

Supplementary document for:

**Sex-specific metabolic pathways associate with Alzheimer's Disease (AD)
endophenotypes in the European Medical Information Framework for AD Multimodal
Biomarker Discovery cohort**

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Supplementary methods and results

Pathway enrichment analysis

The hypergeometric test was performed to identify pathways that are enriched in females and males in collections of AD endophenotypes (diagnosis, CSF markers, cognition, and brain MRI) for metabolites showing associations at the nominal significance level in sex stratified analyses (1)(2). P-values were adjusted for false discovery rate (FDR) at a corrected $P < 0.05$.

Each known metabolite was classified into one of the following eight “super-pathways”: ‘Amino acid’, ‘Carbohydrate’, ‘Cofactors and vitamins’ ‘Energy’, ‘Lipid’, ‘Nucleotide’, ‘Peptide’, and ‘Xenobiotics’ by *Metabolon* based on the Kyoto Encyclopaedia of Genes and Genomes (KEGG) database. Each super-pathway was further subdivided into two or more “sub-pathways”. The original 60 sub-pathways pre-defined by *Metabolon* for all 665 metabolites were employed as reference. Over-representation analyses using the hypergeometric test were performed for the metabolites associated in the sex-stratified analyses with the collections of endophenotypes in females and males respectively. Those containing less than 5 metabolites were excluded, resulting in 34 sub-pathways (10 sub-pathways for diagnosis, 10 for CSF biomarkers, 27 for cognition outcomes and 16 for brain MRI measurements) in the female dataset and 39 sub-pathways (10 sub-pathways for diagnosis, 10 for CSF biomarkers, 26 for cognition outcomes and 18 for brain MRI measurements) in the male dataset. It was revealed that ‘vitamin A metabolism’ ($q = 5.7e-04$) and ‘tryptophan metabolism’ sub-pathways ($q = 2.4e-02$) were enriched for diagnosis in the female group. Three additional sub-pathways were associated with cognition outcomes and four sub-pathways with brain MRI measurements in females (Supplementary Table S2), including ‘acetyl carnitine fatty acid metabolism’ ($q = 8.4e-04$), ‘monohydroxy fatty acid’ ($q = 1.7e-02$), ‘leucine, isoleucine and valine metabolism’ ($q = 4.1e-02$), ‘sphingolipid metabolism’ ($q = 3.4e-$

02), 'phosphatidylinositol (PI)' ($q = 1.9e-02$), 'primary bile acid metabolism' ($q = 3.4e-02$), and 'plasmalogen' ($q = 3.4e-04$). Ceramides were enriched for both cognition ($q = 6.6e-04$) and brain MRI measurements ($q = 1.7e-04$) in males.

The hypergeometric analysis highlighted nine sub-pathways in females and one in males. In females, both vitamin A metabolism (3) and tryptophan metabolism pathways (4) were correlated with diagnosis. The other important sub-pathways in females included acyl carnitine metabolism, phosphatidylinositol, as well as leucine, isoleucine and valine (5) which have been reported as combating oxidative stress, AD pathology or cognition. It has been demonstrated in other studies that the metabolism of some acyl-carnitines is finely connected among different diagnostic groups, as well as with age and sex (6). In males, the ceramides sub-pathway, which has been widely reported to play a role in AD and other neurodegenerative disorders was enriched (7).

Association analyses including *APOE* $\epsilon 4$ as stratification variable

Studies have reported that *APOE* $\epsilon 4$ genotype may exert AD risk in a sex-dependent manner, which has a greater influence on female *APOE* $\epsilon 4$ carrier (8–11). To investigate potential influence of *APOE* $\epsilon 4$ status on the metabolomic level, we also performed association analyses with all 15 AD endophenotypes from four categories, now stratified by *APOE* $\epsilon 4$ status and adjusted for sex. We found that 118 metabolites showed association with AD endophenotypes at nominal significance level in the *APOE* $\epsilon 4$ carrier stratum, while 116 metabolites were predominant in the non-carrier stratum (supplementary table S2). Similarly, there were 22 and 18 metabolites associated with AD endophenotypes in *APOE* $\epsilon 4$ + and *APOE* $\epsilon 4$ – stratum at Bonferroni significance threshold ($P < 8.17e-04$), respectively.

After comparing the metabolites identified in either sex group and *APOE* $\epsilon 4$ carrier stratification analyses (Supplementary Table S1 and Table S2). It was noticed that one metabolite, 2-Hydroxyisocaproic acid, showed association with immediate memory at nominal level in both female and *APOE* $\epsilon 4$ carrier strata (Supplementary Table S3 & Figure S15F). Additionally, the overlaps of metabolites between male statum and *APOE* $\epsilon 4$ carrier stratum at nominal level include LPC (18:2) and methyl glucopyranoside (alpha + beta) (associated with AD), cystathionine (associated with attention), Cer(d18:1/16:0) and GlcCer(d18:1/16:0) (associated with visuoconstruction) (Supplementary Table S3 & Figure S15A-E). Finally, when we investigated further for the cross-over overlapping metabolites that showed association with the the same endophenotype from sex strata at Bonferroni threshold and *APOE* $\epsilon 4$ strata at nominal level, as well as those from *APOE* $\epsilon 4$ starta at Bonferroni threshold and sex starta at nominal level, LPC (18:2) was found to be the only metabolite that associated with AD in males ($P = 1.11\text{e-}03$) and *APOE* $\epsilon 4$ carriers ($P = 3.92\text{e-}04$).

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Supplementary Tables

Table S1. Number of metabolites showed association with each AD endophenotypes in the whole cohort and each sex stratum.

<i>Category</i>	<i>Outcomes</i>	<i>All(*sex)</i> <i>p<0.05</i>	<i>Female</i> <i>p<0.05</i>	<i>Male</i> <i>p<0.05</i>	<i>Female</i> <i>p<8.17e-04</i>	<i>Male</i> <i>p<8.17e-04</i>
Diagnosis	AD/CTL	30	15	13	2	1
CSF markers	P-tau	11	5	5		
	T-tau	2 (38)	6 (15)	1 (13)		
	Amyloid-beta	26	6	7		
Cognition	Attention	13	7	7		
	Executive function	48	16	7		
	Language	27 (152)	6 (66)	19 (60)		
	Memory Delay	27	18	8		
	Memory Immediate	26	19	6		
	Visuoconstruction	34	10	17		
Brain MRI	Hippocampal Left	23	8	10		
	Hippocampal Right	26	6	12		
	Hippocampal Sum	22 (79)	6 (35)	10 (33)		
	Cortical thickness WB	28	9	8		
	Cortical thickness AD	43	21	14		
Total		230	116	100		

WB, whole brain; AD, Alzheimer's disease; CTL, control.

Table S2. Number of metabolites showed association with AD endophenotypes in the whole cohort and each *APOE* $\epsilon 4$ +/- stratum.

<i>Category</i>	<i>Outcomes</i>	<i>All(*APOE $\epsilon 4$ +/-) $p < 0.05$</i>	<i>APOE $\epsilon 4$ + $p < 0.05$</i>	<i>APOE $\epsilon 4$ - $p < 0.05$</i>	<i>APOE $\epsilon 4$ + $p < 8.17e-04$</i>	<i>APOE $\epsilon 4$ - $p < 8.17e-04$</i>
Diagnosis	AD/CTL	42	23	13	7	1
CSF markers	P-tau	65	25	34	1	8
	T-tau	66	24 (40)	37 (60)	- (2)	10 (16)
	Amyloid-beta	31	6	12	1	3
Cognition	Attention	35	16	12	1	2
	Executive function	21	8	8	-	1
	Language	9	3 (62)	3 (41)	2 (8)	1 (5)
	Memory Delay	44	16	8	3	-
	Memory Immediate	32	13	10	2	2
	Visuoconstruction	43	11	4	-	-
Brain MRI	Hippocampal Left	18	8	4	2	-
	Hippocampal Right	12	3	5	1	-
	Hippocampal Sum	15	7 (15)	5 (14)	2 (2)	1
	Cortical thickness WB	14	5	3	-	-
	Cortical thickness AD	17	4	5	-	-
Total			118	116	18	22

WB, whole brain; AD, Alzheimer's disease; CTL, control.

Table S3. Overlap of metabolites showed association with AD endophenotypes in the stratification analyses between female/male group and *APOE* $\epsilon 4$ + group at nominal significance levels ($p < 0.05$).

Sex	AD endophenotypes	<i>APOE</i> $\epsilon 4$ + group
Male	Diagnosis	LPC (18:2)
		methyl glucopyranoside (alpha + beta)
	Attention	Cystathionine
	Visuoconstruction	Cer(d18:1/16:0)
		GlcCer(d18:1/16:0)
Female	Memory Immediate	2-Hydroxyisocaproic acid

Table S4. The associations of the ten sub-pathways with four collections of AD endophenotypes in both sex strata.

Pathways			P-value	q-value
Female	Diagnosis	Vitamin A metabolism	5.73e-05	5.7e-04
		Tryptophan metabolism	4.71e-03	2.4e-02
	Cognition	Acyl Carnitine metabolism	3.10e-05	8.4e-04
		Monohydroxy fatty acid	1.26e-03	1.7e-02
		Leucine, isoleucine and valine metabolism	4.58e-03	4.1e-02
	MRI	Phosphatidylinositol metabolism	1.17e-03	1.9e-02
		Sphingolipid metabolism	4.28e-03	3.4e-02
		Primary bile acid metabolism	6.29e-03	3.4e-02
		Plasmalogen	8.40e-03	3.4e-02
Male	Cognition	Ceramides	2.54e-05	6.6e-04
	MRI	Ceramides	9.60e-06	1.7e-04

Table S5. Bootstrapping results of standard error (SE) and 95% confident interval for AUCs from ROC curves.

	AUC			SE			95% confidence interval		
	Female	Male	All	Female	Male	All	Female	Male	All
VMA + Tryptophan Betaine	0.834	0.639	0.742	0.029	0.046	0.027	0.777 – 0.889	0.546 – 0.733	0.687 – 0.795
Kynurenate	0.589	0.679	0.623	0.043	0.046	0.031	0.505 – 0.672	0.593 – 0.765	0.562 – 0.682
P-tau	0.748	0.783	0.762	0.037	0.042	0.027	0.672 – 0.816	0.697 – 0.862	0.707 – 0.813
T-tau	0.824	0.877	0.845	0.031	0.035	0.023	0.756 – 0.881	0.805 – 0.942	0.798 – 0.887
A β	0.839	0.803	0.824	0.029	0.035	0.022	0.775 – 0.892	0.734 – 0.865	0.781 – 0.866
CSF markers	0.885	0.908	0.894	0.025	0.026	0.018	0.836 – 0.93	0.852 – 0.954	0.858 – 0.926
Covariates	0.826	0.77	0.801	0.031	0.042	0.024	0.763 – 0.886	0.68 – 0.848	0.752 – 0.846
CSF markers + covariates	0.92	0.932	0.921	0.019	0.019	0.014	0.881 – 0.954	0.89 – 0.965	0.893 – 0.948
VMA + Tryptophan Betaine + covariates	0.887	-	0.83	0.024	-	0.023	0.836 – 0.931	-	0.784 – 0.874
Kynurenate + covariates	-	0.815	0.813	-	0.035	0.023	-	0.742 – 0.878	0.766 – 0.854
VMA + Tryptophan betaine + CSF markers + covariates	0.955	-	0.939	0.012	-	0.012	0.93 – 0.978	-	0.914 – 0.962
Kynurenate + CSF markers + covariates	-	0.932	0.921	-	0.02	0.014	-	0.888 – 0.966	0.893 – 0.948

Covariates include age at sampling, education years, sampling batch and *APOE* $\epsilon 4$ status; CSF makers include p-tau, t-tau and A β ; AUC, area under curve; ROC, receiver operating characteristic; VMA, vanillymadelate, A β , Amyloid beta.

Table S6. List of collaborators in European Medical Information Framework (EMIF) consortium.

Organisations	Partner Type	Country
<u>Aarhus Universitetshospital</u>	Academia	Denmark
<u>Agenzia Regionale di Sanità</u>	Academia	Italy
<u>Alzheimer Europe</u>	Patient Organisation	Luxembourg
<u>Amgen</u>	EFPIA	UK
<u>Boehringer Ingelheim International GmbH</u>	EFPIA	Germany
<u>Cambridge Cognition Ltd.</u>	SME	UK
<u>Concentris Research Management GmbH</u>	SME	Germany
<u>Custodix NV</u>	SME	Belgium
<u>Electrophoretics Ltd.</u>	SME	UK
<u>Erasmus Universitair Medisch Centrum Rotterdam</u>	Academia	The Netherlands
<u>European Institute for Health Records</u>	Academia	Belgium
<u>European Molecular Biology Laboratory</u>	Academia	Germany
<u>F. Hoffmann-La Roche AG</u>	EFPIA	Switzerland
<u>Fondazione PENTA – for the Treatment and Care of Children with HIV-ONLUS</u>	Academia	Italy
<u>Genomedics S.R.L.</u>	Academia	Italy
<u>GlaxoSmithKline Research and Development Ltd.</u>	EFPIA	UK
<u>Göteborgs Universitet</u>	Academia	Sweden
<u>Helsingin Yliopisto</u>	Academia	Finland
<u>IDIAP</u>	Academia	Spain
<u>Institut National de la Santé et de la Recherche Médicale</u>	Academia	France
<u>Itä-Suomen Yliopisto</u>	Academia	Finland
<u>Janssen Pharmaceutica NV</u>	EFPIA	Belgium
<u>Karolinska Institutet</u>	Academia	Sweden
<u>King's College London</u>	Academia	UK
<u>Leibniz Institute for Prevention, Research and Epidemiology –BIPS GmbH</u>	Academia	Germany
<u>Maastricht University</u>	Academia	The Netherlands
<u>MAAT France</u>	SME	France
<u>Merck</u>	EFPIA	Germany
<u>Novo Nordisk A/S</u>	EFPIA	Denmark
<u>Pedianet</u>	SME	Italy
<u>Pfizer</u>	EFPIA	UK
<u>Pharmo Cooperatie UA</u>	SME	The Netherlands
<u>Provincia Lombardo-Veneta –Ordine Ospedaliero di San Giovanni di Dio – Fatebenefratelli</u>	Academia	Italy
<u>Servier</u>	EFPIA	France
<u>Synapse Research Management Partners S.L.</u>	SME	Spain
<u>Tartu Ülikool</u>	Academia	Estonia
<u>Teknologian tutkimuskeskus VTT</u>	Academia	Finland
<u>UCB Pharma SA</u>	EFPIA	Belgium
<u>Universidade de Aveiro</u>	Academia	Portugal
<u>Universitat Pompeu Fabra</u>	Academia	Spain
<u>Universiteit Antwerpen</u>	Academia	Belgium

<u>University College London</u>	Academia	UK
<u>University of Copenhagen</u>	Academia	Denmark
<u>University of Exeter</u>	Academia	UK
<u>University of Glasgow</u>	Academia	UK
<u>University of Leicester</u>	Academia	UK
<u>University of Manchester</u>	Academia	UK
<u>University of Oxford</u>	Academia	UK
<u>University Pierre et Marie Curie</u>	Academia	France
<u>Università degli Studi di Pisa</u>	Academia	Italy
<u>Universität Leipzig</u>	Academia	Germany
<u>Universität zu Lübeck (University of Lübeck)</u>	Academia	Germany
<u>Universitätsklinikum Erlangen, Anstalt des Öffentlichen Rechts</u>	Academia	Germany
<u>Vestische Kinder – und Jugendklinik Datteln</u>	Academia	Germany
<u>VIB</u>	Academia	Belgium
<u>VU University Medical Center</u>	Academia	The Netherlands

Supplementary Figures

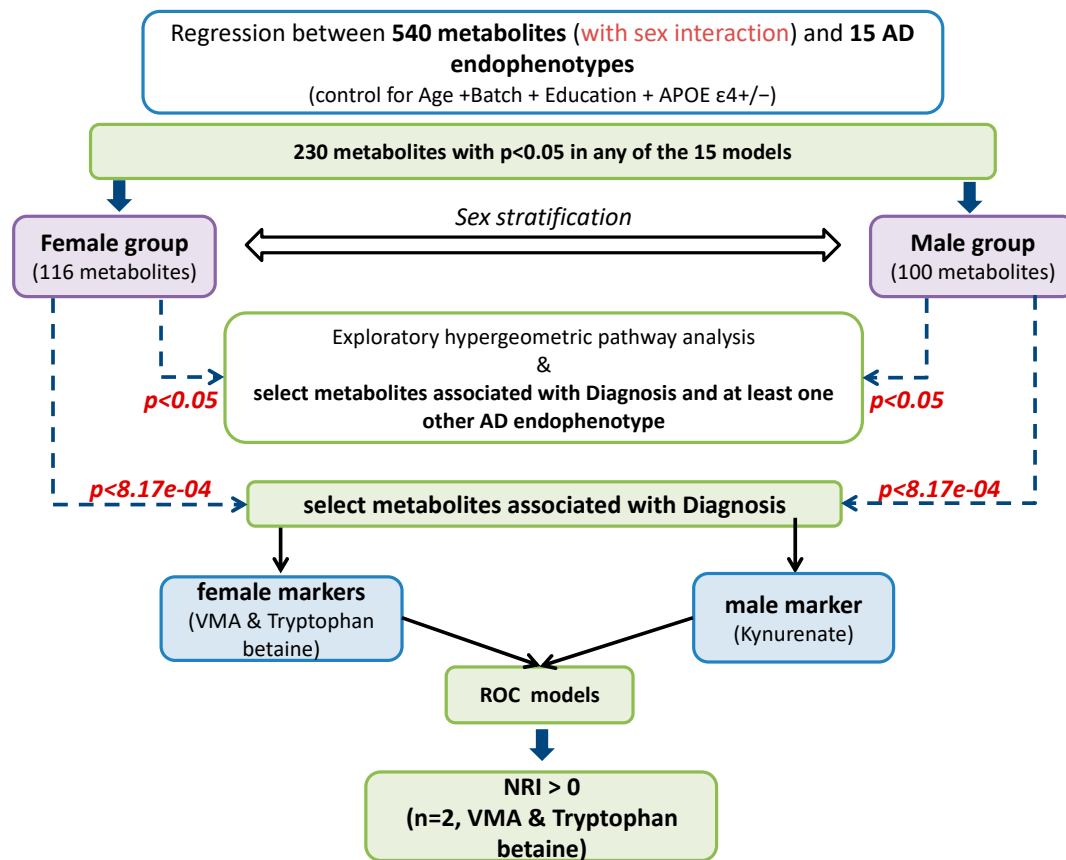


Figure S1. Study workflow. The associations between 540 plasma metabolites with a sex interaction term and 15 AD endophenotypes were investigated using linear/logistic regression. These models were repeated for 230 significant metabolites that showed interactions with sex. Metabolites that i) passed the $P < 0.05$ threshold and correlated with any of 15 AD endophenotypes were further employed for exploratory hypergeometric pathway analysis in four categories of AD endophenotypes; ii) passed the $P < 0.05$ threshold and correlated with both diagnosis as well as any other endophenotype were investigated; iii) passed the $p < 8.17e-04$ threshold in each sex stratum and showed association with diagnosis (AD/CTL) were selected for regression models followed by receiver operating characteristic (ROC) curves to test their prediction abilities in AD, which was further validated using net reclassification index (NRI).

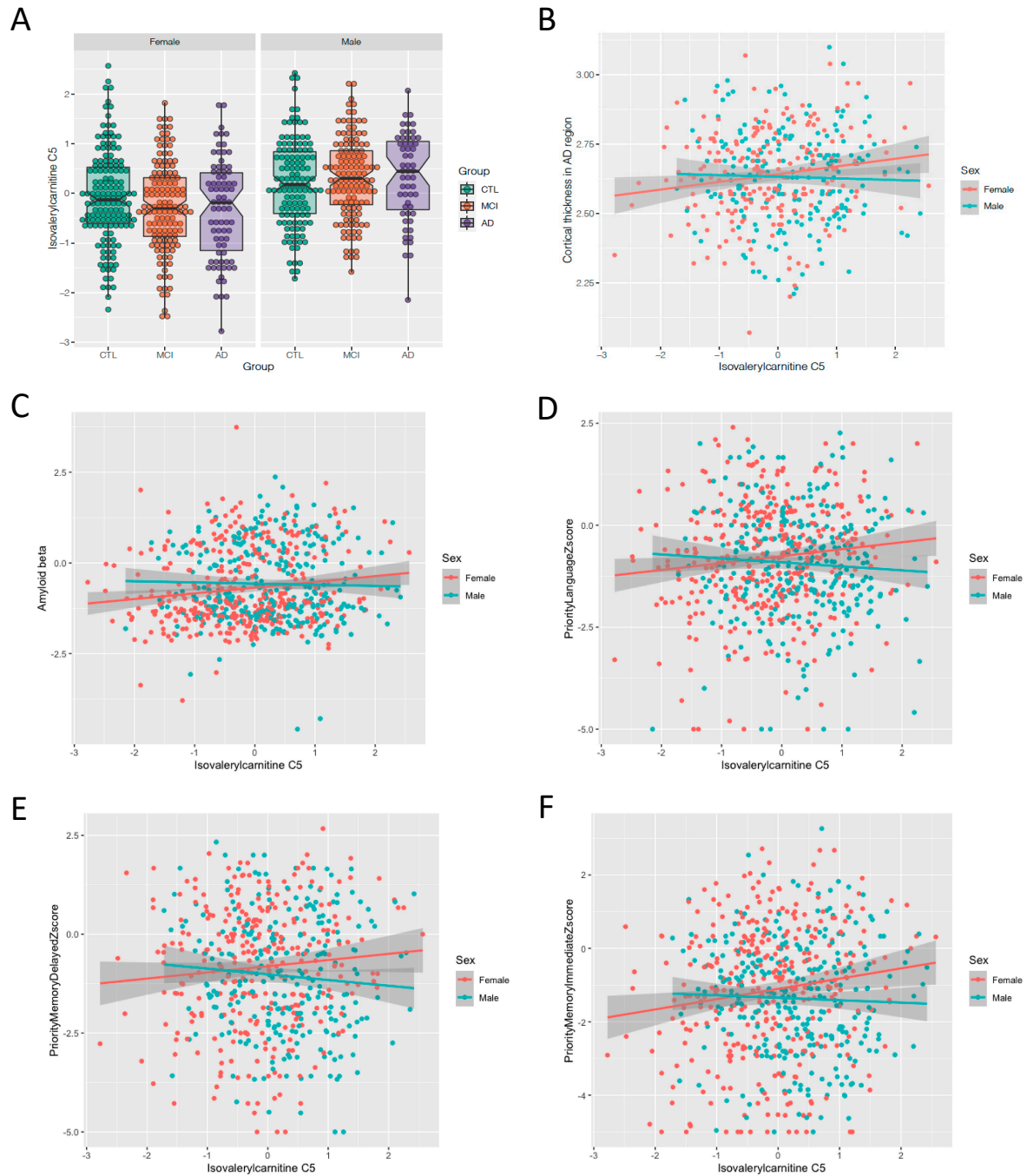


Figure S2. Isovalerylcarnitine C5 showed significant association in the female group with A) diagnosis (AD/CTL) ($\beta = -0.46$, 95% CI = -0.82 to -0.11 , $P = 1.1 \times 10^{-2}$); B) cortical thickness in AD region ($\beta = 0.031$, 95% CI = 0.0085 to 0.053 , $P = 7.3 \times 10^{-3}$); C) amyloid-beta ($\beta = 0.17$, 95% CI = 0.065 to 0.27 , $P = 1.3 \times 10^{-3}$); D) language z-score ($\beta = 0.18$, 95% CI = 0.043 to 0.33 , $P = 1.1 \times 10^{-2}$); E) memory delay z-score ($\beta = 0.19$, 95% CI = 0.0052 to 0.38 , $P = 4.5 \times 10^{-2}$) and F) memory immediate z-score ($\beta = 0.29$, 95% CI = 0.078 to 0.50 , $P = 7.5 \times 10^{-3}$).

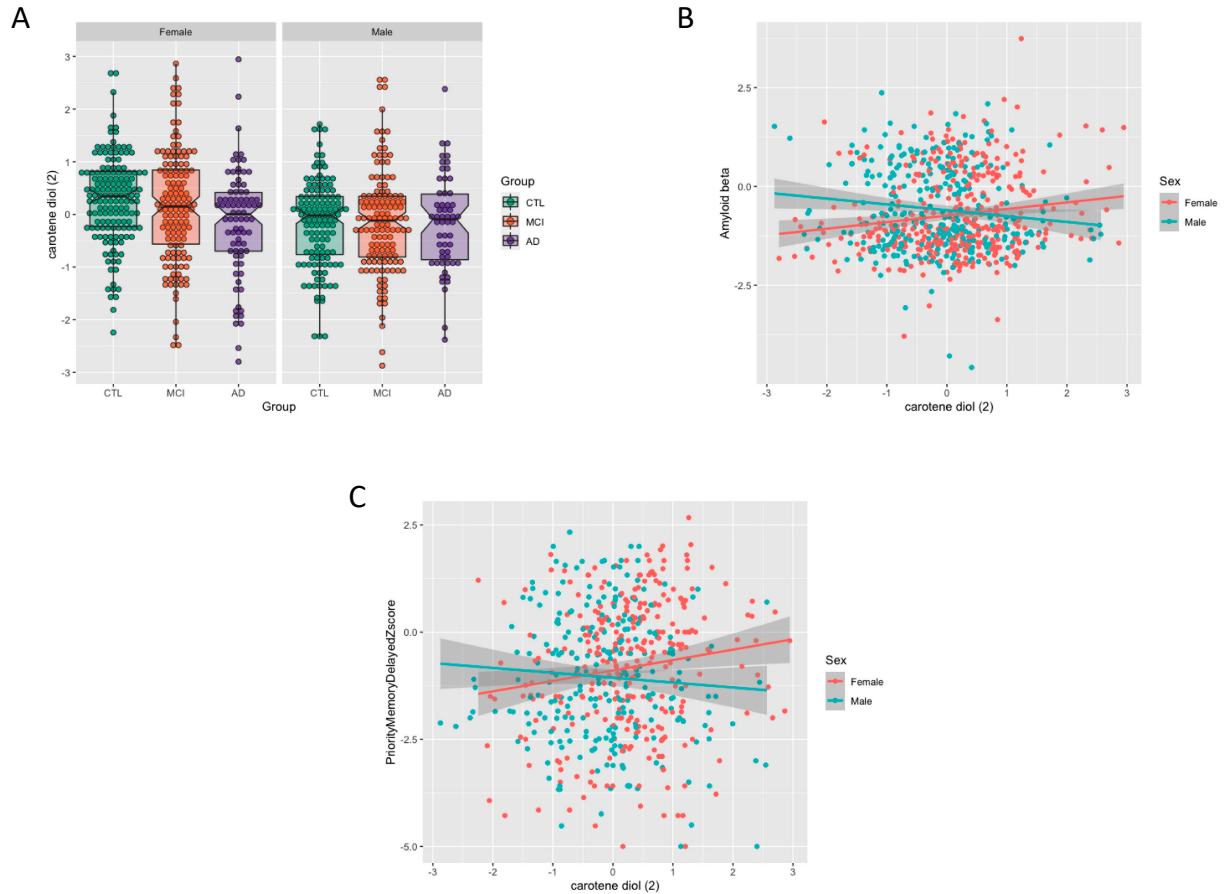


Figure S3. Carotene diol (2) showed significant association in the female group with A) diagnosis (AD/CTL) ($\beta = -0.56$, 95% CI = -0.93 to -0.22, $P = 1.94\text{e-}03$); B) amyloid-beta ($\beta = 0.13$, 95% CI = 0.033 to 0.23, $P = 9.1\text{e-}03$) and C) memory delay z-score ($\beta = 0.022$, 95% CI = 0.036 to 0.40, $P = 1.9\text{e-}02$).

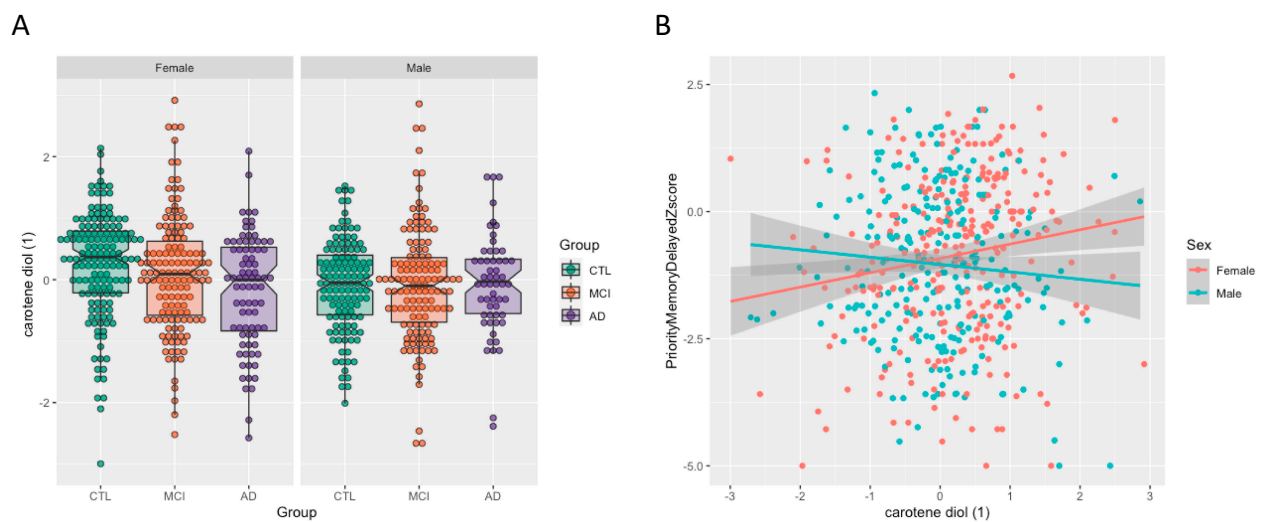


Figure S4. Carotene diol (1) showed significant association in the female group with A) diagnosis (AD/CTL) ($\beta = -0.58$, 95% CI = -0.96 to -0.22, $P = 1.95\text{e-}03$) and B) memory delay z-score ($\beta = 0.21$, 95% CI = 0.021 to 0.40, $P = 3.0\text{e-}02$).

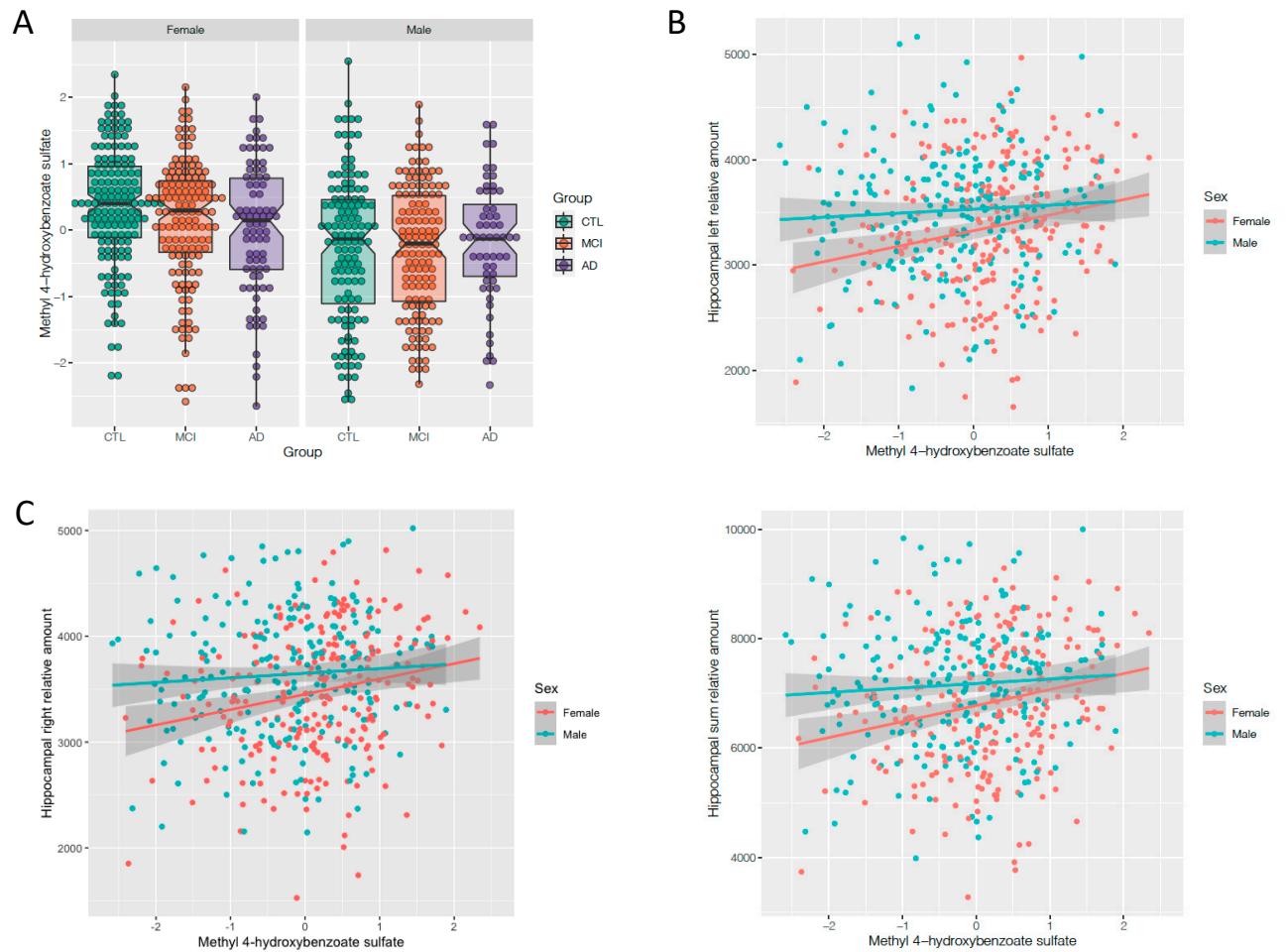


Figure S5. Methyl 4-hydroxybenzoate sulfate showed significant association in the female group with A) diagnosis (AD/CTL) ($\beta = -0.41$, 95% CI = -0.76 to -0.075, $P = 1.8e-02$); B) hippocampal left relative amount ($\beta = 131.99$, 95% CI = 51.86 to 212.13, $P = 1.4e-03$); C) hippocampal right relative amount ($\beta = 123.74$, 95% CI = 45.80 to 201.69, $P = 2.1e-03$) and D) hippocampal total relative amount ($\beta = 255.73$, 95% CI = 104.46 to 407.00, $P = 1.1e-03$).

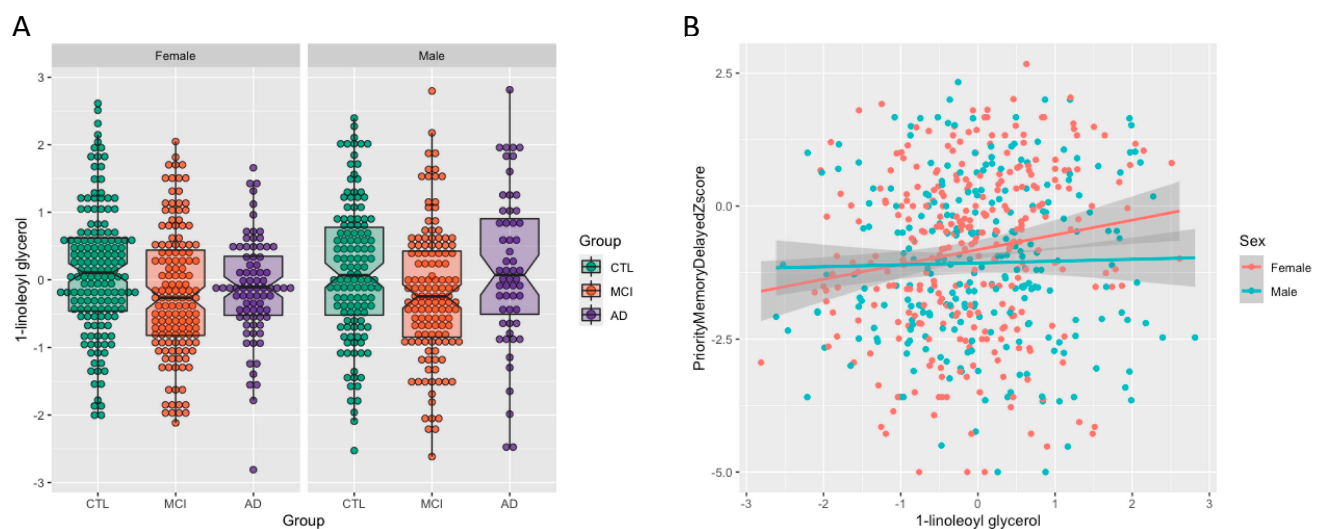


Figure S6. 1-linoleoyl glycerol showed significant association in the female group with A) diagnosis (AD/CTL) ($\beta = -0.57$, 95% CI = -0.98 to -0.18, $P = 4.7e-03$) and B) memory delay z-score ($\beta = 0.27$, 95% CI = 0.09 to 0.46, $P = 3.7e-03$).

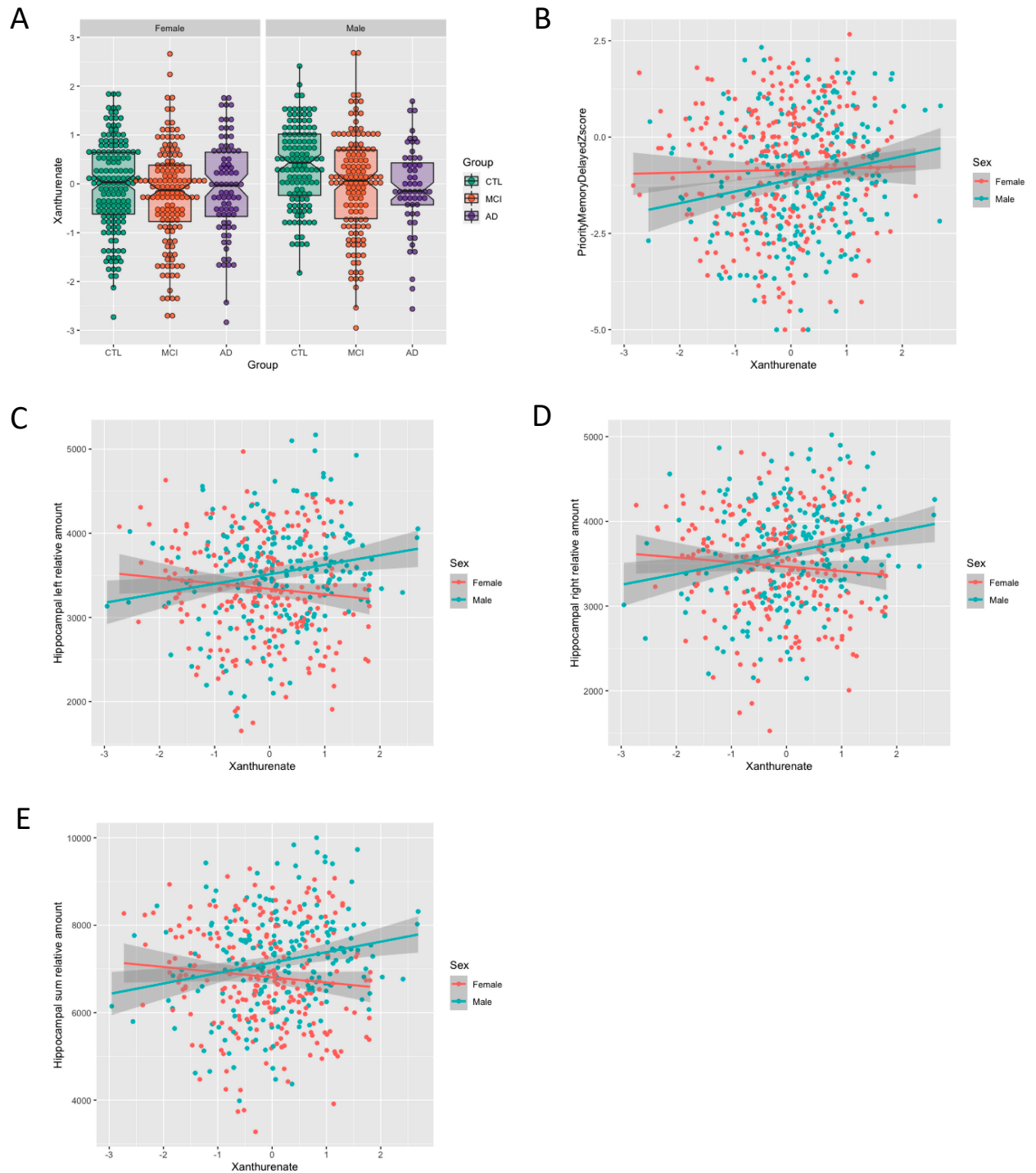


Figure S7. Xanthurenate showed significant association in the male group with A) diagnosis (AD/CTL) ($\beta = -0.73$, 95% CI = -1.18 to -0.31, $P = 1.02e-03$); B) amyloid-beta ($\beta = 0.14$, 95% CI = 0.026 to 0.25, $P = 1.62e-02$); C) hippocampal left relative amount ($\beta = 83.28$, 95% CI = 8.83 to 157.72, $P = 2.9e-02$); D) hippocampal right relative amount ($\beta = 98.28$, 95% CI = 25.45 to 171.11, $P = 8.8e-03$) and E) hippocampal total relative amount ($\beta = 181.57$, 95% CI = 41.18 to 321.95, $P = 1.2e-02$).

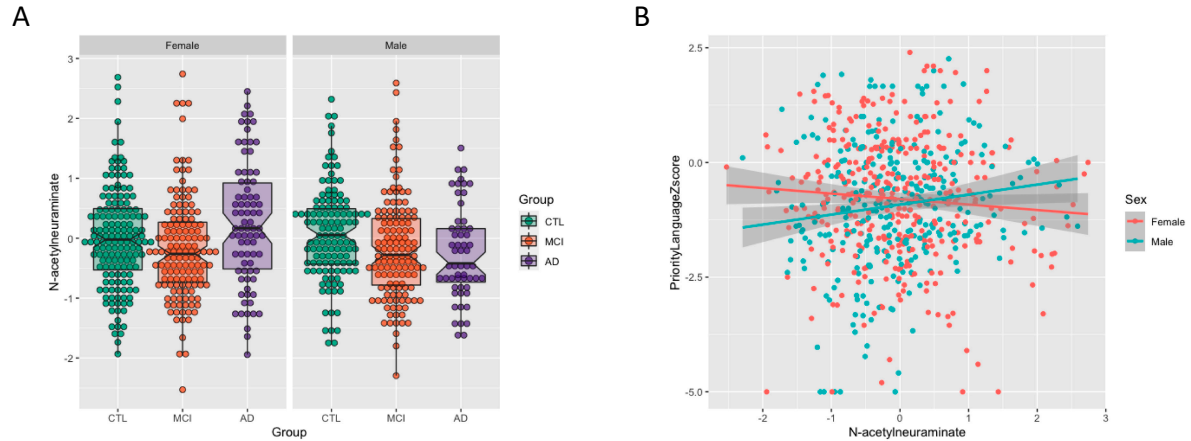


Figure S8. N-acetylneuramine showed significant association in the male group with A) diagnosis (AD/CTL) ($\beta = -0.64$, 95% CI = -1.13 to -0.18, $P = 8.03e-03$) and B) language z-score ($\beta = 0.23$, 95% CI = 0.046 to 0.42, $P = 1.5e-02$).

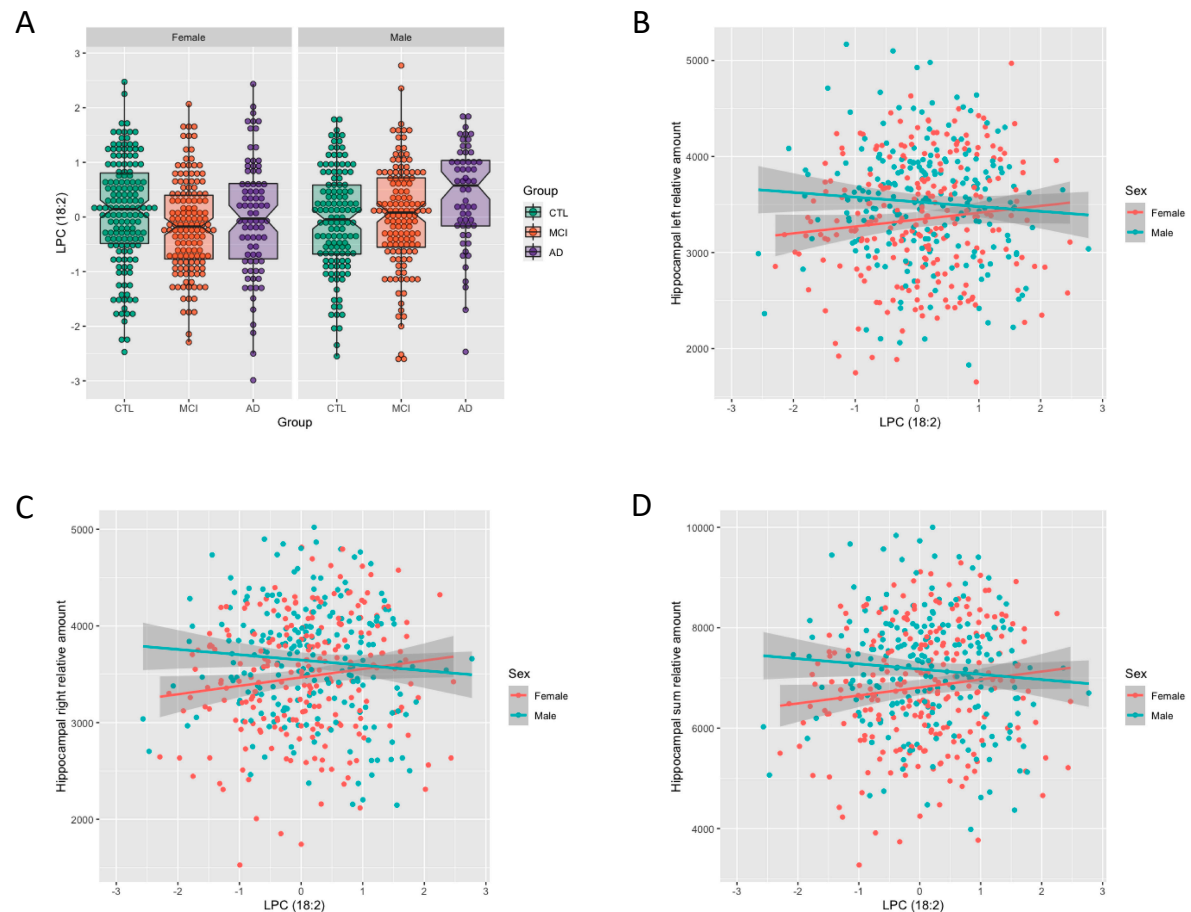


Figure S9. LPC (18:2) showed significant association in the male group with A) diagnosis (AD/CTL) ($\beta = 0.69$, 95% CI = 0.29 to 1.13, $P = 1.1e-03$), B) hippocampal left relative amount ($\beta = -91.03$, 95% CI = -170.63 to -11.43, $P = 2.6e-02$); C) hippocampal right relative amount ($\beta = -98.73$, 95% CI = -176.98 to -20.49, $P = 1.5e-02$) and D) hippocampal total relative amount ($\beta = -189.75$, 95% CI = -340.19 to -39.30, $P = 1.42e-02$).

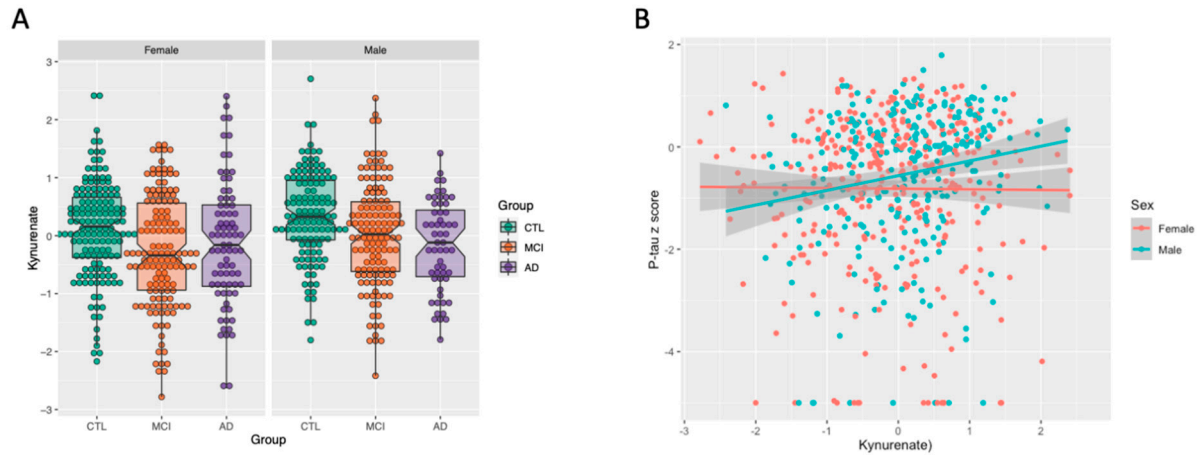


Figure S10. Kynurenate showed significant association in the male group with A) diagnosis (AD/CTL) ($\beta = -1.04$, 95% CI = -1.58 to -0.54, $P = 7.6e-05$) and B) p-tau z-score ($\beta = 0.29$, 95% CI = 0.11 to 0.47, $P = 1.77e-03$).

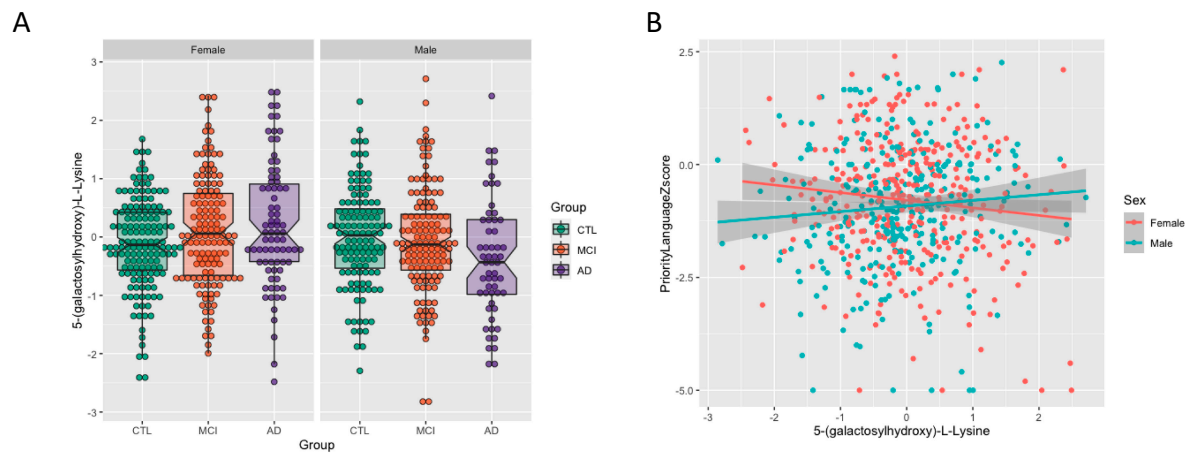


Figure S11. 5-(galactosylhydroxy)-L-Lysine showed significant association in the male group with A) diagnosis (AD/CTL) ($\beta = -0.68$, 95% CI = -1.12 to -0.26, $P = 2.0e-03$) and B) language z-score ($\beta = 0.18$, 95% CI = 0.0062 to 0.35, $P = 4.3e-02$).

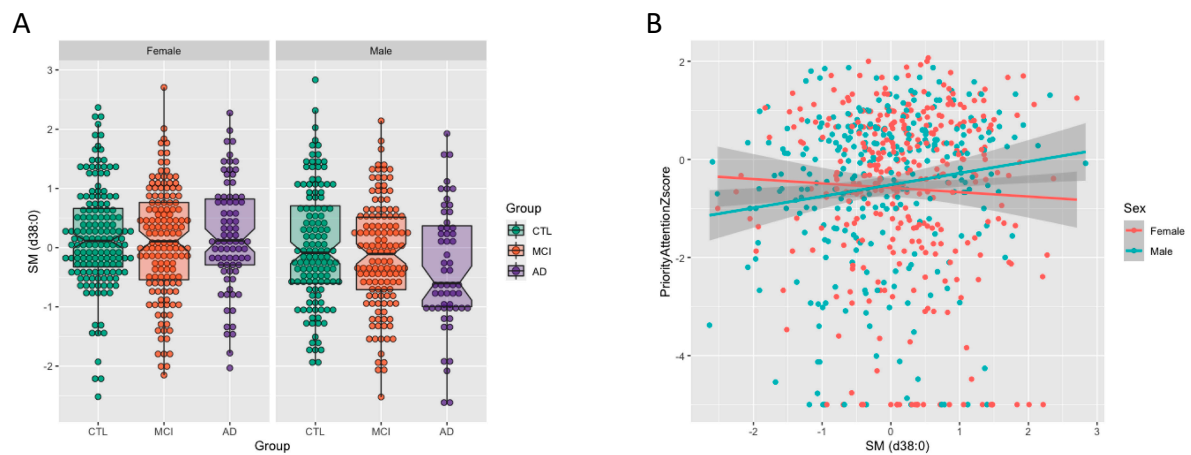


Figure S12. SM (d38:0) showed significant association in the male group with A) diagnosis (AD/CTL) ($\beta = -0.47$, 95% CI = -0.84 to -0.11, $P = 1.2e-02$) and B) attention z-score ($\beta = 0.20$, 95% CI = 0.016 to 0.39, $P = 3.4e-02$).

A	Reference + VMA + Tryptophan betaine			Total	
	Reference	<36.8%	>=36.8%		
	event				NRI_{event}
	<36.8%	7	6	13	$= (6-3)/75$
	>=36.8%	3	59	62	$= 0.04$
	New total	10	65	75	
	Non-event				NRI_{non-event}
	<36.8%	103	4	107	$= (9-4)/129$
	>=36.8%	9	13	22	$= 0.0388$
	New total	112	17	129	NRI = 0.0788
B	Reference + Kynurenate			Total	
	Reference	<34.7%	>=34.7%		
	event				NRI_{event}
	<34.7%	9	0	9	$= (0-0)/52$
	>=34.7%	0	43	43	$= 0$
	New total	9	43	52	
	Non-event				NRI_{non-event}
	<34.7%	79	3	82	$= (3-3)/98$
	>=34.7%	3	13	16	$= 0$
	New total	82	16	98	NRI = 0
C	Reference + VMA + Tryptophan betaine			Total	
	Reference	<35.9%	>=35.9%		
	event				NRI_{event}
	<35.9%	13	8	21	$= (8-2)/127$
	>=35.9%	2	104	106	$= 0.0472$
	New total	15	112	127	
	Non-event				NRI_{non-event}
	<35.9%	183	8	191	$= (8-6)/227$
	>=35.9%	9	27	36	$= 0.0044$
	New total	192	35	227	NRI = 0.0516
D	Reference + Kynurenate			Total	
	Reference	<35.9%	>=35.9%		
	event				NRI_{event}
	<35.9%	21	0	21	$= (0-1)/127$
	>=35.9%	1	105	106	$= -0.0079$
	New total	22	105	127	
	Non-event				NRI_{non-event}
	<35.9%	188	3	191	$= (3-3)/227$
	>=35.9%	3	33	36	$= 0$
	New total	191	36	227	NRI = -0.0079

Figure S13. Net reclassification index table for sex-specific biomarkers. CSF biomarkers and covariates were used as baseline predictors in the reference models. The event, non-event, and total NRI were calculated for A) vanillylmandelate (VMA) and tryptophan betaine in the female sub-dataset; B) kynurenate in the male sub-dataset; C) VMA and tryptophan betaine in the full cohort; D) kynurenate in the full cohort.

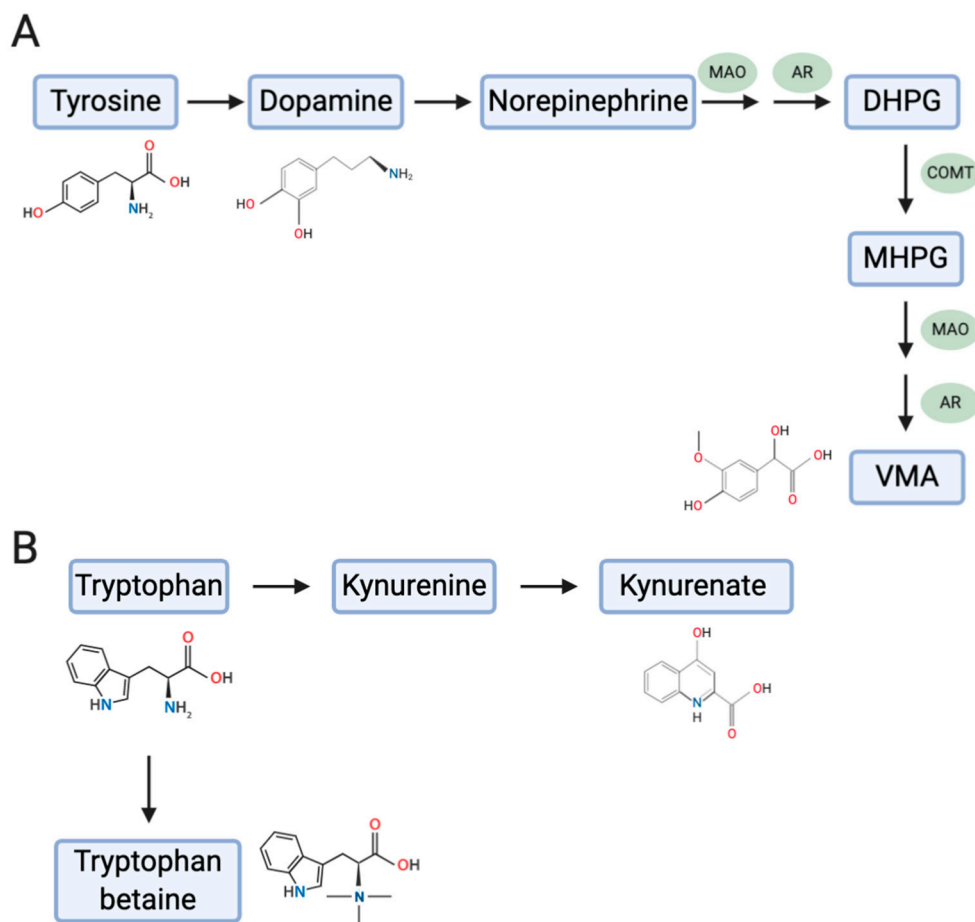


Figure S14. VMA, tryptophan betaine, and kynurenate were generated through tyrosine and tryptophan pathways. A) VMA is an end product of catecholamine metabolism in the tyrosine pathway metabolized by COMT, AR and MAO; B) kynurenate is produced from tryptophan in kynurenine pathway, while tryptophan betaine is mainly generated in plants and through gut microbiota.

VMA, vanillylmandelate; MAO, monoamine oxidase; COMT, catechol-O-methyl transferase; AR, aldehyde reductase; KAT, kynurenine aminotransferase. This figure is created with BioRender.com.

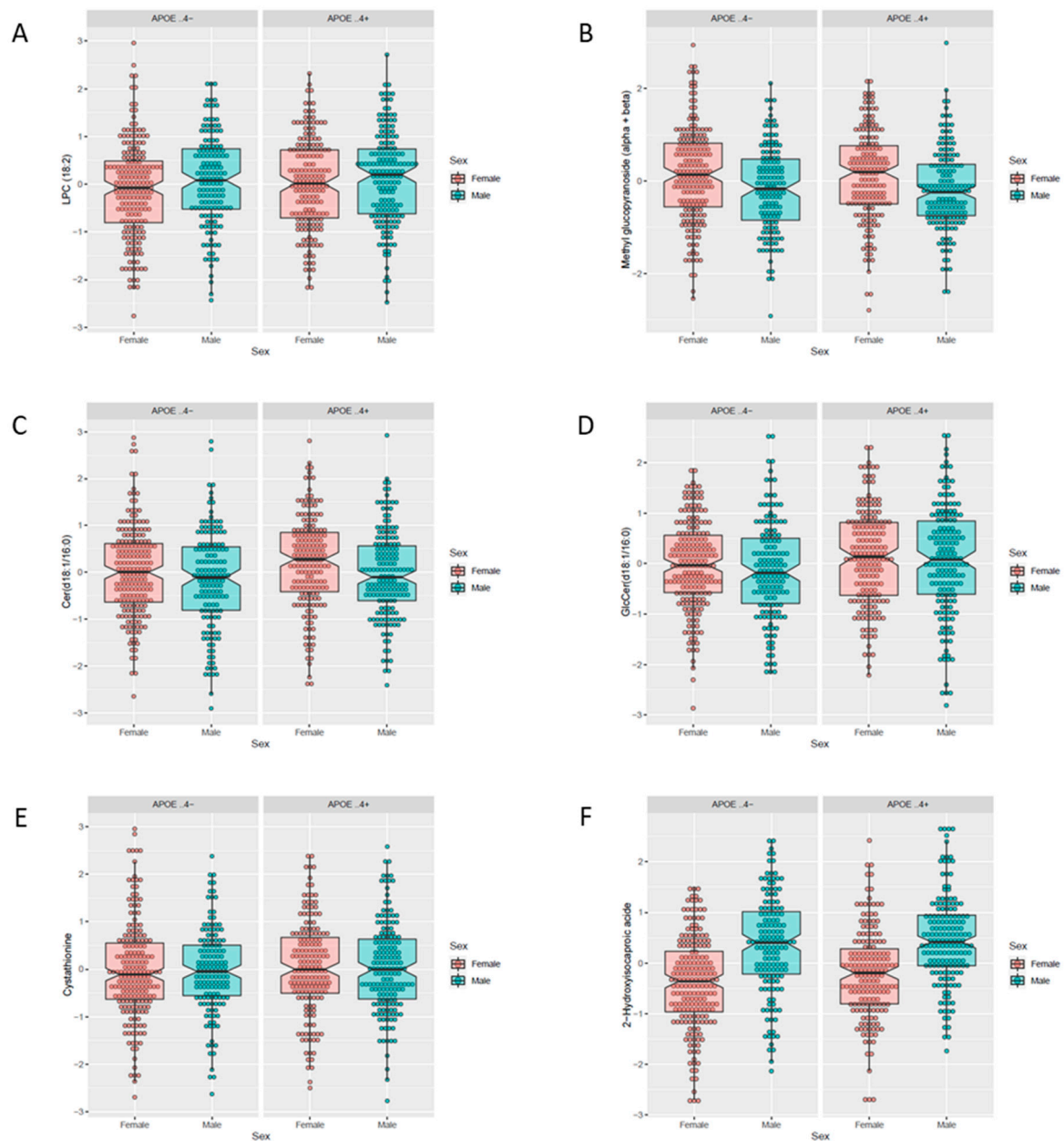


Figure S15. A) LPC (18:2) and B) methyl glucopyranoside (alpha + beta) showed association with AD at nominal level in both male and *APOE* $\epsilon 4$ carrier strata; C) Cer(d18:1/16:0) and D) GlcCer(d18:1/16:0) showed association with visuoconstruction at nominal level in both male and *APOE* $\epsilon 4$ carrier strata; E) cystathionine showed association with attention at nominal level in both male and *APOE* $\epsilon 4$ carrier strata; F) 2-Hydroxyisocaproic acid showed association with immediate memory at nominal level in both female and *APOE* $\epsilon 4$ carrier strata.