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Blood Based Biomarkers for Down Syndrome and Alzheimer's Disease: A Systematic Review

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Abstract

Down syndrome (DS) occurs due to triplication of chromosome 21. Individuals with DS face an elevated risk for development of Alzheimer's disease (AD) due to increased amyloid beta (Aβ) resulting from the over-expression of the amyloid precursor protein found on chromosome 21. Diagnosis of AD among individuals with DS poses particular challenges resulting in an increased focus on alternative diagnostic methods such as blood-based biomarkers. The aim of this review was to evaluate the current state of the literature of blood-based biomarkers found in individuals with DS and particularly among those also diagnosed with AD or in prodromal stages (mild cognitive impairment [MCI]). A systematic review was conducted utilizing a comprehensive search strategy. Twenty-four references were identified, of those, 22 fulfilled inclusion criteria and were selected for further analysis with restriction to only plasma-based biomarkers. Studies found Aβ to be consistently higher among individuals with DS; however, the link between Aβ peptides (Aβ 1–42 and Aβ 1–40) and AD among DS was inconsistent. Inflammatory based proteins were more reliably found to be elevated leading to preliminary work focused on an algorithmic approach with predominantly inflammatory based proteins to detect AD and MCI as well as predict risk of incidence among DS. Separate work has also shown remarkable diagnostic accuracy with the use of a single protein (NfL) as compared to combined proteomic profiles. This review serves to outline the current state of the literature and highlight potential plasma-based biomarkers for use in detecting AD and MCI among this at-risk population.

Keywords

Down syndrome; Alzheimer's disease; plasma; blood-based biomarkers

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CONFLICT OF INTEREST

SEO has multiple patents pending related to precision medicine technologies for neurodegenerative diseases. He is the founding scientist of Cx Precision Medicine and has served on an Advisory Board for Roche Diagnostics. MEP has nothing to disclose.

INTRODUCTION

Down Syndrome (DS) occurs in 1:700 births making it one of the most common genetic disorders in the United States ("Improved national prevalence estimates for 18 selected major birth defects--United States, 1999–2001," 2006; Presson et al., 2013). Children born with DS often present with an increased risk for a variety of health conditions including intellectual disability, physical abnormalities (facial malformations), congenital heart disease, cancer, premature aging, and neurodegenerative disease (Benhaourech, Drighil, & Hammiri, 2016; Bhatnagar, Nizery, Tunstall, Vyas, & Roberts, 2016; Coppus et al., 2012; Fortea et al., 2018; Maloney, Taub, Ravindranath, Roberts, & Vyas, 2015; Tanji et al., 2000). DS results from an extra copy of chromosome 21 and due to this triplication, it is commonly referred to as trisomy 21(Korenberg et al., 1990; Rahmani et al., 1989). Chromosome 21 itself contains around 300 genes, one of those genes encodes for the amyloid precursor protein (APP)(Rahmani et al., 1989; Tanzi et al., 1987).

An over-expression of the APP gene occurs due to this triplication and produces higher rates of APP deposition and accumulation of amyloid beta (Aβ) (Bartha & Soothill, 2005; Wavrant-De Vrieze et al., 1999; Wisniewski, Wisniewski, & Wen, 1985). Such elevations correspond with neuropathological findings that implicate higher amounts of senile plaques and neurofibrillary tangles in individuals with DS (Goldgaber, Lerman, McBride, Saffiotti, & Gajdusek, 1987; Lott & Head, 2019; Robakis et al., 1987; Teipel & Hampel, 2006). Similar neuropathological features are commonly found in Alzheimer's Disease (AD) dementia and it is estimated that by age 40, all individuals with DS present with some form of AD neuropathology(Zana, Janka, & Kalman, 2007). Rates of AD dementia among individuals with DS reach as high as 77% between the ages of 60–69 (Lott & Head, 2019; Zana et al., 2007). Although rare, several case studies have been conducted among individuals with partial trisomy 21(PT21) who are disomic for APP and present without clinical or neuropathological signs of AD dementia (Doran et al., 2017; Prasher et al., 1998). Such findings highlight the link between trisomy 21 and development of AD neuropathology.

Diagnosis of AD dementia can be particularly challenging among individuals with DS due to intellectual disability, which may mask subtle changes in cognitive functioning(Sabbagh & Edgin, 2016). Brief cognitive screeners traditionally used in medically settings to evaluate for AD dementia such as the Mini Mental Status Examination(Folstein, Folstein, & McHugh, 1975) are inappropriate for use within this population due to their low premorbid level of cognitive functioning. To address limitations posed by traditional screening tools, newer measures have been created to specifically evaluate cognitive dysfunction among individuals with lowered intellectual functioning including the Dementia Scale for Mentally Retarded persons (DMR)(Evenhuis, 1992), Test of Severe Impairment(Albert & Cohen, 1992), and the National Task Group (NTG)- Early Detection Screen for Dementia (Esralew et al., 2013).

More specific screening tools such as the Down Syndrome Dementia Scale (Gedye, 1995), Down Syndrome Mental Status Exam(Haxby, 1989), and the Cognitive Scale for Down Syndrome (CS-DS)(Startin, Lowe, Hamburg, Hithersay, & Strydom, 2019) have been further

developed to assess cognitive decline among individuals with DS. However, despite these efforts, research has suggested that early symptoms of AD dementia likely manifest as personality and behavioral changes as well as a decline in executive functioning compared to traditional changes in memory(Ball, Holland, Treppner, Watson, & Huppert, 2008). As with conventional cognitive screening methods, early detection of disease presence may be limited, and subtle changes overlooked. Several of the screening tools specific to DS rely on informant report such as the CS-DS, which is subject to risk of over- or under-reporting of cognitive and functional changes.

Screening tools such as blood-based biomarkers have gained increased support as they are a minimally invasive and serve as a cost-effective means to detect AD dementia even in its prodromal stage (mild cognitive impairment [MCI]). This poses a tremendous advantage to populations such as DS where appropriate screening tools are limited and often completed by informants. Blood-based tools can potentially increase access via rapidly scalable, cost-effective and minimally invasive methods that can complement and enhance other tools, such as cognitive screening tools. A majority of blood-based biomarkers evaluating AD dementia among individuals with DS span blood fraction (serum, plasma) and cerebral spinal fluid (CSF). Understanding changes throughout the disease progression is important particularly in this at-risk population and therefore the aim of this review was to evaluate the current state of the literature of blood-based biomarkers found in individuals with DS as well as evaluate those with DS and an established diagnosis of AD or MCI.

METHODS

A review of the current state of knowledge on blood-based biomarkers of DS with AD dementia was conducted. For this review, the following electronic databases were searched: PubMed/Medline and Scopus by using keywords Down syndrome, blood-based, biomarkers, and Alzheimer's disease. Additional methods for identifying relevant studies included examining cross-references from published reviews and original papers. Studies were limited to those published within the past 10 years. Exclusion criteria also included biomarkers specifically related to DNA/RNA (DNA methylation), cerebrovascular, or immune function (chemokines) to reduce the risk of analyzing mixed or acute pathology as well as biomarkers obtained by means other than blood (i.e. CSF, urine, and neuroimaging).

Blood-based biomarkers linked to just DS as well as DS plus AD dementia are listed in Table 1 and broken down by order of author's last name. As can be seen from Table 1, there is limited consistency in the identified biomarkers with even similar markers showing different directions within the same comparison group (i.e. Aβ peptides among individuals with DS versus healthy control cases). Furthermore, the platform on which the assays were conducted showed a wide range of variability with the greatest level of consistency shown among the use of ELISAs. Research comparing biomarkers across different fractions and platforms has shown little consistency due to the use of different approaches (O'Bryant et al., 2016; O'Bryant et al., 2014).

RESULTS

Out of the 24 studies that were identified, 21 included plasma biomarkers while 2 included serum biomarkers. One study was excluded from the total number because it was an explorative pilot analysis. Additionally, since most of the studies conducted on blood-based biomarkers in individuals with DS were assaying using plasma, we excluded the one study that analyzed only serum biomarkers. After applying exclusion criteria, 22 articles met criteria for inclusion.

The most prolific research conducted examining biomarkers of DS has involved biomarkers of neurodegeneration such as Aβ likely due to its downstream effect from the overexpression of the APP gene. Understanding the role that Aβ peptides play in the development of early aging and dementia has driven research to evaluate Aβ levels throughout the lifespan including gestation, infancy, and adolescence. Findings have shown that plasma Aβ1–42 concentrations are present in fetal blood samples of individuals with and without DS (Bartha & Soothill, 2005). Amniotic samples, however, did not contain this peptide (Bartha & Soothill, 2005). These findings were not shown to correlate with either maternal or gestational age (Bartha & Soothill, 2005). In adolescents (ages 10–15) with DS, Abdel-Meguid and colleagues (2013) found a significant increase in plasma Aβ1–42 concentrations when compared to individuals with DS under the age of 10.

Additional biomarkers of neuronal degeneration aside from Aβ 1–42 have been examined in adolescents with DS as compared to younger children with DS. Abdel-Meguid and colleges (2013) found a significant increase in advanced glycation end production receptors (RAGES) leucocytes. This same research also found a decrease in biomarkers related to neuronal regeneration (i.e. Nestin, CD34) in individuals with DS as compared to healthy controls pointing out a disproportionate balance between the process of degeneration and regeneration particularly among younger individuals with DS (Abdel-Meguid, Abdel-Salam, Abdel Latif, Korraa, & Ismaiel, 2013).

In adults, a high consensus of studies has found elevated plasma Aβ1–42 concentrations among individuals with DS regardless of dementia diagnosis when compared to healthy controls (Hamlett et al., 2017; Iulita et al., 2016; Mehta et al., 2003; Obeid, Hubner, Bodis, & Geisel, 2016). A 6-fold increase in rate of plasma Aβ 1–42 concentrations as well as a 1.5-fold increase in sAPPα concentrations were found when individuals with DS were compared to other individuals with intellectual disabilities (Conti, Galimberti, Piazza, Raggi, & Ferrarese, 2010). Severity of intellectual disability among individuals with DS was shown to be associated with higher plasma Aβ 1–42 concentrations in more profound cases compared to milder cases, similar results were shown for severe cases compared to moderate cases (Matsuoka et al., 2009).

The link between plasma Aβ peptides (Aβ1–42 and Aβ1–40) and AD dementia among individuals with DS is less clear. A number of studies have found higher plasma Aβ1–42 concentrations in those with DS who later went on to develop AD dementia (Coppus et al., 2012; Fortea et al., 2018; Iulita et al., 2016; Lee et al., 2016; Schupf et al., 2007; Schupf et al., 2001). When plasma Aβ1–42 concentrations were split into tertiles (low, middle, high),

Schupf and colleagues (2007) discovered that when compared to the lowest tertile, those in the middle and higher tertiles were 2.0 times as likely to develop AD dementia. This was found to be the case even after adjusting for age, gender, intellectual disability, and APOEe4 carrier status (Schupf et al., 2007). In contrast, other research has shown that plasma Aβ1–42 concentrations are lower among individuals with both DS and AD dementia relative to age-matched controls (Coppus et al., 2012; Head et al., 2011). This also corresponds with CSF findings that reveal lower Aβ1–42 concentrations among individuals with DS compared to healthy controls (Tamaoka et al., 1999; Tapiola, Soininen, & Pirttila, 2001) as well as lower in prodromal and AD dementia groups relative to health controls (Fortea et al., 2018). These findings reflect similar variability in plasma Aβ1–42 observed in the broader AD literature.

Among plasma biomarkers specifically, a decrease in Aβ1–42 concentrations coupled with an increase in proNGF levels correlated with cognitive decline overtime for adults with DS (Iulita et al., 2016). One study found risk for conversion to dementia over a 4 year follow-up was linked to decreased concentrations of Aβ1–42 and ratio of Aβ1–42:Aβ1–40 (Schupf et al., 2010). The Aβ1:42:Aβ1–40 ratio itself has been shown to be higher among individuals with DS as compared to healthy controls (Iulita et al., 2016; Matsuoka et al., 2009). This ratio was also found to be higher among those with DS and AD dementia as compared to those without dementia (Head et al., 2011; Iulita et al., 2016; Lee et al., 2016; Matsuoka et al., 2009). Among ApoeE4 carriers and non-carriers, higher concentrations of the Aβ1–42:Aβ1–40 ratio were identified among those individuals who have been diagnosed with AD dementia for over 4 years relative to those with less than 4 years since diagnosis (Prasher, Sajith, Mehta, Zigman, & Schupf, 2010). This contrasts findings from Schupf and colleagues (2011) who identified that conversion to dementia over 4 years was linked to a decreased ratio of plasma Aβ1–42:Aβ1–40.

Similar to Aβ1–42, conflicting results have been shown for plasma Aβ1–40 with some studies unable to identify a link between DS and AD dementia (Schupf et al., 2007) while other studies have shown elevated levels (Coppus et al., 2012; Fortea et al., 2018; Head et al., 2011; Iulita et al., 2016) or decreased levels (Lee et al., 2016). The link between plasma Aβ1–40 concentrations among individuals with DS and AD dementia may be less dependent on APOEe4 carrier status as both higher rates have been found among APOEe4 carriers as well as non-carriers (Head et al., 2011; Matsuoka et al., 2009). Lower rates of plasma Aβ1–40 were also found among APOEe4 carriers for those with dementia diagnosed over a 4-year time span (Prasher et al., 2010). Other studies indicated that APOEe4 carrier status did not affect either Aβ1–40 or Aβ1–42 levels nor did it increase the risk for dementia or age of onset (Jones, Hanney, Francis, & Ballard, 2009). The limited impact of APOEe4 carrier status may be related to low prevalence rates that fall as low as 20–22% among individuals with DS (Conti et al., 2010; Matsuoka et al., 2009) with that percentage increasing to only 33% for those individuals with DS and AD dementia (Head et al., 2011). Additionally, APOEe2 was not found to exert a protective effect among DS as is usually found (Jones et al., 2009).

Although research efforts have more broadly evaluated the link between tauopathies and AD dementia, fewer studies have been conducted among individuals with DS. This is because

unlike the APP gene, the Tau gene is not directly impacted by the triplication of chromosome 21 (Hamlett et al., 2017). Of the work that has been conducted, research has focused heavily on the link between plasma t-tau in individuals with DS as compared to healthy controls with consistent findings showing elevated levels (Kasai et al., 2017; Lee et al., 2016). Exosomal findings have also revealed increased plasma phosphorylated-tau (P-tau; P-T181-tau and P-S96-tau) in younger individuals with DS that extends into late adulthood (Hamlett et al., 2017). Although the Tau gene itself is not directly impacted, other genes located on chromosome 21 such as superoxide dismutase 1 (SOD1) have been proposed as a mechanism for increasing AD pathology through indirectly dysregulating Tau proteins (Hamlett et al., 2017). SOD has also been considered to be a marker of oxidative stress. Increased total SOD along with other markers of oxidative stress such as MDA in plasma have been identified among children with DS as compared to health controls (He et al., 2016). Glutathione peroxidase (GPx3) also found in plasma works to protect cells from oxidative damage and in children, GPx3 has been shown to be reduced (He et al., 2016). As oxidative stress is considered to play a role in cellular aging, higher levels of SOD and MDA along with lowered levels of GPx3 may play a critical role in the progression of AD neuropathology early on in individuals with DS.

Recent work has examined the utility of blood-based biomarker profiles in detecting clinically-defined MCI (prodromal AD) and AD dementia as well as predicting risk among adults with DS (S. O'Bryant et al., 2018). When applying a previously validated proteomic screen for AD dementia in the general population (O'Bryant et al., 2016; O'Bryant et al., 2014), the proteomic algorithm was able to detect AD dementia (AUC=0.88) and MCI (AUC=0.95). The proteomic profile also predicted risk for incidence of MCI (AUC=0.93) and AD dementia (AUC=0.86). As with AD in the general population, there was a heavy loading of inflammatory based biomarkers in the overall algorithm suggesting the notion of a pro-inflammatory subgroup in AD dementia among those with DS as has been found in AD dementia in the general population (S. O'Bryant et al., 2018). Similar elevations in proteins were identified by Iulita and colleagues (2016) who found higher plasma ProNGF, MPP-1, MMP-3, MMP-9, IFN-y, TNF-α, IL-6, IL-8, and IL-10 among individuals with DS and AD dementia as compared to healthy controls (Iulita et al., 2016). Interestingly, plasma TNF-α, IL-6, and IL-10 were identified as being elevated in those with DS but without dementia (Iulita et al., 2016). Taken together, these studies more consistently point to elevations across multiple inflammatory based biomarkers (pro-and anti-inflammatory) among DS cases as well as those with DS and MCI/AD dementia (Iulita et al., 2016; S. O'Bryant et al., 2018).

Proteomic profiles derived from the identified blood-based biomarkers (referenced above) were able to accurately predict incidence of MCI and AD among those with DS based on an optimized SVM-based risk score of −0.899 and −0.994, respectively (S. O'Bryant et al., 2018). Additional work from Fortea and colleagues (2018) found comparatively lower diagnostic accuracy for plasma biomarkers Aβ1–40, Aβ1–42, and t-tau as compared to NfL, which had a receiver operating characteristic (ROC) of 0.88 for distinguishing DS from those with DS plus prodromal AD. When compared to those with DS and AD dementia, the highest ROC was for NfL, which reached 0.95 (Fortea et al., 2018). Similar results were found when examining the same biomarkers in CSF (Fortea et al., 2018). Plasma NfL

concentrations were also shown to be superior as compared to utilizing a combination of plasma and CSF biomarkers (plasma Aβ1–42; Aβ1–40, CSF Aβ1–42:t-tau, or CSF Aβ1–42:p-tau) (Fortea et al., 2018). In this study, NfL concentrations exhibited a strong plasma-CSF correlation for individuals with DS with a CSF threshold of 624.6 pg/mL shown to produce a sensitivity of 1.00 and specificity of 0.87(Fortea et al., 2018). Additional work has further identified elevated levels of NfL in individuals with DS and dementia as well as in those who developed dementia at follow-up (Strydom et al., 2018).

DISCUSSION

A number of studies have examined a wide range of blood-based biomarkers to help elucidate the link between DS and AD. A major goal of the identification of blood-based biomarkers for AD among individuals with DS is the generation of cost-effective, scalable, and non-invasive first-step methods for screening into novel clinical trials. Work outlined above suggests that blood-based biomarkers have utility in not only detecting prevalent MCI and AD but also predicting those at greatest risk, both of which can be of significant use to trial screening that would decrease costs, increase access while also reducing participant burden. In the future, and when possible, these blood-based biomarkers should be compared against the 2018 AT(N) (β Amyloid deposition, pathologic tau, and neurodegeneration) framework (Jack et al., 2018).

Although AD pathology has been shown in almost all individuals with DS by the age of 40, cognitive changes related to AD often present differently and at a later time-point thus raising the importance of heterogeneity of disease presence and progression. Most of the research efforts have focused on plasma biomarkers, while some included serum and CSF biomarkers. The majority of the findings have shown a strong link with Aβ peptides, primarily Aβ 1–42, which corresponds with the overexpression of APP gene. However, the direction of Aβ peptides has been less consistent as studies have shown both over- and under-expression of Aβ 1–40 and Aβ 1–42. When looking at traditional genetic markers for AD, APOEe4 carrier status appears to have less impact among individuals with DS while APOEe2 has not shown the same protective effect as is usually observed. An increased search in the understanding of non-amyloid pathological pathways will be of tremendous importance in understanding AD among individuals with DS. Additionally, future work should specifically examine the extent that blood-based biomarkers overlap for AD among individuals with and without DS and explore the role biomarkers such as NfL play in traditional neurodegeneration versus the AD neuropathogenesis seen among individuals with DS. The recent NfL work suggests this may be a very promising marker for use in this population; however, additional prospective work is needed to define the exact context of use (COU) where this biomarker may offer utility for advancing trials and/or patient care.

As highlighted in this review, inflammatory markers have been shown more consistently to be altered in both DS and AD in DS. In our preliminary work (Petersen et al., unpublished data), the proteomic profile of AD and MCI among adults with DS was heavily weighted with inflammatory biomarkers. This work, and that by others such as Head and colleagues, suggest that there is a subgroup of adults with DS and AD that have substantial dysfunction in inflammation, which may reflect a specific subgroup (proinflammatory endophenotype)

of patients most likely to benefit from anti-inflammatory interventions or perhaps anti-inflammatory + anti-amyloid interventions. In fact, we have shown that a proinflammatory endophenotype exists in the general population and that this subgroup identifies a subset of AD patients most likely to benefit from NSAID or multi-modal NSAID + anti-amyloid therapy (S. E. O'Bryant et al., 2018). There is also evidence of metabolic dysfunction in DS, which may point towards a different subgroup (metabolic endophenotype) that may benefit from multi-modal amyloid + anti-diabetic medications. Overall, the biological and clinical heterogeneity of AD in DS makes this an ideal scenario for a novel precision medicine trial approach.

The recently established Alzheimer's Biomarker Consortium – Down Syndrome (https://www.nia.nih.gov/research/abc-ds) offers an infrastructure and resource to rapidly advance blood-based biomarkers in AD in DS. Ongoing ABC-DS efforts are seeking to expand and build on findings highlighted here with a goal of the generation of a precision medicine approach for treating and delaying AD in adults with DS. The ABC-DS is examining proteomic, metabolomic, genomic biomarkers in adults with DS and their relation to the development and progression of AD. Additionally, the London Down Syndrome Consortium (LonDownS Consortium) and Down Alzheimer Barcelona Neuroimaging Initiative (DABNI) cohorts are rapidly advancing the science on novel biomarkers for adults with DS. The current status of the field suggests that blood-based biomarkers can have utility in a precision medicine approach for detecting and predicting AD in adults with DS as well as the identification of specific subgroups that may respond to specific therapies. This work needs to be advanced to offer better solutions to families and patients.

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Table 1.

Blood based biomarkers linked with Down syndrome and Alzheimer's disease

Author	Sample	Platform	Blood Fraction	Biomarker	DS	DS + AD	Other
Abdel-Meguid, et al., 2013	N= 30 HC N=23 DS below age 10 N=17 DS age 10–15	ELISA QIAGEN RNA	Plasma	Aβ1-42 RAGE CD34 Nestin	Aβ1-42↑ RAGES↑ Nestin↓ CD34↓		
Bartha and Soothill, 2004	N=17 HC N=13 DS (fetal)	BioSource	Plasma	Aβ1-42			Aβ1-42↑(fetal blood)
Borelli, et al., 2015	N=76 DS N=37 DS-siblings (DSS) N=42 DS-mothers (DSM)	PNGase F Roche Diagnostics	Plasma	N-glycome	H3N4↑ H3N4F1↑ H3N5 ↑ H3N5F1 ↑		
Conti, et al., 2010	N=18 HC N=24 DS N=10 non-DS ID with perinatal brain injury	Biosource Qiagen	Plasma	sAPPα Aβ1-42 APOE4	sAPPα↑		Aβ1-42↑ (DS vs. ID)
Coppus, et al., 2012	N=506 DS	xMAP technology (Luminex200)	Plasma	Aβ1-40 Aβ1-42		Aβ1-40↑	Aβ1-42↑ (developed AD dementia at follow-up) Aβ1-42↓ (AD dementia at baseline)
Fortea, et al., 2018	N=67 HC N=194 DS N=39 DS+ prodromal AD N=49 DS +AD dementia	ELISA	CSF Plasma	Aβ1-40 Aβ1-42 t-tau NfL p-tau	Plasma Aβ1-40↑ Plasma Aβ1-42↑ Plasma NfL↑	Plasma Aβ1-40↑ Plasma t-tau↓ Plasma NfL↑ CSF t-tau↑ CSF p-tau↑ CSF NfL↑	Plasma t-tau↑ (AD dementia vs. HC) Plasma NfL↑ (Prodromal AD and AD dementia vs. HC) CSF Aβ1-42↓ (Prodromal AD and AD dementia vs. HC) CSF t-tau, p-tau, NfL ↑ (Prodromal AD and AD dementia vs. HC)
Hamlett, et al., 2016	N=37 HC N= 80 DS	ELISA	Serum Plasma	Aβ1-42 P-T181-tau P-S96-tau	Aβ1-42↑ P-T181-tau↑ P-S96-tau↑		
He, et al., 2016	N=40 HC N=36 DS (children)		Plasma	SOD GPx3 MDA NOS	SOD ↑ GPx3 ↓ MDA ↑		
Head, et al., 2011	(Study 1) N=11 HC matched to DS N=12 HC matched to AD N=17 DS N=17 possible or	MagNA-Pure ELISA	Plasma	APOE Aβ 1-42 Aβ 1-40		Aβ1-40↑ (with APOEe4)	Aβ1-42↓ (AD vs. HC) Aβ1-42:Aβ1-40↑ (AD vs. HC)

Author	Sample	Platform	Blood Fraction	Biomarker	DS	DS + AD	Other
	probable AD (Study 2) N=52 DS +AD N=26 DS						
Iulita, et al., 2016	N=31 HC N=31 DS	6E10 Western blotting ELISA MesoScale Discovery	Plasma	Aβ 1-40 Aβ 1-42 Aβ 1-38 proNGF neuroserpin tPA MMP-1 MMP-3 MMP-9 TNF-α IL-6 IL-10 IFN-y IL1-β IL-2 IL-4 IL12p70 IL-13 APOE	Aβ 1-40 ↑ Aβ 1-42↑ Aβ1-42:Aβ1-40↑ ProNGF↑ MMP-1↑ MMP-3↑ MMP-9 ↑ TNF-α↑ IL-6↑ IL10↑	Aβ 1-40 ↑ Aβ 1-42↑ Aβ1-42:Aβ1-40↑ IFN-y↑ TNF-α↑ IL-6↑ IL-8↑ IL-10↑	
Jones, et al., 2009	N=60 DS	PCR ELISA	Plasma	Aβ 1-40 Aβ 1-42 APOE		No association	
Kasai, et al., 2017	N=22 HC N=21 DS	Simoa HD-1 (Quanterix)	Plasma	t-tau	t-tau↑		
Lee, et al., 2016	N=78 HC N=62 AD N=35 DS N= 16 DS +AD	IMR XacPro-S, MagQu	Plasma	Aβ 1-40 Aβ 1-42 Tau	Aβ1-40↑ t-tau↑ Aβ1-42↓ Aβ1-42:Aβ1-40↓	Aβ1-40↓ Aβ1-42↑ Aβ1-42:Aβ1-40↑	
Matsuoka, et al., 2009	N=198 DS	Immuno-blotting	Plasma	Aβ 1-40 Aβ 1-42 APOE	Aβ1-40↑ (APOEe4 non-carriers)	Aβ1-42:Aβ1-40↑	Aβ1-42↑ (profound MR vs mild MR) Aβ1-42↑ (severe MR vs moderate MR)
Mehta, et al., 2003	N=50 HC N=50 DS	6E10	Plasma	Aβ 1-40 Aβ 1-42	Aβ1-42↑		
O'Bryant, et al., 2018a	N=356 DS N=42 DS +AD N=54 DS +MCI	MesoScale Discovery	Plasma	FABP B2M PPY CRP ICAM-1 THPO A2M Exotaxin 3 TNF-α Tenascin-C IL-5 IL-6 IL-7 IL-10 IL-18 I-309 Factor VII VCAM1 TARC SAA		IL-6↑ CRP↑ I-309 ↑ IL-10↑ SAA↑ TPO↑ PPY↑ Tenascin C↑ TARC↑	DS + MCI (prodromal AD) IL-10↑ FABP3↑ Exotaxin3↑ SAA↑ IL-5↑ TNF-α↑ I-309↑ PPY↑ IL-7↑ CRP↑
Obeid, et al., 2016	N=44 HC N=31 DS	ELISA	Plasma	Aβ 1-42	Aβ 1-42↑		

Author	Sample	Platform	Blood Fraction	Biomarker	DS	DS + AD	Other
Prasher, et al., 2010	N=83 DS N=44 DS +AD	6E10 Applied Biosystems	Plasma	Aβ1-42 Aβ 1-40 APOE			>4 years dx of AD vs. <4 years Aβ1-40↓ Aβ1-24:Aβ1-40↑ Aβ1-42↑ (APOEe4 non-carrier) Aβ1-42:Aβ1-40↑ (APOEe4 non-carrier) Aβ1-40↓ (APOEe4carriers) Aβ1-42:Aβ 1-40↑ (APOEe4carriers)
Schupf, et al., 2001	N=64 HC N=97 DS N=11 DS +AD	6E10	Plasma	Aβ 1-42 Aβ1-40	Aβ 1-42↑ (APOEe4 carrier vs. non-carriers)	Aβ 1-42↑ (APOEe4 carrier)	
Schupf, et al., 2007	N=207 DS	6E10 PCR	Plasma	Aβ 1-42 Aβ 1-40 APOE		Aβ 1-42↑	Aβ 1-42↑ (dementia at baseline)
Schupf, et al. 2010	N=164 DS N=61 DS +AD N=3 DS+ mixed dementia	6E10 PCR	Plasma	Aβ 1-42 Aβ 1-40 APOE			Conversion to dementia 4-year follow-up Aβ1-40↑ Aβ1-42↓ Aβ1-42:Aβ1-40↓
Strydom et al., 2018	N=94 DS (N=18 dementia at baseline)	HD-1 Simoa (Quanterix)	Plasma	NfL			NfL↑ (dementia at baseline) NfL↑ (dementia at baseline vs. follow-up)

Note: Alzheimer's disease (AD); Amyloid beta (Aβ); Apolipoprotein (APOE), Beta 2 Microglobulin (B2M); C-reactive protein (CRP); Cerebral spinal fluid (CSF); Down syndrome (DS); Enzyme-linked immunosorbent assay (ELISA); Extracellular glutathione peroxidase (GPx3); Fatty acid binding protein (FABP); Healthy Control (HC); High mobility group box-1 (HMGB-1); Intercellular Adhesion Molecule 1 (ICAM1); Intellectual Disability (ID); Interleukin (IL18); Interleukin 1 beta (IL1β); Interleukin 10 (IL10); Interleukin 5 (IL-5); Interleukin 6 (IL6); Interleukin 7 (IL7); Malondialdehyde (MDA); Mental retardation (MR); Mild Cognitive Impairment (MCI); Neurofilament light protein (NfL), Nitric oxide synthase (NOS); Pancreatic polypeptide (PPY); Polymerase chain reaction (PCR); Ribonucleic acid (RNA); s-adenosylhomocysteine (SAH); s-adenosylmethionine (SAM); Soluble amyloid precursor protein alpha (sAPPα); Serum amyloid A (SAA); Superoxide dismutase (SOD); Vascular cell adhesion molecule 1 (VCAM1); Thymus and activation regulated chemokine (TARC); Tenascin C (TNC); Thrombopoietin (THPO); Tumor Necrosis Factor Alpha (TNFα); α2 macroglobulin(A2M).