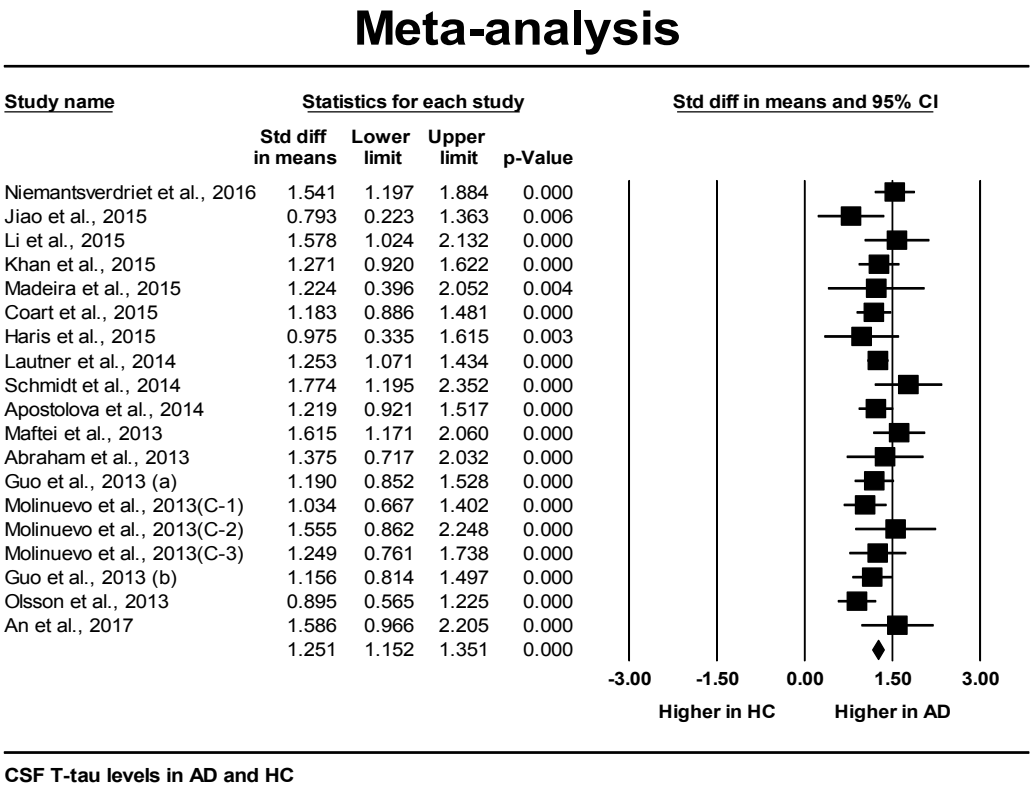


Figure 2.5: Meta-analysis of CSF T-tau concentration in AD and HC subjects. Positive value indicates higher concentration in AD patients, C = cohort.

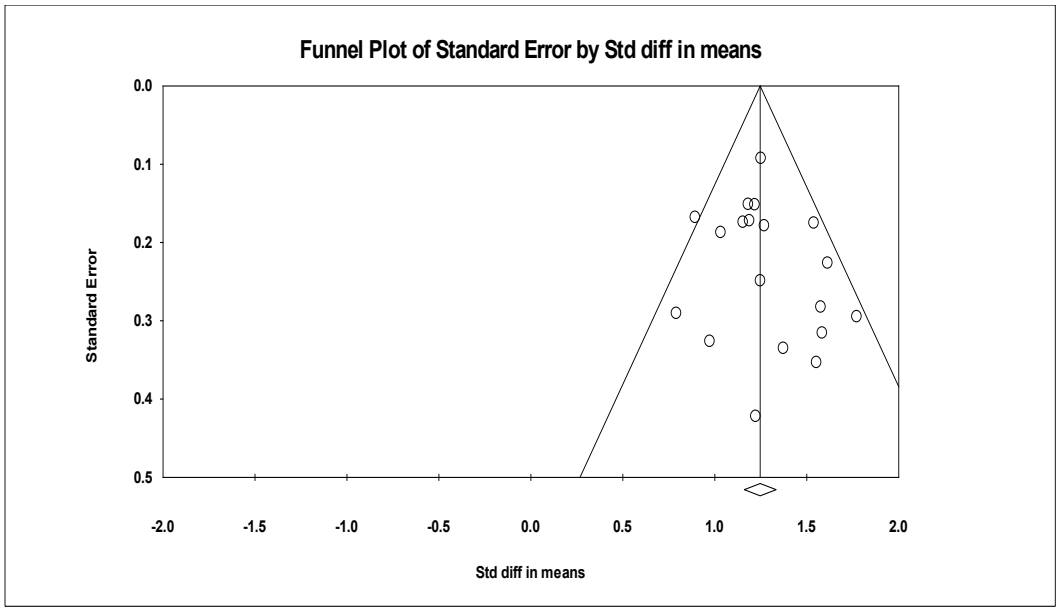


Figure 2.6: Funnel plot depicts the publication bias of CSF T-tau concentration in AD and HC studies.

2.5.4 CSF heart type fatty acid binding protein (hFABP) concentration in AD and HC subjects

To examine the standardized mean difference of CSF hFABP concentration (pg/ml) between AD and HC subjects, only two studies met our inclusion criteria. A total of 165 AD patients and 157 healthy control subjects' data were meta-analyzed using the random effects model. The meta-analysis revealed a large effect size of SMD = 0.819 (CI: 0.589 to 1.050; $P < 0.001$), suggesting higher concentrations of CSF hFABP in AD patients than HC subjects (See **Fig 2.7**). Although, the effect (SMD) is large and highly statistically significant, as we included only two studies with low sample size, it is quite challenging to estimate the average effect. Therefore, more studies with high sample size are required to confirm that CSF hFABP concentration is higher in AD than HC subjects. We did not examine the publication bias and Fail-safe N for this analysis

because of only including two studies. However, the I^2 test indicated (I^2 = 0% with P = 0.518) that there is no study heterogeneity between these study samples.

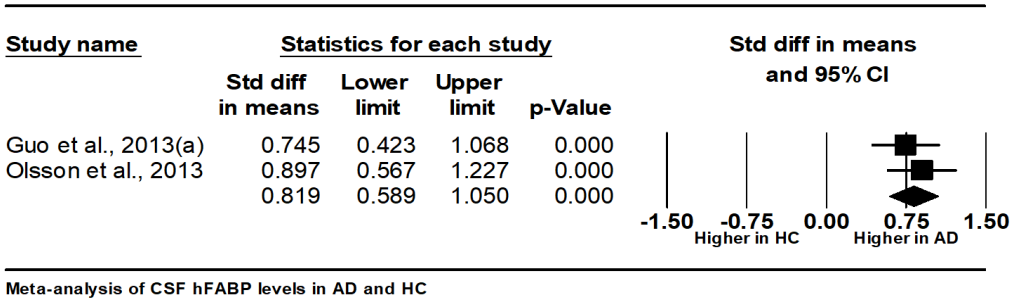


Figure 2.7: Meta-analysis of CSF hFABP concentration in AD and HC subjects. Positive value indicates higher concentration in AD patients.

2.5.5 Plasma $A\beta_{1-42}$ concentration in AD and HC subjects

To estimate the overall effect size (i.e. the SMD), we included 9 studies (meeting our study criteria) comprising of 869 AD patients and 832 HC subjects' summary data meta-analyzed with the random effects model. We found a very negligible effect size of SMD = -0.009 (CI: -0.388 to 0.371; P = 0.964), indicating no difference between plasma $A\beta_{1-42}$ concentration in AD and HC subjects (See fig 8). As the results were not statistically significant (as P = 0.964) it is meaningless to consider measuring the average mean difference of plasma $A\beta_{1-42}$ concentration in AD and HC subjects. As shown on the forest plot (See **Fig 2.8**), the included studies are scattered across the no-effect line (where the SMD = 0), that indicates the literature is very noisy with contrasting results.

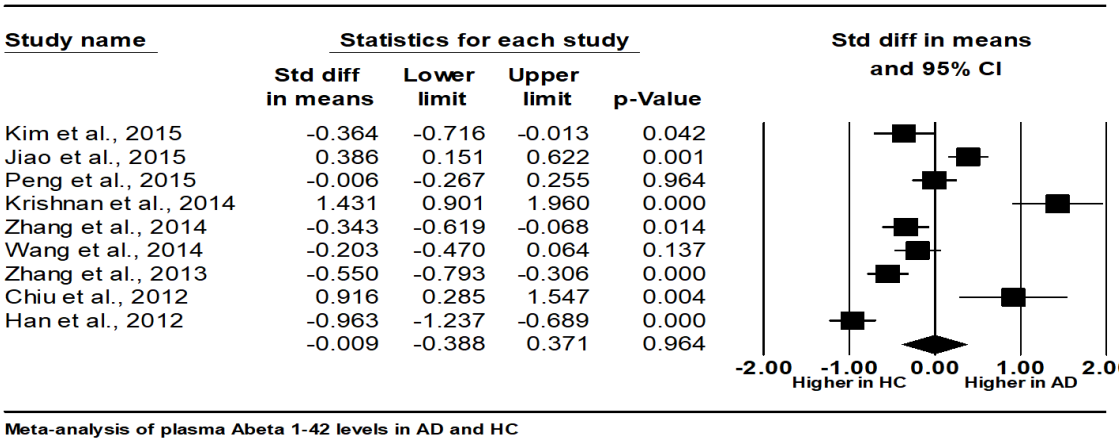


Figure 2.8: Meta-analysis of plasma $A\beta_{1-42}$ concentration in AD and HC subjects. Negative value indicates higher concentration in HC subjects.

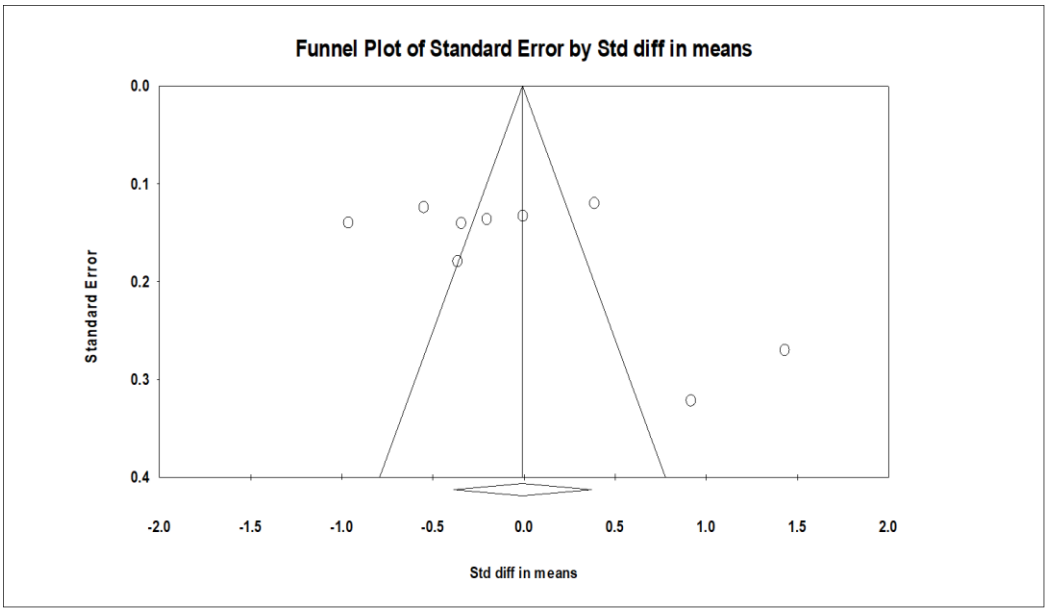


Figure 2.9: Funnel plot depicts the publication bias of Plasma $A\beta_{1-42}$ concentration in AD and HC studies.

The evidence of publication bias was assessed with the funnel plot (see Fig 2.9), that indicates major publication bias among the studies. In addition, we measured study heterogeneity by using I-squared test and found that $I^2 = \sim 93\%$ with $P < 0.001$, which suggests a very large variation of results (i.e. the heterogeneity) across the sampling studies. We did not asses the Fail-Safe number for this analysis because the meta-analysis result is not statistically significant ($P = 0.964$). As indicated in earlier sections, the Fail-safe number test is used in the case of statistically significant results to calculate the number of non-significant findings that may not be published in literature, which would render the meta-analysis results non-significant ($P > 0.05$).

2.5.6 Plasma $A\beta_{1-40}$ concentration in AD and HC subjects

To test the hypothesis of a standardized mean difference of plasma $A\beta_{1-40}$ concentration (pg/ml) between AD and HC subjects, only eight studies were included in this analysis (meeting our study criteria). A total of 839 AD patients' and 792 HC subjects' data were meta-analyzed using the random effects model. Our meta-analysis found an average small effect size of SMD = 0.192 (CI: -0.051 to 0.434; P = 0.121), suggesting a very small increased level of plasma $A\beta_{1-40}$ than HC groups (See **Fig 2.10**). However, such results were not statistically significant (P = 0.121), and hence, there is insufficient evidence to calculate the group level difference (i.e. the SMD) in plasma $A\beta_{1-40}$ concentration between AD and HC groups. As this is a possible small effect, there is a question as to whether further research would be useful to consider an average true effect size of plasma $A\beta_{1-40}$ protein concentration between these two groups in relation to biomarker analysis. That said, even small differences may be important for identifying underlying

mechanisms of pathological change – this remains an empirical question but is unlikely to represent a clinically relevant opportunity.

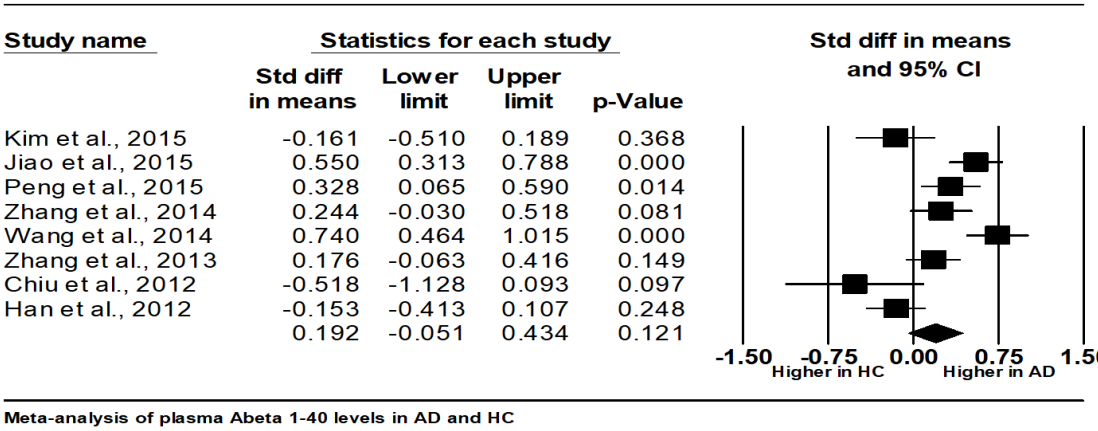


Figure 2.10: Meta-analysis of plasma $A\beta_{1\text{-}40}$ concentration in AD and HC subjects. Positive value indicates higher concentration in AD patients.

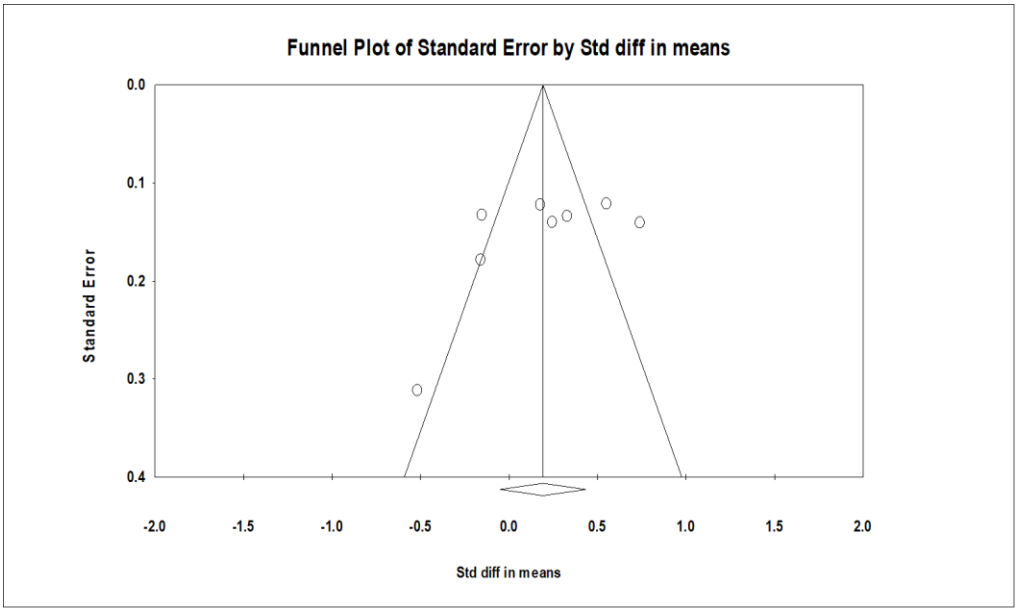


Figure 2.11: Funnel plot depicts the publication bias of Plasma $A\beta_{1\text{-}40}$ concentration in AD and HC studies.

The publication bias was assessed by the funnel plot (see **Fig 2.11**) method, and the same suggests the variation among the sampling studies due to unsymmetrical distribution on the forest plot.

In addition, we examined the study heterogeneity by using I-squared statistics and found the I^2 = ~82% with $P < 0.001$. The I^2 value suggests very large percentage of variation of results among the sampling studies and this value is highly statistically significant. We did not calculate the Fail-safe number for this analysis because our meta-analysis result was statistically non-significant.

2.5.7 Plasma T-tau concentration in AD and HC subjects

To measure the standardized mean difference of plasma T-tau concentration (pg/ml) between AD and HC groups, we included only three studies that met our study criteria. A total of 283 AD patients' and 291 healthy control subjects' data were meta-analyzed by using the random effects model.

Our meta-analysis results found a small effect size of SMD = -0.235 (CI: -0.992 to 0.522; P = 0.543) (see **Fig 2.12**), suggesting a very small decreases level of plasma T-tau in AD patients relative to HC subjects. However, the difference was not statistically significant as the $P > 0.05$. Currently, it is not possible to calculate a true effect size for plasma T-tau proteins in AD and HC groups due to insufficient evidence in the literature. Further studies would be required to measure the true effect.

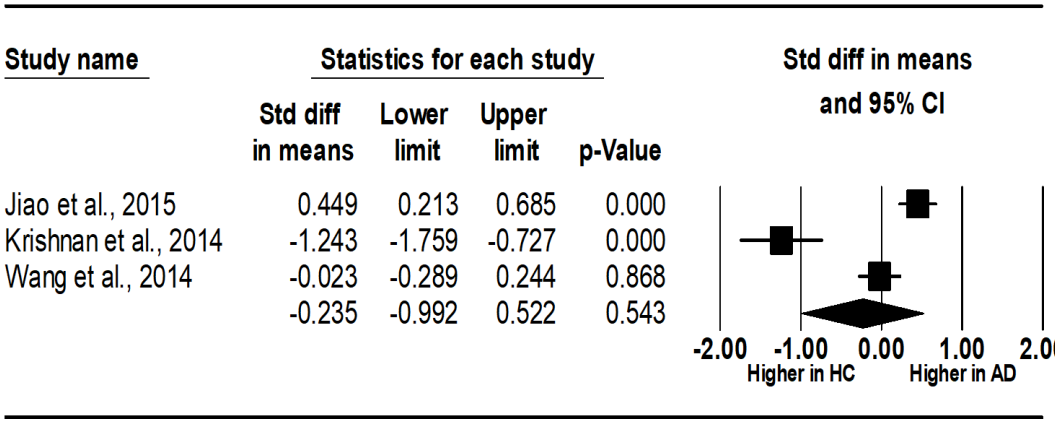


Figure 2.12: Meta-analysis of plasma T-tau concentration in AD and HC subjects. Negative value denotes higher concentration in HC group.

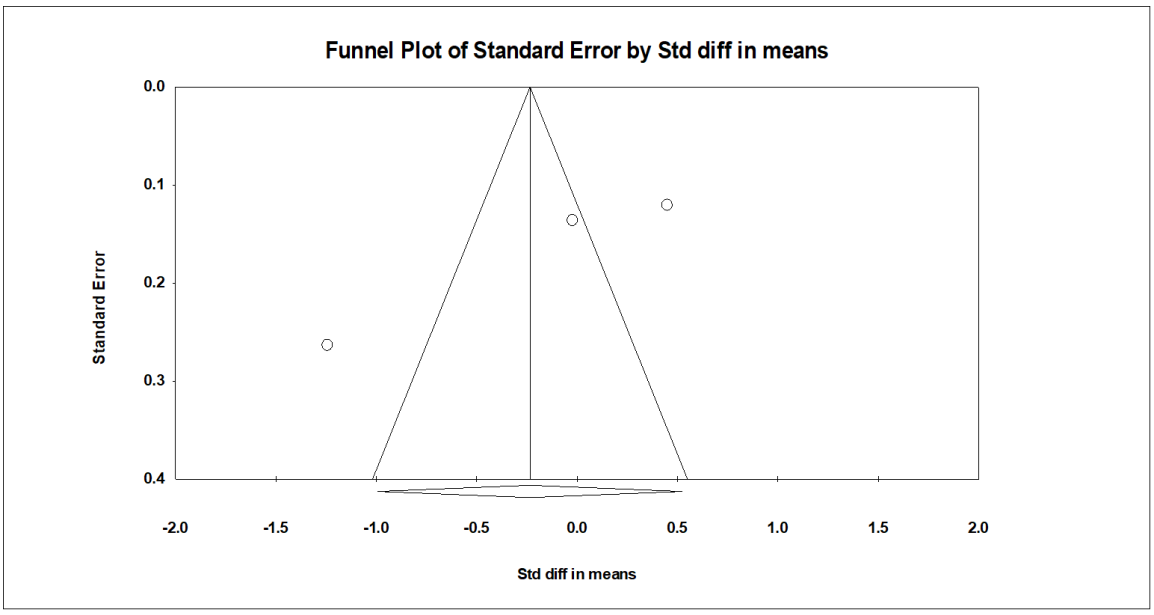


Figure 2.13: Funnel plot depicts the publication bias of plasma T-tau studies.

The funnel plot (see **Fig 2.13**) indicates a major publication bias among these studies. The I-squared statistical test rendered the I^2 = ~94% with $p < 0.001$, that indicates a very large study heterogeneity due to variation among the results of included studies. We did not examine the

Fail-safe number for this analysis because all our meta-analysis results were statistical non-significant.

2.5.8 Plasma Albumin concentration in AD and HC subjects

To measure the standardized mean difference of plasma albumin concentration (g/dL) between the AD and HC groups, we identified four studies that met our study criteria. A total of 551 AD patients' and 491 HC subjects' summary data were meta-analyzed by using the random effects model. We found a moderate effect size of SMD = -0.402 (CI: -0.719 to -0.086; P = 0.013) (see **Fig 2.14**), suggesting a lower concentration of plasma albumin levels in the AD group relative to HC. Although, the results of this analysis are statistically significant (as P = 0.013), due to the small number of studies with low sample sizes it is very difficult to calculate the average standardized mean difference between these two groups. Again, further research would be necessary to determine standardized mean difference.

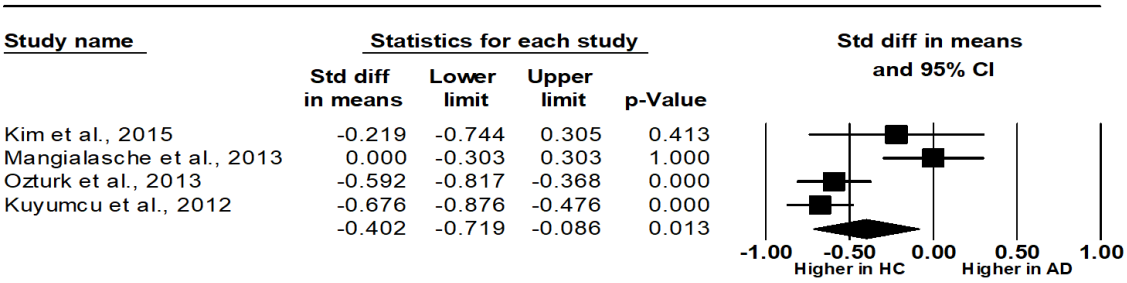


Figure 2.14: Meta-analysis of plasma albumin concentration in AD and HC. Negative value denotes higher concentration in HC group.

The publication bias was assessed with the funnel plot (see **Fig 2.15**), it suggests that there is evidence of publication bias as the sampled studies are not symmetrically distributed on the

forest plot. Furthermore, we examined the I-squared statistics to measure the study heterogeneity. We found the I^2 = ~80% with P = 0.002, which indicates a very large percentage of variation of results among the included studies. As the results of this meta-analysis are statistically significant, the Fail-safe number was calculated, and we found that the Fail-safe N = 38, indicating that 38 studies with a null effect are required to indicate, on the basis of our results, that there is no significant difference of plasma albumin levels between AD and HC groups.

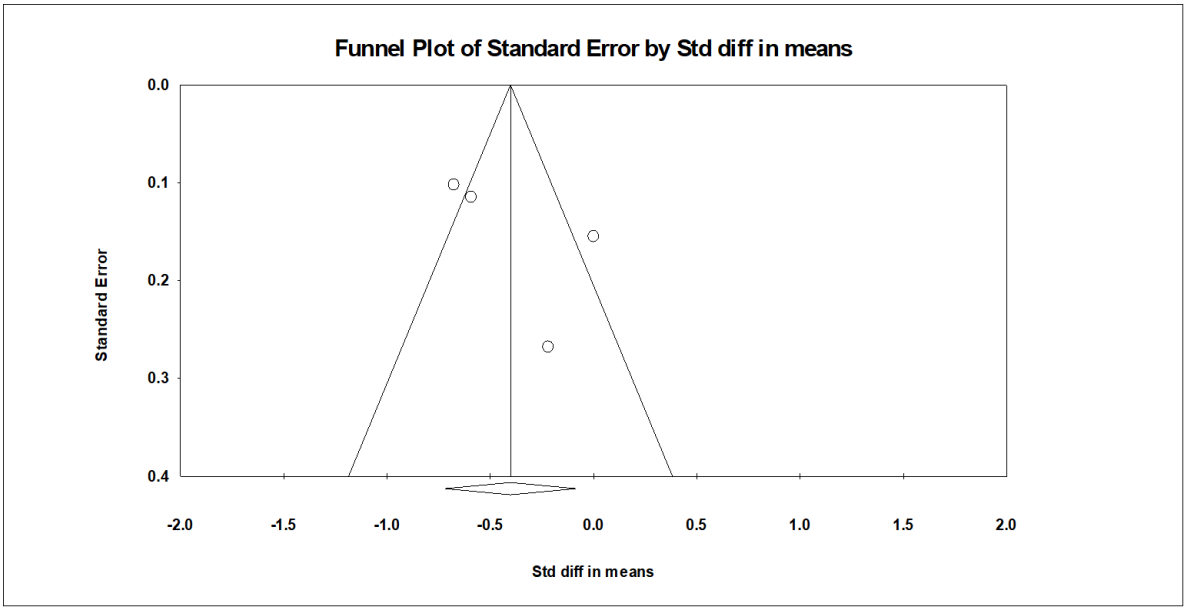


Figure 2.15: Funnel plot depicts the publication bias of Plasma albumin studies.

2.5.9 Plasma interleukin 6 (IL- 6) concentration in AD and HC subjects

To examine the standardized mean difference of plasma IL-6 concentration (pg/ml) between AD and HC groups, we selected only two studies based on our study selection criteria. A total of 194 AD patients' and 107 HC subjects' data were meta-analyzed using the random effects model. We found an overall moderate effect size of SMD = -0.652 (CI: -0.893 to -0.410; P < 0.001) (see **Fig 2.16**), suggesting a higher concentration of IL-6 in HC than AD groups. Although, our meta-

analysis results are supported with statistical significance (P < 0.001), due to the inclusion of only two studies with very low sample size, the results might not be generalizable in the larger population. Hence, we require more evidence for calculation of the true effect size. We did not assess the publication bias in this analysis because of two studies. However, the study heterogeneity was examined with the I -squared test and found that the I^2 = 0% with P = 0.857. It indicates there is no variation of results between these two studies.

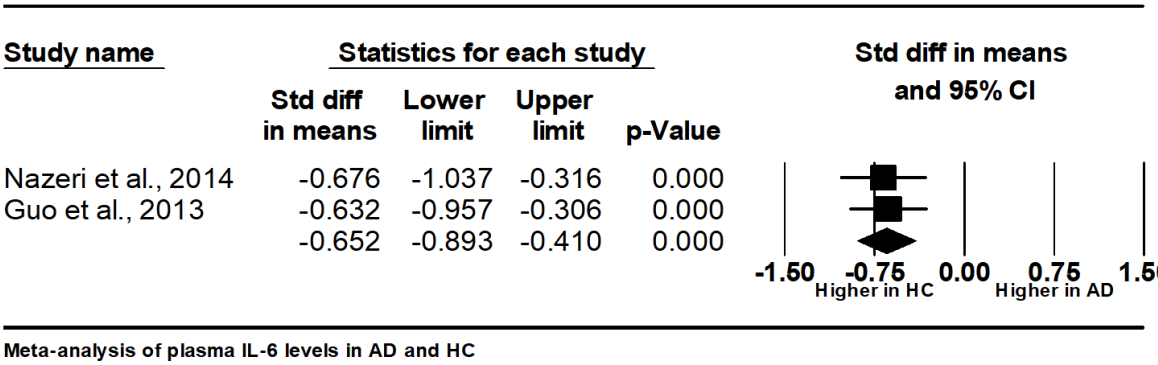
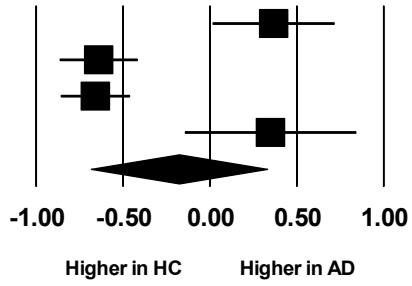


Figure 2.16: Meta-analysis of plasma IL-6 concentration in AD and HC. Negative value denotes higher concentration in HC group.

2.5.10 Plasma creatinine concentration in AD and HC subjects

To examine the overall effect size of plasma creatinine concentration (mg/dL) between AD and HC groups, we included only three studies based on our study selection criteria. A total of 570 patients' and 386 HC subjects' summary data were meta-analyzed using the random effects model. We found an average effect size of SMD = -0.179 (CI: -0.686 to 0.328; P = 0.490) (see **Fig 2.17**), suggesting higher levels of plasma creatinine in HC than AD groups. However, this meta-analysis result was not statistically significant (P = 0.490), and therefore, more studies are

Study name	Statistics for each study				Std diff in means and 95% CI
	Std diff in means	Lower limit	Upper limit	p-Value	
Kim et al., 2015	0.367	0.015	0.718	0.041	
Ozturk et al., 2013	-0.640	-0.865	-0.415	0.000	
Kuyumcu et al., 2012	-0.659	-0.859	-0.459	0.000	
Lin et al., 2018	0.349	-0.145	0.842	0.166	
	-0.179	-0.686	0.328	0.490	



Meta-analysis of plasma creatinine levels in AD and HC

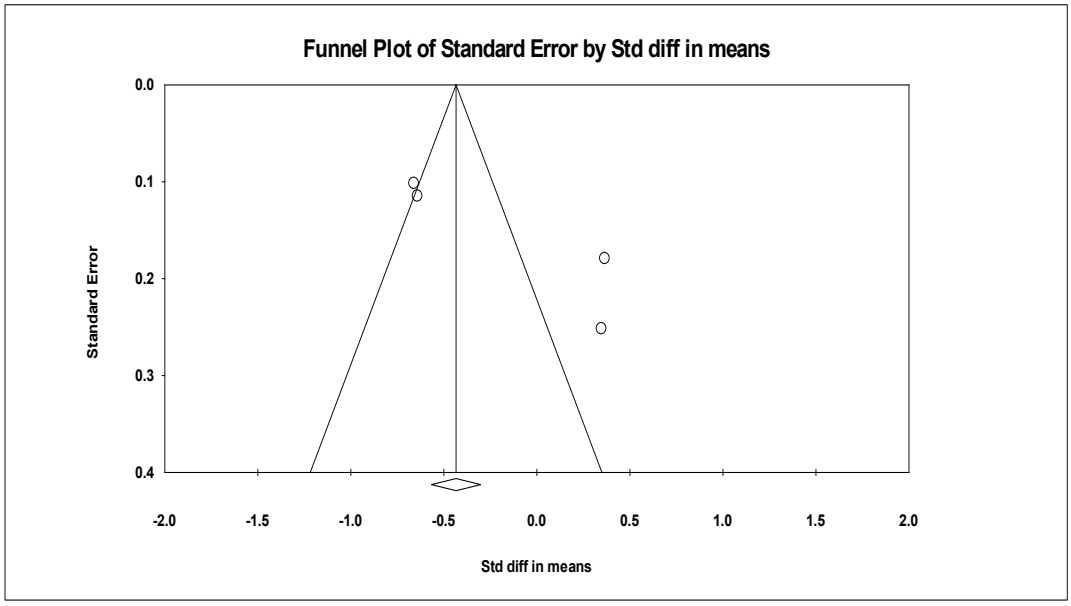


Figure 2.18: Funnel plot depicts the publication bias of Plasma creatinine studies.

required to calculate the true effect size of plasma creatinine concentration between these two groups. In addition, we assessed the publication bias using the funnel plot (see **Fig 2.18**), which

indicates a major publication bias as none of the sampled studies are inside the funnel plot. Furthermore, the study heterogeneity was examined by using the I-squared test, and we found that I^2 = ~92% with P < 0.001, indicating a very large percentage of variation among these study results. Finally, we did not assess the Fail-safe N test because our meta-analysis results are statistically non-significant.

2.5.11 Plasma copper concentration in AD and HC subjects

To measure the average effect size of plasma copper concentration (mg/L) of AD and HC groups, we sampled only three studies comprising 145 AD patients and 115 HC subjects. We meta-analyzed the summary data of these individuals' using the random effects model.

We found a large overall effect size of SMD = 1.186 (CI: 0.192 to 2.181; p = 0.019) (see **Fig 2.19**), suggesting a very high concentration of plasma copper levels in AD than HC groups. However, due to only three studies with very low sample size, this result may not be generalizable in the larger population. Therefore, more evidence is necessary to estimate the true effect size.

Publication bias was assessed by the funnel plot (see **Fig 2.20**), and it demonstrates very high publication bias as none of the studies followed the symmetrical distribution. The I-squared test for study heterogeneity revealed that the I^2 = ~ 92% with P < 0.001, which indicates a very large percentage of variation among the sampled study results. Finally, the Fail-safe N test found that the N =37. Thirty-seven studies with a null effect are required to render the current meta-analysis results as non-significant (P > 0.05) as assessed with the Fail-safe N test.

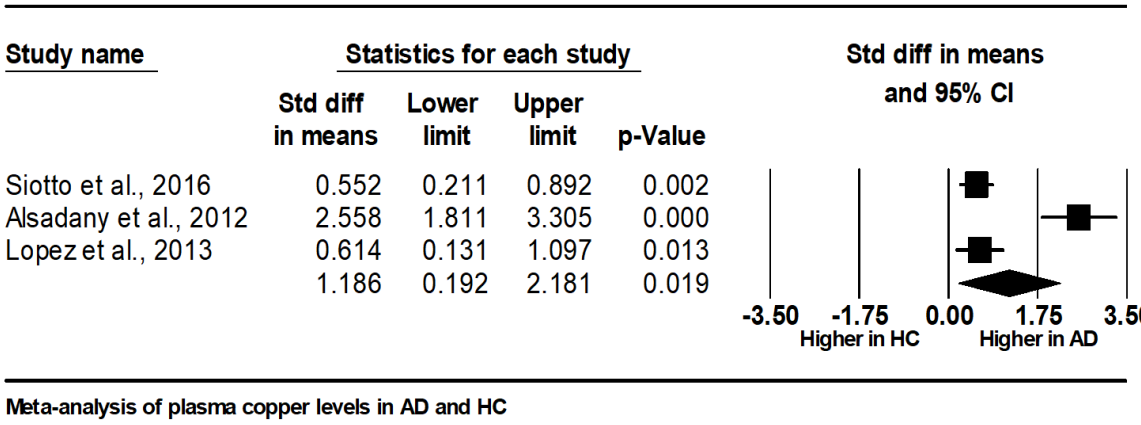


Figure 2.19: Meta-analysis of plasma copper concentration in AD and HC. Positive value indicates higher concentration in AD group.

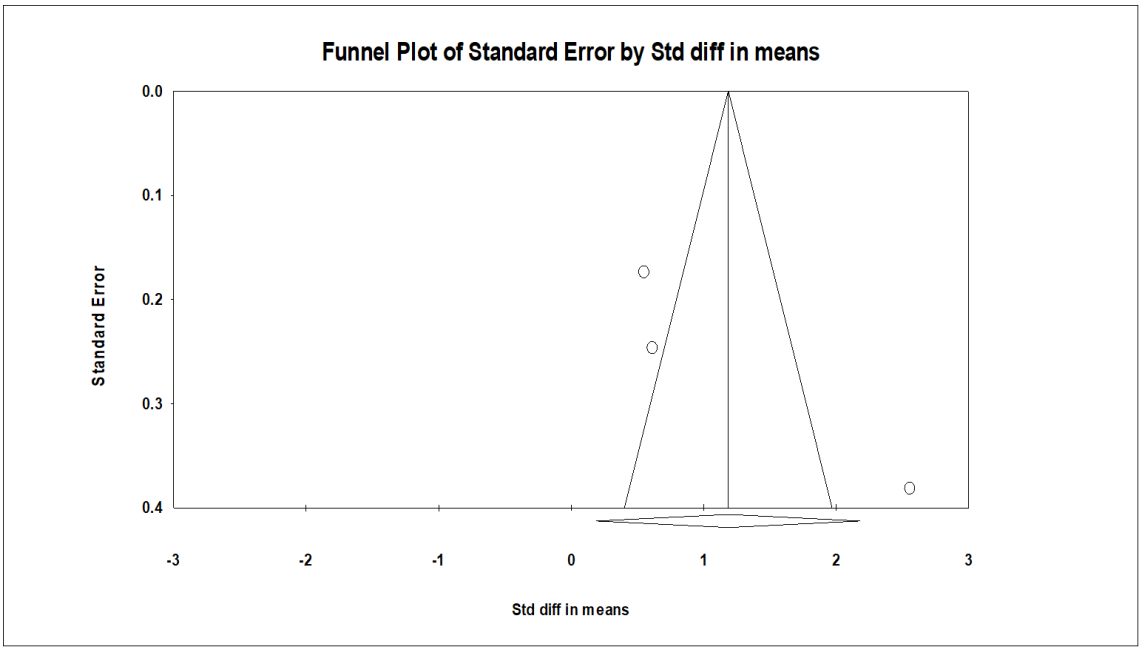


Figure 2.20: Funnel plot depicts the publication bias of Plasma copper studies.

2.5.12 Plasma soluble TNF-α receptor 1 concentration in AD and HC subjects

To measure the overall effect size of plasma soluble TNF-α receptor 1 concentration (pg/ml) in AD and HC, we included only three studies based on our study inclusion criteria. However, one study (Laske et al., 2013) provided data in the two cohorts. So, the same study appeared twice in our analysis as Laske et al., 2013 (C-1) and Laske et al., 2013(C-2) (see Fig 20). A total of 325 AD patients' and 322 HC subjects' data were meta-analyzed by the random effects model. Our meta-analysis results showed an average large effect size of SMD = 1.472 (CI: 0.798 to 2.145; P < 0.001), suggesting a very high concentration of plasma TNF-α receptor 1 in AD than HC groups (see **Fig 2.21**). However, more studies would be needed to confirm this effect in a larger sample size compared to our analysis.

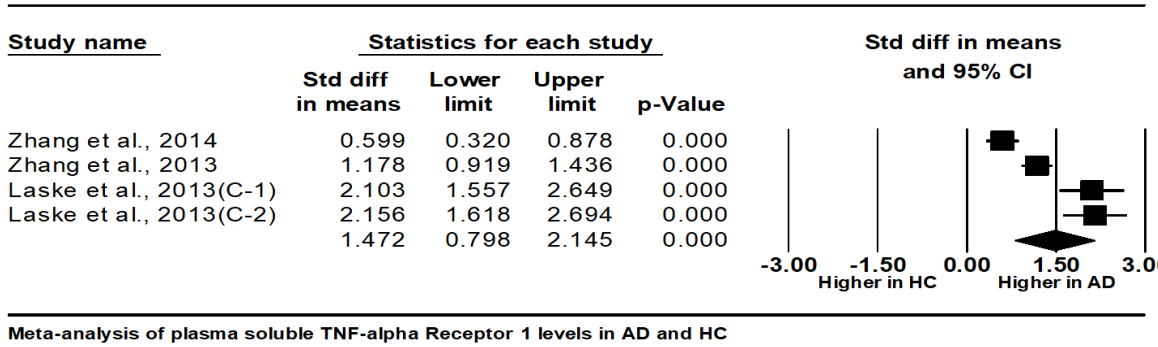


Figure 2.21: Meta-analysis of plasma TNF-α receptor 1 concentration in AD and HC. Positive value indicates higher concentration in AD group.

The funnel plot was created for assessment of publication bias (see **Fig 2.22**), it indicates a very high publication bias as all the sampled studies did not follow the symmetrical distribution the funnel plot analysis. Therefore, more studies are required to calculate a true effect size of the plasma TNF-α receptor 1 concentration between AD and HC groups. In addition, we examined the study heterogeneity by using the I-squared test and found that $I^2 = \sim 93\%$ with $P < 0.001$. The

I-squared value in this analysis suggests a very large study heterogeneity among the results of sampled studies. Finally, the Fail-safe N test yielded N = 208. Indicating that 208 studies with no effect wold be required to indicate no statistically significant difference between the plasma TNF-α receptor 1 concentrations in AD and HC groups.

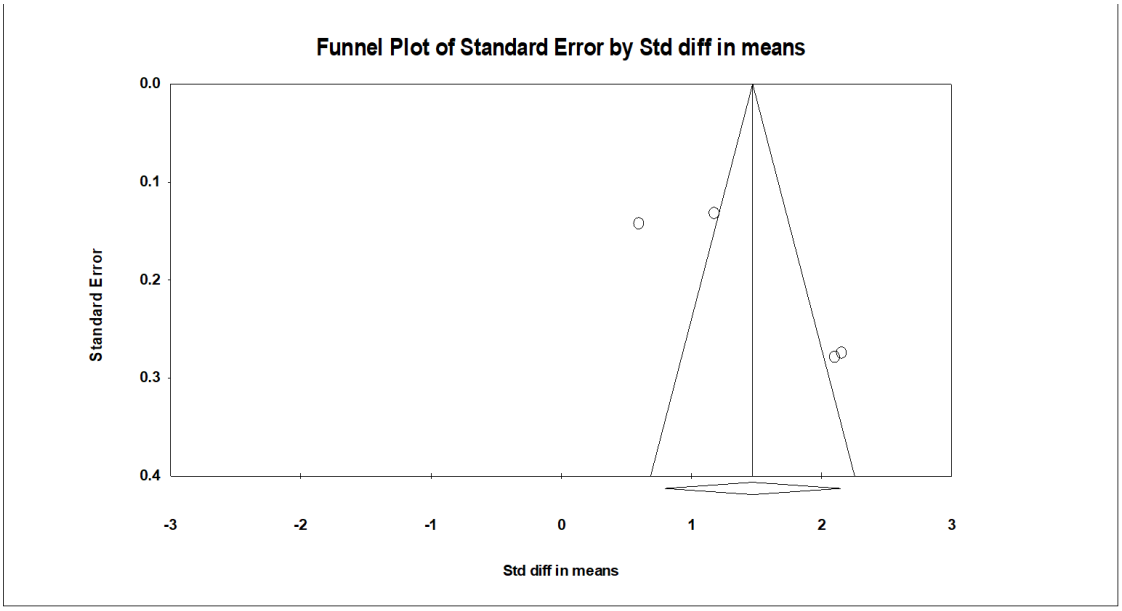


Figure 2.22: Funnel plot depicts the publication bias of plasma soluble TNF alpha receptor 1 studies.

2.5.13 Plasma soluble TNF-α receptor 2 concentration in AD and HC subjects

To examine the overall effect of plasma soluble TNF-α receptor 2 concentration (pg/ml) between AD and HC subjects, we selected only two studies based on our study selection criteria. A total of 243 AD patients and 240 HC subjects' data were meta-analyzed with the random effects model. The meta-analysis found that an average medium effect size of SMD = 0.583 (CI: 0.400 to 0.767; $P < 0.001$) (see **Fig 2.23**), suggesting a high concentration of plasma TNF-α receptor 2 in AD than HC groups. Though, the result is statistically significant, but because of only two

studies with very small sample size it is not possible to measure the true effect size of plasma TNF-α receptor 2 levels between AD and HC groups. Therefore, more studies are required to confirm this effect. The funnel plot for publication bias and the Fail-safe number were not examined because of two studies. However, we measured the study heterogeneity by using the I-squared test and found the $I^2 = 0\%$ with P = 0.487, suggesting no variations of the results among sampled studies.

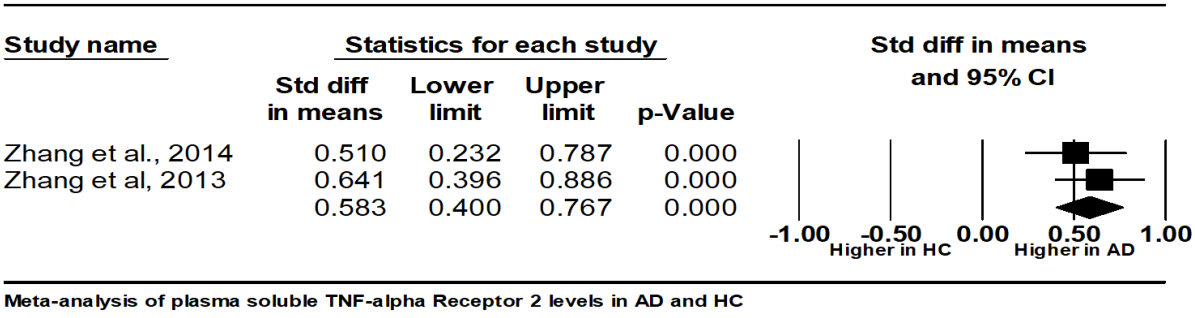


Figure 2.23: Meta-analysis of plasma TNF-α receptor 2 concentration in AD and HC. Positive value indicates higher concentration in AD group.

2.5.14 Urine AD7C-NTP concentration in AD and HC subjects

To measure the overall effect size of urine Alzheimer-associated neuronal thread protein (ng/ml) (AD7c-NTP) between AD and HC subjects, we sampled only two studies based on our stringent study selection criteria. A total of 185 AD patients and 208 HC subjects' summary data were meta-analyzed by using the random effects model. We found an average large effect size of SMD = 2.271 (CI: -1.778 to 6.321; P = 0.272) (see **Fig 2.24**), suggesting a high concentration of urine AD7c-NTP in AD than HC groups. Although, the effect size is very large, but such is not supported with hypothesis significance testing (as the P = 0.272). In addition, because of only

two studies with very low sample size, it is not possible to calculate the true effect size of urine AD7c-NTP concentration in AD and HC subjects. Therefore, more studies are required to estimate the effect interest. We did not examine the publication bias and the Fail-safe number because of two studies. However, we assessed the study heterogeneity using the I-squared test and found the $I^2 = \sim 99\%$ with $P < 0.001$, which indicates a very large study heterogeneity due to the findings of the sampled studies.

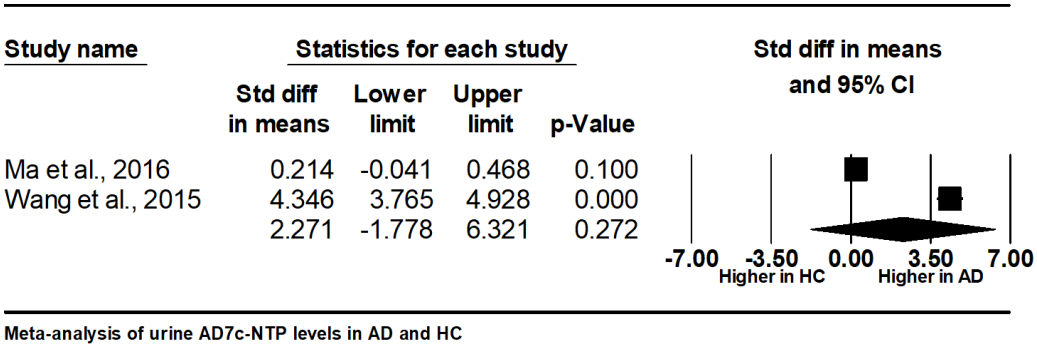


Figure 2.24: Meta-analysis of urine AD7c-NTP concentration in AD and HC. Positive value indicates higher concentration in AD group.

2.6 Discussion

Our meta-analysis results provide a comprehensive analysis of available high-quality recent studies of CSF, blood and urine metabolites of AD patients and HC subjects. Our results on core CSF biomarkers found that the $A\beta_{1\text{-}42}$ concentration was significantly reduced in AD patients, while the T-tau and P-tau_{181p} levels were elevated in AD relative to HC subjects', these findings remain consistent with the other groups' results (see Ferreira et al., 2014; Olsson et al., 2016). The reduced levels of $A\beta_{1\text{-}42}$ proteins in CSF of AD patients may be due to deposition of most of the produced amounts in the form of neuritic plaques inside the brain (Murphy and Levine,

2010). By contrast, the increased levels of CSF T-tau and P-tau in AD patients may be due to excess production of soluble phosphorylated tau proteins from the intraneuronal compartment of brain because of hyperphosphorylation of tau proteins (Noble et al., 2013). All these three established CSF biomarkers of AD were measured by the conventional assays such as Innogenetics, Ghent, Belgium kit or INNOTEST Phospho-Tau (181) kit or INNOTEST ABeta 42 or INNOTEST the multiplexing INNO-BIAAlzBio3 (Ritchie et al., 2017). However, recent studies suggest a large inter laboratory variation in the measurement of biomarkers in AD using research grade assays (Mattsson et al., 2013; Watt et al., 2012).

In addition to these established CSF biomarkers, we also found support for the claim that the hFABP level in CSF is significantly elevated in AD (see Fig 2.7 in the results section). hFABP is a cytosolic long chain fatty acid transport protein that is predominantly expressed in the heart, adipose tissue, kidney and neurons (Colli et al., 2007; Ockner et al., 1972). Although, it is not an established biomarker for AD pathological condition, but due to reported high concentrations in the AD group compared with HC subject (large effect size), this metabolite could be a useful biomarker, if future studies replicate the same effect.

Unlike the CSF Aβ and tau core biomarkers of AD, none of the Plasma biomarkers levels of $A\beta_{1-42}$, Plasma $A\beta_{1-40}$, and Plasma T-tau were significantly different from HC subjects (see table 2.2). Furthermore, none of these metabolites' effect sizes achieved statistical significance, and therefore, are not candidate biomarkers for the differential diagnosis of AD from HC.

Our findings are consistent with other previous meta-analyses of earlier studies which were not included in our analysis (Shanthi et al., 2015; Song et al., 2011).

In addition, many inflammatory markers were found to be elevated in AD than HC controls. Central nervous system inflammation is, beyond age, considered one of the major risk factors of sporadic AD, and neuroinflammation may produce several inflammatory products such as interleukins, TNF-α, homocysteine, Interferon gamma(γ), high sensitivity C-reactive protein (hsCRP) and several others that are quickly released into the blood stream (Delaby et al., 2015; Heneka et al., 2015). Th present analysis supported evidence for two types of TNF-α molecule, namely soluble TNF-α receptor 1 and soluble TNF-α receptor 2, to be significantly elevated in AD compared to the HC subjects. Elevated levels of soluble TNF receptors are associated with the conversion of MCI to AD by stimulating Aβ production and other AD related pathological processes (Buchhave et al., 2010; Diniz et al., 2010). Our meta-analysis results on these elevated inflammatory molecules were consistent with other groups' prior findings (Lai et al., 2017; Swardfager et al., 2010). However, our analysis supported evidence for the observation that plasma IL-6 concentration was significantly reduced in AD than HC groups, which contradicts other groups' results (Lai et al., 2017; Swardfager et al., 2010). Lai et al. (2017), conducting a recent meta-analysis of the serum IL-6 concentration with 40 studies comprising of 2295 AD patients and 2498 HC subjects found a significant elevated level of IL-6 in AD than HC subjects (Lai et al., 2017). The author of the study estimated an average effect size of 0.522 (CI: 0.240 to 0.804; $P < 0.001$) (Lai et al., 2017). Similarly, another meta-analysis examined the peripheral blood IL-6 concentration by combing 14 studies comprising of 985 AD patients and 680 HC subjects, and found an overall increased level of IL-6 in AD than HC individuals (Swardfager et al., 2010). The average effect size of that meta-analysis was 2.86 (CI: 1.68, 4.04; $P < 0.00001$) (Swardfager et al., 2010). In addition, that meta-analysis included a cell culture study (Richartz et al., 2005) that reported diminished level of IL-6 in the AD patients. By contrast, our meta-

analysis on the plasma IL-6 found higher concentrations in HC than AD patients (see Fig 2.16). It may be that because of our stringent study criteria we included only two studies (within the time period) (L. Guo et al., 2013; Nazeri et al., 2014). Our criteria were appropriately stringent and diagnostic criteria used NINCDS-ADRDA (McKhann et al., 1984). The meta-analyses that do not agree with our findings included studies that did not use NINCDS-ADRDA diagnostic criteria. In addition, their investigated HC group comprised subjects with hypertension, diabetes, coronary heart disease, elevated cholesterol, alcohol use, and also reported data other than mean and standard deviation or standard error of mean format (Lai et al., 2017). Therefore, we decided to perform a meta-analysis of the IL-6, combining studies, that were included in the very recent meta-analysis by Lai et al. (2017). Lai and colleagues (2017) performed meta-analysis on the IL-6 level in HC and AD groups by combining 40 studies published before September 2016 (Lai et al., 2017). We assessed those 40 studies with our study inclusion and exclusion criteria (see methods section for our study inclusion and exclusion criteria), unfortunately, only 7 studies (Baranowska-Bik et al., 2008; Bonotis et al., 2008; Bozluolcay et al., 2016; Kamer et al., 2009; Licastro et al., 1997; Rubio-Perez and Morillas-Ruiz, 2013; Zhang et al., 2003) met our criteria. Finally, we recorded the summary data of IL-6 concentration from 9 studies [2 studies from our investigation, and 7 from (Lai et al., 2017)]. A total of 272 AD patients' and 332 HC subjects' data were meta-analyzed together by using the random effects model. Our meta-anlysis results found a very small effect size of SMD = 0.174 (CI: -0.342 to 0.689; P = 0.509) (see **Fig 2.25**), suggesting no difference between the IL-6 concentration in AD and HC group. Therefore, more studies would be required to estimate the true effect size for IL-6 level in HC and AD group.

The publication bias was assessed by the funnel plot (see **Fig 2.26**) method, suggesting a large variation amnong the sampling studies. In addition, we found the I-squared value = 89.667%,

with P < 0.001. We did not estimate the Fail-safe number because the result of our analysis was statistically not significant.

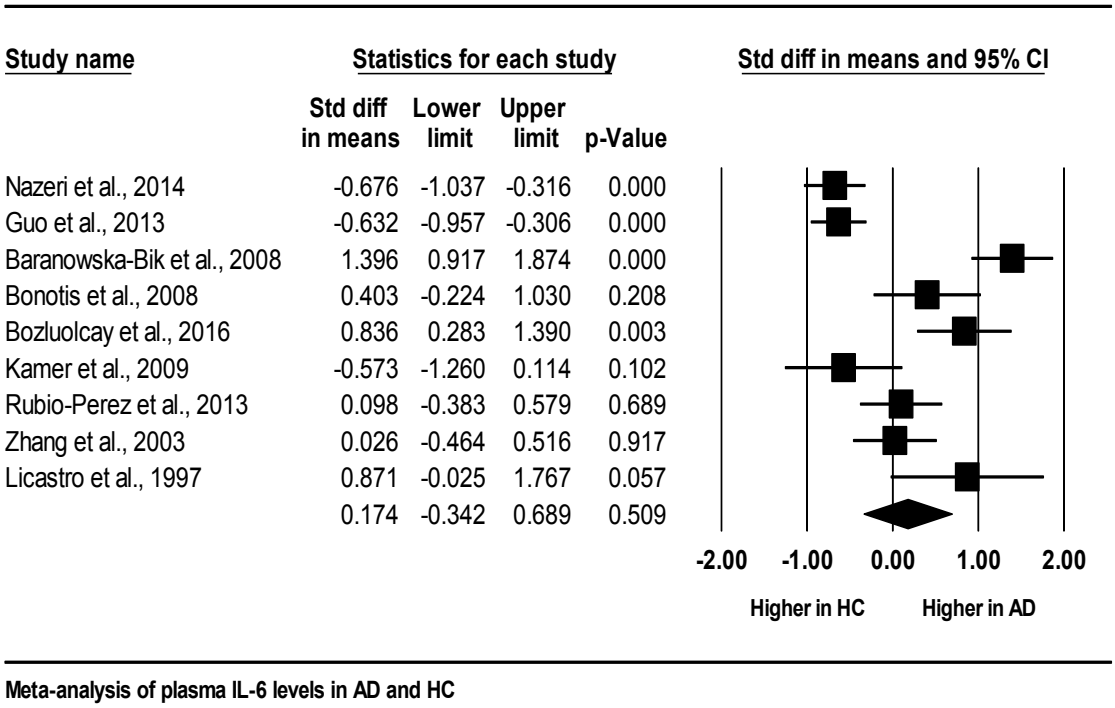


Figure 2.25: Updated meta-analysis of plasma IL-6 concentration in AD and HC subjects. Positive value indicates higher concentration in AD patients'.

In summary, our methods have conformed some strong results for established biomarkers indicating that our approach is valid. There remains possibility a statistical error in the outcome of meta-analysis.

Our findings also supported a reported imbalance of plasma levels of copper, albumin and creatinine. Interesting, the plasma copper level was significantly elevated in AD patients than HC subjects (see Fig 2.19), while the plasma albumin significantly reduced in AD patients (see Fig 2.14).

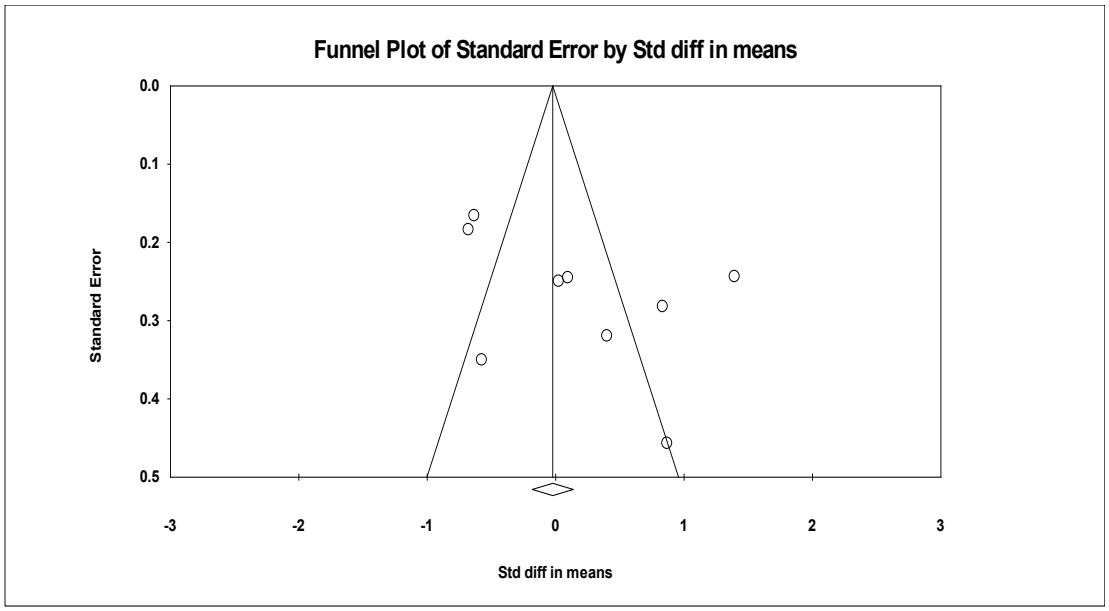


Figure 2.26: Funnel plot depicts the publication bias of plasma IL-6 level in HC and AD for updated studies.

The imbalance of biometal homeostasis, particularly copper, has been associated with AD (Siotto and Squitti, 2018). Due to a high concentration of copper metal in plasma of AD, the serum albumin level is decreased likely because of a copper and albumin interaction, and this may contribute to the development of AD (Shore et al., 1984; Siotto and Squitti, 2018). For one of our meta-analyses on urine AD7c-NTP levels that metabolite appeared to be very high, but the effect was not statistically non-significant in AD patients compared to the HC subjects (see Fig 2.24). AD7c-NTP is a protein predominantly found in the long axonal processes of neurons, and an increase in urine concentration may have been attributed to excess damage of cortical neurons in the early stage of AD dementia (Zhang et al., 2014). Although, this protein concentration in urine is very high AD patients, but it is not currently included in the AD biomarkers list because of insufficient evidence in the literature, and the production of AD7c-NTP by neurodegeneration is not only specific to AD dementia.

It is notable for this meta-analysis we only included recent studies (period between July 2012 to September 2018). This decision was made to assess evidence for biomarkers that did not overlap with prior meta-analyses available at the start of this work.

We excluded many studies because of our stringent study inclusion and exclusion criteria particularly on data reporting format. In addition, we included studies published on the same cohort data set that are measured once [i.e. the ADNI data set (http://adni.loni.usc.edu/)]. Inter-laboratory variation of assays measuring metabolite concentrations remains very high (Mattsson et al., 2013; Noble et al., 2008; Watt et al., 2012). It is perhaps not surprising, therefore, that our indicator of study heterogeneity in the majority of our analysis is very high. The number of studies in each category of analysis (except the CSF core biomarkers of AD) is very low with small sample sizes. Finally, we did not compare any intermediate or subgroup analysis of the MCI and AD (i.e. mild, moderate and severe AD) in this analysis.

2.7 Conclusion

Our findings on CSF indicate that $A\beta_{1\text{-}42}$, T-tau and P-tau_{181P} are the metabolites that discriminate between AD and HC groups with high accuracy. Such findings confirm analysis of previous studies in the literature, and these similarities confirm that our approach is both effective and valid. In addition, the CSF hFABP is an emerging biomarker, which is elevated significantly in AD groups when compared with HC group and warrants further research.

All of our analyses on studies including different plasma Aβ and tau proteins level in AD and HC groups did not find any significant differences. Therefore, currently, there is no rationale for considering them as current of potentially future biomarkers of AD. Although, some

inflammatory related cytokines were found to be significantly elevated in AD compared to HC groups, we observed very high study outcome heterogeneity, indicating a need to be further investigate these with larger AD cohorts. All of these examined peripheral biomarkers may not be only specific to AD dementia. As noted above, the overlapping disease pathology and phenotypic symptoms among different forms of dementia may influence these biomarkers. Therefore, more research is required for classification of the particular clinical characteristics and underlying pathological conditions between AD and non-AD dementia cases.

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Chapter 3: Ante-mortem biofluid metabolite concentrations and their relationship with the severity of Alzheimer's disease dementia: A systematic review and meta-analysis

3.1 Introduction

Dementia is a clinical condition characterized by deterioration of memory and cognitive function, which interferes with social or occupational functioning of an individual (Chertkow et al., 2013). Among the different types of dementia, Alzheimer's disease (AD) is the most prevalent form, comprising up to 75% of all dementia cases in elderly (Qiu et al., 2009). It has been estimated that 36.5 million people were affected with dementia globally in 2010 and this number will exceed 115.4 million by 2050 (Prince et al., 2013). The global costs of dementia were US$ 818 billion in 2015, an increase of 35% of US% 604 billion in 2010 and these costs will exceed the threshold of US$ 1 trillion by 2018 (Wimo et al., 2017). Accumulation of Aβ plaques and neurofibrillary tangles (NFT) in the brain are well established neuropathological hallmarks of AD (Querfurth and LaFerla, 2010). However, around 20-40% of normal ageing individuals and other disease conditions show similar kinds of AD brain pathology (Fjell et al., 2014). Interestingly, the brain pathological conditions in AD appear around 15-20 years before the clinical symptoms appear (Villemagne et al., 2011), and the mean duration of survival is around 8.5 years from the onset of clinical symptoms (Francis et al., 1999).

Generally, AD appears sporadically in old ages and its prevalence nearly doubles in every 5 years after the age of 65 (http://www.alzheimers.net/resources/alzheimers-statistics/) and hence, age is considered the greatest risk factor. The sporadic cases of AD, which develop after age of 65 years known as later age of onset (LOAD), and accounts for more than around 90% of total AD cases (Bertram and Tanzi, 2004; Prince et al., 2013), while about 1-6% of cases of AD develop before the ages of 30 to 65 years and are called early onset of AD (EOAD) (Cruts and Van

Broeckhoven, 1998; Piaceri et al., 2013). EOAD appears mainly due to autosomal dominant mutation of three genes called familial AD and the genes are amyloid precursor protein (APP) gene on chromosome 21, presenilin-1(PS1) gene on chromosome 14, and presenilin-2(PS2) gene on chromosome 1, which comprises around 5% of total cases of AD (Brouwers et al., 2008; Piaceri et al., 2013). In addition, the apolipoprotein E (APoE) gene on chromosome 19 is also associated with the LOAD in both familial and sporadic forms of AD by decreasing the mean age of onset from 84 years to 68 years (Corder et al., 1993). The APoE gene has three alleles such as APoE Ɛ2, APoE Ɛ3 and APoE Ɛ4 and people with single copy of inherited APoE Ɛ4 allele have three fold high risk of developing AD in comparison to other forms of APoE gene, and persons' who carry two copies of APoE Ɛ4 gene, the risk AD increases up to 8-12 fold, while the ApoE ε2 allele decreases the risk of AD (Holtzman et al., 2012; Liu et al., 2013; Loy et al., 2014). Furthermore, people with Down's syndrome (DS) are also associated with high risk of EOAD because DS is a genetic disorder caused by the presence of three copies of chromosome 21 with AAP genes, which plays an important role in production of amyloid-beta (Aβ) in AD (Goedert, 2015).

3.2 Mild Cognitive Impairment

AD proceeds through the mild cognitive impairment (MCI) stage, which is considered as a transition stage between normal ageing and advanced forms of dementia (Petersen, 2011). Interestingly, not all the MCI patients progress to AD or other forms of dementia and they remain stable in this condition after 10 years follow up from the initial diagnosis (Mitchell and Shiri-Feshki, 2009). Patients with MCI are again classified into two subtypes based upon the performance of neuropsychological tests, such as amnestic MCI (aMCI) and non-amnestic MCI (naMCI) (Petersen et al., 2014). The aMCI patients perform poorly on neuropsychological tests

of episodic memory (Tulving, 2002), while patients with aMCI perform poorly on other cognitive domains of neuropsychological tests than memory, such as executive functions, language or visuo-spatial abilities (Petersen et al., 2014). In addition, the MCI patients have impairments in single to multiple cognitive domains and therefore, the MCI patients could be further classified into four possible subtypes, such as (i) aMCI-single domain, (ii) aMCI-multiple domain, (iii) naMCI-single domain and (iv) naMCI-multiple domain (Petersen et al., 2014). Conventionally, the aMCI is generally considered as a prodromal stage for AD, but it might progress to other forms of dementia such as logopenic aphasia, posterior cortical atrophy, frontal lobe-dysexecutive presentation of AD (Petersen, 2016).

3.3 Contemporary diagnosis of the AD and MCI

Conventionally, diagnosis of AD was based on the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (Jack et al., 2011; Mckhann et al., 1984), and other diagnostic criteria such as the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the 10th version of the International Classification of Diseases(ICD-10), and the International Work Group criteria (IWG) (Cummings, 2012; Cummings et al., 2013). In addition, the first clinical characterization of MCI patients was first reported by (Petersen et al., 1999) and subsequently inducted into the clinical research setting for assessment of progression to MCI or AD (Jack et al., 2011; Petersen, 2016; Petersen et al., 2014). Although, the above-mentioned diagnostic criteria are considered as a "gold standard" for diagnosis of AD in living people, sometimes these diagnostic guidelines may give false-positive and false-negative results. For example, a recent study (Edmonds et al., 2016) suggests a 7.1% of false-negative rate for MCI patient diagnosis on conventional diagnostic criteria. After all, the definitive diagnosis of AD is only possible

following autopsy (McKhann et al., 1984). Traditional ante-mortem diagnosis AD is based on clinical symptoms (McKhann et al., 1984), however, by that time much damage already happened to the brain (Villemagne et al., 2011).The failure of all clinical trials of AD therapies (Anderson et al., 2017; Cummings et al., 2017) indicates a current lack of effective drug therapies for AD dementia. Hence, the National Institute on Ageing and Alzheimer's Association (NIA-AA) has redefined AD on the basis of biological construct rather than clinical symptoms, it says "The term "Alzheimer's disease" refers to an aggregate of neuropathologic changes and thus is defined in vivo by biomarkers and by post-mortem examination, not by clinical symptoms" (Jack et al., 2018). However, this new definition of AD is not intended specifically for the clinics but is offered appropriately for clearer understanding of disease etiology from the biomarkers point of view.

3.4 Investigated research questions

Findings from previous autopsy confirmed studies on AD suggest that there is an association between neuropathological changes and AD dementia severity (Arriagada et al., 1992; Bierer et al., 1995; Nelson et al, 2013). However, claims for such an association with living AD patients' has been inconsistent in some studies. In other words, there is a lack of precise evidence on the strength of association between the antemortem biofluid metabolite levels and AD dementia severity, to the best of our knowledge.

In the present work, we explored:

(i) The strength of relationship between biofluid metabolites concentration and severity of AD dementia.

ii) Methodological variations across the studies for clinical application.

Investigated biofluids included:

cerebrospinal fluid (CSF)

blood

plasma

serum

urine

Included studies focussed on analysis of research-identified metabolite concentrations and severity of AD dementia. Antemortem AD patients were diagnosed as probable AD or possible AD as per the NINCDS-ADRDA criteria (McKhann et al., 1984). Severity of dementia is defined as an impairment in global cognition, which can be assessed with any standard neuropsychological test batteries such as the Mini-Mental State Examination (MMSE) score or the Clinical Dementia Rating score (CDR) or the Blessed Dementia Scale and others (Blessed et al., 1968; Folstein et al., 1975; McKhann et al., 1984; Sheehan, 2012).

3.5 Methods

3.5.1 Literature search strategy and study selection

We performed this systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). We searched PubMed data base (https://www.ncbi.nlm.nih.gov/pubmed/) for the maximum number of relevant studies published between July 1, 1984 [time of establishment of current AD diagnosis criteria by (McKhann et al., 1984; Olsson et al., 2016)] to September 5, 2018 by using the keywords ("fluid biomarkers" OR "CSF" OR "cerebrospinal fluid" OR "blood" OR "serum" OR "urine" OR "protein" OR "amyloid beta" OR "tau") AND ("Alzheimer's" OR "mild cognitive

impairment") AND severity. We limited our search only to human species studies written in the English language. We did not include any grey literature sources and only summary estimates of peer reviewed articles were used. These searches retrieved a total of 1722 studies, which were screened by two independent reviewers. We selected studies for our meta-analysis if they met the following inclusion and exclusion criteria.

3.5.2 Inclusion Criteria:

- Original peer-reviewed studies published between July 1, 1984 to September 5, 2018.
- Only human species English language studies were included.
- Studies analyzing the relationship between the antemortem cerebrospinal fluid or peripheral body fluid metabolites concentration and the severity AD dementia.
- Use of clinical diagnosis criteria for AD, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) by (McKhann et al., 1984).
- AD patients' group must be compared with a healthy control group (HC).

3.5.3 Exclusion Criteria

- All animal studies, meta-analyses, review articles, letters, comments, case reports, and unpublished articles.
- Studies that did not report:
    - the correlation coefficient value as an index of effect size measure of the association between the biofluid metabolites concentration and severity of AD dementia.
    - sample size of each subject groups of equal to or greater than ten individuals.
    - report data in a format which can't be convertible in relation to effect size.
- Studies only presenting post-mortem or autopsy or neuroimaging data.

- Healthy control group (HC) comprises participants with other neurological diseases or psychiatric disorders.

Final inclusion and exclusion of studies were decided independently by the two reviewers (M. M & A. G). Any discrepancies in sampling of studies were discussed between the two authors until full agreement was reached, and if such was not resolved between the two reviewers, we took the outcome of three votes including the opinion and vote of a third reviewer.

3.5.4 Data extraction and quality assessment

From the included studies, we recorded the following information:

(i) the first author and the year of publication.

(ii) study design/setting (i.e. longitudinal or cross-sectional)

(iii) sample size

(iv) mean/median age

(v) mean/median MMSE score

(vi) mean/median measured metabolite concentrations of both the AD and HC groups

(vii) AD dementia severity outcome values (i. e. the statistical test results showing the relationship between the biofluid metabolites level and dementia severity).

The strength of association between dementia severity and biofluid metabolites level was reported in different effect size (ES) formats (Rosenthal and DiMatteo, 2001):

(i) Spearman's correlation coefficient (r_s) and Kendell's tau (K_t) are both non-parametric rank correlation for measuring strength of relationship between two variables (i.e. dementia severity and biofluid metabolites concentration.) (Xu et al., 2013).

(ii) Pearson product–moment correlation coefficient or partial correlation (r) (Lee Rodgers and Alan Nice Wander, 1988).

(iii) Standardized beta weights (β) from linear or multiple regression model for predicting the dementia severity on metabolites concentration (Nagelkerke, 1991; Nathans et al., 2012).

(iv) Coefficient of determination (R^2) from linear regression model (Nagelkerke, 1991).

(v) P-value (du Prel et al., 2009) as an effect size measure of association between these two variables.

Data for individual metabolites from CSF and from peripheral blood of were meta-analyzed separately. Articles reporting each metabolite data from the plasma and serum were meta-analyzed together (Olsson et al., 2016). While the majority of our included studies are cross-sectional, a very few studies are longitudinal measurements with clinical follow up. In the case of longitudinal studies, we took only baseline measurement data to meta-analyze with a cross-sectional data approach (Olsson et al., 2016). We decided to perform meta-analysis if there are at least two studies available in each category of metabolite (Olsson et al., 2016; Valentine et al., 2010). For any study that used different scales for grading of dementia severity in AD patients, we changed the sign (i.e. direction of the relationship) of the effect sizes into one direction, which will be equivalent on other scales. For example, both the MMSE and CDR scales (Robert et al., 2010) are used in the assessment of dementia severity in AD patients. Subjects with higher scores (above 24 points) in the MMSE scale are considered in the normal cognition range, while lower scores (below 24 points) are cognitively impaired. However, in case of the CDR scale the AD patients with higher scores (0.5 to 3 points) are considered cognitively impaired, and lower scores (0.5 to 0 points) are cognitively normal. So, both the scales measure the dementia severity

in AD patients, but the scores in these scales are in opposite direction. Hence, signs were changed in one direction to make consistent overall effect sizes that are measured on different scales.

3.5.5 Calculation of effect sizes

The majority of studies included in this meta-analysis report their effect sizes (i.e. the strength of association between metabolite concentration and severity of AD dementia) in the form of Spearman's correlation coefficients (r_s). In addition, we had very few studies that report in the format of Pearson r, and β weights or bivariate regression slopes or R^2 in the linear regression model. Interestingly, we did not have a single study that reports the effect size in the form of standardized β weights that are derived from the multiple regression models or chi square (χ^2) (Rosenthal and DiMatteo, 2001). Combining studies with different effect size measures like Pearson's r, Spearman's r_s, Kendell's tau (K_T) are problematic because of the relative parametric and non-parametric nature of assumptions concerning data distributions. For example, both the r_s and K_T are non-parametric rank order correlations having larger standard errors than r, and hence, for more accurate results, these effect size measures should not normally be combined with the Pearson r (Hunter and Schmidt, 2004). However, this is feasible when there are enough studies available for conducting a coefficient of correlation meta-analysis (Field, 2001; Hunter and Schmidt, 2004; Rosenthal and DiMatteo, 2001). So, we did not omit these studies that report the strength of relationship in different effect sizes index because it might increase the sampling error (Rosenthal and DiMatteo, 2001). Therefore, various transformations were performed on different effect size categories to combinable format, which can be cumulated across the studies. As noted earlier, the majority of our included studies report their effect sizes in r_s format, and for more a conservative approach of converting parametric statistics to non-parametric, we used the

Spearman's correlation coefficients in our meta-analysis. Both the Pearson r and Kendell's tau were approximated to Spearman's correlation coefficient (Chalkidou et al., 2012; Gilpin, 1993; Rupinski and Dunlap, 1996). Similarly, studies reporting effect sizes in R^2 format, we just took the square root of R^2 (Hunter and Schmidt, 2004) and, if a study did not report direction of relationship (i.e. positive or negative correlation), we determined directionality by looking at reported metabolite concentrations and the scale used for measuring dementia severity. Likewise, very few studies that report β weights as an index of effect size derived from the bivariate regression model, those are equal to correlation coefficient r. In addition, if a study only reports P-value as the strength of relationship between two variables, those are converted and combined with other included studies (Rosenthal and DiMatteo, 2001). After all appropriate conversions, the Fisher's Z- transformation was performed to convert each correlation coefficient into a distribution that is approximately normal, and the pooled Z- scores were than back-transformed to the overall correlation coefficients (Chen et al., 2013; Field, 2001). We used Cohen's criteria for interpreting our results to small ($r_s = 0.10$), medium ($r_s = 0.30$) and large ($r_s = 0.50$) the effect sizes (Cohen, 1988).

We employed a random effects model for our analysis because of likely differences in the patient populations and methodological variations in different laboratories across studies (Borenstein et al., 2010; Diener et al., 2009; Hedges and Vevea, 1998). Such models are more conservative and are a better fit to real world data for generalization of findings to a targeted population (Diener et al., 2009). We used Egger's test to create a Funnel plot by plotting standard error against Fisher's z (Egger et al., 1997). We chose to create the funnel plots if at least three studies are available in each category of analysis. Graphical visualization of the Funnel plot showing symmetrical distribution of studies is indicative of no publication bias. We did not perform the fail-safe N and

trim-and-fill (Duval and Tweedie, 2000; Rosenthal and DiMatteo, 2001) to estimate the number studies with negative or null effects that are potentially missing in the literature, which would have been contributed to non-significant results; because (i) most of our results are statistically non-significant, and (ii) after applying inclusion and exclusion criteria to potential studies for inclusion, our final analysis included a small number of studies are available in each category of analysis.

We used the Comprehensive Meta-Analysis Version 3.0 software program (https://www.meta-analysis.com/) for all our analyses (Bax et al., 2007; Borenstein et al., 2009).

3.6 Results

The initial PubMed search retrieved 1722 articles, and the abstracts of each study were screened for eligibility. Thirteen hundred and forty-four articles were excluded because of those studies were studies on animals, failed to analyze the relationship between biofluid metabolites concentration with severity of dementia, or presenting only neuroimaging data. Only 378 studies were assessed fully for eligibility with our study inclusion and exclusion criteria as noted earlier. Of these, 161 studies report only post-mortem data, 86 did not follow the standard diagnostic criteria, or had a sample size of less than 10, or the control group comprised other psychiatric/neurological disorder. In addition, 48 studies did not perform the relevant analysis or failed to report effect sizes, 57 studies were single studies (see **Table 3.3** for single study characteristic details) or had a statistical reporting problem.

Finally, 26 studies (20 cross-sectional and 5 longitudinal) were included in our analysis. Out of that set, 18 studies examined CSF metabolite relationship to severity of AD, while 10 studies analyzed the relationship between blood metabolite levels and severity of AD dementia. Of

these, two studies (DeKosky et al., 2003; Oishi et al., 1996) reported data on both the CSF and blood biomarkers. In addition, many studies reported data on multiple metabolites that in relationship to AD severity (See **Table 3.1 & Table 3.2** for included study characteristic details). In the CSF category, we conducted meta-analysis on eight metabolites comprising total of AD n = 678 patients. Analyzed CSF metabolites were CSF $A\beta_{42}$ (7 studies), t-tau (7 studies), P-tau (3 studies), Aβ oligomers (2 studies), α1-antichymotrypsin (ACT; 2 studies), Pyruvate (2 studies), Insulin (2 studies) and norepinephrine (2 studies). Similarly, in the blood biomarkers category, we performed meta-analysis on four metabolites comprising a total of AD n = 826 patients. These metabolites were 1,6-Diphenyl-1,3,5-hexatriene (DPH; 2 studies), ACT (3 studies), Brain-derived neurotrophic factor (BDNF; 3 studies) and interleukin-18 (IL-18; 2 studies). Details of these studies were discussed in the latter sections.

All results are depicted in the form of forest plots (Lewis, 2001) derived by computing the overall effect sizes (Button et al., 2013; Crombie, 2013) with 95% confidence interval (CI), and p-values (Cumming and Maillardet, 2006). P-values of less than or equal to 0.05 ($P \leq 0.05$) were considered statistically significant for e of our examined hypotheses.

Table 3.1: Characteristics of included CSF metabolite studies

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF metabolite levels and severity of dementia in AD patients only.
(Jagust et al., 2009)	AD =10 HC = 11	$A\beta_{42}$, P-tau, t-tau ADNI data set, Longitudinal	MMSE	R = 0.01 for $A\beta_{42.}$ R = 0.28 for P-tau R = 0.26 for t-tau.
(Riemenschneider et al., 2000)	AD = 75 HC = 30	$A\beta_{42}$ Cross-sectional	MMSE	*r = 0.332 for $A\beta_{42}$
(Andreasen et al., 1999)	AD = 53 HC = 21	$A\beta_{42}$ Longitudinal	MMSE	**r_s= - 0.02 for $A\beta_{42.}$
(Mulder et al., 2002)	AD = 20 HC = 20	$A\beta_{42,}$ t-tau, Cross-sectional	MMSE	*r = 0.13 for $A\beta_{42.}$ * r = 0.37 for t-tau.
(Rosén et al., 2012)	AD = 75 HC= 65	$A\beta_{42,}$ $A\beta_{40,}$ P-tau, t-tau, Cross-sectional	MMSE	**r_s = 0.12 for $A\beta_{42,}$ **r_s = 0.12 for t-tau * r = 0.16 for P-tau * r = -0.08 for $A\beta_{40.}$
(Vemuri et al., 2009)	AD = 98 HC = 109	$A\beta_{42,}$ P-tau, t-tau. ADNI data set. Cross-sectional	MMSE	**r_s = 0.03 for $A\beta_{42,}$ **r_s =-0.13 for t-tau **r_s = -0.09 for

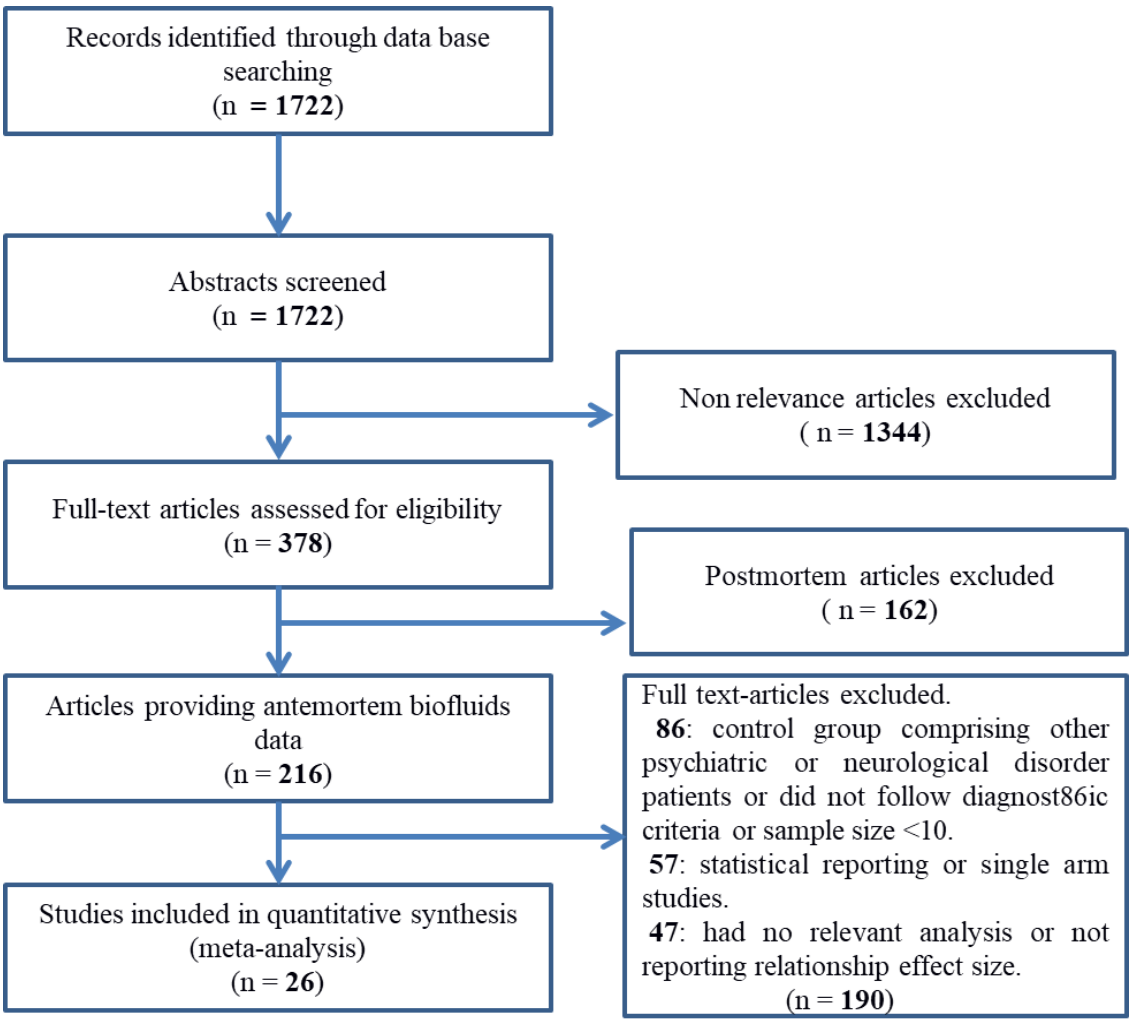
				P-tau
Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF metabolite levels and severity of dementia in AD patients only.
(Lin et al., 2009)	AD = 28 HC = 21	$A\beta_{42,}$ t-tau Cross-sectional	MMSE	**r_s = 0.005 for $A\beta_{42}$ **r_s = -0.279 for t-tau
(Riemenschneider et al., 1996)	AD = 22 HC = 19	t-tau Cross-sectional	MMSE	** r_s = -0.203 for t-tau
(Munroe et al., 1995)	AD = 24 HC = 14	t-tau Longitudinal	MMSE	*r = -0.03 for t-tau
(Santos et al., 2012)	AD = 14 HC = 12	Aβ oligomers Longitudinal	MMSE	**r_s = -0.65 for Aβ oligomers.
(Fukumoto et al., 2010)	AD = 18 HC = 25	Aβ oligomers Longitudinal	MMSE	*r = -0.402 for Aβ oligomers
(Oishi et al., 1996)	AD = 10 HC = 10	ACT, Norepinephrine	MMSE	**r_s = -0.19 for ACT **r_s = -0.49 for Norepinephrine.
(DeKosky et al., 2003)	AD = 34 HC = 16	ACT	MMSE, CDR, etc.	* r = -0.30 for ACT levels
(Parnetti et al., 2000)	AD = 41 HC = 44	Pyruvate	MMSE	**r_s = -0.81 for Pyruvate.
(L. Parnetti et al., 1995)	AD = 30 HC= 23	Pyruvate	MMSE	*r = -0.41 for Pyruvate.
(Molina et al., 2002)	AD = 27 HC = 16	Insulin	MMSE	*r = -0.15 for insulin.

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF metabolite levels and severity of dementia in AD patients only.
(Craft et al., 1998)	AD = 25 HC = 14	Insulin	MMSE	*r = 0.52 for insulin.
(Elrod et al., 1997)	AD = 74 HC = 42	Norepinephrine	MMSE	*r = -0.43 for Norepinephrine.
	Total AD = 678 Total HC = 512			

Table legends: AD = Alzheimer's disease, ADNI = Alzheimer's Disease Neuroimaging Initiative, ACT = α1-antichymotrypsin, Aβ = Amyloid beta, BDNF = Brain-derived neurotrophic factor, HC =Healthy Control, MCI = Mild Cognitive Impaired, MMSE = Mini Mental State Examination, CDR = Clinical Dementia Rating, DPH = 1,6-Diphenyl-1,3,5-hexatriene, P-tau = hyperphosphorylated tau, t-tau = total tau, IL = Interleukin, OD = Other Dementia, *r = Pearson's correlation coefficient, **r_s = Spearman's correlation coefficient, K_T = Kendell's tau, R^2 = Coefficient of determination, R = Strength of relationship between metabolite levels and severity of AD derived from the linear regression analysis, β = Beta coefficient from linear regression analysis. P = P-vale., TARC = Texas Alzheimer's Research Consortium.

Table 3.2: Characteristics of included blood metabolite studies

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between blood metabolite levels and severity of dementia in AD patients only.
(Zubenko et al., 1987a)	AD = 24 HC = 36	Platelet DPH	MMSE	*r = -0.73 for DPH anisotropy
(Zubenko et al., 1987b)	AD = 51 HC =50	Platelet DPH	MMSE	*r = -0.60 for DPH anisotropy.
(DeKosky et al., 2003)	AD =359 HC = 113	Plasma ACT	MMSE	P = 0.0075 for plasma ACT.
(Hinds et al., 1994)	AD = 36 HC =16	Serum ACT	MMSE	*r = 0.06 for serum ACT.
(Oishi et al., 1996)	AD = 10 HC = 10	Serum ACT	MMSE	**r_s = -0.24 for serum ACT.
(Siuda et al., 2017)	AD =134 HC =80	Serum BDNF	MMSE	**r_s = -0.01 for serum BDNF.
(Laske et al., 2006)	AD =30 HC = 10	Serum BDNF	MMSE	K_T = 0.486 for serum BDNF.
(O'Bryant et al., 2009)	AD = 99 HC = 99	Serum BDNF TARC data set	MMSE, CDR	P = 0.72 for serum BDNF.
(Chen et al., 2014)	AD = 53 HC = 53	Serum IL-18	MMSE	**r_s = -0.356 for serum IL-18.
(Bossù et al., 2008)	AD = 30 HC = 25	Serum IL-18	MMSE	*r = -0.407 for serum IL-18.



Flowchart 3.1 Study selection process.

3.6.1 Effect CSF $A\beta_{1-42}$ levels on severity of AD dementia

To test the hypothesis concerning the relationship of CSF $A\beta_{1-42}$ levels on severity of AD dementia, we estimated the overall effect size across seven studies (two longitudinal) comprising 359 AD patients. We found a non-significant average effect size (in random meta-analytic method) of r_s (Spearman correlation coefficient) = - 0.032 (CI: -0.180 - 0.118, Z = -0.419, P =

0.675) suggesting no effect on disease severity. There is insufficient evidence to examine the relationship between CSF $A\beta_{1-42}$ concentrations and severity of AD, and hence, more research is required to confirm the strength of that relationship if it exists.

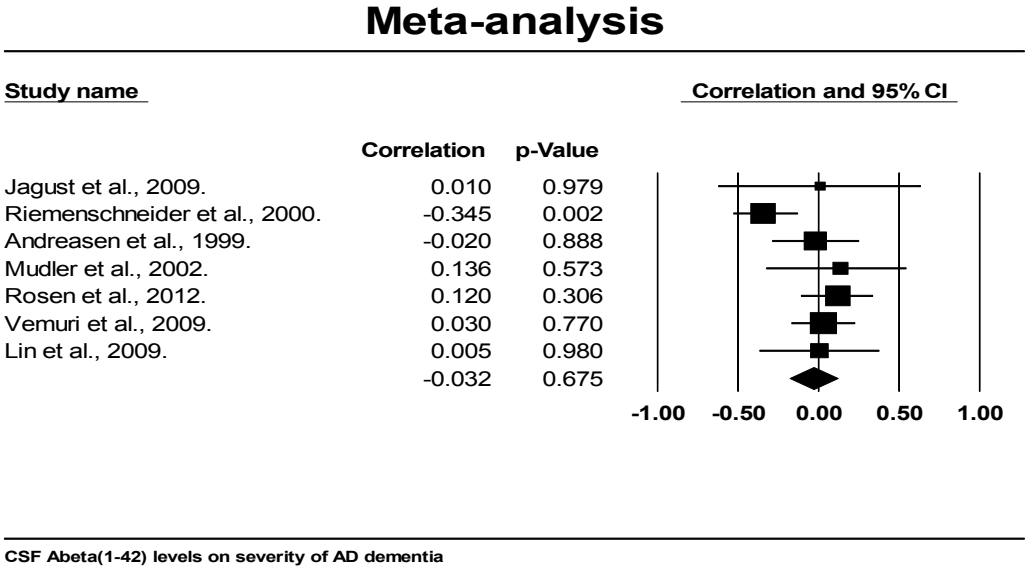


Figure 3.1: Forest plot of the overall correlation coefficient for CSF $A\beta_{1-42}$ levels on severity of AD dementia.

All the seven studies included in this meta-analysis indicate a non-significant or negligible relationship between CSF $A\beta_{1-42}$ levels and severity of AD, as it is depicted on the above forest plot (**Figure 3.1**) that the confidence intervals of each study touch the no-effect line. By contrast, one study (Riemenschneider et al., 2000) suggests a significant medium effect (r_s = - 0.345) on this forest plot. The authors of the above study reported a Pearson correlation coefficient value (r = 0.332; P = 0.026) without any sign, which suggests a positive correlation between CSF $A\beta_{1-42}$ levels and severity of AD, however, we corrected this typographical error by analyzing the raw

data (i.e. CSF $A\beta_{1-42}$ levels were reduced significantly in AD group and the severity of dementia is assessed with the MMSE scale) (Riemenschneider et al., 2000). In addition, another study (Nitsch et al., 1995) met our study inclusion criteria in this category, but we did not include in our analysis because it does not specify the particular type of Aβ concentration which correlates with AD severity. We created a funnel plot using Egger's test to assess the publication bias by plotting the standard error against Fisher's Z (Fisher, 1925; Stuck et al., 1998).The funnel plot (**Figure 3.2**) shows very minimal publication bias.

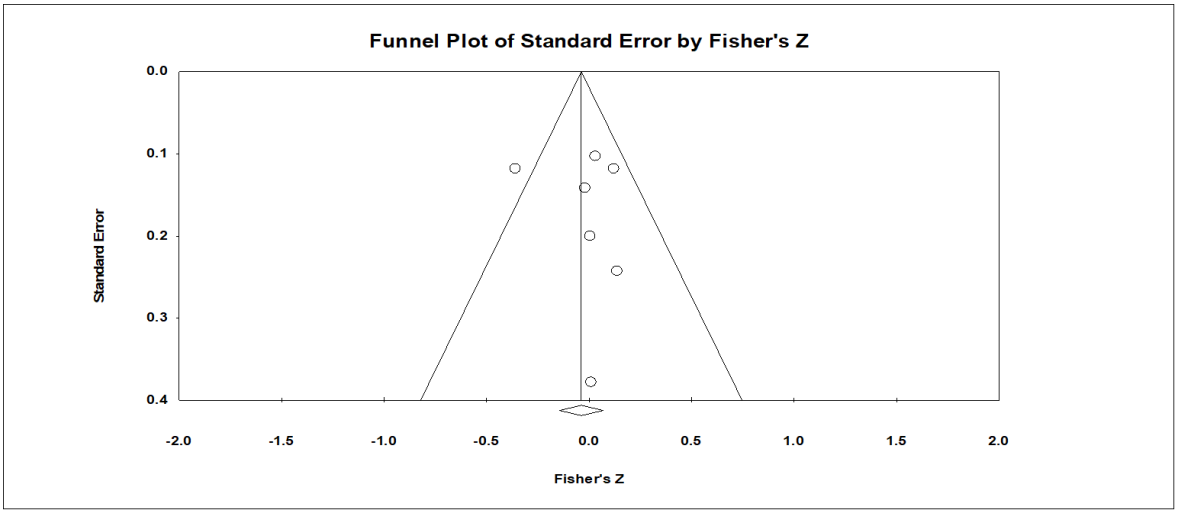


Figure 3.2: Funnel plot depicts very minimal publication bias for CSF $A\beta_{1-42}$ studies on severity of AD.

3.6.2 Effect of CSF total tau (t-tau) protein levels on severity of AD dementia

To examine the effect of CSF t-tau protein concentrations on AD severity, we calculated average effect size across seven studies (AD; n = 277). Our analysis found a non-significant effect size of r_s = -0.018 (CI: -0.179 - 0.143; Z = -0.220; P = 0.826) on cognitive functions of AD group. All the seven studies included in this analysis show statistically non-significant effects close to zero, while one study (Mulder et al., 2002) indicates a medium effect size, but it is not statistically

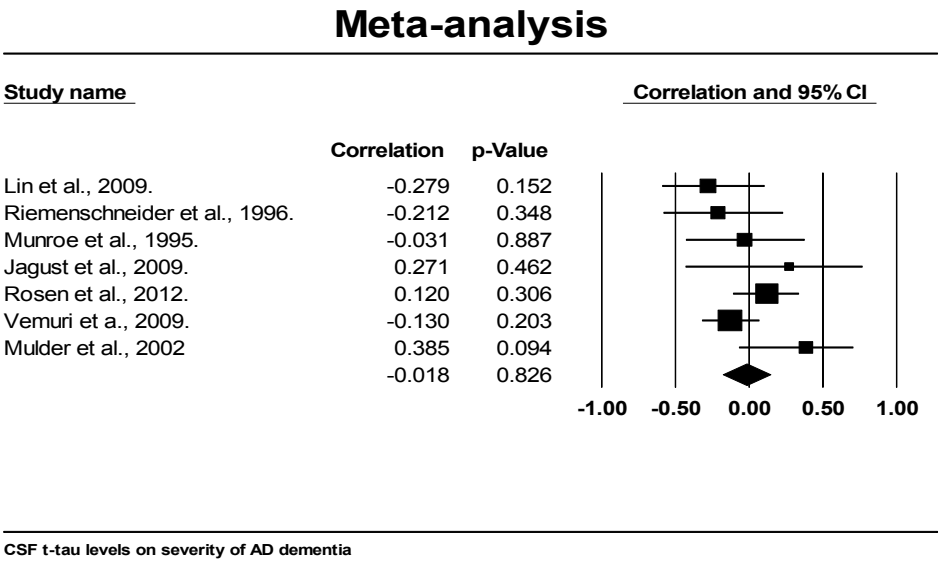


Figure 3.3 Forest plot of the overall correlation coefficient for CSF t-tau levels on severity of AD dementia

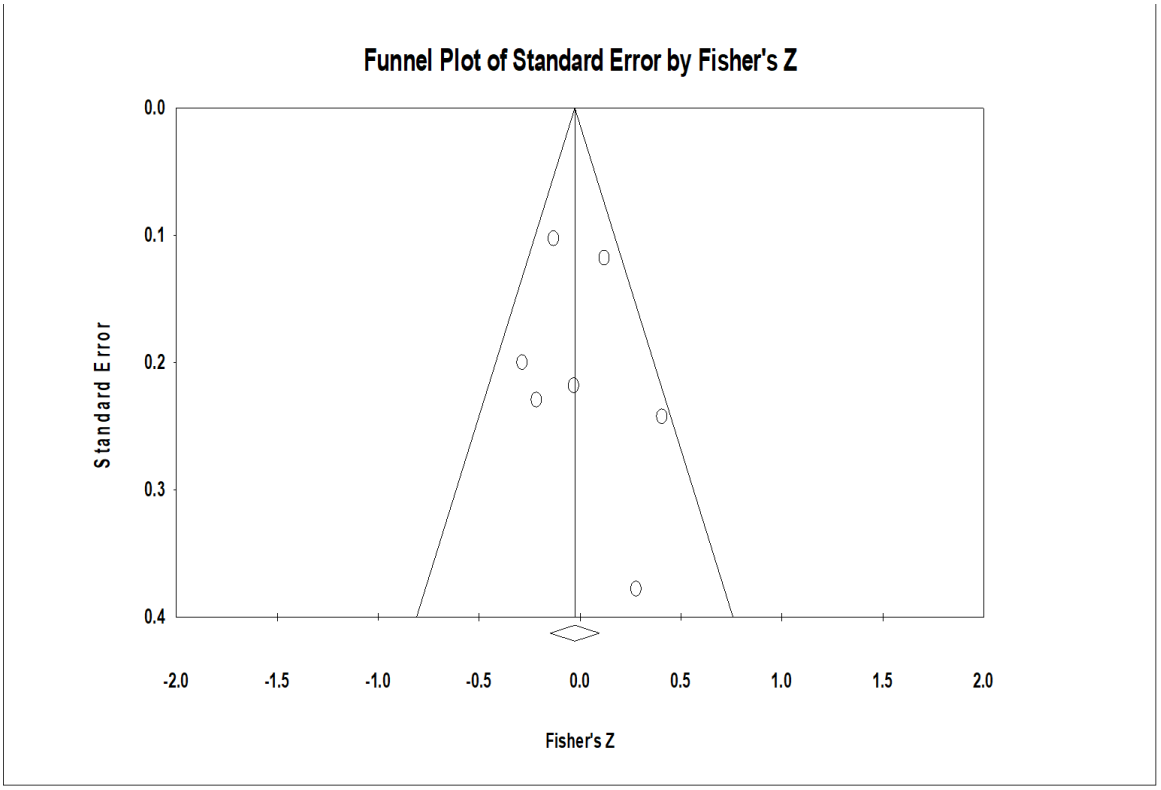


Figure 3.4: Funnel plot depicting no publication bias for CSF t-tau studies on severity.

significant. In addition, we did not include one study in our analysis because the authors reported a significant correlation between CSF t-tau levels and severity of AD assessed in the ADAS-cog scale, however, such correlation between these two variables was not found in the MMSE scale (Wallin et al., 2006). It is quite evident from the above analysis (**Figure 3.3**) that CSF t-tau protein levels are not correlated with severity of AD, and the overall effect is not significant. In addition, a funnel plot (**Figure 3.4**) indicates no publication bias.

3.6.3 Effect CSF phosphorylated tau protein (p-tau) levels on severity of AD

To test the strength of relationship between CSF p-tau protein levels and severity of dementia, three studies met our inclusion criteria (AD; n =183). Our analysis did not find any significant difference with average effect size (r_s) = 0.051 (CI: -0.161 - 0.260; Z = 0.470; P = 0.639).

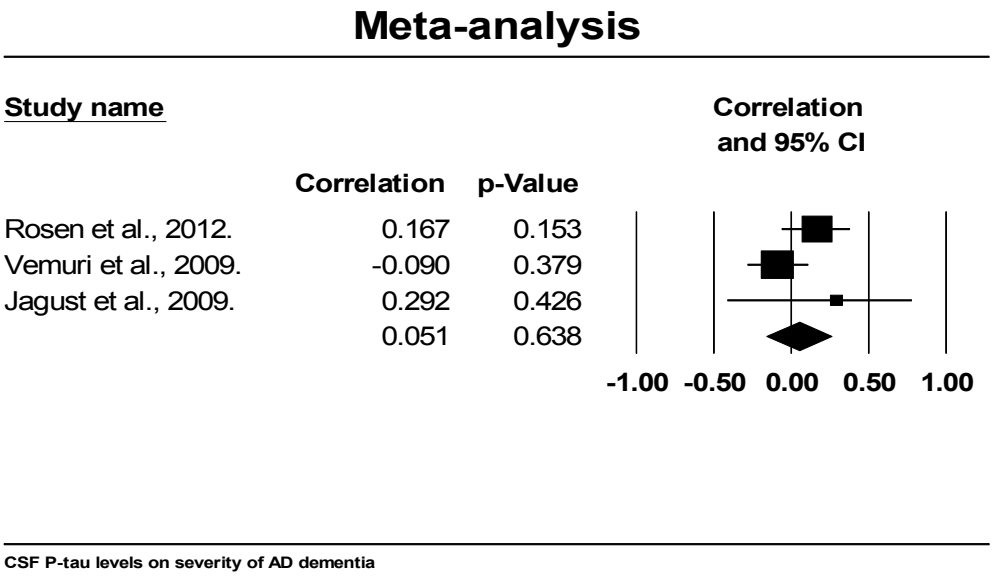


Figure 3.5 Forest plot of the overall correlation coefficient for CSF P-tau levels on severity of AD dementia.

It is intuitively difficult to make any confident statement about the strength of relationship between CSF p-tau levels and severity of with only three studies. Hence, more studies will be required to measure the strength of association between CSF p-tau metabolite concentrations and severity of AD dementia.

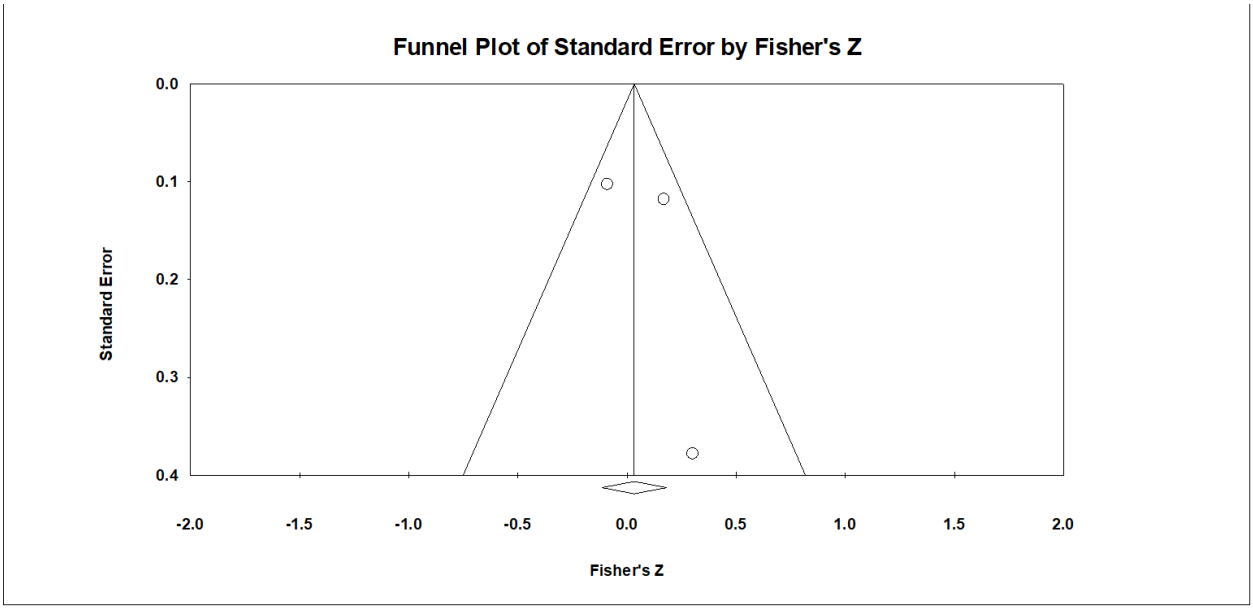


Figure 3.6 Funnel plot showing no publication bias for CSF P-tau studies on severity of AD.

All three studies included in this analysis (**Figure 3.5**) did not show any significant relationship between these two variables, and all effect sizes are scattered around the zero-effect line. In addition, three more studies (Fellgiebel et al., 2009; Ravaglia et al., 2008; Wallin et al., 2006) met our inclusion criteria, however, we did not include in our analysis because (i) the authors of study (Wallin et al., 2006) reported that there is a strong positive correlation between CSF p-tau and severity of cognitive impairment in AD patients as assessed by the Alzheimer's Disease Assessment Scale-cognition sub-scale (ADAS-Cog) (Rosen et al., 1984), however, they failed to find any positive correlations between CSF biomarkers and severity of AD using the MMSE scale. (ii) Similarly, the study (Ravaglia et al., 2008) performed correlational analysis between

CSF p-tau levels and MMSE scores (r = -0.33; p=0.006), but it did not give details of the AD group investigated. (iii) Likewise, another study (Fellgiebel et al., 2009) examined the strength of relationship between CSF p-tau levels with AD severity by combing an AD and MCI group together. The funnel plot (**Figure 3.6**) shows no publication bias for this category of analysis.

3.6.4 Effect of CSF Aβ Oligomers concentration and severity of AD

For this analysis, only two longitudinal studies met our inclusion criteria (AD; n = 32). We observed a strong negative correlation r_s = - 0.526 (CI: -0.748 - -0.197, Z = -2.979, P = 0.003) between CSF Aβ oligomers level and severity of AD dementia. Although, our analysis resulted in a statistically significant association between these two variables, with only to two studies and very small sample sizes, the analysis is inconclusive. In addition, one study from the above

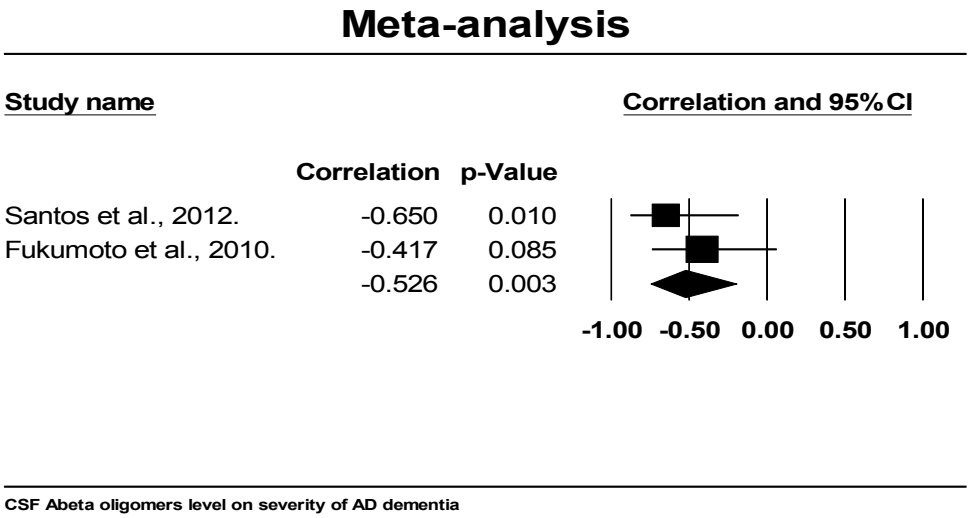


Figure 3.7 Forest plot of the overall correlation coefficient for CSF Aβ oligomers level on severity of AD dementia.

Analysis (**Figure 3.7**) shows a statistical non-significant effect because the CI is crossing the zero-effect line (Fukumoto et al., 2010).Therefore, more studies are necessary to replicate this effect. We did not assess the publication bias as there were only two studies to assess.

3.6.5 Effect of CSF alpha-1-antichymotrypsin levels (ACT) levels on AD dementia

To examine the effect of CSF ACT levels in cognition of AD dementia, only two studies met our inclusion criteria (AD; n = 44). We did not find a significant difference by averaging effect size r_s = - 0.290 (CI: -0.549 - 0.019; Z = -1.842; P = 0.06) (**Figure 3.8**). Therefore, more studies are required to examine the effect of CSF ACT levels on AD severity. We did not assess the publication bias for this analysis because there were only two studies in this analysis.

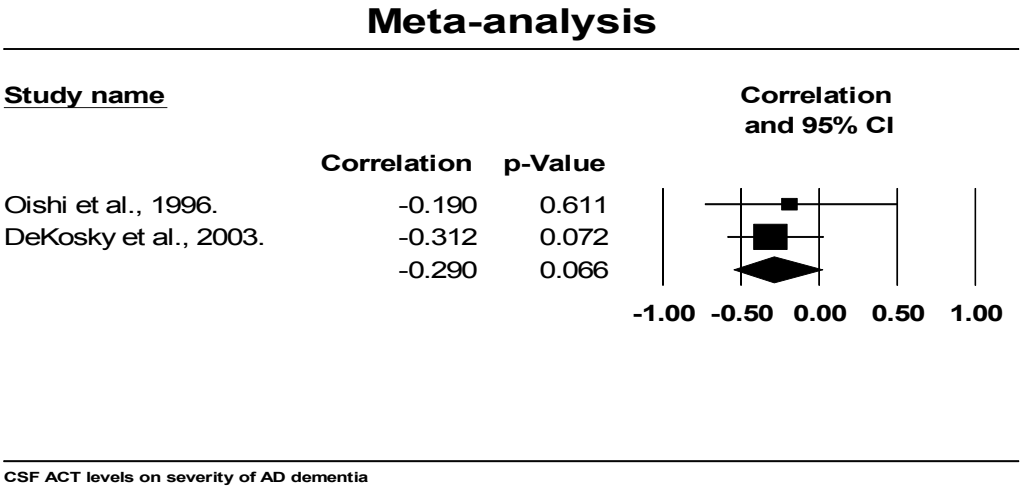


Figure 3.8 Forest plot of the overall correlation coefficient for CSF ACT levels on severity of AD dementia.

3.6.6 Effect of CSF pyruvate levels on severity of AD dementia

To assess the average effect size of CSF pyruvate levels on severity of AD, we again had only two studies (Parnetti et al., 2000, 1995) that met our criteria (AD; n = 71). We found a strong

significant negative correlation (r_s) = -0.661 (CI: -0.898 - -0.129; Z = -2.342; P =0.019) (**Figure 3.9**) between these two variables. However, both the studies were published by the same group, and in order to confirm this strong negative correlation between CSF pyruvate levels and severity of AD dementia, its replication by other groups will be necessary. Publication bias was not assessed for this group because of two studies.

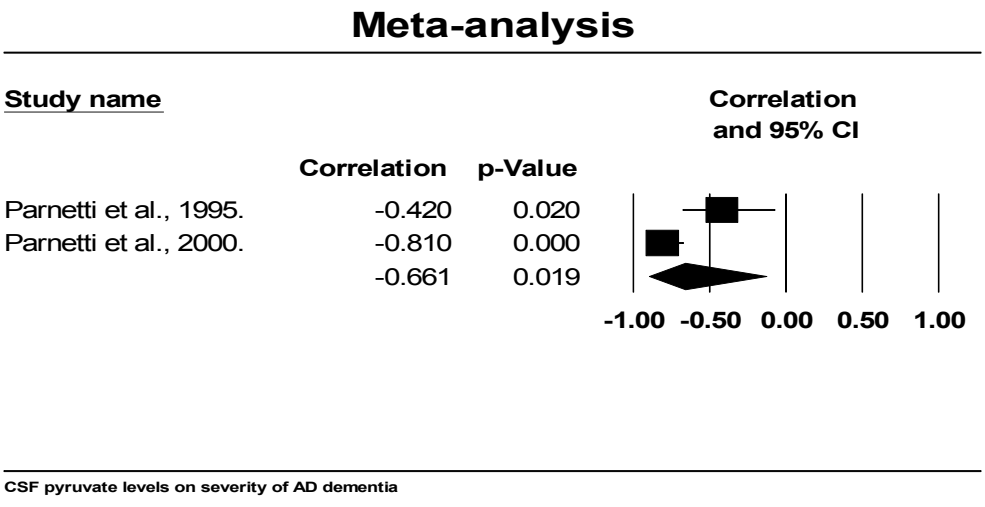


Figure 3.9 Forest plot of the overall correlation coefficient for the CSF pyruvate levels on severity of AD dementia.

3.6.7 Effect of CSF Insulin levels on severity of AD dementia

To examine the effect of CSF insulin levels on severity of AD dementia, again, only two studies met our inclusion criteria (AD; n = 52). We found a non-significant average effect of r_s = 0.215 (CI: -0.480 – 0.745; Z = 0.578; P = 0.563). One study (Craft et al., 1998) reported a strong positive correlation (r_s = 0.537; P = 0.005) between CSF insulin levels and severity AD, while other one (Molina et al., 2002) suggests no significant relationship (see **Figure 3.10**). So, the

overall effect is statistically not significant, and hence, more evidence is required to measure the effect of CSF insulin levels on severity of AD dementia.

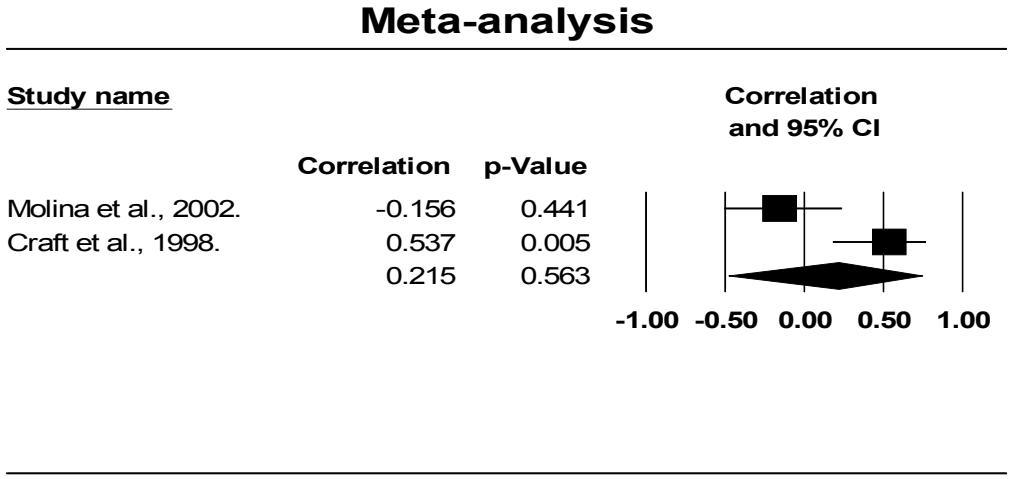


Figure 3.10 Forest plot of the overall correlation coefficient for the CSF insulin levels on severity of AD dementia.

3.6.8 Effect of CSF norepinephrine concentrations on severity of AD dementia

For this category of analysis, we estimated the combined effect size of CSF norepinephrine concentrations on severity of AD. Ultimately, only two studies met our study selection criteria (AD; n = 84).

We found a significant medium average effect size r_s = - 0.450 (CI: -0.609 - -0.257; Z = -4.281, P < 0.001), suggesting a medium negative correlation between CSF norepinephrine levels and severity of AD dementia (**Figure 3.11**). Although, the above analysis shows a significant negative correlation between these two variables, it requires more evidence because of only two studies.

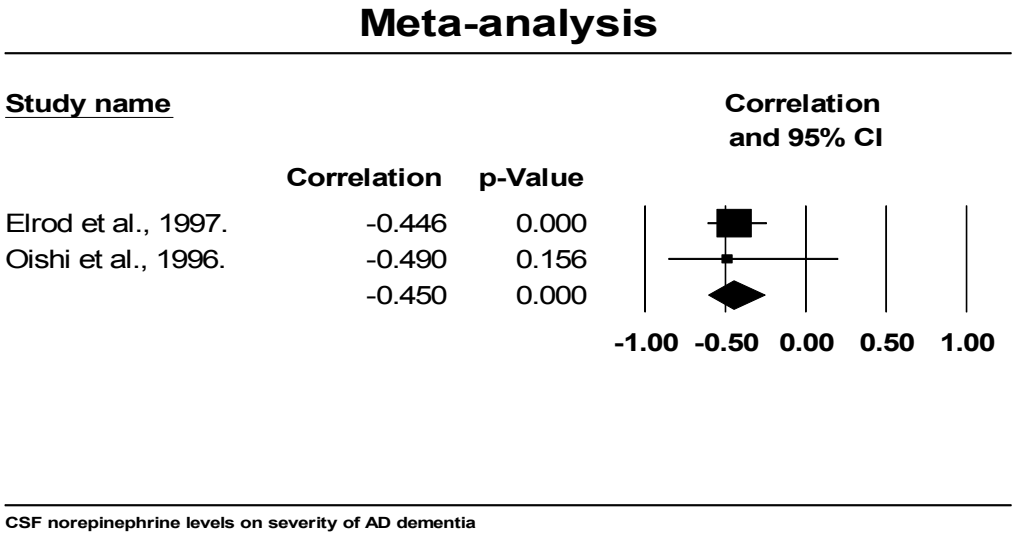


Figure 3.11 Forest plot of the overall correlation coefficient for the CSF norepinephrine levels on severity of AD dementia.

3.6.9 Effect of plasma alpha-1-antichymotrypsin levels (ACT) levels on severity of AD dementia

To examine the average effect of Plasma ACT levels on AD severity, three studies met our inclusion criteria (AD; n = 405). Our analysis found a significant effect size of (r_s) = -0.126 (CI: -0.221- -0.028; Z = -2.521; P = 0.012), suggesting a small effect. From the above forest plot (**Figure 3.12**), two studies (Hinds et al., 1994; Oishi et al., 1996) reported the effect sizes in the form of correlation coefficient, while other one (DeKosky et al., 2003) reported in the form of p-values. Although, the overall effect size shows a negative correlation between plasma ACT levels and severity of AD, but with two included studies (Hinds et al., 1994; Oishi et al., 1996) we did not find any significant difference. Therefore, it requires more evidence to confirm the effect of plasma ACT levels on cognitive functions of AD patients. Publication bias was not found in this analysis (see **Figure 3.13**).

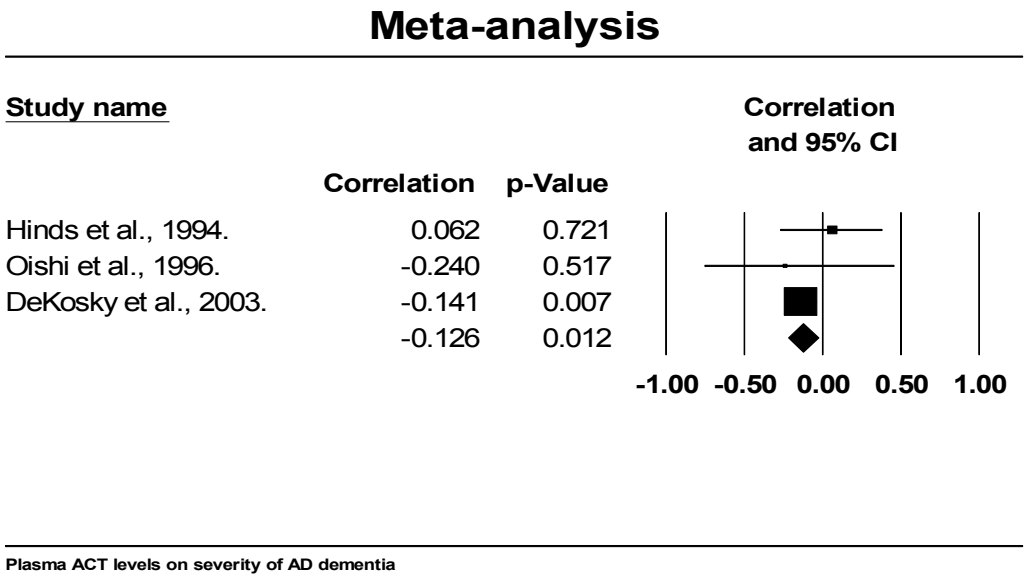


Figure 3.12 Forest plot of the overall correlation coefficient for the Plasma ACT levels on severity of AD dementia.

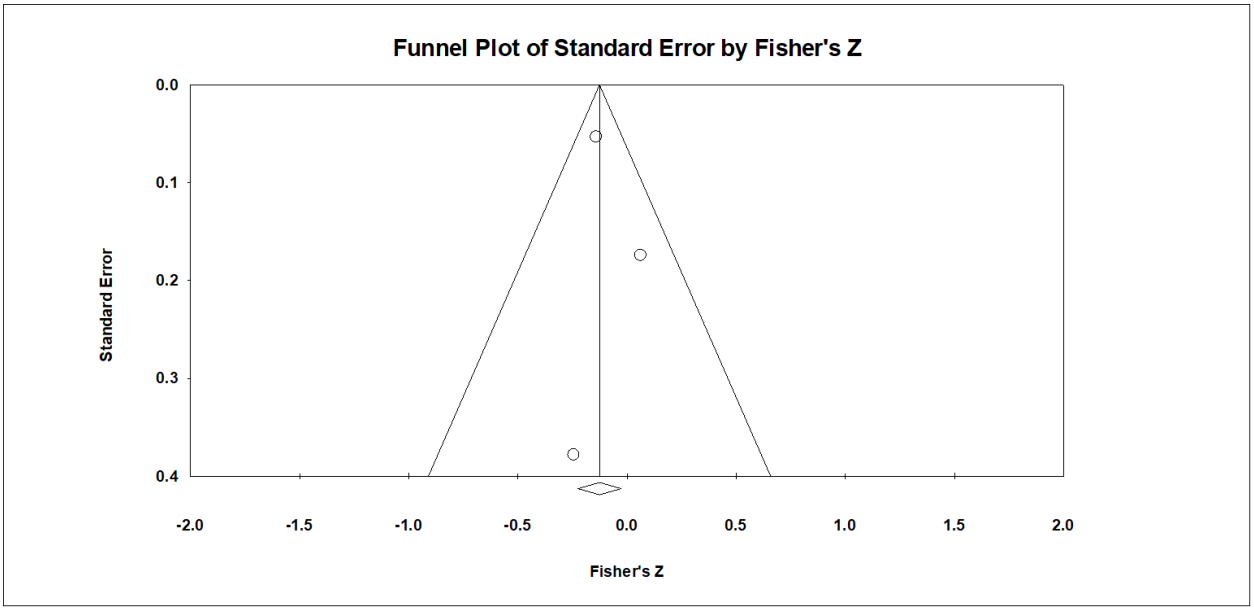


Figure 3.13 Funnel plot depicting publication bias for plasma ACT levels on severity of AD studies.

3.6.10 Effect of plasma Brain-derived neurotrophic factor (BDNF) levels on severity of AD

To test the effect of plasma BDNF levels, only three studies (AD; n =263) that met our inclusion criteria. We found a non-significant average effect size of (r_s) = 0.231 (CI: -0.135 – 0.542; Z = 1.242; P = 0.214). As it is shown on the above forest plot (**Figure 3.14**), two studies (O'Bryant et al., 2009; Siuda et al., 2017) indicated no relationship of plasma BDNF levels to cognition, while other one (Laske et al., 2006) reporting a large positive correlation between these two variables. It is quite clear from the above analysis, that there is a large variation in effect sizes, and hence it requires more evidence to examine the true effect of plasma BDNF levels on severity of AD patients.

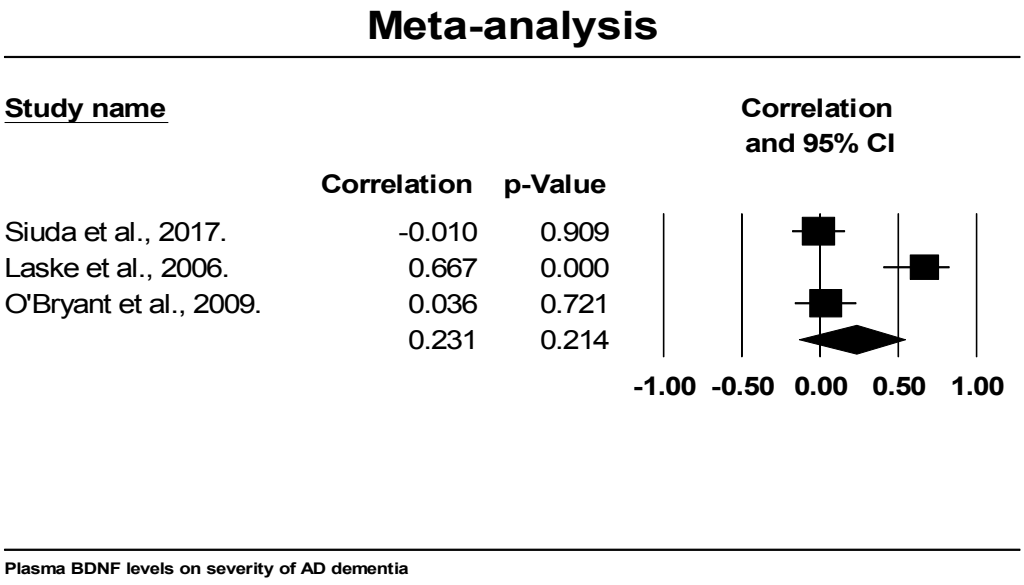


Figure 3.14 Forest plot of the overall correlation coefficient for the Plasma BDNF levels on severity of AD dementia.

In addition, another study (Konukoglu et al., 2012) which met our inclusion criteria, but we did not include in our analysis because it reports two correlation coefficient values between serum BDNF levels and the MMSE scores of two AD patient groups: (i) AD group without treatment

(AD; n = 22; r = 0.422; P < 0.01), and (ii) AD group treated with cholinesterase inhibitors (CEI) (AD+ CEI; n = 32; r = -0.357; P < 0.005). In our study inclusion and exclusion criteria, we did not consider drug treated AD patients as an excluding criterion. This is the first study (Konukoglu et al., 2012), we have come across, which reports a strong effect of CEI on cognitive functions of AD patients.

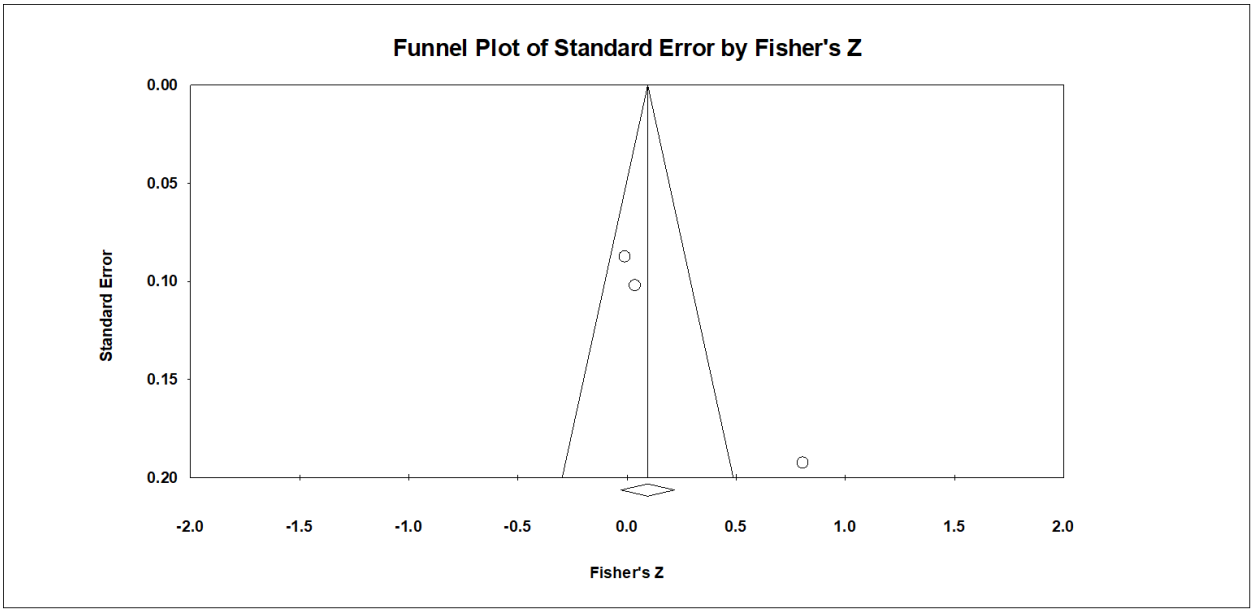


Figure 3.15 Funnel plot depicting publication bias for plasma BDNF studies.

In addition, it is quite evident in the literature that none of the drugs were proved to be effective for AD patients (Anderson et al., 2017; Cummings et al., 2017). Therefore, we excluded this study from our analysis (Konukoglu et al., 2012).

The funnel plot (**Figure 3.15**) indicates a variation in study findings.

3.6.11 Effect of abnormal platelet membrane fluidity on AD severity

To examine the effect of 1,6-Diphenyl-1,3,5-hexatriene (DPH; as a measure of abnormal platelet membrane fluidity) on severity of AD, two studies met our study inclusion criteria (AD; n = 75)

(Zubenko et al., 1987a, 1987b).We found significant combined effect size of (r_s) = -0.661 (CI: -0.774 - -0.507; Z = -6.602; P< 0.001), suggesting a strong negative correlation between abnormal platelet membrane fluidity and cognitive functions of AD patients (see F**igure 3.16**). Such effects need to be replicated by other groups because both the studies were published by the same group. Hence, more evidence from other groups is necessary to confirm this effect.

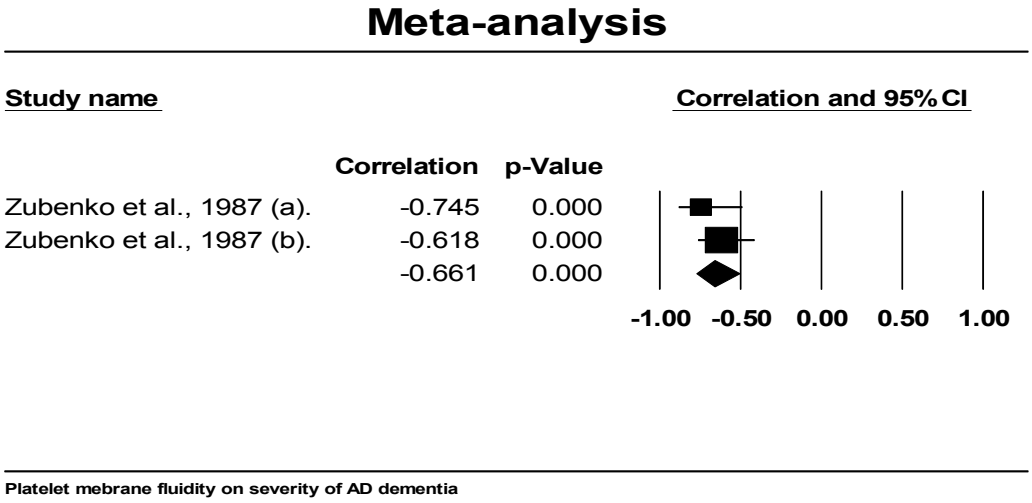


Figure 3.16 Forest plot of the overall correlation coefficient for the Platelet membrane fluidity on severity of AD dementia.

3.6.12 Effect of serum Interleukin-18 (IL-18) levels on severity of AD dementia

We examined the overall effect of serum IL-18 levels on severity of AD dementia. Two studies met our inclusion criteria (AD; n = 83). We found a significant overall effect size of (r_s) = -0.380 (CI: -0.553 - -0.174; Z = -3.506; P < 0.001), suggesting a medium negative correlation with severity of AD (see **Figure 3.17**). Because of only two studies with a relatively small group of AD patients, it is difficult to estimate the true combined effect size for these two parameters. Hence, more studies are required to examine the true effect of serum IL-18 on severity of AD dementia.

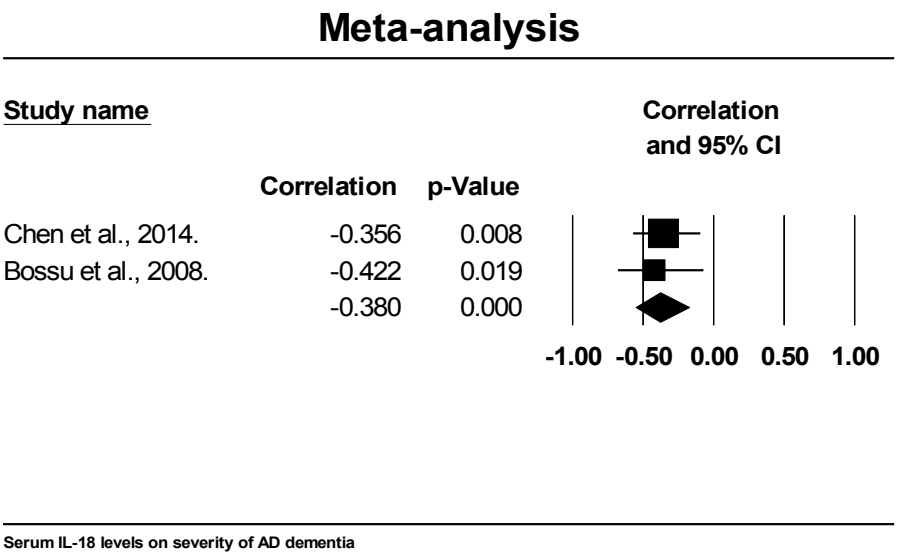


Figure 3.17 Forest plot of the overall correlation coefficient for the serum IL-18 levels on severity of AD dementia.

Table 3.3: Characteristics of single arm studies

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Nitsch et al., 1995)	AD = 19 HC = 10	CSF Aβ	BDS	*r = -0.666 for CSF Aβ
(Costa et al., 2011)	AD = 18 HC = 15	CSF galanin and α-MSH	MMSE	**r_s = 0.53 for CSF total and complexed IgG galanin autoabs. **r_s = 0.5 for CSF levels of free IgG α-MSH autoAbs
(Comi et al., 2010)	AD = 67 HC = 69	CSF Osteopontin	MMSE	**r_s = 0.58 for CSF Osteopontin.
(Arlt et al., 2008)	AD =80 HC = 80	CSF ADMA Plasma triglycerides	MMSE	**r_s = 0.26 for CSF ADMA. **r_s = -0. 28 for Plasma triglycerides.
(Lavados et al., 2008)	AD =13 HC = 12	Redox-active CSF iron	CDR-TBS	R^2 = 0.7839 (negative) for Redox-active CSF iro

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Peskind et al., 2001)	AD = 68 HC = 28	CSF S100B	MMSE	*r = 0.322 for CSF S100B.
(Minthon et al., 1997)	AD = 34 HC = 40	CSF Somatostatin and Neuropeptide Y	MMSE	**r_s = -0.42 for CSF somatostatin.
(L Parnetti et al., 1995)	AD = 31 HC = 11	CSF and Serum NSE	MMSE	R^2 = 0.36 (negative) for CSF NSE
(Pomara et al., 1989)	AD = 15 HC =10	CSF CRF-LI	GNI	*r = 0.62 for CSF CRF.
(Xue et al., 2012)	AD = 56 HC = 20	Plasma endothelial microparticles	MMSE	**r_s = -0.603 for CD31+ / CD42- counts. **r_s = -0.582 for CD62e+ / CD42- counts. **r_s = -0.340 for CD31+ / CD42+ counts.
(Desideri et al., 2008)	AD = 120 HC = 40	Plasma soluble CD 40 ligand	MMSE	**r_s = -0.574 for CD 40 levels.

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Scali et al., 2002)	AD = 40 HC = 36	Neutrophils CD11b and fibroblasts PGE 2.	ADL	**r_s = 0.354 for CD 11b basal values.
(Nilsson and Gustafson, 2004)	AD =85 HC = 51	Plasma homocysteine	Berger scale	**r_s = 0.42 for plasma homocysteine .
(Velayudhan et al., 2012)	AD = 270 HC = 50	Plasma transthyretin levels. Machine learning study	MMSE	R^2 = 0.2 (positive) for transthyretin.
(Muck-Seler et al., 2009)	AD = 74 HC = 49	Platelet serotonin level and MAO-B activity.	MMSE	**r_s = 0.299 for serotonin. **r_s = 0.327 for MAO-B activity.
(Laske et al., 2008)	AD = 30 HC = 20	Plasma soluble Glycoprotein VI and β-thromboglobulin.	MMSE	K_T = 0.271 for Glycoprotein VI. K_T = 0.214 for β-thromboglobulin.
(Merched et al., 2000)	AD = 56 HC = 59	Serum Apolipoprotein AI (Apo AI)	MMSE	R = 0.50 for serum Apo AI levels.

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Konukoglu et al., 2012)	AD = 22 AD + CEI group = 32 HC = 20	Serum BDNF	MMSE	**r_s = 0.422 for BDNF levels of AD group. **r_s = -0.357 for BDNF levels of AD + CEI group.
(Hye et al., 2014)	AD = 476 HC = 452	Plasma proteins : ApoE, CFH, NCAM, Aβ 40, A1AcidG, Clusterin. Machine learning study	MMSE	*r = -0.15 for ApoE. *r = -0.104 for CFH. *r = -0.114 for NCAM. *r = -0.161 for Aβ 40. *r = -0.135 for A1AcidG. *r = -0.135 for clusterin.
(O'Bryant et al., 2013)	AD = 284 HC = 557	Serum C-reactive protein.	MMSE	β = -1.26 for C-reactive protein.
(Song et al., 2015)	AD = 121 HC = 43	Serum haptoglobin	MMSE	**r_s = -0.301 for haptoglobin levels.
(Murialdo et al., 2000)	AD = 25 HC = 12	Serum Insulin like growth factor-1 (IGF-1)	MMSE	K_T = 0.287 for IGF-1 levels.

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Kálmán et al., 1997)	AD= 41 HC = 24	Serum Interleukin-6 (IL-6) levels	MMSE	**r_s = 0.48 for IL-6 levels.
(Chao et al., 1994)	AD = 19 HC = 22	Serum TGF-β levels	GDS	*r = 0.45 for TGF-β levels.
(Hatanaka et al., 2015)	AD = 72 HC = 53	Plasma dROM levels	MMSE	**r_s = -0.332 for dROM levels.
(Galbusera et al., 2004)	AD = 52 HC = 15	Plasma lipid peroxidation measured by TBARS assay.	MMSE	R^2 = 0.21 (positive) for plasma TBARC levels.
(Huang et al., 2015)	AD = 110 HC = 50	Plasma VCAM-1, ICAM-1 and E-selectin levels	CDR sum of box scores	*r = 0.258 for VCAM-1 levels. *r = -0.001 for ICAM-1 levels. *r = 0.070 for E-selectin levels.
(Choi et al., 2011)	AD = 61 HC = 35	Plasma chitinase 3-like 1 protein (CHI3L1) levels	MMSE	**r_s = 0.225 for CHI3L1 levels.
(Smith et al., 2011)	AD = 34 HC = 34	Plasma Feutin-A and TNF-α levels	MMSE	**r_s = 0.504 for Feutin-A levels.

				**r_s = -0.363 for TNF-α levels.
Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Kim et al., 2008)	AD = 51 HC = 57	Plasma soluble fractalkine levels	MMSE	*r = 0.347 for fractalkine levels.
(Wang et al., 2008)	AD = 36 HC = 10	Plasma β-carotene, leutin, RBC DHA, LDL-cholestrol levels.	MMSE	**r_s = 0.43 for leutin levels. **r_s = 0.37 for β-carotene levels. **r_s = 0.34 for RBC DHA levels. **r_s = -0.38 for LDL-cholestrol levels.
(Goodenowe et al., 2007)	AD = 256 HC = 68	Serum Ethanolamine plasmalogen level	ADAS-cog	R^2 = 0.99 for Ethanolamine plasmalogen levels.
(Zoia et al., 2005)	AD = 10 HC = 10	Fibroblast cell culture: EAAT 1 expression, EAAT 1 mRNA	MMSE	R^2 = 0.4881 for EAAT1 expression. R^2 = 0.6904 (negative) for EAAT1

				mRNA.
Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Pratico et al., 2000)	AD = 14 HC = 10	CSF 8,12-iso-iPF2alpha-VI levels	MMSE	R^2 = 0.15 (negative) for 8,12-iso-iPF2alpha-VI levels.
(Kokkonen et al., 2017)	AD = 115 HC = 40	Serum Bullous Pemphigoid 180 (BP180)	MMSE	**r_s = -0.287 for BP180 levels.
(Zhuang et al., 2016)	AD = 78 HC = 39	Serum ACE activity	MMSE	**r_s = -0.29 for ACE activity.
(Bulati et al., 2015)	AD = 35 HC = 15	Cell culture: B cell ligands	MMSE	R^2 = 0.536 for CD19+ absolute number.
(Schmidt et al., 2013)	AD = 33 HC = 33	CSF Melanin-concentrating hormone (MCH) levels	MMSE	*r = -0.362 for MCH levels.
(Valenti et al., 2013)	AD = 25 HC = 22	Blood Glutaminyl Cyclase levels	MMSE	**r_s = -0.607 for Glutaminyl Cyclase mRNA levels.

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Öztürk et al., 2013)	AD = 197 HC = 133	Red cell distribution width (RDW) percentage.	MMSE	*r = -0.453 for RDW percentage.
(Khalil et al., 2012)	AD = 39 HC = 20	Serum and HDL mediated cholestrol efflux percentage.	MMSE	R^2 = 0.17 (negative) for serum mediated cholestrol efflux. R^2 = 0.11 (negative) for HDL-mediated cholestol efflux.
(Armentero et al., 2011)	AD = 20 HC = 20	Peripheral protein kinase B expression	MMSE	*r = -0.584 for protein kinase B expression.
(Chaves et al., 2010)	AD = 54 HC = 66	Serum S100B and NSE levels	MMSE	**r_s = -0.35 for S100B levels. **r_s = -0.48 for NSE levels.
(Hogervosrt and Smith, 2002)	AD = 66 HC = 62	Serum Folate and Estradiol levels	MMSE	B = -0.92 for serum folate levels.

Study first author's name & year of publication.	Sample size (n) of AD & HC groups only	Investigated metabolites recorded for our analysis only & study design	Scales used for assessing dementia severity in AD patients	Strength of relationship between CSF/blood metabolite levels and severity of dementia in AD patients only.
(Leblhuber et al., 1999)	AD = 24 HC = 14	Serum neopterin levels	MMSE	**r_s = -0.435 for neopterin levels.
(Fischer et al., 1997)	AD = 41 HC = 19	Serum transferrin and ferritin levels	MMSE	**r_s = 0.411 for transferrin levels. **r_s = -0.420 for ferritin levels.
(Zhu et al., 2018)	AD =51 HC = 51	Serum haptoglobin	CDR	**r_s = 0.354 for serum haptoglobin levels.
(Dysken et al., 1992)	AD = 55 HC = 41	Peripheral lymphocyte counts	MMSE	*r = 0.19 for lymphocyte counts.

Table legends: Aβ = Amyloid beta, AutoAbs = autoantibodies, ApoE = Apolipoprotein E, ADMA = Asymmetrical dimethylarginine, ADL = Activities of Daily Living, BDS = Blessed dementia scale, BDNF = Brain-derived neurotrophic factor, CD = cluster of differentiation, CDR = Clinical Dementia Rating, CFH = Compliment factor H, CDR-TBS = CDR- Total box score, CRF-LI = Corticotropin-releasing factor-like immunoreactivity, CEI = cholinesterase inhibitors, dROM = diacron reactive oxygen metabolite, GNI = global neuropsychological impairment, GDS = Global Deterioration Scale, MSH = melanocyte-stimulating hormone, MAO-B = monoamine oxidase type B, NSE = neuron-specific enolase, NCAM =Neural Cell adhesion

molecule, PGE 2 = prostaglandin-E2, TGF-β = Transforming growth factor β, TBARS = Thiobarbitururic acid reactive substance, *r = Pearson's correlation coefficient, **r_s = Spearman's correlation coefficient, K_T = Kendell's tau, R^2 = Coefficient of determination, R = Strength of relationship between metabolite levels and severity of AD derived from the linear regression analysis, β = Beta coefficient from linear regression analysis. B value = strength of association between two variables derived from multiple regression, P = P-value, VCAM-1 = vascular cell adhesion molecule-1, ICAM-1 = Intracellular cell adhesion molecule-1, TNF-α = Tumor necrosis factor-α, RBC = Red blood cell, LDL = Low density lipoprotein, DHA= docosahexaenoic acid, ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale, EAAT = Excitatory amino acid transporter, mRNA = messenger Ribonucleic acid, ACE = Angiotensin converting enzyme.

3.7 Discussion

To the best of our knowledge, our analysis provides the first quantitative examination of literature describing the relationships of both CSF and blood biomarkers and cognitive functions in AD dementia. Across 26 included studies comprising of total 1504 AD patients, we did not find any significant effect of the core biomarkers (Lai et al., 2017; Olsson et al., 2016) on the severity of AD. However, some of the CSF biomarkers such as Aβ oligomers (AD = 32; average r_s = -0.526; P =0.003), norepinephrine (AD = 84; average r_s = -0.450; P = 0.001) and pyruvate (AD = 71; average r_s = -0.661; P = 0.019) indicate a strong inverse correlation with severity of AD. Similarly, some blood-based biomarkers such as plasma ACT (AD = 405; overall r_s = -0.126; P = 0.012), serum IL-18 (AD = 83; r_s = -0.380; P = 0.001), and abnormal platelet membrane fluidity (Zubenko et al., 1987a) (AD = 75; r_s = -0.661; P = 0.001) demonstrate a

significant predictive relationship with the severity of AD. Although, these analyses demonstrate a significant predictive relationship of AD dementia severity, based on the small numbers of studies with relatively small patient sample size that met our study criteria, it is not clear that these findings are generalizable to the broader AD patient population and further research is needed.

Previous meta-analyses on differential diagnosis of AD from normal ageing show significant group level differences in both CSF and peripheral biomarkers (Kokkinou et al., 2014; Lai et al., 2017; Olsson et al., 2016; Zhang et al., 2014). Such biomarkers may prove useful for distinguishing AD patients from HC. Nevertheless, our analysis of evidence for these biomarkers with respect to dementia severity indicates that there is insufficient evidence in the literature to make definitive statements. In addition, the failure of all the clinical trials to date, targeted to underlying pathology AD (Anderson et al., 2017; Cummings et al., 2017), indicate a current lack of effective drug therapies for AD dementia. This may be due to excessive damage in to the brain prior to clinical symptom onset (Villemagne et al., 2011), or to our insufficient understanding with respect to diagnosis and disease progression. Although, abnormal aggregation protein clumps define AD as a unique kind of neurodegenerative disorder in the brain (Jack et al., 2018), similar patterns of disease pathology and presentation of clinical symptoms in some other forms of dementia and normal ageing are also evident in the literature (Fjell et al., 2014; Raz et al., 2016). Finally, some of our investigated biomarkers in both CSF and blood indicate a significant inverse correlation with the severity of AD. Again, future studies are needed to clarify the relevance of these findings.

Our meta-analysis has several limitations: (i) we may have missed some published studies analyzing the strength association of between biofluid markers and dementia severity, (ii) we

only included studies published in English (iii) we included two studies from the ADNI data set, which measured raw data from same samples as other studies, (iv) we did not assess any grey literature. It is interesting to note in the context of this form of analysis, with an appropriate reliance of the quality of study design and reported data, that our study criteria only allowed inclusion of 20% of identified studies for our analysis: because of inadequate statistical reporting, existence of only single studies and other methodological problems.

3.8 Conclusions

This meta-analysis, which was conducted by quantitative examination of literature from July 1984 to September 2018, combined effect sizes across 26 studies that measured the strength of relationship between biofluid markers on the severity of AD dementia, we found there is insufficient evidence in the literature for predicting dementia severity from biofluid biomarker concentrations. However, some of our results indicate a strong correlation between some biomarker levels and cognitive functions in AD patients. These effects need to be confirmed by additional future research.

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Chapter 4: Biofluid metabolites concentration and their relationship with the age at onset of Alzheimer's disease dementia: A systematic review

4.1 Introduction

Among different kinds of dementia, Alzheimer's disease (AD) is the most common, and comprises around 72% of all dementia cases (Qiu et al., 2009). Abnormal protein aggregations in the brain define AD as a unique neurodegenerative disorder among different forms of dementia (Jack et al., 2018). These protein clumps are extracellular deposition of amyloid beta (Aβ) in the form of senile plaques, and intracellular deposition neurofibrillary tangles (NFT), which is made up of hyperphosphorylated tau proteins (Armstrong, 2009). AD precedes through an intermediate stage called mild cognitive impairment (MCI) (Petersen, 2016), which is the transition stage between normal healthy controls and full dementia. Interestingly, all the MCI subjects do not progress to dementia or AD even after 10 years of follow-up (Mitchell and Shiri-Feshki, 2009). Therefore, now the MCI, has gained much attention in the research domain to better understand the AD mechanism and progression.

The majority of AD cases appears sporadically in the population, with age of onset of 65 years or older known as late-onset of AD (LOAD), typically sporadic cases are seen in the late 70’ through the 80’s (Kukull et al., 2002) and hence, increasing age is generally considered as the greatest risk factor for dementia (Fiest et al., 2016; Shea et al., 2016). The cut-off point of 65 years old is however, a sociological partition with regard to the employment and retirement age, which has no particular biological significance on this cut-off point (Rossor et al., 2010). Similarly, those AD cases which occur before the age of 65 years are generally considered as the early-onset of AD (EOAD) (Wu et al., 2012). The rate of EOAD is around 6.1% (Zhu et al., 2015), and these EOAD cases are mainly because of the genetic mutation of three genes such as

presenilin 1 (PSEN1), presenilin (PSEN2), and amyloid precursor protein (APP) (Shea et al., 2016). Recent systematic reviews and meta-analyses suggest that the patients with mutation of PSEN 1 gene have earliest age of onset at 43.3 ± 8.6 years, while patients with PSEN 2 and APP gene mutations have later age of onset with longer disease duration (Ryman et al., 2014; Shea et al., 2016). In addition, another gene named apoliporotein E(APoE) gene on chromosome 19 is associated with LOAD of both the familial and sporadic cases of AD (Reitz and Mayeux, 2014; Tanzi, 2012).There are three allelic variants of the APoE gene (ApoE ε2, APoE ε3, and ApoE ε4) and people with ApoE ε4 are at major genetic risk for LOAD, whereas APoE ε2 is associated with longevity and a lower risk of AD (Suri et al., 2013). However, the most recent meta-analysis on the effect of APOE ε3/ ε4 genotype and gender on the risk of AD suggests that both the men and women are at equal odds (Bland and Altman, 2000) of developing AD, but interestingly, women are at increased risk for early ages (Neu et al., 2017).

To date, there are many systematic reviews and meta-analyses on the effect of genotypes, gender and environmental factors for risk of developing AD in both EOAD and LOAD cases (see: (Farrer et al., 1997; Killin et al., 2016; Neu et al., 2017; Ryman et al., 2014; Shea et al., 2016)). However, there is a current lack of systematic review and meta-analysis on the relationship of biofluid metabolite levels and age at onset of AD dementia.

As biofluid metabolites are among important ante-mortem markers AD, we decided to investigate whether there is evidence in the literature for a relationship between age at onset of AD dementia and biofluid metabolite concentrations. Age at onset of AD dementia is defined as the early or late onset of AD dementia (i.e. only sporadic AD cases) without genetic mutation of familial AD cases (Rossor et al., 2010; Tanzi, 2012). Different types of biofluid biomarkers including cerebrospinal fluid (CSF), blood, serum, plasma, urine, and saliva were included in our

analysis. Only clinical studies analyzing the relationship between the biofluid metabolites level of living AD patients and age at onset of AD were included. The antemortem diagnosis of AD patients is based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA criteria for probable AD or possible AD (McKhann et al., 1984).

4.2 Methods

We conducted this systematic review and meta-analysis according the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher et al., 2009). We searched the PubMed database (https://www.ncbi.nlm.nih.gov/pubmed/) from July 1, 1984 (the first diagnostic criteria of AD were reported by McKhann et al., (1984)) to September 5, 2018 for the maximum number of relevant studies (McKhann et al., 1984; Olsson et al., 2016). We used the search words ("age of onset" OR "early onset" OR "late onset" OR "correlation") AND ("biomarker" OR "CSF" OR "cerebrospinal fluid" OR "blood" OR "serum" OR "urine" OR "protein" OR "amyloid beta" OR "tau") AND ("accuracy" OR "sensitivity" OR "specificity" OR "ROC" OR "receiver operator characteristic") AND ("Alzheimer's" OR "mild cognitive impairment" OR "normal ageing"). We restricted our search to the human species peer reviewed studies, which are written in English language only. A total of 357 studies were recorded, and out of that, only 15 studies were selected through the abstract screening. In addition to that, we had also included 17 articles from references list searching. After that, full text of all the 32 articles was assessed independently by the two reviewers (M.M & A.G) for the eligibility of quantitative synthesis. Any disagreements between the two reviewers were resolved by discussion with a third reviewer, until the final agreement was reached. Finally, the studies were selected if they met the following inclusion and exclusion criteria.

4.2.1 Inclusion Criteria

- Original peer-reviewed studies published between July 1, 1984 to September 5, 2018.
- Only human species English language studies were included.
- Studies analyzing the relationship between the biofluid metabolites concentration with the age at onset of AD dementia.
- Use of clinical diagnosis criteria for AD, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 1984).
- AD patients' group must be compared with a healthy control group (HC).

4.2.2 Exclusion Criteria

- All animal studies, meta-analyses, review articles, letters, comments, case reports, and unpublished articles.
- Studies did not report the correlation coefficient value as an index of effect size measure of the association between the biofluid metabolites concentration and age at onset of AD dementia or the sample size of each subject groups or fewer than ten individuals or report data in a format which can't be convertible.
- Studies only presenting post-mortem or autopsy or neuroimaging data.
- When a healthy control group (HC) comprises participants with other neurological diseases or psychiatric disorders.

4.3 Results and discussion

The PubMed data base search retrieved 357 records, and the abstracts of all the records were screened for eligibility. Three hundred and forty-two articles were excluded because they were studies on animals or did not analyze the relationship between biofluid metabolites concentration and age at onset of AD dementia, presented only neuroimaging or post-mortem data, were reviews or meta-analyses.

In addition, 17 studies were included from our previous systematic review and meta-analysis on biofluid metabolite levels and severity of AD dementia. Consequently, the text of 32 studies was assessed fully for inclusion eligibility for meta-analysis with our study inclusion and exclusion criteria as mentioned above. Of these, 6 studies had control groups, which comprised other psychiatric or neurological disorders, 20 studies did not perform the relevant analysis or had statistical reporting errors. Finally, only 6 studies (with total 128 AD patients and 111 healthy controls) met our inclusion criteria for quantitative synthesis of data. Out of seven studies, 3 studies measured the relationship between CSF biomarker levels and age at onset of AD dementia, 3 studies performed such analysis using possible blood biomarkers, and one study assessed the same on both CSF and blood metabolites (See details in **Table 4.1**). Unfortunately, all these studies differed from each other in terms of category of metabolites and body fluids. Valentine et al. (2010) has suggested that to conduct a meta-analysis for a logical conclusion, we need at least two studies in the same category of biomarkers (Valentine et al., 2010). Hence, we were not able to perform meta-analysis to get an overall effect size (Rosenthal and DiMatteo, 2001) because of insufficient data in each category of biomarkers.

A myriad of clinical studies has been published on potential body fluid biomarker levels in AD, MCI, and healthy controls (HC) subjects to examine possible differential diagnosis (see recent

meta-analyses: Lai et al., 2017; Olsson et al., 2016). Unfortunately, very few studies have focussed on the relationship between age at onset of AD with body fluid biomarkers. During our systematic review of literature from July 1, 1984 to March 15, 2018, we found the first study, which was published by Alom and colleagues in 1990. That study was conducted on 20 AD patients and 19 HC subjects to investigate the relationship of CSF neuropeptide Y levels with age at onset of AD and degree of cognitive impairment (Alom et al., 1990). The authors reported that AD patients had lower mean concentrations of CSF neuropeptide Y levels than the HC group. However, they did not find any significant correlation (Pearson $r = 0.22$; $P > 0.05$) between levels and age at onset in AD patients (Alom et al., 1990). Similarly, a CSF insulin study on AD and HC subjects, found that there are no significant differences in overall insulin levels between these two groups (Molina et al., 2002). The authors performed correlational analysis between CSF insulin levels and age at onset of AD patients, and found no significant correlation (Pearson $r = 0.01$) between these two variables (Molina et al., 2002). However, another study (with sample size of AD = 37, HC = 32) from the same group reported significant negative correlations between CSF taurine levels and age at onset of AD (Pearson $r = -0.34$; $P< 0.05$), while CSF histidine levels had a medium positive correlation (Pearson $r =0.44$; $P< 0.05$) with the same variable of age at onset of AD (Molina et al., 1998). The strength of correlation for small ($r = 0.10$), medium ($r = 0.30$) and large ($r = 0.50$) is based on Cohen's criteria (Cohen, 1988). Likewise, another study (sample sizes AD = 16, HC = 13) claimed that reduction of platelet enzyme phospholipase A_2 activity correlates (Spearman $r = 0.43$; $P < 0.10$) with the early onset of illness in AD patients (Gattaz et al., 1996). A medium strength correlation was reported between phospholipase A_2 activity and early onset of illness in AD patients (Cumming and Maillardet,

2006) . The remaining study that our review identified (sample sizes AD =12, HC = 13) claimed that platelet membrane fluidity is correlated (Pearson r

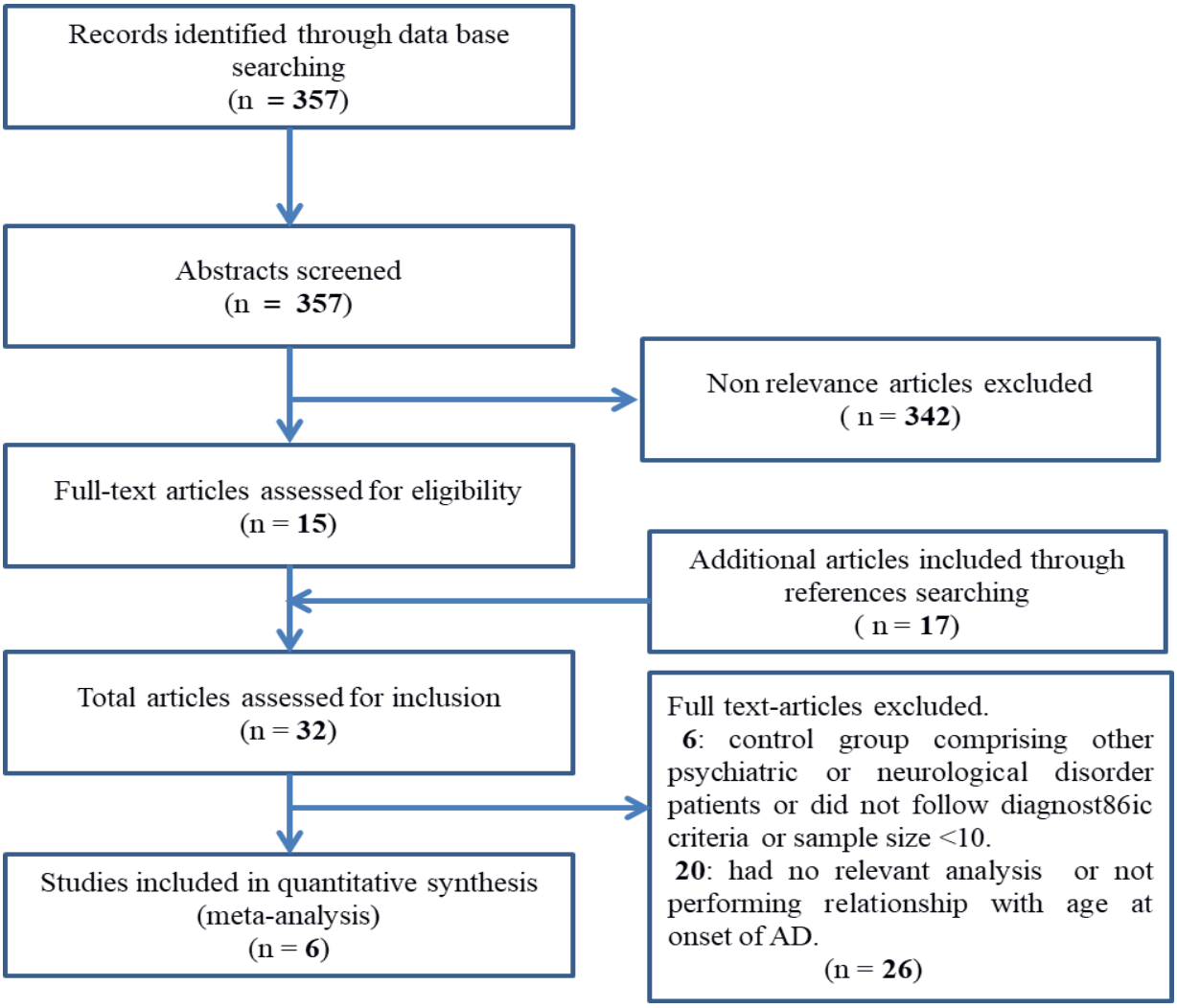
Table 4.1: **Characteristics of age at onset of AD included studies**

Study first author's name and year of publication	Sample size (n) of AD and HC group only	Investigated metabolites	Effect size matrix for prediction coefficient or correlation between age at onset of AD and metabolites level
(O'Brien et al., 1996)	AD = 16 HC = 18	Cortisol response (HPA axis activity)	*r = 0.73 for HPA axis activity (Peak cortisol level)
(Alom et al., 1990)	AD = 20 HC = 19	CSF neuropeptide Y	*r = 0.22 between CSF neuropeptide Y and age at onset.
(Molina et al., 2002)	AD = 27 HC = 16	CSF insulin	*r = 0.01 between CSF insulin levels and age at onset.
(Molina et al., 1998)	AD = 37 HC = 32	CSF taurine, histidine	*r = -0.34 for CSF taurine. *r = 0.44 for CFS histidine.
(Gattaz et al., 1996)	AD = 16 HC = 13	Platelet PLA_2	**r_s = 0.43 for platelet PLA2 activity and EOAD
(Piletz et al., 1991)	AD =12 HC = 13	Platelet membrane fluidity (as measured by low DPH anisotropy)	*r = -0.057 for membrane fluidity and age at onset
	Total AD = 128 Total HC = 135		

Table legends: AD = Alzheimer's disease, CSF = Cerebrospinal fluid, HC = Healthy controls, HPA = hypothalamic-pituitary-adrenal (HPA), IL = Interleukin, *r = Pearson's correlation

coefficient, **r_s = Spearman's correlation. PLA_2 = Phospholipase A2, DPH = 1,6-diphenyl-1,3,5-hexatriene,).

= -0.057; P = 0.026) with age at onset of AD (Piletz et al., 1991). For each of these cases described above, our included studies have very low sample size and are not sufficient evidence to determine accurate effect sizes: these findings must need to be replicated before any significant weight may be placed on the significance of their findings.



Flowchart 4.1 Study selection process.

4.1 Conclusion

Our systematic review of literature indicates clearly that there is a paucity of evidence for estimating the relationship between age at onset of AD dementia and biofluid metabolite levels. Although six studies were identified that attempted to examine the strength of relationship between these variables, it is not possible to calculate the average effect size by meta-analytic methods because of single category studies. For meta-analytic synthesis of evidence in terms of calculating the average effect size, we need to have at least two studies in the same category (Valentine et al., 2010). Due to insufficient evidence in the current state of literature, it is not possible to predict the age at onset of AD dementia of sporadic cases from body fluid biomarkers. More research is required in the context of predicting age at onset of AD dementia from biomarkers. Future investigations into the important question of whether body fluid metabolites correlate with age at onset of AD may provide additional knowledge that will contribute to improved diagnosis and prognosis, particularly in relation to early prediction of AD dementia.

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Chapter 5: A systematic review on neuroimaging biomarkers of Alzheimer's disease: an overview towards early diagnosis, classification and prediction of course of illness

5.1 Introduction

Dementia is a condition characterized by the loss of memory and other cognitive abilities which affects individuals' daily life activities (Rowe & Villemagne, 2013). Among different forms of dementia (Camicioli, 2004; Shaik & Varma, 2012), Alzheimer's disease (AD) accounts up to 50-75% (Fiest et al., 2016; Qiu et al., 2009b; Reitz and Mayeux, 2014), and is considered as a "major killer" in the elderly (Katzman, 2008). AD was first described by Dr. Alois Alzheimer more than a century ago, however, the abnormal protein deposits associated with AD were isolated over the past three decades (Goedert, 2015). According to the World Alzheimer Report 2018, It has been estimated that around 50 million people are lived with dementia in 2017, and this prevalence will exceed 131.5 million in 2050. The worldwide financial burden of dementia was around 818 billion US$ in 2015, and this amount is predicted to exceed 1 trillion US$ by 2018 (Wimo et al., 2017). Although, the exact cause of AD is still unclear, the extracellular accumulation of beta-amyloid (Aβ) and intraneuronal tau proteins in the form of plaques and neurofibrillary tangles (NFT) respectively, defines AD as a distinct type of neurodegenerative disorder that leads to dementia (Armstrong, 2009; Goedert & Spillantini, 2006; Hyman et al., 2012; Jack et al., 2018). AD appears mainly sporadically, and the sporadic form accounts up to 90% or more of incidence, at a later age of onset (Bertram & Tanzi, 2004). Around 5% of AD cases develop through genetic mutation (Cruts & Van Broeckhoven, 1998). AD dementia that appears symptomatically before the age 65 years is generally considered as early age at onset of AD (EOAD) (Shea et al., 2016; X.-C. Zhu et al., 2015), which is mainly caused by the autosomal

dominant mutation of three genes: the amyloid precursor protein (APP) gene on chromosome 21, the presenilin-1(PS1) gene on chromosome 14, and the presenilin-2(PS2) gene on chromosome 1 (Brouwers, Sleegers, & Van, 2008). The late onset of AD (LOAD) typically develops after age of 65, and hence, old age is the greatest risk factor for sporadic cases of AD (Guerreiro & Bras, 2015). In addition, the apolipoprotein E (APoE) gene on chromosome 19 expresses three alleles: APoE Ɛ2, APoE Ɛ3 and APoE Ɛ4. The inheritance of APoE Ɛ4 allele is associated with the late onset of AD in both familial and sporadic cases (Neu et al., 2017) by decreasing mean age at onset from 84 to 68 years (Corder et al., 1993). Furthermore, people with Down's syndrome (DS) are also associated with high risk for early onset of AD because DS is caused by the presence of three copies of chromosome 21 with AAP genes, which plays an important role of Aβ production in AD (Goedert, 2015).

AD progresses through an intermediate stage known as the Mild Cognitive Impairment (MCI), which is characterized by a clinical condition of cognitive and memory impairment without affecting significantly to the individuals' daily life activities (Petersen et al., 2009). MCI is further classified into two subcategories namely amnestic (aMCI) and non-amnestic (nMCI) (Petersen et al., 2014). Individuals' with aMCI show clinically significant memory impairment as noticed by self and their family members of increasing forgetfulness, which does not meet the criteria for diagnosis of dementia or AD (Petersen et al., 2009). Similarly, people with nMCI show subtle impairment in attention, languages, or visuospatial functions, but not impairment of memory, and may further progress to other forms of dementia such as frontotemporal lobar degeneration or dementia with Lewy bodies (Molano et al., 2010; Petersen, 2009). Brain damage in AD is an ongoing process, which may begin 20 or more years before clinical symptoms appear (Jack et al., 2009; Reiman et al., 2012; Villemagne et al., 2013). The main clinical symptomatic

hallmark of AD and some MCI is a deficit of episodic memory (Carlesimo & Oscar-Berman, 1992; Jack et al., 2011). Episodic memory is the ability to encode, retain and retrieve content of autobiographical experiences of a person's daily life, and it is supported both in animals and humans by the medial temporal lobe (MTL) including the hippocampus with other cortical and sub-cortical structures (Bonnici, Chadwick, & Maguire, 2013; Dickerson & Eichenbaum, 2010).

The conventional clinical diagnosis of AD is based on the guidelines of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (McKhann et al., 1984), and it has been revised and modified into separate diagnosis and research criteria based on specific patterns of cognitive and structural or biological changes on AD pathology (Dubois et al., 2010; Jack et al., 2018; Mckhann et al., 2011). In addition, the Alzheimer's Disease Assessment Scale-Cognitive Behaviour section (ADAS-Cog) is considered as the "gold standard" for diagnosis of MCI but sometimes it gives false-positive and false-negative results (Edmonds et al., 2015; Hobart et al., 2013; Posner et al., 2013). For example, a longitudinal study by Edmonds et al., (2016) comprising of 520 individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://adni.loni.usc.edu/), who were originally identified as "cognitively normal" based on ADNI diagnostic criteria (Petersen et al., 2010) identified 37 subjects as the MCI based on the actuarial neuropsychological diagnostic criteria (Bondia et al., 2014). Finally, the authors concluded that the false-negative rate of MCI is 7.1% and the impact of "missed" cases of MCI could affect the clinical practice, research studies, and clinical trials of suspected AD (Edmonds et al., 2016). Currently the absolute diagnosis of AD can only be confirmed at autopsy, or rarely – brain biopsy (Vinters, 2014).

The inaccessibility of living human brain tissue for diagnosis of AD underscores the proposal that in vivo imaging modalities have an advantage for better understanding of this disease's underlying pathological process by serving as a "window in the brain" (Johnson, et al., 2012). In this systematic review, we assessed the utility of multimodal neuroimaging biomarkers for diagnosis and distinguishing AD patients from the normal ageing controls and MCI subjects. We also consider the prediction of the course of illness in AD from MCI.

5.2 Imaging biomarkers in AD brain pathology

A biomarker or biological marker can be defined as a characteristic which is measured and evaluated as an indicator of normal biological processes or pathological processes or to detect the pharmacological responses to a specific therapeutic intervention (Biomarkers Definitions Working Group, 2001). There are five biomarkers have been constructed to be used in clinical trials and in advanced diagnostic criteria. These biomarkers fall into two categories such as the beta amyloid (Aβ) plaque biomarkers and tau-related neurodegeneration biomarkers (Clifford & Holtzman, 2013).Three out of five biomarkers are imaging measurements while the other two are cerebrospinal fluid (CSF) protein analytes. Amyloid beta (Aβ) deposition related biomarkers are (i) decreased concentration of CSF Aβ42 due to progressive deposition in the brain, and (ii) positron emission tomography (PET) for amyloid imaging. However, other the three biomarkers are tau protein related neurodegeneration such as (i) increased level of CSF total tau (t-tau), (ii) hyperphosphorylated tau (p-tau), and (iii) atrophy on structural magnetic resonance imaging (MRI) or hypometabolism of flurodeoxyglucose (FDG) on PET (Clifford & Holtzman, 2013; Jack et al., 2018).In addition, the functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) modalities are being extensively investigated as potential biomarkers in

research domain. The main goal of these biomarkers is to demonstrate the pathological condition of AD by measuring the Aβ plaques and NFT in brain and CSF.

Each of the five biomarkers mentioned above, constructed for use in clinical trials and in advanced diagnostic criteria biomarker types, has a unique pattern of strength and weakness in disease diagnosis and prediction, and sometimes these biomarkers may lead to misdiagnosis. This is probably due to the similar spatiotemporal evolution of AD, healthy ageing and other related dementia (Johnson et al., 2012). For instance, around 20 - 40% of healthy elderly non-demented individuals have similar functional pathology to AD with decline in episodic memory and other cognitive abilities such as mental speed and executive function (Fjell et al., 2014; Jack et al., 2010). Therefore, the classification of normal ageing subjects from the early stages of dementia is quite challenging, and it needs to be understood very clearly for better understanding of pathological process, progression and clinical symptoms underlying AD.

5.3 Receiver operating characteristic (ROC) curve

The goals of AD biomarker research include the pursuit of indicators for ante-mortem diagnosis and early prediction of onset of disease with high accuracy, sensitivity and specificity. To achieve this in the field of neuroimaging, signal detection methodology is being widely employed using parameters derived from receiver operator characteristic (ROC) curves to achieve estimates of these quantities (Zhu, Zeng, & Wang, 2010). The ROC curve displays diagnostic test accuracy expressed in sensitivity (i.e true positive rate) against 1-specificity (i.e false positive rate). This is illustrated by the confusion matrix of figure from Zhu, Zeng, & Wang (2010).

For example, results from a diagnostic test aiming to measure occurrence of a disease could represent a true positive (TP), true negative (TN), false negative (FN) or false positive (FP)

decision. The TP indicates the presence of disease, while the TN indicates absence of the disease (Zhu, Zeng, & Wang, 2010). Similarly, if the diagnostic test result indicates presence of a disease in a person who actually doesn't have the disease that is a FP result. The reciprocal case applies for FN case (Zhu, Zeng, & Wang, 2010). All these confusion matrix quantities are mostly used to describe the SN, SP and accuracy of a diagnostic test [see details Table 5.1, adapted from (Zhu, Zeng, & Wang, 2010)].

Outcome of the diagnostic test	Condition (e.g. Disease) As determined by the Standard of Truth		
	Positive	Negative	Row Total
Positive	TP	FP	TP+FP (Total number of subjects with positive test)
Negative	FN	TN	FN + TN (Total number of subjects with negative test)
Column total	TP+FN (Total number of subjects with given condition)	FP+TN (Total number of subjects without given condition)	N = TP+TN+FP+FN (Total number of subjects in study)

Table 5.1 Confusion matrix. TP = true positive, TN = true negative, FN = false negative, FP = false positive.

SN = TP/TP+FN (Number of true positive assessment)/(Number of all positive assessment).

SP = TN/TN+FP (Number of true negative assessment)/(Number of all negative assessment).

Accuracy = TN+TP/TN+TP+FN+FP (Number of correct assessments)/Number of all assessments).

The ROC area under the curve (AUC) represents the accuracy of a diagnostic test by plotting the SN (i.e true positive rate) in y-coordinate against 1-SP (i.e false positive rate) in x-coordinate (see **Fig 5.1**). The ideal coordinates (0, 1) represent the performance of a diagnostic test that perfectly classifies the presence or absence of a disease condition in a population with 100% sensitivity and 100% specificity. When such classification only achieved 50% SN and 50% SP by the diagnostic test is called random classification. The cut-point in the ROC space (i.e AUC) represents the trade-off between SN and SP for increasing SN of a diagnosis while accompanying with the decreased of SP (Zhu, Zeng, & Wang, 2010).

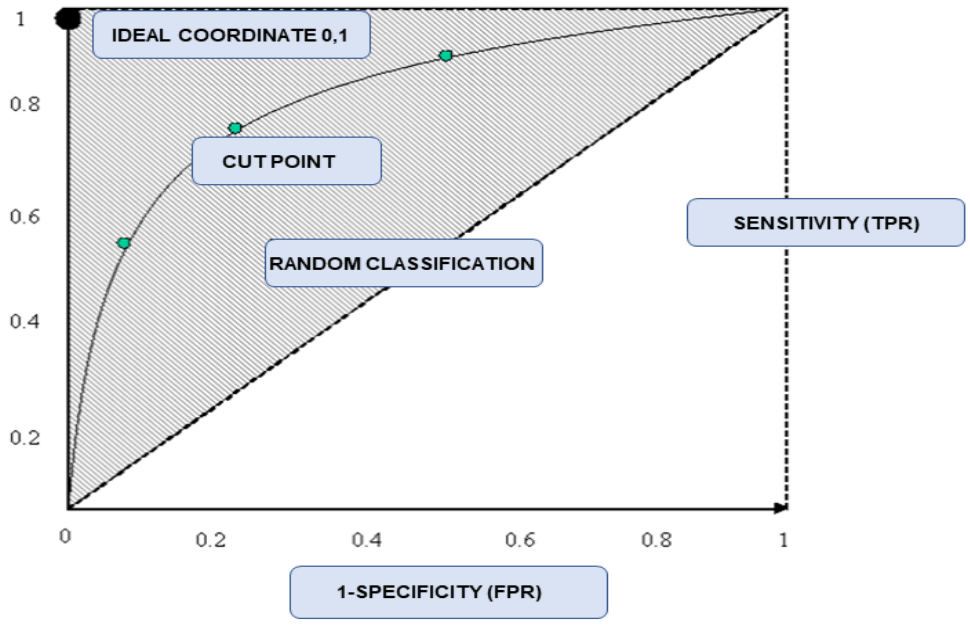

Figure 5.1 Receiver operating characteristic curve. Adapted and modified from (Zhu, Zeng, & Wang, 2010).

5.4 Methodology

For this systematic review, we identified relevant studies in the PubMed data base (https://www.ncbi.nlm.nih.gov/pubmed/). We searched studies from July 01, 1984 to January September 5, 2018 using the key words ("biomarker" OR "machine learning" OR "classifier") AND ("accuracy" OR "sensitivity" OR "specificity" OR "ROC" OR "receiver operator characteristic") AND ("diagnosis" OR "prognosis" OR "prediction") AND ("magnetic resonance imaging" OR MRI OR fMRI OR "functional magnetic resonance imaging" OR PET OR "positron emission tomography" OR "diffusion tensor imaging" OR DTI OR "magnetic resonance spectroscopy" OR MRS OR "Single-photon emission computed tomography" OR SPECT) AND ("alzheimer's" OR "mild cognitive impairment" OR "normal ageing"). We limited our search to English language studies involving human species only. A total of 248 initial hits were returned, and out of these, we selected only 145 studies based on our following inclusion and exclusion criteria. MCI has not been considered as a main comparator group in the majority of this thesis. In this systematic analysis of evidence from neuroimaging there is a considerable amount of data describing MCI – AD contrasts. For this reason, this section of the thesis includes comparative analysis of MCI where appropriate.

5.4.1 Inclusion criteria

(i) Only peer reviewed neuroimaging studies published between July 01, 1984 [first reported AD diagnostic criteria (McKhann et al., 1984)] to September 5, 2018.

(ii) Studies reporting accuracy or sensitivity and specificity or receiver operating characteristic (ROC) area under the curve (W. Zhu, Zeng, & Wang, 2010).

(iii) Studies classifying AD, MCI and healthy controls (HC) or discriminating between aMCI

vs nMCI or predicting progression of conversion to AD or MCI.

5.4.2 **Exclusion criteria**:

(i) Studies only report fluid biomarkers data or autopsy data.

(ii) All meta-analyses or conference proceeding or review articles or animal model studies.

(iii) Studies did not report numerical data of accuracy or sensitivity and specificity or receiver operating characteristic (ROC) area under curve or sample size in subject groups.

In addition to the selected studies, we have also cited many background studies, meta-analysis and systematic reviews. All selected studies are reported in tabular (see details **Table 5.1**) form after the SPECT imaging in AD section.

5.5 Structural MRI in AD:

MRI is a non-invasive imaging method for acquiring brain images and can be configured to be sensitive to various aspects of brain structures like water, fat, and iron etc. It is one of the constructed neuroimaging biomarkers widely used in clinics and in the research domain to assess atrophies in AD specifically grey matter volume changes the brain and also monitors the pattern of disease progression (Clifford & Holtzman, 2013). Brain atrophy in AD is thought to be caused by the deposition Aβ protein, which may ultimately lead to the death of neurons and glial cells and considered as a major contributor in the AD pathology (Johnson et al., 2012). The earliest site of Aβ deposition occurs and follows by five distinct neuroanatomical phases in the brain such as neocortex, allocortex, diencephalic-striatal-basal forebrain, brain stem, and cerebellum with most advanced Aβ pathology (Thal et al., 2002). Conversely, a study by Jack et al, (2010) suggested that Aβ deposition might be a less sensitive biomarker for tracking disease progression

in AD. However, the earliest site of NFTs deposition occurs in the trans-entorhinal region followed by neocortical association areas and subcortical nuclei, and then spreads to other areas of MTL (Braak & Braak, 1991). Furthermore, a recent review (Fjell et al., 2014) revealed that brain atrophy in AD progresses by entorhinal cortex and hippocampus in the MTL, then extends to other association areas in medial parietal, lateral temporal and frontal regions, finally spreads out to all regions of cortex. The annual atrophy rate of MCI people is much higher than normal people and it increases with the people who further develop to AD as suggested by the above study. The rates of atrophy difference in different parts of the brain like whole-brain, entorhinal cortex, hippocampus, temporal lobe volumes, and ventricular enlargement are highly correlated with changes in cognitive performances and offer validated markers for tracking disease progression (Frisoni et al., 2010). For example, MTL atrophy can simply be assessed by visual inspection of T1-weighted coronal section (a standard structural MRI image), and it offers around 80-85% of sensitivity and specificity to distinguish from AD patients to cognitively normal individuals, but it provides slightly lower sensitivity and specificity for diagnosis of aMCI (Frisoni et al., 2010). Another autopsy confirmed cohort study (Burton et al., 2009) on visual rating of MTL atrophy shows high diagnostic accuracy with sensitivity of 91% and specificity of 94% among AD, dementia with Lewy bodies (DLB) and vascular cognitive impairment (VCI). Furthermore, Schuff et al., (2009) demonstrated that normal subjects with APOE ε4 carrier have a faster hippocampal loss than non-carriers and the accelerated hippocampal loss may be an indicator of AD pathology. Likewise, another study (Mcdonald et al., 2009) demonstrated that the progressive cerebral atrophy in AD is not uniform throughout the brain, and the clinical impairment stage is associated with increased atrophy rates in neocortical areas, early stage with medial temporal cortex, and finally in the later stage the atrophy rates are

larger in prefrontal, posterior temporal, parietal and cingulate cortex. However, there is a wealth of evidence which suggests that many psychiatric disorders like major depression, borderline personality disorder and post-traumatic stress disorder etc. are associated with reduced hippocampal volume (Frodl et al., 2006; Hickie et al., 2005; Schmahl et al., 2009).

5.6 Diagnosis of AD with structural MRI: Prediction of conversion

Two promising biomarkers of AD, structural MRI and CSF protein concentrations, respectively, provide early predictive information about the conversion of MCI to AD, but structural MRI has slightly better prediction of conversion from aMCI to AD than CSF biomarkers (Vemuri, Weigand, & Trojanowski, 2009). It is well accepted that all AD patients' progress through an MCI stage and some may remain in this transitional stage until death. However, irreversible brain damage in AD is an ongoing process, which may begin 20 or more years before clinical findings appear (Villemagne et al., 2013). Therefore, there has been a lot of interest in prediction of AD from the prodromal stage for early diagnosis and targets for therapeutic interventions to halt or delay the progression. A meta-analysis (Y., Z.-X., & Wei, 2009) demonstrated that MTL atrophy has around 72.8% sensitivity and 81% specificity for predicting conversion of aMCI patients to dementia. Another meta-analysis (Karow et al., 2010),which included 826 AD patients and 1027 elderly cognitively normal subjects, found that MTL atrophy was the strongest change observed in AD dementia. In addition, hippocampal volume reduction of 20% is already present at a mild stage of AD as estimated by the above study. Furthermore, another meta-analytic study (Schroeter et al., 2009) involving 1351 patients and 1097 healthy control subjects showed that early AD affects structurally the (trans-) entorhinal and hippocampal regions, and functionally, the inferior parietal lobules and precuneus. Therefore, the most reliable predictor of AD from aMCI appears to be atrophy in the (trans-) entorhinal area/hippocampus and

hypometabolism/hypoperfusion in the inferior parietal lobules (Schroeter et al., 2009). However, the annual conversion rate of AD from aMCI is around 10-15%, while only 1-2% normal elderly persons progress to AD (Petersen, 2009). Furthermore, Fischer et al., (2007) reported the conversion rates of AD from aMCI and nMCI are 48.7% and 26.8% respectively. In addition to that, people with MCI show a high probability of developing to full AD after 2.5 years and both the subtypes of MCI develop frequently to AD and related dementia. Moreover, a meta-analysis (Mitchell & Shiri-Feshki, 2009) on progression of MCI to AD and to related dementia reported that 50% of people with MCI convert to dementia, and the annual conversion rate is approximately 7% to dementia and AD and 2% to vascular dementia. Interestingly, the other half of the people with MCI will not progress to AD after 10 years as suggested by the above study. Another study, however, suggested that approximately 80% of aMCI subjects progress to dementia within 6 years (Petersen, 2004).

A number of studies have been published with reference to hippocampal atrophy rates in normal ageing (NA), MCI, and AD to monitor and predict the disease progression. A meta-analysis (Barnes et al., 2009) on 595 AD patients and 212 matched controls demonstrated that the annualized hippocampal volume loss rates for AD patients and normal controls (mean age of 69-83 years) were estimated to be 4.66% and 1.41% respectively within 95% of the confidence interval (CI). However, an MRI study (Sluimer et al., 2009) demonstrated that hippocampal atrophy rate is the best classifier of MCI and control groups, while whole brain atrophy rate discriminates AD from MCI groups. Finally, the authors stated that regional hippocampal atrophy rates are the strongest predictors of AD progression. In a recent meta-analysis (Tabatabaei-jafari, Shaw, & Cherbuin, 2015) on cerebral atrophy of MCI patients revealed that the volume reduction is higher in different brain areas: such as 2.2-fold higher in the

hippocampus, 1.5-fold in the entorhinal cortex, and 1.8-fold in the whole brain. However, atrophy rates may vary with different methodological considerations. For instance, an ADNI study (Mouiha et al., 2011) of 683 subjects used Surgical Navigation Technologies (SNT) and FreeSurfer software, and the authors found that the monthly whole hippocampal atrophy rate of different subject groups on FreeSurfer is AD = 0.77% (standard deviation (SD) = 0.84), MCI = 0.49% (SD = 0.79) and Control = 0.12% (SD = 0.87); while in STN these rates are AD = 0.59% (SD = 0.33), MCI = 0.40% (SD = 0.32) and Control = 0.22% (SD = 0.20) . In contrast, the annual atrophy rates in normal healthy older adults are found to be 0.2–0.5% for gross brain volume reduction, 0.79–2.0% for the hippocampus, and 0.3–2.4% for the entorhinal cortex (Fjell et al., 2014).

5.7 Machine learning Approach

A great deal of work has been reported on machine-learning techniques such as support vector machines (SVM) for disease diagnosis, transition prediction and treatment prognosis from structural and functional brain images of AD, MCI, and normal healthy ageing subjects with high accuracy. A specific set of algorithms is used to train the SVMs on well-characterized data such as normal ageing and AD brain scans to test the new scans against a training set for automatic classification of different groups such as MCI, AD and NA with high sensitivity and specificity (Klo et al., 2008). A linear SVM study included 85 pathologically proven AD patients, 91 normal ageing subjects and 19 frontotemporal lobar degeneration (FTLD) patients, and the authors compared each subject group on the basis of grey matter segmentation of the whole brain and antero-medial lobe volume of interest for analysis (Klo et al., 2008). By using the SVM classification in confirmed AD-patients versus controls group, up to 95% AD cases were correctly classified with 95% sensitivity and 95% specificity. Considering the grey matter of the

antero-medial lobe volume of interest analysis, up to 90% AD cases were correctly classified with 85% sensitivity and 95% specificity (Klo et al., 2008). Furthermore, for classification between mild AD versus controls of the whole brain images, up to 81.1% cases were classified correctly with 60.6% sensitivity and 93.0% specificity, and when this analysis was restricted only to the MTL, it further increases accuracy to 85.6% with sensitivity of 75.8% and specificity of 91.2% (Klo et al., 2008). Finally, the classification between AD versus a FTLD group showed 89.2% cases were correctly identified by using whole brain analysis with sensitivity of 94.7% and specificity of 83.3% (Klo et al., 2008). Likewise, another machine-learning cohort study(Mitchell et al., 2009), included 107 non-demented non-depressed subjects initially, and then sub-classified into 22 pure aMCI subjects, 54 multi-domain MCI (mdMCI) subjects, 10 nMCI subjects and 21 "worried well" subjects. After 2 years of follow up study, 59% of mdMCI progressed to dementia with only 5% improved, and 18% of pure aMCI progressed and 41% improved. In the case of nMCI subjects, 70% were improved (Mitchell et al., 2009). Similarly, another recent SVM study(Long et al., 2016) reported on the classification of MCIs from healthy controls by examining the MRI data from 29 MCI patients and 33 healthy controls. In that study, the authors classified the MCIs and normal controls with an accuracy of up to 96.77%, sensitivity and specificity were 93.10% and 100 respectively. The above study also found the most discriminating features for classification mainly on the default-mode network associated areas like hippocampus, parahippocampal gyrus, posterior cingulate gyrus and middle frontal gyrus, and subcortical regions such as lentiform nucleus and the amygdala (Long et al., 2016). However, due to the small sample size of many studies, fine-grained interpretation of results may not be warranted as it may undermine power (Schnack & Kahn et al., 2016).

In the past decade, many quantitative studies in AD have been published on voxel-based morphometry (VBM) in contrast with a region of interest (ROI) approach. Briefly, VBM is a data analysis technique for MRI, which detects regional grey matter, white matter concentrations, cerebrospinal fluid partitions, and anatomical standardization between different subject groups by voxel-wise comparison in an automated fashion (Ashburner & Friston, 2000; Matsuda, 2013). However, a VBM meta-analytic study suggested that the grey matter reduction in the left hippocampus and parahippocampal gyrus is more in aMCI patients who convert to AD, and therefore, left MTL atrophy appears to be the most consistent neurostructural biomarker for predicting conversion AD from aMCI (Ferreira et al., 2011). In addition, MTL structures like amygdala, hippocampus, and thalamus may be preserved in normal ageing, while cortical regions like frontal and insular areas are frequently atrophied in normal ageing (Matsuda, 2013).

In summary, structural MRI has the potential to detect significant brain changes in different stages of AD and related dementia with high accuracy as explained earlier. Furthermore, Harper and colleagues recently published a study on MRI visual rating scales in the diagnosis of dementia by evaluating 184 subsequently post-mortem confirmed cases (Harper et al., 2016) and the study distinguished each pathological group from controls with an accuracy of 0.86-0.97 in relation to area under receiver-operator curves. However, atrophy in MTL is considered as a key marker for diagnosis of AD and early prediction from the MCI stage. In addition, the progressive atrophy rate in the whole brain, hippocampus and MTL is significantly more than the normal ageing, and these different patterns of atrophy could offer helpful predictive information about the conversion to AD from the MCI stage. Conversely, it has been well documented that some normal healthy older individuals possess AD-like neuropathology. Consequently, it is sometimes quite challenging to use MRI to distinguish normal ageing, MCI and AD patients. In addition,

perhaps surprisingly, an earlier MCI study for comparison of structural MRI and the cognitive assessment tests for prediction of AD from its prodromal stage suggested that the cognitive assessment tests produce a better prediction of probable AD from aMCI than the volumetric measurement of the whole brain, ventricle, entorhinal cortex, or hippocampus (Fleisher et al., 2008). Therefore, there are some pitfalls in structural MRI, which undermine the accuracy of diagnosis and prediction of AD. Johnson and colleagues (2012) described some of the limitations in the structural MRI (Johnson et al., 2012),these are (i) It cannot directly detect the involved proteins, (ii) It cannot assess brain function, (iii) Progressive pattern of cerebral atrophies may also be found in related dementia and other diseases, (iv) Study variability due to inter scanner variations and differences in patient sample, (v) Lack of enough longitudinal studies. Therefore, by combining all other biomarkers might offer utmost accuracy of early diagnosis, prediction of conversion and prognosis of AD.

5.8 Functional MRI (fMRI) in AD

Functional magnetic resonance imaging (fMRI) is a non-invasive neuroimaging technique, which measures the brain activity by detecting tissue perfusion, blood-volume changes, or changes in the concentration of oxygen in the form of blood oxygenation level–dependent (BOLD) contrast mechanism (Logothetis, 2008). It is an indirect measure of neuronal activity during certain tasks, and the BOLD responses are believed to reflect neuronal activity due to changes in the concentration of blood oxyhemoglobin to deoxyhemoglobin ratio (Logothetis et al., 2001). As mentioned earlier, a symptomatic hallmark of AD is the deficit of episodic memory and other cognitive functions, and is supported by hippocampus and MTL, but in contrast, musical memory is well preserved in many AD patients (Stelzer et al., 2015). Therefore, the majority of previous fMRI studies on AD and MCI mostly focused on the hippocampus and

related areas of MTL to show different activation patterns in various episodic memory tasks. However, AD patients show decreased activity in hippocampal and parahippocampal regions during episodic memory encoding tasks relative to normal subjects (Dickerson & Sperling, 2008). In a quantitative meta-analysis (Schwindt & Black, 2009) on fMRI and PET studies of episodic memory activation in AD demonstrated that control subjects show consistently greater activity in several regions, including MTL and frontal pole, while patients show increased activity in ventral lateral prefrontal cortex and other regions. Furthermore, a recent meta-analysis (Terry et al., 2015) of fMRI studies including total 409 subjects (healthy older adults (HOA) = 200, MCI = 131, and AD = 89) on the activation pattern associated with episodic memory in AD, MCI and HOA explained that the MCI subjects show greater activation in the cerebellum compared to the HOA, where as AD patients show hypoactivation in MTL. In addition, HOA subjects show more activation in the right hippocampus than the AD patients. Finally, the authors suggested that more evidence is required before considering hyperactivation of MTL as an early biomarker of AD. Several fMRI studies have reported decreased MTL activity in MCI subjects and genetic at-risk subjects compared to normal subjects, while many other studies showed increased MTL activity in symptomatic individuals, who are at risk for AD dementia (Johnson et al., 2012; Sperling, 2011). Furthermore, a subgroup of MCI subjects when compared to a clinically stable group showed greater activation in MTL, who further progressed to cognitive decline over 2.5 years of follow up (Dickerson et al., 2004). Another longitudinal MCI study (5.9 years of follow up) (Miller et al., 2008) on hippocampal activation for the prediction of degree and rate of cognitive decline found that greater hippocampal activation predicts greater degree and subsequent rate of cognitive decline. In addition, results from whole-brain analysis suggest that the hippocampal formation is the only brain region where its activation predicts cognitive

decline and many factors known to be affecting cognitive decline within MCI, including baseline level of clinical impairment, age, education, and hippocampal volume (Miller et al., 2008). Likewise, another study (Dickerson et al., 2005) suggested that the MCI group shows hyperactivation in the MTL and the hippocampus compared to normal controls, whereas the AD patients show hypoactivation in the hippocampus and the entorhinal cortex. However, the above study hypothesized that the MTL hyperactivation is an early course of prodromal AD and it subsequently decreases as the disease progresses (Dickerson et al., 2005). Furthermore, another meta-analysis (Nellessen et al., 2014) on episodic memory related brain activation patterns in AD suggested that the MCI subjects show hyperactivation within the right hippocampus during memory encoding, while the left hippocampus and the fusiform gyrus show hypoactivation during retrieval tasks. In contrast, the AD patients show increased activation in the precuneus (PCU) during memory encoding, whereas the right hippocampus shows hypoactivation during retrieval tasks (Nellessen et al., 2014).

5.9 Resting-state fMRI in AD

The use of resting-state fMRI (rsfMRI) focussing on the default mode network (DMN) is an interesting approach in fMRI to study brain connectivity in various neuropsychiatric disorders without any external stimuli, and it is very useful measure of critical brain functions such as movement, vision, audition, language, episodic memory, executive function, and salience detection (Greicius, 2008; Greicius et al., 2004; Krajcovicova et al., 2014). In rsfMRI, the subjects do not have to perform any tasks, but instead, they are asked to stay quiet inside the scanner with closing their eyes for several minutes to localize the functional connectivity between different areas of the brain at rest (Greicius, 2008; Vemuri et al., 2012). An early study on AD reported that the prominent coactivation of the hippocampus in all groups of subjects

suggests that the DMN is closely associated with episodic memory processing. (Greicius et al., 2004) In addition, AD patients show decreased resting-state activity in the posterior cingulate and hippocampus, and this disrupted DMN could be used as an early AD biomarker with sensitivity of 85% and a specificity of 77% (Greicius et al., 2004). Furthermore, a recent machine learning ADNI study (Khazaee et al., 2016) reported on rsfMRI classification of AD, MCI, and healthy control (HC) subjects and achieved 93.3% of accuracy on automatic classification. In addition, the authors estimated hub nods (brain networks) and the numbers found to be 12, 10, and 9 for HC, MCI and AD respectively, which indicates AD patients may have more disruption in brain networks as the disease progresses. Moreover, AD selectively seems to disrupt highly connected hubs of the brain network such as the medial and lateral prefrontal cortex, parietal cortices, insula, and thalamus, and this alteration in brain networks tightly correlates with the patients' cognitive performance (Dai et al., 2015). Conversely, a longitudinal study (Sheline et al., 2010) including 100 cognitively normal subjects suggested that the APOE Ɛ4 allele also disrupts the rsfMRI connectivity of the precuneus to several other regions in the absence of amyloid plaques or decreased CSF Aβ42. However, the first voxel-level quantitative meta-analysis (Jacobs et al., 2013) on default mode connectivity in 1196 AD patients and 1255 controls demonstrated that the subcortical areas of the brain act as a modulator between DMN connectivity and task-related activation. In addition to that, the MCI stage shows disrupted DMN function in the ventral posterior cingulate cortex (PCC) and the precuneus (PCU) leading to compensatory task-related increased deactivation in AD. Finally, they concluded that AD is a syndrome that starts by damage in neural networks and followed by cognitive deficits (Jacobs et al., 2013). Furthermore, a recent meta-analysis (Lau et al., 2016) on rsfMRI of aMCI patients has shown that regional resting-state functional connectivity is

disrupted more in aMCIs than controls, including the posterior cingulate cortex, right angular gyrus, right parahippocampal gyrus, left fusiform gyrus, left supramarginal gyrus and bilateral middle temporal gyri.

In summary, both fMRI and rsfMRI are promising neuroimaging techniques for detecting brain changes in cognitive tasks and at rest. By synthesizing previous research evidence, it is clear that the pattern of brain activity is significantly different in AD, MCI and HOA subjects. Disruption of DMN functional connectivity and reduced MTL activity are already present in the MCI stage. In addition, the hypoactivation of MTL and the hippocampus is observed in latter stages of dementia. Based on these results, rsfMRI of the DMN in relation to brain connectivity might have the potential for the early stage diagnosis of AD and prediction of conversion from the prodromal stage of dementia with more than 90% accuracy.

However, there are some pitfalls associated with fMRI studies (Johnson et al., 2012). For example: (i) It is quite problematic for severely cognitive impaired subjects, (ii) It is very prone to wrong interpretation of results due to subjects head motion and physiological noises (iii) Inter-individual variability in cognition-related activity in different brain regions, and (iv) It can not directly detect the involved neuropathology of AD.

5.10 Diffusion Tensor Imaging (DTI) in AD

DTI is a non-invasive neuroimaging technique, which allows detection of white matter integrity and the magnitude and degree of anisotropy in tissues by reflecting water retention capacity across the fiber tracts in the brain of healthy controls as well as the disease suspected subjects' (Alexander et al., 2007). Fractional anisotropy (FA) and mean diffusivity (MD) measure the directional flow of water molecule and average diffusion of water in the white matter

respectively (Alexander et al., 2007; Oishi et al., 2011), which are mainly analyzed in AD studies. In addition to grey matter volume changes, the white matter abnormalities in AD and MCI patients, particularly in the MTL and associated areas involved in episodic memory impairment have been demonstrated (Stebbins & Murphy, 2009). However, a DTI meta-analysis (Sexton et al., 2011) suggested that the FA value of AD and MCI patients decreases in all white matter regions except parietal, occipital and internal capsular regions, while the MD value increases in all regions in AD and MCI except occipital and frontal regions in case of MCI. Moreover, a meta-analysis (Clerx et al., 2012) on comparison of DTI and the MTL atrophy measurements in AD. In their study, the authors included 2791 and 8122 subjects for DTI and MRI studies respectively, and they found that the MTL atrophy differentiates significantly between AD and controls [effect size (ES) of 1.32 –1.98], MCI and controls (ES of 0.61–1.46). However, in DTI studies, the total cingulum FA value best discriminates between AD and controls (ES of 1.73) and the parahippocampal cingulum FA between MCI and controls (ES = − 1.17) (Clerx et al., 2012).In addition, the hippocampal MD value best discriminates between AD and controls (ES = −1.17) and between MCI and controls (ES = −1.00) (Clerx et al., 2012). Finally, they concluded that the MD values of the frontal, parietal, occipital and temporal lobe have more discriminating power than FA values, and the ES of MTL atrophy measurements is equal or greater than the DTI measurements. In contrast, a prospective study (Fellgiebel et al., 2006) has shown that the hippocampal MD is superior to the volumetric measurements and the increased MD value of the left hippocampus predicts conversion of MCI to dementia with in 18 months. However, another study (Chua et al., 2009) has reported that the DTI of posterior cingulate cortex differentiates between MCI and cognitively normal subjects with an accuracy of 85.1%.

To date, a few machine-learning DTI studies have been reported for the prediction of conversion from MCI to AD. For example, a recent machine-learning study (Dyrba et al., 2015) on comparison of MRI and DTI data has suggested that DTI provides better prediction accuracy in than grey matter volumes in the prodromal stages of AD with a maximum accuracy of 77%. Furthermore, another machine-learning study (Dyrba et al., 2013) by the same group included 137 patients with clinically probable AD and 143 healthy elderly controls demonstrated that the SVM classifies AD and normal controls with an accuracy of 80% for FA and 83% for MD. In addition, a DTI study has demonstrated that the cognitively normal elderly subjects' with APOE Ɛ4 allele positive show decreased cognitive performance as well as grey and white matter changes in the medial temporal cortex than APOE Ɛ4 allele negative individuals' (Honea et al., 2009). Interestingly, a multicenter study (Li et al., 2013) included 53 early-stage AD and 30 normal aging volunteers for differentiating early-stage AD and normal aging reported that the bilateral MD values of hippocampus and pallidum, and of the right thalamus and caudate are significantly increased in the early-stage of AD ($P < 0.05$). In their study, the authors classified early-stage AD and normal aging using the MD values of bilateral hippocampi and pallidums, and combination of two imaging modalities (such as MRI and DTI) with an accuracy of 84.7% and 93.1% respectively.

In summary, DTI provides promising results for diagnosis and prediction of conversion AD from the early stages. Furthermore, the neuroanatomical structures such as cingulum bundle, fornix and corpus callosum are more susceptible to early disease processes (Acosta-Cabronero & Nestor, 2014). In addition, the MTL and associated areas involved in episodic memory are also affected much before clinical symptoms of AD appear. However, increased MD and decreased FA values in the hippocampus and MTL could value as a potential biomarker for early predicting

the AD. Due to advancement of the machine-learning and its application into the neuroimaging studies of AD, it is now, therefore, possible to predict the disease with certain accuracy. In contrast, multiple overlapping pathologies of AD and similar neuropathological conditions of normal ageing contribute to misclassification of AD, MCI, healthy controls and related dementia by using DTI. Therefore, further investigation is required before considering DTI as a potential biomarker to be used in clinics for early diagnosis, classification and predicting the conversion AD from MCI with more than 95% accuracy.

5.11 Flurodeoxyglucose positron emission tomography (FDG-PET) in AD

FDG-PET is an established in vivo biomarker for AD, which is used to measure the pattern of glucose metabolism in the brain as an indicative of synaptic activity (Segobin et al., 2015). PET imaging using FDG as a glucose analog to vizualize the pattern of cerebral metabolism in normal healthy aging as well as disease conditions (Shivamurthy et al., 2015). Several FDG-PET studies have been reported on the pattern of cerebral glucose metabolism in AD, MCI and normal aging (NC), and well the pattern of FDG uptake and metabolism shows much tighter correlation with autopsy (Johnson et al., 2012). However, a recent review (Kato et al., 2016) has demonstrated that the AD patients show hypometabolism in the brain areas such as parieto-temporal association area, posterior cingulate or precuneus and the hypometabolism in the inferior parietal lobe, posterior cingulate and precuneus predicts the conversion of MCI to AD. In contrast, normal ageing shows hypometabolism in the anterior cingulate and anterior temporal lobe, along with regional atrophy (Kato et al., 2016),while the aMCIs show less severe hypometabolism of glucose in the posterior cingulate cortex as compared to AD and the lateral parietal cortex does not show any abnormalities in glucose metabolism in case of the aMCIs (Shivamurthy et al., 2015). In addition, a 12-month longitudinal FDG-PET multi-regional study (Gray et al., 2012)

including 321 ADNI participants achieved the classification accuracy 88% between AD vs NC, while this value reduced to 68% when they performed the discrimination between stable MCI (sMCI) and progressive (pMCI). Furthermore, the above study was replicated by Rodrigues & Silveira, (2014), where they conducted their study by including 223 subjects from ADNI on the whole brain voxel-based morphometry instead of defined regions of analysis. The replicated study (Rodrigues & Silveira, 2014) achieved 92.6% of classification accuracy between AD vs normal control, and 70.2% for MCI vs normal controls. However, a recent multi-modality study (Xu, Wu, Chen, & Yao, 2015) of three imaging modalities such as volumetric MRI, FDG-PET, and Florbetapir PET performed the classification of AD, MCI and NC. The authors of the study included 113 AD patients, 110 MCI patients and 117 NC subjects from ADNI and achieved classification accuracy of 94.8% for AD vs. NC, 74.5% for MCI vs. NC, and 77.8% for pMCI vs. sMCI (Xu et al., 2015).

Over the past few years, there has been increasing interest in application of machine learning algorithms in classification and predicting the conversion of AD from MCI. For instance, in a meta-analytic study (Zhang et al., 2012) on the comparison of diagnostic accuracy of FDG-PET and Pittsburgh Compound B (PiB) PET suggested that both the FDG-PET and PiB-PET have the potential of predicting conversion of AD from MCI. However, FDG-PET yielded diagnostic accuracy of 78.7% sensitivity and 74.0% specificity, while PiB-PET shows 93.5% sensitivity and 56.2% specificity (Zhang et al., 2012). Moreover, in an FDG-PET conversion study (Mosconi et al., 2004) demonstrated that the regional glucose metabolic rate of the inferior parietal cortex predicts conversion to AD with an accuracy of 84%, whereas an APOE Ɛ4 positive aMCI subject group provides excellent discrimination relative to aMCI APOE Ɛ4 negative nonconverters: with 100% sensitivity, 90% specificity, and 94% accuracy. Finally, the authors concluded that the

combination of APOE Ɛ4 genotype and FDG-PET might improve the prediction of conversion accuracy (Mosconi et al., 2004). Likewise, another ADNI conversion study on FDG-PET (Landau et al., 2010) including 200 cognitively normal older subjects, 400 MCIs and 200 early AD patients showed that 17.2% of MCI people convert to AD annually. In addition, the MCI subjects with abnormal FDG-PET and episodic memory are 11.7 times more likely to develop AD as suggested by the authors of this study with an accuracy of 76%, sensitivity of 82% and specificity of 70% (Landau et al., 2010). In addition, a recent multicenter longitudinal study (Ito et al., 2015) has shown the potential of 18-FDG-PET in predicting the development AD with MCI for a period of 3 years. In their study, the authors included 114 MCI patients from 9 participating institutions and found that 47% of MCI patients progressed to clinical diagnosis of probable AD. Furthermore, the visual assessment of PET scans during 3-year follow-up for predicting the conversion of AD from MCI offered a diagnostic accuracy of 68%, while the optimized PET score showed promising predictive information of the AD from MCI with in 2 years and the overall diagnostic accuracy was 83%, with sensitivity of 70%, and specificity of 90% (Xu et al., 2015).

In summary, the FDG-PET is a valid biomarker of AD and it provides robust information about the brain metabolism in AD and related dementia. As described previously, the FDG-PET findings in AD suggest the hypometabolic pattern of glucose particularly in the parieto-temporal association area, posterior cingulate or precuneus in the brain could be used as a biomarker for diagnosis with an accuracy ranged from 80% to 95%. The pattern of FDG hypometabolism not only provides predictive information about AD, but also may discriminate between different subject groups with normal cognition, MCI and clinical AD (Montagne et al., 2016). Despite of FDG-PET's greater accuracy rates in the diagnosis of AD and MCI, an autopsy is required for

confirmation of AD cases. In addition, there are certain limitations of FDG-PET studies in AD (Johnson et al., 2012) including: (i) FDG-PET scans are relatively expensive and its scanners are less available, (ii) It involves intravenous injection of radioactive substances, and (iii) its metabolism pattern can't directly indicate AD-related brain pathology and seen in some cognitively normal individuals and non-AD related dementia.

5.12 Amyloid PET in AD

Amyloid PET is one of the validated biomarkers of AD neuropathology for the human brain. Briefly, the amyloid PET is a molecular imaging techinque that uses different radionuclides as ligands for amyloid imaging (Jack, Barrio, & Kepe, 2013; Klunk et al., 2004; Quigley, Colloby, & Brien, 2011). The first human amyloid specific tracer was 11C-Pittsburgh Compound-B (PIB), which was reported by Klunk et al., (2004). In their study, the authors analyzed 16 mild AD patients and 9 controls with PIB and found that the AD patients showed over 1.5 fold increase of PIB retention in the frontal cortex, parieto-temporal cortex, occipital cortex and the striatum than controls (Klunk et al., 2004). After the major breakthrough of PIB ligand, several fluorine-18 (18F) labelled amyloid compounds like Florbetapir, Flutametamol, Florbetaben and AZD-4694 have been developed to trace amyloid plaques [see reviews: (Adlard et al., 2014; Jack et al., 2013; Mathis et al., 2012)]. The main function of these amyloid tracers is to detect cerebral β-amyloidosis and show only postive signal to amyloid pathology and negative signals to prion pathology, α-synucleopathy and pure tauopathy (Burack et al., 2010; Drzezga et al., 2008; Villemagne et al., 2009). In addition, an amyloid positive PET scan refers to the presence of moderate-to-frequent plaques, while a negative scan indicates few-to-no amyloid plaques on neuropathological examination of the human brain (Ossenkoppele et al., 2015). However, a longitudinal study period from May 22, 1985 through October 15, 2008) of 135 elderly cognitive

normal individuals suggested smaller volumes in the hippocampus, temporal neocortex, anterior cingulate, and posterior cingulate of PIB positive (+) subjects than PIB negative (-) subjects (Storandt et al., 2009). Further investigation of these PIB(+) subjects showed impairment in episodic memory as well as working memory and visuospatial abilities associated with increasing Aβ levels and reduced hippocampal volume (Storandt et al., 2009). Moreover, MCI subjects with PIB(+) are more likely to convert to AD than PIB(-) subjects, and are significantly associated with clinical diagnosis, age, and APOE genotype (Okello et al., 2009; Ossenkoppele et al., 2015). In contrast, around 30% cognitively normal and 60% MCI subjects showed PIB+ in amyloid PET imaging, further confirmed in autopsy studies, which also suggest similar kind AD pathology in MCI subjects [see review: (Jack et al., 2013)]. In recent years, there is promising evidence on amyloid imaging for the diagnosis and prediction of AD from MCI. For instance, a recent Cochrane study (Zhang et al., 2014) on evaluating the diagnostic test accuracy of 11C-PIB scans of MCI patients, who progress to AD dementia has revealed the sensitivities between 83% to 100% and specificities between 46% - 88%. In their study, the authors meta-analyzed 247 participants, and found that 112 subjects progressed to AD dementia. Despite having good sensitivity in their study, Zhang et al., (2014) recommended not to use 11C-PIB in MCI subjects in clinical practice because of lack of defined thresholds for determination of test positivity and a high cost-effective investigation. Moreover, another meta-analysis on 352 MCI subjects for predicting the accuracy of Aβ imaging of MCIs to AD conversion demonstrated that sensitivities between 83.3% to 100% and specificities between 41.1% to 100% (Ma et al., 2014). In addition, the latest meta-analysis (Morris et al., 2016) on 18F amyloid PET tracers such as Florbetapir, Flutametamol, and Florbetaben revealed no difference in diagnostic accuracy of the three beta-amyloid radiotracers for the diagnosis of AD. Furthermore, the authors of that study suggested all

these amyloid tracers work better when used to classify between AD and healthy controls (Morris et al., 2016).

In summary, amyloid PET is a valuable imaging technique for diagnosis of AD by demonstrating amyloid tracer retention in the brain. Visual analysis of 18F-labelled amyloid PET scans achieves a sensitivity of 90% and specificity of 85% for discriminating AD from normal controls, while quantitative analysis offers a sensitivity of 90% and specificity of 84% (Morris et al., 2016). Although, Aβ imaging achieves high sensitivity for prediction of AD from MCI, the specificity remains low as compared to sensitivity and some cognitively normal individuals have the same kind of pathology. Furthermore, predictive accuracy increases when using APoE genotyping combined with amyloid PET. Despite considering amyloid PET imaging a validated biomarker for AD, there are some limitations in its application(Johnson et al., 2012). These are (i) It is not a good surrogate biomarker of the progression AD from the early dementia stages. (ii) It is a costly technique for measurement of Aβ42, when compared with CSF Aβ42 measurements. (iii) It can't assess the function of the human brain. (iv) A negative amyloid PET scan can't indicate anything about non-AD dementia etiology, but MRI and FDG-PET might provide information about frontotemporal or vascular pathology of the brain.

5.13 Magnetic Resonance Spectroscopy (MRS) in AD

Magnetic resonance spectroscopy (MRS) is a non-invasive in vivo imaging technique that provides information about changing biochemical metabolites in the brain (Currie et al., 2013). By using MRS, the commonly detected metabolite concentrations are N-acetylaspartate (NAA), myo-Inositol (mI), choline (Cho), creatine (Cr), glutamate, and glutamine (GLx). Each of these metabolite concentrations in the brain is associated with different neurodegenerative disorders. However, the metabolite ratios such as NAA/Cr, Cho/Cr, mI/Cr, mI/NAA, NAA/mI, and GLx/Cr

are commonly assessed in AD. In an early MRS autopsy study, comparing AD patients and normal subject's brain showed that a decrease in NAA metabolite level (Klunk et al., 1992). The low concentration of NAA level is correlated with plaque and tangle density and also regarded as a neuronal marker, synthesized in mtochondria (Graff-Radford & Kantarci, 2013; Wang et al., 2015). In addition to reduced NAA level, the Cho concentration is increased in AD and it may be due to break down of glycerophosphocholine and phosphocholine present in cellular membrane (Klein, 2000). Presymptomatic subjects with APoE Ɛ4 status have shown decreased levels of NAA/mI and NAA/Cr ratios, around 10-25% compared to normal controls (Godbolt et al., 2006). Furthermore, with reference to Cr and mI concentrations in AD, Cr levels are thought to be stable and hence used as a reference, while mI is elevated due to increased activation and proliferation of glia (Graff-Radford & Kantarci, 2013; Wang et al., 2015). Interestingly, a novel MRS study has been reported on the brain antioxidant glutathione (GSH) level for discriminating AD, MCI, and HC in the frontal cortex and the hippocampus (Mandal et al., 2015). In their study, the authors discriminated AD from HC with an accuracy of 100% (sensitivity of 100% and specificity of 100%) by measuring the bilateral hippocampal GSH level, discriminating HC from MCI with an accuracy of 93.1% (sensitivity of 87.5% and specificity of 100%) in left hippocampal GSH level, and MCI from AD with an accuracy of 96.3% (sensitivity of 91.7% and specificity of 100%) in GSH levels of the bilateral frontal cortex (Mandal et al., 2015).

Over recent years, numerous studies have been investigated and reported on using MRS technique to distinguish AD patients from MCIs and controls. However, a recent meta-analysis comprising 1282 AD patients and 1519 HC subjects suggested that AD patients have reduced NAA levels in the posterior cingulate (PC) and bilateral hippocampus compared to controls (Wang et al., 2015). In addition, the PC of AD patients show decreased NAA/Cr ratio, while the

mI/Cr metabolite ratio is elevated, but unfortunately, the authors did not assess this quantitatively (Wang et al., 2015). Some MRS studies reported on distinguishing AD from controls with a high sensitivity of 90% in the temporo-parietal region and a 95% specificity in the medial occipital lobe (Graff-Radford & Kantarci, 2013; Kantarci et al., 2002). Moreover, NAA/Cr ratio of the PC cortex discriminates AD from MCI with a sensitivity of 80% and specificity of 65% (Kantarci et al., 2002). However, a cohort MRS study of 53 MCI patients demonstrated that NAA/Cr ratio predicted AD from MCI with a sensitivity of 100% and specificity of 75%, with a positive predictive value of 83% and a 100% negative predictive value (Modrego, Fayed, & Pina, 2005). In addition, Fayed et al., (2012) reported that the NAA/Cr ratio of the PC gyrus predicts AD from MCI with a sensitivity of 82% and a specificity 72%, which correlates with clinical scales of dementia. Furthermore, a meta-analyis comprising of 607 MCI patients and 862 healthy controls revealed that consistent metabolite changes in the PC cortex, hippocampus, and the peritrigonal white matter are observed in MCI patients, and NAA level may be the most reliable metabolite for discriminating MCI from healthy controls (Tumati, Martens, & Aleman, 2013).

In summary, the MRS is an imaging tool, which could be used in diagnosis AD and MCI by interpreting the metabolite ratios in the brain. As described above, NAA is a neuronal marker that appears to be reduced significantly before clinical symptoms appear. In addition, mI level is increased particularly in the occipital, temporal, parietal, and frontal areas of AD patients. Furthermore, the NAA/Cr ratio of the PC cortex best discriminates AD from MCI and controls, it also predicts AD from MCI with high accuracies. Despite recent advances in MRS, there are certain pitfalls such as lack of standardized methodology, overlap of spectral patterns between different pathologies (i.e low specificity), lack of reimbursement, and lack of treatment options

in most dementias (Gao & Barker, 2014).Therefore, more research is needed to validate MRS as a potential biomarker for AD.

5.14 Single-photon emission-computed tomography (SPECT) in AD

Single-photon emission computed tomography (SPECT) is a functional nuclear imaging technique that provides different physiological and pathological information of the living brain through cerebral blood flow measurement (Yeo et al., 2013). SPECT imaging requires injection of a single-photon emitting radionuclide to the patient's blood stream, and after its radioactive decay a photon is emitted and detected by the gamma-camera (Knoll, 1983; Piccinelli & Garcia, 2016; Theodore, 2017). The radionuclides technetium-99m (99m-Tc) and iodine-123 (123-I) are mainly used in SPECT imaging. For brain SPECT imaging, two most commonly used tracers are 99mTc-hexamethylpropyleneamine (99mTc-HMPAO) and 99mTc-ethylcysteine dimer (99m Tc-ECD), which distribute in the brain to assess regional cerebral blood flow (rCBF) (Yeo et al., 2013). Perfusion SPECT studies in AD are based on the specific regional pattern of hypoperfusion, which corresponds to glucose consumption and reflects neuronal activity (Knoll, 1983). Numerous SPECT studies have been reported in AD for diagnosis, discriminating AD from healthy ageing and other forms of dementia, and predicting AD from MCI. AD patients exhibit reduced cerebral blood flow in the temporal and parietal association cortex, the posterior cingulate cortex, the precuneus areas, and the frontal cortex in more advanced cases of AD, while subjects with MCI show hyperperfusion, particularly in the posterior cingulate, which could be used as a risk factor for developing AD (Knoll, 1983). Interestingly, MCI subjects compared to cognitively normal controls show 23% less rCBF in the mesotemporal regions and 17% in the anterior cingulum, while no further reduction of rCBF is observed in mild AD (Luckhaus et al., 2008). The rCBF of amygdala is reduced to 20% in MCI subjects compared to normal controls

and it further declines to 28% in mild AD cases (Luckhaus et al., 2008). Furthermore, another comparison study reported by the same research group examined different patterns of rCBF between mild AD and MCI (Luckhaus et al., 2010). Reduced brain volume in both the right and left amygdala and the right hippocampus was observed, but interestingly no apparent changes in rCBF of these brain regions were shown. The authors did not find any correlation between the hippocampal and amygdalar brain volumes with regards to rCBF in both MCI and mild AD (Luckhaus et al., 2010). Furthermore, a systematic review (Yeo et al., 2013) on diagnostic utility of 99m Tc-HMPAO and 99m Tc-ECD SPECT imaging in dementia suggested a discrimination between AD vs FTD with sensitivity of 79.7% and specificity of 79.9%, AD vs VaD with sensitivity of 74.5% and specificity of 72.4%, AD vs DLB with a sensitivity of 70.2% and specificity of 76.2%, and finally AD vs HC with sensitivity of 76.1% and specificity of 85.4%. In addition, many machine learning studies on classification of AD from HC and MCI using SPECT imaging have been published. For example, a SPECT study of 91 subjects using the SVM classification achieved an accuracy of 92.31% for distinguishing AD from HC (López et al., 2009). Likewise, another SVM study on SPECT imaging comprising of 41 healthy controls and 38 suspected AD patients performed a classification accuracy of 98.6% with a sensitivity of 97.3% sensitivity and a specificity of 100% (Chaves et al., 2009).

Table 5.2 Characteristics of included studies

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Zhang et al. (2018)	HC = 183 MCI = 296 AD = 129	MRI	AD vs HC	0.92
Valenzuela et al., (2018)	HC = 59 cMCI = 74 ncMCI = 74 AD = 87	MRI	AD vs HC	94.4%
Fang et al. (2018)	HC = 190 MCI = 305 AD = 335	MRI	AD vs HC	96.54%
Tan et al. (2018)	HC = 540 AD = 411	MRI	AD vs HC	83.33%
Choi and Jin. (2018)	HC =182 cMCI= 79 ncMCI = 92 AD = 139	FDG-PET Amyloid-PET	AD vs HC Prediction of AD from MCI	96% 84.2%
Belathur Suresh et al. (2018)	HC = 269 HC = 137	MRI	AD vs HC	90.32%
Park et al. (2017)	HC = 41 AD = 57	MRI RsFMRI	AD vs HC	91.7%
Wu et al. (2017)	HC = 47 MCI = 99 AD = 62	Amyloid PET	AD vs HC	86.1%
Kim and Lee. (2017)	HC = 208 cMCI= 69 ncMCI = 281 AD = 160	MRI	AD vs HC MCI vs HC	92.84% 78.28%
De Marco et al. (2017)	HC = 50 MCI = 50	MRI RsfMRI	HC vs MCI	94%
Li et al. (2017)	HC = 117 MCI = 110 AD = 113	MRI FDG-PET Amyloid PET	AD vs HC HC vs MCI	98.5% 82.8%
Mathotaarachchi et al. (2017)	sMCI = 230 pMCI = 43	Amyloid PET	sMCI vs pMCI	84%

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Doan et al. (2017)	HC = 31 HCY = 324 MCI = 78 SCI = 38 AD = 137	MRI	AD vs HC	0.93
Chen et al. (2017)	HC=54 MCI = 54	DTI fMRI	HC vs MCI	78.70%
Bouallègue et al. (2017)	HC = 157 SMC =95 MCI = 301 AD = 124	Amyloid PET CSF markers	Diagnosis of AD	85%
Hojjati et al. (2017)	cMCI = 18 nc MCI= 62	RsfMRI	cMCI vs ncMCI	91.4%
Long et al. (2017)	HC = 135 sMCI =132 pMCI = 95 AD = 65	MRI	HC vs AD pMCI vs HC	96.5% 91.74%
Beheshti et al. (2017)	HC = 162 sMCI = 65 pMCI = 71 AD = 160	MRI	HC vs AD sMCI vs pMCI	94.73% 75%
Suk et al. (2017)	HC = 226 sMCI = 226 pMCI = 167 AD = 186	MRI	HC vs AD sMCI vs pMCI	90.28% 73.28%
(Shi et al., 2018)	HC = 52 cMCI = 43 ncMCI = 56 AD = 51	MRI PET	HC vs AD cMCI vs ncMCI	97.13% 78.88%
Ortiz et al. (2016)	HC=229 MCI=401 AD= 118	MRI	AD vs HC sMCI vs AD HC vs MCI	0.90 0.84 0.83
Martinez-Murcia et al. (2016)	HC=180 AD=180	MRI	AD vs HC	90.9%
Harper et al. (2016)	HC=73 AD=101 DLB=28 FTLD=55	MRI	AD vs HC	92%

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Suppa et al. (2016)	aMCI=198	MRI	Prediction of AD from aMCI	0.79
Zhang et al. (2016)	HC=98 AD=28	MRI	AD vs HC	92.81%
Ardekani et al. (2016)	HC=22 pAD=43	MRI	AD vs HC	97%
Lu et al. (2015)	HC=75 AD=70	FDG-PET	AD vs HC	Sen.88.89% Spe. 90%
Wang et al. (2015)	HC=98 AD=28	MRI	AD vs HC	93.05%
Dukart et al. (2016)	HC=122 AD=144 sMCI=265 cMCI=177	MRI, FDG-PET, Amyloid-PET Neuropsychology Genetics	sMCI vs cMCI	87%
Anandh et al. (2016)	HC=55 MCI=30 AD=30	MRI	AD vs HC MCI vs AD	98.45% 97.31%
Coupe et al. (2015)	HC=225 AD=192 sCN=309 cCN=37	MRI	sCN vs cCN	72.5%
Zheng et al. (2015)	HC=189 AD=198 MCI=163	MRI	AD vs HC AD converter vs non-converter	92.11% 79.37%
Xie et al. (2015)	HC=64 aMCI=64	MRI DTI	HC vs aMCI	83.59%
Palmqvist et al. (2015)	HC=268 MCI-AD=98	amyloid-PET CSF bimarker	HC vs MCI-AD (with PET only)	0.92
Xu et al. (2015)	HC=117 MCI=110 AD=113	MRI FDG-PET amyloid-PET	AD vs HC MCI vs HC pMCI vs sMCI	94.8% 74.5% 77.8%
Schreiber et al. (2015)	MCI=104	amyloid-PET (Visual analysis)	MCI to AD conversion (rate of conversion= 15.2% within a mean of 1.6 years	Sen. 79% Spe. 96%

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Gorji and Haddadnia, (2015)	HC=148 MCI=172 AD=180	MRI	AD vs MCI HC vs MCI	94.88% 95.59%
Beltrachini et al. (2015)	HC=21 MCI=29	Rs fMRI Cognitive tests	HC vs MCI	0.9559
Sui et al. (2015)	HC=48 AD=59 MCI=43	Rs fMRI	HC vs MCI	81%
Martínez-Torteya et al. (2015)	HC=469 MCI=893 AD=280	MRI, FDG-PET Cognitive tests, etc	HC vs AD HC vs MCI MCI vs AD	0.85 0.79 0.80
Liu et al. (2015)	HC=14 MCI=12 AD=14	MRI amyloid-PET	AD vs HC MCI vs HC	1.00 0.89
Mandal et al. (2015)	HC=49 MCI=41 AD=40	MRS	 MCI vs HC MCI vs AD	Sen. 87.5% Spe. 100% Sen. 91.7% Spe. 100%
Khazaee et al. (2015)	HC=20 AD=20	fMRI	HC vs AD	100%
Farzan et al. (2015)	HC=30 AD=30	MRI	HC vs AD	91.7%
Cheng et al. (2015)	HC=52 cMCI=43 ncMCI=56 AD=51	MRI FDG-PET CEF	MCI vs NC MCI vs AD cMCI vs ncMCI	86.41% 82.71% 79.4%
Challis et al. (2015)	HC=39 MCI=50 AD=27	Rs fMRI	HC vs aMCI AD vs aMCI	79% 97%
Cheng et al. (2015a)	HC=52 cMCI=43 ncMCI=56 AD=51	MRI PET CSF	Prediction of conversion of MCI	80.1%
Zhang et al. (2015)	HC=24 MCI=36	Rs fMRI	HC vs MCI	87.5%

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Prestia et al. (2015)	pMCI=29 sMCI=44	MRI FDG-PET CSF	Prediction of AD (FDG-PET)	Sen. 100% Spe. 36%
Dyrba et al. (2015)	HC=25 MCI-Aβ42(+) =35 MCI-Aβ42(-) =35	MRI DTI	MCI-Aβ42(+) vs MCI-Aβ42(-) HC vs MCI-Aβ42(+)	68% 77%
Liu et al. (2015)	HC=128 pMCI=117 sMCI=117 AD=97	MRI	AD vs HC pMCI vs sMCI	92.51% 78.88%
Apostolova et al. (2015)	PiB SUVR ≥ 1.5 = 41 PiB SUVR< 1.5 = 19	amyloid-PET CSF	Progression of MCI to AD (with PiB-PET)	71%
Ito et al. (2015)	MCI=114	MRI FDG-PET	Prediction of AD from MCI	83%
Hall et al. (2015)	SCI= 231 MCI=544	MRI CSF Cognitive tests	Predicting AD progression to AD	75%
Kaneko et al. (2014)	PiB(-) = 22 PiB(+) =40	amyloid-PET	PiB(+) vs PiB(-)	Sen. 0.925 Spe. 0.955
Raamana et al. (2014)	HC=42 sd-aMCI= 38 md-aMCI= 32	MRI	HC vs md-aMCI HC vs sd-aMCI sd-aMCI vs md-aMCI	0.74 0.67 0.67
Lebedev et al. (2014)	HC=225 aMCI=165 AD=185	MRI APoE genotyping	HC vs AD MCI to AD conversion	Sen. 88.6% Spe. 92.0% Sen. 83.3% Spe. 81.3%
Moradi et al. (2015)	HC=231 AD=200 pMCI=164 sMCI=100 uMCI=130	MRI Cognitive tests	pMCI vs sMCI pMCI vs sMCI (with MRI only)	0.9020 0.7661

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Farhan et al. (2014)	HC=48 AD=37	MRI	AD vs HC	93.75%
Prasad et al. (2015)	HC=50 eMCI=78 lMCI=38 AD=38	DWI	HC vs AD HC vs eMCI HC vs lMCI eMCI vs lMCI	78.2% 59.2% 68.2% 63.4%
Eskildsen et al. (2015)	HC=231 sMCI=238 pMCI=161 AD=198	MRI	Prediction of conversion of AD	72%
Suppa et al. (2015)	AD=44 non-AD=35 Intermediate AD=21	MRI	Diagnosing AD in the whole sample	84%
Willette et al. (2014)	HC=93 MCI=162 AD=65	MRI	HC vs AD MCI vs AD sMCI vs pMCI	94.3% 81.4% 80%
Nazeri et al. (2014)	HC=49 MCI=300 AD=85	MRI Plasma proteomics	HC vs AD prediction of AD from MCI	Sen. 93% Spe. 92% 94%
Han et al. (2014)	HC=33 AD=89	MRI	AD vs HC (70-74 yrs. group)	0.88
Li et al. (2014)	HC=142 MCI=141 AD=80	MRI	HC vs AD HC vs MCI	82.84% 61.53%
Ivanoiu et al. (2015)	HC=31 SCI=21 aMCI=27 naMCI=12	MRI FDG-PET amyloid-PET Neuropsychol-ogical tests	HC vs MCI (combining all biomarkers)	Sen. 72 Spe. 84%
Hye et al. (2014)	HC=452 nMCI=169 cMCI=51 AD=467	MRI Plasma protein analysis Genotyping	predicting progression to AD	87%
Young et al.(2014)	HC=92 MCI=129 AD=64	MRI CSF Cognitive tests	HC vs AD HC vs MCI Predicting AD from	99% 76%

			MCI	77%
Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Li et al. (2014b)	HC=15 AD=21	MRI DTI	HC vs AD	94.3%
Tong et al. (2014)	HC=231 sMCI=238 pMCI=167 AD=198	MRI	HC vs AD sMCI vs pMCI	89% 79%
Bron et al. (2014)	HC=32 early AD=32	MRI ASL	HC vs early AD (combining both modalities)	91%
Guerrero et al. (2014)	HC=309 sMCI=114 pMCI=116 early-MCI=229 AD=106	MRI	HC vs AD pMCI vs sMCI HC vs eMCI	86% 71% 65%
Apostolova et al. (2014)	HC=111 MCI=182 AD=95	MRI CSF Genotyping	HC vs AD HC vs MCI MCI vs AD	0.85 0.79 0.70
Segovia et al. (2014)	sMCI=20 MCI-AD=26	PET Neuropsychol-ogical tests	Diagnosis (combining both biomarkers)	89%
Ferrarini et al. (2014)	HC=75 MEM=31 MEMnos=31	MRI	HC vs MEM HC vs MEMnos	0.66 0.64
Steenland et al. (2014)	HC=191(no-conversion =163 + conversion to AD/MCI=28)	MRI CSF Neuropsychol-ogical tests	prediction of progression to MCI/AD	65%
Zhang et al. (2014)	HC=117 MCI=187	MRI	Diagnosis of MCI	Sen. 80.2%
Dubey et al. (2014)	HC=191 sMCI=177 cMCI=142 AD=138	MRI Proteomics	HC vs AD HC vs MCI HC vs cMCI & AD	87.225% 67.729% 89.771%
Trzepacz et al. (2014)	cMCI=20 ncMCI=30	MRI PiB-PET FDG-PET Genotyping	Prediction of AD from MCI (combining MRI and PiB-PET)	76%

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Adaszewski et al. (2013)	HC=137 ncMCI=61 cMCI=142 AD=108	MRI	Diagnosis of HC AD cMCI	 80.30% 73.5% 63.7%
Park et al. (2013)	HC=30 MCI=30 cMCI=12	MRI	HC vs MCI prediction of conversion to AD	0.73 83%
Liu et al. (2013)	HC=138 cMCI=97 sMCI=93 AD=86	MRI	HC vs AD cMCI vs AD cMCI vs sMCI predicting conversion to AD	0.90 0.57 0.66 0.68
Dyrba et al. (2013)	HC=143 AD=137	DTI	HC vs AD	0.83
Yang et al. (2013)	HC=17 MCI=18 AD=17	MRI	HC vs AD HC vs MCI	94.12% 88.89%
Tosun et al. (2013)	HC=46 MCI=215	MRI PiB-PET Genotyping	prediction of amyloidosis in MCI	0.88
Martínez-Murcia et al. (2013)	SPECT data set: HC=41 Possible AD =29 Probable AD =22 Certain AD =4 FDG-PET data set: HC=101 AD=95	 SPECT FDG-PET	AD vs HC (with SPECT) AD vs HC (with FDG-PET)	96.9% 91.3%
Yan et al. (2013)	HC=98 Suspected AD=100	MRI	HC vs AD	0.90
Thiele et al. (2013)	HC=70 AD=71 FTD=31	FDG-PET	HC vs AD	between 89%-98%
Liu et al. (2014)	HC=229 MCI=225 AD=198	MRI	HC vs AD HC vs MCI	92.0% 85.3%

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Prestia et al. (2013)	Prodromal AD=24 sMCI=51	MRI FDG-PET CSF	predicting conversion to AD (with only MRI)	Sen. 46% Spe. 76%
Diciotti et al. (2012)	HC=29 mild AD=51	MRI	HC vs mild AD	86%
Liu et al. (2012)	HC=227 MCI=220 AD=196	MRI	HC vs AD HC vs MCI	between 0.87-0.91 0.79-0.85
Illán et al. (2012)	HC=41 AD=56	SPECT	HC vs AD	92.78%
Choo et al. (2012)	pMCI=26 sMCI=51	FDG-PET CSF Genotyping Neuropsychol-ogical tests	Prediction of progression to AD (with FDG-PET)	0.83
Lunnon et al. (2013)	HC=266 MCI=257 AD=258	MRI Blood biomarkers	HC vs AD (with MRI only)	76.0%
Eskildsen et al. (2013)	HC=226 MCI=862 AD=194	MRI	HC vs AD Predicting AD from MCI	92.0% 73.5%
Sabuncu and Van Leemput, (2012)	HC=150 AD=150	MRI	HC vs AD	0.93
Vandenberghe et al. (2013)	HC=25 MCI=20 probable AD = 20	MRI amyloid-PET	HC vs AD (amyloid-PET visual reads) HC vs AD (with MRI)	100% 85.2%
Chaves et al. (2012)	SPECT data: HC=41 Possible- AD=30 probable-AD=22 Certain-AD=4 FDG-PET :	SPECT FDG-PET	HC vs AD groups (with SPECT imaging) HC vs AD	92.7% 90.11%

	HC= 75 AD=75		(with PET imaging)	
Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Yu et al. (2012)	cMCI=25 ncMCI=38	MRI FDG-PET CSF Cognitive tests Genotyping	Predicting aMCI to AD(all biomarkers) with MRI only	81% 78%
Grydeland et al. (2013)	HC=71 AD=78	MRI	HC vs AD	0.79
Westman et al. (2012)	HC=111 MCI=162 AD=96	MRI CSF	HC vs AD (by combining all) HC vs MCI Predicting AD from MCI	91.8% 77.6% 58.6% to 66.4%
Toussaint et al. (2012)	HC=80 sMCI=40 cMCI=40 probable-AD=80	FDG-PET	HC vs pAD sMCI vs cMCI	92% 80%
Shao et al. (2012)	HC=21 mild-AD=17 AD-MCI=23	DTI	HC vs AD HC vs AD-MCI mild AD vs AD-MCI	95% 90% 85%
O'Dwyer et al. (2012)	HC=40 MCI=33	DTI	HC vs MCI	Sen. 93.0% Spe. 92.8%
Liu et al. (2012a)	HC=229 MCI=225 AD=198	MRI	HC vs AD HC vs MCI	98.80% 87.85%
Farzan et al. (2011)	HC=30 AD=30	MRI	HC vs AD	90%
Wolz et al. (2011)	HC=231 sMCI=238 pMCI=167 AD=198	MRI	HC vs AD sMCI vs pMCI HC vs pMCI	Sen. 93% Spe. 85% Sen.67% Spe. 69% Sen. 86% Spe. 82%

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Aksu et al. (2011)	HC=180 MCI=300 AD=120	MRI	Prediction of MCI to AD	between 0.75 to 0.83
Dai et al. (2012)	HC=22 AD=16	MRI Rs fMRI	HC vs AD	89.74%
Zhang and Shen, (2012)	HC=50 cMCI=43 ncMCI=48 AD=45	MRI FDG-PET CSF	HC vs AD HC vs MCI cMCI vs ncMCI	0.933 0.832 0.739
Padilla et al. (2012)	SPECT data: NOR=41 AD=56 FDG-PET: HC=52 MCI=114 AD=53	SPECT FDG-PET	NOR vs AD (with SPECT) HC vs AD (with FDG-PET)	91.42% 86.59%
Graña et al. (2011)	HC=25 AD=20	DTI	HC vs AD	97%
Mattila et al. (2011)	HC=199 sMCI=190 pMCI=154 AD=163	MRI CSF Cognitive tests	Predicting conversion of MCI to AD	75.5%
Jack et al. (2011)	sMCI=173 AD converter =135	MRI	Predicting progression of MCI to AD	0.678
Chincarinicor et al. (2011)	HC=189 ncMCI=166 cMCI=136 AD=144	MRI	HC vs AD HC vs cMCI ncMCI vs cMCI	0.97 0.92 0.74
Abdulkadir et al. (2011)	HC=266 probable-AD=191	MRI	HC vs probable-AD	87
Nho et al. (2010)	HC=226 MCI=389 AD=182	MRI	HC vs AD Predicting MCI to AD conversion	90.5% 72.3%
Costafreda et al. (2011)	HC=88 MCI=103 AD=71	MRI	Predicting MCI to AD conversion	80%

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Ewers et al. (2012)	HC=101 MCI-AD=58 MCI-non-AD =72 AD=81	MRI CSF Neuropsychol ogical data	HC vs AD cMCI vs ncMCI MCI-AD vs MCI-non-AD. Predicting conversion to AD	79.7% 68.5% 76.3% 68.5%
Hinrichs et al. (2011)	HC=66 MCI=119 AD=48	MRI FDG-PET Neuropsychol ogical data	HC vs AD (with imaging data) Predicting MCI to AD (with imaging biomarkers)	0.876 0.9737
Polikar et al. (2010)	HC=36 AD=37	MRI EEG FDG-PET	HC vs AD (with all imaging modalites)	80.08%
Wee et al. (2011)	HC=17 MCI=10	DTI	HC vs MC	88.89%
Karow et al. (2010)	HC=80 MCI=156 sdMCI=69 AD=68	MRI FDG-PET	HC vs AD (with MRI & FDG-PET) AD vs MCI (with MRI & FDG-PET)	0.899 & 0.706 0.751 & 0.626
Zhuang et al. (2010)	HC=252 aMCI=96 naMCI=69	DTI	HC vs aMCI	74.8%
Cuingnet et al. (2011)	HC=162 cMCI=76 ncMCI=134 AD=137	MRI	HC vs AD HC vs cMCI	Sen. 81% Spe. 95% Sen. 57% Spe. 96%
Koch et al. (2012)	HC=21 MCI=17 AD=15	Rs fMRI	HC vs AD	97.2%
Luckhaus et al. (2010)	HC=12 MCI=30 AD=15	Perfusion-weighted MRI	HC vs AD MCI vs AD	100% 0.894

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
Fritzsche et al. (2010)	HC=15 MCI=18 AD=15	MRI	HC vs AD cMCI vs ncMCI Prediction of AD from MCI	90.0% 83.3% 77.8%
Hinrichs et al. (2009)	HC=82 AD=77	MRI FDG-PET	HC vs AD (with both the modalities)	81.00%
Huang et al. (2010)	HC=67 MCI=116 AD=49	FDG-PET	HC vs AD	Sen. 88% Spe. 88%
López et al. (2009)	HC=41 Possible AD=27 Probable AD=19 Certain AD=4	SPECT	HC vs AD	92.31%
Chaves et al. (2009)	HC=41 Suspected AD=38	SPECT	HC vs AD	98.3%
Chua et al. (2009)	HC=153 aMCI=55 naMCI=41	DTI	HC vs aMCI vs naMCI	Sen. 80% Spe.60.3%
Hinrichs et al. (2009a)	HC=94 AD=89	MRI FDG-PET Neuropsychol ogic-al data	HC vs AD (with MRI) (with FDG-PET)	82% 84%
Salas-Gonzalez et al. (2009)	HC=41 Probable AD=38	SPECT	HC vs AD	99%
Chupin et al. (2009)	HC=166 MCI=294 AD=145	MRI	HC vs AD MCI vs HC cMCI vs ncMCI	Sen. 80% Spe. 79% Sen. 63% Spe. 63% Sen. 65% Spe. 68%
Davatzikos et al.(2009)	HC=175 MCI=15 AD=56	MRI	HC vs AD	0.89

Study 1st author name and year of publication	Sample size (N) in each group	Techniques	Comparison/ Prediction of AD	Reported Max. Accuracy (%)/ ROC/AUC
McEvoy et al. (2009)	HC=139 MCI=175 mild AD=84	MRI	HC vs AD	89%
Misra et al. (2009)	cMCI=27 ncMCI=76	MRI	cMCI vs ncMCI	81.5%
Klöppel et al. (2008)	HC=34 AD=52 FTLD=19	MRI	HC vs AD	95%
Duchesne et al. (2008)	HC=75 Probable- AD=75	MRI	HC vs AD	92%
Fritzsche et al. (2008)	HC=27 MCI=16 AD=25	MRI	HC vs MCI	Sen. 81% Spe. 80%
Herholz et al. (2002)	HC=110 Probable-AD=395	FDG-PET	HC vs AD	Sen. 93% Spe. 93%

Table legends: HC = healthy controls, sCN = stable cognitively normal, cCN = converter CN, MCI = mild cognitive imapirment, DLB = dementia with lewy bodies, FTLD = frontotemporal lobar degeneration, FTD = frontotrmporal dementia, pAD = probable AD, aMCI = amnestic MCI, sMCI = stable MCI, cMCI = converter MCI, ncMCI = non-converter MCI, MCI-AD = mild cognitive impairment who later developed AD dementia, sd-aMCI = single domain aMCI, md-aMCI = multi domain aMCI, uMCI = unknown MCI, eMCI = early MCI, lMCI = late MCI, CSF = Cerebrospinal fluid, ROC = receiver operating characteristic curve, AUC = area under curve, MRI = Magnetic resonance imaging, PET = positron emission tomography, FDG-PET = fluorodeoxyglucose PET, fMRI = functional magnetic resonance imaging, Rs fMRI = resting state fMRI, DTI = diffusion tensor imaging, DWI = diffusion weighted imaging, MRS = magnetic resonance spectroscopy, ASL = arterial spin labeling, EEG = electroencephalogram, Aβ42(+) = beta amyloid positive, Aβ42(-) = beta amyloid negative, PiB = Pittsburgh compound

B, SUVR= Pittsburgh compound Bstandard uptake value ratio, SCI = subjective cognitive impairment, MEM = individuals with memory deficits, MEMnos = individuals with memory deficits not otherwise specified, NOR = subjects not affected by AD, Sen. = sensitivity, Spe. = specificity.

5.15 Conclusion

AD is a multifaceted disease with pathological hallmarks of beta amyloid plaques and neurofibrillary tangle. The use of structural, functional, and molecular neuroimaging biomarkers in the AD brain could provide better disease diagnosis, prognosis and prediction. As discussed above, no single imaging technique could achieve 100% classification accuracy because of their unique strengths and weaknesses. In addition, the overlapping symptomatology and pathological conditions among different forms of dementia and some normal individuals are quite challenging for absolute antemortem diagnosis of AD diagnosis and prediction. Although combining all the imaging techniques could provide high accuracy in classifying AD from HC, high cost and limited availability preclude this for regular clinical use. MCI is a prodromal stage for all AD, but all the MCI patients do not progress to AD or other dementia even after 10 year of follow up investigation (Mitchell & Shiri-Feshki, 2009). In addition, the clinical diagnosis of MCI is challenging and associated with a high rate of misdiagnosis because of overlapping symptomatic and pathologic characteristics like healthy ageing. Therefore, there is an urgent need of biomarker(s) for early detection or prediction of AD or related dementia, particularly from the MCI stage, which could be a key target for therapeutic intervention to halt or delay the onset of AD.

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Chapter 6: Conclusion and future directions

6.1 Summary of findings

The key goals of this PhD thesis were

(i) To assess the diagnostic value of biofluid markers for classifying AD dementia from normal ageing with systematic review and meta-analysis procedure of the recent literature (**Chapter 2**).

(ii) To assess the predictive value for Alzheimer's disease (AD) dementia of body fluid metabolites using systematic review and meta-analysis methods (**chapter 3**).

(iii) To investigate the relationship between age at onset of AD dementia and biofluid markers with a systematic review process (**Chapter 4**).

(iv) To assess the utility of neuroimaging techniques for differential diagnosis of AD dementia from healthy ageing, and for predicting the progression of AD dementia from the mild cognitive impairment (MCI) stage with a systematic review of literature (**Chapter 5**).

In chapter 2, we investigated the differences of peripheral body fluid metabolite concentrations between AD patients and healthy ageing individuals (HC) using systematic review and meta-analysis procedures (Borenstein et al., 2010; Hedges and Vevea, 1998). Our meta-analysis confirmed that the well-established CSF biomarkers of AD such as $A\beta_{1\text{-}42}$,T-tau and P-tau_{181p} proteins level were significantly different from healthy controls. CSF $A\beta_{1\text{-}42}$ levels were found to be significantly decreased in AD patients relative to healthy individuals. In addition, our meta-analyses supported reports that CSF T-tau and P-tau_{181p} levels are significantly elevated in AD patients relative to healthy control subjects. Our findings confirm other groups' findings on the established CSF biomarkers for differential diagnosis of AD versus HC [see (Ferreira et al., 2014; Olsson et al.,

2016)]. In addition, our results support the claim that another CSF metabolite called heart type fatty acid binding protein (hFABP) is significantly elevated in AD groups relative to the HC group. Furthermore, our analysis of studies on plasma Aβ and tau proteins concentrations did not support any significant differences between AD and HC groups. Our analysis also supported the proposal that some inflammatory related cytokines (Turner et al., 2014) may be significantly elevated in AD. Unlike the other cytokines, we found support for the observation that IL-6 concentrations were significantly reduced in AD group relative to healthy controls, which contradicts some previous findings (Lai et al., 2017; Swardfager et al., 2010). This contradictory result may be due to the fact that we included only two studies (Guo et al., 2013; Nazeri et al., 2014) with total 194 AD patients and 107 HC subjects for our analysis based on published results from the Alzheimer's Disease Neuroimaging Initiative (ADNI) (http://adni.loni.usc.edu/) cohort. In addition, there are many emerging biomarkers were reported in the literature, but due to limited studies and very high study heterogeneity (Higgins and Thompson, 2002) across the laboratories, those findings are not clearly supported. Therefore, more research is necessary for classification of AD and non-AD dementia and healthy controls with using body fluid metabolites.

In chapter 3, we examined the relationship between antemortem biofluid marker concentrations and their relationship with the dementia severity. Different types of biofluid, including cerebrospinal fluid (CSF), blood, serum, plasma, and urine, were investigated. The majority of our findings were statistically non-significant. The established body fluid biomarkers of AD dementia are:

1 Reduced concentration of CSF amyliod beta 1-42 ($A\beta_{1\text{-}42}$) protein

2 Increased concentration of CSF total tau (T-tau) and phoshorylated tau ($P\text{-}tau_{181p}$) proteins (Alzheimer's Association, 2018; Blennow et al., 2012).

From our analysis, none of these established CSF biomarkers seem to predictive of AD dementia based on differences in concentration.

CSF $A\beta_{1-42}$,T-tau and P-tau_{181p} protein levels also did not show any significant correlation with severity of AD dementia. However, the analysis supported the claims that some other CSF metabolites including Aβ oligomers, norepinephrine, and pyruvate may be negatively correlated with the severity of AD dementia. These metabolite concentrations were inversely correlated with the severity of AD dementia, but due to the small number of studies with low sample sizes in the included study set, these findings may not be generalizable to a larger population.

Similarly, our analysis supported some reports of changes in blood-based metabolites, including plasma alpha-1-antichymotrypsin (ACT), serum interleukin-18 (IL-18) concentrations and abnormal platelet membrane fluidity. These showed a statistically significant inverse correlation with the severity of AD. Although, some of our analyses of biofluid metabolites suggest significant effects, because of insufficient numbers of studies, small sample sizes, study design and inter laboratory variations (Mattsson et al., 2013; Noble et al., 2008; Watt et al., 2012), these findings may not also generalize more broadly. Therefore, our systematic investigation of AD dementia severity from the body fluid metabolites indicates that there is insufficient evidence in the literature to quantify the effect (Rosenthal and DiMatteo, 2001). In addition, there are many single studies claiming correlations between peripheral biofluid metabolites and AD dementia severity, that need to be replicated with larger sample sizes. Based on our current analysis, further research is necessary to attempt to extend and confirm some of these findings.

In chapter 4, our aim was to predict the age at onset of sporadic AD dementia from biofluid metabolites by using the systematic review and meta-analysis procedure. Therefore, we examined the relationship between different types of body fluid metabolites and age at onset of AD dementia. Unfortunately, we found only 6 studies that met our study inclusion and exclusion criteria, which reported inconsistent results. It was not possible to quantify the effect sizes using meta-analytic methods because each study analyzed the strength of relationship age at onset of AD dementia with

different metabolites. To reach a firm logical conclusion of findings using meta-analysis method, we need to least two studies in the same category (Valentine et al., 2010).Therefore, we were not able to measure the average effect size between these two variables. Hence, our investigation into the literature suggests that there is insufficient evidence for measuring the strength of the relationship between age at onset of AD dementia and body fluid metabolites concentration. Therefore, more research is necessary for attempts at predicting age at onset of AD dementia from peripheral biomarkers.

In chapter 5, we discussed the diagnostic accuracy (Leeflang et al., 2008) of major neuroimaging techniques for classifying AD dementia from controls by a systematic review process. We mainly focused on the machine learning (Falahati et al., 2014; Pellegrini et al., 2018) literature on magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), diffusion tensor imaging (DTI), magnetic resonance spectroscopy (MRS), and Single-photon emission computed tomography (SPECT) (Ferreira and Busatto, 2011; Valkanova and Ebmeier, 2014). Neuroimaging studies reported classification accuracy or sensitivity or specificity or receiver operating characteristic (ROC) area under curve (Zhu et al., 2010) were targeted. We found that studies combined application of different neuroimaging techniques perform better diagnostic classification accuracy between AD and healthy controls (more than 95% accuracy). However, some small sample size machine learning studies reported 100% accuracy, which may not be generalizable in lager population (Schnack and Kahn, 2016). We also found many studies that reported very high sensitivity (more than 95%) for classification between AD and HC, but their specificity remains very low. In addition, due to the overlapping pathological conditions among different kinds of dementia and some normal individuals it is quite challenging given our current knowledge set, to even theoretically approach differential diagnosis of AD from healthy controls with 100% sensitivity and specificity. Although, the combination of multiple

neuroimaging techniques offers a very high accuracy in classifying AD from HC, but due to high cost and availability, it is not possible to incorporate into all clinical settings.

6.2 Conclusion and future direction

AD dementia is a multifaceted neurodegenerative disease with pathological hallmarks of beta amyloid plaques and neurofibrillary tangle. Although, these protein clumps are not the causal for AD pathogenesis, their accumulation in the brain defines AD as a unique neurodegenerative disorder (Alzheimer's Association, 2018). Symptomatic hallmarks of AD dementia vary from patient to patient, including impairment of episodic memory and other cognitive functions.

It is of great interest that AD pathogenesis may begin over a decade before the onset of clinical symptoms, and the symptoms gradually deteriorate from preclinical to intermediate and clinical conditions. The intermediate stage of dementia is called mild cognitive impairment (MCI), where a person with MCI, while exhibiting some decline in cognition, may be functionally active enough to carry out daily life activities. Evidence suggests that the individuals with MCI condition are high risk of developing AD or other forms of dementia. However, studies also suggest that all the MCI subjects do not progress to AD or related dementia even 10 years after initial diagnosis (Mitchell and Shiri-Feshki, 2009; Ward et al., 2013). Therefore, the early diagnosis of dementia or AD particularly from MCI stage would be very helpful for development of therapeutic intervention for attempted enhancement of cognition by physical or mental activities (Farina et al., 2014; Groot et al., 2016) to halt or delay the onset of deteriorating dementia symptoms. In addition, the early diagnosis of MCI subjects would not only enable the researchers to carry out important clinical trials, but also these affected individual future patients can make legal, financial and end-of-life plans, while they are cognitively intact (Alzheimer's Association, 2018).

The findings of AD research in the literature are inconsistent, and it significantly varies among studies. The main objective of this PhD investigation was to estimate the true effect size across the large volume of data as accurately as possible, and to quantify the existence of study variabilities in the AD literature by using systematic review and meta-analytic methods. Meta-analysis is a statistical method for combining different studies to get the highest level of evidence from the literature, and now, it is widely used in clinical and applied research for the evaluation of evidence, policy making, grant applications, and many other fields as well (Borenstein et al., 2009). Our meta-analytic methods confirmed the analysis of previous studies in literature, and these parallel findings confirm that our approach is both effective and valid. Unfortunately, very few studies met our study inclusion criteria from the literature. The majority of studies was excluded because of data format, limited statistical reporting, and considering neurologically disordered individuals' as a healthy control for their comparative analysis with AD group. Our meta-analysis only examined the group level differences in the metabolite concentration, and predicting AD dementia from the metabolite concentration, which may not be generalizable in the individual level. We did not perform meta-analysis on subgroups' level like the MCI, aMCI, naMCI (Petersen et al., 2014), and comparison among different forms of dementia (Camicioli, 2004). We did not perform any analysis on moderator variables like age, sex, gender, and years of education, that may influence our findings. Despite an extensive search, we may have missed some potential studies in the literature, which may affect our results. Many studies with small sample size are not reliable and false positive findings may be high (Button et al., 2013). In addition, we combined high quality studies with low quality studies (Rosenthal et al., 2001), that may influence the true effect size. Therefore, future research should continue to examine these pitfalls for better AD diagnosis, prognosis and early prediction based on biomarkers.

To date, more than 244 drugs were clinically tested in between 2002-2012 for the treatment of AD dementia, but unfortunately, none of them proved to be effective (Alzheimer's Association, 2018; Cummings et al., 2017). However, only six drugs, namely the rivastigmine, galantamine, donepezil, tacrine, memantine, and donepezil combined with memantine are currently being used to treat for a partial symptomatic relief of mild to moderate AD dementia patients' (Alzheimer's Association, 2018). Majority of disease modifying pharmacological interventions for AD treatment were targeted to Aβ peptide fragments. Among those, the passive immunotherapy through monoclonal antibodies targeting to different Aβ species is the most elaborately studied and continually being developed to treat AD (van Dyck, 2018). Briefly, there are two types of Aβ immunotherapies for AD, such as the active and passive immunotherapy (van Dyck, 2018). In active Aβ immunotherapy, a segment of Aβ or a similar antigen is administered to the patients' body to stimulate the immune response to produce own antibody against Aβ (van Dyck, 2018). Although, initial clinical trials worked in many patients', but due to adverse side effects and lack of immune response or inconsistent, particularly in elderly patients', it was however, terminated [see details in (van Dyck, 2018)]. By contrast, in passive immunotherapy for AD, the preformed monoclonal antibodies are administered into the patients' body to boost the immune system for the purpose of clearing Aβ plaques or to prevent the Aβ aggregation (van Dyck, 2018). It is a high cost associated procedure because it requires repeated production and injection of antibodies (van Dyck, 2018). Unfortunately, all the clinical trials targeted to passive immunotherapy of Aβ have failed, and a possible explanation for the failures of all these trials that they all were set in the late stage of AD process (Petersen et al., 2014;van Dyck, 2018). Therefore, new clinical trials are going on particularly targeting preclinical and prodromal stages of AD (Petersen et al., 2014), and hopefully, the findings may open new avenues for AD research [see details (van Dyck, 2018)]. Furthermore, in future, if research ethics regulations allow, development of another advanced gene editing

method called the clustered regularly interspaced short palindromic repeats (CRISPR) [see recent review (Adli, 2018)] may be useful for treating familial forms of AD.

Recent advanced computational methods in the domains of machine-learning, data mining, and artificial intelligence, with advanced algorithms and advanced statistical models, are proving to be very useful tools for disease diagnosis, predictions of course of disease transition prediction and treatment prognosis (Klo et al., 2008;Young et al., 2018). Interestingly, these algorithms recognize data patterns in the training set and perform classification on new data sets (i.e. testing set) at the individual case level (Klo et al., 2008;Young et al., 2018). Future work should continue with these advanced techniques for improved public health through automatic disease diagnosis, the possibility of this leading to new clinical treatment options and yielding information that will lead us to a better understanding of disease processes.

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