Gut and Serum Metabolites and Alzheimer's: Exploring the Link Between Metabolite Levels and the Risk of Developing Alzheimer's

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Abstract—Alzheimer's disease is a fatal neurodegenerative disorder marked by inflammation and gradual cognitive decline. Recent research has revealed that gut microbiome affect the functioning of the brain, while at the same time, disease, and inflammation can also alter the gut microbiota. The composition, and function patterns of the gut microbiome was also found to be varied between the sexes during late adulthood, with it being mainly determined by biological sex. Analyzing the gut and serum metabolite data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, this exploratory analysis indicated that several gut bacteriamodulated metabolites are sex-dependent even at late adulthood stage. Moreover, several gut metabolites highlight possible correlation with the risk of developing Alzheimer's disease, prior to symptom development. As the demographic distribution of subjects with normal baseline who later developed cognitive impairment was low, the results should be interpreted cautiously. This work has implications in the predictive modeling of Alzheimer's risk.

Keywords—Alzheimer's disease, gut metabolites, serum metabolites, ADNI

I INTRODUCTION

Alzheimer's disease is a neurodegenerative disease threatening elderly health and life quality [1]–[4]. The defining features of Alzheimer disease (AD) include neuroinflammation and gradual cognitive decline [2], [3]. The behavioral symptoms of AD correlate with the accumulation of plaques and tangles, and they are a direct consequence of the damage and destruction of synapses that mediate memory and cognition [2].

Recent research showed evidence that the gut microbiota is involved in the pathogenesis of Alzheimer's disease [3], [5], [6] via a constant bidirectional communication through the gut-brain axis [3], [7], [8]. The gut microbiota consists of a commensal grouping of microbes that inhabit the gastrointestinal tract [3]. Various studies show that intestinal microbes affect the functioning of the brain, such as learning, and memory functions [1], [3], [8], [9]. Changes in the gut microbiota, collectively known as dysbiosis, was found to increase the permeability of the intestine, alter the permeability of the blood-brain barrier, and elevate proinflammatory mediators causing neurodegeneration, also associated with Alzheimer's disease [3], [7], [10]-[14]. In addition, gut flora-regulated metabolites were identified in cerebrospinal fluid, showing correlation with AD [15]. Furthermore, metabolic syndrome and associated serum metabolites such as lipoproteins, lipid molecules, fatty acids, and glycoproteins also feature an association with the risk of Alzheimer's [16]–[20].

In addition to gut and serum metabolites, current literature highlights some differences in the microbiota between sexes during adulthood [21]. These differences are said to be minimized during late adulthood (after menopause), where the gut microbiota taxonomy, and functionality present in women is more similar to men [21]. On the other hand, research show that there are equally notable alterations in aging populations that likely impact signalling between the gut microbiome and brain [22]. Agerelated changes to gut microbes has been reported in relation to measures of frailty, nutritional status, metabolic profiles, and markers of inflammation [22]-[24]. Moreover, the composition and function patterns of the gut microbiome was also found to be varied between the sexes during late adulthood [25], [26], with male gut microbiome exhibiting greater resistance to oxidative stress compared to females, while the species associated with healthy aging dominated among healthy females [26]. Research also consider that factors driving female-male differences in the microbiota seem to be mainly determined by biological sex [21], [27] Hence, association with sex should be considered for studies concerning gut metabolites and disease [23], [25].

Early risk detection of Alzheimer's from when subjects are still cognitively normal could improve prognosis and intervention strategies. Successful therapeutic intervention would benefit from early likelihood detection before cognitive impairment become evident [2].

This study aimed to explore the link between the gut and serum metabolites, and the risk of developing Alzheimer's disease. Specifically, it aimed to determine if there are specific microbe-mediated metabolite that can be used as predictors in the mathematical modelling of the likelihood of getting Alzheimer's disease. In addition, possible sex-based interaction with the metabolite levels was also evaluated.

II DATA AND METHODS

II.A Data Sources

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD) [28].

• Human participant data

The demographic data was obtained from the adnimerge dataset. This table merges together several of the key variables from various case report forms and biomarker lab summaries across the ADNI protocols (ADNII , ADNIGO, and ADNI2) [29].

• Gut microbial metabolite data

The data was obtained from the ADMC U Hawaii UPLC-MS/MS Gut Metabolites Serum Longitudinal [ADNI1,GO,2] dataset. A panel of 104 representative gut microbial metabolites including bile acids in human serum samples was measured using both ultraperformance liquid chromatography coupled with mass spectrometry (UPLC-MS/MS) [3].

• Serum metabolite data

The data was from the ADNINIGHTINGALELONG, and the ADNINIGHTINGALE2 datasets of the ADNI database (adni.loni.usc.edu). Blood biomarkers were analyzed using Nuclear Magnetic Resonance (NMR) assay based on the methods developed by the Nightingale Health. The assay quantified 250 metabolic biomarkers, covering biomarkers multiple biological pathways including lipids, lipoprotein subclass profiling with lipid concentrations within 14 subclasses, fatty acid composition, and various low-molecular metabolites including amino acids, ketone bodies and gluconeogenesis-related metabolites from the ADNI 1/GO/2 cohorts' human serum samples [31], [32].

II.B Data Processing

The metabolites dataset were merged with the corresponding patient baseline diagnoses, gender, and age. The duplicate patient entries were imputed with the mean of the corresponding metabolite values. Moreover, the metabolite data was screened to include only the patient entries with a normal baseline diagnosis. This was done with the aim of finding metabolites that can be used as a predictor of Alzheimer's when the patients are still of normal cognitive performance. All analyses were done using Pandas [33], Matplotlib [34], Statsmodels [35] in Python 3.11.4.

II.C Data Exploration

The patients are classified based on their corresponding diagnoses at the end of the longitudinal study. In order to determine if there are possible Alzheimer's predictors out of the quantified gut and serum metabolites, the histogram for each metabolite, were visually analyzed, to see if there are distinct data clusters based on the end diagoses of the patients. These distinct data clusters are important because distinct separation lead to a more defined decision boundary, which then minimizes the classification errors in the predictive model [36]. All analyses were done using Pandas [33], Matplotlib [34], Statsmodels [35], Seaborn [37], and Plotly [38] in Python 3.11.4.

II.D Statistical Analysis

The sex-dependency of the metabolite values were analyzed with one-way analysis of variance (ANOVA) at $\alpha = 0.05$ to see if there exists a statistically significant difference in the mean metabolite values between male and female patients. This was performed using the metabolite data from the patients that were normal at baseline and did not develop any cognitive impairment at the end of the longitudinal study. This was designed in order to exclude bidirectional

interactions of health (diagnosis) on the gut metabolite levels, and look solely on the sex-dependency of the metabolite levels on normal healthy subjects. The difference between groups was also quantified using the Cohen's d.

To supplement the data exploration results, each metabolite was tested with one-way analysis of variance (ANOVA) at $\alpha=0.05$ to see if there exists a statistically significant difference in the mean metabolite values between the (normal baseline) patients that stayed normal, developed MCI, and those that were finally diagnosed with AD at the end of the longitudinal study. If the metabolite showed statistically significant differences between sex groups, the ANOVA was done for corresponding sex. The Bonferroni correction ($\alpha=0.0167$) was also applied as a post hoc adjustment in order to control Type I error when comparing multiple groups. The difference between groups was also quantified using the Cohen's d.

All analyses were done using Pandas [33], Matplotlib [34], Statsmodels [35], Numpy [39], and Seaborn [37] in Python 3.11.4.

III RESULTS

III.A Lack of Longitudinal Data

Fig. 1 provides the patient demographics for the gut metabolites from the ADNI database. There were 352 patients that started with a healthy baseline, of which, 171 (48.6 %) are female, and 181 (51.4 %) are male. Out of the female patients, 23 (13 %) developed MCI and 8 (5 %) developed AD, whereas in male patients, 35 (19 %) developed MCI, and 9 (5 %) developed AD at the end of the longitudinal study.

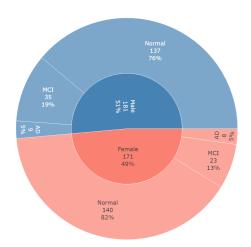


Fig. 1 Distribution of subjects who started normal at baseline in the gut metabolites data.

The patient demographics for the serum metabolites from the ADNI database is provided in Fig. 2. There were 458 patients that started with a normal baseline, of which, 233 (50.9 %) are female, and 225 (49.1 %) are male. Out of the female patients, 26 (11 %) developed MCI and 8 (3 %) developed AD, whereas 43 (19 %) male patients developed MCI, and 10 male patients (4 %) developed AD at the end of the longitudinal study.

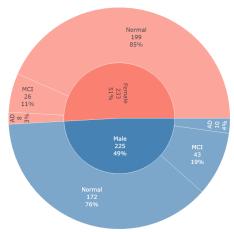


Fig. 2 Distribution of subjects who started normal at baseline in the serum metabolites data.

III.B Sex-dependent Gut Metabolites

The gut metabolites that showed statistically significant difference are shown in Table I. The test statistic for other gut metabolites are tabulated in Appendix A.

Table I Gut metabolites that showed statistically significant difference in the mean at baseline between male (n = 137) and female (n = 140) patients that did not develop any type of cognitive disorder.

3-Hydroxybutyric Acid (C4H8O3)	Metabolite	p-value α= 0.05	Cohen's d	Group with higher mean
Decanoic Acid (C10H20O2) 0.0006 -0.3684 Female Dodecanoic Acid (C13H24O2) 0.0074 -0.2873 Female Tridecanoic Acid (C13H26O2) 0.0008 -0.3112 Female Myristic Acid (C14H28O2) 0.0000 -0.4531 Female Palmitic Acid (C16H32O2) 0.0000 -0.4120 Female Palmitoleic Acid (C16H30O2) 0.0000 -0.4120 Female Heptadecanoic Acid (C17H34O2) 0.0006 -0.3127 Female Heptadecanoic Acid (C18H36O2) 0.0000 -0.8600 Female Stearic Acid (C18H36O2) 0.0000 -0.7898 Female Gleic Acid (C18H32O2) 0.0000 -0.7098 Female Linoleic Acid (C18H32O2) 0.0000 -0.6577 Female Gamma-Linolenic Acid (C18H30O2) 0.0000 -0.7452 Female I0,13-Nonadecadienoic Acid (C18H34O2) 0.0000 -0.7452 Female Eicosadienoic Acid (C20H36O2) 0.0000 -0.5231 Female Bicosapentaenoic Acid (C22H32O2) 0.0000 -0.4436 Female <td>3-Hydroxybutyric Acid (C4H8O3)</td> <td>0.0488</td> <td>-0.2108</td> <td>Female</td>	3-Hydroxybutyric Acid (C4H8O3)	0.0488	-0.2108	Female
Dodecanoic Acid (C13H26O2) 0.0074 -0.2873 Female Tridecanoic Acid (C13H26O2) 0.0008 -0.3112 Female Myristic Acid (C14H28O2) 0.0000 -0.8233 Female Pentadecanoic Acid (C16H30O2) 0.0000 -0.4120 Female Palmitic Acid (C16H30O2) 0.0000 -1.0869 Female Heptadecanoic Acid (C17H34O2) 0.0036 -0.3127 Female Heptadecenoic Acid (C17H31O2) 0.0000 -0.8600 Female Stearic Acid (C18H36O2) 0.0000 -0.8600 Female Gleic Acid (C18H34O2) 0.0000 -0.7098 Female Linoleic Acid (C18H34O2) 0.0000 -0.6577 Female Alpha-Linolenic Acid (C18H30O2) 0.0000 -0.8388 Female Alpha-Linolenic Acid (C20H36O2) 0.0000 -0.7452 Female Eicosadienoic Acid (C20H36O2) 0.0000 -0.5231 Female Arachidonic Acid (C20H36O2) 0.0000 -0.4437 Female Eicosapentaenoic Acid (C22H32O2) 0.0000 -0.4386 Female <td>Pelargonic Acid (C8H1802)</td> <td>0.0300</td> <td>-0.2323</td> <td>Female</td>	Pelargonic Acid (C8H1802)	0.0300	-0.2323	Female
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Eicosadienoic Acid (C20H36O2) 0.0000 -0.5231 Female 8,11,14-Eicosatrienoic Acid (C20H34O2) 0.0002 -0.4069 Female Arachidonic Acid (C20H32O2) 0.0000 -0.4436 Female Eicosapentaenoic Acid (C20H30O2) 0.0003 -0.3275 Female Docosahexaenoic Acid (C22H36O2) 0.0000 -0.4386 Female Docosapentaenoic Acid (C22H36O2) 0.0000 -0.5949 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.5309 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.6171 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.6171 Female L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.7216 Male L-Valine 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Tryptophan 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 1-Hydroxyisovaleric Acid <	Alpha-Linolenic Acid (C18H30O2)	0.0000	-0.7452	Female
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Arachidonic Acid (C20H32O2) 0.0000 -0.4436 Female Eicosapentaenoic Acid (C20H3OO2) 0.0023 -0.3275 Female Docosahexaenoic Acid (C22H32O2) 0.0000 -0.4386 Female Docosapentaenoic Acid (C22H36O2) 0.0000 -0.5949 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.5309 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.6171 Female Beta Alanine 0.0000 0.7216 Male L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Methionine 0.0000 0.4937 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male L-Tryptophan 0.0011 0.3806 Male Indoleacetic Acid 0.003 0.3151 Male Cheinodeoxycholic Acid 0.0030 0.3192 Male <td>Eicosadienoic Acid (C20H36O2)</td> <td>0.0000</td> <td>-0.5231</td> <td>Female</td>	Eicosadienoic Acid (C20H36O2)	0.0000	-0.5231	Female
Eicosapentaenoic Acid (C20H30O2) 0.0023 -0.3275 Female Docosahexaenoic Acid (C22H32O2) 0.0000 -0.4386 Female Docosapertaenoic Acid (C22H36O2) 0.0000 -0.5949 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.5309 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.6171 Female Beta Alanine 0.0000 0.7216 Male L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male 1Indoleacetic Acid 0.0033 0.3151 Male Cholic Acid 0.0033 0.3151 Male Chenodeoxycholic Acid 0.0000 0.4845 Male Chenodeoxycholic Acid 0.0016 0.3400 Male <	8,11,14-Eicosatrienoic Acid (C20H34O2)	0.0002	-0.4069	Female
Docosahexaenoic Acid (C22H32O2) 0.0000 -0.4386 Female Docosatetraenoic Acid (C22H36O2) 0.0000 -0.5949 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.5309 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.6171 Female Beta Alanine 0.0000 0.7216 Male L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Heucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male Cholic Acid 0.0033 0.3192 Male Chenodeoxycholic Acid 0.0000 0.4845 Male Muricholic Acid/Hyocholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male	Arachidonic Acid (C20H32O2)	0.0000	-0.4436	Female
Docosahexaenoic Acid (C22H32O2) 0.0000 -0.4386 Female Docosatetraenoic Acid (C22H36O2) 0.0000 -0.5949 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.5309 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.6171 Female Beta Alanine 0.0000 0.7216 Male L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Heucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male Cholic Acid 0.0033 0.3192 Male Chenodeoxycholic Acid 0.0000 0.4845 Male Muricholic Acid/Hyocholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male	Eicosapentaenoic Acid (C20H30O2)	0.0023	-0.3275	Female
Docosapentaenoic Acid (C22H34O2) 0.0000 -0.5309 Female Docosapentaenoic Acid (C22H34O2) 0.0000 -0.6171 Female Beta Alanine 0.0000 0.7216 Male L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Methionine 0.0000 0.4937 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male Chenocleoxycholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Muricholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0129 0.2665 Male Norcholic Acid <td></td> <td>0.0000</td> <td>-0.4386</td> <td>Female</td>		0.0000	-0.4386	Female
Docosapentaenoic Acid (C22H34O2) 0.0000 -0.6171 Female Beta Alanine 0.0000 0.7216 Male L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Methionine 0.0000 0.5354 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Muricholic Acid 0.0129 0.2665 Male Morcholic Acid 0.0129 0.2665 Male Morcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid	Docosatetraenoic Acid (C22H36O2)	0.0000	-0.5949	Female
Beta Alanine 0.0000 0.7216 Male L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Methionine 0.0000 0.5354 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Murocholic Acid 0.0129 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 <td< td=""><td>Docosapentaenoic Acid (C22H34O2)</td><td>0.0000</td><td>-0.5309</td><td>Female</td></td<>	Docosapentaenoic Acid (C22H34O2)	0.0000	-0.5309	Female
L-Aspartic Acid 0.0361 -0.2243 Female L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Methionine 0.0000 0.5354 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0020 0.2320 Male Murocholic Acid 0.0129 0.2665 Male Morcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.02	Docosapentaenoic Acid (C22H34O2)	0.0000	-0.6171	Female
L-Proline 0.0000 0.5622 Male L-Valine 0.0000 0.4453 Male L-Methionine 0.0000 0.5354 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0129 0.2665 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0234 -0.2428 Female	Beta Alanine	0.0000	0.7216	Male
L-Valine 0.0000 0.4453 Male L-Methionine 0.0000 0.5354 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	L-Aspartic Acid	0.0361	-0.2243	Female
L-Methionine 0.0000 0.5354 Male L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	L-Proline	0.0000	0.5622	Male
L-Leucine 0.0000 0.4937 Male L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	L-Valine	0.0000	0.4453	Male
L-Tryptophan 0.0011 0.3514 Male 3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0129 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	L-Methionine	0.0000	0.5354	Male
3-Hydroxyisovaleric Acid 0.0004 0.3806 Male Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0090 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	L-Leucine	0.0000	0.4937	Male
Indoleacetic Acid 0.0033 0.3151 Male 3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0090 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	L-Tryptophan	0.0011	0.3514	Male
3-Methyl-2-oxovaleric Acid 0.0000 0.4845 Male Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0090 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	3-Hydroxyisovaleric Acid	0.0004	0.3806	Male
Cholic Acid 0.0030 0.3192 Male Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0090 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	Indoleacetic Acid	0.0033	0.3151	Male
Chenodeoxycholic Acid 0.0016 0.3400 Male Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0090 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	3-Methyl-2-oxovaleric Acid	0.0000	0.4845	Male
Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0090 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	Cholic Acid	0.0030	0.3192	Male
Muricholic Acid/Hyocholic Acid 0.0020 0.3320 Male Isolithocholic Acid 0.0090 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	Chenodeoxycholic Acid	0.0016	0.3400	Male
Isolithocholic Acid 0.0090 0.2800 Male Murocholic Acid 0.0129 0.2665 Male Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female		0.0020	0.3320	Male
Norcholic Acid 0.0234 0.2428 Male Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	Isolithocholic Acid	0.0090	0.2800	Male
Cis-Aconitic Acid 0.0407 -0.2471 Female Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	Murocholic Acid	0.0129	0.2665	Male
Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	Norcholic Acid	0.0234	0.2428	Male
Glycochodeoxycholic Acid 0.0327 0.2579 Male Apocholic Acid 0.0234 -0.2428 Female	Cis-Aconitic Acid	0.0407	-0.2471	Female
Apocholic Acid 0.0234 -0.2428 Female	Glycochodeoxycholic Acid	0.0327		Male
1		0.0234	-0.2428	Female
	Lithocholic Acid 3-Sulfate	0.0040		Male

III.C Sex-dependent Serum Metabolites

Table II Serum metabolites that showed statistically significant difference in the mean at baseline between male (n = 172) and female (n = 199) patients that did not develop any cognitive impairment.

Metabolite	p-value α= 0.05	Cohen's	Group with higher mean
Total Cholesterol	0.0000	-0.6733	Female
Non-HDL Cholesterol	0.0000	-0.4335	Female
Remnant cholesterol; non-HDL, non-LDL - cholesterol	0.0000	-0.4352	Female
Clinical LDL Cholesterol	0.0001	-0.4060	Female
Cholesterol in LDL	0.0001	-0.4104	Female
Cholesterol in HDL Triglycerides in LDL particles	0.0000	-0.7732	Female Female
Triglycerides in HDL particles Triglycerides in HDL particles	0.0003	-0.3783 -0.3419	Female
Total Phospholipids	0.0000	-0.8719	Female
Phospholipids in LDL particles	0.0003	-0.3845	Female
Phospholipids in HDL particles Total Cholesteryl Esters	0.0000 0.0000	-0.8901 -0.6945	Female Female
Cholesteryl Esters in HDL particles	0.0264	-0.0943	Female
Cholesteryl Esters in HDL particles	0.0001	-0.3990	Female
Cholesteryl Esters in HDL particles	0.0000	-0.7568	Female
Total Free Cholesterol Free Cholesterol in LDL particles	0.0000 0.0001	-0.5994 -0.4250	Female Female
Free Cholesterol in HDL particles	0.0001	-0.4230	Female
Total Lipids	0.0000	-0.6690	Female
Lipids in LDL particles	0.0001	-0.4153	Female
Lipids in HDL particles Total Lipoprotein Particle Concentrations	0.0000 0.0000	-0.8641 -0.8939	Female Female
Very Low Density Lipoprotein Particles	0.0459	-0.2085	Female
Low Density Lipoprotein Particles	0.0072	-0.2815	Female
High Density Lipoprotein Particles	0.0000	-0.8827	Female
Size of VLDL Size of LDL	0.0382 0.0013	0.2166 -0.3363	Male Female
Size of HDL	0.0000	-0.5332	Female
Apolipoprotein B	0.0026	-0.3157	Female
Apolipoprotein A-1	0.0000	-0.8984	Female
Ratio of Apolipoprotein B to A-1 Phosphoglycerides	0.0067 0.0000	0.2841 -0.9667	Male Female
Ratio of Triglycerides to Phosphoglycerides	0.0088	0.2742	Male
Cholines	0.0000	-0.9616	Female
Phosphatidylcholines Sphingarmyoling	0.0000 0.0000	-0.9443 -0.8381	Female Female
Sphingomyelins Total Fatty Acids	0.0000	-0.6459	Female
Estimated Degree of Unsaturation	0.0000	-0.4546	Female
Omega-3 Fatty Acids	0.0000	-0.5970	Female
Omega-6 Fatty Acids Polyunsaturated Fatty Acids (mmol/l)	0.0000 0.0000	-0.7159 -0.7664	Female Female
Monounsaturated Fatty Acids; 16:1, 18:1	0.0000	-0.7604	Female
Saturated Fatty Acids (mmol/l)	0.0000	-0.5967	Female
18:2, Linoleic Acid (mmol/l)	0.0000	-0.5547	Female
22:6, Docosahexaenoic Acid (mmol/l) Glutamine (mmol/l)	0.0000 0.0227	-0.6803 0.2382	Female Male
Glycine (mmol/l)	0.0000	-0.5507	Female
Histidine (mmol/l)	0.0049	0.2950	Male
Total Branched-Chain Amino Acids	0.0000	0.6596	Male
Isoleucine Leucine	0.0000 0.0000	0.8205 0.5849	Male Male
Valine	0.0000	0.5455	Male
Tyrosine	0.0114	0.2646	Male
Glucose	0.0150	0.2545	Male
GlycA Inflammatory Biomarker Total cholesterol in medium VLDL	0.0002 0.0073	-0.3951 -0.2811	Female Female
Free cholesterol in medium VLDL	0.0276	-0.2303	Female
Free cholesterol in small VLDL	0.0232	-0.2374	Female
Concentration of very small VLDL particles	0.0000	-0.4601	Female
Total lipids in very small VLDL Phospholipids in very small VLDL	0.0000 0.0002	-0.4533 -0.3983	Female Female
Total cholesterol in very small VLDL	0.0002	-0.4935	Female
Cholesterol esters in very small VLDL	0.0000	-0.5035	Female
Free cholesterol in very small VLDL	0.0000	-0.4324	Female
Triglycerides in very small VLDL	0.0170	-0.2496	Female

Metabolite	p-value α= 0.05	Cohen's d	Group with higher mean
Concentration of IDL particles	0.0000	-0.4544	Female
Total lipids in IDL	0.0000	-0.6014	Female
Phospholipids in IDL	0.0000	-0.5615	Female
Total cholesterol in IDL	0.0000	-0.5854	Female
Cholesterol esters in IDL	0.0000	-0.5833	Female
Free cholesterol in IDL	0.0000	-0.5781	Female
Triglycerides in IDL	0.0001	-0.4191	Female
Concentration of large LDL particles	0.0014	-0.3355	Female
Total lipids in large LDL	0.0000	-0.4866	Female
Phospholipids in large LDL	0.0000	-0.4446	Female
Total cholesterol in large LDL	0.0000	-0.4802	Female
Cholesterol esters in large LDL	0.0000	-0.4702	Female
Free cholesterol in large LDL	0.0000	-0.4945	Female
Triglycerides in large LDL	0.0000	-0.4514	Female
Total lipids in medium LDL particles	0.0070	-0.2825	Female
Phospholipids in medium LDL particles	0.0038	-0.3030	Female
Total cholesterol in medium LDL particles	0.0114	-0.2647	Female
Cholesterol esters in medium LDL particles	0.0236	-0.2367	Female
Free cholesterol in medium LDL particles	0.0021	-0.3225	Female
Triglycerides in medium LDL particles	0.0042	-0.2997	Female
Concentration of small LDL particles	0.0205	-0.2422	Female
Total lipids in small LDL particles	0.0109	-0.2664	Female
Phospholipids in small LDL particles	0.0178	-0.2478	Female
Total cholesterol in small LDL particles	0.0103	-0.2686	Female
Cholesterol esters in small LDL particles	0.0073	-0.2807	Female
Free cholesterol in small LDL particles	0.0407	-0.2138	Female
Concentration of very large HDL particles	0.0000	-0.4532	Female
Total lipids in very large HDL particles	0.0001	-0.4139	Female
Phospholipids in very large HDL particles	0.0001	-0.4083	Female
Total cholesterol in very large HDL particles	0.0002	-0.3972	Female
Cholesterol esters in very large HDL particles		-0.4348	Female
Free cholesterol in very large HDL particles	0.0188	-0.2457	Female
Triglycerides in very large HDL particles	0.0001	-0.4011	Female
Concentration of large HDL particles	0.0000	-0.6181	Female
Total lipids in large HDL particles	0.0000	-0.6254	Female
(Phospholipids in large HDL particles	0.0000	-0.6572	Female
Total cholesterol in large HDL particles	0.0000	-0.5723	Female
Cholesterol esters in large HDL particles	0.0000	-0.5663	Female
Free cholesterol in large HDL particles	0.0000	-0.5890	Female
Triglycerides in large HDL particles (0.0000	-0.5731	Female
Concentration of medium HDL particles	0.0000	-0.8921	Female
Total lipids in medium HDL particles	0.0000	-0.9104	Female
Phospholipids in medium HDL particles	0.0000	-0.9257	Female
Total cholesterol in medium HDL particles	0.0000	-0.8426	Female
Cholesterol esters in medium HDL particles	0.0000	-0.8248	Female
Free cholesterol in medium HDL particles	0.0000	-0.8963	Female
Triglycerides in medium HDL particles	0.0005	-0.3683	Female
Concentration of small HDL particles	0.0000	-0.5694	Female
Total lipids in small HDL particles	0.0000	-0.6660	Female
Phospholipids in small HDL particles	0.0000	-0.7318	Female
Total cholesterol in small HDL particles	0.0000	-0.5919	Female
Cholesterol esters in small HDL particles	0.0000	-0.5066	Female
Free cholesterol in small HDL particles	0.0000	-0.7834	Female

The test statistic for other serum Metabolites are shown in Appendix B.

III.D Gut and Serum Metabolites showing possible relation with Alzheimer's disease

TABLE III GUT AND SERUM METABOLITES THAT SHOWED SIGNIFICANT DIFFERENCES AT BASELINE FOR FEMALE PATIENTS

Metabolite	End Diagnosis Comparison	Corrected p-value	η²	Cohen's
Glycine ^a	MCI vs AD	0.0033	0.0421	-1.4881
Indoleacetic Acida	Normal vs AD	0.0085	0.0676	-1.1036
Allolithocholic Acida	Normal vs AD	0.0005	0.0574	-1.3978
Monounsaturated Fatty Acids (%) ^b	Normal vs. MCI	0.0128	0.0382	0.6019

^aGut metabolite ^bSerum metabolite

TABLE IV GUT METABOLITES THAT SHOWED SIGNIFICANT DIFFERENCES AT BASELINE FOR MALE PATIENTS

Metabolite	End Diagnosis Comparison	Corrected p-value	η^2	Cohen's d
Caprylic Acid	Normal vs AD	0.0056	0.0667	-1.0914
Hippuric Acid	Normal vs AD	0.0021	0.0346	-1.1928
Indoleacetic Acid	Normal vs MCI	0.0026	0.0653	-0.6432

Indoleacetic acid (p-value = 0.0085), allolithocholic acid (p-value = 0.0005) showed statistically significant difference in the baseline mean of female patients (n = 171) that stayed normal (n = 140) and those that developed AD (n = 8). Moreover, baseline glycine levels of those that developed MCI (n = 23) and those that developed AD also showed a significant difference (p-value = 0.0033). Furthermore, statistical analysis revealed a meaningful difference in the mean (p-value = 0.0128) of the baseline serum concentration of monounsaturated fatty acids in the female patients (n = 233) that developed MCI (n = 26) and those that did not develop the cognitive impairment (n = 199). There results are summarized in Table III.

In male patients (n = 181) there was a significant difference between mean values at the baseline levels of caprylic acid (p-value = 0.0056), and hippuric acid (p-value = 0.0021) between patients that developed AD, and those who stayed cognitively normal (Table IV). Additionally, indole acetic acid (p-value = 0.0026) at baseline showed statistically validated difference between normal patients and those that developed MCI.

When the whole cohort of normal baseline patients were analyzed without separating for sex, the baseline glycine metabolite level showed statistically significant difference (p-value = 0.0090) between patients that stayed normal and those who developed MCI.

IV DISCUSSION

The potential for early quantification of the risk of developing Alzheimer's disease is crucial for the elderly population. Currently diagosis involves the collection of cerebrospinal fluid (CSF) via a spinal tap where the levels of proteins associated with Alzheimer's and related dementias are measured [40]. Brain scans, such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET), are also done to support an Alzheimer's diagnosis or rule out other possible causes for symptoms [40]. These tests are expensive, and are usually done when symptoms are apparent to the patient. Hence, it is of an advantage to find a good predictor of Alzheimer's risk, before signs of neurodegeneration appear.

In this study, the lack of longitudinal data on patients that had a normal baseline and later progressed to MCI or AD made it difficult to explore the relationship of gut and serum metabolites to the risk of developing neurodegenerative disease. In this regard, it is difficult to use the measurement values as possible predictor for the quantification of the likelihood of getting the disease in the future. Another hurdle in designing the predictive model is the lack of distinctive end diagnosis clusters at baseline. This could be attributed to the underrepresentation of patients who started without any cognitive impairment, and later on progressed to MCI or AD.

Several studies point out that the observed sexdifferences in gut microbiota in the population of old adults to be more related to biological sex than sex hormones alone [25]–[27]. Moreover, the gut microbiome communicates bidirectionally with the brain, termed as the microbiota-gutbrain axis, shown to likely contrubute to sex differeces in the susceptibility to neuropsychiatric conditions [27]. In this study, multiple gut and serum metabolites showed statistically significant difference in normal male and female patients. This shows that sex differences should be accounted for when considering metabolite levels in the prediction of the risk of developing AD.

Recent research also show increasing evidence on the role of bile acids in neuroinflammation, and stress response through bidirectional interactions within the gut-brain axis[3], [7], [8], [41]. Bile acids are the end products of human cholesterol metabolism, which is produced by human and gut microbiota [1], [41]-[43]. The presence of primary and secondary bile acid metabolites at the serum level were found to be related with amyloid proteins and tau in the cerebrospinal fluid of AD patients, as well as with brain atrophy and cerebral glucose metabolism dysfunction [1]. Bile acids can enter the systematic circulation, and cross the blood-brain barrier [7], [13], [41], [44]. The bile acid pool and composition is manipulated by the gut microbiota, being dependent on the metabolic capacity of the microbial flora, antibiotics, and diet [43], [45], [46]. Primary bile acids are metabolized by bacteria in the gut to secondary bile acids, such as deoxycholic acid (DCA), and lithocholic acid (LCA) [10], [43]. While specific studies on allolithocholic acid are limited, research has shown that alterations in bile acid profiles, including secondary bile acids like lithocholic acid, are associated with cognitive impairment in Alzheimer's disease [44], [47].

Other bacteria-modulated metabolites including hippurate and indoleacetate, the conjugate bases of hippuric acid, and indoleacetic acid, were also found to be detectable within the cerebrospinal fluid [15]. Indoleacetic acid is a gut microbial metabolite derived from tryptophan. Tryptophan metabolites were also shown to correlate with neurological disorders suggesting a connection between gut microbial metabolites, and cognitive impairment [4], [10], [13], [48]. Hippuric acid was also found to be statistically different in male patients that later developed MCI, and those that stayed normal. Hippuric acid is a metabolite resulting from the glycine conjugation of benzoic acid or from the gut bacterial metabolism of phenylalanine [49]. Hippuric acid levels has been proposed as an aging biomarker as serum hippuric acid level can be influenced by the presence of age-related conditions, including frailty, and cognitive impairment [49]. Another study within the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort also found that higher plasma levels of caprylic acid were inversely associated with the risk of developing MCI among cognitively normal individuals [50].

Glycine is the smallest nonessential amino acid, and has been associated with neurotherapeutic effects by inhibiting oxidative stress [51]. It has also been shown to influence synaptic plasticity, and cognitive functions [52]. In oxidative stress and neurotoxicity associated with AD, glycine residues within the amyloid betapeptide were found to be implicated [53]. Although the aforementioned studies suggest that glycine, and its interactions within the brain may play a role in Alzheimer's disease, there are not many studies describing a direct association of glycine with the risk of AD, warranting further research into its potential therapeutic applications in this field.

For serum metabolites, serum lipid levels has been associated with current AD biomarkers and AD clinical symtpoms [54]–[57]. Polyunsaturated fatty acids and

docosahexaenoic acid (DHA) were found to be lower on both MCI and AD patients which suggest a role in Alzheimer's pathology [56]. Dietary intake of monounsaturated fatty acids was also shown to be associated with reduced risk of AD [56], [58] On the other hand, some found no significant association between serum monounsaturated fatty acids, and the risk of AD [55], [56]. Overall, while some studies suggest a protective role of monounsaturated fatty acids against cognitive decline and AD, others do not find a significant association. Additionally, the gut microbiome also show a biderectional interaction

In summary, it is difficult to attribute specific gut and serum metabolites to the risk of developing AD as the metabolic pathways are often overlapping, and a full understanding of how these metabolites interact with the host is still lacking [10]. The results also did not lead to specific metabolites that can consistently distinguish between all diagnostic groups, prior to symptom development. However, this data exploration showed interesting findings that could be looked at more closely in the future.

V CONCLUSION AND RECOMMENDATION

This exploratory analysis indicated that several gut bacteria-modulated metabolites are sex-dependent even at late adulthood stage. Hence, it would be useful to factor in sex-differences when using metabolite levels in predicting the risk of AD. Moreover, several gut metabolites including allolithocholic acid, indoleacetic acid, hippuric acid, and glycine showed significant difference between end diagnostic groups, highlighting possible correlation with the risk of developing Alzheimer's diesease, prior to symptom development. As the demographic distribution of subjects with normal baseline and later developed cognitive impairment was low, the results should be interpreted cautiously. Additionally, the metabolite values were measured as the serum abundace, which may not be directly comparable to other research results which studied gut metabolites using the stool sample. Most published research also performed the measurements between diagnostic groups when the patients already exhibited cognitive decline, which does not elliminate the effects of altered gut microbiome as caused by inflammation, neurodegenerative disease, and frailty. Further research is needed in order to verify the suitability of specific serum metabolites in the predictive modelling of the likelihood of future Alzheimer's diagnosis.

Future investigation should focus on longitudinal studies which also cover the baseline values before symptoms of neurodegeneration occur, for patients who later developed cognitive impairment. This will increase the quality of the comparison between future diagnostic groups at baseline level, as well as the possibility of finding suitable predictors that can consistently be used for the predictive modelling of AD risk.

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VI APPENDIX A

Gut metabolites that did not show statistically significant difference in the mean at baseline between male (n = 137) and female (n = 140) patients that did not develop any type of cognitive disorder.

Variable Corrected p-value Hyodeoxycholic Acid 0.7985 Methylsuccinic Acid 0.9087 Formic Acid (HCOOH) 0.6769 Ursocholic Acid 0.2387 Ketolithocholic Acid 0.7527 Glycoursodeoxycholic Acid 0.0914 Adipic Acid 0.0914 Glycocholic Acid (Isoursodeoxycholic acid) 0.1298 Glycocholic Acid 0.799 Glycocholic Acid 0.1061 Deoxycholic Acid 0.0952 Tauroursodeoxycholic Acid 0.1183 Lithocholic Acid 0.7442 Heptanoic Acid (C7H1402) 0.1678 Caprylic Acid (C8H1602) 0.6018 Glycolic Acid 0.7299 L-Lysine 0.775 Butyric Acid (C4H803) 0.6019 Taurodeoxycholic Acid 0.3396 L-Alpha Amiobutyric Acid 0.284 L-Malic Acid 0.5178 Glycohyocholic Acid 0.5178 Glycohyocholic Acid 0.575 Jebrydrocholic Acid 0.582 Urside Acid		
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Caprylic Acid (C8H1602) 0.6018 Glycolic Acid 0.7299 L-Lysine 0.775 Butyric Acid (C4H803) 0.6019 Taurodeoxycholic Acid 0.3396 L-Alpha Amiobutyric Acid 0.284 Undecanoic Acid (C11H22O2) 0.9234 L-Malic Acid 0.5178 Glycohyocholic Acid 0.906 Valeric Acid 0.1758 Isocitric Acid 0.1758 Isocitric Acid 0.1485 Ursodeoxycholic Acid 0.6982 Glycolithocholic Acid 0.6982 Glycolithocholic Acid 0.6588 Glycine 0.0721 Tauro-muricholic Acid 0.6223 Tauro-muricholic Acid 0.871 Suberic acid 0.7058 Propionic Acid (C3H6O2) 0.4132 Undecylenic Acid (C1H20O2) 0.3621 Oxoglutaric Acid 0.1355 Allolithocholic Acid (Isoallolithocholic acid) 0.0994 Glycodeoxycholic Acid 0.1355 L-Histidine 0.0974 L-Tyrosine 0	Lithocholic Acid	0.7442
Glycolic Acid	Heptanoic Acid (C7H1402)	0.1678
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Butyric Acid (C4H803) Taurodeoxycholic Acid L-Alpha Amiobutyric Acid Undecanoic Acid (C11H22O2) 0.9234 L-Malic Acid 0.5178 Glycohyocholic Acid Valeric Acid 0.1758 Isocitric Acid 0.1851 Ursodeoxycholic Acid 0.1851 Ursodeoxycholic Acid 0.6982 Glycolithocholic Acid 0.6982 Glycolithocholic Acid 0.6982 Glycine 0.0721 Taurocholic Acid 0.871 Suberic acid 0.7058 Propionic Acid (C3H6O2) 0.4132 Undecylenic Acid (C1H20O2) 0.3621 Oxoglutaric Acid 0.1884 Glyceric Acid 0.1884 Glyceric Acid 0.1884 Glyceric Acid 0.1355 Allolithocholic Acid (Isoallolithocholic acid) 0.0994 Glycodeoxycholic Acid 0.1993 L-Histidine 0.0974 L-Tyrosine 0.2048 Pyroglutamic Acid 0.1994 Hexanoic Acid (C6H12O2) 0.0795 3-Dehydrocholic Acid 0.1539 Dehydrolithocholic Acid 0.823 L-Aspargine 0.7384 Indolepropionic Acid 0.5887 L-Alanine 0.1179 Citric Acid 0.0848 23-Nordeoxycholic Acid 0.2862 Hippuric Acid 0.948 Acetic Acid (C2H4O2) 0.3881 L-Serine	Glycolic Acid	0.7299
Taurodeoxycholic Acid L-Alpha Amiobutyric Acid Undecanoic Acid (C11H22O2) L-Malic Acid O.5178 Glycohyocholic Acid O.906 Valeric Acid O.1758 Isocitric Acid O.1857 7-Dehydrocholic Acid Ursodeoxycholic Acid O.6982 Glycolithocholic Acid O.6982 Glycine O.0721 Taurocholic Acid O.6223 Tauro-muricholic Acid O.871 Suberic acid O.7058 Propionic Acid (C3H6O2) Undecylenic Acid (C1H2OO2) Oxoglutaric Acid O.1884 Glyceric Acid O.8934 Succinic acid O.1355 Allolithocholic Acid (Isoallolithocholic acid) O.9994 Glycodeoxycholic Acid L-Tyrosine Volume Acid (C6H12O2) O.0994 Hexanoic Acid (C6H12O2) O.0795 J-Dehydrocholic Acid O.1994 Hexanoic Acid (C4H8O3) Dehydrolithocholic Acid O.823 L-Aspargine O.7384 Indolepropionic Acid O.829 P-Cresol Sulfate O.5647 12-Ketolithocholic Acid O.8887 L-Alanine O.1179 Citric Acid O.8881 Acetic Acid (C2H4O2) O.3881 L-Serine	L-Lysine	0.775
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Undecanoic Acid (C11H22O2) 0.9234 L-Malic Acid 0.5178 Glycohyocholic Acid 0.906 Valeric Acid 0.1758 Isocitric Acid 0.5574 7-Dehydrocholic Acid 0.1485 Ursodeoxycholic Acid 0.6982 Glycolithocholic Acid 0.6588 Glycine 0.0721 Taurocholic Acid 0.871 Suberic acid 0.7058 Propionic Acid (C3H6O2) 0.4132 Undecylenic Acid (C3H6O2) 0.3621 Oxoglutaric Acid 0.1884 Glyceric Acid 0.8934 Succinic acid 0.1385 Allolithocholic Acid (Isoallolithocholic acid) 0.0994 Glycodeoxycholic Acid 0.953 L-Histidine 0.0974 L-Tyrosine 0.2048 Pyroglutamic Acid 0.1994 Hexanoic Acid (C6H1202) 0.0795 3-Dehydrocholic Acid 0.1539 Dehydrolithocholic Acid 0.4099 Isobutyric Acid (C4H803) 0.823 L-Aspargine 0.7384 <td>Taurodeoxycholic Acid</td> <td>0.3396</td>	Taurodeoxycholic Acid	0.3396
L-Malic Acid 0.5178 Glycohyocholic Acid 0.906 Valeric Acid 0.1758 Isocitric Acid 0.5574 7-Dehydrocholic Acid 0.1485 Ursodeoxycholic Acid 0.6982 Glycolithocholic Acid 0.6588 Glycine 0.0721 Taurocholic Acid 0.871 Suberic acid 0.7058 Propionic Acid (C3H6O2) 0.4132 Undecylenic Acid (C1H20O2) 0.3621 Oxoglutaric Acid 0.1884 Glyceric Acid 0.8934 Succinic acid 0.1355 Allolithocholic Acid (Isoallolithocholic acid) 0.0994 Glycodeoxycholic Acid 0.953 L-Histidine 0.0974 L-Tyrosine 0.2048 Pyroglutamic Acid 0.1994 Hexanoic Acid (C6H1202) 0.0795 3-Dehydrocholic Acid 0.1539 Dehydrolithocholic Acid 0.4099 Isobutyric Acid (C4H803) 0.823 L-Aspargine 0.7384 Indolepropionic Acid 0.5647	L-Alpha Amiobutyric Acid	0.284
Glycohyocholic Acid	Undecanoic Acid (C11H22O2)	0.9234
Valeric Acid 0.1758 Isocitric Acid 0.5574 7-Dehydrocholic Acid 0.1485 Ursodeoxycholic Acid 0.6982 Glycolithocholic Acid 0.6588 Glycine 0.0721 Taurocholic Acid 0.871 Suberic acid 0.7058 Propionic Acid (C3H6O2) 0.4132 Undecylenic Acid (C1H20O2) 0.3621 Oxoglutaric Acid 0.1884 Glyceric Acid 0.8934 Succinic acid 0.1355 Allolithocholic Acid (Isoallolithocholic acid) 0.0994 Glycodeoxycholic Acid 0.953 L-Histidine 0.0974 L-Tyrosine 0.2048 Pyroglutamic Acid 0.1994 Hexanoic Acid (C6H1202) 0.0795 3-Dehydrocholic Acid 0.1539 Dehydrolithocholic Acid 0.4099 Isobutyric Acid (C4H803) 0.823 L-Aspargine 0.7384 Indolepropionic Acid 0.5647 12-Ketolithocholic Acid 0.5887 L-Alanine 0.1179	L-Malic Acid	0.5178
Valeric Acid 0.1758 Isocitric Acid 0.5574 7-Dehydrocholic Acid 0.1485 Ursodeoxycholic Acid 0.6982 Glycolithocholic Acid 0.6588 Glycine 0.0721 Taurocholic Acid 0.871 Suberic acid 0.7058 Propionic Acid (C3H6O2) 0.4132 Undecylenic Acid (C1H20O2) 0.3621 Oxoglutaric Acid 0.1884 Glyceric Acid 0.8934 Succinic acid 0.1355 Allolithocholic Acid (Isoallolithocholic acid) 0.0994 Glycodeoxycholic Acid 0.953 L-Histidine 0.0974 L-Tyrosine 0.2048 Pyroglutamic Acid 0.1994 Hexanoic Acid (C6H1202) 0.0795 3-Dehydrocholic Acid 0.1539 Dehydrolithocholic Acid 0.4099 Isobutyric Acid (C4H803) 0.823 L-Aspargine 0.7384 Indolepropionic Acid 0.5647 12-Ketolithocholic Acid 0.5887 L-Alanine 0.1179	Glycohyocholic Acid	0.906
7-Dehydrocholic Acid Ursodeoxycholic Acid O.6982 Glycolithocholic Acid O.6588 Glycine O.0721 Taurocholic Acid O.6223 Tauro-muricholic Acid O.871 Suberic acid Propionic Acid (C3H6O2) Undecylenic Acid (C11H20O2) Oxoglutaric Acid O.8934 Glyceric Acid O.8934 Succinic acid O.1355 Allolithocholic Acid (Isoallolithocholic acid) Olycodeoxycholic Acid CTyrosine Pyroglutamic Acid Hexanoic Acid (C6H1202) O.0795 3-Dehydrocholic Acid Dehydrolithocholic Acid Dehydrolithocholic Acid O.1539 Dehydrolithocholic Acid D.1539 Dehydrolithocholic Acid D.823 L-Aspargine D.7384 Indolepropionic Acid D.8299 p-Cresol Sulfate D.5647 12-Ketolithocholic Acid D.5887 L-Alanine D.1179 Citric Acid D.3881 L-Serine D.7126		0.1758
Ursodeoxycholic Acid 0.6982 Glycolithocholic Acid 0.6588 Glycine 0.0721 Taurocholic Acid 0.6223 Tauro-muricholic Acid 0.871 Suberic acid 0.7058 Propionic Acid (C3H6O2) 0.4132 Undecylenic Acid (C11H20O2) 0.3621 Oxoglutaric Acid 0.1884 Glyceric Acid 0.8934 Succinic acid 0.1355 Allolithocholic Acid (Isoallolithocholic acid) 0.0994 Glycodeoxycholic Acid 0.953 L-Histidine 0.0974 L-Tyrosine 0.2048 Pyroglutamic Acid 0.1994 Hexanoic Acid (C6H1202) 0.0795 3-Dehydrocholic Acid 0.1539 Dehydrolithocholic Acid 0.4099 Isobutyric Acid (C4H803) 0.823 L-Aspargine 0.7384 Indolepropionic Acid 0.8299 p-Cresol Sulfate 0.5647 12-Ketolithocholic Acid 0.5887 L-Alanine 0.1179 Citric Acid 0.948 <td>Isocitric Acid</td> <td>0.5574</td>	Isocitric Acid	0.5574
Glycolithocholic Acid Glycine Glycine 10.0721 Taurocholic Acid 0.6223 Tauro-muricholic Acid 0.871 Suberic acid 0.7058 Propionic Acid (C3H6O2) Undecylenic Acid (C11H2OO2) 0.3621 Oxoglutaric Acid 0.1884 Glyceric Acid 0.8934 Succinic acid 0.1355 Allolithocholic Acid (Isoallolithocholic acid) 0.0994 Glycodeoxycholic Acid L-Histidine 0.0974 L-Tyrosine 9.2048 Pyroglutamic Acid Hexanoic Acid (C6H12O2) 3-Dehydrocholic Acid 0.1539 Dehydrolithocholic Acid 0.1539 Dehydrolithocholic Acid 0.4099 Isobutyric Acid (C4H8O3) 0.823 L-Aspargine 0.7384 Indolepropionic Acid 0.5887 L-Alanine 0.1179 Citric Acid 0.2862 Hippuric Acid Acetic Acid (C2H4O2) 0.3881 L-Serine 0.7126	7-Dehydrocholic Acid	0.1485
Glycine	Ursodeoxycholic Acid	0.6982
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L-Serine 0.7126		

VII APPENDIX B

Serum metabolites that did not show statistically significant difference in the mean at baseline between male (n = 172) and female (n = 199) patients that did not develop any cognitive impairment.

Triglycerides in very large HDL particles (%)	Variable	
Free Cholesterol in VLDL particles (mmol/l)		p-value
Cholesterol esters in IDL particles (%)		
Free cholesterol in IDL particles (%)		
Total cholesterol in large VLDL particles (%) 0.8043 Citrate (mmol/l) 0.1506 Concentration of medium LDL particles (mmol/l) 0.127 Free cholesterol in medium LDL particles (mmol/l) 0.7939 17iglycerides in large VLDL (mmol/l) 0.7939 17iglycerides in VLDL particles (mmol/l) 0.9933 17iglycerides in very large VLDL (mmol/l) 0.9933 17iglycerides in very large VLDL (mmol/l) 0.9933 17iglycerides in very large VLDL (mmol/l) 0.9933 17iglycerides in wery large VLDL (mmol/l) 0.9933 17iglycerides in wery large VLDL (mmol/l) 0.9932 Phospholipids in medium LDL particles (%) 0.5927 Phospholipids in small LDL particles (%) 0.5927 17otal Triglycerides (mmol/l) 0.505 17otal Triglycerides (mmol/l) 0.6059 17otal Triglycerides (mmol/l) 0.6059 17otal Triglycerides (mmol/l) 0.6059 17otal Triglycerides (mmol/l) 0.6027 17otal Triglycerides (mmol/l) 0.6027 17otal Triglycerides (mmol/l) 0.2215 17otal princip to the property of the property		
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Free cholesterol in extremely large VLDL particles (%) 0.6839	Lactate (mmol/l)	
	Free cholesterol in extremely large VLDL particles (%)	0.6839

APPENDIX B

Serum metabolites that did not show statistically significant difference in the mean at baseline between male (n = 172) and female (n = 199) patients that did not develop any cognitive impairment.

Variable	p-value
Phospholipids in small VLDL particle (%)	0.0509
Total cholesterol in very small VLDL particles (%)	0.0872
Phospholipids in small VLDL (mmol/l)	0.057
Phospholipids in very large HDL particles (%)	0.0509
Free cholesterol in very large VLDL particles (%)	0.617
Triglycerides in large VLDL particles (%)	0.371
Phospholipids in very small VLDL particles (%)	0.8777
Phospholipids in chylomicrons and extremely large VLDL (mmol/l)	0.4402
Triglycerides in extremely large VLDL particles (%)	0.5556
Polyunsaturated Fatty Acids (%)	0.6553
Omega-6 Fatty Acids (%)	0.0577
Free cholesterol in very large VLDL (mmol/l)	0.7321
Total cholesterol in IDL particles (%)	0.1164
Total cholesterol in very large VLDL particles (%)	0.2611
Concentration of small VLDL particles (mmol/l)	0.2848
Phenylalanine (mmol/l)	0.8053
Total cholesterol in chylomicrons and extremely large VLDL (mmol/l)	0.6449
Free cholesterol in large VLDL particles (%)	0.1918
Total cholesterol in large HDL particles (%)	0.749
Total cholesterol in small VLDL (mmol/l)	0.0957
Ratio of Omega-6 to Omega-3 Fatty Acids	0.0556
Cholesterol esters in large VLDL particles (%)	0.2454
Cholesterol esters in large LDL particles (%)	0.3607
Phospholipids in very large VLDL (mmol/l)	0.6119
Total cholesterol in small VLDL particle (%)	0.3527
Triglycerides in small VLDL particles (%)	0.1996
Free cholesterol in very small VLDL particles (%)	0.6173
Albumin (g/l)	0.1556
Free cholesterol in chylomicrons and extremely large VLDL (mmol/l)	0.5533
Triglycerides in large LDL particles (%)	0.8905
Triglycerides in large HDL particles (%)	0.2874
Triglycerides in medium VLDL (mmol/l)	0.567
Triglycerides in small HDL particles (mmol/l)	0.4946
Triglycerides in medium LDL particles (%)	0.4561