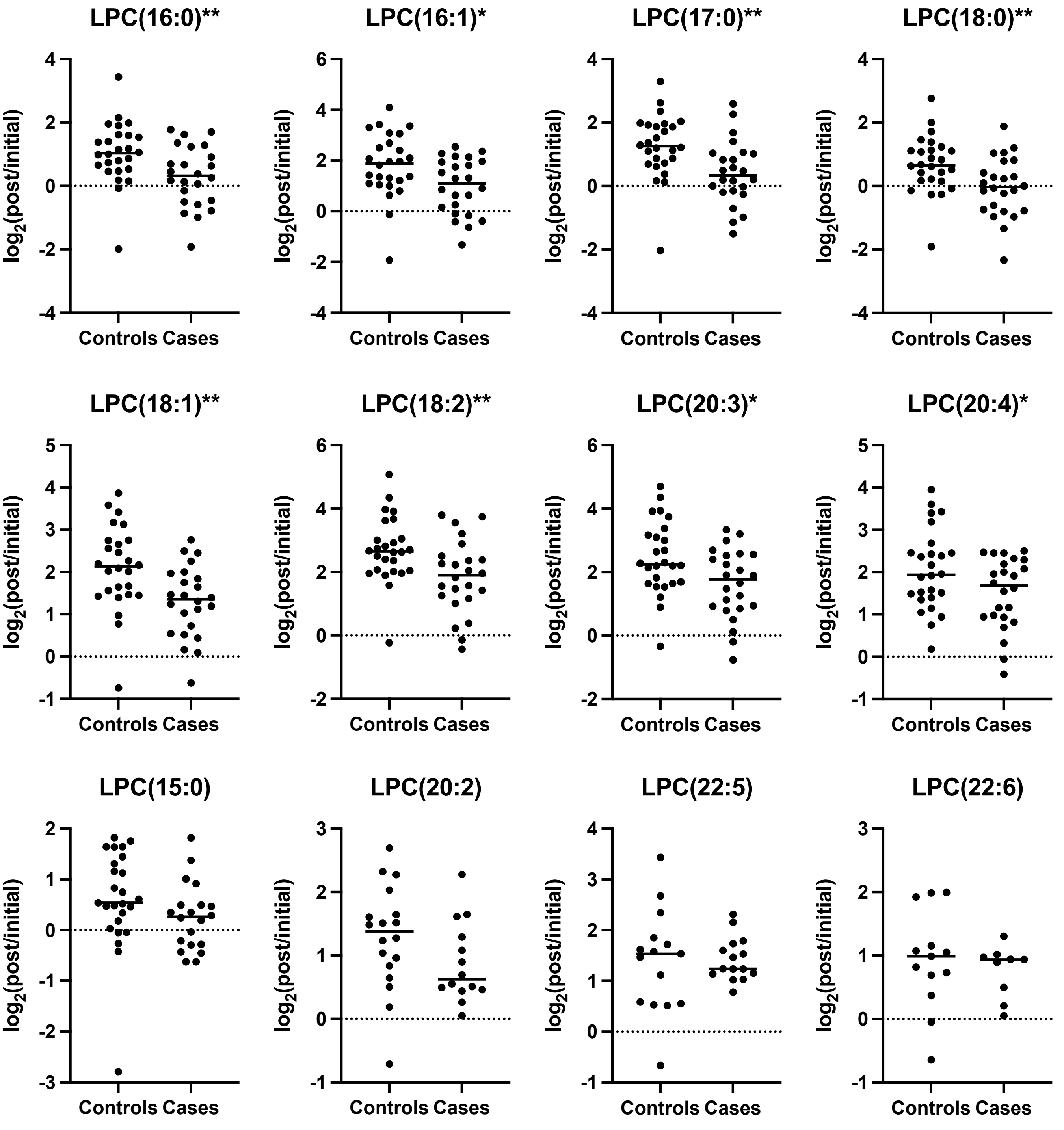
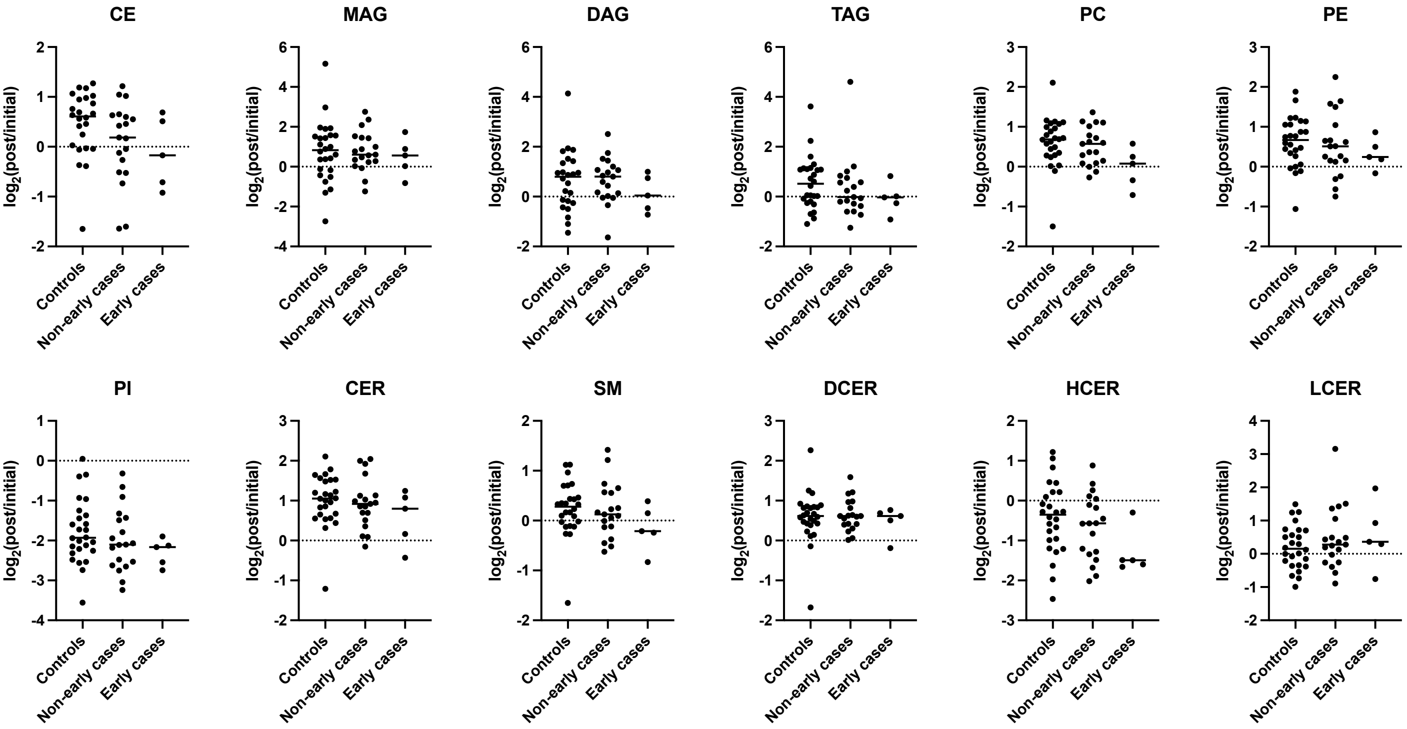


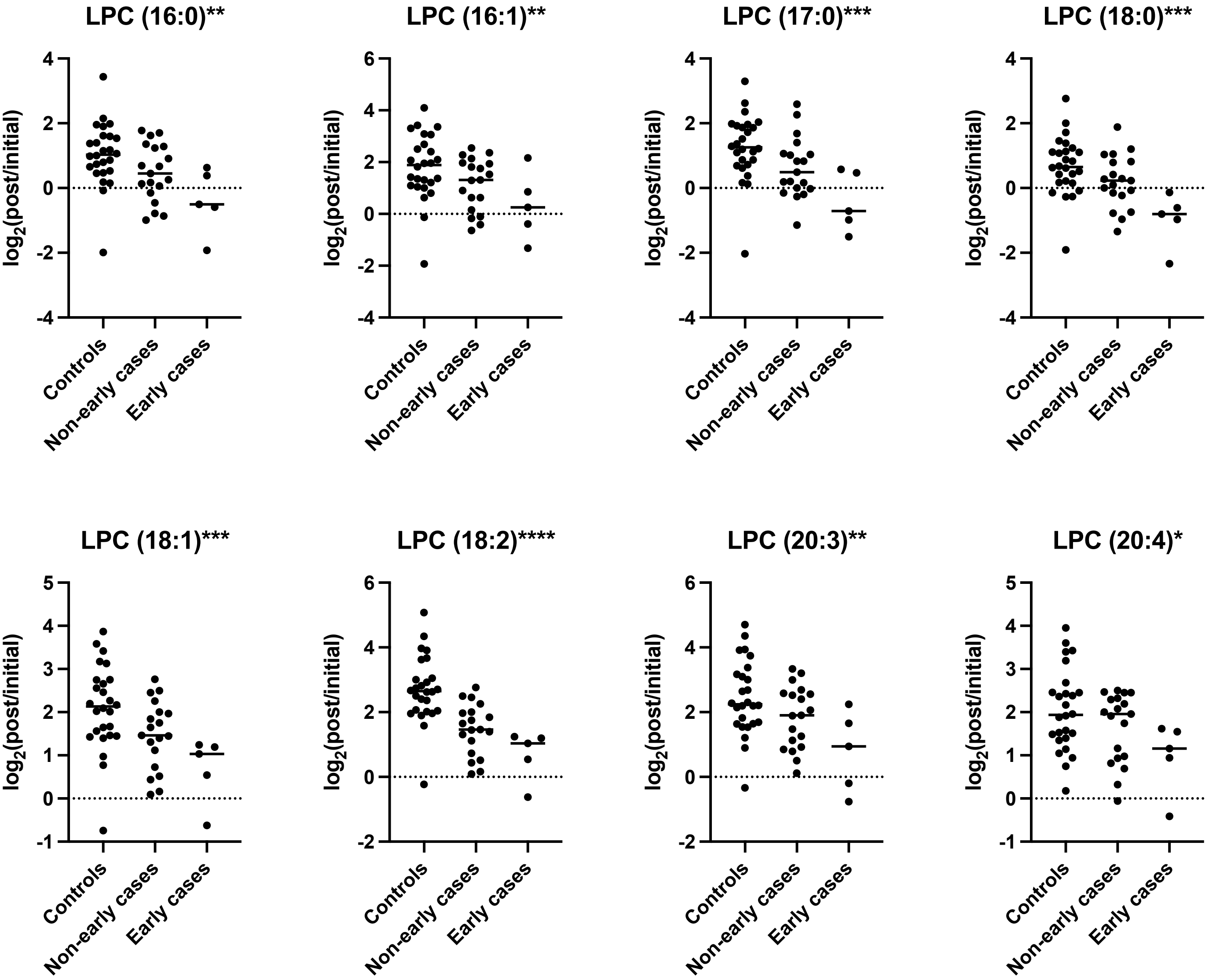
**Supplemental Figure 1. Individual LPC species show attenuated induction-associated increases in AAP cases.**

Eight LPC species exhibit significantly reduced post-induction to initial ratios in cases compared with controls. *P < 0.05, **P < 0.01; unpaired t test with Welch's correction.



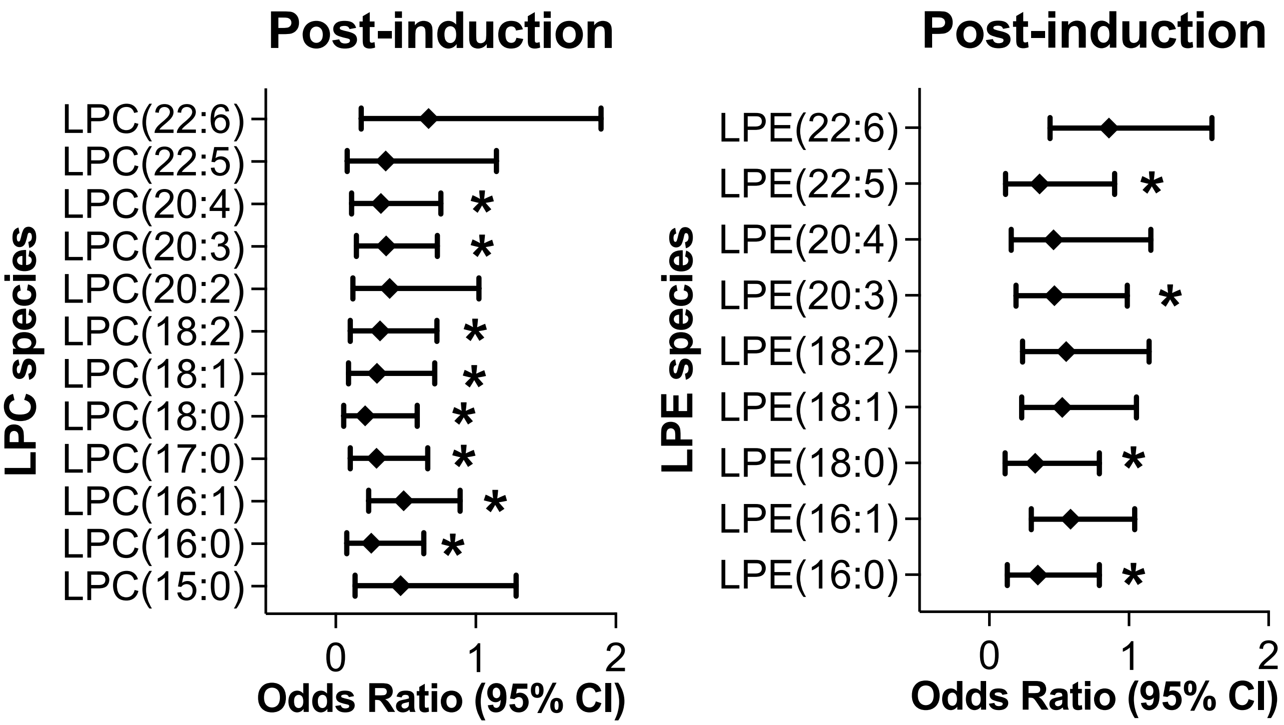
**Supplemental Figure 2. Lipid classes other than LPC and LPE do not show timing-dependent differences.**

Linear trend testing shows no significant differences across controls, non-early cases, and early cases for lipid classes other than LPC and LPE.



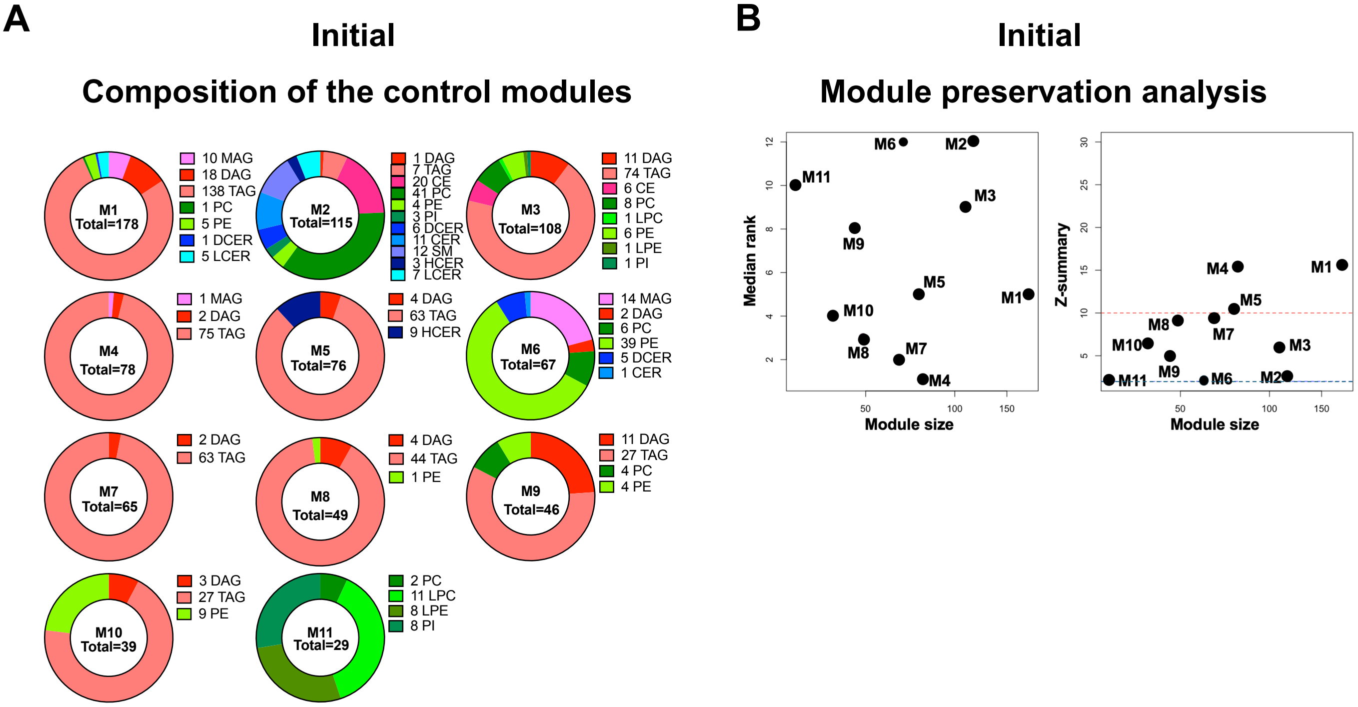
**Supplemental Figure 3. Reduced post/initial LPC ratios in cases across eight LPC species, with the lowest ratios in early cases.**

Post-induction to initial ratios for eight LPC species, stratified by group (controls, non-early cases, early cases).**P < 0.01, ***P < 0.001, ****P < 0.0001, linear trend test.



**Supplemental Figure 4. Selected post-induction LPC and LPE species are associations with reduced AAP risk.**

Forest plots display odds ratios (ORs) and 95% confidence intervals (CIs) for AAP per 1-unit increase in $\log_2$ post-induction lipid concentration for individual LPC (left) and LPE (right) species. *indicates 95% confidence interval (CI) does not cross 1.



A Initial

Composition of the control modules

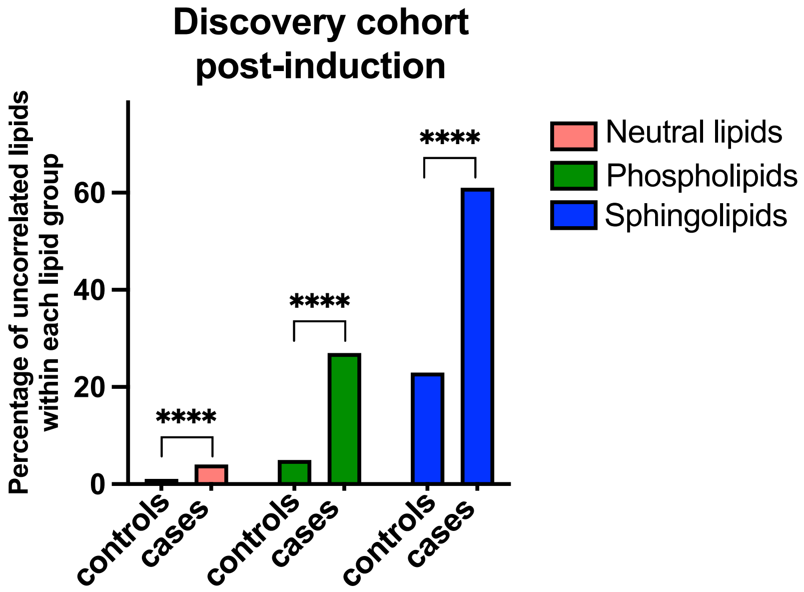
B Initial

Module preservation analysis

**Supplemental Figure 5. WGCNA identifies non-preserved lipid modules at baseline.**

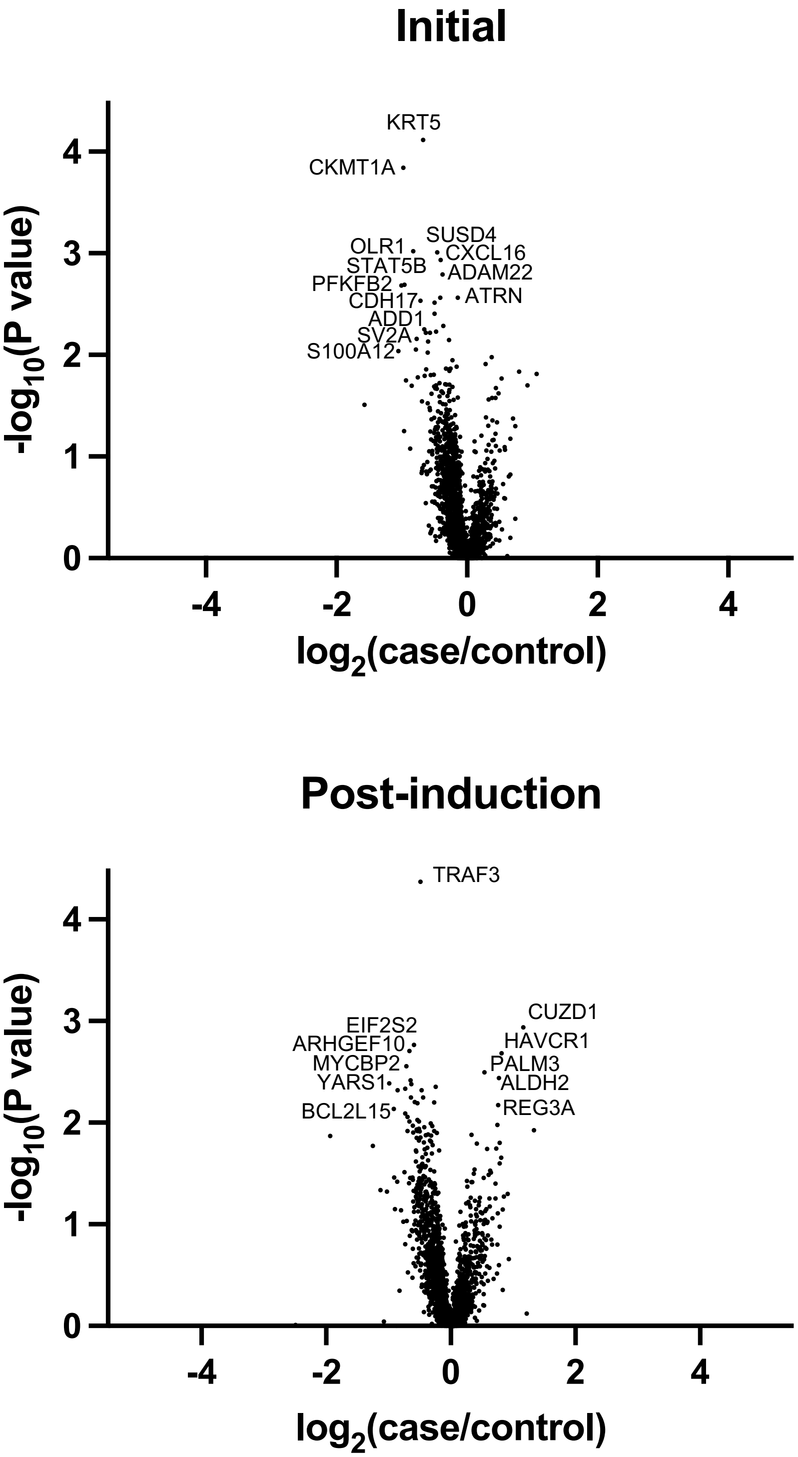
(A) Lipid module composition at the initial timepoint in controls.

(B) Module preservation analysis identifies three non-preserved modules in cases, including one (M11) enriched for LPC species.



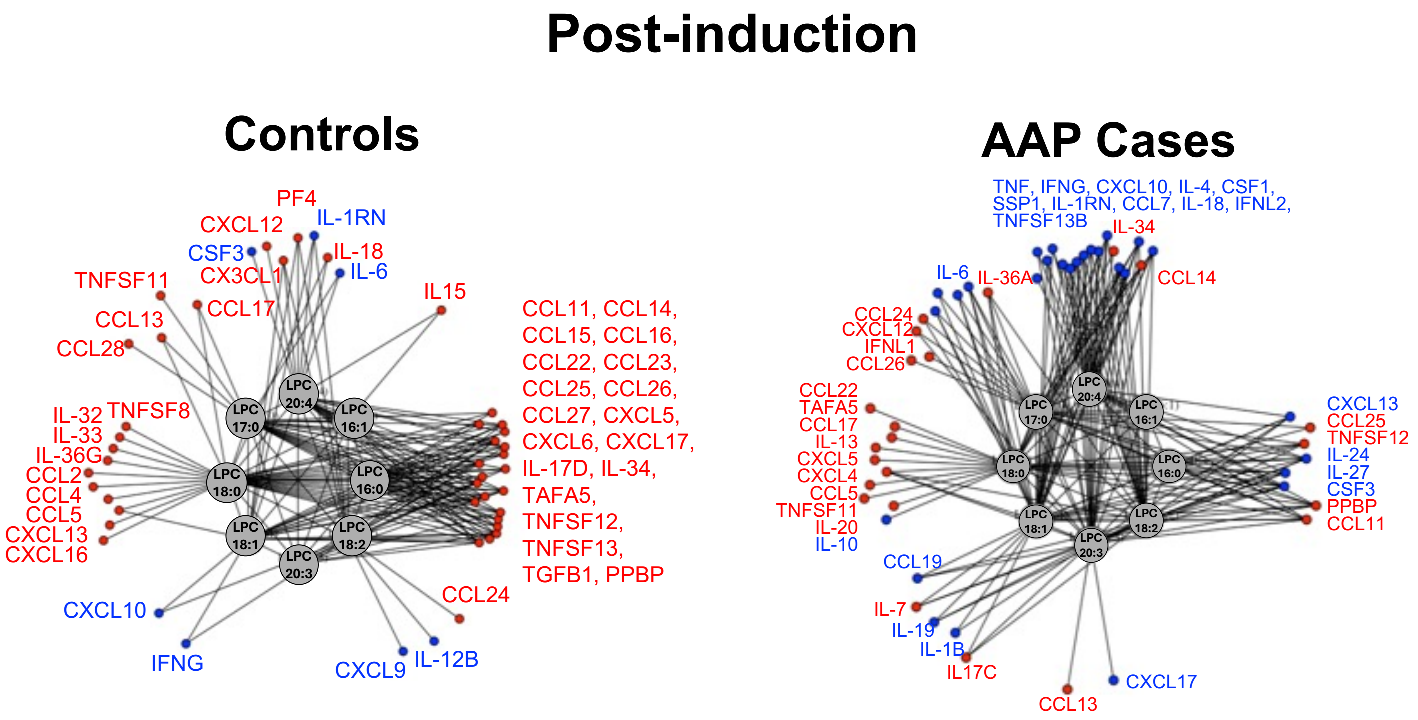
**Supplemental Figure 6. Increased proportion of uncorrelated lipid species in AAP cases post-induction in the discovery cohort.**

Cases exhibit a significantly higher proportion of uncorrelated lipid species compared with controls, consistent with network-level dysregulation. ****P < 0.0001.



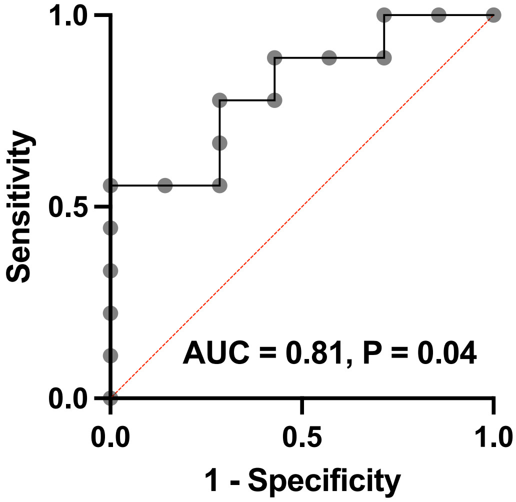
**Supplemental Figure 7. Differential protein expression at baseline and post-induction.**

Volcano plots showing differentially expressed proteins between cases and controls at each timepoint. Only proteins with $P < 0.01$ were annotated where space allowed.



**Supplemental Figure 8. Divergent LPC–cytokine association patterns in cases and controls.**

Network plots illustrate widespread remodeling of LPC–cytokine associations in cases relative to controls post-induction. Each circle represents a cytokine, with red indicating a significant positive association and blue indicating a negative association between the cytokine and the LPC ($Q < 0.05$).



**Supplemental Figure 9. IL-18/LPC(18:0) ratio discriminates AAP risk in very high-risk ALL.**

Receiver operating characteristic analysis demonstrates discriminatory performance of the IL-18/LPC(18:0) ratio within the very high-risk subgroup.

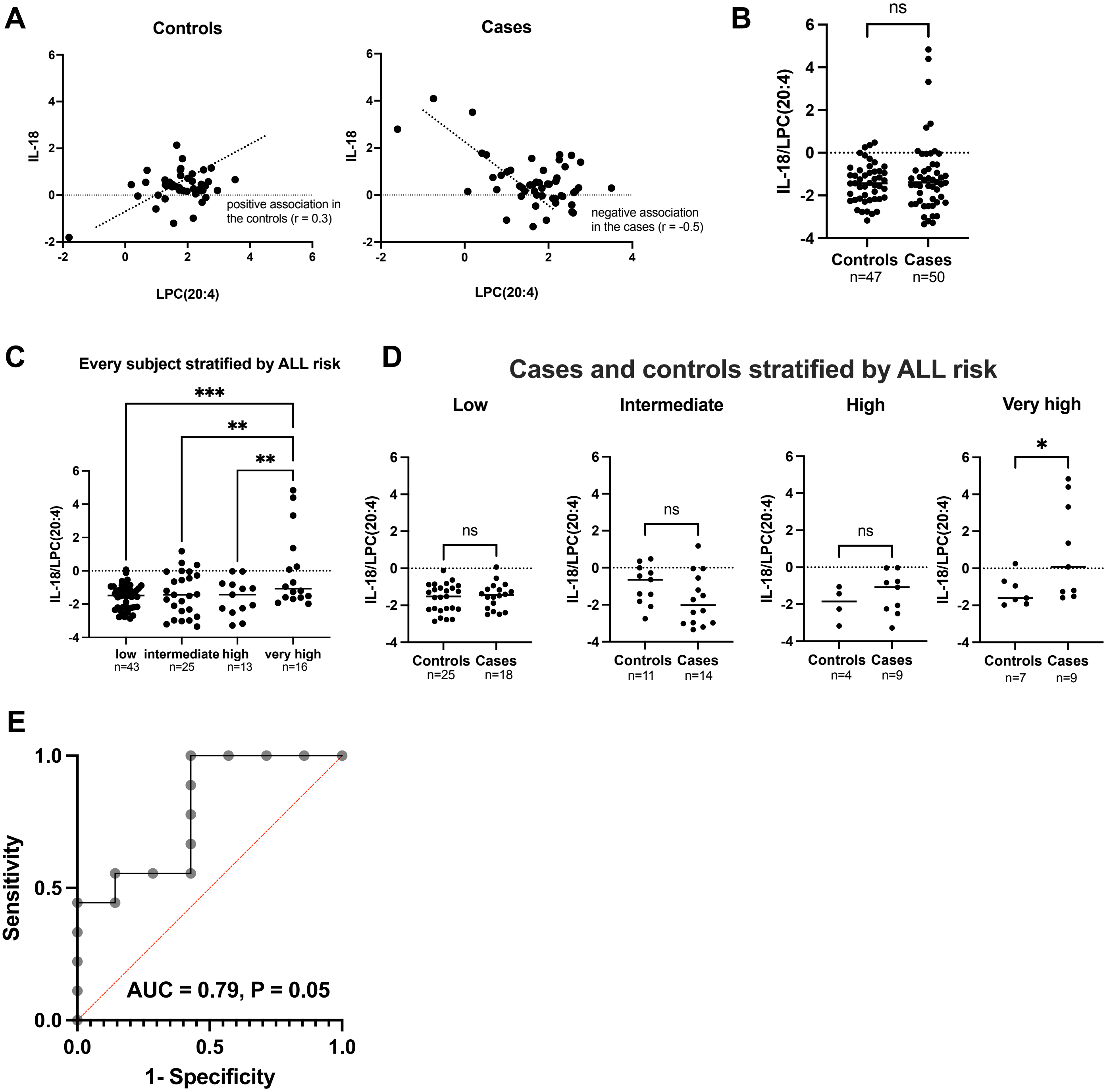


**Fig. S10. Parallel IL-18/LPC(20:4) association patterns mirror LPC(18:0) findings.**

Correlation (A), ratio (B), and stratified analyses (C-E) show similar IL-18–LPC(20:4) dynamics, reinforcing the IL-18/LPC signature.

**Supplemental Table 1. Structural classification of lipids: backbone, head group, and conjugation properties**

| Lipid group | Lipid class | Backbone | Head group | Number of conjugated fatty acid | Number of conjugated phosphate |
|---|---|---|---|---|---|
| neutral lipid | monoacylglycerol (MAG) | glycerol | NA | 1 | 0 |
| | diacylglycerol (DAG) | glycerol | NA | 2 | 0 |
| | triacylglycerol (TAG) | glycerol | NA | 3 | 0 |
| | cholesteryl ester (CE) | sterol | NA | 1 | 0 |
| phospholipid | phosphatidylcholine (PC) | glycerol | choline | 2 | 1 |
| | lysophosphatidylcholine (LPC) | glycerol | choline | 1 | 1 |
| | phosphatidylethanolamine (PE) | glycerol | ethanolamine | 2 | 1 |
| | lysophosphatidylethanolamine (LPE) | glycerol | ethanolamine | 1 | 1 |
| | phosphatidylinositol (PI) | glycerol | inositol | 2 | 1 |
| sphingolipid | dihydroceramide (DCER) | sphinganine | NA | 1 | 0 |
| | ceramide (CER) | sphingosine | NA | 1 | 0 |
| | sphingomyelin (SM) | sphingosine | phosphocholine | 1 | 1 |
| | hexosylceramide (HCER) | sphingosine | hexose | 1 | 0 |
| | lactosylceramide (LCER) | sphingosine | lactose | 1 | 0 |

**Supplemental Table 2. Overview of biostatistical methods for data analysis**

| Methods | Purposes | Pros | Cons | Figure | Table |
|---|---|---|---|---|---|
| Principal Component Analysis (PCA) | Exploratory analysis and visualization of lipids on a two-dimensional plot by timepoints and subject groups, using the first two principal components of lipids that explain majority of variation in all lipids. | Intuitive by plotting the lipids on a two-dimensional plot through dimension deduction for identifying group and time differences, batch effects and outliers; useful for initial examination. | Subjective way to examine the differences between subjects groups or timepoints; provides limited interpretability. | 1E, G, 3D | |
| Linear mixed-effects regression model | Rigorous statistical modeling approach to test lipid expression differences between the subject groups and over time by taking lipids measured at multiple timepoints into account, adjusting for baseline covariates. | Accounts for time, group, and interaction effects in one model. | Power may be reduced with small smaple sizes, especially in the discovery cohort | 2A, 4A | S3-4, 9 |
| Class enrichment analysis through one-sided Fisher exact tests | To examine whether the lipid class containing differentially represented lipids are statistically significant enriched. | A rigorous way to examine whether the lipid class contains differentially represented lipids is beyond what would be expected by chance; one-sided tests answer the hypothesis whether the lipid class is enriched with significantly differentially represented lipids ( "over representation") compared to two-sided tests which only answer if there is any differences in the number of significant differentially represented lipids. | Require prior hypothesis on the direction of the test when using the one-sided testing approach; lack identification of under respresentation. | 2B | |
| Multivariable logistic regression | To examine the effect of lipids on the risk of developing pancreatitis, adjusting for baseline covariates. | A rigorous parametric regression to examine the association between the covariate and a binary outcome; odds ratio with 95% confidence interval can be obtained with intuitive interpretation for developing pancreatitis. | Require a moderate sample size especially for rare events. | 2E | |

| | | | | | |
|---|---|---|---|---|---|
| WGCNA (weighted gene co-expression network analysis) | Identify lipid clusters and assess the correlation patterns between subject groups. | It has a rigorous rationale and statistical procedure through weighted correlation and topology to identify the correlation patterns and give information about "whether correlations within lipids are different between two groups". Module eigengene can be further used as a representative of a module to perform more analysis on module level. More rigorous than Spearman rank correlation which can only subjectly see the differences in correlation patterns between groups. | Sensitive to the choice of some parameters (e.g., soft threshold, monimum node size); subjective in determining the unpreserved module as Z-summary is sensitive to the module size and the threshold is subjective, but still more objective than visually comparing Spearman correlations between groups. | 3E-F, S5 | S5-6, 8 |
| Two-sided two-sample proportion test | Examine the proportion of lipids uncorrelated with any other modules within each lipid group between cases and controls. | easy interpretation of comparing two proportions in two independent groups; widely used. | Has size requirements especially requiring larger sample size if the proportion is close to 0 or 1. | S6 | |
| Pathway enrichment analysis through one-sided Fisher exact tests | To examine whether the pathway containing differentially expressed proteins are statistically significant enriched. | A rigorous way to examine whether the pathway containing differentially expressed proteins is beyond what would be expected by chance; one-sided tests answer the hypothesis whether the pathway is enriched with significant differentially expressed proteins("over representation”) compared to two-sided tests which only answer if there is any differences in the number of significant differentially expressed proteins. | Require prior hypothesis on the direction of the test when using the one-sided testing approach; lack identification of under respresentation. | 4B | |

**Supplemental Table 3. Linear mixed-effects regression analysis of lipid class concentrations at initial and post-induction timepoints, and their ratios (post/initial) between cases and controls**

| **Lipid group** | **Lipid class** | **Initial** | | | **Post-induction** | | | **Post/intial ratio** | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | tstat | P value | Q value | tstat | P value | Q value | tstat | P value | Q value |
| neutral lipid | DAG | 0.814 | 0.661 | 0.993 | -0.459 | 0.876 | 0.876 | -0.056 | 0.955 | 0.970 |
| | MAG | -0.108 | 0.993 | 0.993 | -0.476 | 0.867 | 0.876 | 0.038 | 0.970 | 0.970 |
| | TAG | -0.287 | 0.949 | 0.993 | -0.666 | 0.757 | 0.876 | -0.868 | 0.390 | 0.682 |
| | CE | 0.609 | 0.792 | 0.993 | -1.951 | 0.105 | 0.421 | -2.105 | 0.041 | 0.191 |
| phospholipid | PC | 0.505 | 0.851 | 0.988 | -1.757 | 0.16 | 0.26 | -1.045 | 0.302 | 0.604 |
| | **LPC** | 0.696 | 0.738 | 0.988 | -3.584 | **0.001** | **0.005** | -2.850 | **0.007** | **0.092** |
| | PE | -0.140 | 0.988 | 0.988 | -1.363 | 0.321 | 0.402 | -0.544 | 0.589 | 0.750 |
| | LPE | -0.412 | 0.899 | 0.988 | -2.384 | **0.038** | **0.095** | -2.268 | 0.028 | 0.191 |
| | PI | 0.670 | 0.755 | 0.988 | -1.195 | 0.415 | 0.42 | -1.109 | 0.273 | 0.604 |
| sphingolipid | DCER | -0.729 | 0.717 | 0.950 | -0.974 | 0.554 | 0.554 | 0.290 | 0.773 | 0.902 |
| | CER | -1.106 | 0.469 | 0.950 | -1.863 | 0.127 | 0.318 | -0.717 | 0.477 | 0.743 |
| | SM | 0.657 | 0.763 | 0.950 | -1.301 | 0.354 | 0.443 | -0.587 | 0.560 | 0.750 |
| | HCER | 0.360 | 0.922 | 0.950 | -1.493 | 0.258 | 0.431 | -1.345 | 0.185 | 0.604 |
| | LCER | -0.284 | 0.950 | 0.950 | 2.127 | 0.071 | 0.318 | 1.236 | 0.223 | 0.604 |

tstat: the ratio of the difference in a number’s estimated value from its assumed value to its standard error.

**Supplemental Table 4. Differentially presented lipids species identified post-induction ($P < 0.05$)**

| Lipid group | Lipid species | $\log_2$(case/control) | -log(P value) |
|---|---|---|---|
| **neutral lipid** | DAG(14:0/20:0) | -0.77 | 1.60 |
| | TAG54:5-FA18:0 | -0.70 | 1.44 |
| | TAG54:6-FA18:2 | -0.72 | 1.43 |
| | TAG54:7-FA18:1 | -0.69 | 1.48 |
| | TAG54:7-FA18:2 | -0.84 | 1.62 |
| | TAG54:7-FA18:3 | -0.81 | 1.61 |
| | TAG54:8-FA18:2 | -0.95 | 1.97 |
| | TAG54:8-FA18:3 | -0.99 | 1.85 |
| | TAG55:6-FA20:3 | 0.11 | 1.50 |
| | CE(12:0) | -0.94 | 1.68 |
| | CE(14:0) | -0.52 | 1.44 |
| | CE(15:0) | -0.54 | 1.92 |
| | CE(17:0) | -0.56 | 1.81 |
| **phospholipid** | PC(14:0/20:3) | -0.69 | 2.54 |
| | PC(14:0/20:4) | -0.40 | 1.55 |
| | PC(16:0/20:2) | -0.44 | 1.84 |
| | PC(16:0/20:3) | -0.53 | 1.76 |
| | PC(16:0/20:5) | -0.85 | 1.36 |
| | PC(16:0/22:4) | -0.41 | 1.45 |
| | PC(16:0/22:5) | -0.47 | 1.61 |
| | PC(18:0/20:3) | -0.47 | 1.52 |
| | PC(18:0/22:5) | -0.47 | 1.86 |
| | PC(18:2/20:3) | -0.40 | 1.94 |
| | PC(18:2/20:4) | -0.32 | 1.69 |
| | LPC(16:0) | -0.59 | 2.89 |
| | LPC(16:1) | -0.62 | 1.98 |
| | LPC(17:0) | -0.66 | 2.65 |
| | LPC(18:0) | -0.59 | 2.67 |
| | LPC(18:1) | -0.57 | 2.32 |
| | LPC(18:2) | -0.54 | 1.90 |
| | LPC(20:3) | -0.71 | 2.62 |
| | LPC(20:4) | -0.56 | 2.07 |
| | PE(18:2/16:1) | -0.52 | 1.99 |
| | PE(O-18:0/20:3) | -0.54 | 1.82 |
| | PE(P-16:0/18:2) | -0.64 | 2.23 |
| | PE(P-16:0/20:3) | -0.76 | 2.68 |
| | PE(P-18:0/18:2) | -0.65 | 2.32 |
| | PE(P-18:0/20:3) | -0.85 | 2.67 |
| | PE(P-18:0/20:5) | -0.93 | 2.00 |
| | PE(P-18:1/18:2) | -0.54 | 1.71 |
| | PE(P-18:1/20:3) | -0.75 | 2.18 |
| | LPE(16:0) | -0.50 | 2.22 |
| | LPE(18:0) | -0.51 | 2.04 |
| | LPE(22:5) | -0.60 | 1.34 |
| | PI(18:0/20:3) | -0.39 | 1.48 |
| **sphingolipid** | CER(24:0) | -0.42 | 1.63 |
| | DCER(22:2) | -0.70 | 2.04 |
| | LCER(24:1) | 1.10 | 1.62 |

In the Metabolon lipid nomenclature system, the letter indicates the lipid class, while the content in parentheses specifies the conjugated fatty acid. The first number represents the number of carbon atoms in the fatty acid chain, and the second number denotes the number of double bonds.

**Supplemental Table 5. Non-preserved lipid species identified at initial in the discovery cohort**

| Lipid group | Lipid Species |
|---|---|
| neutral lipid | MAG(14:0) |
| | MAG(16:0) |
| | MAG(17:0) |
| | MAG(18:0) |
| | MAG(18:1) |
| | MAG(18:2) |
| | MAG(18:3) |
| | MAG(20:1) |
| | MAG(20:2) |
| | MAG(20:3) |
| | MAG(20:4) |
| | MAG(22:4) |
| | MAG(22:5) |
| | MAG(22:6) |
| | DAG(16:1/20:0) |
| | DAG(16:1/20:2) |
| | DAG(16:1/22:6) |
| | TAG55:7-FA15:0 |
| | TAG58:6-FA16:0 |
| | TAG58:7-FA20:4 |
| | TAG58:8-FA20:3 |
| | TAG58:8-FA20:4 |
| | TAG58:9-FA20:4 |
| | TAG58:10-FA20:4 |
| | CE(12:0) |
| | CE(14:0) |
| | CE(14:1) |
| | CE(15:0) |
| | CE(16:0) |
| | CE(16:1) |
| | CE(17:0) |
| | CE(18:0) |
| | CE(18:1) |
| | CE(18:2) |
| | CE(18:3) |
| | CE(18:4) |
| | CE(20:2) |
| | CE(20:3) |
| | CE(20:4) |
| | CE(22:0) |
| | CE(22:1) |
| | CE(22:4) |
| | CE(22:5) |
| | CE(24:1) |
| | PC(14:0/18:1) |
| | PC(14:0/18:2) |
| | PC(14:0/20:3) |
| | PC(14:0/20:4) |
| | PC(15:0/18:1) |
| | PC(15:0/18:2) |
| | PC(16:0/16:0) |
| | PC(16:0/16:1) |

| | |
|---|---|
| phospholipid | PC(16:0/18:0) |
| | PC(16:0/18:1) |
| | PC(16:0/18:2) |
| | PC(16:0/20:1) |
| | PC(16:0/20:2) |
| | PC(16:0/20:3) |
| | PC(16:0/20:4) |
| | PC(16:0/22:4) |
| | PC(16:0/22:5) |
| | PC(17:0/18:1) |
| | PC(17:0/18:2) |
| | PC(17:0/20:3) |
| | PC(17:0/20:4) |
| | PC(18:0/16:1) |
| | PC(18:0/18:0) |
| | PC(18:0/18:1) |
| | PC(18:0/18:2) |
| | PC(18:0/20:2) |
| | PC(18:0/20:3) |
| | PC(18:0/20:4) |
| | PC(18:0/22:4) |
| | PC(18:0/22:5) |
| | PC(18:1/16:1) |
| | PC(18:1/18:1) |
| | PC(18:1/18:2) |
| | PC(18:1/20:2) |
| | PC(18:1/20:3) |
| | PC(18:1/20:4) |
| | PC(18:1/22:4) |
| | PC(18:1/22:5) |
| | PC(18:2/16:1) |
| | PC(18:2/18:2) |
| | PC(18:2/18:3) |
| | PC(18:2/20:2) |
| | PC(18:2/20:3) |
| | PC(18:2/20:4) |
| | PC(18:2/22:5) |
| | PC(20:0/18:1) |
| | PC(20:0/18:2) |
| | PC(20:0/20:3) |
| | PC(20:0/20:4) |
| | LPC(15:0) |
| | LPC(16:0) |
| | LPC(16:1) |
| | LPC(17:0) |
| | LPC(18:0) |
| | LPC(18:1) |
| | LPC(18:2) |
| | LPC(20:2) |
| | LPC(20:3) |
| | LPC(20:4) |
| | LPC(22:5) |
| | PE(18:0/18:0) |
| | PE(18:0/18:1) |
| | PE(18:0/20:2) |
| | PE(18:1/16:1) |

PE(18:1/20:4)
PE(18:1/22:5)
PE(18:2/16:1)
PE(O-16:0/18:1)
PE(O-16:0/18:2)
PE(O-16:0/20:4)
PE(O-16:0/22:4)
PE(O-16:0/22:5)
PE(O-16:0/22:6)
PE(O-18:0/18:1)
PE(O-18:0/18:2)
PE(O-18:0/20:3)
PE(O-18:0/20:4)
PE(O-18:0/22:4)
PE(O-18:0/22:5)
PE(O-18:0/22:6)
PE(P-16:0/18:1)
PE(P-16:0/18:2)
PE(P-16:0/20:3)
PE(P-16:0/20:4)
PE(P-16:0/22:4)
PE(P-16:0/22:5)
PE(P-16:0/22:6)
PE(P-18:0/16:0)
PE(P-18:0/18:1)
PE(P-18:0/18:2)
PE(P-18:0/20:3)
PE(P-18:0/20:4)
PE(P-18:0/22:5)
PE(P-18:0/22:6)
PE(P-18:1/16:0)
PE(P-18:1/18:1)
PE(P-18:1/18:2)
PE(P-18:1/20:3)
PE(P-18:1/20:4)
PE(P-18:1/22:4)
PE(P-18:1/22:5)
PE(P-18:1/22:6)
PE(P-18:2/20:4)
LPE(16:0)
LPE(16:1)
LPE(18:0)
LPE(18:1)
LPE(18:2)
LPE(20:3)
LPE(20:4)
LPE(22:5)
PI(16:0/18:1)
PI(16:0/18:2)
PI(16:0/20:4)
PI(18:0/16:1)
PI(18:0/18:1)
PI(18:0/18:2)
PI(18:0/20:3)
PI(18:0/20:4)
PI(18:1/18:1)

| | |
|---|---|
| | PI(18:1/18:2) |
| | PI(18:1/20:4) |
| sphingolipid | DCER(16:0) |
| | DCER(18:0) |
| | DCER(18:1) |
| | DCER(20:0) |
| | DCER(20:1) |
| | DCER(22:0) |
| | DCER(22:1) |
| | DCER(22:2) |
| | DCER(24:0) |
| | DCER(24:1) |
| | DCER(26:1) |
| | CER(14:0) |
| | CER(16:0) |
| | CER(18:0) |
| | CER(18:1) |
| | CER(20:0) |
| | CER(20:1) |
| | CER(22:0) |
| | CER(22:1) |
| | CER(24:0) |
| | CER(24:1) |
| | CER(26:0) |
| | CER(26:1) |
| | SM(14:0) |
| | SM(16:0) |
| | SM(18:0) |
| | SM(18:1) |
| | SM(20:0) |
| | SM(20:1) |
| | SM(22:0) |
| | SM(22:1) |
| | SM(24:0) |
| | SM(24:1) |
| | SM(26:0) |
| | SM(26:1) |
| | HCER(18:1) |
| | HCER(20:1) |
| | HCER(22:1) |
| | LCER(14:0) |
| | LCER(16:0) |
| | LCER(18:1) |
| | LCER(20:1) |
| | LCER(24:0) |
| | LCER(24:1) |
| | LCER(26:0) |

**Supplemental Table 6. Uncorrelated lipid species identified post-induction in the discovery cohort**

| Lipid group | Controls | Cases |
|---|---|---|
| neutral lipid | | MAG(14:0) |
| | | MAG(14:1) |
| | | MAG(16:1) |
| | | MAG(18:1) |
| | | MAG(20:2) |
| | | MAG(20:3) |
| | | MAG(20:4) |
| | | MAG(20:5) |
| | | MAG(22:4) |
| | | MAG(22:5) |
| | | MAG(24:1) |
| | TAG57:9-FA22:6 | |
| | | CE(16:0) |
| | | CE(18:0) |
| | | CE(18:1) |
| | | CE(18:3) |
| | CE(20:0) | CE(20:0) |
| | CE(20:1) | CE(20:1) |
| | | CE(20:2) |
| | | CE(20:3) |
| | | CE(20:4) |
| | | CE(22:0) |
| | | CE(22:1) |
| | CE(22:2) | CE(22:2) |
| | | CE(22:4) |
| | | CE(22:5) |
| | | CE(22:6) |
| | | CE(24:0) |
| | | CE(24:1) |
| phospholipid | | PC(16:0/18:0) |
| | | PC(16:0/20:3) |
| | | PC(16:0/22:5) |
| | | PC(16:0/22:6) |
| | | PC(17:0/18:2) |
| | | PC(17:0/20:3) |
| | | PC(17:0/20:4) |
| | | PC(18:0/18:0) |
| | | PC(18:0/20:3) |
| | | PC(18:0/20:4) |
| | | PC(18:0/22:4) |
| | | PC(18:0/22:5) |
| | | PC(18:0/22:6) |
| | | PC(18:1/20:3) |
| | | PC(18:1/22:5) |
| | | PC(18:2/20:5) |
| | | PC(18:2/22:5) |
| | | PC(18:2/22:6) |
| | | PC(20:0/20:3) |
| | | PC(20:0/20:4) |
| | | LPC(16:0) |
| | | LPC(16:1) |
| | LPC(17:0) | LPC(17:0) |
| | | LPC(18:0) |

| | | |
|---|---|---|
| | | LPC(18:1) |
| | LPC(18:2) | LPC(18:2) |
| | | LPC(20:2) |
| | | LPC(20:3) |
| | | LPC(20:4) |
| | | LPC(22:5) |
| | | LPC(22:6) |
| | | PE(18:1/22:0) |
| | | PE(O-16:0/22:6) |
| | | PE(O-18:0/22:6) |
| | PE(P-16:0/22:6) | PE(P-16:0/22:6) |
| | PE(P-18:0/20:5) | |
| | PE(P-18:0/22:6) | PE(P-18:0/22:6) |
| | PE(P-18:1/22:6) | PE(P-18:1/22:6) |
| | LPE(18:2) | LPE(18:2) |
| | | LPE(20:3) |
| | | LPE(20:4) |
| | | LPE(22:5) |
| | | LPE(22:6) |
| | | PI(18:0/18:2) |
| | | PI(18:0/20:3) |
| | PI(18:0/20:4) | PI(18:0/20:4) |
| sphingolipid | | DCER(18:0) |
| | | DCER(18:1) |
| | | DCER(20:0) |
| | | DCER(20:1) |
| | | DCER(22:0) |
| | | DCER(22:2) |
| | | DCER(24:0) |
| | | DCER(24:1) |
| | DCER(26:0) | DCER(26:0) |
| | | CER(18:0) |
| | | CER(18:1) |
| | | CER(20:0) |
| | | CER(20:1) |
| | | CER(22:0) |
| | | CER(22:1) |
| | | CER(24:0) |
| | | SM(16:0) |
| | SM(18:0) | SM(18:0) |
| | SM(18:1) | SM(18:1) |
| | | SM(20:0) |
| | SM(20:1) | SM(20:1) |
| | | SM(22:0) |
| | SM(22:1) | SM(22:1) |
| | SM(24:0) | SM(24:0) |
| | | SM(24:1) |
| | SM(26:0) | |
| | SM(26:1) | |
| | | HCER(14:0) |
| | | HCER(16:0) |
| | | HCER(18:0) |
| | | HCER(18:1) |
| | | HCER(20:0) |
| | | HCER(20:1) |
| | | HCER(22:0) |

| | |
|---|---|
| | HCER(22:1) |
| | HCER(24:0) |
| | HCER(24:1) |
| LCER(16:0) | LCER(16:0) |
| LCER(18:1) | |
| LCER(22:0) | |
| LCER(24:0) | |
| LCER(24:1) | LCER(24:1) |
| LCER(26:1) | |

**Supplemental Table 7. 814 lipid species overlap between discovery and validation cohorts**

| Lipid group (# species, %) | Lipid class (# species, %) |
|---|---|
| neutral lipids (627, 77.0) | MAG (25, 3.1)<br>DAG (58, 7.1)<br>TAG (518, 63.6)<br>CE (26, 3.2) |
| phospholipids (128, 15.7) | PC (59, 7.2)<br>LPC (11, 1.4)<br>PE (48, 5.9)<br>LPE (8, 1.0)<br>PI (2, 0.2 ) |
| sphingolipids (59, 7.3) | DCER (13, 1.6)<br>CER (12, 1.5)<br>SM (12, 1.5)<br>HCER (12, 1.5)<br>LCER, (10, 1.2) |

**Supplemental Table 8. Non-preserved lipid species identified at post-induction in the validation cohort**

| | |
|---|---|
| neutral lipid | MAG(18:4) |
| | CE(12:0) |
| | CE(14:0) |
| | CE(14:1) |
| | CE(15:0) |
| | CE(16:0) |
| | CE(16:1) |
| | CE(17:0) |
| | CE(18:0) |
| | CE(18:1) |
| | CE(18:2) |
| | CE(18:3) |
| | CE(18:4) |
| | CE(20:2) |
| | CE(20:3) |
| | CE(20:4) |
| | CE(20:5) |
| | CE(22:0) |
| | CE(22:4) |
| | CE(22:5) |
| | PC(14:0/18:1) |
| | PC(14:0/18:2) |
| | PC(14:0/20:3) |
| | PC(14:0/20:4) |
| | PC(15:0/18:1) |
| | PC(15:0/18:2) |
| | PC(16:0/18:2) |
| | PC(16:0/20:1) |
| | PC(16:0/20:4) |
| | PC(16:0/20:5) |
| | PC(16:0/22:4) |
| | PC(16:0/22:5) |
| | PC(17:0/18:1) |
| | PC(17:0/18:2) |
| | PC(17:0/20:3) |
| | PC(17:0/20:4) |
| | PC(18:0/18:2) |
| | PC(18:0/20:4) |
| | PC(18:0/20:5) |
| | PC(18:0/22:4) |
| | PC(18:0/22:5) |
| | PC(18:1/18:2) |
| | PC(18:1/18:3) |
| | PC(18:1/20:4) |
| | PC(18:1/20:5) |
| | PC(18:1/22:4) |
| | PC(18:1/22:5) |
| | PC(18:2/16:1) |
| | PC(18:2/18:2) |
| | PC(18:2/18:3) |
| | PC(18:2/20:3) |
| | PC(18:2/20:4) |

| | |
|---|---|
| phospholipid | PC(20:0/18:2) |
| | PC(20:0/20:4) |
| | LPC(15:0) |
| | LPC(16:0) |
| | LPC(16:1) |
| | LPC(17:0) |
| | LPC(18:0) |
| | LPC(18:1) |
| | LPC(18:2) |
| | LPC(20:2) |
| | LPC(20:3) |
| | LPC(20:4) |
| | LPC(22:5) |
| | PE(O-16:0/22:5) |
| | PE(O-18:0/20:4) |
| | PE(O-18:0/22:5) |
| | PE(P-16:0/18:1) |
| | PE(P-16:0/18:2) |
| | PE(P-16:0/20:3) |
| | PE(P-16:0/20:4) |
| | PE(P-16:0/22:4) |
| | PE(P-16:0/22:5) |
| | PE(P-18:0/18:1) |
| | PE(P-18:0/18:2) |
| | PE(P-18:0/20:3) |
| | PE(P-18:0/20:4) |
| | PE(P-18:0/22:4) |
| | PE(P-18:0/22:5) |
| | PE(P-18:1/18:1) |
| | PE(P-18:1/18:2) |
| | PE(P-18:1/20:3) |
| | PE(P-18:1/20:4) |
| | PE(P-18:1/22:5) |
| | LPE(16:0) |
| | LPE(18:0) |
| | LPE(18:1) |
| | LPE(22:5) |
| | PI(18:0/20:4) |
| sphingolipid | DCER(24:0) |
| | CER(24:0) |
| | CER(26:0) |
| | SM(14:0) |
| | SM(16:0) |
| | SM(20:0) |
| | SM(20:1) |
| | SM(22:0) |
| | SM(22:1) |
| | SM(24:0) |
| | SM(26:0) |
| | SM(26:1) |
| | HCER(14:0) |
| | HCER(16:0) |
| | HCER(18:0) |
| | HCER(20:0) |
| | HCER(22:0) |
| | HCER(24:0) |

| | | |
|---|---|---|
| | HCER(24:1) | ;; |
| | LCER(18:1) | |
| | LCER(20:1) | |

Lipid species labeled in black were within the non-preserved module (M2), while those labeled in blue were within the modestly non-preserved module (M6).

**Supplemental Table 9. Differentially expressed proteins ($P < 0.05$) in cases and controls across three sampling conditions**

| Initial | Post-induction | Post/Initial |
|---|---|---|
| ACYP1 | AARSD1 | ACE2 |
| ADAM22 | ACAN | ADAMTS4 |
| ADAMTS1 | ACE2 | ADAMTSL2 |
| ADD1 | ACYP1 | APCS |
| ANXA1 | AK1 | ARHGEF10 |
| APCS | ALDH2 | ARTN |
| APOA1 | ALDH5A1 | ATP1B3 |
| APOB | AMPD3 | BRK1 |
| APOD | ANXA1 | C1QTNF1 |
| ARHGEF1 | ANXA11 | C1QTNF5 |
| ASRGL1 | ANXA3 | C1S |
| ATP1B3 | APRT | CABP2 |
| AZU1 | ARHGEF1 | CBS |
| BRAP | ARHGEF10 | CCL19 |
| BRDT | ARHGEF12 | CCN4 |
| BRK1 | ATXN3 | CCN5 |
| CDH17 | BCL2L15 | CDH4 |
| CEACAM21 | BLVRB | CEACAM5 |
| CFB | CA3 | CFB |
| CKMT1A | CALCOCO1 | CFHR5 |
| CKMT1B | CC2D1A | CKMT1A |
| CLU | CCL20 | CKMT1B |
| CNST | CCS | COL18A1 |
| CSPG4 | CCT5 | COL3A1 |
| CST6 | CD300LG | COL4A1 |
| CTHRC1 | CDH17 | CPXM2 |
| CTSD | CEACAM5 | CRX |
| CXCL16 | CEP85 | CSF3 |
| DKK3 | CHAC2 | CSRP3 |
| DLK1 | CHMP1A | CUZD1 |
| DNAJB2 | CRADD | CXADR |
| DPP7 | CRYGD | CXCL17 |
| DSG3 | CSF2 | CXCL8_Cardiometabolic |
| DTX3 | CSF2RB | CXCL8_Inflammation |
| EFNB2 | CTSE | CXCL8_Neurology |
| EIF2AK2 | CUZD1 | CXCL8_Oncology |
| ENO2 | CXCL13 | DUOX2 |
| EPHB6 | CXCL8_Inflammation | ECHS1 |
| F13B | CXCL8_Oncology | EDN1 |
| FGF19 | DARS1 | EFNB2 |
| FGFBP1 | DCTN1 | EIF5 |
| GBP1 | DGKA | FOXO1 |

GFRA3
GPHA2
HSPG2
HYAL1
ICAM2
ICAM5
IFNAR1
IL-17D
IPCEF1
KIRREL2
KRT5
LCN15
LEG1
LGALS3
LGMN
LILRA4
LPA
LRG1
LTB
LY9
LZTFL1
MBL2
MFAP5
MRPL58
MUC16
MYCBP2
NDRG1
NOP56
NPTXR
NTRK2
OLR1
PDE5A
PFKFB2
PLA2G4A
PPP1R12A
PTH
PTPRK
PTPRN2
PZP
RELT
RGMA
RNASE4
S100A12
SAA4
SCRIB_Neurology_II

DNAJB1
DNAJB2
DPP7
DSG3
DTYMK
ECHS1
EIF2AK2
EIF2S2
EIF4E
ENOX2
ENPP5
ENPP6
EPHA1
EPHX2
EVI5
FARSA
FCGR2A
FCRLB
FGFBP1
GAST
GCLM
GGCT
GKN1
GLRX
GMPR
HAVCR1
ICA1
IKBKG
IL-10
INPP5D
IRAK4
KIAA0319
KLK13
KLK8
LARP1
LRTM2
LYPLA2
LZTFL1
MFAP3L
MNDA
MYCBP2
NCF2
NFE2
NFKB1
NOP56

GCLM
HLA-E
ICAM2
IFNAR1
IGFL4
IGSF3
IL-18R1
IL-32
IL-6_Cardiometabolic
IL-6_Inflammation
IL-6_Neurology
IL-6_Oncology
ITGB1BP1
KRT18
KRT5
LAMB1
LBP
LEG1
LPA
LRG1
LY9
LYPD8
MBL2
MMP10
NEDD9
NPTN
NPTX2
NUB1
PAFAH2
PALM3
PGA4
PLA2G2A
PPIE
PRR4
PTPRK
PTPRM
PVR
REG3A
RELT
RGL2
S100A13
SAA4
SCIN
SCT
SERPINA7

SCT
SLAMF1
SLITRK1
SPON1
SRP14
STAT5B
SUSD4
SV2A
TCP11
TET2
THBS4
TIGAR
TIGIT
TNR
TPD52L2
TPP1
TRIM40
TSC1
UNC5D
VASP
WFIKKN1

NPTN
NPTXR
NRTN
NT5C3A
NTRK2
OTUD6B
PALM3
PDAP1
PDE5A
PFKFB2
PIK3AP1
PLA2G2A
PLPBP
PPP1R12A
PPP1R2
PRKRA
PSAPL1
PTRHD1
RAB44
RASSF2
REG3A
RSPO1
RSPO3
S100A4
SAMD9L
SDHB
SERPINI2
SFRP1
SH3GLB2
SHBG
SKAP1
SLITRK1
SNX9
SPINK4
SPOCK1
STAMBP
STAT5B
TANK
TAX1BP1
TBC1D17
TBCA
TBCC
TNFSF12
TNIP1
TOP2B

SFRP4
SOWAHA
SPON2
SRPX
SUSD4
TCP11
TIGIT
TNFRSF6B
TNFRSF8
TRIM25
TRIM40
TSPAN1
TSPAN7
VMO1
VWA1
WFIKKN1

| |
|---|
| TRAF3 |
| TRIM25 |
| TSPAN1 |
| TXN |
| TXNDC9 |
| UNC5D |
| USP25 |
| VASP |
| VTA1 |
| YARS1 |

## Supplemental Table 10. Top 10 signigicant enriched pathways identified in proteomics

| Pathway | Number of total proteins within the pathway | Number of significant differentially expressed proteins within the pathway | P value | Q value |
|---|---|---|---|---|
| Senescence-Associated Secretory Phenotype (SASP) | 17 | 8 | 8.15E-08 | 0.00017 |
| Interleukin-10 signaling | 42 | 10 | 3.17E-06 | 0.00326 |
| Cellular Senescence | 28 | 8 | 7.15E-06 | 0.00490 |
| MAPK1 (ERK2) activation | 6 | 4 | 3.04E-05 | 0.01249 |
| Interleukin-6 signaling | 6 | 4 | 3.04E-05 | 0.01249 |
| Interleukin-4 and Interleukin-13 signaling | 57 | 10 | 5.53E-05 | 0.01893 |
| RAF-independent MAPK1/3 activation | 8 | 4 | 1.33E-04 | 0.02740 |
| MAPK3 (ERK1) activation | 8 | 4 | 1.33E-04 | 0.02740 |
| CD163 mediating an anti-inflammatory response | 8 | 4 | 1.33E-04 | 0.02740 |
| ATF4 activates genes in response to endoplasmic reticulum stress | 8 | 4 | 1.33E-04 | 0.02740 |

**Supplemental Table 11. List of LPC species and cytokines included in the association**

| LPC species | Cytokine |
|---|---|
| LPC(16:0) | CCL2 |
| LPC(16:1) | CCL3 |
| LPC(17:0) | CCL4 |
| LPC(18:0) | CCL5 |
| LPC(18:1) | CCL7 |
| LPC(18:2) | CCL8 |
| LPC(20:3) | CCL11 |
| LPC(20:4) | CCL13 |
| | CCL14 |
| | CCL15 |
| | CCL16 |
| | CCL17 |
| | CCL18 |
| | CCL19 |
| | CCL20 |
| | CCL21 |
| | CCL22 |
| | CCL23 |
| | CCL24 |
| | CCL25 |
| | CCL26 |
| | CCL27 |
| | CCL28 |
| | CSF1 |
| | CSF2 |
| | CSF3 |
| | CX3CL1 |
| | CXCL1 |
| | CXCL3 |
| | CXCL5 |
| | CXCL6 |
| | CXCL10 |
| | CXCL11 |
| | CXCL12 |
| | CXCL13 |
| | CXCL14 |
| | CXCL16 |
| | CXCL17 |
| | CXCL8-cardiometabolic |
| | CXCL8-inflammation |
| | CXCL8-neurology |
| | CXCL8-oncology |
| | CXCL9 |
| | CYTL1 |
| | FLT3LG |
| | IFNG |
| | IFNL1 |
| | IFNL2 |
| | IFNW1 |
| | IL-1A |
| | IL-1B |
| | IL-1RN |

IL-2
IL-3
IL-4
IL-5
IL-6-cardiometabolic
IL-6-inflammation
IL-6-neurology
IL-6-oncology
IL-7
IL-9
IL-10
IL-11
IL-12A_IL-12B
IL-12B
IL-13
IL-15
IL-16
IL-17A
IL-17C
IL-17D
IL-17F
IL-18
IL-19
IL-20
IL-22
IL-24
IL-25
IL-27A
IL-31
IL-32
IL-33
IL-34
IL-36A
IL-36G
LECT2
LIF
OSM
PF4
PPBP
SCGB1A1
SPP1
TAFA5
TGFB1
TGFB2
TNF-cardiometabolic
TNF-inflammation
TNF-neurology
TNF-oncology
TNFSF8
TNFSF9
TNFSF10
TNFSF11
TNFSF12
TNFSF13
TNFSF13B
TNFSF14

| | |
|---|---|
| | XCL1 |
| | CXCL8, IL-6 and TNF were measured in 4 different panels and are considered distinct proteins. |

**Supplemental Table 12. Baseline characteristics of 16 subjects with VHR ALL**

| | Controls | | | AAP cases | | |
|---|---|---|---|---|---|---|
| | **N** | **%** | **Median (range)** | **N** | **%** | **Median (range)** |
| **Total no. of subjects** | 7 | | | 9 | | |
| **Age at diagnosis, y** | | | 8 (1~15) | | | 6 (1 ~15) |
| 1 ~ 10 | 5 | 71.4 | | 7 | 77.8 | |
| 10 ~ 15 | 2 | 28.6 | | 2 | 22.2 | |
| **Sex** | | | | | | |
| Female | 2 | 28.6 | | 4 | 44.4 | |
| Male | 5 | 71.4 | | 5 | 55.6 | |