Supplementary Material

Targeted Metabolomic Analysis in Alzheimer's Disease Plasma and Brain Tissue in Non-Hispanic Whites

Supplementary Methods

Sample filtration

The counts of samples presented in the main text are the final counts following a sample filtering procedure. The filtering was performed (1) to attain relative sample homogeneity without cases of rare features, which could not be reliably controlled for in the statistical analysis due to their low occurrence, nor cases with major central nervous system co-morbidities, and (2) to improve reliability of the diagnosis group assignment.

We received 77 controls and 100 Alzheimer's disease (AD) plasma samples with matched distributions of sex, age, and *apolipoprotein E* (*APOE*) ε4 carriers. Following the selection criteria, we removed 9 participants with inconsistent diagnosis during follow-up visits, 3 participants with a low number of follow-up visits (required to guarantee short-time diagnosis consistency) and 3 participants of minority race or ethnicity. There was one site that collected only 4 samples, and these were excluded, bringing the final number of plasma samples to 94 AD and 64 controls.

For the second cohort, we received brain samples of 40 AD and 40 controls. We applied the selection criteria and excluded 1 AD with multiple sclerosis, 1 AD with hippocampal sclerosis, 1 AD marked "abnormal", and 2 controls with mild cognitive impairment. After excluding 4 cases of racial and ethnical minorities, the final number of used samples is 35 AD and 36 controls. 1 AD case and 4 controls had missing indicator of Hispanic ethnicity and were not removed from the analysis.

Plate configuration

Each plate contained 3 blanks (phosphate buffered saline for plasma, 85% ethanol in phosphate buffered saline for cortex) and 4-6 repeats of a quality control sample. Samples were randomized across the plates. Plasma samples were run on 4 plates together with samples from another source (another project) and different characteristics and these samples were not included in plate normalization or analysis. Cortex samples were run on 2 plates together with two other equally-sized diagnostic groups (33 and 32 subjects) from a related project, obtained from the same source and with a similar sociodemographic profile. Therefore, these samples were formally included in plate normalization and the statistical analysis as separate diagnostic groups to improve statistical power for estimation of the effect of regression covariates, and thus, indirectly improving statistical power for estimation of the AD effect. This allowed us to include more covariates and resulted in detection of significantly more altered lipid species in the cortex cohort (indeed, owing to shorter confidence intervals), whereas the number of detected altered small molecules remained virtually unchanged.

Data preprocessing

Plate normalization

To account for batch effects, plates were normalized (per metabolite) by scaling through median normalization (as recommended by Biocrates, the kit manufacturer): For a given metabolite, values of reference samples in each plate are scaled by such a factor so that their median is equivalent to the median of values of all reference samples before normalization. As the reference samples, we used the analyzed human samples rather than quality control samples, because this approach is expected to cause a smaller normalization error owing to the large sample count per plate despite the biological variability. To achieve unbiased normalization in this case, the reference samples need to have identical diagnosis group distribution across the plates, which was possible due to stratified sample randomization across the plates. This rule was strictly enforced even in cases where some values were treated as missing by appropriately matching the number of reference samples in each diagnosis group across the plates, reducing them as needed, starting from those with extreme values to maintain the overall median for the group as if estimated from the original number of samples without reducing its accuracy.

Limits of detection (LODs)

LODs were calculated as mean + 2 standard deviations of signal in blanks. Metabolites with more than 50% values below LOD in both AD and controls were filtered out. Values below LOD were not adjusted, since they represent the best estimate of the true values. However, strictly zero values were adjusted: Based on our experience with the kit, zero values obtained in the flow-injection mode are likely to represent mismeasurements and were regarded as missing values, whereas zero values obtained in the chromatography mode represent minimal values and were interpolated as half of the minimal non-zero value for the given metabolite to avoid strict zeros, since strict zeros are biologically unlikely. The rationale behind the special treatment of flow-injection values is that in certain cases of low-abundant metabolites the flow-injection signal is so weak and noisy that it temporarily submerges under the baseline and the signal integration software discards the whole transition, resulting in 0. The evidence comes from the behavior of quality control samples where there can be a jump to 0, even though the other values are above the level of detection and quantified in other samples even for lower concentrations. Therefore, the flow-injection 0 values can be a result of misintegration and are treated as missing rather than 0. This affected 0.57% flow-injection values in the cortex cohort (0.57% controls, equally 0.57% AD) and 2.6% flow-injection values in the plasma cohort (3.9% controls, 1.6% AD). The non-randomness in the missingness between the groups in the latter case suggests that some of the values are results of truly low-abundant signal. However, we followed a conservative approach and preferred to possibly decrease the statistical power by considering these values missing/unknown (pulling groups together if the assumption is wrong) than to risk creating false group differences by setting them to minimal values (pushing groups apart if the assumption is wrong).

Calculated analytes

Metabolic indicators were calculated according to Biocrates Metabo*INDICATOR*™ formulas [1]. Ratios with zeros were treated as missing values.

Data transformation

In *R* environment [2], we applied Box-Cox transformation with *R* package *car* [3] to better approximate Gaussian distributions. Outliers were detected and adjusted with conventional Tukey's fencing (k=1.5) [4] to protect against skewing the means by extreme values while not reducing the variance greatly compared to outlier removal. Finally, the values were standardized with respect to control samples to facilitate comparison of regression coefficients in the statistical analysis.

Missing values

The statistical analysis requires all regressors to be non-missing. Therefore, several missing sociodemographic values were imputed: In the plasma dataset, missing body mass index (BMI) values of 9 participants were interpolated through manual review of BMI data from their other visits (linear interpolation if possible or next available value in case of the first visit), and missing indicator of thyroid disorder of 1 participant was imputed as disorder negative. In the cortex dataset, missing BMI values of 4 participants and length of education of 6 participants were imputed as a mean value conditional on the diagnosis group and sex. The values of analytes (metabolites and metabolic indicators) are modelled as dependent variables and samples with missing values (not to be confused with values below LOD) are not imputed as they do not contribute to the model.

Statistical methods

Differential analysis

For the primary study objective, exploring which analytes are differentially present in AD, both tissue cohorts were modeled separately as a multivariable multiple regression, where the dependent values are individual analytes and the independent values are AD diagnosis, demographics and other clinical data potentially reflected in the metabolism (see section Covariates below). The regression was realized as a series of bootstrapped de-sparsified lasso linear regression models with *R* package *hdi* (high-dimensional inference) [5] with 1 model per each analyte and cohort: Lasso regularization, with the underlying lasso coefficient internally identified by 10-fold cross-validation, was chosen to prevent overfitting in presence of a relatively large number of regressors with respect to the number of samples (especially in the cortex dataset). De-sparsification is needed to identify reliable confidence intervals and p-values which would otherwise be biased in lasso settings due to regularization, and no special regressor selection is necessary. Bootstrapping (N = 1000) was also used, as it has been shown to successfully recover reliable estimator distributions even in the presence of non-Gaussian-distributed residuals [6]. Values of dependent variables were standardized, so the unit of the regression coefficients is 1 standard deviation on the distribution of values (of the respective analyte) of control samples.

Heteroscedasticity control

Robust estimation of variance ("sandwich" method) and robust bootstrapping ("wild" method) are recommended to prevent bias and inconsistency in the presence of heteroscedasticity [6]. This approach was applied when the Breusch-Pagan test [7] (*R* package *lmtest* [8]) for heteroscedasticity achieves evidence with p-value ≤ 0.2. This less stringent value is used instead of the conventional 0.05 since it is preferred to err on the side of falsely detected heteroscedasticity rather than falsely undetected heteroscedasticity.

False discovery rate (FDR) control

For each regressor of interest (primarily AD diagnosis, but we also report on sex-specific changes), its 2-tailed p-values across all models were controlled for FDR via the q-value approach with the *R* package *q-value* [9], for which metabolites and metabolic indicators were processed separately. FDR 0.05 was used as the threshold for statistical significance.

Covariates and collinearity

The complete list of covariates for both cohorts includes: age, sex, education, count of *APOE* ε4 alleles, BMI, diabetes mellitus, hypertension, thyroid disorder, and depression; for the plasma cohort also: hypercholesterolemia, cardiovascular disorder, smoking (100 life-time cigarettes), vitamin E supplementation, collection site, freezer storage duration, and hours of fasting before blood draw; and for the cortex cohort: hyperlipidemia, argyrophilic grains, cerebral white matter rarefaction, cerebral amyloid angiopathy, coronary artery disease, gastro-esophageal reflux disease, osteoporosis, peripheral neuropathy, urinary incontinence, benign prostatic hypertrophy, hearing impairment, cancer, tremor, renal disease, statins, prazoles, multivitamin, calcium, vitamin D, beta blockers, freezer storage duration, and postmortem interval. All time covariates were log-transformed to model exponential effects (as for decay). All regressors which indicate presence or absence (diagnosis, medication, etc.) were included because they were present in at least 20 cases, less frequent disorders or medications were not analyzed. This condition was relaxed for diabetes mellitus in plasma dataset and renal disorder in cortex dataset for their notoriously large impact on metabolism. Assessment of collinearity among all regressors was based on the magnitude of Pearson's correlation coefficients and adjusted generalized variable inflation factor (GVIF) calculated with *R* package *car* [8]. Besides mini-mental state examination score [10] and anti-dementia medication, which were not included among regressors, there was no significant collinearity (all Pearson's $r < 0.6$ and adjusted GVIF < 2.5).

Pathway analysis

We downloaded definitions of human metabolic pathways from KEGG [11] and SMPDB [12] as publicly available on December 7, 2021 and matched them with the measured metabolites. Since certain measurements in the performed assay may represent multiple isoforms undistinguishable by the mass spectra and each isoform can have its own annotations and pathway memberships, we accounted for this by assigning the measured metabolites into all pathways with any of the possible isoforms of the metabolite. Multiple metabolites remained unassigned to any pathway, especially the ones related to microbial activity. Therefore, we created a custom metabolite set with only microbial metabolites (indoles, 5-aminovaleric acid, trimethylamine N-oxide, *para*-cresol sulfate, and secondary bile acids). Only metabolic pathways with 4 or more assigned metabolites were analyzed. We followed the statistical approach of ChemRICH enrichment analysis [13] which relies on application of one-sided Kolmogorov-Smirnov test over the distribution of p-values of metabolites assigned to the same pathway using the uniform distribution as a reference. The advantage of this approach is that the test is done over p-values, which can be obtained from any comparative model, in our case the main regression model, so the covariates are considered. This is in contrast with currently available pathway tools, which, besides having problems with pairing multiple isoforms to a single measurement, cannot include covariates in the analysis, resulting in less effective analysis and potentially even false positive results. We also performed FDR control via q-values [9].

Diagnosis prediction

As the secondary objective, we searched for possible biomarkers, for which we applied the extreme gradient boosting (XGBoost) machine learning method with *R* package *xgboost* [14] using a linear base model and logistic objective, to build a model to predict the diagnosis (AD versus control), evaluated via 10x10-fold nested cross-validation. We used standardized, randomly partitioned data with stratification by the diagnosis group. We adjusted for covariates related to sample collection and handling (freezer storage duration, postmortem intervals, and blood draw fasting times) by regressing out their effects identified in the regression models. This modification is a necessary precaution to avoid bias caused by uneven freezer storage durations between the diagnostic groups in the cortex cohort and at the same time to increase the power by factoring out these confounders. The only hyperparameter used for tuning was the number of algorithm iterations, which was optimized via the inner 10-fold cross-validation with stratification by the diagnosis group, never seeing the external test fold for evaluation. The performance of predictions on test folds was evaluated with the area under receiver operating characteristic (ROC) curve (AUC) score computed with *R* package *pROC* [15] and DeLong's test was used for comparison of differences between two ROC curves. The average performance of cross-validation results of 20 repeats with different randomization of folds is reported and compared with two reference models—a model with basic sociodemographic information (sex, age, education, BMI, *APOE* ε4) and a model with randomly generated data (with 5 features as in the basic model, also 20x repeated). Additionally, we used feature selection through step-wise reduction of the least-important feature in each step and cross-validated its performance in the similar manner as before. The importance in the XGBoost model is represented by the absolute value of regression coefficients. Once the cross-validated performance was calculated, we used all data to train the final model (the best possible model in terms of bias [16]) and applied the stepwise feature reduction. More precisely, we averaged 100 different randomizations of the final model (i.e., each time with different randomizations of cross-validation folds for hyperparameter tuning) for robustness in the reported importance weights and feature selection. Then, we plotted the average feature importance against the average feature rank (order during the feature reduction process) to identify the top 30 features. In our opinion, both of these scores provide meaningful information about the feature performance, so we combined these scores by fitting a logarithmic trend and applying cut-offs perpendicular (using piecewise linear approximation) to the trend line for selecting the top features.

Demographic comparison, associations, odds ratio, and relative risk

We compared key covariates between AD cases and controls with Welch's t-test (continuous variables) and Fisher's exact test (binomial variables). Further, we explored associations between the AD diagnosis and un-matched covariates in terms of odds ratio with a series of univariable logistic regression models with profile likelihood confidence intervals, FDR-controlled with Benjamini-Hochberg procedure [17]. Estimated risk ratio for a purpose of comparison was computed with a log-binomial regression model with profile likelihood confidence interval, averaged over 100 randomizations of bootstrapping of controls to approximate 10% prevalence of AD among elderly population [18].

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Supplementary Table 1. Regression Coefficients of Individual Lipid Species Altered in AD Plasma or Frontal Cortex

	Plasma			Frontal cortex		
Metabolite	**Effect[a]**	**CI$_{95}$**	**FDR[b]**	**Effect[a]**	**CI$_{95}$**	**FDR[b]**
Acylcarnitines						
C2	-5%	(-38% – 27%)	0.20	61%	(17% – 107%)	0.031
C3	35%	(2% – 65%)	0.017	85%	(36% – 109%)	0.007
C3-DC (C4-OH)	NA[c]	NA[c]	NA[c]	82%	(36% – 128%)	0.007
C4	7%	(-28% – 40%)	0.19	67%	(26% – 112%)	0.027
C5	-21%	(-60% – 18%)	0.08	75%	(33% – 123%)	0.015
C5-DC (C6-OH)	NA[c]	NA[c]	NA[c]	47%	(4% – 88%)	0.049
C8	53%	(12% – 95%)	0.008	NA[c]	NA[c]	NA[c]
C10	44%	(-1% – 89%)	0.023	NA[c]	NA[c]	NA[c]
C12	NA[c]	NA[c]	NA[c]	68%	(33% – 106%)	0.007
C12:1	19%	(-17% – 52%)	0.09	50%	(9% – 91%)	0.046
C14	NA[c]	NA[c]	NA[c]	58%	(21% – 98%)	0.015
C14:1	18%	(-15% – 50%)	0.08	61%	(23% – 100%)	0.015
C14:1-OH	NA[c]	NA[c]	NA[c]	72%	(27% – 114%)	0.015
C16	28%	(-9% – 67%)	0.05	55%	(5% – 104%)	0.048
C16:1	-27%	(-68% – 13%)	0.06	53%	(10% – 97%)	0.034
C16:1-OH	NA[c]	NA[c]	NA[c]	61%	(13% – 106%)	0.039
C16:2	NA[c]	NA[c]	NA[c]	65%	(15% – 116%)	0.015
C18	37%	(-2% – 76%)	0.023	50%	(2% – 97%)	0.07
Sphingomyelins						
SM C16:0	22%	(-9% – 52%)	0.05	61%	(18% – 105%)	0.027
SM C16:1	16%	(-11% – 46%)	0.07	63%	(23% – 104%)	0.015
SM C24:1	8%	(-23% – 39%)	0.17	43%	(7% – 77%)	0.049
SM C26:1	24%	(-6% – 56%)	0.047	38%	(5% – 71%)	0.042
SM (OH) C14:1	6%	(-24% – 37%)	0.17	55%	(12% – 100%)	0.031
SM (OH) C22:1	16%	(-10% – 46%)	0.07	46%	(8% – 79%)	0.042
SM (OH) C22:2	4%	(-22% – 32%)	0.17	46%	(11% – 84%)	0.048
Ceramides						
Cer(d16:1/18:0)	30%	(-4% – 62%)	0.034	19%	(-26% – 60%)	0.34
Cer(d16:1/20:0)	35%	(4% – 68%)	0.014	-9%	(-51% – 29%)	0.44
Cer(d16:1/22:0)	26%	(-8% – 61%)	0.047	36%	(-16% – 87%)	0.18
Cer(d16:1/23:0)	25%	(-8% – 57%)	0.048	-4%	(-48% – 42%)	0.53
Cer(d18:1/14:0)	30%	(-3% – 69%)	0.028	63%	(19% – 102%)	0.007
Cer(d18:1/16:0)	38%	(5% – 75%)	0.012	95%	(40% – 151%)	0.007
Cer(d18:1/18:0)	63%	(23% – 102%)	0.003	44%	(4% – 82%)	0.06
Cer(d18:1/18:1)	31%	(-6% – 69%)	0.037	23%	(-14% – 60%)	0.20
Cer(d18:1/20:0(OH))	50%	(18% – 85%)	0.003	36%	(2% – 71%)	0.07
Cer(d18:1/20:0)	76%	(42% – 112%)	0.001	22%	(-20% – 61%)	0.23
Cer(d18:1/22:0)	61%	(23% – 97%)	0.001	37%	(3% – 74%)	0.06
Cer(d18:1/23:0)	63%	(29% – 99%)	0.003	34%	(0% – 67%)	0.07
Cer(d18:1/24:0)	49%	(15% – 81%)	0.004	35%	(2% – 68%)	0.07
Cer(d18:1/24:1)	59%	(21% – 94%)	0.003	36%	(1% – 72%)	0.07
Cer(d18:1/25:0)	53%	(14% – 91%)	0.004	29%	(-7% – 63%)	0.13
Cer(d18:1/26:0)	43%	(5% – 80%)	0.014	26%	(-9% – 61%)	0.16
Cer(d18:1/26:1)	73%	(29% – 115%)	0.001	36%	(3% – 73%)	0.06

Metabolite	Plasma			Frontal cortex		
	Effect[a]	CI_{95}	FDR[b]	Effect[a]	CI_{95}	FDR[b]
Cer(d18:2/16:0)	45%	(6% – 83%)	0.009	18%	(-28% – 65%)	0.36
Cer(d18:2/18:0)	68%	(31% – 103%)	0.001	11%	(-31% – 57%)	0.42
Cer(d18:2/20:0)	47%	(10% – 82%)	0.009	-4%	(-48% – 43%)	0.53
Cer(d18:2/22:0)	31%	(-4% – 66%)	0.028	18%	(-19% – 53%)	0.27
Cer(d18:2/23:0)	27%	(-6% – 61%)	0.035	36%	(1% – 72%)	0.07
Cer(d18:2/24:0)	32%	(-6% – 70%)	0.034	38%	(6% – 74%)	0.049
Cer(d18:2/24:1)	37%	(4% – 69%)	0.014	40%	(3% – 75%)	0.06
Cer(d18:0/24:0)	66%	(32% – 100%)	0.001	NA[c]	NA[c]	NA[c]
Cer(d18:0/24:1)	76%	(40% – 114%)	0.001	33%	(-7% – 72%)	0.13
Glycosylceramides						
HexosylCer(d18:1/23:0)	12%	(-18% – 43%)	0.11	39%	(5% – 74%)	0.049
HexosylCer(d18:1/26:1)	51%	(18% – 87%)	0.004	37%	(3% – 72%)	0.07
HexosylCer(d18:2/20:0)	NA[c]	NA[c]	NA[c]	44%	(9% – 82%)	0.039
HexosylCer(d18:2/22:0)	17%	(-18% – 52%)	0.10	47%	(14% – 80%)	0.027
HexosylCer(d18:2/23:0)	25%	(-7% – 57%)	0.039	43%	(7% – 76%)	0.031
HexosylCer(d18:2/24:0)	9%	(-22% – 38%)	0.14	45%	(12% – 77%)	0.007
DihexosylCer(d18:1/16:0)	10%	(-24% – 44%)	0.16	45%	(5% – 81%)	0.046
DihexosylCer(d18:1/18:0)	36%	(3% – 68%)	0.013	37%	(0% – 70%)	0.07
DihexosylCer(d18:1/20:0)	53%	(15% – 90%)	0.001	37%	(4% – 72%)	0.048
DihexosylCer(d18:1/22:0)	44%	(20% – 73%)	0.003	39%	(1% – 78%)	0.07
DihexosylCer(d18:1/24:0)	41%	(13% – 67%)	0.003	53%	(19% – 87%)	0.022
DihexosylCer(d18:1/24:1)	15%	(-17% – 47%)	0.11	47%	(14% – 82%)	0.015
TrihexosylCer(d18:1/16:0)	23%	(-5% – 56%)	0.037	65%	(21% – 107%)	0.007
TrihexosylCer(d18:1/18:0)	19%	(-14% – 49%)	0.08	84%	(31% – 140%)	0.022
Phosphatidylcholines						
PC aa C24:0	29%	(-1% – 61%)	0.024	-12%	(-50% – 31%)	0.39
PC aa C26:0	36%	(3% – 68%)	0.017	-37%	(-81% – 10%)	0.13
PC aa C28:1	15%	(-14% – 43%)	0.09	54%	(12% – 95%)	0.034
PC aa C30:0	27%	(-6% – 61%)	0.044	-18%	(-60% – 25%)	0.32
PC aa C32:0	40%	(5% – 74%)	0.009	-23%	(-66% – 21%)	0.26
PC aa C32:1	31%	(-2% – 62%)	0.023	17%	(-23% – 55%)	0.34
PC aa C32:2	37%	(2% – 69%)	0.014	-2%	(-43% – 37%)	0.53
PC aa C32:3	36%	(10% – 70%)	0.007	9%	(-31% – 51%)	0.44
PC aa C34:1	36%	(4% – 65%)	0.011	11%	(-47% – 70%)	0.48
PC aa C34:2	61%	(27% – 97%)	0.001	14%	(-30% – 58%)	0.38
PC aa C34:3	53%	(23% – 86%)	0.001	-3%	(-42% – 34%)	0.49
PC aa C34:4	46%	(18% – 79%)	0.001	5%	(-39% – 46%)	0.48
PC aa C36:1	36%	(6% – 65%)	0.011	13%	(-27% – 51%)	0.38
PC aa C36:2	54%	(27% – 90%)	0.001	24%	(-16% – 59%)	0.19
PC aa C36:3	51%	(18% – 84%)	0.004	7%	(-38% – 51%)	0.48
PC aa C36:4	64%	(27% – 99%)	0.001	-9%	(-52% – 34%)	0.45
PC aa C38:3	28%	(-5% – 61%)	0.032	22%	(-25% – 68%)	0.32
PC aa C38:4	51%	(14% – 83%)	0.005	-23%	(-63% – 20%)	0.28
PC aa C38:5	51%	(21% – 85%)	0.001	-8%	(-54% – 40%)	0.49
PC aa C40:3	9%	(-19% – 39%)	0.13	45%	(7% – 86%)	0.048
PC aa C40:4	72%	(37% – 108%)	0.001	-29%	(-75% – 15%)	0.23
PC aa C40:5	66%	(34% – 102%)	0.001	-5%	(-54% – 49%)	0.49

Metabolite	Plasma			Frontal cortex		
	Effect[a]	CI_{95}	FDR[b]	Effect[a]	CI_{95}	FDR[b]
PC aa C42:1	-8%	(-38% – 21%)	0.17	48%	(14% – 85%)	0.027
PC aa C42:4	26%	(-5% – 58%)	0.032	56%	(14% – 98%)	0.015
PC aa C42:5	29%	(-1% – 61%)	0.024	37%	(-8% – 81%)	0.13
PC aa C42:6	30%	(-3% – 62%)	0.026	30%	(-13% – 75%)	0.18
PC ae C30:0	10%	(-20% – 43%)	0.13	58%	(15% – 101%)	0.034
PC ae C32:1	15%	(-13% – 44%)	0.10	54%	(19% – 93%)	0.034
PC ae C32:2	10%	(-18% – 43%)	0.12	48%	(11% – 85%)	0.031
PC ae C34:0	30%	(0% – 61%)	0.022	-35%	(-77% – 12%)	0.18
PC ae C34:2	41%	(10% – 76%)	0.007	46%	(5% – 84%)	0.06
PC ae C34:3	31%	(-1% – 66%)	0.023	50%	(9% – 89%)	0.042
PC ae C36:0	28%	(-2% – 59%)	0.032	-38%	(-85% – 8%)	0.13
PC ae C36:2	32%	(-1% – 64%)	0.023	38%	(0% – 72%)	0.07
PC ae C36:3	40%	(6% – 73%)	0.008	43%	(2% – 81%)	0.06
PC ae C36:4	56%	(23% – 89%)	0.003	66%	(29% – 106%)	0.007
PC ae C36:5	36%	(4% – 66%)	0.014	93%	(44% – 144%)	0.015
PC ae C38:3	24%	(-6% – 53%)	0.035	40%	(1% – 80%)	0.06
PC ae C38:4	48%	(14% – 79%)	0.004	41%	(-8% – 92%)	0.12
PC ae C38:5	44%	(8% – 80%)	0.004	64%	(26% – 101%)	0.007
PC ae C38:6	16%	(-16% – 47%)	0.11	58%	(18% – 97%)	0.027
PC ae C40:1	31%	(-1% – 63%)	0.022	-21%	(-50% – 14%)	0.21
PC ae C40:4	34%	(1% – 65%)	0.019	45%	(5% – 85%)	0.049
PC ae C40:5	26%	(-7% – 57%)	0.043	45%	(2% – 84%)	0.07
PC ae C42:1	33%	(2% – 64%)	0.017	-11%	(-48% – 25%)	0.42
PC ae C42:5	10%	(-21% – 39%)	0.13	46%	(7% – 84%)	0.042
Lysophosphatidylcholines						
LysoPC a C14:0	30%	(-4% – 63%)	0.029	-28%	(-65% – 6%)	0.13
LysoPC a C16:0	56%	(23% – 91%)	0.001	-28%	(-69% – 8%)	0.15
LysoPC a C16:1	51%	(12% – 89%)	0.006	-43%	(-85% – -3%)	0.06
LysoPC a C18:0	49%	(14% – 81%)	0.006	-26%	(-65% – 12%)	0.19
LysoPC a C18:1	56%	(23% – 87%)	0.001	-39%	(-88% – 9%)	0.15
LysoPC a C18:2	76%	(42% – 105%)	0.001	-14%	(-51% – 29%)	0.38
LysoPC a C20:3	58%	(26% – 91%)	0.001	-18%	(-56% – 23%)	0.29
LysoPC a C20:4	70%	(32% – 104%)	0.001	-37%	(-73% – -1%)	0.07
LysoPC a C26:1	32%	(-1% – 62%)	0.023	43%	(1% – 85%)	0.07
LysoPC a C28:0	29%	(-1% – 63%)	0.024	44%	(-1% – 92%)	0.08
LysoPC a C28:1	21%	(-4% – 49%)	0.042	39%	(-3% – 81%)	0.10
Cholesteryl esters						
CE(16:1)	29%	(-5% – 65%)	0.031	NA[c]	NA[c]	NA[c]
CE(17:1)	24%	(-8% – 55%)	0.048	-19%	(-64% – 27%)	0.33
CE(18:2)	27%	(-3% – 61%)	0.029	-30%	(-73% – 14%)	0.18
CE(18:3)	32%	(5% – 62%)	0.010	2%	(-34% – 39%)	0.53
CE(20:1)	29%	(-2% – 61%)	0.026	3%	(-39% – 44%)	0.53
CE(20:4)	34%	(2% – 69%)	0.019	15%	(-20% – 48%)	0.30
CE(22:0)	NA[c]	NA[c]	NA[c]	67%	(17% – 119%)	0.027
CE(22:2)	39%	(9% – 69%)	0.004	-40%	(-90% – 10%)	0.12
CE(22:5)	53%	(23% – 87%)	0.001	NA[c]	NA[c]	NA[c]
Diglycerides						

Metabolite	Plasma			Frontal cortex		
	Effect[a]	CI_{95}	FDR[b]	Effect[a]	CI_{95}	FDR[b]
DG(14:0_18:1)	NA[c]	NA[c]	NA[c]	56%	(18% – 93%)	0.015
DG(16:0_18:1)	47%	(12% – 82%)	0.006	65%	(29% – 103%)	0.007
DG(16:0_18:2)	55%	(23% – 90%)	0.003	84%	(45% – 125%)	0.007
DG(16:0_20:3)	NA[c]	NA[c]	NA[c]	57%	(24% – 91%)	0.007
DG(16:1_18:1)	43%	(3% – 80%)	0.014	NA[c]	NA[c]	NA[c]
DG(17:0_18:1)	32%	(-4% – 69%)	0.032	44%	(8% – 86%)	0.06
DG(18:0_20:4)	NA[c]	NA[c]	NA[c]	66%	(26% – 100%)	0.007
DG(18:1_18:1)	40%	(7% – 73%)	0.012	55%	(12% – 91%)	0.034
DG(18:1_18:2)	42%	(8% – 74%)	0.009	31%	(-12% – 75%)	0.18
DG(18:2_18:2)	39%	(8% – 72%)	0.007	24%	(-15% – 72%)	0.18
DG(18:2_18:3)	33%	(-1% – 71%)	0.023	20%	(-24% – 61%)	0.30
DG(18:2_20:4)	NA[c]	NA[c]	NA[c]	52%	(12% – 92%)	0.039
Triglycerides						
TG(14:0_32:2)	31%	(-1% – 62%)	0.024	NA[c]	NA[c]	NA[c]
TG(14:0_34:0)	33%	(1% – 65%)	0.021	NA[c]	NA[c]	NA[c]
TG(14:0_34:1)	39%	(4% – 70%)	0.013	NA[c]	NA[c]	NA[c]
TG(14:0_34:2)	42%	(10% – 74%)	0.006	44%	(-1% – 92%)	0.08
TG(14:0_34:3)	46%	(14% – 82%)	0.004	-37%	(-83% – 8%)	0.11
TG(14:0_35:1)	39%	(8% – 69%)	0.007	16%	(-27% – 57%)	0.33
TG(14:0_35:2)	38%	(6% – 70%)	0.007	25%	(-18% – 70%)	0.25
TG(14:0_36:1)	37%	(7% – 69%)	0.008	6%	(-31% – 46%)	0.48
TG(14:0_36:2)	40%	(11% – 69%)	0.004	28%	(-15% – 68%)	0.18
TG(14:0_36:3)	48%	(16% – 80%)	0.005	NA[c]	NA[c]	NA[c]
TG(14:0_36:4)	48%	(14% – 80%)	0.004	59%	(15% – 101%)	0.031
TG(14:0_38:4)	50%	(19% – 83%)	0.004	11%	(-30% – 54%)	0.41
TG(14:0_38:5)	55%	(21% – 91%)	0.001	-26%	(-75% – 26%)	0.26
TG(16:0_28:1)	32%	(-1% – 65%)	0.023	-18%	(-64% – 24%)	0.33
TG(16:0_28:2)	30%	(-2% – 63%)	0.028	NA[c]	NA[c]	NA[c]
TG(16:0_30:2)	40%	(7% – 70%)	0.008	NA[c]	NA[c]	NA[c]
TG(16:0_32:0)	42%	(8% – 78%)	0.009	NA[c]	NA[c]	NA[c]
TG(16:0_32:1)	39%	(6% – 73%)	0.012	NA[c]	NA[c]	NA[c]
TG(16:0_32:2)	44%	(11% – 75%)	0.005	9%	(-45% – 57%)	0.47
TG(16:0_32:3)	45%	(11% – 78%)	0.009	29%	(-13% – 69%)	0.18
TG(16:0_33:1)	37%	(4% – 69%)	0.012	NA[c]	NA[c]	NA[c]
TG(16:0_33:2)	45%	(12% – 77%)	0.007	NA[c]	NA[c]	NA[c]
TG(16:0_34:0)	45%	(15% – 81%)	0.004	NA[c]	NA[c]	NA[c]
TG(16:0_34:1)	47%	(16% – 82%)	0.005	NA[c]	NA[c]	NA[c]
TG(16:0_34:2)	56%	(23% – 91%)	0.001	NA[c]	NA[c]	NA[c]
TG(16:0_34:3)	58%	(24% – 93%)	0.001	NA[c]	NA[c]	NA[c]
TG(16:0_34:4)	51%	(15% – 86%)	0.004	NA[c]	NA[c]	NA[c]
TG(16:0_35:1)	48%	(17% – 81%)	0.003	19%	(-33% – 74%)	0.34
TG(16:0_35:2)	46%	(14% – 79%)	0.005	NA[c]	NA[c]	NA[c]
TG(16:0_35:3)	53%	(24% – 87%)	0.001	-12%	(-52% – 31%)	0.38
TG(16:0_36:2)	45%	(13% – 77%)	0.005	NA[c]	NA[c]	NA[c]
TG(16:0_36:3)	49%	(21% – 80%)	0.001	-3%	(-45% – 38%)	0.52
TG(16:0_36:4)	54%	(24% – 84%)	0.004	-18%	(-59% – 27%)	0.34
TG(16:0_36:5)	61%	(32% – 97%)	0.001	-17%	(-54% – 21%)	0.31

Metabolite	Plasma Effect[a]	Plasma CI_{95}	Plasma FDR[b]	Frontal cortex Effect[a]	Frontal cortex CI_{95}	Frontal cortex FDR[b]
TG(16:0_36:6)	53%	(21% – 84%)	0.001	NA[c]	NA[c]	NA[c]
TG(16:0_37:3)	40%	(7% – 72%)	0.009	NA[c]	NA[c]	NA[c]
TG(16:0_38:1)	45%	(11% – 82%)	0.005	NA[c]	NA[c]	NA[c]
TG(16:0_38:2)	47%	(13% – 81%)	0.005	29%	(-17% – 83%)	0.23
TG(16:0_38:3)	52%	(21% – 83%)	0.003	-5%	(-40% – 30%)	0.48
TG(16:0_38:4)	58%	(30% – 90%)	0.001	23%	(-22% – 68%)	0.24
TG(16:0_38:5)	58%	(24% – 96%)	0.001	0%	(-37% – 38%)	0.55
TG(16:0_38:6)	54%	(18% – 92%)	0.004	31%	(-7% – 69%)	0.13
TG(16:0_38:7)	43%	(6% – 82%)	0.010	40%	(-8% – 89%)	0.14
TG(16:0_40:6)	55%	(21% – 90%)	0.001	14%	(-23% – 51%)	0.38
TG(16:0_40:7)	38%	(1% – 74%)	0.017	-6%	(-53% – 44%)	0.50
TG(16:1_28:0)	33%	(-1% – 64%)	0.023	24%	(-23% – 72%)	0.29
TG(16:1_30:1)	41%	(5% – 74%)	0.009	NA[c]	NA[c]	NA[c]
TG(16:1_32:0)	41%	(6% – 76%)	0.014	NA[c]	NA[c]	NA[c]
TG(16:1_32:1)	37%	(1% – 71%)	0.019	NA[c]	NA[c]	NA[c]
TG(16:1_32:2)	44%	(10% – 79%)	0.006	NA[c]	NA[c]	NA[c]
TG(16:1_33:1)	44%	(10% – 81%)	0.007	NA[c]	NA[c]	NA[c]
TG(16:1_34:0)	44%	(8% – 78%)	0.005	4%	(-33% – 40%)	0.49
TG(16:1_34:1)	46%	(11% – 83%)	0.004	NA[c]	NA[c]	NA[c]
TG(16:1_34:2)	54%	(22% – 91%)	0.003	NA[c]	NA[c]	NA[c]
TG(16:1_34:3)	56%	(21% – 90%)	0.003	NA[c]	NA[c]	NA[c]
TG(16:1_36:1)	44%	(9% – 78%)	0.007	NA[c]	NA[c]	NA[c]
TG(16:1_36:2)	36%	(5% – 72%)	0.012	-14%	(-58% – 30%)	0.38
TG(16:1_36:3)	42%	(15% – 76%)	0.001	44%	(1% – 89%)	0.07
TG(16:1_36:4)	46%	(13% – 80%)	0.005	26%	(-16% – 66%)	0.21
TG(16:1_36:5)	56%	(22% – 91%)	0.001	NA[c]	NA[c]	NA[c]
TG(16:1_38:3)	54%	(21% – 88%)	0.001	NA[c]	NA[c]	NA[c]
TG(16:1_38:4)	56%	(24% – 88%)	0.001	NA[c]	NA[c]	NA[c]
TG(16:1_38:5)	63%	(30% – 102%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:0_32:1)	41%	(8% – 76%)	0.007	39%	(-12% – 92%)	0.12
TG(17:0_34:1)	42%	(8% – 73%)	0.006	54%	(1% – 112%)	0.07
TG(17:0_34:2)	52%	(15% – 84%)	0.003	48%	(-10% – 98%)	0.14
TG(17:0_34:3)	54%	(22% – 88%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:0_36:3)	48%	(20% – 79%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:0_36:4)	46%	(15% – 76%)	0.004	4%	(-50% – 58%)	0.52
TG(17:1_32:1)	41%	(6% – 73%)	0.009	NA[c]	NA[c]	NA[c]
TG(17:1_34:1)	42%	(10% – 75%)	0.007	NA[c]	NA[c]	NA[c]
TG(17:1_34:2)	55%	(33% – 87%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:1_34:3)	51%	(17% – 83%)	0.003	NA[c]	NA[c]	NA[c]
TG(17:1_36:3)	48%	(21% – 79%)	0.001	29%	(-12% – 71%)	0.17
TG(17:1_36:4)	56%	(27% – 87%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:1_36:5)	53%	(20% – 87%)	0.001	52%	(-1% – 99%)	0.08
TG(17:1_38:5)	57%	(23% – 89%)	0.001	40%	(-15% – 91%)	0.15
TG(17:1_38:6)	62%	(25% – 96%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:1_38:7)	70%	(37% – 105%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:2_34:2)	56%	(22% – 86%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:2_34:3)	36%	(0% – 71%)	0.022	NA[c]	NA[c]	NA[c]

Metabolite	Plasma			Frontal cortex		
	Effect[a]	CI_{95}	FDR[b]	Effect[a]	CI_{95}	FDR[b]
TG(17:2_36:2)	55%	(30% – 91%)	0.001	-3%	(-41% – 38%)	0.51
TG(17:2_36:3)	58%	(23% – 95%)	0.003	NA[c]	NA[c]	NA[c]
TG(17:2_36:4)	50%	(17% – 84%)	0.004	6%	(-46% – 56%)	0.50
TG(17:2_38:5)	50%	(17% – 85%)	0.004	-12%	(-55% – 31%)	0.41
TG(17:2_38:6)	63%	(25% – 99%)	0.001	NA[c]	NA[c]	NA[c]
TG(17:2_38:7)	60%	(23% – 96%)	0.001	9%	(-33% – 52%)	0.44
TG(18:0_30:1)	29%	(-5% – 63%)	0.032	50%	(6% – 92%)	0.05
TG(18:0_32:0)	43%	(6% – 79%)	0.012	NA[c]	NA[c]	NA[c]
TG(18:0_32:1)	40%	(4% – 73%)	0.014	NA[c]	NA[c]	NA[c]
TG(18:0_32:2)	45%	(13% – 80%)	0.004	NA[c]	NA[c]	NA[c]
TG(18:0_34:2)	53%	(21% – 84%)	0.001	NA[c]	NA[c]	NA[c]
TG(18:0_34:3)	56%	(21% – 88%)	0.003	NA[c]	NA[c]	NA[c]
TG(18:0_36:1)	35%	(1% – 65%)	0.016	15%	(-29% – 56%)	0.38
TG(18:0_36:2)	44%	(11% – 78%)	0.004	NA[c]	NA[c]	NA[c]
TG(18:0_36:3)	51%	(16% – 83%)	0.001	NA[c]	NA[c]	NA[c]
TG(18:0_36:4)	53%	(18% – 86%)	0.001	20%	(-24% – 65%)	0.29
TG(18:0_36:5)	57%	(24% – 90%)	0.001	13%	(-33% – 59%)	0.42
TG(18:0_38:6)	52%	(15% – 87%)	0.005	NA[c]	NA[c]	NA[c]
TG(18:0_38:7)	56%	(20% – 95%)	0.005	36%	(-1% – 75%)	0.08
TG(18:1_26:0)	27%	(-6% – 60%)	0.041	NA[c]	NA[c]	NA[c]
TG(18:1_28:1)	37%	(5% – 69%)	0.015	NA[c]	NA[c]	NA[c]
TG(18:1_30:0)	38%	(6% – 72%)	0.013	NA[c]	NA[c]	NA[c]
TG(18:1_30:1)	38%	(4% – 73%)	0.012	-4%	(-51% – 42%)	0.52
TG(18:1_30:2)	43%	(8% – 78%)	0.004	NA[c]	NA[c]	NA[c]
TG(18:1_31:0)	36%	(6% – 67%)	0.008	86%	(39% – 134%)	0.007
TG(18:1_32:0)	47%	(12% – 81%)	0.004	NA[c]	NA[c]	NA[c]
TG(18:1_32:1)	45%	(14% – 80%)	0.004	NA[c]	NA[c]	NA[c]
TG(18:1_32:2)	48%	(16% – 80%)	0.003	NA[c]	NA[c]	NA[c]
TG(18:1_32:3)	53%	(22% – 83%)	0.001	NA[c]	NA[c]	NA[c]
TG(18:1_33:0)	43%	(11% – 76%)	0.005	NA[c]	NA[c]	NA[c]
TG(18:1_33:1)	37%	(8% – 68%)	0.009	NA[c]	NA[c]	NA[c]
TG(18:1_33:2)	43%	(13% – 75%)	0.004	28%	(-12% – 64%)	0.21
TG(18:1_33:3)	42%	(9% – 71%)	0.007	NA[c]	NA[c]	NA[c]
TG(18:1_34:1)	44%	(18% – 77%)	0.003	NA[c]	NA[c]	NA[c]
TG(18:1_34:2)	49%	(20% – 82%)	0.001	NA[c]	NA[c]	NA[c]
TG(18:1_34:3)	49%	(15% – 80%)	0.004	10%	(-37% – 56%)	0.45
TG(18:1_34:4)	49%	(17% – 81%)	0.003	5%	(-32% – 42%)	0.49
TG(18:1_35:2)	45%	(15% – 75%)	0.004	36%	(-5% – 79%)	0.12
TG(18:1_35:3)	46%	(14% – 76%)	0.003	26%	(-16% – 67%)	0.20
TG(18:1_36:0)	44%	(8% – 79%)	0.005	NA[c]	NA[c]	NA[c]
TG(18:1_36:1)	43%	(10% – 78%)	0.005	22%	(-11% – 56%)	0.19
TG(18:1_36:2)	47%	(11% – 81%)	0.004	NA[c]	NA[c]	NA[c]
TG(18:1_36:3)	52%	(21% – 86%)	0.001	-14%	(-57% – 33%)	0.41
TG(18:1_36:4)	53%	(21% – 89%)	0.001	33%	(-7% – 75%)	0.14
TG(18:1_36:5)	54%	(18% – 87%)	0.004	26%	(-18% – 67%)	0.24
TG(18:1_36:6)	50%	(18% – 82%)	0.003	NA[c]	NA[c]	NA[c]
TG(18:1_38:5)	53%	(18% – 87%)	0.004	31%	(-11% – 73%)	0.15

Metabolite	Plasma			Frontal cortex		
	Effect[a]	CI_{95}	FDR[b]	Effect[a]	CI_{95}	FDR[b]
TG(18:1_38:6)	41%	(4% – 78%)	0.014	24%	(-20% – 64%)	0.24
TG(18:1_38:7)	45%	(6% – 82%)	0.007	8%	(-38% – 56%)	0.46
TG(18:2_28:0)	36%	(2% – 69%)	0.014	NA[c]	NA[c]	NA[c]
TG(18:2_30:0)	42%	(6% – 73%)	0.009	-6%	(-52% – 41%)	0.49
TG(18:2_30:1)	48%	(17% – 83%)	0.004	23%	(-26% – 72%)	0.28
TG(18:2_31:0)	44%	(12% – 78%)	0.004	28%	(-25% – 82%)	0.26
TG(18:2_32:0)	54%	(26% – 85%)	0.001	2%	(-39% – 43%)	0.54
TG(18:2_32:1)	54%	(25% – 86%)	0.004	19%	(-27% – 63%)	0.31
TG(18:2_32:2)	52%	(20% – 83%)	0.003	-27%	(-67% – 12%)	0.16
TG(18:2_33:0)	45%	(11% – 76%)	0.004	13%	(-50% – 71%)	0.45
TG(18:2_33:1)	41%	(8% – 70%)	0.005	22%	(-27% – 76%)	0.31
TG(18:2_33:2)	39%	(10% – 70%)	0.007	50%	(8% – 94%)	0.046
TG(18:2_34:0)	51%	(23% – 83%)	0.001	NA[c]	NA[c]	NA[c]
TG(18:2_34:1)	46%	(17% – 76%)	0.001	7%	(-31% – 46%)	0.46
TG(18:2_34:2)	46%	(15% – 79%)	0.004	0%	(-34% – 34%)	0.54
TG(18:2_34:3)	51%	(18% – 83%)	0.003	0%	(-41% – 43%)	0.54
TG(18:2_34:4)	52%	(20% – 87%)	0.003	14%	(-33% – 58%)	0.42
TG(18:2_35:1)	45%	(17% – 81%)	0.001	NA[c]	NA[c]	NA[c]
TG(18:2_35:2)	41%	(13% – 72%)	0.004	18%	(-18% – 52%)	0.29
TG(18:2_35:3)	46%	(13% – 79%)	0.003	31%	(-10% – 69%)	0.15
TG(18:2_36:0)	57%	(26% – 89%)	0.001	14%	(-32% – 64%)	0.42
TG(18:2_36:1)	54%	(25% – 88%)	0.003	17%	(-30% – 69%)	0.36
TG(18:2_36:2)	52%	(18% – 87%)	0.004	NA[c]	NA[c]	NA[c]
TG(18:2_36:3)	48%	(18% – 82%)	0.001	27%	(-15% – 66%)	0.18
TG(18:2_36:4)	47%	(17% – 80%)	0.003	38%	(-4% – 78%)	0.11
TG(18:2_36:5)	49%	(18% – 83%)	0.003	8%	(-38% – 49%)	0.44
TG(18:2_38:4)	57%	(28% – 88%)	0.001	-5%	(-48% – 40%)	0.49
TG(18:2_38:5)	66%	(31% – 101%)	0.001	81%	(31% – 129%)	0.007
TG(18:2_38:6)	42%	(5% – 76%)	0.013	9%	(-35% – 55%)	0.44
TG(18:3_30:0)	43%	(10% – 74%)	0.004	NA[c]	NA[c]	NA[c]
TG(18:3_32:0)	55%	(24% – 88%)	0.001	NA[c]	NA[c]	NA[c]
TG(18:3_32:1)	58%	(27% – 90%)	0.003	NA[c]	NA[c]	NA[c]
TG(18:3_33:2)	42%	(9% – 73%)	0.010	NA[c]	NA[c]	NA[c]
TG(18:3_34:0)	60%	(26% – 92%)	0.001	NA[c]	NA[c]	NA[c]
TG(18:3_34:1)	61%	(27% – 93%)	0.001	23%	(-20% – 66%)	0.25
TG(18:3_34:2)	59%	(27% – 95%)	0.001	15%	(-27% – 59%)	0.36
TG(18:3_34:3)	52%	(19% – 85%)	0.003	13%	(-28% – 55%)	0.39
TG(18:3_35:2)	41%	(8% – 74%)	0.008	31%	(-9% – 65%)	0.16
TG(18:3_36:1)	60%	(30% – 92%)	0.001	7%	(-36% – 49%)	0.48
TG(18:3_36:2)	53%	(21% – 89%)	0.001	2%	(-36% – 41%)	0.54
TG(18:3_36:3)	48%	(15% – 84%)	0.004	-18%	(-62% – 25%)	0.32
TG(18:3_36:4)	47%	(13% – 81%)	0.004	45%	(-11% – 101%)	0.13
TG(18:3_38:5)	60%	(21% – 93%)	0.001	35%	(-13% – 76%)	0.15
TG(18:3_38:6)	52%	(19% – 89%)	0.001	14%	(-39% – 62%)	0.42
TG(20:0_32:3)	54%	(25% – 83%)	0.004	NA[c]	NA[c]	NA[c]
TG(20:0_32:4)	50%	(23% – 82%)	0.001	NA[c]	NA[c]	NA[c]
TG(20:0_34:1)	44%	(10% – 76%)	0.007	NA[c]	NA[c]	NA[c]

Metabolite	Plasma			Frontal cortex		
	Effect[a]	CI_{95}	FDR[b]	Effect[a]	CI_{95}	FDR[b]
TG(20:1_30:1)	42%	(9% – 73%)	0.004	8%	(-38% – 58%)	0.44
TG(20:1_31:0)	NA[c]	NA[c]	NA[c]	69%	(12% – 115%)	0.031
TG(20:1_32:1)	43%	(9% – 79%)	0.008	3%	(-42% – 47%)	0.52
TG(20:1_32:2)	50%	(16% – 78%)	0.001	10%	(-41% – 61%)	0.46
TG(20:1_32:3)	47%	(14% – 79%)	0.004	15%	(-31% – 59%)	0.38
TG(20:1_34:0)	53%	(17% – 84%)	0.001	NA[c]	NA[c]	NA[c]
TG(20:1_34:1)	39%	(9% – 73%)	0.007	12%	(-25% – 49%)	0.36
TG(20:1_34:2)	47%	(15% – 76%)	0.004	NA[c]	NA[c]	NA[c]
TG(20:1_34:3)	49%	(19% – 80%)	0.003	NA[c]	NA[c]	NA[c]
TG(20:2_32:0)	55%	(20% – 91%)	0.004	63%	(21% – 107%)	0.015
TG(20:2_32:1)	58%	(32% – 94%)	0.001	1%	(-46% – 49%)	0.54
TG(20:2_34:1)	52%	(22% – 83%)	0.003	0%	(-52% – 48%)	0.54
TG(20:2_34:2)	56%	(32% – 89%)	0.001	-49%	(-95% – -4%)	0.07
TG(20:2_34:3)	60%	(34% – 94%)	0.001	NA[c]	NA[c]	NA[c]
TG(20:2_34:4)	45%	(9% – 79%)	0.009	NA[c]	NA[c]	NA[c]
TG(20:2_36:5)	82%	(47% – 118%)	0.001	-1%	(-42% – 41%)	0.54
TG(20:3_32:0)	53%	(21% – 86%)	0.001	NA[c]	NA[c]	NA[c]
TG(20:3_32:1)	54%	(20% – 88%)	0.003	41%	(-14% – 93%)	0.16
TG(20:3_32:2)	55%	(19% – 89%)	0.004	NA[c]	NA[c]	NA[c]
TG(20:3_34:0)	47%	(13% – 82%)	0.006	NA[c]	NA[c]	NA[c]
TG(20:3_34:1)	52%	(17% – 83%)	0.003	31%	(-13% – 78%)	0.17
TG(20:3_34:2)	60%	(27% – 92%)	0.001	NA[c]	NA[c]	NA[c]
TG(20:3_34:3)	52%	(21% – 86%)	0.004	47%	(0% – 91%)	0.08
TG(20:3_36:3)	51%	(20% – 83%)	0.003	-5%	(-46% – 35%)	0.49
TG(20:3_36:4)	59%	(25% – 93%)	0.001	34%	(-12% – 78%)	0.16
TG(20:3_36:5)	64%	(30% – 98%)	0.001	40%	(-15% – 89%)	0.18
TG(20:4_30:0)	37%	(3% – 73%)	0.017	NA[c]	NA[c]	NA[c]
TG(20:4_32:0)	56%	(18% – 95%)	0.004	NA[c]	NA[c]	NA[c]
TG(20:4_32:1)	54%	(17% – 90%)	0.004	NA[c]	NA[c]	NA[c]
TG(20:4_32:2)	54%	(18% – 89%)	0.003	NA[c]	NA[c]	NA[c]
TG(20:4_33:2)	58%	(23% – 94%)	0.001	NA[c]	NA[c]	NA[c]
TG(20:4_34:0)	60%	(21% – 100%)	0.001	27%	(-13% – 68%)	0.20
TG(20:4_34:1)	59%	(22% – 95%)	0.001	55%	(8% – 99%)	0.048
TG(20:4_34:2)	69%	(44% – 104%)	0.001	-16%	(-63% – 27%)	0.36
TG(20:4_34:3)	69%	(34% – 104%)	0.001	NA[c]	NA[c]	NA[c]
TG(20:4_35:3)	67%	(36% – 105%)	0.001	NA[c]	NA[c]	NA[c]
TG(20:4_36:2)	61%	(31% – 93%)	0.001	22%	(-15% – 62%)	0.23
TG(20:4_36:3)	64%	(34% – 94%)	0.001	18%	(-23% – 61%)	0.34
TG(20:4_36:4)	68%	(35% – 103%)	0.001	21%	(-31% – 72%)	0.31
TG(20:4_36:5)	55%	(17% – 91%)	0.004	-28%	(-76% – 20%)	0.21
TG(22:0_32:4)	54%	(21% – 85%)	0.001	NA[c]	NA[c]	NA[c]
TG(22:1_32:5)	36%	(3% – 72%)	0.017	0%	(-40% – 42%)	0.54
TG(22:2_32:4)	48%	(13% – 79%)	0.005	NA[c]	NA[c]	NA[c]
TG(22:4_32:0)	59%	(23% – 93%)	0.003	50%	(-2% – 102%)	0.09
TG(22:4_32:2)	61%	(26% – 99%)	0.003	NA[c]	NA[c]	NA[c]
TG(22:4_34:2)	73%	(45% – 107%)	0.001	NA[c]	NA[c]	NA[c]
TG(22:5_32:0)	53%	(15% – 89%)	0.004	30%	(-12% – 72%)	0.18

Metabolite	Plasma			Frontal cortex		
	Effect[a]	**CI_{95}**	**FDR**[b]	**Effect**[a]	**CI_{95}**	**FDR**[b]
TG(22:5_32:1)	60%	(23% – 97%)	0.003	26%	(-15% – 66%)	0.22
TG(22:5_34:1)	58%	(18% – 97%)	0.001	NA[c]	NA[c]	NA[c]
TG(22:5_34:2)	67%	(30% – 105%)	0.001	NA[c]	NA[c]	NA[c]
TG(22:5_34:3)	64%	(29% – 99%)	0.001	25%	(-10% – 59%)	0.17

aa, diacyl; ae, acyl-alkyl; CE, cholesteryl ester; Cer, ceramide; CI_{95}, 95% confidence interval; C*n*, acylcarnitine C*n*:0; DG, diglyceride; FDR, false discovery rate; NA, not available; PC, phosphatidylcholine; SM, sphingomyelin; TG, triglyceride.

[a] AD regression coefficient in units of 1 standard deviation of the distribution of controls.

[b] FDR control with q-values following bootstrapped p-values of multivariable de-sparsified L1-regularized linear regression models. FDR ≤ 0.05 is rounded to 3 decimal places and highlighted in red (upregulated) and blue (downregulated).

[c] Value not available when the metabolite was not sufficiently detected (in at least 50% of samples in either group above the limit of detection).

Supplementary Table 2. Regression Coefficients of Metabolites Altered in Plasma in Males Compared to Females

Metabolite	Plasma		
	Effect[a]	**CI_{95}**	**FDR[b]**
Microbiome-related metabolites			
3-Indoleacetic acid	36%	(2% – 69%)	0.039
Glycocholic acid	47%	(11% – 87%)	0.026
Methylhistidine metabolism			
β-Alanine	50%	(21% – 81%)	0.009
Carnosine	62%	(23% – 97%)	0.004
Homocysteine metabolism			
Betaine	46%	(7% – 86%)	0.029
Choline	36%	(3% – 70%)	0.046
Polyamines			
Spermidine	61%	(27% – 99%)	0.004
Steroids			
DHEAS	50%	(17% – 76%)	0.012
Omega-3 fatty acids			
EPA	-37%	(-70% – -2%)	0.046
Amino acids			
Aspartate	59%	(30% – 94%)	0.009
Glutamate	44%	(14% – 74%)	0.012
Glycine	-59%	(-93% – -30%)	0.004
Isoleucine	73%	(39% – 107%)	0.004
Leucine	74%	(38% – 107%)	0.004
Tryptophan	37%	(3% – 73%)	0.040
Valine	77%	(45% – 112%)	0.004
Others amino acid related			
α-Aminoadipic acid	86%	(53% – 122%)	0.004
α-Aminobutyric acid	59%	(21% – 101%)	0.009
Creatinine	97%	(65% – 134%)	0.004
Homoarginine	54%	(19% – 80%)	0.004
Tryptophan betaine	55%	(14% – 95%)	0.022
Neurotransmitters			
Serotonin	44%	(5% – 73%)	0.029
Fatty acids			
FA(18:1)	-29%	(-61% – 0%)	0.050
Acylcarnitines			
C3	44%	(11% – 77%)	0.015
Sphingomyelins			
SM C16:0	-50%	(-80% – -17%)	0.004
SM C16:1	-78%	(-106% – -52%)	0.004
SM C18:0	-55%	(-89% – -22%)	0.009
SM C18:1	-70%	(-104% – -41%)	0.004
SM C20:2	-108%	(-148% – -72%)	0.004
SM C24:1	-40%	(-69% – -9%)	0.022
SM (OH) C14:1	-61%	(-92% – -30%)	0.004
SM (OH) C16:1	-47%	(-81% – -17%)	0.009
SM (OH) C22:1	-62%	(-92% – -38%)	0.004

Metabolite	Plasma		
	Effect[a]	**CI$_{95}$**	**FDR**[b]
SM (OH) C22:2	-93%	(-121% – -67%)	0.004
Ceramides			
Cer(d16:1/18:0)	-45%	(-79% – -11%)	0.020
Cer(d16:1/23:0)	-43%	(-74% – -12%)	0.015
Cer(d18:1/18:1)	-49%	(-85% – -11%)	0.026
Cer(d18:1/20:0(OH))	-39%	(-71% – -4%)	0.043
Cer(d18:1/23:0)	-38%	(-75% – -2%)	0.047
Cer(d18:1/25:0)	-53%	(-91% – -16%)	0.012
Cer(d18:2/16:0)	-65%	(-105% – -26%)	0.004
Cer(d18:2/23:0)	-55%	(-88% – -18%)	0.012
Cer(d18:2/24:1)	-38%	(-70% – -4%)	0.037
Glycosylceramides			
HexosylCer(d16:1/22:0)	-53%	(-87% – -19%)	0.004
HexosylCer(d16:1/24:0)	-52%	(-84% – -21%)	0.004
HexosylCer(d18:1/16:0)	-36%	(-69% – -4%)	0.034
HexosylCer(d18:1/18:0)	-45%	(-78% – -7%)	0.037
HexosylCer(d18:1/18:1)	-54%	(-82% – -22%)	0.009
HexosylCer(d18:1/20:0)	-45%	(-77% – -7%)	0.033
HexosylCer(d18:1/23:0)	-47%	(-76% – -14%)	0.017
HexosylCer(d18:1/26:0)	-45%	(-78% – -10%)	0.015
HexosylCer(d18:2/22:0)	-46%	(-81% – -11%)	0.024
HexosylCer(d18:2/23:0)	-65%	(-100% – -32%)	0.004
HexosylCer(d18:2/24:0)	-41%	(-72% – -7%)	0.017
DihexosylCer(d18:1/14:0)	-35%	(-66% – -2%)	0.046
DihexosylCer(d18:1/18:0)	-37%	(-70% – -4%)	0.042
DihexosylCer(d18:1/20:0)	-43%	(-81% – -6%)	0.040
TrihexosylCer(d18:1/16:0)	-64%	(-92% – -34%)	0.004
TrihexosylCer(d18:1/18:0)	-66%	(-99% – -35%)	0.004
TrihexosylCer(d18:1/24:1)	-58%	(-89% – -26%)	0.004
TrihexosylCer(d18:1_20:0)	-36%	(-71% – -3%)	0.044
TrihexosylCer(d18:1_22:0)	-37%	(-71% – -5%)	0.033
Phosphatidylcholines			
PC aa C28:1	-76%	(-106% – -48%)	0.004
PC aa C30:0	-62%	(-95% – -30%)	0.004
PC aa C32:0	-40%	(-76% – -7%)	0.024
PC aa C32:1	-62%	(-95% – -27%)	0.004
PC aa C32:2	-76%	(-108% – -41%)	0.004
PC aa C32:3	-105%	(-134% – -74%)	0.004
PC aa C34:1	-34%	(-65% – 0%)	0.050
PC aa C34:2	-42%	(-74% – -6%)	0.034
PC aa C34:3	-94%	(-126% – -61%)	0.004
PC aa C34:4	-86%	(-119% – -56%)	0.004
PC aa C36:0	-37%	(-68% – -6%)	0.022
PC aa C36:1	-44%	(-74% – -15%)	0.017
PC aa C36:2	-60%	(-93% – -31%)	0.004
PC aa C36:3	-50%	(-83% – -15%)	0.015
PC aa C36:4	-39%	(-73% – -3%)	0.037

	Plasma		
Metabolite	**Effect**[a]	**CI$_{95}$**	**FDR**[b]
PC aa C36:5	-52%	(-83% – -20%)	0.004
PC aa C36:6	-67%	(-96% – -36%)	0.004
PC aa C38:0	-47%	(-79% – -16%)	0.015
PC aa C38:3	-59%	(-91% – -27%)	0.012
PC aa C38:4	-49%	(-91% – -16%)	0.009
PC aa C38:5	-84%	(-120% – -52%)	0.004
PC aa C38:6	-35%	(-67% – -1%)	0.046
PC aa C40:1	-36%	(-64% – -6%)	0.031
PC aa C40:3	-47%	(-75% – -19%)	0.009
PC aa C40:4	-36%	(-73% – 0%)	0.050
PC aa C40:5	-68%	(-105% – -35%)	0.004
PC aa C40:6	-46%	(-77% – -16%)	0.020
PC aa C42:0	-46%	(-76% – -16%)	0.004
PC aa C42:1	-35%	(-63% – -5%)	0.037
PC aa C42:5	-61%	(-91% – -31%)	0.004
PC aa C42:6	-72%	(-104% – -38%)	0.004
PC ae C30:0	-45%	(-77% – -15%)	0.004
PC ae C30:1	-57%	(-88% – -22%)	0.004
PC ae C30:2	-76%	(-106% – -46%)	0.004
PC ae C32:1	-43%	(-71% – -10%)	0.015
PC ae C32:2	-72%	(-101% – -43%)	0.004
PC ae C34:0	-29%	(-59% – 0%)	0.050
PC ae C34:1	-55%	(-85% – -23%)	0.009
PC ae C34:2	-61%	(-90% – -25%)	0.009
PC ae C34:3	-58%	(-88% – -26%)	0.004
PC ae C36:1	-45%	(-74% – -15%)	0.015
PC ae C36:2	-39%	(-73% – -5%)	0.022
PC ae C36:3	-53%	(-84% – -21%)	0.004
PC ae C36:4	-40%	(-72% – -5%)	0.036
PC ae C36:5	-36%	(-67% – -3%)	0.039
PC ae C38:0	-68%	(-98% – -36%)	0.004
PC ae C38:2	-37%	(-69% – -5%)	0.039
PC ae C38:3	-39%	(-71% – -9%)	0.020
PC ae C38:5	-36%	(-72% – -3%)	0.043
PC ae C38:6	-59%	(-91% – -27%)	0.009
PC ae C40:1	-45%	(-77% – -14%)	0.017
PC ae C40:2	-47%	(-77% – -17%)	0.012
PC ae C40:3	-39%	(-67% – -8%)	0.024
PC ae C40:6	-40%	(-73% – -7%)	0.022
PC ae C42:0	-45%	(-77% – -13%)	0.015
PC ae C42:1	-52%	(-83% – -20%)	0.012
PC ae C42:2	-50%	(-78% – -22%)	0.004
PC ae C42:3	-40%	(-66% – -7%)	0.020
Lysophosphatidylcholines			
LysoPC a C14:0	-38%	(-71% – -5%)	0.034
LysoPC a C16:1	-65%	(-103% – -23%)	0.004
LysoPC a C26:1	-36%	(-64% – -6%)	0.034

Metabolite	Plasma		
	Effect[a]	CI_{95}	FDR[b]
LysoPC a C28:1	-74%	(-100% – -49%)	0.004
Cholesteryl esters			
CE(14:0)	-49%	(-81% – -15%)	0.012
CE(14:1)	-52%	(-86% – -18%)	0.015
CE(15:0)	-38%	(-68% – -8%)	0.026
CE(15:1)	-40%	(-72% – -5%)	0.043
CE(16:1)	-71%	(-106% – -39%)	0.004
CE(17:1)	-38%	(-70% – -5%)	0.037
CE(18:2)	-36%	(-73% – -6%)	0.034
CE(18:3)	-67%	(-97% – -40%)	0.004
CE(20:4)	-34%	(-67% – -1%)	0.046
CE(20:5)	-42%	(-73% – -10%)	0.017
CE(22:5)	-54%	(-88% – -23%)	0.009
Diglycerides			
DG(16:0_18:2)	42%	(9% – 74%)	0.009
DG(18:1_18:1)	44%	(14% – 80%)	0.012
DG(18:1_18:2)	53%	(21% – 86%)	0.004
DG(18:2_18:2)	49%	(16% – 82%)	0.017
Triglycerides			
TG(16:0_36:2)	41%	(5% – 75%)	0.036
TG(16:0_36:3)	43%	(11% – 68%)	0.017
TG(16:0_36:4)	40%	(5% – 66%)	0.036
TG(16:0_38:2)	38%	(2% – 74%)	0.046
TG(16:0_38:3)	47%	(12% – 73%)	0.017
TG(16:0_38:4)	36%	(4% – 57%)	0.020
TG(16:0_40:6)	39%	(2% – 73%)	0.039
TG(16:0_40:7)	45%	(8% – 82%)	0.026
TG(16:0_40:8)	39%	(3% – 73%)	0.044
TG(17:0_36:3)	45%	(13% – 70%)	0.012
TG(17:0_36:4)	42%	(10% – 75%)	0.017
TG(17:1_36:3)	37%	(2% – 65%)	0.046
TG(17:2_36:4)	38%	(2% – 75%)	0.042
TG(17:2_38:5)	47%	(13% – 82%)	0.017
TG(17:2_38:6)	46%	(10% – 80%)	0.024
TG(18:0_36:2)	37%	(5% – 69%)	0.034
TG(18:0_36:3)	44%	(9% – 76%)	0.022
TG(18:0_36:4)	44%	(13% – 78%)	0.004
TG(18:0_38:6)	42%	(7% – 76%)	0.031
TG(18:1_33:2)	37%	(6% – 68%)	0.034
TG(18:1_34:2)	39%	(7% – 66%)	0.031
TG(18:1_35:2)	38%	(5% – 70%)	0.020
TG(18:1_35:3)	32%	(1% – 63%)	0.049
TG(18:1_36:1)	41%	(6% – 79%)	0.031
TG(18:1_36:2)	51%	(15% – 87%)	0.012
TG(18:1_36:3)	54%	(21% – 85%)	0.004
TG(18:1_36:4)	46%	(14% – 79%)	0.009
TG(18:1_38:5)	35%	(2% – 70%)	0.044

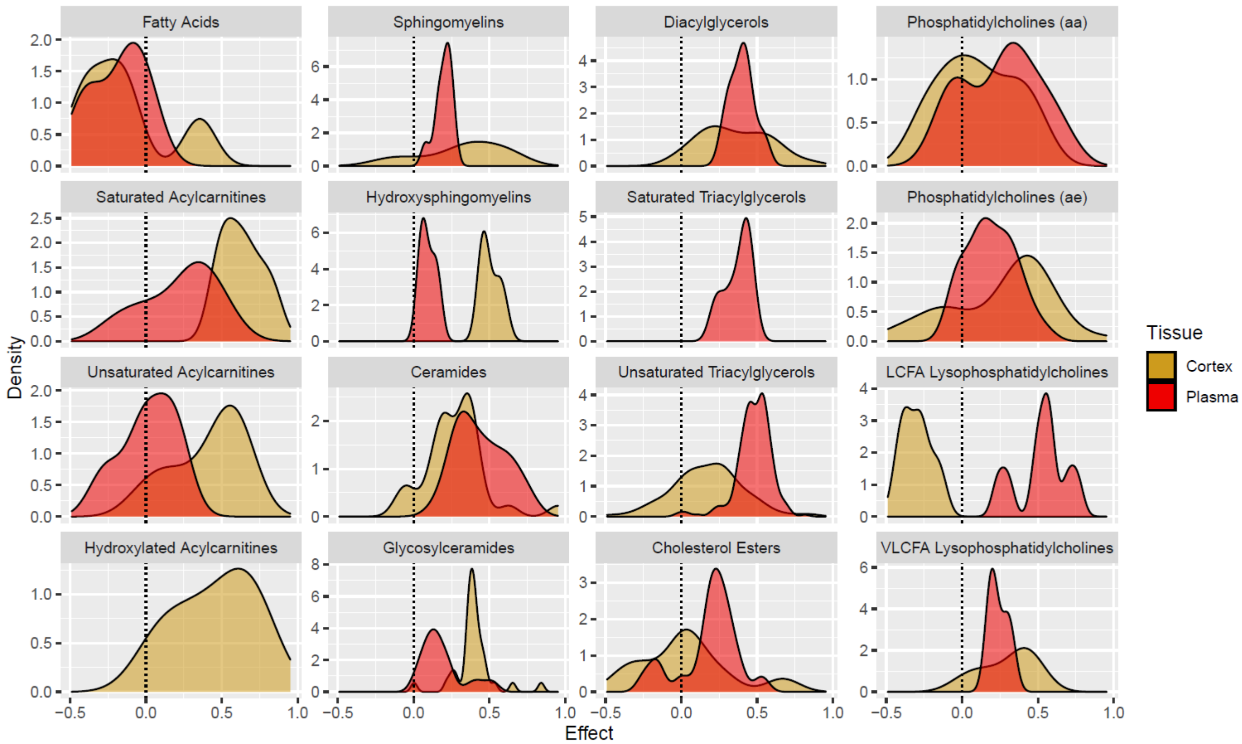
Metabolite	Plasma		
	Effect[a]	CI_{95}	FDR[b]
TG(18:2_33:0)	33%	(0% – 66%)	0.050
TG(18:2_33:1)	34%	(1% – 64%)	0.046
TG(18:2_33:2)	38%	(8% – 68%)	0.017
TG(18:2_34:0)	36%	(3% – 61%)	0.040
TG(18:2_34:1)	42%	(8% – 68%)	0.009
TG(18:2_34:2)	42%	(8% – 68%)	0.024
TG(18:2_35:1)	42%	(12% – 68%)	0.012
TG(18:2_35:2)	41%	(9% – 67%)	0.026
TG(18:2_35:3)	34%	(2% – 64%)	0.040
TG(18:2_36:0)	35%	(1% – 68%)	0.046
TG(18:2_36:1)	46%	(12% – 78%)	0.020
TG(18:2_36:2)	53%	(18% – 89%)	0.004
TG(18:2_36:3)	46%	(9% – 76%)	0.012
TG(18:2_36:4)	36%	(3% – 67%)	0.039
TG(18:2_38:4)	35%	(0% – 60%)	0.047
TG(20:0_32:3)	49%	(15% – 76%)	0.012
TG(20:0_32:4)	41%	(8% – 67%)	0.034
TG(20:1_34:0)	39%	(3% – 74%)	0.044
TG(20:1_34:1)	40%	(2% – 76%)	0.047
TG(20:1_34:2)	36%	(1% – 64%)	0.047
TG(20:2_34:1)	45%	(13% – 73%)	0.015
TG(20:2_34:2)	36%	(4% – 59%)	0.037
TG(20:3_34:0)	36%	(3% – 68%)	0.043
TG(22:0_32:4)	39%	(8% – 73%)	0.022
TG(22:5_34:1)	42%	(9% – 79%)	0.022
TG(22:5_34:2)	40%	(4% – 76%)	0.039
TG(22:6_34:1)	40%	(3% – 77%)	0.046
TG(22:6_34:2)	41%	(5% – 78%)	0.040

aa, diacyl; ae, acyl-alkyl; CE, cholesteryl ester; Cer, ceramide; CI95, 95% confidence interval; C*n*, acylcarnitine C*n*:0; DG, diglyceride; DHEAS, dehydroepiandrosterone sulfate; EPA, eicosapentaenoic acid; FA, fatty acid; FDR, false discovery rate; PC, phosphatidylcholine; SM, sphingomyelin; TG, triglyceride.

[a] Male sex regression coefficient in units of 1 standard deviation of the distribution of controls.

[b] FDR control with q-values following bootstrapped p-values of multivariable de-sparsified L1-regularized linear regression models. FDR ≤ 0.05 is rounded to 3 decimal places and highlighted in red (upregulated) and blue (downregulated).

Supplementary Figure 1. Distributions of AD Regression Coefficients for Lipids by Class



Distribution of regression coefficients of lipid species in cortex and plasma with the reference dotted line crossing zero representing no effect in AD, i.e., matching controls. All lipid classes covered by the assay are included. The groups were formed so as to best highlight the differences between distributions. This visualization facilitates the interpretation of how each lipid class is altered, e.g., whether the group as a whole or its subset. aa, diacyl; ae, acyl-alkyl; LCFA, long-chain fatty acid; VLCFA, very long-chain fatty acid.

Supplementary Figure 2. Example Boxplots of Altered Metabolites and Metabolic Indicators

Boxplots, overlayed with individual values, of several representative metabolites (top part) and metabolic indicators (bottom part), which we found altered in both AD plasma (odd rows) and cortex (even rows). This figure serves as an illustrative example of the magnitue of the alterations. The differences are relatively small with respect to the variation, not constituting precise biomarkers. Note that no other confounding effects (e.g., age) are visualized except for sex subgrouping. 5-AVA, 5-aminovaleric acid; Cer, ceramide; DG, diglyceride; Hex2Cer, dihexosylceramide; t4-OH-Pro, *trans*-4-hydroxyproline; TG, triglyceride.