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Plasma metabolites associated with biomarker evidence of neurodegeneration in cognitively normal older adults

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Alphabetical list of abbreviations

AC: Acylcarnitine

AD: Alzheimer's disease

ADMA: Asymmetric dimethylarginine

ALS: Amyotrophic lateral sclerosis

APOE: Apolipoprotein E genotype

A β : Amyloid- β

A β -: Low brain amyloid- β load

A β +: High brain amyloid- β load

BP: Blood pressure

C: *APOE* ϵ 4 carriers

CE: Cholesteryl ester

CKD: Chronic kidney disease

CSF: Cerebrospinal fluid

DASS: Depression, anxiety, stress scales

DG: Diglyceride

FBB: ^{18}F -Florbetaben

HRAM-MS: High-resolution accurate mass - mass spectrometer

KARVIAH: Kerr Anglican Retirement Village initiative in ageing health

LLOD: Lower limit of detection

Lyso-PC: Lyso- phospholipid with choline head group

MCI: Mild cognitively impaired

Met-SO: Methionine sulfoxide

MMSE: Mini-mental state examination

MoCA: Montreal cognitive assessment

MRI: Magnetic resonance imaging

NC: *APOE* ϵ 4 non-carriers

NF-L: Neurofilament light chain

NO: Nitric oxide

NOS: Nitric oxide synthase

PC: Phospholipid with choline head group

PD: Parkinson's disease

PET: Positron emission tomography

QC: Quality control

SDMA: Symmetric dimethylarginine

Simoa: Single molecule array

SM: Sphingomyelin

SUVR: Standard uptake value ratio

t4OH-Pro: Trans-4-hydroxyproline

TG: Triglyceride

UHPLC: Ultra-high-performance liquid chromatography

Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that currently has no cure. Identifying biochemical changes associated with neurodegeneration prior to symptom onset, will provide insight into the biological mechanisms associated with neurodegenerative processes, that may also aid in identifying potential drug targets. The current study therefore investigated associations between plasma neurofilament light chain (NF-L), a marker of neurodegeneration, with plasma metabolites that are products of various cellular processes. Plasma NF-L, measured by ultrasensitive Single molecule array (Simoa) technology (Quanterix) and plasma metabolites, measured by mass-spectrometry (AbsoluteIDQ® p400HR kit, BIOCRATES), were assessed in the Kerr Anglican Retirement Village Initiative in Ageing Health (KARVIAH) cohort comprising 100 cognitively normal older adults. Metabolites belonging to biogenic amine (creatinine, symmetric dimethylarginine, asymmetric dimethylarginine; ADMA, kynurenine, trans-4-hydroxyproline), amino acid (citrulline, proline, arginine, asparagine, phenylalanine, threonine) and acylcarnitine classes were observed to have positive correlations with plasma NF-L, suggesting a link between neurodegeneration and biological pathways associated with neurotransmitter regulation, nitric oxide homeostasis, inflammation and mitochondrial function. Additionally, after stratifying participants based on low/high brain amyloid- β load ($A\beta$ -/+) assessed by positron emission tomography, only ADMA, proline, arginine, asparagine, phenylalanine and acylcarnitine species continued to correlate with NF-L in the $A\beta$ + group, suggesting that the association of these metabolites with neurodegeneration may be relevant to AD-related neuropathology. Metabolites identified to be associated with plasma NF-L may have the potential to serve as prognostic markers for neurodegenerative diseases, however, further studies are required to validate the current findings in an independent cohort, both cross-sectionally and longitudinally.

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, characterised by extracellular amyloid- β (A β) deposits, intracellular tau aggregates and neuronal loss (Masters *et al.* 2015). In 2019, nearly 50 million people worldwide were estimated to have AD or another form of dementia and this statistic is expected to escalate to over 150 million by 2050 (Alzheimer's Disease International 2019). Currently AD is incurable, despite significant investments in clinical trials targeted towards effective treatments. Identifying metabolites associated with neurodegeneration prior to symptomatic manifestation of the disease may examine the problem from a different perspective and help to reveal early pathological steps in the cellular mechanisms involved in the AD neurodegenerative process. It may also provide further insight into the identification of potential drug targets for AD and other neurodegenerative diseases.

Neurofilament light chain (NF-L), an axonal cytoskeletal protein, is increased in the cerebrospinal fluid (CSF) and blood in several neurodegenerative diseases, including AD (Backstrom *et al.* 2015; Pijnenburg *et al.* 2015; Scherling *et al.* 2014; Novakova *et al.* 2017; Gaiottino *et al.* 2013; Hansson *et al.* 2017; Zetterberg *et al.* 2016; Mattsson *et al.* 2017). This

increase has been attributed to the axonal damage occurring in neurodegenerative disorders, resulting in increased neuronal NF-L release into the interstitial fluid with subsequent diffusion into the CSF and blood. Therefore, CSF and blood NF-L levels are increasingly being recognised as features of neurodegeneration.

In AD, CSF NF-L concentrations have been reported to correlate with disease pathology and poorer cognitive performance (Zetterberg *et al.* 2016). Further, blood NF-L concentrations have also been reported to correlate with AD pathology and cognitive performance in cognitively normal older adults, mild cognitively impaired (MCI) and/or AD individuals (Chatterjee *et al.* 2018b; Mattsson *et al.* 2017). Similar findings have been reported in familial AD, where blood NF-L concentrations were higher in pre-symptomatic familial AD individuals, and predicted cognitive changes (Preische *et al.* 2019; Weston *et al.* 2017; Weston *et al.* 2019).

Within the current study, we investigated associations between plasma NF-L, a marker of neurodegeneration, and plasma metabolites that reflect various cellular processes. Additionally, the current study also evaluated associations between plasma NF-L and plasma metabolites separately in individuals at risk of AD, characterised by high brain A β load assessed by positron emission tomography (PET), given that the abnormal build-up of A β in the brain begins up to two decades prior to AD symptom onset (Villemagne *et al.* 2013; Asih *et al.* 2014). Further, for metabolites that associated with NF-L, correlations were investigated with cognitive performance, hippocampal volume and brain A β load.

Methods

Participants

All participants from the Kerr Anglican Retirement Village Initiative in Ageing Health (KARVIAH) met the inclusion and exclusion screening criteria. The inclusion criteria comprised an age range of 65-90 years, good general health and no known significant cerebral vascular disease, fluency in English, adequate or corrected vision and hearing, and no dementia or other pathological cognitive impairment based on a Montreal Cognitive Assessment (MoCA) score ≥ 26 . The study neuropsychologist assessed MoCA scores between 18-25, on a case by case basis, using age and education adjusted norms (Rossetti *et al.* 2011). The exclusion

criteria comprised, previous diagnosis of dementia, presence of acute functional psychiatric disorder, history of stroke, depression (based on the depression, anxiety, stress scales; DASS) and uncontrolled hypertension (systolic BP>170 or diastolic BP>100). One-hundred and five participants out of the 134 volunteers meeting the inclusion/exclusion criteria underwent blood collection, neuroimaging and neuropsychometric evaluation, while the remaining volunteers either declined neuroimaging or withdrew from the study. Of these 105 participants, 100 were considered cognitively normal based on their Mini Mental State Examination score (MMSE ≥ 26) and were included in the current study. All volunteers provided written informed consent prior to participation and the Bellberry Human Research Ethics Committee, Australia (reference no. 2012-09-1086) and the Macquarie University Human Research Ethics Committee (reference no. 5201701078) provided approval for the study. This study was not pre-registered. This study utilized the entire cohort size available that met the set inclusion/exclusion criteria, and therefore no blinding was required.

Blood collection and APOE genotyping

Prior to blood withdrawal in the morning, all participants fasted overnight for a minimum of ten hours. The blood drawn was fractionated as described previously (Ellis *et al.* 2009), and stored at -80°C , in 2015. Apolipoprotein E (*APOE*) genotype was determined from purified genomic DNA extracted from 0.5 ml whole blood as previously described (Goozee *et al.* 2018).

Measurement of NF-L

The ultra-sensitive Single molecule array (Simoa) assay platform (Quanterix, Billerica, MA) was employed to measure plasma NF-L concentrations in 2018. All calibrators were run in duplicate. Samples were diluted 4-fold and run in singlicates. Two quality control (QC) samples were run in duplicates at the beginning and end of each plate (Chatterjee *et al.* 2019). A QC sample with a concentration of 12.1 pg/mL had repeatability and intermediate precision of 20.2%, and a QC sample with a concentration of 155.8 pg/mL had repeatability of 14.6% and intermediate precision of 14.9%.

Measurement of plasma metabolites

Employing a targeted metabolomics approach, endogenous plasma metabolite concentrations were measured in 2019 using the AbsoluteIDQ® p400 HR kit (BIOCRATES Life Science AG, Innsbruck, Austria) on an ultra-high-performance liquid chromatography (UHPLC - Thermo Scientific™ Vanquish™) interfaced with a high-resolution, accurate mass, mass spectrometer

(HRAM-MS - Thermo Scientific™ Q Exactive Plus™) platform. The AbsoluteIDQ® p400 HR kit can measure up to 408 endogenous metabolites quantitatively (amino acids and biogenic amines) and semi-quantitatively (acylcarnitines, sphingolipids, choline head group phospholipids, diglycerides and triglycerides) (https://biocrates.com/wp-content/uploads/2020/02/Biocrates_p400_metabolites.pdf).

Within the current study, plasma samples were de-identified, randomised and blinded prior to being analysed according to the manufacturer's protocol. Test samples were run in singlicates, however a quality control sample (QC2; provided by the manufacturers) was placed after every 19-20 test samples in each kit plate (resulting in five QC2 replicates/plate) to examine consistency in quantitative performance throughout the analysis of each plate and for normalising intra-plate and inter-plate variation (refer to Supplementary Material). Within the current study, metabolites with >40% of measurements below the lower limit of detection (LLOD) were excluded from analysis (Toledo *et al.* 2017). Based on this criteria, 216 metabolite species in the plasma were analysed within the current study, consistent with a report by Thompson and colleagues (Thompson *et al.* 2019).

Neuropsychological testing

The MMSE (Folstein *et al.* 1975) scores were utilised as the primary measure for global cognitive ability assessment within the current study. The MMSE scores range from 0-30, with higher scores indicating better cognitive function and a cut off score below 26 was used for screening out the potential dementia patients. A primary cognitive performance outcome measure was calculated by generating a global composite score for each participant that included verbal and visual episodic memory, as well as, working memory and executive function as described previously (Chatterjee *et al.* 2018b). The specific neuropsychological tests used to generate the global composite score have been listed in Table 1.

Assessment of brain A β load via PET

Participants underwent A β PET imaging with ¹⁸F-Florbetaben (FBB) and magnetic resonance imaging (MRI) at Macquarie Medical Imaging in Sydney within three months of blood collection. A 4x5 min static scan was acquired 50 min post intravenous injection of FBB. Brain A β load was calculated using CapAIBL (Zhou *et al.* 2014; Bourgeat *et al.* 2015) as the mean standard uptake value ratio (SUVR) of the neocortical region including the frontal, superior parietal, lateral temporal, lateral occipital, and anterior and posterior cingulate regions

normalized to the cerebellar cortex. A cut-off score of 1.35 SUVR was used to categorise participants with low brain A β load (A β -, SUVR<1.35, n=65) and high brain A β load (A β +, SUVR $\geq$ 1.35, n=35). Ninety-six of the 100 participants from the KARVIAH cohort underwent 3D MRI as described previously using a General Electric 3Tesla scanner (Model 750W) (Goozee *et al.* 2017). Hippocampal volumes were calculated from the T1 MRI images acquired and was normalized to the total intracranial volume comprising the cerebrospinal fluid, grey matter and white matter.

Statistical analyses

Descriptive statistics including means and standard deviations were calculated for A β - and A β + groups. Chi-square tests were employed to compare categorical variables between A β - and A β + groups. Pearson's correlation coefficient was employed to investigate correlations between plasma NF-L and plasma metabolite concentrations in all participants. Additionally, partial correlations were used to investigate correlations between plasma metabolite concentrations and plasma NF-L after adjustment for covariates, age, sex, *APOE* ϵ 4 carrier status and body mass index (BMI), in all participants. Further, plasma metabolites that correlated with plasma NF-L in all participants, before and after adjusting for covariates, were further investigated for their association with plasma NFL after stratification of participants based on A β -/+ status, using Pearson's correlation coefficient and partial correlations. For plasma metabolites that correlated with plasma NF-L, Pearson's correlation coefficient and partial correlations, adjusting for the aforementioned covariates, were employed to investigate correlations between plasma metabolite concentrations and cognitive performance, hippocampal volume and brain A β load in all participants. Continuous response variables were natural log transformed as necessary, to better approximate normality (based on $p>.05$, Shapiro-Wilk test). No test for outliers was conducted. All participants from the Kerr Anglican Retirement Village Initiative in Ageing Health (KARVIAH) cohort met the inclusion and exclusion screening criteria. Therefore, no sample size calculation was carried out a priori, and no blinding was required - the entire cohort was utilized. All analyses were carried out using IBM® SPSS® Version 23.

Results

Participant characteristics

Study participant characteristics including sex, age, BMI, education, *APOE* $\epsilon 4$ carriage, MMSE scores, hippocampal volume, plasma NF-L and brain A β load are presented in Table 2. On stratifying participants based on A β -/+ status, no significant differences in participant characteristics were observed between the two groups, except for a significantly higher *APOE* $\epsilon 4$ carrier frequency in the A β + group compared to the A β - group, as expected (Polvikoski *et al.* 1995).

Association between AD risk factors (age, sex and APOE $\epsilon 4$ carriage) and plasma metabolites

Plasma metabolites observed to have significant associations with age and sex within the KARVIAH cohort are presented in Supplementary Table 1 and Supplementary Table 2, respectively. Briefly, the biogenic amines creatinine, symmetric dimethylarginine (SDMA) and methionine sulfoxide (Met-SO); the amino acids citrulline and proline; acylcarnitine (AC) and lyso-phospholipid with choline head group (lyso-PC) species correlated positively with age. The amino acid tryptophan along with PC, sphingomyelin (SM), cholesteryl ester (CE), diglyceride (DG) and triglyceride (TG) species were observed to correlate inversely with age (Supplementary Table 1). Furthermore, the biogenic amine creatinine; the amino acids, aspartate, glutamic acid, isoleucine, methionine, proline, valine and leucine; and species belonging to the AC, lyso-PC and TG classes were significantly lower in females; whereas the amino acid glycine along with metabolite species within the PC, SM, CE and DG classes were observed to be significantly higher in females (Supplementary Table 2). No significant differences in plasma metabolites were observed between *APOE* $\epsilon 4$ non-carriers (NC) and carriers (C), except for DG(44:3) ($p=0.030$, NC (mean $\pm$ SD): 2.23 ± 1.51 μ M, C: 3.07 ± 1.74 μ M).

Correlation between plasma NF-L and plasma metabolites

The biogenic amines, creatinine, SDMA, asymmetric dimethylarginine (ADMA), kynurenine and trans-4-hydroxyproline (t4OH-Pro) had positive associations with plasma NF-L levels, both, before and after adjusting for potential confounding variables such as age, sex, *APOE* $\epsilon 4$ carriage and BMI in all participants (Table 3, Figure 1A). After stratifying the cohort based on brain A β load status (A β -/+), creatinine and SDMA continued to correlate with plasma NF-L in both, A β - and A β + participants, before and after adjusting for the potential confounding variables. Kynurenine correlated significantly with plasma NF-L in A β - and A β + participants before adjusting for covariates, however, after adjusting for covariates kynurenine correlated

significantly with plasma NF-L in A β ⁺ participants and a trend level significance was observed in A β ⁻ participants. ADMA correlated with plasma NF-L only in A β ⁺ participants (Table 4).

Additionally, the amino acids citrulline, proline, arginine, asparagine, phenylalanine and threonine were observed to have positive correlations with plasma NF-L, before and after adjusting for covariates (Table 3, Figure 1B). After stratifying the cohort based on brain A β load, citrulline correlated with plasma NF-L in both A β ⁻ and A β ⁺ participants, while proline, arginine, asparagine and phenylalanine correlated with plasma NF-L only in A β ⁺ participants (Table 4).

Further, the acylcarnitine species AC(0:0), AC(2:0), AC(8:1), AC(10:0), AC(10:1), AC(10:2), AC(10:3), AC(12:1) and AC(14:1), were observed to have a positive correlation with plasma NF-L levels before and after adjusting for potential confounding variables (Table 3, Figure 1C). After stratifying the cohort based on brain A β load, all the above-mentioned AC species, except AC(8:1), correlated significantly with plasma NF-L, in A β ⁺ participants only (Table 4).

Correlation of cognitive performance, hippocampal volume and brain A β load with plasma metabolites associated with NF-L

The biogenic amines creatinine and SDMA, the amino acids phenylalanine and threonine and the acylcarnitine species AC(0:0), AC(8:1), AC(10:0), AC(10:2), AC(10:3), AC(12:1) and AC(14:1), were observed to correlate inversely with the global composite score before adjusting for covariates, however, only threonine and AC(12:1) correlated significantly with the global composite score after adjusting for potential confounding factors, age, sex, *APOE* ϵ 4 carriage and BMI (Table 5). Further, creatinine, ADMA and the acylcarnitine species AC(3:0), AC(8:1), AC(10:2) and AC(10:3), were observed to correlate inversely with hippocampal volume before adjusting for covariates, while the acylcarnitine species AC(10:0) was observed to correlate positively with brain A β load both before and after adjusting for the potential confounding factors (Table 5).

Discussion

The present study is the first to report on correlations between neurodegeneration, as assessed by the biomarker NF-L, and plasma metabolites representing various cellular processes. Significant associations were found between NF-L and metabolite species belonging to the

biogenic amine, amino acid and acylcarnitine classes, reflecting a link between neurodegeneration and biological pathways associated with neurotransmitter regulation, nitric oxide homeostasis, inflammation and mitochondrial function. Within the current study, we also found significant correlations between plasma metabolites that associated with biomarker evidence of neurodegeneration, and cognition, hippocampal volume and brain A β load.

The biogenic amine creatinine, correlated positively with plasma NF-L, suggesting a positive association between plasma creatinine levels and neurodegeneration. Creatinine was also observed to correlate inversely with cognitive performance and hippocampal volume within the current study. Blood creatinine levels have previously been reported to be higher in AD patients compared to healthy controls (Gonzalez-Dominguez *et al.* 2014) and also associate inversely with cognitive performance and brain volume (Rajagopalan *et al.* 2013). Furthermore, higher CSF creatinine levels have been reported in neurodegenerative diseases, such as AD and multiple sclerosis (van der Velpen *et al.* 2019; Lazzarino *et al.* 2017). In addition, longitudinal studies have reported that increased blood creatinine levels are associated with an increased risk of cognitive impairment and dementia, and faster rate of cognitive decline (Kurella *et al.* 2005; Khatri *et al.* 2009; Etgen *et al.* 2009; Seliger *et al.* 2015; Seliger *et al.* 2004). Our observations within the present study are in line with the above reports. While the exact mechanism behind these associations is not yet understood, a possible neurotoxic effect of creatinine could be mediated by its inhibitory potential towards gamma-aminobutyric acid receptors (De Deyn *et al.* 2009). Interestingly, in contrast to observations in the current study, lower blood creatinine concentrations have been reported in amyotrophic lateral sclerosis (ALS) patients compared to healthy controls, that also inversely correlated with severity (Lawton *et al.* 2012; Lawton *et al.* 2014). These contrasting findings could be attributed to the fact that loss of muscle mass is a feature of ALS and plasma creatinine is a function of muscle mass; while participants within the current study were asymptomatic healthy older adults. Alternatively, as creatinine is a well-known biomarker of renal function, this may reflect the fact that co-morbid renal disease is much less prevalent in ALS (Mitchell *et al.* 2015).

Plasma levels of the biogenic amines SDMA and ADMA, and the amino acids arginine and citrulline, involved in the nitric oxide (NO) production pathway, correlated positively with biomarker evidence of neurodegeneration, plasma NF-L. Further, SDMA had a significant inverse correlation with cognitive performance while ADMA showed an inverse correlation with cognitive performance with a trend towards statistical significance. Within the NO

pathway, nitric oxide synthase (NOS) catalyses the conversion of arginine to NO and citrulline. It is well known that NO has several beneficial functions given its antioxidant, anti-apoptotic and vasodilation enhancing properties (Leiper & Vallance 1999; Dimmeler *et al.* 1999). However, ADMA has NOS inhibitory properties and SDMA can inhibit cellular arginine uptake, thereby negatively affecting NO production. Therefore, our observations of positive associations of SDMA and ADMA with the plasma neurodegeneration marker were expected. In line with our observations, increased blood ADMA and SDMA levels have previously been reported to be associated with cognitive impairment, neuronal injury and neurodegenerative diseases (McEvoy *et al.* 2014; Pikula *et al.* 2009; Luneburg *et al.* 2012; Arlt *et al.* 2008; Selley 2003; Kirbas *et al.* 2016; Javadiyan *et al.* 2012). The positive associations of plasma arginine and citrulline with NF-L could be attributed to the inhibition of cellular uptake of plasma arginine by SDMA, and consequently, plasma arginine could be converting to plasma citrulline via ornithine (Marini 2012).

Notably, several of the metabolites that positively correlated with NF-L in the present study have also previously been reported as biomarkers of renal function, particularly creatinine and SDMA (Oliva-Damaso *et al.* 2019; Kielstein *et al.* 2006; Kassirer 1971; Schmidt & Baylis 2000). Interestingly, SDMA has been reported as having superior performance compared to other established glomerular filtration rate estimation (eGFR) methods in some populations (Kielstein *et al.* 2011). This is because almost all SDMA is cleared by renal filtration (Kakimoto & Akazawa 1970). We found that both creatinine and SDMA had strong associations with NF-L, supporting the possibility of renal dysfunction being associated with neurodegenerative changes. We also observed significant associations between plasma NF-L, and eGFR and urea (Supplementary Table 3), showing associations of NF-L with other renal parameters. It is important to note that the cohort used in this study was in good general health as specified by the inclusion criteria, therefore, individuals with severe kidney or other chronic disease would have been excluded. However, most people with chronic kidney disease (CKD) are asymptomatic until the late stages. Nevertheless, significant associations were also observed between plasma NF-L, and creatinine and SDMA in cohort participants not considered to be at-risk for CKD (based on creatinine levels $\leq 90 \mu\text{M}$ and $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$) and in participants reporting no past or present kidney disease (Supplementary Table 4). Results of the current study suggest that plasma metabolites linked to renal dysfunction are associated with biomarker evidence of neurodegeneration, however, the observed correlations in the present study are not attributed to a current kidney disease

diagnosis. It should also be noted that our knowledge on NF-L clearance from the blood is limited. Whether or not renal clearance is important will be an important topic in future studies.

Additionally, plasma kynurenine levels correlated positively with NF-L levels. This was expected, as discussed in detail previously (Chatterjee *et al.* 2019). The kynurenine pathway is upregulated in neuroinflammatory conditions and, associations of several metabolites from the kynurenine pathway (including kynurenine) with neurodegenerative diseases have been reported previously (Chatterjee *et al.* 2018a; Chang *et al.* 2018; Schwarz *et al.* 2013; Giil *et al.* 2017; Schwarcz *et al.* 2012; Lim *et al.* 2017; Jacobs *et al.* 2019).

Plasma proline levels were also found to correlate positively with NF-L. In line with this observation, a previous metabolomics study reported higher plasma proline levels in AD patients compared to controls (Wang *et al.* 2014); and Ibáñez and colleagues reported that CSF proline concentrations (along with other metabolites) could potentially be used to track AD progression (Ibanez *et al.* 2012). Given that proline has been reported to lower glutamate uptake in rat cerebral cortex *in vitro* and *in vivo* (Delwing *et al.* 2007), it could be posited that the positive association observed between proline and NF-L is attributed to the disruption in glutamate homeostasis with higher proline levels. However, further studies are required to validate this hypothesis.

Plasma levels of asparagine were also observed to have a positive correlation with plasma NF-L. Given that asparagine plays a role in the biosynthesis of glycoproteins (N-glycosylation), it could be posited that the positive correlation between asparagine and plasma NF-L may reflect a positive association between the propensity for post-translational modifications and plasma NF-L. The role of glycosylation in AD pathogenesis has been reviewed previously (Schedin-Weiss *et al.* 2014). However, in contrast to our observations, CSF asparagine levels have previously been reported to be lower in AD patients compared to controls (Jimenez-Jimenez *et al.* 1998). Further, Fiandaca and colleagues reported lower mean asparagine plasma levels in individuals with preclinical AD compared to controls (Fiandaca *et al.* 2015). Therefore, further studies are required to validate the associations observed between plasma asparagine and NF-L within the current study.

Additionally, the amino acid phenylalanine was observed to have a positive correlation with NF-L, and a negative correlation with cognitive performance in the present study. In line with our observations, higher plasma phenylalanine concentrations have previously been observed in individuals with amnesic MCI and AD compared to healthy controls (Ravaglia *et al.* 2004).

Higher levels of this amino acid have been associated with delirium (Flacker & Lipsitz 2000; van der Mast *et al.* 1999). Phenylalanine is a precursor for catecholamines. It has been posited that higher phenylalanine levels may result in brain damage by mechanisms including competition with other large neutral amino acids for transport carriers across the blood brain barrier, decreased protein synthesis in the brain, abnormalities in amine neurotransmitter systems and higher myelin turnover (Surtees & Blau 2000). Higher threonine levels were reported in advanced Parkinson's disease (PD) patients compared to early PD patients, suggesting an increase in plasma threonine concentrations with PD progression (Figura *et al.* 2018). These observations are in line with our observations of a positive correlation between threonine and NF-L.

Lastly, within the current study, levels of acylcarnitine species were observed to correlate positively with plasma NF-L. Several acylcarnitine species also had an inverse correlation with cognitive performance and hippocampal volume, and AC(10:0) showed a positive correlation with brain A β load. Acylcarnitines reportedly have protective neurobiological functions including maintaining synaptic morphology and neurotransmitter signalling (Gorini *et al.* 1996; Laschi *et al.* 1990; Bertoni-Freddari *et al.* 1994; Bertoni-Freddari *et al.* 1996; Curti *et al.* 1989; Davis *et al.* 1993; Piovesan *et al.* 1995; Imperato *et al.* 1989) as well as regulating brain energy (Pettegrew *et al.* 2000; Aureli *et al.* 1990; Aureli *et al.* 1994; Rosenthal *et al.* 1992). Lower blood acylcarnitine concentrations have been reported in individuals with amnesic MCI and AD compared to controls (Mapstone *et al.* 2014; Cristofano *et al.* 2016). The positive associations observed between NF-L and acylcarnitine species within the current study are therefore in the opposite direction of what was expected and may reflect a compensatory mechanism within the pre-symptomatic stages of neurodegeneration. However, in line with the current observations, acylcarnitines have also been reported to ameliorate A β associated oxidative stress and cell death *in vitro* (Dhitavat *et al.* 2002), therefore, further validation studies are required.

Interestingly, after stratifying participants by brain A β status (A β -/A β +), ADMA, proline, arginine, asparagine, phenylalanine and acylcarnitine species correlated with NF-L only in the A β + group, suggesting that the association of these metabolites with neurodegeneration may be relevant to early AD neuropathology. However, creatinine, SDMA and citrulline correlated with NF-L in both A β - and A β + individuals. Additionally, kynurenine correlated with NF-L significantly in A β + individuals and a trend towards statistical significance ($p=.051$) was observed in A β - participants. These observations may reflect previously reported observations

of increased plasma or CSF NF-L not being specifically associated with brain A β pathology but rather as a feature reflecting both the intensity and the extent of neurodegeneration. For example, elevated NF-L in primary tauopathies with no A β pathology, such as multiple system atrophy, progressive supranuclear palsy and corticobasal degeneration have been reported compared to controls (Hansson *et al.* 2017), suggesting that NF-L concentrations are not driven by brain A β load, which likely resulted in the observation of A β -/+ status independent associations between some plasma metabolites and NF-L. Therefore, such metabolites may serve as markers that may denote neurodegeneration that is not specific to AD.

Limitations acknowledged within the current study include the modest sample size employed, and the cross-sectional nature of the study. Additionally, in comparison to plasma NF-L being employed as a biomarker for neurodegeneration within the current study, CSF NF-L could have served as a more accurate measure of neurodegeneration. However, plasma NF-L has been reported to correlate strongly with CSF NF-L with correlation coefficients $>.75$, showing that plasma NF-L is representative of the axonal disruption manifesting in the CSF (Mattsson *et al.* 2017; Zetterberg & Blennow 2018). Another possible limitation is that medication use, and diet were not accounted for in the analyses, which may have affected the outcome. Further, given the modest sample size, adjustments for multiple comparisons were not made as the current study aimed to generate scientific hypotheses that will be critically tested in the future. However, if adjustments for multiple comparisons were to be considered, using Bonferroni correction, $p < 0.00023$ ($0.05/216$ metabolites) would be considered significant, leaving the association of creatinine, SDMA and citrulline with NF-L significant even after adjusting for multiple comparisons.

To conclude, the current study identified plasma metabolites that are associated with plasma NF-L, a biomarker for neurodegeneration, providing valuable insights into biological pathways that are triggered in neurodegenerative processes. Additionally, metabolites identified to be associated with plasma NF-L within the current study may have the potential to serve as prognostic markers for neurodegenerative diseases. However, further studies are required to validate the current findings in an independent cohort both cross-sectionally and longitudinally, employing CSF NF-L in parallel with plasma NF-L. Additionally, the specificity of the metabolites for AD would also need to be determined in future studies.

--Human subjects --

Involves human subjects:

If yes: Informed consent & ethics approval achieved:

=> if yes, please ensure that the info "Informed consent was achieved for all subjects, and the experiments were approved by the local ethics committee." is included in the Methods

ARRIVE guidelines have been followed:

No

=> if it is a Review or Editorial, skip complete sentence => if No, include a statement in the "Conflict of interest disclosure" section: "ARRIVE guidelines were not followed for the following reason:

No animals were used in the current study "

(edit phrasing to form a complete sentence as necessary).

=> if Yes, insert in the "Conflict of interest disclosure" section:

"All experiments were conducted in compliance with the ARRIVE guidelines." unless it is a Review or Editorial

Conflicts of interest: HZ has served at scientific advisory boards for Denali, Roche Diagnostics, Wave, Samumed and CogRx, has given lectures in symposia sponsored by Fujirebio, Alzecure and Biogen, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (all outside the submitted work). KB has served as a consultant, at advisory boards, or at data monitoring committees for Abcam, Axon, Biogen, Julius Clinical, Lilly, MagQu, Novartis, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program, outside the submitted work.

=> if 'none', insert "The authors have no conflict of interest to declare."

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Tables

Table 1. List of neuropsychological tests used to generate the global composite score. The global composite score was generated from the mean of the z-score measures of the tests listed below.

Test	Reference
Rey Auditory Verbal Learning Test (RAVLT) List A, short delay, long delay	(Estevez-Gonzalez <i>et al.</i> 2003)
Logical Memory (LM) I and II (WMS-III; Story A only)	(Elwood 1991)
Rey Complex Figure Test (RCFT) 3 min and RCFT 30 min	(Meyers & Meyers 1995)
Wechsler Adult Intelligence Scale – Third edition (WAIS–III) Digit Span backward	(Wechsler 1987)
WAIS–III Digit Symbol Substitution Test (DSST)	(Wechsler 1997)
D-KEFS Category Fluency (Boys Names) and Switching (Fruits and Furniture) Tasks	(Delis <i>et al.</i> 2001)
MMSE	(Folstein <i>et al.</i> 1975)

Table 2. Study participant characteristics. Participant characteristics including sex, age, body mass index (BMI), education, *APOE* $\epsilon 4$ status, mini mental state examination (MMSE) score, global composite score, hippocampal volume (HV; normalised with intracranial volume), neurofilament light chain concentrations (NF-L) and brain A β load (represented by the standard uptake value ratio (SUVR) of the ligand ^{18}F -Florbetaben in the neocortical region normalised with that in the cerebellum) are presented for all participants, and stratified by brain A β load status, i.e. A β - (SUVR<1.35) and A β + (SUVR $\geq$ 1.35). Chi-square tests or linear models were employed, as appropriate. p represents p-values for comparison of participant characteristics between A β - and A β + groups. p<0.05 was considered significant and is presented in bold font. N represents the number of participants.

	All participants	A β -	A β +	p
N	100	65	35	-
Sex (M/F)	32/68	19/46	13/22	0.419
Age (years, mean $\pm$ SD)	78.18 $\pm$ 5.52	77.62 $\pm$ 5.56	79.23 $\pm$ 5.38	0.165
BMI (kg/m ² , mean $\pm$ SD)	27.62 $\pm$ 4.56	27.39 $\pm$ 4.48	28.06 $\pm$ 4.74	0.486
Education (years, mean $\pm$ SD)	14.43 $\pm$ 3.26	14.85 $\pm$ 3.37	13.64 $\pm$ 2.92	0.078

nAPOE ε4 carriers (%)	21 (21)	5 (7.69)	16 (45.71)	<0.0001
MMSE (mean ±SD)	28.61±1.15	28.51±1.16	28.80±1.11	0.225
Global composite score (mean ±SD)	0.00±0.55	0.07±0.49	-.13±0.63	0.080
HV% (mean ±SD, n=96, left and right lobes)	0.195±0.02; 0.199±0.0204	0.195±0.0201; 0.199±0.0214	0.194±0.0197; 0.200±0.0186	0.805; 0.891
NF-L (pg/mL, mean±SD)	36.38±17.78	35.24±17.28	38.50±18.76	0.384
Brain Aβ load (SUVR, mean ±SD)	1.35±0.32	1.16±0.09	1.71±0.26	-

Table 3. Plasma metabolites correlating with plasma neurofilament light chain. Correlations were investigated using Pearson's correlation coefficient (r) and partial correlations (r^a), adjusting for age, sex, *APOE* ε4 carrier status and body mass index (BMI), in all participants. Metabolites significantly correlating with NF-L both before and after adjusting for covariates have been reported. † represents metabolites that were natural log transformed to better approximate normal distribution. SDMA: symmetric dimethylarginine, ADMA: asymmetric dimethylarginine, t4OH-Pro: trans-4-hydroxyproline, AC: acylcarnitine.

Analyte	r	p	r ^a	p
<i>Biogenic amines</i>				
Creatinine †	.544	0.000000005	.558	0.000000003
SDMA †	.560	0.000000001	.503	0.00000002
ADMA	.250	0.012	.228	0.026
Kynurenine †	.315	0.001	.358	0.0003
t4OH-Pro †	.243	0.015	.221	0.031
<i>Amino acids</i>				
Citrulline †	.428	0.000009	.390	0.00009
Proline †	.297	0.003	.260	0.010
Arginine	.233	0.020	.296	0.003
Asparagine	.271	0.006	.251	0.014
Phenylalanine	.210	0.036	.215	0.036
Threonine	.253	0.011	.208	0.042
<i>Acylcarnitines</i>				
AC(0:0)	.294	0.003	.288	0.004
AC(2:0)	.248	0.013	.260	0.011
AC(8:1) †	.348	0.0004	.207	0.043
AC(10:0)	.370	0.0001	.356	0.0004
AC(10:1)	.343	0.0005	.296	0.003
AC(10:2) †	.417	0.00002	.289	0.004
AC(10:3) †	.401	0.00003	.295	0.004
AC(12:1)	.364	0.0002	.343	0.001
AC(14:1) †	.338	0.001	.267	0.009

Table 4. Plasma metabolites correlating with plasma neurofilament light chain, in participants stratified by A β status. Correlations were investigated using Pearson's correlation coefficient (r) and partial correlations (r^a), adjusting for age, sex, *APOE* ϵ 4 carrier status and body mass index (BMI). Participants were categorised as A β -/+ based on their brain A β load measured via positron emission tomography using ligand ¹⁸F-Florbetaben. † represents metabolites that were natural log transformed to better approximate normal distribution. SDMA: symmetric dimethylarginine, ADMA: asymmetric dimethylarginine, t4OH-Pro: trans-4-hydroxyproline, AC: acylcarnitine. p<0.05 was considered significant and is presented in bold font.

Analyte	A β -				A β +			
	r	p	r ^a	p	r	p	r ^a	p
<i>Biogenic amines</i>								
Creatinine †	.506	0.00002	.506	0.00003	.610	0.0001	.627	0.0002
SDMA †	.527	0.00001	.439	0.0004	.610	0.0001	.638	0.0001
ADMA	.170	0.177	.140	0.282	.368	0.030	.357	0.049
Kynurenine †	.265	0.033	.251	0.051	.395	0.019	.560	0.001
t4OH-Pro †	.153	0.224	.177	0.173	.431	0.010	.324	0.075
<i>Amino acids</i>								
Citrulline †	.380	0.002	.305	0.017	.506	0.002	.590	0.0005
Proline †	.193	0.124	.108	0.406	.434	0.009	.473	0.007
Arginine	.151	0.229	.223	0.084	.350	0.039	.482	0.006
Asparagine	.139	0.268	.127	0.330	.459	0.005	.441	0.013
Phenylalanine	.129	0.307	.073	0.575	.320	0.061	.450	0.011
Threonine	.101	0.424	.171	0.189	.448	0.007	.264	0.152
<i>Acylcarnitines</i>								

AC(0:0)	.221	0.077	.186	0.152	.406	0.016	.587	0.001
AC(2:0)	.227	0.069	.140	0.282	.310	0.070	.580	0.001
AC(8:1) †	.299	0.016	.169	0.193	.457	0.006	.319	0.080
AC(10:0)	.318	0.010	.251	0.051	.437	0.009	.631	0.0001
AC(10:1)	.264	0.034	.153	0.240	.455	0.006	.580	0.001
AC(10:2) †	.372	0.002	.236	0.067	.517	0.001	.371	0.040
AC(10:3) †	.330	0.007	.182	0.160	.542	0.001	.476	0.007
AC(12:1)	.309	0.012	.224	0.083	.431	0.010	.596	0.0004
AC(14:1) †	.290	0.019	.139	0.286	.418	0.012	.620	0.0002

Table 5. Association of cognitive performance, hippocampal volume and brain A β load with plasma metabolites correlating significantly with plasma NF-L. Correlations were investigated using Pearson's correlation coefficient (r) and partial correlations (r^a), adjusting for age, sex, *APOE* ϵ 4 carrier status and body mass index (BMI) in all participants. Cognitive performance was calculated by generating a global composite score as described in the Methods section. † represents metabolites that were natural log transformed to better approximate normal distribution. SDMA: symmetric dimethylarginine, ADMA: asymmetric dimethylarginine, t4OH-Pro: trans-4-hydroxyproline, AC: acylcarnitine. p<0.05 was considered significant.

	Cognitive performance				Left hippocampus volume				Right hippocampus volume				Brain A β load			
Analyte	r	p	r ^a	p	r	p	r ^a	p	r	p	r ^a	p	r	p	r ^a	p
<i>Biogenic amines</i>																
Creatinine †	-.348	0.0004	-.156	0.130	-.226	0.027	-.081	0.441	-.202	0.049	-.038	0.721	.140	0.165	.067	0.516
SDMA †	-.258	0.009	-.115	0.263	-.162	0.114	-.055	0.600	-.178	0.082	-.059	0.578	.151	0.133	.074	0.476
ADMA	-.170	0.092	-.136	0.186	-.064	0.535	-.021	0.840	-.210	0.040	-.162	0.122	.062	0.542	.039	0.706
Kynurenine †	-.091	0.369	-.039	0.706	-.126	0.223	-.081	0.444	-.170	0.097	-.109	0.302	.113	0.263	.053	0.610
t4OH-Pro †	-.168	0.094	-.144	0.162	-.082	0.426	-.054	0.611	-.028	0.785	.022	0.837	-.027	0.787	-.028	0.787
<i>Amino acids</i>																
Citrulline †	-.153	0.128	-.051	0.623	-.092	0.375	-.021	0.842	-.080	0.439	-.002	0.981	-.006	0.956	-.010	0.923
Proline †	-.170	0.090	-.042	0.682	-.124	0.228	-.015	0.885	-.163	0.114	-.032	0.764	.149	0.140	-.002	0.984
Arginine	-.149	0.139	-.153	0.138	.006	0.953	.017	0.871	-.104	0.312	-.101	0.339	.046	0.652	.062	0.550
Asparagine	-.137	0.175	-.096	0.354	-.094	0.365	-.062	0.559	-.113	0.272	-.085	0.422	.049	0.629	.070	0.496
Phenylalanine	-.220	0.028	-.173	0.092	-.044	0.670	.014	0.894	-.087	0.401	-.022	0.837	.089	0.379	.050	0.629
Threonine	-.266	0.008	-.227	0.026	-.142	0.167	-.104	0.325	-.112	0.276	-.066	0.529	.042	0.675	.042	0.684
<i>Acylcarnitines</i>																
AC(0:0)	-.238	0.017	-.178	0.082	-.116	0.261	-.055	0.601	-.197	0.055	-.131	0.214	.159	0.115	.133	0.198

AC(2:0)	-0.143	0.157	-0.075	0.467	-0.153	0.136	-0.097	0.355	-0.191	0.062	-0.133	0.207	.015	0.883	-.012	0.904
AC(8:1) †	-.222	0.027	-.083	0.424	-.272	0.007	-.182	0.083	-.279	0.006	-.172	0.100	.160	0.112	.123	0.232
AC(10:0)	-.231	0.021	-.155	0.131	-.166	0.107	-.106	0.313	-.102	0.324	-.041	0.701	.221	0.027	.229	0.025
AC(10:1)	-.179	0.075	-.082	0.426	-.099	0.336	-.032	0.760	-.053	0.605	.011	0.917	.125	0.214	.164	0.109
AC(10:2) †	-.258	0.009	-.121	0.240	-.223	0.029	-.135	0.200	-.216	0.034	-.123	0.243	.073	0.468	.089	0.388
AC(10:3) †	-.198	0.048	-.028	0.783	-.280	0.006	-.180	0.085	-.257	0.011	-.148	0.160	.100	0.321	.057	0.583
AC(12:1)	-.283	0.004	-.237	0.020	-.145	0.158	-.105	0.321	-.145	0.159	-.114	0.280	.192	0.055	.174	0.090
AC(14:1) †	-.259	0.009	-.180	0.079	-.083	0.422	-.006	0.955	-.151	0.142	-.075	0.476	.155	0.123	.124	0.229

Figures

Figure 1. Correlation between plasma NF-L and plasma metabolites in all participants.

Correlation of plasma NF-L with A. Biogenic amines, creatinine, symmetric dimethylarginine (SDMA), asymmetric dimethylarginine (ADMA), kynurenine and trans-4-hydroxy proline (t4OH-Pro), B. Amino acids, citrulline, proline, arginine, asparagine, threonine and phenylalanine and C. Acylcarnitine species using Pearson's correlation coefficient (r). Concentrations of plasma NF-L and metabolites (as necessary) were natural log transformed to better approximate normality. $P < .05$ was considered significant. Number of participants = 100.

Figures

Figure 1. Correlation between plasma NF-L and plasma metabolites in all participants.

Correlation of plasma NF-L with A. Biogenic amines, creatinine, symmetric dimethylarginine (SDMA), asymmetric dimethylarginine (ADMA), kynurenine and trans-4-hydroxy proline (t4OH-Pro), B. Amino acids, citrulline, proline, arginine, asparagine, threonine and phenylalanine and C. Acylcarnitine species using Pearson's correlation coefficient (r). Concentrations of plasma NF-L and metabolites (as necessary) were natural log transformed to better approximate normality. $P < .05$ was considered significant. Number of participants = 100.

A. Biogenic amines

B. Amino acids

C. Acylcarnitines

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