Exploring Pre- and Postmenopausal Breast Cancer Risk Factors through Metabolomics and Risk Prediction Modeling

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EXPLORING PRE- AND POSTMENOPAUSAL BREAST CANCER RISK FACTORS THROUGH METABOLOMICS AND RISK PREDICTION MODELING

by

Kristen Brantley

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ABSTRACT

Evidence suggests that breast cancer, long recognized as a hormonal disease, also has a metabolic component influencing its development. However, etiologic mechanisms of breast cancer, including those related to metabolism, remain elusive given its heterogenous nature. Investigation of metabolomics can provide information on biochemical processes key to breast cancer development. Further, because some breast cancer risk factors differ by menopausal status at diagnosis, evaluating metabolomics and risk factors by menopausal groups is important to capture underlying disease mechanisms. Research into risk factors with opposing associations with pre- vs. postmenopausal breast cancers will allow better understanding of the biologic development of this disease.

In this dissertation, I explore potential etiologic mechanisms for pre- and postmenopausal breast cancer through metabolomics and examine differences in risk factor profiles based on menopausal status at diagnosis. In **Chapter 1** I took an agnostic approach to examine metabolite associations with breast cancer risk in a nested matched case-control study (N cases=939, N controls=939) in the Nurses' Health Study (NHS). I uncovered several metabolite groups associated with risk of breast cancer, including cholesteryl esters (inversely associated with risk), triacylglycerols (TAGS) with <3 double bonds (positively associated with risk), and TAGs with ≥ 3 double bonds (inversely associated with risk). I noted changing associations between metabolite groups and breast cancer risk dependent on timing of measurement. **In Chapter 2**, I took a closer look at adiposity as a risk factor for pre- and postmenopausal breast cancer and evaluated metabolomic profiles for adiposity measures. I found that metabolomic scores were often more informative than self-reported measures for adiposity in determining breast cancer risk, suggesting metabolic dysregulation as a key etiologic component to

breast cancer. I also found that metabolite profiles for adiposity measures were similar by menopausal status, though associations with risk were opposite. In **Chapter 3**, I developed a risk prediction model for premenopausal breast cancer to identify risk factors important to development of this disease. I found that many risk factors identified as significant in primarily postmenopausal cohorts were similarly important for premenopausal breast cancer, including premenopausal duration, ever having a birth, time from menarche to first birth, height, alcohol use, BMI in young adulthood, family history of breast cancer, and history of benign breast disease.

Overall, this dissertation suggests that mechanisms of metabolic dysregulation are key components for breast cancer development. Differences seen in risk of pre- vs. postmenopausal breast cancer with respect to certain risk factors, such as adiposity, may be explained by differential action of metabolic dysregulation across the life-course. Discovery that most reproductive and hormonal risk factors for premenopausal breast cancer align with those for postmenopausal breast cancer supports the notion that metabolic dysregulation may be a key element to distinguish the two diseases. Evaluation of the factors of metabolic dysregulation that may be responsible for differences in pre-vs. postmenopausal breast cancer risk can enhance knowledge about etiologic mechanisms for development of breast cancer over time.

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INTRODUCTION

Breast cancer is the leading cause of cancer among women worldwide, with 2.3 million new cases diagnosed in 2020.[1] Over the past 10 years, incidence has continued to rise at a modest rate in developed nations, while rates have accelerated in transitioning countries.[1] Breast cancer is the fifth leading cause of cancer mortality worldwide, accounting for 6.9% of all cancer deaths.[1] The five-year survival rate is high among women diagnosed with stage I or stage II breast cancer (80-90%), though survival for late-stage diagnoses remains low (24%).[2] Given the widespread nature of this disease, working toward prevention by gaining insight into risk factors and etiologic mechanisms is key.

Breast cancer is a heterogeneous disease, with several molecular subtypes that exhibit different prognostic features. Importantly, breast cancer characteristics differ based on whether diagnosis occurs before or after menopause. The vast majority of breast cancers are diagnosed after menopause. However, diagnosis before menopause generally results in a more aggressive form of the disease that is associated with worse prognosis.[3] In addition, early detection of breast cancer is more difficult for younger women, as premenopausal women tend to have higher breast density, making identification of tumors in mammograms even more elusive.[4,5] Due to these inherent differences, there is a need to study breast cancer separately by menopausal status at diagnosis.

Several breast cancer risk factors have already been identified across the life-course, with most research focusing on primarily postmenopausal breast cancers. Most prominently, characteristics associated with increased estrogen burden over time are associated with increased breast cancer risk.[6] These include earlier age at menarche, later age at menopause, and use of postmenopausal hormone therapy.[7] Pregnancy is associated with an initial increase in breast cancer risk, followed by a decline in risk that grows over time and with additional births.[8] The few known modifiable risk factors associated with breast cancer include exogenous estrogen exposure, adiposity, and alcohol intake.[9]

When examining risk factors, an additional layer of complexity is added due to differential associations of risk factors based on menopausal status at diagnosis. Although childhood adiposity is consistently associated with lower risk of both pre- and postmenopausal breast cancer, adulthood adiposity is differentially associated with risk by menopausal status.[10,11] For instance, adiposity, measured

any time while a woman is premenopausal, is inversely associated with premenopausal breast cancer.[12] However, adulthood adiposity, measured either before or after menopause, is consistently associated with an increased risk of postmenopausal breast cancer.[13,14] Premenopausal breast cancer is less well understood than postmenopausal breast cancer due to more limited cases of premenopausal breast cancer in existing cohort studies. Overall, understanding of etiologic mechanisms underlying risk factors for breast cancer remains elusive given the complexity of this disease. To start, we may begin thinking of cancer as a metabolic disease.

The recognition of cancer as a metabolic disease stems from the central idea of the Warburg effect, wherein Otto Warburg identified differential uptake of glucose between tumors and normal tissue and use of aerobic instead of anaerobic glycolysis by tumor cells to survive.[15] As a natural progression for the study of metabolic disease, we can use the new field of metabolomics to explore biochemical processes that contribute to risk and ultimately may help explain risk factor relationships. The metabolome is defined as a complete collection of metabolites found in a given organelle, cell, organ, biofluid, or organism.[16] Individual metabolites are essentially any small molecule that is detectable, including endogenous compounds such as amino acids, lipids, and nucleic acids, and their breakdown products, as well as exogenous compounds from the diet or environment, such as food additives or pollutants.[17] The sensitivity of the metabolome to internal and external variables, such as age or diet, makes it ideal for studying how risk factors relate to breast cancer on a biochemical level. Metabolites can be measured via mass spectrometry instruments: liquid chromatography (LC-MS), gas chromatography (GC-MS), capillary electrophoresis (CE-MS), integration ion mobility (IMS-MS) or through nuclear magnetic resonance (NMR technology).[17] Compounds are identified through detection of peaks and spectral deconvolution. In terms of measurement, tissues can be used, though blood is often preferred, given ease of collection and evidence that it serves as a good proxy for all parts of an organism.[18]

Metabolomic studies over the past decade have advanced our understanding of breast cancer. For example, the finding that metabolomic spectra differ based on molecular subtypes reveals information about differential action of breast cancer subtypes as well.[19] Discovery of oncometabolites, endogenously produced metabolites that initiate or sustain tumorigenesis, have led to targeted

prevention efforts.[20] Metabolomic analyses have also revealed potential to predict treatment response or anticipate recurrence.[19]

While metabolomics can help us understand the biologic basis for disease, given the limited knowledge on premenopausal breast cancer, we also need to continue uncovering general risk factors for disease. Current risk prediction models are most interpretable for postmenopausal breast cancers, given the limited number of premenopausal cases involved in derivation.[7,8,21] As noted, the degree to which risk factors predictive of postmenopausal breast cancer risk similarly predict premenopausal breast cancer is unclear. Identification of novel or consistent risk factors will provide a framework for future work at the biochemical level to identify etiologic mechanisms of risk.

In **Chapter 1**, I begin by presenting an agnostic evaluation of how metabolites and metabolite groups relate to overall breast cancer risk, via a study that was completed in majority postmenopausal women. In **Chapter 2**, I delve into a specific risk factor, adiposity, and examine the relationship between adiposity-related metabolites with pre- and postmenopausal breast cancers. Contrasting how metabolomic data informs us about pre- vs. postmenopausal breast cancer can allow us to better understand why differences in risk occur at different stages in life. In **Chapter 3**, I explore the potential contribution of breast cancer risk factors established for postmenopausal breast cancer in premenopausal breast cancer, and test candidate risk factors for inclusion in a premenopausal risk prediction model. Identification of risk factors specific to premenopausal breast cancer will allow further exploration of the biochemical processes behind these relationships. Through this dissertation, I seek to add to our understanding of pre- and postmenopausal breast cancer etiology, with the long-term goal of accelerating prevention efforts.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249.

2. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and breast cancer. Available at dietandcancerreport.org

3. Rosenberg SM, Partridge AH. Management of breast cancer in very young women. Breast. 2015;24 Suppl 2:S154-158.

4. Checka CM, Chun JE, Schnabel FR, Lee J, Toth H. The relationship of mammographic density and age: implications for breast cancer screening. *AJR Am J Roentgenol*. 2012;198(3):W292-295.

5. Heer E, Harper A, Escandor N, Sung H, McCormack V, Fidler-Benaoudia MM. Global burden and trends in premenopausal and postmenopausal breast cancer: a population-based study. *Lancet Glob Health*. 2020;8(8):e1027-e1037.

6. Rosner B, Colditz GA. Nurses' health study: log-incidence mathematical model of breast cancer incidence. *J Natl Cancer Inst*. 1996;88(6):359-364.

7. Rice MS, Tworoger SS, Hankinson SE, et al. Breast cancer risk prediction: an update to the Rosner-Colditz breast cancer incidence model. *Breast Cancer Res Treat*. 2017;166(1):227-240.

8. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol*. 2000;152(10):950-964.

9. Maas P, Barrdahl M, Joshi AD, et al. Breast Cancer Risk from Modifiable and Nonmodifiable Risk Factors Among White Women in the United States. *JAMA Oncol*. 2016;2(10):1295-1302.

10. Baer HJ, Tworoger SS, Hankinson SE, Willett WC. Body fatness at young ages and risk of breast cancer throughout life. *Am J Epidemiol*. 2010;171(11):1183-1194.

11. Andersen ZJ, Baker JL, Bihrmann K, Vejborg I, Sørensen TIA, Lynge E. Birth weight, childhood body mass index, and height in relation to mammographic density and breast cancer: a register-based cohort study. *Breast Cancer Res*. 2014;16(1):R4.

12. Premenopausal Breast Cancer Collaborative Group, Schoemaker MJ, Nichols HB, et al. Association of Body Mass Index and Age With Subsequent Breast Cancer Risk in Premenopausal Women. JAMA Oncol. 2018;4(11):e181771.

13. White KK, Park S-Y, Kolonel LN, Henderson BE, Wilkens LR. Body size and breast cancer risk: the Multiethnic Cohort. Int J Cancer. 2012;131(5):E705-716. doi:10.1002/ijc.27373

14. Harris HR, Willett WC, Terry KL, Michels KB. Body fat distribution and risk of premenopausal breast cancer in the Nurses' Health Study II. J Natl Cancer Inst. 2011;103(3):273-278.

15. Warburg O., Wind F. and Negelein E. (1927) The metabolism of tumors in the body. J. Gen. Physiol. 8, 519–530

16. Wishart DS, Tzur D, Knox C, et. al. HMDB: the human metabolome database. Nucleic Acids Res 35, Database: D521–D526, 2007.

17. Wishart DS. Metabolomics for Investigating Physiological and Pathophysiological Processes. Physiol Rev. 2019;99(4):1819-1875.

18. Psychogios N, Hau DD, Peng J, et al. The human serum metabolome. PLoS One 6: e16957, 2011.

19. McCartney A, Vignoli A, Biganzoli L, et al. Metabolomics in breast cancer: A decade in review. *Cancer Treat Rev*. 2018;67:88-96.

20. Ward PS, Patel J, Wise DR, Abdel-Wahab O, et. al. The common feature of leukemia-associated IDH1 and IDH2 mutations is a neomorphic enzyme activity converting alpha-ketoglutarate to 2-hydroxyglutarate. Cancer Cell 17: 225–234, 2010.

21. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81(24):1879-1886.

CHAPTER 1

Title: Plasma metabolites and breast cancer risk among postmenopausal women in the Nurses' Health Study

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ABSTRACT

Metabolite profiles reflect the integrated impact of the genome and exogenous exposures on the metabolic state and may provide insight into biologic mechanisms contributing to breast cancer development. To better understand this, we explored the association between pre-diagnostic plasma metabolites (N=307) and invasive breast cancer among women in the Nurses' Health Study. Plasma metabolites were profiled for cases and controls via liquid chromatography tandem mass spectrometry (LC-MS) using samples taken ≥10 years prior to diagnosis (distant, N=939 cases), and <10 years prior to diagnosis (proximate, N=592 cases).

Multivariable conditional logistic regression adjusting for standard breast cancer risk factors was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for a 2.5 standard deviation change in metabolite level, using the number of effective tests to account for testing multiple correlated hypotheses. Changes over time were assessed using cross-classification of high v. low levels of metabolites at each time point and through latency analysis. Metabolite set enrichment analysis (MSEA) was used to group molecularly-similar metabolites based on pre-defined classes. Weighted gene co-expression network analysis (WGCNA) identified data-driven metabolite modules based on their interconnectedness; associations between resulting module scores and breast cancer risk were examined. Multiple testing in MSEA and WGCNA was accounted for using the false discovery rate.

Though no individual metabolites were significantly associated with breast cancer risk, several patterns emerged. At the distant timepoint, cholesteryl esters were inversely associated with risk [e.g.: C22:5 CE OR = 0.82, 95% CI=0.75-0.9]. TAGs with ≥3 double bonds were inversely associated with breast cancer at the proximate timepoint [e.g.: C58:7 TAG OR=0.81, 95% CI=0.72-0.92]. MSEA showed negative enrichment (corresponding to an inverse association with breast cancer) of cholesteryl esters at the distant (normalized enrichment score (NES)=-2.26, p_{adj}=0.02) timepoint. Though positive enrichment of TAGs with <3 double bonds was observed at both time points, TAGs with ≥3 double bonds were significantly inversely associated with breast cancer at the proximate time point (NES=-2.91, padj=0.03). Overall, the results suggest that cholesteryl esters may be inversely related to early development of

breast cancer, while TAGs with many double bonds appear inversely associated with development of breast cancer closer to diagnosis.

INTRODUCTION

Metabolite profiles reflect the integrated impact of the genome and exogenous exposures on the metabolic state and may provide insight into biologic mechanisms contributing to disease development. It is particularly important to study metabolomics in diseases with limited knowledge on etiological mechanisms, such as breast cancer. Breast cancer is the most common cancer among women worldwide.[1] The use of metabolomics can help reveal insights into biologic mechanisms of development. A handful of recent studies have explored metabolite associations with breast cancer incidence,[2-9] though only a few have taken an agnostic approach to explore the metabolomics of breast cancer,[3,8,9] instead focusing on weight-associated or nutritional metabolites. Among the studies that have explored metabolites overall with respect to breast cancer risk, one had a very small sample size (N=84 cases),[8] and all used different metabolomic platforms for measurement. All studies thus far have only captured metabolite profiles at a single point in time. We sought to add to the literature on metabolomics and breast cancer and identify potential pathways of etiologic interest. Here we used an agnostic approach in the Nurses' Health Study to investigate associations between metabolite levels, measured prior to diagnosis, and future breast cancer risk. We also examined how these measures changed over time, using measures from two different blood collections, approximately 10 years apart.

MATERIAL & METHODS

Cohort

We conducted a nested case-control study within the Nurses' Health Study (NHS), a prospective cohort of 121,700 female nurses that was started in 1976. Biennial follow up questionnaires collect risk factor information as well as new disease diagnoses. Blood samples were collected in 1989-1990 from 32,826 cohort members, aged 43-69 years at blood collection. A subset of these women (N=18,743) provided a second blood sample between 2000-2002. Breast cancer cases were identified by self-report

and confirmed by medical record review. Deaths were captured by next of kin, postal service, or review of the National Death Index. Cases were all women diagnosed with invasive breast cancer between 2000-2010 who provided a blood sample at either time point (N=939 for distant 1989-90 blood collection; N=592 for proximate 2000-02 blood collection). Controls were matched to cases on factors at each blood draw, including age (+/- 1 year), month (±1 month), time of day (±2 h), fasting status (≥10 h since a meal vs.<10 h or unknown), postmenopausal hormone use (yes/no), and menopausal status (pre/post/unknown).

Metabolite Profiling

Plasma metabolites were profiled at the Broad Institute of MIT and Harvard (Cambridge, MA). Two different liquid chromatography tandem mass spectrometry (LC/MS-MS) platforms were used for identification of metabolites, designed to measure polar metabolites and lipids, and free fatty acids, described elsewhere.[10-13] Specifics on measurement procedures are described in a previous publication.[14] Briefly, matched case-control pairs were distributed randomly within batch, pooled reference samples were included every 20 samples, and 64 quality controls were randomly distributed. Measures were standardized using the ratio of the value of the sample to the value of the nearest pooled reference multiplied by the median of all reference values for the metabolite. For metabolites measured with multiple metabolomics platforms, the assay laboratory provided a list of the preferred measurement platform. For metabolites measured multiple times with the same platform, the metabolite with the lowest CV was used for analysis. Metabolites that had poor stability due to delay in processing were excluded (N=51).[13] Following this initial data cleaning, a total of 307 known metabolites were successfully measured and included in the study. Metabolites were annotated by superclass, class, and subclass distinctions.

Covariates

Identified risk factors for breast cancer were included as covariates in the analyses, including the following: (1) weight factors: BMI at age 18 (kg/m2) & weight change since age 18 (kg); (2) reproductive factors: age at first birth and parity (nulliparous, 1-2 kids <25 y, 1-2 kids 25+ y, 3+ kids <25y, 3+ kids 25+ y), age at menarche (years) & breastfeeding history (yes/no); (3) disease history factors: history of

benign breast disease (yes/no) & family history of breast cancer (yes/no), and (4) lifestyle factors: physical activity (MET-hours/week) & alcohol intake (g/day), hormone use as a combination of oral contraceptive and/or menopausal hormone therapy (yes/no).

Statistical Analysis

Individual Metabolites

Metabolites with <10% missing were imputed with ½ the minimum value (N=39 at distant blood collection, N=0 at proximate blood collection). Metabolites with >10% missing (N=15 at distant blood collection, N=16 at proximate blood collection) were not imputed. We used probit transformation for all metabolites. Multivariable conditional logistic regression (CLR) was used to determine the association of individual metabolites with breast cancer at both distant and proximate blood collections.

Four different models were run to explore the influence of covariates on the results: (1) CLR, unadjusted for other covariates; (2) CLR, adjusted for BMI at age 18; (3) CLR, adjusted for BMI at age 18 and weight change since age 18; (4) CLR adjusted for BMI at age 18, weight change since age 18 (kg), and all reproductive, lifestyle, and disease history variables noted above.

Unconditional logistic regression (UCLR) with additional adjustment for matching factors was used to assess the association between metabolites and ER+ and ER- breast cancers. ER- models were not adjusted for hormone status at blood draw, as there was no variation of this variable.

We accounted for testing for multiple correlated hypotheses by calculating the number of effective tests among controls by performing a principal components analysis of all metabolites and calculating the number of PCs that explained 99.5% of the total variance.[15] For this method, $p_{adj}=p_{unadjusted}$/number of effective tests. This method has been shown to have similar performance to permutation-based multiple comparison testing correction.[15] All models were assessed looking at a 2.5 standard deviation (SD) increase in metabolites, representing the comparison for 90th-10th percentile of metabolite value.

In a separate analysis, we explored the association of presence vs. absence of metabolites with >10% missingness with breast cancer risk; no significant associations were identified.

Difference and Average

Correlations between metabolite measurements at distant and proximate time points were assessed using Spearman correlations, both unadjusted, and adjusted for fasting, age at blood draw, and weight change since age 18. This was restricted to the subset of participants with both blood measures available (N=592 cases). The value of studying the difference between metabolites was assessed using logistic regression, including metabolite measures at both time points in the same regression along with an interaction term; the p-value for the interaction term was used to determine potential interest in the difference measures.

The difference of metabolite levels at proximate – distant blood collection was analyzed via logistic regression, including only those participants with both blood measures. All models included the distant blood metabolite level and were interpreted as a 2.5 SD change in metabolite level from distant to proximate blood, adjusted for distant blood, e.g.: $\text{logit}(Y)=\beta_0 + \beta_1(X_1) + \beta_0(X_2-X_1)$, where X_1 is the metabolite level at distant blood, and X_2 is the metabolite at proximate blood. For both average and difference analyses, fasting status was assessed as a combination of fasting status between the two time points (fasting at both, fasting at neither, fasting at one), and combined menopausal status (premenopausal at both, postmenopausal at both, switch from pre- to postmenopausal). The remaining covariates were taken from the proximate blood collection.

Cross classification

To further assess the changing influence of metabolites on breast cancer based on measurement time, we conducted a cross-classification analysis. Only individuals with metabolite measures for both blood samples were included in the analysis. Metabolites were classified for participant as below the median value, or equal to or greater than the median value at each time point. Unconditional logistic regression with adjustment for matched factors (as defined above in the difference analysis) was used to determine the association between metabolite levels that increased (<median to ≥median), decreased (≥median to <median), or remained ≥ the median value from distant to proximal time points and breast cancer risk, compared to metabolites that were below the median value at both time points.

Latency analysis

To add to our understanding of how risk changes over time based on metabolite levels, we conducted a latency analysis. The analysis considered metabolite levels at both time points, as well as the time from blood draw to diagnosis for each measure. The following equation was applied to our sample:

$$\log\left(\frac{p}{1-p}\right) = \beta x_1 e^{-\lambda t_1} + \beta x_2 e^{-\lambda t_2} \cong \beta x_1(1-\lambda t_1) + \beta x_2(1-\lambda t_2)$$
$$= \beta_1(x_1 + x_2) - \beta_2(x_1 t_1 + x_2 t_2)$$

The parameter $\beta_2=\beta\lambda$, and λ is a dampening parameter representing the influence of time from blood collection to diagnosis on the association between metabolite level and risk. A positive λ suggests more importance of the proximal time point measure to the association between metabolite and breast cancer risk, while a negative value suggests more importance to the distant time point. The calculation of λ is simply $-\beta_2/\beta_1$, as calculated from our logistic regression analysis. The significance that time of blood collection represents is equivalent to the p-value for the β_2. This analysis was modeled both linearly (as shown above), and quadratically as shown below.

$$\log\left(\frac{p}{1-p}\right) = \beta x_1 e^{-\lambda_1 t_1 - \lambda_2 t_1^2} + \beta x_2 e^{-\lambda_1 t_2 - \lambda_2 t_2^2} \cong \beta x_1(1-\lambda_1 t_1 - \lambda_2 t_1^2) + \beta x_2(1-\lambda_1 t_2 - \lambda_2 t_2^2)$$
$$= \beta_1(x_1 + x_2) - \beta_2(x_1 t_1 + x_2 t_2) - \beta_3(x_1 t_1^2 + x_2 t_2^2)$$

In this equation $\beta_3 = \beta\lambda_2$ and $\beta_2 = \beta\lambda_1$.

Metabolite Set Enrichment Analysis

Metabolites were grouped based on biologic or molecular similarities. The subclasses provide a way to classify metabolites based on structural similarities. Metabolite set enrichment analysis (MSEA) combines the effect estimates from logistic regressions performed on individual metabolites by defined groups, to determine a summary Enrichment Score (ES) and Normalized Enrichment Score (NES) adjusted for group size. All MSEA models are thus adjusted for the same covariates listed above in the individual metabolite analyses. The ES represents the degree to which the metabolite set is overrepresented compared to other sets when analyzing breast cancer as the outcome of interest; where a positive ES represents a significant positive enrichment in breast cancer (i.e., a harmful association), while a significant negative score indicates a group that is negatively enriched in breast cancer (i.e., a protective association). P-values are adjusted using the False Discovery Rate (FDR) to account for multiple comparisons.[16]

Weighted metabolite co-expression network analysis

Weighted gene (metabolite) co-expression network analysis (WGCNA) in R was used to identify metabolite modules associated with breast cancer risk. This analysis process is described in detail elsewhere.[17] Briefly, a gene (or in our case, metabolite) co-expression network is constructed using the absolute values of the correlation coefficients between metabolites to identify interconnected "nodes" based on a threshold value of similarity. Hierarchical clustering based on scale-free topology is used to identify densely interconnected metabolites from the identified network, and modules are identified by using a Dynamic Tree Cut method.[18] Within each subset of interest, (overall BC, ER+ BC, and ER- BC), all metabolites were assigned a module score based on their loading on the first principal component of each module, which was either negative or positive. Module scores were derived in control subjects at each time point separately. These scores were then related to breast cancer risk via UCLR. The resulting OR represents the association of a particular module with breast cancer risk. The loading status of individual metabolites into each module was examined to determine the influence of individual metabolites on the resultant module association. Key metabolites driving module scores were also identified by examining their corresponding loadings on each module.[17]

RESULTS

Descriptive

A total of 939 cases and 939 controls were included for distant blood collection analysis, and 592 cases and 592 controls were included for the proximate blood collection. At first blood collection, mean age was 55 years (SD=6.9); 25% of women were premenopausal (**Table 1.1**). At the second blood draw, 98% of women were postmenopausal. Family history of breast cancer, particularly at second collection, was higher among cases (23%) compared to controls (15%). As expected, weight gain since age 18 was higher at the second blood draw; at both time points cases tended to have approximately 2kg more weight gain compared to controls.

Table 1.1. Descriptive characteristics of participants in NHS who provided blood samples at distant and proximate dates.*

Characteristic	Distant Blood		Proximate Blood	
	Case (N=939)	Control (N=939)	Case (N=592)	Control (N=592)
Age at blood draw (mean (SD))	55.5 (6.9)	55.6 (6.9)	66.4 (6.9)	66.5 (6.8)
Fasting at blood draw (N (%))	626 (67%)	683 (73%)	515 (87%)	547 (92.4)
Menopausal status & PMH use at blood draw (N (%))				
Premenopausal	239 (26%)	240 (26%)	3 (1%)	5 (1%)
Postmenopausal, no PMH use	288 (31%)	289 (31%)	188 (32%)	186 (31%)
Postmenopausal, PMH use	293 (13%)	292 (31%)	393 (66%)	395 (67%)
Unknown	0	0	8 (1%)	6 (1%)
Age at menarche (mean (SD))	12.5 (1.4)	12.6 (1.4)	12.5 (1.4)	12.6 (1.4)
Nulliparous (N (%))	90 (9.6)	75 (8.0)	51 (8.6)	35 (5.9)
Parity (mean (SD))^	3.1 (1.4)	3.2 (1.6)	3.1 (1.3)	3.2 (1.6)
Age at first birth (mean (SD)) ^	25 (3.1)	25 (3.1)	24.9 (3.1)	24.7 (3.0)
Breastfeeding history (N (%))^	604 (64%)	583 (62%)	399 (67%)	381 (64%)
History of benign breast disease (%)	492 (52%)	430 (46%)	53 (50%)	47 (50%)
Family history of breast cancer (%)	136 (15%)	101 (11%)	135 (23%)	87 (15%)
Weight change from age 18 to blood draw in kg (mean (SD))	12.3 (10.9)	10.6 (11.2)	15.1 (12.8)	13.5 (12.8)
BMI at blood draw kg/m² (mean (SD))	25.7 (4.3)	25.2 (4.7)	26.7 (5.0)	26.4 (5.1)
Average alcohol consumption at blood draw in g/day (mean (SD))	7.0 (9.8)	5.9 (8.2)	6.7 (9.2)	5.8 (7.7)
Activity level at blood draw in MET-hours/week (mean (SD))	15.4 (18.8)	15.9 (17.6)	25.7 (42.0)	23.4 (31.7)

*Distant blood draw was >10 years before diagnosis date for cases. Proximate blood draw was <=10 years before diagnosis date for cases.
^ Among parous women

Individual metabolite associations with breast cancer

Conditional logistic regression results at distant and proximate time points did not reveal any metabolites that were significantly associated with breast cancer risk after adjusting for the number of effective tests (NEF distant=193, NEF proximate=186, p-value adj. T1=0.0003, p-value adj. T2=0.0002) (**Supplemental Tables 1.1a & 1.1b**). Despite the lack of significance at this level, several metabolites and classes of metabolites stood out as nominally significant (**Table 1.2**). In particular, the amino acid phenylalanine was positively associated with breast cancer risk at both distant (odds ratio (OR)=1.41, 95% confidence interval (CI)=1.08-1.85; nominal p-value=0.01), and proximate time points (OR= 1.76, 95% CI=1.25-2.48; nominal p-value=0.001). Similar positive associations at both time points were seen for the amino acid proline. When examining groups of metabolites, we found strong positive associations

for triacylglycerols (TAGs) with <3 double bonds at the distant time point, (e.g.: C51:0 TAG OR= 1.3, 95% CI=1.01-1.68; nominal p-value=0.04). At the proximate time point, several TAGs with high numbers of double bonds were inversely associated with breast cancer risk (e.g.: C56:10 TAG OR= 0.64, 95% CI=0.47-0.87; nominal p-value=0.005).

The majority of metabolites with >10% missingness were drug related metabolites and were not significantly associated with breast cancer risk (**Supplemental Tables 1.2a & 1.2b**).

While most associations remained consistent for ER+ and ER- breast cancer separately, several metabolites were associated in opposite directions for ER+ vs. ER- breast cancers (**Table 1.3**; **Supplemental Tables 1.3a & 1.3b (ER+), Supplemental Tables 1.4a & 1.4b (ER-)**), though most did not demonstrate significant heterogeneity. For example, at the proximate time point TAGs with <3 double bonds were strongly positively associated with ER+ breast cancers, but suggestively inversely associated with ER- breast cancers (e.g.: C52:0 TAG ER+ OR= 1.49, 95% CI=1.04-2.15; nominal p-value=0.03; ER- OR= 0.55, 95% CI=0.27-1.10; nominal p-value=0.09, p-het=0.25).

Table 1.2. Odds ratios for breast cancer risk comparing 90th to 10th percentiles of selected metabolites^ measured at distant or proximate blood.

				Unadjusted		Multivariate Adjusted†	
Metabolite Name	**HMDB ID**	**Class**	**Sub Class**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
Distant Blood							
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.50 (1.17-1.94)	0.002	1.41 (1.08-1.85)	0.012
proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.37 (1.07-1.75)	0.012	1.33 (1.03-1.72)	0.032
homoarginine	HMDB0000670*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.41 (1.11-1.80)	0.005	1.3 (1.01-1.68)	0.039
lysine	HMDB0000182	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.38 (1.08-1.77)	0.011	1.31 (1.01-1.69)	0.040
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	0.80 (0.64-1.01)	0.064	0.73 (0.57-0.93)	0.010
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.72 (0.57-0.92)	0.007	0.73 (0.57-0.93)	0.012
C51:0 TAG	HMDB0031106*	Glycerolipids	Triacylglycerols	1.46 (1.15-1.86)	0.002	1.30 (1.01-1.68)	0.044
C22:5 LPC	HMDB0010403*	Glycerophospho-lipids	Glycerophospho-cholines	0.78 (0.61-0.99)	0.041	0.78 (0.60-1.00)	0.047
C22:0 LPE	HMDB0011520	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.69 (0.54-0.89)	0.004	0.75 (0.58-0.98)	0.035
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.82 (0.65-1.03)	0.088	0.78 (0.61-0.99)	0.039
thyroxine	HMDB0000248	NA	NA	1.50 (1.16-1.95)	0.002	1.56 (1.19-2.05)	0.001
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and conjugates	1.42 (1.1-1.84)	0.008	1.35 (1.02-1.77)	0.035
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	1.38 (1.07-1.77)	0.014	1.32 (1.01-1.72)	0.039
guanosine	HMDB0000133	Purine nucleosides	NA	0.77 (0.61-0.97)	0.027	0.78 (0.61-0.99)	0.041
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesterol esters	0.61 (0.48-0.77)	<0.001	0.67 (0.52-0.86)	0.002

Table 1.2 (continued). Odds ratios for breast cancer risk comparing 90th to 10th percentiles of selected metabolites

C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesterol esters	0.70 (0.55-0.88)	0.003	0.69 (0.54-0.89)	0.004
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesterol esters	0.75 (0.60-0.95)	0.016	0.74 (0.58-0.95)	0.017
Proximate Blood							
2-aminohippuric acid	NA**	Benzene and substituted derivatives	Benzoic acids and derivatives	1.39 (1.01-1.93)	0.046	1.45 (1.02-2.06)	0.038
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	1.38 (1.02-1.85)	0.034	1.41 (1.03-1.94)	0.032
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, analogues	1.77 (1.29-2.42)	<0.001	1.76 (1.25-2.48)	0.001
proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, analogues	1.52 (1.12-2.07)	0.007	1.59 (1.13-2.22)	0.007
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, analogues	1.55 (1.15-2.08)	0.004	1.56 (1.12-2.17)	0.009
leucine	HMDB0000687	Carboxylic acids and derivatives	Amino acids, peptides, analogues	1.50 (1.12-2.02)	0.007	1.48 (1.06-2.06)	0.02
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, analogues	1.39 (1.03-1.89)	0.033	1.45 (1.06-2.00)	0.022
serine	HMDB0000187	Carboxylic acids and derivatives	Amino acids, peptides, analogues	1.35 (0.99-1.85)	0.058	1.46 (1.05-2.02)	0.023
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	Amino acids, peptides, analogues	0.78 (0.58-1.03)	0.081	0.71 (0.53-0.96)	0.026
betaine	HMDB0000043	Carboxylic acids and derivatives	Amino acids, peptides, analogues	1.27 (0.91-1.79)	0.164	1.47 (1.03-2.12)	0.035
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.67 (0.5-0.91)	0.010	0.71 (0.52-0.97)	0.030
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	1.5 (1.07-2.1)	0.018	1.58 (1.11-2.24)	0.012
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.60 (0.44-0.82)	0.001	0.59 (0.42-0.82)	0.002
C56:9 TAG	HMDB0005448*	Glycerolipids	Triacylglycerols	0.68 (0.51-0.91)	0.010	0.64 (0.46-0.87)	0.004
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	0.69 (0.52-0.93)	0.013	0.63 (0.46-0.86)	0.004

Table 1.2 (continued). Odds ratios for breast cancer risk comparing 90th to 10th percentiles of selected metabolites

C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	0.70 (0.52-0.94)	0.017	0.64 (0.47-0.87)	0.005
C54:8 TAG	HMDB0010518*	Glycerolipids	Triacylglycerols	0.70 (0.52-0.94)	0.017	0.65 (0.47-0.88)	0.006
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	0.70 (0.52-0.94)	0.017	0.64 (0.47-0.88)	0.006
C56:8 TAG	HMDB0005392*	Glycerolipids	Triacylglycerols	0.69 (0.51-0.93)	0.015	0.66 (0.48-0.90)	0.008
C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	0.67 (0.50-0.91)	0.010	0.66 (0.47-0.90)	0.010
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	0.69 (0.51-0.93)	0.014	0.66 (0.48-0.90)	0.010
C56:7 TAG	HMDB0005462*	Glycerolipids	Triacylglycerols	0.74 (0.55-0.99)	0.044	0.68 (0.50-0.94)	0.017
C58:6 TAG	HMDB0005458*	Glycerolipids	Triacylglycerols	0.68 (0.49-0.92)	0.013	0.68 (0.49-0.94)	0.018
C52:7 TAG	HMDB0010517*	Glycerolipids	Triacylglycerols	0.76 (0.57-1.02)	0.065	0.69 (0.50-0.94)	0.019
C54:7 TAG	HMDB0005447*	Glycerolipids	Triacylglycerols	0.73 (0.54-0.97)	0.031	0.70 (0.51-0.95)	0.021
C60:12 TAG	HMDB0005478*	Glycerolipids	Triacylglycerols	0.76 (0.56-1.02)	0.071	0.71 (0.51-0.98)	0.035
C52:6 TAG	HMDB0005436*	Glycerolipids	Triacylglycerols	0.79 (0.59-1.06)	0.114	0.73 (0.53-0.99)	0.046
C18:3 LPC	HMDB0010387*	Glycerophospho-lipids	Glycerophospho-cholines	1.40 (1.04-1.90)	0.026	1.40 (1.02-1.93)	0.035
C16:1 LPC	HMDB0010383*	Glycerophospho-lipids	Glycerophospho-cholines	1.39 (1.04-1.87)	0.028	1.39 (1.02-1.89)	0.038
C16:0 LPC	HMDB0010382	Glycerophospho-lipids	Glycerophospho-cholines	1.40 (1.04-1.89)	0.026	1.38 (1.01-1.89)	0.042
C18:1 LPC	HMDB0002815*	Glycerophospho-lipids	Glycerophospho-cholines	1.32 (0.97-1.79)	0.072	1.39 (1.01-1.93)	0.046
C38:6 PE	HMDB0009102*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.76 (0.55-1.05)	0.091	0.69 (0.49-0.97)	0.035
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	1.39 (1.04-1.87)	0.028	1.40 (1.03-1.9)	0.030
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	Ceramides	1.62 (1.18-2.22)	0.003	1.72 (1.23-2.40)	0.002
C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	Ceramides	1.46 (1.08-1.98)	0.014	1.42 (1.04-1.94)	0.028
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	Ceramides	1.43 (1.06-1.94)	0.020	1.39 (1.01-1.92)	0.044

Table 1.2 (continued). Odds ratios for breast cancer risk comparing 90th to 10th percentiles of selected metabolites

^Selected metabolites are those with nominal p value <0.05 in fully adjusted models among metabolites with <10% missingness. Missing values were imputed with 1/2 the minimum value. Results sorted by class, subclass & p-value for fully adjusted model.
† Multivariate model adjusted for: BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (MET-hrs/week). P values are nominal p-values before correction for multiple testing.
*Representative HMDBID
**No HMDBID

Table 1.3. Odds ratios for breast cancer risk comparing 90th to 10th percentiles of selected metabolite levels^ measured at distant or proximate blood, by ER status of case.

				ER+		ER-	
Metabolite Name	**HMDB ID**	**Class**	**Subclass**	**OR (95% CI)†**	**p value**	**OR (95% CI)†**	**p value**
Distant Blood							
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	0.67 (0.50-0.90)	0.007	1.02 (0.57-1.82)	0.952
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, analogues	0.70 (0.53-0.94)	0.016	0.69 (0.39-1.23)	0.214
citrulline	HMDB0000904	Carboxylic acids and derivatives	Amino acids, peptides, analogues	0.74 (0.55-0.99)	0.045	0.82 (0.46-1.46)	0.496
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	0.59 (0.44-0.79)	<0.001	1.12 (0.61-2.06)	0.715
C3 carnitine	HMDB0000824	Fatty Acyls	Fatty acid esters	0.72 (0.54-0.97)	0.029	1.16 (0.64-2.10)	0.621
C4 carnitine	HMDB0002013	Fatty Acyls	Fatty acid esters	0.69 (0.52-0.92)	0.012	0.91 (0.50-1.64)	0.748
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.70 (0.53-0.93)	0.015	0.94 (0.52-1.68)	0.823
C34:2 DAG	HMDB0007103*	Fatty Acyls	Lineolic acids and derivatives	1.50 (1.12-2.02)	0.007	1.49 (0.81-2.78)	0.203
C36:3 DAG	HMDB0007219*	Fatty Acyls	Lineolic acids and derivatives	1.35 (1.01-1.80)	0.040	1.29 (0.70-2.39)	0.419
C32:0 DAG	HMDB0007098*	Glycerolipids	Diacylglycerols	1.44 (1.06-1.94)	0.018	1.49 (0.80-2.77)	0.209
C34:1 DAG	HMDB0007102*	Glycerolipids	Diacylglycerols	1.38 (1.03-1.87)	0.034	1.41 (0.75-2.66)	0.284
C52:4 TAG	HMDB0005363*	Glycerolipids	Triacylglycerols	1.43 (1.07-1.90)	0.015	1.22 (0.67-2.25)	0.518
C50:2 TAG	HMDB0005377*	Glycerolipids	Triacylglycerols	1.44 (1.06-1.96)	0.021	1.26 (0.67-2.38)	0.476
C50:1 TAG	HMDB0005360*	Glycerolipids	Triacylglycerols	1.42 (1.05-1.93)	0.027	1.24 (0.66-2.33)	0.508
C52:2 TAG	HMDB0005369*	Glycerolipids	Triacylglycerols	1.39 (1.02-1.88)	0.035	1.25 (0.67-2.36)	0.479
C50:3 TAG	HMDB0005433*	Glycerolipids	Triacylglycerols	1.38 (1.02-1.86)	0.035	1.45 (0.78-2.73)	0.245
C51:1 TAG	HMDB0042104*	Glycerolipids	Triacylglycerols	1.38 (1.02-1.86)	0.036	1.46 (0.79-2.68)	0.227
C43:2 TAG	HMDB0043169*	Glycerolipids	Triacylglycerols	1.37 (1.01-1.85)	0.041	1.46 (0.80-2.67)	0.220

Table 1.3 (continued). Odds ratios for breast cancer risk comparing 90th to 10th percentiles of selected metabolite levels

C55:2 TAG	HMDB0042226*	Glycerolipids	Triacylglycerols	1.35 (1.00-1.82)	0.047	1.18 (0.64-2.19)	0.591
C22:5 LPC	HMDB0010403*	Glycerophospho-lipids	Glycerophospho-cholines	0.58 (0.43-0.77)	<0.001	0.71 (0.39-1.27)	0.248
C18:2 LPC	HMDB0010386*	Glycerophospho-lipids	Glycerophospho-cholines	0.64 (0.47-0.87)	0.005	0.78 (0.41-1.49)	0.453
C20:5 LPC	HMDB0010397	Glycerophospho-lipids	Glycerophospho-cholines	0.65 (0.48-0.88)	0.006	0.82 (0.43-1.54)	0.535
C18:1 LPC	HMDB0002815*	Glycerophospho-lipids	Glycerophospho-cholines	0.68 (0.51-0.91)	0.011	0.96 (0.52-1.74)	0.889
C18:0 LPC	HMDB0010384	Glycerophospho-lipids	Glycerophospho-cholines	0.69 (0.51-0.93)	0.014	1.09 (0.58-2.03)	0.789
C36:5 PC plasmalogen-B	HMDB0011220*	Glycerophospho-lipids	Glycerophospho-cholines	0.75 (0.57-0.99)	0.043	0.84 (0.47-1.47)	0.534
C22:0 LPE	HMDB0011520	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.65 (0.48-0.88)	0.005	0.96 (0.51-1.80)	0.900
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.72 (0.54-0.95)	0.022	0.72 (0.41-1.27)	0.254
C36:5 PE plasmalogen	HMDB0011410*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.73 (0.55-0.97)	0.028	0.84 (0.48-1.47)	0.542
serotonin	HMDB0000259	Indoles and derivatives	Tryptamines and derivatives	1.37 (1.04-1.81)	0.025	1.03 (0.59-1.80)	0.925
C20:4 LPC	HMDB0010395	NA	NA	0.66 (0.50-0.88)	0.004	0.94 (0.52-1.67)	0.823
thyroxine	HMDB0000248	NA	NA	1.50 (1.11-2.04)	0.009	2.16 (1.15-4.13)	0.018
C20:1 LPE	HMDB0011512*	NA	NA	0.69 (0.52-0.92)	0.011	0.71 (0.39-1.30)	0.270
trigonelline	HMDB0000875	NA	NA	0.71 (0.53-0.95)	0.021	0.66 (0.37-1.18)	0.161
carnitine	HMDB0000062	Organonitrogen compounds	Quaternary ammonium salts	0.73 (0.54-0.99)	0.041	1.12 (0.60-2.07)	0.729
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	1.26 (0.95-1.69)	0.110	1.85 (1.04-3.33)	0.037
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	1.34 (1.00-1.79)	0.054	2.02 (1.13-3.64)	0.019

Table 1.3 (continued). Odds ratios for breast cancer risk comparing 90th to 10th percentiles of selected metabolite levels

C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesterol esters	0.52 (0.39-0.70)	<0.001	0.65 (0.35-1.18)	0.160
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesterol esters	0.61 (0.46-0.82)	0.001	0.60 (0.33-1.10)	0.103
C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesterol esters	0.65 (0.49-0.86)	0.003	0.55 (0.30-1.01)	0.054
C20:4 CE	HMDB0006726	Steroids and steroid derivatives	Cholesterol esters	0.67 (0.50-0.89)	0.006	0.77 (0.42-1.38)	0.374
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesterol esters	0.68 (0.51-0.91)	0.010	0.99 (0.53-1.83)	0.965
C20:3 CE	HMDB0006736*	Steroids and steroid derivatives	Cholesterol esters	0.73 (0.55-0.96)	0.026	0.69 (0.38-1.25)	0.225
C18:1 CE	HMDB0000918*	Steroids and steroid derivatives	Cholesterol esters	0.72 (0.54-0.97)	0.030	0.77 (0.41-1.42)	0.404
Proximate Blood							
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	0.64 (0.45-0.91)	0.014	0.52 (0.26-1.03)	0.062
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	1.46 (1.02-2.08)	0.038	2.33 (1.14-4.81)	0.020
proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.52 (1.04-2.21)	0.029	1.67 (0.80-3.50)	0.171
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.48 (1.03-2.14)	0.035	1.31 (0.62-2.79)	0.487
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.47 (1.00-2.16)	0.049	0.89 (0.41-1.91)	0.760
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.60 (0.42-0.86)	0.004	1.46 (0.72-2.97)	0.289
C52:0 TAG	HMDB0005365*	Glycerolipids	Triacylglycerols	1.49 (1.04-2.15)	0.030	0.55 (0.27-1.10)	0.093
C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	0.68 (0.48-0.98)	0.037	0.55 (0.26-1.15)	0.113
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	0.69 (0.48-0.98)	0.038	0.60 (0.29-1.23)	0.160

Table 1.3 (continued). Odds ratios for breast cancer risk comparing 90th to 10th percentiles of selected metabolite levels

C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	0.69 (0.48-0.99)	0.043	0.61 (0.29-1.27)	0.189
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.68 (0.47-0.99)	0.044	0.67 (0.32-1.37)	0.272
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	0.69 (0.49-0.99)	0.045	0.70 (0.34-1.46)	0.345
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	0.70 (0.49-0.99)	0.046	0.83 (0.41-1.70)	0.614
C52:1 TAG	HMDB0005367*	Glycerolipids	Triacylglycerols	1.45 (1.01-2.09)	0.047	0.86 (0.42-1.74)	0.668
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	1.56 (1.09-2.23)	0.015	0.98 (0.49-1.97)	0.956
guanosine	HMDB0000133	Purine nucleosides	NA	1.45 (1.02-2.06)	0.039	0.71 (0.35-1.42)	0.332
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	Ceramides	1.50 (1.05-2.16)	0.027	1.89 (0.95-3.82)	0.071
C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	Ceramides	1.48 (1.03-2.13)	0.035	1.28 (0.63-2.59)	0.488
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	Ceramides	1.48 (1.02-2.15)	0.037	1.26 (0.61-2.60)	0.533
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesteryl esters	0.69 (0.49-0.98)	0.040	1.08 (0.56-2.10)	0.814
hydroxyproline	HMDB0000725	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.77 (0.54-1.10)	0.157	2.03 (1.01-4.15)	0.048
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	0.80 (0.55-1.14)	0.218	2.44 (1.19-5.07)	0.015
C45:0 TAG	HMDB0042093*	Glycerolipids	Triacylglycerols	1.16 (0.80-1.67)	0.465	0.67 (0.33-1.34)	0.039
C22:0 LPE	HMDB0011520	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.66-1.39)	0.818	2.39 (1.16-5.01)	0.018
deoxyguanosine	HMDB0000085	NA	NA	1.18 (0.83-1.68)	0.346	0.47 (0.23-0.98)	0.043
methyl N-methylanthra-nilate	HMDB0034169	NA	NA	1.10 (0.78-1.55)	0.580	0.50 (0.25-0.98)	0.045
kynurenic acid	HMDB0000715	Quinolines and derivatives	Quinoline carboxylic acids	0.97 (0.67-1.41)	0.888	2.14 (1.03-4.5)	0.041

^Selected metabolites are those with <10% missingness and a nominal p<0.05 for either ER+ or ER- breast cancers. Results sorted by class, subclass, and p-value for fully adjusted model. Metabolites in **bold** represent those chosen as top hits for ER- breast cancer.
† Multivariate model adjusted for: BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week). P values are nominal p-values before correction for multiple testing.
*Representative HMDBID

Due to the differences noted in the association of TAGs with breast cancer by number of double bonds, this relationship was further explored by examining ORs by number of carbon atoms and number of double bonds in TAGs (**Figure 1.1**). We found a strong inverse association for TAGs with increasing carbon atoms and double bonds at the proximate time point. This inverse association was not notable for the distant time point, though we did see a trend of a more positive association with risk given lower number of carbon atoms and double bonds at the distant time point. Based on these findings, we grouped the subclass "TAGs" into two distinct segments for further analysis (TAGs with ≥3 vs. TAGs with <3 double bonds).

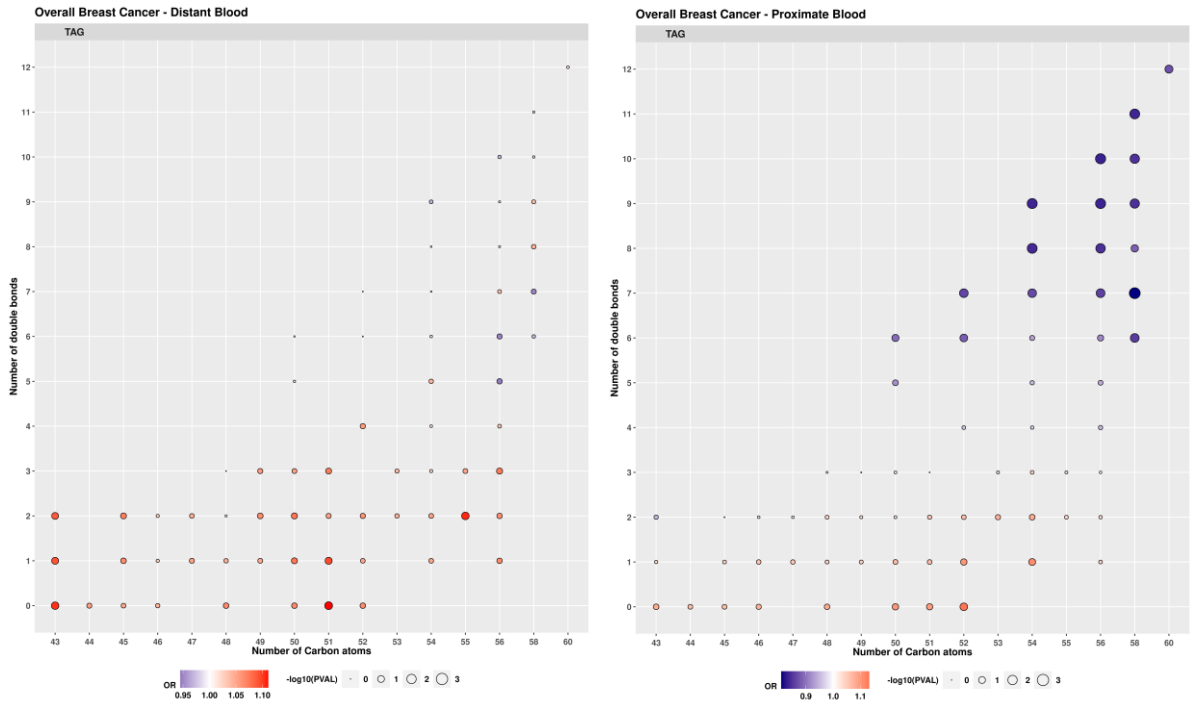

Figure 1.1. Odds ratios for breast cancer risk comparing 90th to 10th percentile of triacylglycerols, by number of Carbon atoms and double bonds at distant & proximate blood. Models are for CLR, fully adjusted for: BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (MET-hrs/week). Y axis is number of double bonds, X axis is number of Carbon atoms. Protective associations are shown in blue, harmful associations are shown in red.

Association between metabolite subclasses and breast cancer risk

MSEA results mirrored those found in individual metabolite analyses and revealed several subclasses of metabolites significantly associated with breast cancer risk after the FDR correction (**Figure 1.2, Supplemental Tables 1.5a & 1.5b**).

TAGs with <3 double bonds at the distant timepoint were strongly positively associated with risk of overall, ER+, and ER- breast cancers. This trend remained at the proximate blood draw for ER+ breast cancers, but no association was observed for ER- breast cancers. TAGs with ≥3 double bonds were strongly inversely associated with breast cancer at the proximate blood draw for overall, ER+, and ER- breast cancers; however, at the distant blood draw this group had a significant positive association with ER+ breast cancer risk.

Another group of interest was cholesteryl esters, which appeared strongly inversely associated with risk at the distant time point, and less strongly, though still inversely associated with risk, at the proximate time point. Glycerophospholipids, Glycerophosphoethanolamines, and glycerophosphocholines all appeared inversely associated with risk at the distant time point for ER+ breast cancers, though associations were weaker and not significant at the proximate time point. Similarly, diacylglycerols (DAGs) were strongly positively associated with risk at the distant time point; while the association remained in the same direction, DAGs were less strongly associated at the proximate time point. Further, the group amino acids, peptides, and analogues was positively associated with overall, ER+ and ER- breast cancer at the proximate blood, though the result was stronger for ER- v. ER+ breast cancers. This group was not significantly associated with breast cancer risk at the distant time point.

Metabolite modules associated with breast cancer risk

WGCNA defined 12 metabolite modules at distant collection, and 11 at proximate (Supplemental Figures 1.1a & 1.1b**, Supplemental Table 1.6**). At both time points, Module 1, the grey module, represents those metabolites that were left over after correlation analyses determined other metabolite groupings. While modules were not defined by one particular subclass, it was notable that most had a majority of one subclass, or a split between two subclass distinctions.

Metabolite module groupings and corresponding associations with breast cancer are displayed in Figure 3; key metabolites driving module scores are highlighted. At the distant time point, there were no modules that were significantly associated with breast cancer risk for overall breast cancer (**Supplemental Table 1.7a & 1.7b**). One module, defined by several glycerophospholipids and TAGs with high numbers of double bonds, was suggestively inversely associated with ER+ breast cancer (M7 red OR=0.66, 95% CI=0.49-0.89; nominal p-value=0.01, FDR adjusted p-value=0.08). TAGs with high numbers of double bonds were negatively weighted in this module, while glycerophospholipids were mainly positively weighted (**Supplemental Figure 1.2**). Thus, individuals with a high module 6 score, defined by more glycerophospholipids and fewer TAGs with ≥3 double bonds, have a decreased risk of ER+ breast cancer. This result corresponds with the MSEA findings for the distant time point that TAGs ≥3 double bonds are positively associated with ER+ breast cancer risk, and glycerophospholipids are inversely associated with risk (**Figure 1.2**).

While glycerophospholipids as a group were not significantly associated with ER+ breast cancer in MSEA, our significant results from the WGCNA highlight the importance of a few key glycerophospholipids including C20:4 LPC (OR comparing 90th to 10th percentile=0.66, 95% CI=0.50-0.88, p=0.004) and C18:2 LPC (OR =0.64, 95% CI=0.47-0.87, p=0.005) (ORs from Supplemental Table 1.3). At the proximate time point, no modules were associated with breast cancer risk for overall, ER+, or ER- breast cancer. Despite this, associative patterns that arose in module groupings appeared to align with MSEA results; for example, metabolite module M3 (Supplemental Table 1.6), defined by positively weighted amino acids and negatively weighted TAGs with high double bonds, was positively associated with breast cancer risk, which is expected given the associations seen for these groups of metabolites at the proximate time point (Figure 1.2).

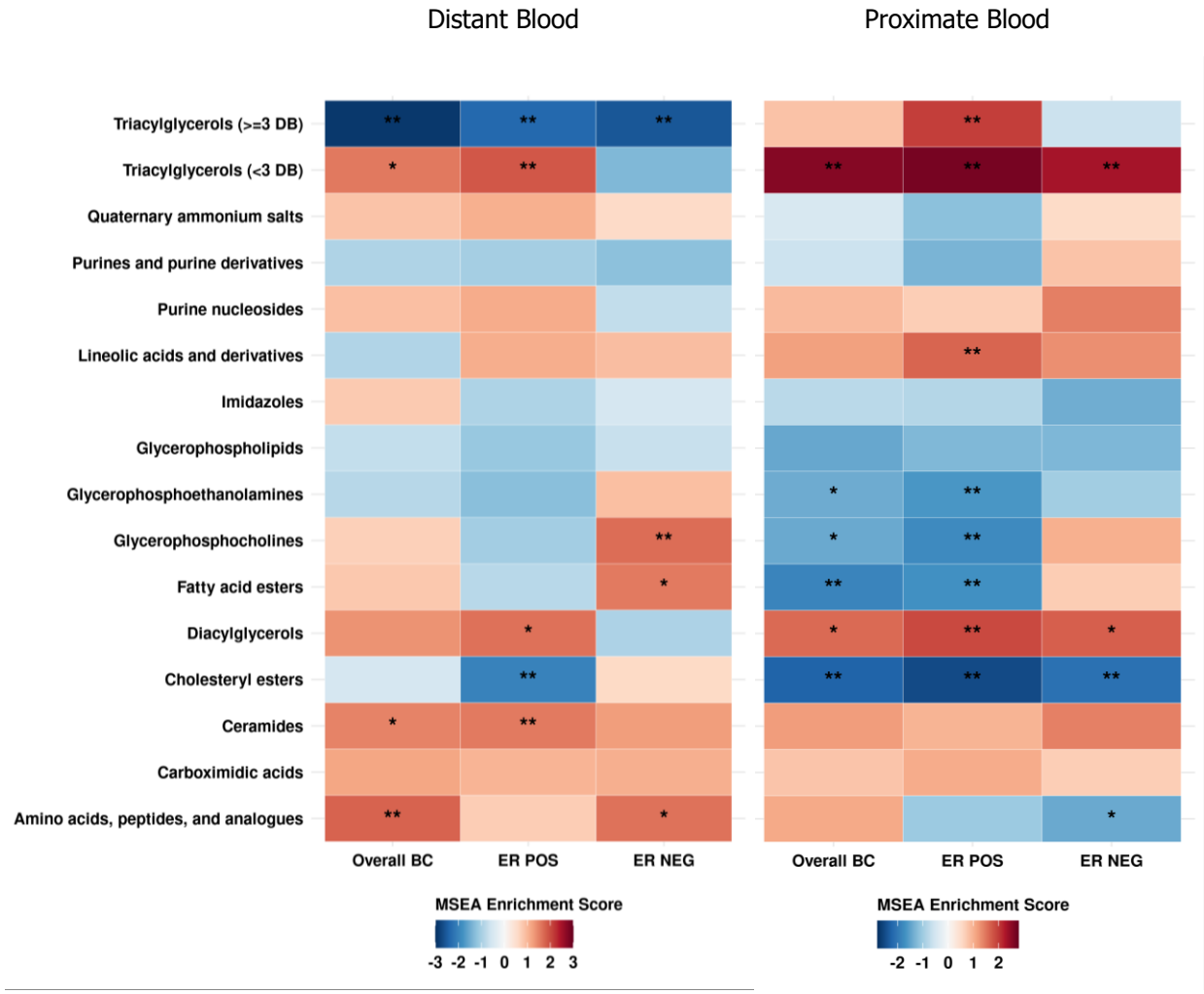

Figure 1.2. Gene set enrichment analysis by subclass of metabolites for overall, ER+, and ER- breast cancer, distant (≥10y before dx) & proximate blood (<10y before dx). Overall breast cancer results use conditional logistic regression; ER status specific models use unconditional logistic regression models adjusted for matched factors. Models are fully adjusted for the following: BMI at age 18, weight change from age 18 to blood draw, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (MET-hrs/week). Stars denote p-values adjusted by FDR: * (padj <0.2); ** (padj<0.05). Darker blue is a more negative enrichment score; darker red is a more positive enrichment score.

Average & Difference between distant and proximate blood draws

Metabolites with the most significant difference measures between blood draws included TAGs with ≥3 double bonds appeared at the top of the list (**Table 1.4**). A 2.5 SD increase in TAGs with ≥3 db from distant to proximate blood measure was associated with a reduced risk of breast cancer (e.g.: for C56:10 TAG OR=0.62, 95% CI=0.43-0.88; nominal p-value=0.007).

To determine if averaging metabolite levels across 10 years was appropriate, metabolite correlations between the two time points were analyzed. The majority showed a spearman correlation between 0.4-0.5 (**Supplemental Table 1.8 & Supplemental Figure 1.3**). Analysis of metabolite associations with breast cancer risk taking the average of both time points revealed similarities with individual time point analyses, though some metabolite associations were somewhat weakened based on opposing associations, while others were strengthened by consistent associations (**Supplemental Table 1.9**). MSEA analysis of average values highlighted the strong inverse association seen for cholesteryl esters (**Supplemental Figure 1.4**), and the strong positive association seen for TAGS with <3 double bonds. However, TAGS with ≥3 double bonds showed strongly inverse associations for overall and ER- BC on average, but null associations with ER+ breast cancer, due to opposing directions of association at distant and proximate bloods.

Cross-classification and latency analyses

The cross-classification analysis draws attention to several metabolites that were noteworthy in both measurements. Cross-classification of selected metabolites based on comparison to median values at each time point are included in **Table 1.5**. Metabolites shown are those that appeared as a top hit (nominal p-value for individual metabolite analysis at least one time point<0.05). Additional metabolites were assessed if they appeared with a p-value <0.05 in the difference analysis (see Table 1.4). Further, metabolites with strong associations (p<0.01) in cross-classification analysis were examined; those that demonstrated differing associations with breast cancer based on time of measurement were also included.

Phenylalanine, which appeared positively associated with breast cancer at both distant and proximate time points, demonstrated a strong positive association with breast cancer for individuals with

levels that were equal to or above the median value at both time points (OR=1.52, 95% CI=1.06-2.04, p=0.01). This was also true for those who had measured phenylalanine ≥ median value at either time point, solidifying the results that this metabolite is positively associated with breast cancer regardless of time of measurement. The triacylglycerol C58:11 TAG demonstrated a significant inverse association with breast cancer when considering an increase in metabolite level over time compared to a consistently low metabolite level (OR=0.66, 95% CI=0.46-0.94), but a null association with breast cancer for a decrease in metabolite level (OR=1.27, 95% CI=0.88-1.82). This mirrors general findings in individual analyses suggesting TAGs with high numbers of double bonds are protective against breast cancer at the proximate time point.

The latency analysis revealed that for most metabolites deemed important at either time point, or in difference analysis, the proximate time point contributed more strongly to breast cancer risk (**Table 1.6**). The dampening parameter λ based on the linear model was positive for all metabolites previously acknowledged as top hits, and 23 of 59 had significant p-values. For example, for triacylglycerol C56:7 TAG λ=0.07 and p=0.02. This general finding matches the positive ORs seen when examining the difference analysis for each of these metabolites (see Table 1.4). None of the metabolites appeared to follow a quadratic model for latency. Apart from those metabolites highlighted in Table 1.7 and 1.7b, our findings demonstrate similar associations by time point, with the proximate time point as the strongest determinant of association with breast cancer.

Table 1.4. Odds ratios for breast cancer risk for 2.5-unit SD difference in proximate-distant metabolite measures for metabolites with nominal p-value <0.05.

Metabolite	HMDB ID	Class	Subclass	OR (95% CI)	p value	Spearman correlation†
N-alpha-acetylarginine	HMDB0004620	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.86 (1.25-2.78)	0.002	0.461
2-aminooctanoic acid	HMDB0000991	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.67 (0.48-0.93)	0.019	0.502
aminoisobutyric acid	HMDB0001906	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.65 (0.45-0.93)	0.020	0.412
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.43 (1.01-2.03)	0.044	0.403
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	1.47 (1.03-2.11)	0.033	0.351
C58:9 TAG	HMDB0005463	Glycerolipids	Triacylglycerols	0.60 (0.42-0.85)	0.004	0.380
C56:9 TAG	HMDB0005448	Glycerolipids	Triacylglycerols	0.60 (0.42-0.86)	0.005	0.487
C58:11 TAG	HMDB0010531	Glycerolipids	Triacylglycerols	0.60 (0.42-0.86)	0.005	0.301
C56:10 TAG	HMDB0010513	Glycerolipids	Triacylglycerols	0.62 (0.43-0.88)	0.007	0.374
C56:7 TAG	HMDB0005462	Glycerolipids	Triacylglycerols	0.62 (0.43-0.88)	0.008	0.495
C58:7 TAG	HMDB0005471	Glycerolipids	Triacylglycerols	0.64 (0.45-0.90)	0.010	0.416
C56:8 TAG	HMDB0005392	Glycerolipids	Triacylglycerols	0.64 (0.46-0.90)	0.010	0.432
C54:8 TAG	HMDB0010518	Glycerolipids	Triacylglycerols	0.65 (0.46-0.91)	0.013	0.463
C54:9 TAG	HMDB0010498	Glycerolipids	Triacylglycerols	0.65 (0.46-0.92)	0.015	0.545
C58:10 TAG	HMDB0005476	Glycerolipids	Triacylglycerols	0.64 (0.45-0.92)	0.015	0.549

Table 1.4 (continued). Odds ratios for breast cancer risk for 2.5-unit SD difference in proximate-distant metabolite measures

C60:12 TAG	HMDB0005478	Glycerolipids	Triacylglycerols	0.64 (0.45-0.92)	0.017	0.548
C58:8 TAG	HMDB0005413	Glycerolipids	Triacylglycerols	0.67 (0.48-0.95)	0.023	0.455
C52:7 TAG	HMDB0010517	Glycerolipids	Triacylglycerols	0.68 (0.48-0.97)	0.032	0.383
C58:6 TAG	HMDB0005458	Glycerolipids	Triacylglycerols	0.70 (0.49-0.98)	0.037	0.433
C54:7 TAG	HMDB0005447	Glycerolipids	Triacylglycerols	0.71 (0.51-0.99)	0.045	0.467
C18:1 LPC	HMDB0002815	Glycerophospho-lipids	Glycerophosphocholines	1.47 (1.06-2.06)	0.022	0.493
C18:0 LPC	HMDB0010384	Glycerophospho-lipids	Glycerophosphocholines	1.45 (1.05-2.01)	0.026	0.499
C40:9 PC	HMDB0008731	Glycerophospho-lipids	Glycerophosphocholines	0.67 (0.46-0.98)	0.039	0.426
C38:6 PC	HMDB0007991	Glycerophospho-lipids	Glycerophosphocholines	0.67 (0.46-0.98)	0.040	0.490
C18:3 LPC	HMDB0010387	Glycerophospho-lipids	Glycerophosphocholines	1.38 (1.01-1.90)	0.047	0.487
C38:6 PE	HMDB0009102	Glycerophospho-lipids	Glycerophosphoethanol-amines	0.64 (0.44-0.92)	0.017	0.522
C22:0 LPE	HMDB0011520	Glycerophospho-lipids	Glycerophosphoethanol-amines	1.44 (1.03-2.03)	0.035	0.434
C20:1 LPE	HMDB0011512	Glycerophospho-lipids	Glycerophosphoethanol-amines	1.40 (1.00-1.94)	0.048	0.420
C22:6 LPE	HMDB0011526	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.70 (0.49-1.00)	0.048	0.457

tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	1.42 (1.02-1.98)	0.039	0.467
ribothymidine	HMDB0000884	Pyrimidine nucleosides	Pyrimidine nucleosides	1.49 (1.03-2.16)	0.033	0.502
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	Ceramides	1.57 (1.12-2.20)	0.009	0.370
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	Ceramides	1.48 (1.04-2.12)	0.030	0.505
C24:1 Ceramide (d18:1)	HMDB0004953	Sphingolipids	Ceramides	1.44 (1.01-2.04)	0.043	0.655
C18:3 CE	HMDB0010370	Steroids and steroid derivatives	Cholesteryl esters	1.53 (1.07-2.19)	0.021	0.548
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesteryl esters	1.44 (1.04-2.02)	0.030	0.395

* Representative HMDBID

^ All models adjusted for distant blood measure. Estimate is for difference proximate-distant blood measure. Results are sorted by class, subclass, and p-value for Model 2. ORs are for unconditional logistic regressions adjusted for BMI at age 18, weight change from 18 to blood draw, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week). P values are nominal p-values before correction for multiple testing.

† Correlations between proximate and distant time point, adjusted for fasting status and age at blood draw

Table 1.5. Multivariate adjusted odds ratios† for breast cancer risk comparing cross-classification of metabolite levels as below or above/equal to the median value at distant and proximate timepoints for metabolites identified as top hits at either time point, or identified in difference analyisis with $p<0.05$.

			Low-Low	Increase^		Decrease^		High-High		
Metabolite Name	**HMDB ID**	**Class**	OR (95% CI)	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value	Sp‡
Identified as top hits at either time point										
N1,N12-diacetyl-spermine	HMDB0002172	Carboximidic acids and derivatives	1.0 (ref)	1.07 (0.75-1.52)	0.71	1.00 (0.71-1.41)	0.99	1.41 (1.06-1.88)	0.02	0.49
betaine	HMDB0000043	Carboxylic acids and derivatives	1.0 (ref)	1.22 (0.86-1.73)	0.27	1.14 (0.80-1.62)	0.48	1.11 (1.06-1.49)	0.49	0.47
homoarginine	HMDB0000670*	Carboxylic acids and derivatives	1.0 (ref)	1.12 (0.78-1.60)	0.55	1.42 (0.99-2.04)	0.06	1.11 (1.06-1.48)	0.46	0.52
isoleucine	HMDB0000172	Carboxylic acids and derivatives	1.0 (ref)	1.41 (1.00-2.00)	0.05	1.22 (0.87-1.72)	0.25	1.41 (1.06-1.89)	0.02	0.37
leucine	HMDB0000687	Carboxylic acids and derivatives	1.0 (ref)	1.23 (0.87-1.75)	0.24	1.10 (0.78-1.56)	0.58	1.28 (1.06-1.71)	0.09	0.37
lysine	HMDB0000182	Carboxylic acids and derivatives	1.0 (ref)	0.92 (0.65-1.30)	0.62	1.15 (0.81-1.62)	0.44	1.32 (0.06-1.77)	0.06	0.44
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	1.0 (ref)	1.01 (0.67-1.52)	0.96	0.90 (0.60-1.35)	0.61	0.79 (1.06-1.03)	0.08	0.73
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	1.0 (ref)	1.30 (0.89-1.90)	0.18	0.82 (0.56-1.19)	0.29	1.07 (1.06-1.41)	0.62	0.65
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	1.0 (ref)	1.45 (1.03-2.05)	0.03	1.41 (1.00-2.00)	0.05	1.52 (1.06-2.04)	0.01	0.33
proline	HMDB0000162	Carboxylic acids and derivatives	1.0 (ref)	1.53 (1.08-2.17)	0.02	1.16 (0.82-1.66)	0.40	1.28 (1.06-1.71)	0.10	0.46
serine	HMDB0000187	Carboxylic acids and derivatives	1.0 (ref)	1.22 (0.86-1.72)	0.27	1.26 (0.89-1.78)	0.20	1.13 (1.06-1.52)	0.40	0.42

Table 1.5 (continued). Multivariate adjusted odds ratios† for breast cancer risk comparing cross-classification of metabolite levels

C5:1 carnitine	HMDB0002366	Fatty Acyls	1.0 (ref)	1.27 (0.89-1.81)	0.18	0.89 (0.63-1.27)	0.53	0.93 (1.06-1.24)	0.62	0.46
C5-DC carnitine	HMDB0013130	Fatty Acyls	1.0 (ref)	0.92 (0.63-1.35)	0.69	0.88 (0.60-1.30)	0.52	0.81 (0.06-1.06)	0.13	0.63
myristoleic acid	HMDB0002000	Fatty Acyls	1.0 (ref)	1.06 (0.75-1.51)	0.74	0.89 (0.62-1.28)	0.53	1.21 (1.06-1.61)	0.19	0.50
C51:0 TAG	HMDB0031106*	Glycerolipids	1.0 (ref)	1.13 (0.80-1.58)	0.49	1.13 (0.80-1.58)	0.50	1.27 (1.06-1.71)	0.11	0.31
C52:6 TAG	HMDB0005436*	Glycerolipids	1.0 (ref)	0.78 (0.54-1.11)	0.17	0.91 (0.64-1.31)	0.62	1.00 (0.06-1.33)	1.00	0.47
C52:7 TAG	HMDB0010517*	Glycerolipids	1.0 (ref)	0.66 (0.46-0.93)	0.02	1.03 (0.72-1.46)	0.89	0.94 (0.06-1.26)	0.70	0.46
C54:7 TAG	HMDB0005447*	Glycerolipids	1.0 (ref)	0.68 (0.48-0.96)	0.03	1.08 (0.76-1.52)	0.67	0.86 (0.06-1.16)	0.34	0.38
C54:8 TAG	HMDB0010518*	Glycerolipids	1.0 (ref)	0.62 (0.43-0.88)	0.01	1.01 (0.71-1.44)	0.96	0.86 (0.06-1.15)	0.31	0.43
C54:9 TAG	HMDB0010498*	Glycerolipids	1.0 (ref)	0.65 (0.46-0.93)	0.02	1.11 (0.78-1.58)	0.57	0.77 (0.06-1.02)	0.07	0.47
C56:10 TAG	HMDB0010513*	Glycerolipids	1.0 (ref)	0.78 (0.55-1.11)	0.17	1.21 (0.84-1.73)	0.30	0.88 (0.06-1.17)	0.37	0.49
C56:7 TAG	HMDB0005462*	Glycerolipids	1.0 (ref)	0.60 (0.42-0.86)	0.01	0.82 (0.57-1.17)	0.27	1.07 (0.06-1.43)	0.65	0.50
C56:8 TAG	HMDB0005392*	Glycerolipids	1.0 (ref)	0.76 (0.53-1.06)	0.11	1.12 (0.79-1.58)	0.52	1.00 (0.06-1.34)	0.99	0.43
C56:9 TAG	HMDB0005448*	Glycerolipids	1.0 (ref)	0.67 (0.47-0.95)	0.02	0.92 (0.65-1.31)	0.65	0.91 (0.06-1.22)	0.54	0.49
C58:10 TAG	HMDB0005476*	Glycerolipids	1.0 (ref)	0.97 (0.68-1.37)	0.85	1.36 (0.95-1.93)	0.09	0.87 (0.06-1.17)	0.36	0.49
C58:11 TAG	HMDB0010531*	Glycerolipids	1.0 (ref)	0.66 (0.46-0.94)	0.02	1.27 (0.88-1.82)	0.20	0.85 (0.06-1.13)	0.28	0.52
C58:6 TAG	HMDB0005458*	Glycerolipids	1.0 (ref)	0.70 (0.49-1.00)	0.05	0.92 (0.65-1.32)	0.66	0.89 (0.06-1.20)	0.44	0.43
C58:7 TAG	HMDB0005471*	Glycerolipids	1.0 (ref)	0.72 (0.51-1.02)	0.07	1.19 (0.83-1.69)	0.35	0.83 (0.06-1.11)	0.22	0.42
C58:9 TAG	HMDB0005463*	Glycerolipids	1.0 (ref)	1.05 (0.74-1.49)	0.77	1.43 (1.01-2.04)	0.04	0.89 (1.06-1.18)	0.41	0.47

Table 1.5 (continued). Multivariate adjusted odds ratios† for breast cancer risk comparing cross-classification of metabolite levels

C60:12 TAG	HMDB0005478*	Glycerolipids	1.0 (ref)	0.89 (0.63-1.27)	0.52	1.15 (0.81-1.64)	0.44	0.91 (0.06-1.21)	0.53	0.50
C16:0 LPC	HMDB0010382	Glycerophospholipids	1.0 (ref)	1.07 (0.76-1.51)	0.69	0.97 (0.69-1.36)	0.85	1.25 (1.06-1.68)	0.14	0.30
C16:1 LPC	HMDB0010383*	Glycerophospholipids	1.0 (ref)	1.22 (0.86-1.72)	0.27	1.16 (0.82-1.64)	0.40	1.34 (1.06-1.79)	0.05	0.38
C18:1 LPC	HMDB0002815*	Glycerophospholipids	1.0 (ref)	1.08 (0.76-1.53)	0.68	0.75 (0.53-1.06)	0.11	1.08 (1.06-1.44)	0.61	0.38
C18:3 LPC	HMDB0010387*	Glycerophospholipids	1.0 (ref)	1.11 (0.79-1.56)	0.55	1.08 (0.77-1.52)	0.64	1.33 (1.06-1.79)	0.06	0.30
C22:0 LPE	HMDB0011520	Glycerophospholipids	1.0 (ref)	1.48 (1.04-2.12)	0.03	0.90 (0.63-1.27)	0.53	0.78 (1.06-1.04)	0.09	0.42
C22:5 LPC	HMDB0010403*	Glycerophospholipids	1.0 (ref)	1.00 (0.71-1.41)	0.98	0.71 (0.51-1.00)	0.05	0.83 (1.06-1.12)	0.22	0.40
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospholipids	1.0 (ref)	1.08 (0.77-1.53)	0.64	1.01 (0.72-1.41)	0.96	0.86 (1.06-1.16)	0.33	0.40
tryptophan	HMDB0000929	Indoles and derivatives	1.0 (ref)	1.35 (0.95-1.92)	0.10	0.98 (0.69-1.39)	0.92	1.11 (1.06-1.48)	0.49	0.40
thyroxine	HMDB0000248	NA	1.0 (ref)	0.99 (0.69-1.41)	0.95	1.35 (0.95-1.92)	0.09	1.25 (0.06-1.67)	0.12	0.41
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	1.0 (ref)	1.36 (0.96-1.93)	0.08	1.26 (0.89-1.79)	0.19	1.53 (1.06-2.05)	0.00	0.43
2-methylguanosine	HMDB0005862	Purine nucleosides	1.0 (ref)	1.22 (0.87-1.71)	0.24	1.44 (1.03-2.02)	0.03	1.45 (1.06-1.99)	0.02	0.24
guanosine	HMDB0000133	Purine nucleosides	1.0 (ref)	1.13 (0.81-1.57)	0.48	0.77 (0.55-1.07)	0.13	0.75 (1.06-1.03)	0.08	0.19
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	1.0 (ref)	1.70 (1.20-2.42)	0.00	1.51 (1.06-2.14)	0.02	1.39 (1.06-1.87)	0.03	0.41
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	1.0 (ref)	1.29 (0.91-1.85)	0.15	1.03 (0.72-1.46)	0.87	1.37 (1.06-1.83)	0.03	0.49
C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	1.0 (ref)	1.34 (0.94-1.91)	0.10	1.17 (0.83-1.67)	0.37	1.42 (1.06-1.91)	0.02	0.46
C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	1.0 (ref)	1.11 (0.78-1.57)	0.58	0.86 (0.60-1.23)	0.42	0.85 (1.06-1.13)	0.26	0.49
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	1.0 (ref)	0.84 (0.59-1.20)	0.34	0.86 (0.61-1.23)	0.41	0.67 (0.06-0.89)	0.01	0.48

Table 1.5 (continued). Multivariate adjusted odds ratios† for breast cancer risk comparing cross-classification of metabolite levels

C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	1.0 (ref)	1.24 (0.87-1.78)	0.24	0.86 (0.60-1.24)	0.42	0.78 (1.06-1.04)	0.09	0.47
Identified in difference analysis with significant interaction										
2-aminooctanoic acid	HMDB0000991	Carboxylic acids and derivatives	1.0 (ref)	0.86 (0.60-1.24)	0.43	0.62 (0.43-0.89)	0.01	0.98 (0.74-1.29)	0.88	0.46
amino-isobutyric acid	HMDB0001906	Carboxylic acids and derivatives	1.0 (ref)	0.90 (0.63-1.27)	0.54	1.15 (0.54-1.63)	0.43	0.97 (0.73-1.30)	0.84	0.50
C58:8 TAG	HMDB0005413	Glycerolipids	1.0 (ref)	1.38 (0.98-1.95)	0.07	0.82 (0.07-1.15)	0.25	1.00 (0.75-1.34)	0.99	0.46
C18:0 LPC	HMDB0010384	Glycerophospholipids	1.0 (ref)	0.77 (0.54-1.10)	0.16	1.56 (0.16-2.24)	0.01	0.96 (0.72-1.28)	0.77	0.35
C20:1 LPE	HMDB0011512	Glycerophospholipids		0.80 (0.56-1.15)	0.23	1.59 (0.23-2.28)	0.01	1.13 (0.84-1.50)	0.42	0.37
C22:6 LPE	HMDB0011526	Glycerophospholipids	1.0 (ref)	0.85 (0.59-1.22)	0.39	1.35 (0.39-1.94)	0.10	1.15 (0.87-1.53)	0.33	0.43
C38:6 PC	HMDB0007991	Glycerophospholipids	1.0 (ref)	0.93 (0.65-1.32)	0.67	1.49 (0.67-2.14)	0.03	1.05 (0.79-1.41)	0.74	0.55
C38:6 PE	HMDB0009102	Glycerophospholipids	1.0 (ref)	1.04 (0.74-1.47)	0.82	0.92 (0.82-1.30)	0.63	0.92 (0.68-1.22)	0.55	0.55
C40:9 PC	HMDB0008731	Glycerophospholipids	1.0 (ref)	1.01 (0.71-1.42)	0.96	0.78 (0.96-1.09)	0.15	0.91 (0.67-1.22)	0.51	0.55
ribothymidine	HMDB0000884	Pyrimidine nucleosides	1.0 (ref)	1.07 (0.76-1.51)	0.70	0.98 (0.70-1.39)	0.93	0.96 (0.72-1.29)	0.79	0.55
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	1.0 (ref)	0.90 (0.63-1.29)	0.56	1.27 (0.56-1.83)	0.19	1.06 (0.80-1.40)	0.71	0.40

† Multivariate regression models include: BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week). P values are nominal p-values before correction for multiple testing.

^ All models compared to group with metabolites remaining below the median at both time points

* Representative HMDBID

ǂ Spearman correlation between proximate and distant blood draw measures, adjusted for fasting status and age at blood draw, and weight change from age 18 to blood draw.

Table 1.6. Latency analysis based on linear & quadratic multivariate adjusted models,[†] for metabolites with nominal p-values <0.05 in individual analyses or significant interaction in difference analyses.

			Linear model^		**Quadratic model^**			
Metabolite Name	**HMDB ID**	**Class**	**λ**	**p value**	**λ1**	**p value (λ1)**	**λ2**	**p value (λ2)**
Identified by nominal p-value in individual analysis								
N1,N12-diacetyl-spermine	HMDB0002172	Carboximidic acids and derivatives	0.054	0.013	-0.044	0.886	0.004	0.612
betaine	HMDB0000043	Carboxylic acids and derivatives	0.063	0.031	0.083	0.324	-0.001	0.584
homoarginine	HMDB0000670*	Carboxylic acids and derivatives	0.156	0.419	0.427	0.831	-0.019	0.714
isoleucine	HMDB0000172	Carboxylic acids and derivatives	0.101	0.181	0.126	0.302	-0.004	0.203
leucine	HMDB0000687	Carboxylic acids and derivatives	0.069	0.023	0.111	0.645	-0.004	0.540
lysine	HMDB0000182	Carboxylic acids and derivatives	0.025	0.821	0.152	0.541	-0.004	0.510
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	0.069	0.101	0.110	0.848	-0.001	0.946
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	0.041	0.156	0.095	0.024	-0.002	0.089
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	0.015	0.818	0.320	0.620	-0.009	0.579
proline	HMDB0000162	Carboxylic acids and derivatives	0.412	0.638	0.115	0.207	-0.003	0.172
serine	HMDB0000187	Carboxylic acids and derivatives	0.026	0.749	0.133	0.087	-0.004	0.074
C5:1 carnitine	HMDB0002366	Fatty Acyls	0.108	0.577	0.093	0.027	-0.002	0.078
C5-DC carnitine	HMDB0013130	Fatty Acyls	0.052	0.383	0.062	0.793	0.001	0.919

Table 1.6 (continued). Latency analysis based on linear & quadratic multivariate adjusted models

myristoleic acid	HMDB0002000	Fatty Acyls	0.047	0.074	0.137	0.462	-0.005	0.337
C51:0 TAG	HMDB0031106*	Glycerolipids	-0.003	0.985	0.104	0.333	-0.003	0.325
C52:6 TAG	HMDB0005436*	Glycerolipids	0.056	0.424	0.104	0.167	-0.002	0.262
C52:7 TAG	HMDB0010517*	Glycerolipids	0.076	0.131	0.107	0.115	-0.002	0.182
C54:7 TAG	HMDB0005447*	Glycerolipids	0.062	0.009	0.088	0.580	-0.001	0.796
C54:8 TAG	HMDB0010518*	Glycerolipids	0.072	0.082	0.089	0.536	-0.001	0.760
C54:9 TAG	HMDB0010498*	Glycerolipids	0.063	0.021	0.098	0.481	-0.002	0.659
C56:10 TAG	HMDB0010513*	Glycerolipids	0.057	0.007	0.075	0.719	0.000	0.969
C56:7 TAG	HMDB0005462*	Glycerolipids	0.065	0.024	0.024	0.926	0.002	0.739
C56:8 TAG	HMDB0005392*	Glycerolipids	0.071	0.069	0.264	0.554	-0.012	0.318
C56:9 TAG	HMDB0005448*	Glycerolipids	0.062	0.002	-0.596	0.800	0.042	0.505
C58:10 TAG	HMDB0005476*	Glycerolipids	0.068	0.027	0.181	0.551	-0.008	0.352
C58:11 TAG	HMDB0010531*	Glycerolipids	0.071	0.137	-0.874	0.823	0.062	0.557
C58:6 TAG	HMDB0005458*	Glycerolipids	0.082	0.175	0.152	0.666	-0.006	0.515
C58:7 TAG	HMDB0005471*	Glycerolipids	0.073	0.088	1.013	0.849	-0.073	0.611
C58:9 TAG	HMDB0005463*	Glycerolipids	0.070	0.124	0.224	0.468	-0.010	0.248
C60:12 TAG	HMDB0005478*	Glycerolipids	0.083	0.227	0.158	0.266	-0.006	0.145

Table 1.6 (continued). Latency analysis based on linear & quadratic multivariate adjusted models

C16:0 LPC	HMDB0010382	Glycerophospholipids	0.064	0.077	0.092	0.191	-0.002	0.365
C16:1 LPC	HMDB0010383*	Glycerophospholipids	0.055	0.002	0.109	0.239	-0.003	0.309
C18:1 LPC	HMDB0002815*	Glycerophospholipids	0.105	0.250	0.089	0.139	-0.002	0.327
C18:3 LPC	HMDB0010387*	Glycerophospholipids	0.051	0.013	0.097	0.102	-0.002	0.209
C22:0 LPE	HMDB0011520	Glycerophospholipids	0.069	0.063	0.087	0.064	-0.002	0.203
C22:5 LPC	HMDB0010403*	Glycerophospholipids	0.078	0.314	0.082	0.210	-0.001	0.443
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospholipids	0.072	0.064	0.100	0.277	-0.002	0.345
tryptophan	HMDB0000929	Indoles and derivatives	0.075	0.244	0.160	0.281	-0.006	0.145
thyroxine	HMDB0000248	NA	0.052	0.003	0.078	0.240	-0.001	0.474
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	0.047	0.105	0.159	0.118	-0.005	0.063
2-methylguanosine	HMDB0005862	Purine nucleosides	0.062	0.016	0.073	0.479	-0.001	0.633
guanosine	HMDB0000133	Purine nucleosides	0.053	0.194	0.140	0.115	-0.004	0.076
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	0.042	0.510	0.113	0.268	-0.002	0.370
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	0.063	0.030	0.092	0.359	-0.001	0.561
C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	0.058	0.004	0.112	0.045	-0.003	0.074

Table 1.6 (continued). Latency analysis based on linear & quadratic multivariate adjusted models

C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	0.076	0.089	0.071	0.275	-0.001	0.650
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	0.064	0.027	0.099	0.207	-0.002	0.251
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	0.071	0.095	0.048	0.639	0.000	0.966
Identified in difference analysis with significant interaction								
2-aminooctanoic acid	HMDB0000991	Carboxylic acids and derivatives	0.061	0.079	0.099	0.072	-0.002	0.132
aminoisobutyric acid	HMDB0001906	Carboxylic acids and derivatives	0.060	0.002	0.032	0.820	0.002	0.682
C58:8 TAG	HMDB0005413	Glycerolipids	0.059	0.037	0.161	0.183	-0.006	0.084
C18:0 LPC	HMDB0010384	Glycerophospholipids	0.059	0.003	0.080	0.187	-0.001	0.469
C20:1 LPE	HMDB0011512	Glycerophospholipids	0.061	0.094	0.099	0.146	-0.002	0.238
C22:6 LPE	HMDB0011526	Glycerophospholipids	0.061	0.117	1.444	0.754	-0.078	0.524
C38:6 PC	HMDB0007991	Glycerophospholipids	0.062	0.028	0.253	0.474	-0.011	0.243
C38:6 PE	HMDB0009102	Glycerophospholipids	0.062	0.020	0.055	0.713	0.000	0.910
C40:9 PC	HMDB0008731	Glycerophospholipids	0.064	0.034	0.247	0.504	-0.011	0.271
ribothymidine	HMDB0000884	Pyrimidine nucleosides	0.062	0.006	0.207	0.306	-0.008	0.118
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	0.058	0.073	0.077	0.459	-0.001	0.703

† Multivariate regression models include: BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week). P values are nominal p-values before correction for multiple testing. See methods for dampening models (linear v quadratic).

^ Linear and quadratic models are defined in the Methods section

* Representative HMDBID

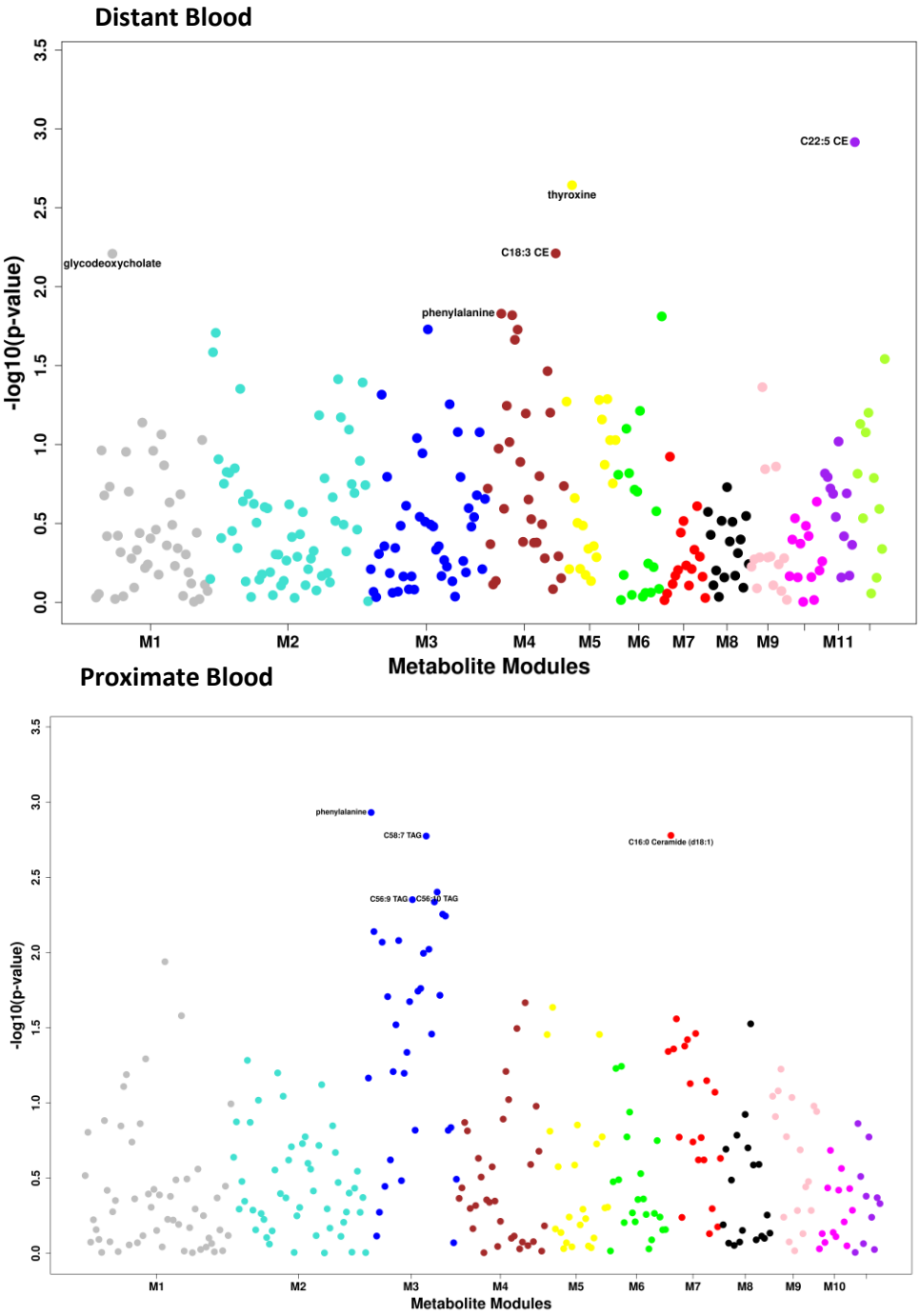

Figure 1.3. Metabolite associations with overall breast cancer risk (by Module grouping) at distant (top) and proximate (bottom) blood.

DISCUSSION

In this prospective cohort study examining the association between 307 plasma metabolites and risk of breast cancer, we identified several metabolite groups, defined based on similar biochemical structure, that were associated with breast cancer risk. Individual metabolites did not reach statistical significance with correction for multiple comparisons in our analyses; however, associations informed a deeper dive into the interconnectedness of metabolites and consequent associations. Examined by subclass, cholesteryl esters were associated with a reduced risk of breast cancer, whereas amino acids and derivatives were associated with increased breast cancer risk. The association between breast cancer and the subclass TAGs was seemingly dependent on double bond status; TAGs with ≥3 double bonds, i.e., highly unsaturated, were inversely associated, while TAGs with <3 double bonds were positively associated with risk. The unique ability to assess metabolite measures at two different time points also highlighted the potential for metabolites to independently influence different stages of breast cancer development, as several associations appeared to change based on time between blood draw and diagnosis.

Our results add novel knowledge and provide support for several findings from other similar agnostic metabolomic approaches. For example, a nested case-control study in EPIC (with 1,624 cases), examined 127 metabolites in prediagnostic samples, where diagnosis ≥2 years post-measurement.[9] While we did not see exact similarities between individual metabolite results in EPIC and our study, we did notice associations on the metabolite class level tended to concur. For example, we did not observe an inverse association between C2 carnitine and breast cancer as seen in EPIC, though we did observe an inverse association between high levels of carnitines and risk in general, with C5-DC carnitine appearing inversely related to breast cancer with a nominal p value <0.05 at both collected blood samples. This finding for carnitines was also supported in a recent study looking at 1,275 metabolites in prediagnostic serum in a nested case-control study of 782 postmenopausal breast cancer cases and controls within the Cancer Prevention Study 2,[3] in which acyl fatty acid derivatives of carnitine were inversely associated with risk. The carnitine system has been implicated in enhancing metabolic flexibility needed in cancer cells,[19] and the importance of carnitine in breast cancer development should be examined further.

Phosphatidylcholines appeared inversely associated with risk in EPIC; we found nominally significant inverse association between several glycerophosphocholines (which are derivatives of phosphatidylcholines) and risk, especially for ER+ breast cancer. This is interesting considering dietary intake of choline, including choline intake from glycerophosphocholines, was found to be inversely related to breast cancer risk in a Chinese case-control study.[20] Corresponding to this finding, in an earlier study within the EPIC-Heidelberg cohort, Kuhn et. al. found higher levels of lysophosphatidylcholines (lysoPCs) were associated with decreased breast cancer risk,[6] which was suggestive, though not statistically significant, in our study (e.g.: C18:0 LPC OR=0.78, 95% CI=0.6-1.01, p=0.06). In contrast, Moore et. al. found a positive association between glycerophosphocholines and breast cancer risk,[3] which was not mirrored in our study or in EPIC. The associations may be highly dependent on side chains of interest; because each study measured a slightly different set of metabolites, direct comparisons are impossible, though it appears this group may be important in breast cancer development.

Investigators in EPIC found an inverse association between arginine and breast cancer risk, which was not measured in our study. However, increased levels of the arginine derivative N-alpha-acetylarginine in our study were positively associated with risk (RR=1.45, 95% CI=1.06-2.00, p=0.02) for the proximate time point; this metabolite has been associated with oxidative stress in in vivo rat models.[21] With this joint evidence, we may consider the metabolism of arginine as a potential pathway of interest for breast cancer risk as well.

Yoo's study in the Korean Cancer Prevention Study II was of much smaller scale (N=84 cases), though their findings mimicked some of what we found. Overall, the authors found amino acid metabolism, fatty acid metabolism, and linoleic acid metabolism to differ between cases and controls.[8] Pathway analysis matched our finding that amino acid metabolism may be an important driver in breast cancer development (Figure 2). The authors observed an increased risk of breast cancer for higher expression of metabolites involved in phenylalanine, tyrosine, and tryptophan biosynthesis. It is interesting to note that downregulation of amino acid levels was apparent in cases at diagnosis compared to controls,[22,23] suggesting that the tumor-specific metabolic reprogramming focuses on use of amino acids. Perhaps a high level of amino acids many years prior to diagnosis provides a hospitable

environment for tumor cells that will later use these amino acids to drive their formation. In our analysis phenylalanine was one of the strongest hits at both the distant and proximate time points (e.g.: RR proximate blood=1.76, 95% CI=1.25-2.48, p=0.001). The importance of this metabolite may be further highlighted by the need for cancer cells to uptake phenylalanine to survive; in fact, a recent study used nanoparticles coated with phenylalanine to target and cause cancer cells to self-destruct.[24] Proline also appeared nominally significant in our analyses (RR proximate blood=1.59, 95% CI=1.13-2.22, p=0.007); this amino acid has been shown to play a key role in metabolic reprogramming important for cancer cell survival.[25] Further supporting our amino acid findings, plasma levels of amino acids including valine, lysine, arginine, glutamine were associated with increased breast cancer risk in SU.VI.MAX cohort. This study used untargeted NMR metabolomic profiles to assess 206 breast cancer cases and 396 controls.[5]

Remaining studies exploring circulating metabolites and breast cancer risk did not take an agnostic approach in identifying metabolites, and instead focused on nutritionally associated metabolites,[4,7] or BMI-associated metabolites.[2] Tobias et. al. examined BCAAs and obesity-related cancers, finding no associations with breast cancer risk.[4] In contrast, as we have reported separately,[14] we found nominally significantly increased risk of breast cancer with branched-chain amino acids valine, leucine, and isoleucine at the proximate blood (Supplemental Table 1b). In Moore's BMI-associated metabolite analysis within the Prostate, Lung, Colorectal, and Ovarian cancer screening (PLCO) cohort, acylcarnitines 3-methylglutarylcarnitine and 2-methylbutyrylcarnitine were associated with increased breast cancer risk,[2] contrasting with the finding of the agnostic analysis within CPS 2.[3] While our study generally agrees with the agnostic analysis, finding inverse associations with breast cancer risk for carnitines and derivatives, we did note a handful of carnitines that were positively associated with risk of breast cancer. Carnitines positive association with breast cancer may represent break down products of animal sources of protein. Higher levels of acylcarnitines have been associated with increased meat consumption, and higher blood concentrations may be indicative of changes in mitochondrial function and β-oxidation.[26,27] The combined evidence suggests a more complex relationship between the carnitine system and breast cancer risk.

Uniquely, in our study we observed a strong inverse association between cholesteryl esters as a subclass and breast cancer risk. Cholesteryl esters form the components of cholesterol, high density lipoprotein (HDL) and low-density lipoprotein (LDL), levels of which have been associated with risks of prostate[28] and breast cancer, [29] though epidemiologic evidence for these associations remain inconsistent.[30] In addition, laboratory studies and in vivo studies suggest cholesterol metabolism as a driver for breast cancer tumor growth.[31] Plasma levels of HDL and LDL are heavily influenced by the common medication statins, making them difficult to study independently; thus, it is notable that a mendelian randomization study found that genetically elevated HDL and LDL was associated with increased breast cancer risk.[32] The role of cholesteryl esters in lipid transport and lipid metabolism is of interest, as lipid metabolic reprogramming has been documented in cancer cells.[33] Our finding of an inverse association of cholesteryl esters with breast cancer risk was more notable at the distant time point. While the biologic basis for this difference over time is unclear, based on our results we hypothesize that women with more prominent cholesteryl ester profiles earlier in life may be more likely to benefit from their protective effect, making cholesterol metabolism across the life course an important avenue for further research.

A novel finding in our study, triacylglycerols were significantly associated with breast cancer risk, but in opposite directions depending on the size and number of carbon atom double bonds. Recent studies in the diabetes literature have shown that lipid composition is important in the association between lipids and diabetes.[34] This may be linked to the influence that TAGs have on insulin action; TAGs of low carbon atoms and low double bonds are associated with insulin resistance and consequently with diabetes, while TAGs of high carbon atoms and high double bonds are not typically represented in insulin resistant individuals and are more represented in individuals with normal insulin function.[34] Insulin signaling is a marker for metabolic health, which is a predictor of breast cancer risk.[35,36] Insulin signaling is responsible for activating the mitogen activated protein kinase (MAPK) and PI3K/Akt pathways, which promote cancer cell proliferation and invasion.[37] In addition, several TAGS with many double bonds and carbon atoms are associated with higher fish intake,[38] indicating a potential protective mechanism of dietary fish intake. More generally, polyunsaturated, omega-3, and omega-6 fatty acids are associated

with a higher alternative healthy eating index (AHEI) score,[39] further demonstrating potential of dietary intake to influence metabolite levels and future breast cancer risk. Again, we observed a difference in the relative importance of these measures when comparing distant and proximate blood timepoints. Women with high levels of TAGs with high double bond content at the proximal timepoint appeared to be at lower risk of breast cancer than women with similarly high levels at the distant time point. Conversely, women with high levels of TAGs with low double bond content at the distant time point had a higher risk of developing breast cancer than those women with high levels of TAGs with low double bond content at the proximal time point. In contrast to our findings, lower plasma levels of unsaturated lipids were associated with a higher risk of breast cancer in the SU.VI.MAX cohort.[5] Further research is needed to parse apart why these relationships change over time.

There are several differences between our study and previous studies evaluating metabolites and breast cancer risk. Importantly, the platforms used for metabolomic profiling are not directly comparable, which may account for the inconsistencies between studies.[3] Moreover, the timing of blood collections and median time from blood draw to diagnosis differed in these studies. Because we found differences between two blood collection time points and associations with risk, this may be an important factor for comparison. Studies with shorter median follow-up times may better capture the underlying tumor metabolic reprogramming as opposed to pre-tumorigenic factors contributing to risk, and this should be considered in interpretation.

There are several strengths of our study. First, we had the ability to control for covariates at the time of metabolite measure, as data were collected for all pertinent covariates every two years with follow-up questionnaires, and on blood draw specific questionnaires. We were thus able to have ample control for known breast cancer risk factors. Second, our study was the first to assess how metabolites associated with breast cancer change over time, with samples taken covering a period 0-20 years prior to cancer diagnosis. While others have examined lag-times between blood draw and diagnosis,[6,9] differences between time points have not been assessed. The measurement of metabolites on two separate platforms, and selection of measurement based on platform-specific performance was important in retrieving accurate metabolite profiles as well.

While the metabolomic platforms used for profiling were a strength of our study, these also represent a limitation in our ability to compare results to those of other studies using different methods. While we were able to assess by ER status of breast cancer, the small sample size for ER- breast cancers made it difficult to assess individual differences by ER status. We were unable to investigate premenopausal breast cancer, as most women in NHS were already postmenopausal by the second blood draw.

In conclusion, we found several metabolite subclasses that may be of further interest to explore with respect to etiology of breast cancer, including cholesteryl esters, amino acids, and TAGs. Moreover, our findings clarified some previous findings, supporting the idea that carnitine metabolism and glycerophosphocholines may be involved in reduction of breast cancer risk. Future studies will be needed to determine the intricacies of the biologic mechanisms contributing to breast cancer risk.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global Cancer Statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin, in press.

2. Moore SC. Metabolomics and breast cancer: scaling up for robust results. BMC Med. 2020 Jan 31;18(1):18.Moore SC, Playdon MC, Sampson JN, et al. A Metabolomics Analysis of Body Mass Index and Postmenopausal Breast Cancer Risk. *J Natl Cancer Inst*. 2018;110(6):588-597.

3. Moore SC, Mazzilli KM, Sampson JN, et al. A Metabolomics Analysis of Postmenopausal Breast Cancer Risk in the Cancer Prevention Study II. *Metabolites*. 2021;11(2).

4. Tobias DK, Hazra A, Lawler PR, et al. Circulating branched-chain amino acids and long-term risk of obesity-related cancers in women. *Sci Rep*. 2020;10(1):16534.

5. Lécuyer L, Victor Bala A, Deschasaux M, et al. NMR metabolomic signatures reveal predictive plasma metabolites associated with long-term risk of developing breast cancer. *Int J Epidemiol*. 2018;47(2):484-494.

6. Kühn T, Floegel A, Sookthai D, et al. Higher plasma levels of lysophosphatidylcholine 18:0 are related to a lower risk of common cancers in a prospective metabolomics study. *BMC Med*. 2016;14:13.

7. Playdon MC, Ziegler RG, Sampson JN, et al. Nutritional metabolomics and breast cancer risk in a prospective study. *Am J Clin Nutr*. 2017;106(2):637-649.

8. Yoo HJ, Kim M, Kim M, et al. Analysis of metabolites and metabolic pathways in breast cancer in a Korean prospective cohort: the Korean Cancer Prevention Study-II. Metabolomics. 2018;14(6):85.

9. His M, Viallon V, Dossus L, et al. Prospective analysis of circulating metabolites and breast cancer in EPIC. *BMC Medicine*. 2019;17(1):178.

10. Mascanfroni ID, Takenaka MC, Yeste A, et al. Metabolic control of type 1 regulatory T cell differentiation by AHR and HIF1-α. *Nat Med*. 2015;21(6):638-646.

11. O'Sullivan JF, Morningstar JE, Yang Q, et al. Dimethylguanidino valeric acid is a marker of liver fat and predicts diabetes. *J Clin Invest*. 2017;127(12):4394-4402.

12. Paynter, N.P., et al., Metabolic predictors of incident coronary heart disease in women. *Circulation*, 2018. 137(8): p. 841-853.

13. Townsend MK, Clish CB, Kraft P, et al. Reproducibility of metabolomic profiles among men and women in 2 large cohort studies. *Clin Chem*. 2013;59(11):1657-1667.

14. Zeleznik OA, Eliassen AH, Kraft P, et al. A Prospective Analysis of Circulating Plasma Metabolites Associated with Ovarian Cancer Risk. *Cancer Res*. 2020;80(6):1357-1367.

15. Gallois A, Mefford J, Ko A, et al. A comprehensive study of metabolite genetics reveals strong pleiotropy and heterogeneity across time and context. *Nature Communications*. 2019;10(1):4788.

16. Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. Biometrika. 2006;93(3):491–507

17. Langfelder P, Horvath S. WGCNA: an R package for weighted correlation network analysis. *BMC Bioinformatics*. 2008;9:559.

18. Langfelder P, Zhang B, Horvath S. Defining clusters from a hierarchical cluster tree: the Dynamic Tree Cut package for R. *Bioinformatics*. 2008;24(5):719-720.

19. Melone MAB, Valentino A, Margarucci S, Galderisi U, Giordano A, Peluso G. The carnitine system and cancer metabolic plasticity. *Cell Death Dis*. 2018;9(2):228.

20. Zhang C-X, Pan M-X, Li B, et al. Choline and betaine intake is inversely associated with breast cancer risk: a two-stage case-control study in China. *Cancer Sci*. 2013;104(2):250-258.

21. Sasso S, Dalmedico L, Delwing-Dal Magro D, Wyse ATS, Delwing-de Lima D. Effect of N-acetylarginine, a metabolite accumulated in hyperargininemia, on parameters of oxidative stress in rats: protective role of vitamins and L-NAME. *Cell Biochem Funct*. 2014;32(6):511-519.

22. Yuan B, Schafferer S, Tang Q, et al. A plasma metabolite panel as biomarkers for early primary breast cancer detection. Int J Cancer. 2019;144(11):2833-2842.

23. Jové M, Collado R, Quiles JL, et al. A plasma metabolomic signature discloses human breast cancer. Oncotarget. 2017;8(12):19522-19533.

24. Zhuoran Wu, Hong Kit Lim, Shao Jie Tan, Archana Gautam, Han Wei Hou, Kee Woei Ng, Nguan Soon Tan, Chor Yong Tay. Potent-By-Design: Amino Acids Mimicking Porous Nanotherapeutics with Intrinsic Anticancer Targeting Properties. Small, 2020; 16 (34)

25. Burke L, Guterman I, Palacios Gallego R, et al. The Janus-like role of proline metabolism in cancer. *Cell Death Discov*. 2020;6:104.

26. Rebholz CM, Zheng Z, Grams ME, et al. Serum metabolites associated with dietary protein intake: results from the Modification of Diet in Renal Disease (MDRD) randomized clinical trial. *Am J Clin Nutr*. 2019;109(3):517-525.

27. Bouchard-Mercier A, Rudkowska I, Lemieux S, Couture P, Vohl M-C. The metabolic signature associated with the Western dietary pattern: a cross-sectional study. *Nutr J*. 2013;12:158.

28. Allott EH, Howard LE, Cooperberg MR, et al. Serum lipid profile and risk of prostate cancer recurrence: Results from the SEARCH database. *Cancer Epidemiol Biomarkers Prev*. 2014;23(11):2349-2356.

29. Pelton K, Coticchia CM, Curatolo AS, et al. Hypercholesterolemia induces angiogenesis and accelerates growth of breast tumors in vivo. *Am J Pathol*. 2014;184(7):2099-2110.

30. Cedó L, Reddy ST, Mato E, Blanco-Vaca F, Escolà-Gil JC. HDL and LDL: Potential New Players in Breast Cancer Development. *J Clin Med*. 2019;8(6).

31. Danilo C, Frank PG. Cholesterol and breast cancer development. *Curr Opin Pharmacol*. 2012;12(6):677-682.

32. Johnson KE, Siewert KM, Klarin D, et al. The relationship between circulating lipids and breast cancer risk: A Mendelian randomization study. *PLoS Med*. 2020;17(9):e1003302.
33. Beloribi-Djefaflia S, Vasseur S, Guillaumond F. Lipid metabolic reprogramming in cancer cells. *Oncogenesis*. 2016;5:e189.

34. Rhee EP, Cheng S, Larson MG, et al. Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. *J Clin Invest*. 2011;121(4):1402-1411.

35. Iyengar NM, Arthur R, Manson JE, et al. Association of Body Fat and Risk of Breast Cancer in Postmenopausal Women With Normal Body Mass Index: A Secondary Analysis of a Randomized Clinical Trial and Observational Study. *JAMA Oncol*. 2019;5(2):155-163.

36. Park Y-MM, White AJ, Nichols HB, O'Brien KM, Weinberg CR, Sandler DP. The association between metabolic health, obesity phenotype and the risk of breast cancer. *Int J Cancer*. 2017;140(12):2657-2666.

37. Yee LD, Mortimer JE, Natarajan R, Dietze EC, Seewaldt VL. Metabolic Health, Insulin, and Breast Cancer: Why Oncologists Should Care About Insulin. *Front Endocrinol (Lausanne)*. 2020;11:58.

38. Mazzilli KM, McClain KM, Lipworth L, et al. Identification of 102 Correlations between Serum Metabolites and Habitual Diet in a Metabolomics Study of the Prostate, Lung, Colorectal, and Ovarian Cancer Trial. *J Nutr*. 2020;150(4):694-703.

39. Akbaraly T, Würtz P, Singh-Manoux A, et al. Association of circulating metabolites with healthy diet and risk of cardiovascular disease: analysis of two cohort studies. *Sci Rep*. 2018;8(1):8620.

CHAPTER 2

A metabolomic analysis of adiposity measures and pre- and postmenopausal breast cancer risk in the Nurses' Health Studies

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ABSTRACT

Adiposity is a known risk factor for many chronic diseases, including postmenopausal breast cancer. However, adiposity is consistently inversely associated with premenopausal breast cancer risk, a discrepancy that has yet to be fully explained. Moreover, standard measures of adiposity such as body mass index (BMI) and waist circumference may not reflect one's metabolic health, and thus may not be the best indicators for breast cancer risk.

In this nested case-control study of 1651 breast cancer cases and 1651 matched controls from the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHSII), we explored metabolite associations with adiposity measures, and subsequently with breast cancer risk. First, we selected metabolites correlated with BMI, waist circumference, weight change since age 18, or derived fat mass, and developed a metabolomic score for each measure using LASSO regression. We assigned women a metabolomic adiposity score for each measure and used logistic regression, adjusted for breast cancer risk factors, to investigate the association between this score and breast cancer risk. All analyses were stratified by menopausal status at blood draw, and further stratified by menopausal status at diagnosis. We further explored risk of ER+ and ER- breast cancer within each group.

Across adiposity measures, metabolite correlations were very similar. Between 80 and 100 metabolites were identified for each measure as having a strong ($r \geq |0.15|$) significant correlation (Benjamini Hochberg FDR p-value $p<0.05$). Metabolites with the largest correlations included TAGs and DAGs with few double bonds, glycerophosphocholines, and branched-chain amino acids. LASSO-developed models were strongly predictive of self-reported adiposity measures (R^2 range: 0.32-0.50). Metabolites selected among only premenopausal or only postmenopausal women were very similar, and scores were highly correlated with scores developed in all women (r=0.94-0.96). Regression of metabolomic scores on breast cancer risk revealed similar and generally stronger associations compared with self-reported measures. Higher metabolomic adiposity scores were generally inversely related to breast cancer risk among premenopausal women, though only the metabolomic weight change score was statistically significant (odds ratio (OR) Q4 v. Q1=0.72, 95% confidence interval (CI)=0.53-0.96, p-trend=0.05). Among postmenopausal women, significant positive trends with risk were observed for

higher metabolomic adiposity scores (e.g., metabolomic waist circumference score OR Q4 v. Q1= 1.55, 95% CI=1.08-2.22, p-trend=0.01).

Groups of metabolites particularly influential in the relationship between adiposity and breast cancer risk, glycerophosphocholines and branched-chain amino acids, are closely linked to insulin resistance and thus representative of metabolic dysregulation. Our findings suggest that metabolomic scores may be more predictive of breast cancer risk then self-reported measures. This supports the idea that metabolic dysregulation may be a better representative risk factor for breast cancer than adiposity measures alone. In addition, the same metabolites were identified to represent adiposity in pre- and postmenopausal women despite the fact that the associations between metabolomic scores and breast cancer risk were in opposing directions depending on menopausal status. This suggests that metabolic dysregulation may act differentially on pre- vs. postmenopausal breast cancer. Exploration of these metabolites and their role in adiposity-related breast cancer risk should be further explored.

INTRODUCTION

Body mass index (BMI) is a recognized risk factor for postmenopausal breast cancer, with higher adiposity associated with increased risk.[1-8] However, evidence consistently shows higher BMI is associated with a decreased risk of premenopausal breast cancer,[1,3,4,6,7,9-12] though the reasons for these conflicting relationships remain unclear. There are several different ways to examine adiposity among women, and determining which measure is the most representative of the underlying biology of adiposity remains elusive. Measures of waist circumference and weight change in adulthood have been used to capture adiposity;[13,14] in addition, fat mass, while difficult to collect directly, may represent adiposity in adulthood better than BMI alone.[15] It is also possible that none of these measures adequately provides insight into one's underlying metabolic health, which may be a more robust overall indicator of risk.

To better understand the relationship between adiposity and breast cancer we need to explore the biologic mechanisms behind the associations. Metabolomic analyses allow us to evaluate the contribution of metabolites, small molecules that are breakdown products within blood or urine, to various phenotypes. Several studies have identified metabolites that are associated with adiposity

measures, such as BMI or waist circumference.[16-20] While one has explored the association between BMI-related metabolites and postmenopausal breast cancer,[17] none to date have used metabolomic data to develop adiposity scores reflective of metabolic health. Here we derived a metabolomic score for different adiposity measures and examined the association between this score and breast cancer risk, by menopausal status. We seek to add knowledge about the metabolic profiles of these adiposity measures, determine if metabolomic scores can be used to assess risk and are beneficial beyond standard measures, and finally, to explore how metabolic state influences the development of breast cancer and whether these influences differ by menopausal status.

METHODS

Study Population

Participants included women in the Nurses' Health Study (NHS) and NHSII who were part of a breast cancer nested case-control study. Both the NHS and the NHSII are long-running prospective cohorts, started in 1976 and 1989, respectively. Case-control participants included 1188 NHS women who provided a blood sample (collected 2000-2002), and 2119 NHSII women who provided a blood sample (collected 1996-1999) and had metabolites profiled. Cases were women with a breast cancer diagnosis after blood collection and before 2010 (NHS) or 2011 (NHSII); controls were matched to cases by menopausal status at diagnosis (pre/post/unknown), and age (+/- 1 year), month (±1 month), time of day (±2 h), fasting status (≥8 h since a meal vs.<8 h or unknown), menopausal status and hormone use (premenopausal, postmenopausal, hormone user, postmenopausal, non-user, unknown) at blood draw. Risk factor information is collected in both cohorts via biennial questionnaires. Breast cancer cases were identified by self-report and confirmed by medical record review. Deaths were captured by next of kin, postal service, or review of the National Death Index.

Metabolomic Profiles

Metabolites were profiled by Dr. Clary Clish's lab at the Broad Institute of MIT and Harvard (Cambridge, MA) using liquid chromatography tandem mass spectrometry (LC/MS-MS) platforms designed to measure polar metabolites and lipids.[21-24] Matched case-control pairs were distributed

randomly within batch. Pooled reference samples were included every 20 samples and blinded quality control samples were also randomly distributed. Measures were standardized using the ratio of the value of the sample to the value of the nearest pooled reference multiplied by the median of all reference values for the metabolite. After removing metabolites impacted by delayed sample processing, as was utilized in both cohorts (ICC and Spearman rho <0.75 comparing immediately vs. within 24 to 48-hours post collection N=51 in NHS, N=52 in NHSII, there were 306 metabolites measured in NHS and 394 metabolites measured in NHSII.[24] For the primary analysis, metabolites were excluded if the blinded quality control samples CV was ≥25% (NHS N=47, NHSII N=53), though all metabolites were included in a sensitivity analysis. Metabolites with 0-<10% missingness (N=20 in NHS, N=320 in NHSII) were imputed with ½ the minimum value; metabolites with ≥10% missingness were excluded (N=2 in NHS, N=22 in NHSII). Finally, all metabolites that were included in both NHS and NHSII (N=248) were assessed in analyses.

Exposure & Covariate Measurement

Adiposity measures assessed included BMI (kg/m^2), waist circumference (cm), weight change since age 18 (kg), and predicted fat mass. BMI and weight change were assessed at blood draw. Waist circumference was assessed in 2000 for NHS and in 1993 for NHSII. Fat mass was derived from measures of age, weight, height, waist circumference, and race, through the National Health and Nutrition Examination Survey (NHANES)-developed equation for women which strongly predicts dual-energy x-ray absorptiometry (DXA)-measured fat mass (R^2=0.90).[15]

Additional covariates included standard breast cancer risk factors, selected at time of blood draw from corresponding questionnaires or prior reports for non-time-varying covariates: age at menarche, age at first birth and parity, breastfeeding history, history of benign breast disease, BMI at age 18 (kg/m^2), alcohol consumption (g/day) at blood draw, and physical activity level (MET-hrs/week) at blood draw. Missing values for these covariates were imputed with median values.

Statistical Methods

Derivation of metabolomics score for adiposity measures

A metabolomics-based score was derived for each adiposity measure separately. First, all individuals missing the adiposity measure of interest were removed from the analysis. BMI analyses further excluded extreme outliers: women with BMI >60 or <15 kg/m^2. Spearman correlations between probit-transformed metabolites and the adiposity measure, adjusted for case-control status and age at blood draw, were calculated. Metabolites with a correlation ≥|0.15| with the adiposity measure, and a Benjamini Hochberg FDR p-value <0.05 were selected to be carried forward in model development.[25] LASSO regression with cross-validation was used to select metabolites for inclusion in each model, resulting in a metabolomic adiposity score. LASSO regression is advantageous to derive unbiased estimates for our models; however, collinearity can still be an issue in variable selection. The LASSO equation will eliminate metabolites (by reducing the coefficients to zero) in the model if they are not deemed strong predictors of the outcome variable. However, when two metabolites are highly correlated, the penalty will apply to one of two correlated metabolites, and the model will arbitrarily choose one metabolite over another. While this is not completely unavoidable, we performed a sensitivity analysis using Ridge regression to avoid dropping correlated metabolites in our models.

Sensitivity analyses were also conducted by limiting derivation of the metabolomic equation to controls only and comparing selected metabolites with those derived using both cases and controls. In addition, the derivation of metabolomic scores was done in premenopausal and postmenopausal women separately and compared with the results using all women. Percent weight change, as opposed to continuous weight change in kg, was also assessed.

Association of adiposity measures (self-reported/derived, and metabolomic scores) with breast cancer

Unconditional logistic regression was used to assess the association between self-reported and metabolomic adiposity scores and breast cancer risk to maintain the maximum number of subjects given exclusions among cases or controls for missing adiposity scores. All analyses were stratified by menopausal status at blood draw, and secondarily by menopausal status at diagnosis. Models controlled for all matched factors and covariates listed above. We also evaluated increasing quartiles of the exposure of interest, with quartile cutpoints determined among all women for each measure. Trends for quartile analyses were calculated by modeling the median of each quartile as a continuous variable. P-

values <0.05 were considered statistically significant. Risk of estrogen receptor (ER) positive and negative breast cancer were assessed separately, using relevant ER subtype cases and all controls. We also assessed risk associated with cross-classified metabolomic scores and self-reported measures, using above or below the median values to form groups.

RESULTS

Descriptive characteristics

The analysis cohort included 1651 cases and 1651 controls. Descriptive characteristics are included in **Table 2.1**. Average age at blood draw was 52.3y (SD=11.7) for cases and 52.6y (SD=11.7) for controls. Most participants were fasting at blood draw (75% of cases, 81% of controls). About half of the participants (53%) were premenopausal at blood draw, and approximately 27% were premenopausal at diagnosis. Missingness varied by adiposity measures, with <2% for BMI, and <4% for weight change since age 18. However, approximately 35% of the participants were missing waist circumference and predicted fat mass measures.

Metabolomic scores for adiposity measures

Selection of metabolites

Out of 248 metabolites measured, a large proportion were selected as significantly correlated with each adiposity measure: 99 for BMI (N participants=3249), 79 for waist circumference (N=2212), 101 for weight change (N=3198), and 91 for fat mass (N=2140) (**Table 2.2**). Overlaps in selected metabolites for each adiposity measure were substantial. All metabolites with a significant Spearman correlation with waist circumference were included as correlated among the other three measures. For fat mass, all correlated metabolites were also significantly correlated with BMI, and all except one of the metabolites selected (carnitine) were significantly correlated with weight change. Metabolites with the highest correlations with adiposity measures tended to be consistent across all adiposity measures. Among the top ten correlated metabolites for each adiposity measure, overlapping metabolites included several triacylglycerols (TAGs) and diacylglycerols (DAGs) with 0-2 double bonds, such as C52:2 TAG, C50:1 TAG, C50:2 TAG, C32:1 DAG, C34:1 DAG, C34:2 DAG, as well as uric acid and valine. For example,

C52:2 TAG was strongly correlated with BMI (r=0.39), waist circumference (r=0.33), weight change (r=0.39), and fat mass (r=0.37). Directions of correlations for metabolites was consistent across adiposity measures as well; for example, cholesteryl ester C18:2 CE was inversely correlated with all measures.

Table 2.1. Descriptive characteristics of participants in the Nurses' Health Studies.*

Characteristic	Case	Control
N Participants	1651	1651
NHS2	1059	1059
NHS	592	592
Age at blood draw (mean (SD))	52.3 (11.7)	52.6 (11.7)
Fasting at blood draw (N (%))	1242 (75%)	1338 (81%)
Menopausal status at blood draw (N (%))		
Premenopausal	823 (53%)	819 (53%)
Postmenopausal	715 (46%)	719 (47%)
Unknown	8 (0.5%)	6 (0.4%)
Current hormone use (any) (N (%))	1052 (64%)	1060 (64%)
Current postmenopausal hormone use (N (%))	715 (46%)	719 (47%)
Age at diagnosis (mean (SD))	59.2 (10.7)	NA
Menopausal status at diagnosis (N (%))		
Premenopausal	453 (27%)	453 (27%)
Postmenopausal	1070 (65%)	1081 (66%)
Unknown	128 (7.8%)	117 (7.1%)
Age at menarche, years (mean (SD))	12.5 (1.4)	12.5 (1.4)
Nulliparous (N (%))	275 (17%)	231 (14%)
Parity, children (mean (SD))^	2.6 (1.2)	2.7 (1.3)
Age at first birth, years (mean (SD))^	26 (4.1)	26 (4.1)
Breastfeeding history (N (%))^	1067 (65%)	1069 (65%)
History of benign breast disease (N (%))	619 (38%)	511 (31%)
Family history of breast cancer (N (%))	319 (19%)	201 (12%)
BMI at age 18 in kg/m^2 (mean (SD))	20.8 (2.8)	21.2 (3.0)
Alcohol consumption at blood draw, g/day (mean (SD))	4.9 (7.9)	4.2 (6.5)
Activity level at blood draw, MET-hours/week (mean (SD))	20.7 (28.2)	20.0 (22.8)
BMI, kg/m^2 (mean (SD))	25.6 (5.3)	26.0 (5.7)
Missing (N (%))	26 (1.6%)	14 (0.8%)
Weight change since age 18, kg (mean (SD))	13.0 (12.6)	13.0 (13.2)
Missing (N (%))	57 (3.5%)	47 (2.8%)
Waist circumference, cm (mean (SD))	81.8 (13.2)	82.1 (13.7)
Missing (N (%))	538 (33%)	534 (32%)
Fat Mass (kg) (mean (SD))	26.8 (8.9)	26.9 (8.9)
Missing (N (%))	579 (35%)	568 (34%)
Waist to hip ratio (mean (SD))	0.8 (0.1)	0.8 (0.1)
Missing (N (%))	545 (33%)	539 (33%)

*All measures taken at blood draw unless otherwise noted. Blood draw 2000-2002 for NHS, 1996-1999 for NHS2.

^ Among parous women

Table 2.2. Metabolites identified as significantly associated with adiposity measure (FDR p-value<0.05) and with correlation >=|0.15|.

			BMI		Waist Circumference		Weight Change		Fat Mass	
HMDBID	Metabolite Name	Class	r*	p value^	r*	p value^	r*	p value^	r *	p value^
HMDB0000714	hippurate	Benzene and substituted derivatives					-0.18	1.1E-45		
HMDB0000064	creatine	Carboxylic acids and derivatives					0.16	1.0E-35		
HMDB0000123	glycine	Carboxylic acids and derivatives	-0.20	2.5E-58	-0.16	5.5E-27	-0.21	6.4E-64	-0.18	2.4E-30
HMDB0000128	guanidinoaceti c acid	Carboxylic acids and derivatives	-0.21	5.1E-66	-0.19	1.4E-35	-0.22	4.6E-71	-0.20	8.0E-38
HMDB0000158	tyrosine	Carboxylic acids and derivatives	0.27	1.2E-111	0.22	7.5E-48	0.28	8.0E-117	0.27	3.1E-72
HMDB0000159	phenylalanine	Carboxylic acids and derivatives	0.22	2.7E-68	0.18	4.1E-32	0.22	9.4E-72	0.23	9.9E-54
HMDB0000161	alanine	Carboxylic acids and derivatives	0.27	1.4E-106	0.20	4.5E-41	0.28	1.2E-110	0.26	8.7E-69
HMDB0000162	proline	Carboxylic acids and derivatives	0.21	1.4E-65	0.17	2.6E-28	0.22	1.9E-71	0.22	1.4E-45
HMDB0000172	isoleucine	Carboxylic acids and derivatives	0.31	2.9E-143	0.26	9.6E-69	0.33	6.0E-163	0.31	1.4E-96

Table 2.2 (continued). Metabolites identified as significantly associated with adiposity measure

HMDB0000182	lysine	Carboxylic acids and derivatives	0.18	1.7E-46			0.19	3.5E-54	0.16	7.1E-26
HMDB0000687	leucine	Carboxylic acids and derivatives	0.30	2.4E-134	0.26	3.7E-67	0.32	1.2E-155	0.31	9.8E-94
HMDB0000883	valine	Carboxylic acids and derivatives	0.37	5.5E-212	0.30	5.7E-91	0.39	2.7E-226	0.37	3.3E-135
HMDB0029416	NMMA	Carboxylic acids and derivatives	0.18	1.8E-49			0.19	1.3E-51	0.17	6.6E-28
HMDB0000201	C2 carnitine	Fatty Acyls	0.16	3.0E-39						
HMDB0000688	C5 carnitine	Fatty Acyls	0.25	1.2E-91	0.19	1.7E-37	0.25	1.4E-89	0.24	2.3E-58
HMDB0000705	C6 carnitine	Fatty Acyls	0.19	1.8E-52			0.18	1.1E-47		
HMDB0000824	C3 carnitine	Fatty Acyls	0.23	2.1E-81	0.18	3.1E-31	0.21	2.0E-63	0.23	8.4E-50
HMDB0013127	C4-OH carnitine	Fatty Acyls	0.25	3.1E-95	0.20	5.9E-41	0.23	5.6E-75	0.21	1.3E-42
HMDB0007103	C34:2 DAG	Fatty Acyls	0.35	7.0E-189	0.31	6.7E-100	0.37	2.3E-204	0.35	1.1E-119
HMDB0007132	C34:3 DAG	Fatty Acyls	0.33	6.1E-166	0.32	2.1E-105	0.36	2.9E-189	0.34	1.0E-115
HMDB0007219	C36:3 DAG	Fatty Acyls	0.23	5.3E-75	0.24	5.1E-59	0.25	5.6E-91	0.24	1.1E-54
HMDB0007248	C36:4 DAG	Fatty Acyls	0.16	1.9E-39	0.20	3.4E-42	0.20	7.8E-57	0.18	1.4E-32
HMDB0007098	C32:0 DAG	Glycerolipids	0.32	1.3E-155	0.25	2.1E-64	0.33	1.5E-165	0.30	1.1E-90
HMDB0007099	C32:1 DAG	Glycerolipids	0.36	3.0E-200	0.30	1.9E-90	0.38	1.0E-211	0.36	1.7E-125
HMDB0007100	C34:0 DAG	Glycerolipids	0.28	9.1E-114	0.21	1.0E-45	0.29	1.9E-123	0.25	1.8E-63
HMDB0007102	C34:1 DAG	Glycerolipids	0.37	8.3E-207	0.31	6.1E-97	0.38	6.0E-213	0.35	1.8E-124
HMDB0007199	C38:5 DAG	Glycerolipids	0.27	4.4E-111	0.22	7.6E-50	0.28	1.1E-112	0.27	2.2E-69
HMDB0007216	C36:1 DAG	Glycerolipids	0.34	4.6E-174	0.28	2.5E-78	0.34	2.5E-175	0.32	2.7E-100
HMDB0007218	C36:2 DAG	Glycerolipids	0.34	2.2E-169	0.29	5.5E-87	0.33	6.4E-166	0.32	2.7E-100

Table 2.2 (continued). Metabolites identified as significantly associated with adiposity measure

HMDB0005356	C48:0 TAG	Glycerolipids	0.24	3.4E-88	0.16	2.7E-26	0.25	2.0E-88	0.21	1.8E-44
HMDB0005357	C50:0 TAG	Glycerolipids	0.27	1.6E-107	0.19	2.4E-35	0.27	5.8E-110	0.24	3.4E-54
HMDB0005359	C48:1 TAG	Glycerolipids	0.29	1.4E-124	0.21	3.0E-46	0.29	5.6E-127	0.27	4.7E-69
HMDB0005360	C50:1 TAG	Glycerolipids	0.37	5.7E-203	0.28	6.5E-79	0.37	3.2E-201	0.33	3.1E-110
HMDB0005362	C51:2 TAG	Glycerolipids	0.27	1.3E-108	0.20	1.1E-38	0.27	5.1E-104	0.26	4.2E-65
HMDB0005363	C52:4 TAG	Glycerolipids	0.16	3.8E-39	0.21	2.9E-43	0.19	4.1E-54	0.18	4.1E-32
HMDB0005367	C52:1 TAG	Glycerolipids	0.35	1.1E-185	0.27	1.3E-73	0.35	5.8E-184	0.32	7.7E-100
HMDB0005369	C52:2 TAG	Glycerolipids	0.39	3.3E-236	0.33	9.1E-111	0.39	1.3E-226	0.37	1.3E-139
HMDB0005376	C48:2 TAG	Glycerolipids	0.29	1.0E-121	0.21	1.4E-43	0.29	1.7E-122	0.27	1.4E-69
HMDB0005377	C50:2 TAG	Glycerolipids	0.37	5.5E-212	0.29	1.1E-86	0.37	2.0E-205	0.35	1.7E-120
HMDB0005385	C54:5 TAG	Glycerolipids	0.23	1.7E-79	0.18	1.9E-31	0.24	4.5E-81	0.22	2.1E-46
HMDB0005403	C54:2 TAG	Glycerolipids	0.30	2.8E-138	0.26	1.3E-65	0.30	7.5E-133	0.28	1.9E-78
HMDB0005410	C56:3 TAG	Glycerolipids	0.17	2.3E-42			0.17	5.9E-44	0.16	6.8E-27
HMDB0005432	C48:3 TAG	Glycerolipids	0.30	2.2E-132	0.22	7.8E-51	0.31	2.1E-142	0.28	3.8E-75
HMDB0005433	C50:3 TAG	Glycerolipids	0.33	2.1E-168	0.28	7.1E-78	0.34	4.8E-174	0.32	6.8E-102
HMDB0005436	C52:6 TAG	Glycerolipids	0.22	1.1E-71	0.21	2.2E-44	0.25	3.9E-88	0.21	3.2E-45
HMDB0010411	C46:0 TAG	Glycerolipids	0.21	2.4E-66			0.22	2.2E-69	0.19	1.4E-34
HMDB0010412	C46:1 TAG	Glycerolipids	0.26	2.4E-96	0.18	1.4E-32	0.26	2.2E-100	0.24	4.4E-54
HMDB0010419	C46:2 TAG	Glycerolipids	0.28	7.2E-113	0.20	4.6E-40	0.29	1.5E-123	0.25	4.4E-63
HMDB0010471	C50:5 TAG	Glycerolipids	0.28	1.9E-113	0.23	3.8E-53	0.30	1.2E-133	0.26	3.7E-65
HMDB0010497	C50:6 TAG	Glycerolipids	0.25	9.4E-93	0.19	2.5E-38	0.28	3.4E-111	0.23	4.6E-52
HMDB0010517	C52:7 TAG	Glycerolipids	0.21	7.2E-68	0.18	1.2E-32	0.24	1.2E-82	0.20	5.6E-40
HMDB0011701	C51:3 TAG	Glycerolipids	0.23	5.5E-75	0.22	1.6E-47	0.24	2.2E-82	0.23	7.7E-54
HMDB0011706	C49:2 TAG	Glycerolipids	0.20	9.0E-59			0.21	1.2E-62	0.18	5.8E-33
HMDB0031106	C51:0 TAG	Glycerolipids	0.22	2.6E-68			0.22	6.9E-73	0.19	9.8E-37
HMDB0042076	C47:2 TAG	Glycerolipids	0.24	6.1E-87	0.16	7.3E-27	0.25	1.6E-92	0.22	3.5E-49
HMDB0042103	C49:3 TAG	Glycerolipids	0.24	4.1E-84	0.18	1.6E-32	0.25	5.4E-89	0.23	5.8E-53
HMDB0042104	C51:1 TAG	Glycerolipids	0.33	1.0E-159	0.24	5.5E-58	0.34	1.4E-171	0.30	1.9E-89
HMDB0042196	C53:2 TAG	Glycerolipids	0.26	2.8E-103	0.22	4.8E-49	0.26	1.4E-96	0.26	1.2E-66

Table 2.2 (continued). Metabolites identified as significantly associated with adiposity measure

HMDB0042226	C55:2 TAG	Glycerolipids	0.26	2.4E-98	0.19	9.0E-37	0.26	8.9E-99	0.23	1.3E-53
HMDB0002815	C18:1 LPC	Glycerophospho-lipids	-0.22	2.7E-69	-0.18	1.6E-34	-0.23	3.0E-80	-0.21	1.8E-42
HMDB0007870	C30:1 PC	Glycerophospho-lipids	0.16	4.3E-40			0.16	9.9E-36		
HMDB0007873	C32:1 PC	Glycerophospho-lipids	0.21	2.2E-63			0.19	6.3E-54	0.17	5.4E-29
HMDB0007874	C32:2 PC	Glycerophospho-lipids					0.16	8.4E-37		
HMDB0008047	C38:3 PC	Glycerophospho-lipids	0.35	5.5E-187	0.24	1.2E-58	0.34	2.9E-171	0.31	1.2E-92
HMDB0008138	C36:4 PC-B	Glycerophospho-lipids	0.19	5.3E-54			0.18	3.4E-47	0.17	5.2E-28
HMDB0010386	C18:2 LPC	Glycerophospho-lipids	-0.28	1.3E-116	-0.23	3.6E-55	-0.28	1.5E-118	-0.27	8.4E-72
HMDB0010397	C20:5 LPC	Glycerophospho-lipids	-0.27	4.1E-109	-0.23	1.2E-52	-0.28	1.5E-110	-0.26	1.8E-68
HMDB0010404	C22:6 LPC	Glycerophospho-lipids	-0.16	1.1E-39			-0.16	1.9E-38	-0.16	1.9E-25
HMDB0011208	C34:1 PC plasmalogen	Glycerophospho-lipids	-0.24	7.7E-82	-0.21	1.9E-46	-0.25	9.7E-89	-0.23	2.2E-51
HMDB0011211	C34:3 PC plasmalogen	Glycerophospho-lipids	-0.23	4.0E-79	-0.22	2.9E-50	-0.23	8.3E-74	-0.23	2.6E-52
HMDB0011239	C34:1 PC plasmalogen-B	Glycerophospho-lipids	-0.23	3.0E-80	-0.20	8.1E-41	-0.24	1.1E-84	-0.24	2.7E-55
HMDB0011243	C36:2 PC plasmalogen	Glycerophospho-lipids	-0.25	1.4E-91	-0.22	5.2E-51	-0.24	2.2E-84	-0.25	5.4E-63
HMDB0011310	C36:4 PC plasmalogen	Glycerophospho-lipids	-0.27	1.5E-110	-0.24	1.1E-57	-0.29	1.1E-121	-0.26	2.1E-65

Table 2.2 (continued). Metabolites identified as significantly associated with adiposity measure

HMDB0008942	C38:2 PE	Glycerophospho-lipids	-0.18	6.2E-48	-0.19	1.9E-35	-0.17	2.4E-40	-0.20	1.8E-39
HMDB0008993	C36:1 PE	Glycerophospho-lipids	0.18	3.9E-46			0.19	4.0E-52		
HMDB0008994	C36:2 PE	Glycerophospho-lipids	0.16	8.7E-38			0.18	4.5E-47		
HMDB0009003	C38:4 PE	Glycerophospho-lipids	0.19	1.0E-55	0.15	4.3E-24	0.19	9.9E-54	0.18	3.1E-32
HMDB0009016	C36:1 PE plasmalogen	Glycerophospho-lipids	-0.26	3.7E-101	-0.22	1.6E-47	-0.26	6.5E-102	-0.25	1.8E-59
HMDB0011520	C22:0 LPE	Glycerophospho-lipids	-0.29	3.3E-124	-0.23	2.2E-52	-0.29	5.6E-127	-0.27	5.8E-74
HMDB0007883	C34:4 PC	Glycerophospho-lipids	0.19	5.4E-51			0.20	4.1E-58	0.15	9.4E-23
HMDB0010391	C20:1 LPC	Glycerophospho-lipids	-0.22	3.8E-70	-0.18	1.1E-32	-0.20	3.6E-56	-0.20	8.8E-38
HMDB0011210	C34:2 PC plasmalogen	Glycerophospho-lipids	-0.29	1.7E-121	-0.28	3.7E-77	-0.31	1.8E-145	-0.28	1.1E-78
HMDB0011244	C36:3 PC plasmalogen	Glycerophospho-lipids	-0.29	1.7E-127	-0.28	2.5E-78	-0.28	1.7E-113	-0.30	4.4E-91
HMDB0000289	urate	Imidazopyrimidin es	0.38	4.8E-215	0.29	7.0E-84	0.34	1.7E-174	0.34	8.8E-115
HMDB0000875	trigonelline	NA					-0.15	5.0E-35		
HMDB0000767	pseudouridine	Nucleoside and nucleotide analogues	0.21	3.4E-68	0.20	3.8E-39	0.17	3.9E-44	0.23	1.1E-49
HMDB0000062	carnitine	Organonitrogen compounds	0.16	5.2E-38					0.16	1.7E-26

Table 2.2 (continued). Metabolites identified as significantly associated with adiposity measure

HMDB0001563	1-methyl-guanosine	Purine nucleosides	0.21	4.3E-64	0.17	2.7E-29	0.20	1.6E-55	0.20	6.8E-41
HMDB0004824	N2,N2-dimethyl-guanosine	Purine nucleosides	0.26	1.0E-99	0.24	4.1E-56	0.23	1.9E-75	0.26	2.0E-67
HMDB0001431	pyridoxamine	Pyridines and derivatives	0.19	6.2E-56			0.20	1.5E-60	0.18	3.3E-31
HMDB0005923	N4-acetylcytidine	Pyrimidine nucleosides	0.26	3.4E-101	0.22	1.0E-50	0.21	6.5E-62	0.26	1.1E-65
HMDB0004949	C16:0 Ceramide (d18:1)	Sphingolipids	0.16	1.1E-38						
HMDB0004952	C22:0 Ceramide (d18:1)	Sphingolipids	0.24	3.1E-85	0.18	5.0E-34	0.26	9.3E-99	0.19	1.1E-36
HMDB0004956	C24:0 Ceramide (d18:1)	Sphingolipids					0.16	3.3E-38		
HMDB0012097	C14:0 SM	Sphingolipids	0.16	5.3E-36						
HMDB0000067	cholesterol	Steroids and steroid derivatives	0.18	4.8E-46			0.17	1.1E-42		
HMDB0000610	C18:2 CE	Steroids and steroid derivatives	-0.33	2.3E-168	-0.29	1.2E-85	-0.34	5.6E-168	-0.32	8.4E-103
HMDB0000885	C16:0 CE	Steroids and steroid derivatives	-0.31	3.4E-139	-0.26	3.7E-67	-0.31	2.3E-145	-0.27	8.6E-74
HMDB0000918	C18:1 CE	Steroids and steroid derivatives	-0.32	1.4E-149	-0.28	1.1E-81	-0.32	4.8E-155	-0.30	1.2E-91

Table 2.2 (continued). Metabolites identified as significantly associated with adiposity measure

HMDB0006725	C14:0 CE	Steroids and steroid derivatives	-0.18	3.3E-48	-0.18	2.3E-33	-0.20	7.6E-59	-0.18	2.2E-31
HMDB0006726	C20:4 CE	Steroids and steroid derivatives	-0.22	1.7E-69	-0.19	7.4E-37	-0.24	9.8E-84	-0.20	2.1E-38
HMDB0006731	C20:5 CE	Steroids and steroid derivatives					-0.18	2.1E-47		
HMDB0006733	C22:6 CE	Steroids and steroid derivatives	-0.31	2.5E-139	-0.25	9.4E-62	-0.31	1.3E-145	-0.27	5.7E-73
HMDB0010370	C18:3 CE	Steroids and steroid derivatives	-0.19	1.3E-51	-0.19	7.4E-35	-0.20	7.9E-60	-0.19	6.8E-36
HMDB0010375	C22:5 CE	Steroids and steroid derivatives	-0.31	2.2E-141	-0.25	8.6E-62	-0.33	2.1E-163	-0.28	2.2E-79

*Spearman correlation adjusted for age at blood draw and case-control status. Sorted by absolute value of correlation. Bolded items were selected in LASSO model.

^FDR adjusted p value

LASSO selection of these significantly correlated metabolites resulted in 75 metabolites for BMI, 52 for waist circumference, 81 for fat mass, and 91 for weight change (**Table 2.3**). Variability in adiposity measures explained by metabolite scores was generally high, as evidenced by R^2 values from each equation: BMI=0.50; weight change=0.42; fat mass=0.45; waist circumference=0.32. The majority of selected metabolites were lipids.

Metabolites with large coefficients for a one-SD change in BMI included the glycerophosphocholines C38:3 PC and C18:1 LPC, and diacylglycerol C36:2 DAG (Table 2.3). The top five metabolites influencing weight change included glycerophosphocholine C38:3 PC, cholesterol esters C20:4 CE, C14:0 CE, and C22:5 CE, and triacylglycerol C56:3 TAG. Top metabolites selected for waist circumference were cholesterol ester C20:4 CE, triacylglycerol C52:1 TAG, glycerophospholipid C36:3 PC plasmalogen, glycerophosphoethanolamine C38:2 PE, and diacylglycerol C34:3 DAG. Fat mass metabolomic score creation relied on heavily on glycerphosphocholines C38:3 PC, C22:6 LPC, and C18:1 LPC, glycerophospholipid C36:3 plasmalogen, and cholesterol ester C20:5 CE. Glycerophosphocholine C38:3 PC and cholesterol ester C20:4 CE were strongly predictive of waist circumference, weight change, fat mass, and BMI.

Sensitivity analyses – selection of metabolites in different populations

Metabolites identified as well-correlated with adiposity measures ($r \geq |0.15|$) were very similar when examining only the controls compared to all participants. For BMI, all metabolites with correlations $\geq |0.15|$ in the full participant group also had correlations $\geq |0.15|$ among controls only. Ten unique metabolites had correlations $\geq |0.15|$ when examining controls-only ($r = |0.15\text{-}0.17|$); the correlation coefficients were not materially different when examining contributions for the full participant dataset (r in full group ranged from 0.12-<0.15). In addition, metabolomic scores in controls only v. cases and controls were strongly correlated, with Pearson correlations ≥0.94 for BMI, weight change, waist circumference, and fat mass.

Table 2.3. Coefficients for probit-transformed metabolites in predictive models for each adiposity measure, for 1-SD increase in adiposity measure.*

HMDB ID	Metabolite Name	Class	Coefficients			
			BMI (R2=0.50)	Waist Circumference (R2=0.32)	Weight change (R^2=0.42)	Fat Mass (R^2=0.45)
(Intercept)				6.137	1.015	3.074
HMDB0000714	hippurate	Benzene and substituted derivatives			-0.041	
HMDB0000064	creatine	Carboxylic acids and derivatives			0.014	
HMDB0000123	glycine	Carboxylic acids and derivatives	-0.019	-0.03	-0.053	-0.036
HMDB0000128	guanidinoacetic acid	Carboxylic acids and derivatives	-0.058	-0.07	-0.048	-0.051
HMDB0000158	tyrosine	Carboxylic acids and derivatives	0.078	0.113	0.072	0.1
HMDB0000159	phenylalanine	Carboxylic acids and derivatives	-0.007	-0.024	-0.001	0.018
HMDB0000161	alanine	Carboxylic acids and derivatives	0.014		0.008	0.005
HMDB0000162	proline	Carboxylic acids and derivatives	0.032	0.05	0.056	0.04
HMDB0000172	isoleucine	Carboxylic acids and derivatives	0.01		0.037	-0.004
HMDB0000182	lysine	Carboxylic acids and derivatives	-0.082		-0.043	-0.093
HMDB0000687	leucine	Carboxylic acids and derivatives	-0.132	-0.08	-0.127	-0.129

Table 2.3 (continued). Coefficients for probit-transformed metabolites in predictive models for each adiposity measure

HMDB0000883	valine	Carboxylic acids and derivatives	0.153	0.089	0.122	0.178
HMDB0029416	NMMA	Carboxylic acids and derivatives	0.044		0.04	0.048
HMDB0007132	C34:3 DAG	Fatty Acyls		0.151		
HMDB0007248	C36:4 DAG	Fatty Acyls		0.003		
HMDB0013127	C4-OH carnitine	Fatty Acyls		0.08		
HMDB0000201	C2 carnitine	Fatty Acyls	-0.099			
HMDB0000688	C5 carnitine	Fatty Acyls	0.002		0.049	0
HMDB0000705	C6 carnitine	Fatty Acyls			0.002	
HMDB0000824	C3 carnitine	Fatty Acyls	0.014		-0.045	-0.016
HMDB0007103	C34:2 DAG	Fatty Acyls				-0.053
HMDB0007132	C34:3 DAG	Fatty Acyls	0.076		0.136	0.158
HMDB0007219	C36:3 DAG	Fatty Acyls				0.324
HMDB0007248	C36:4 DAG	Fatty Acyls	0.13		0.184	0.099
HMDB0013127	C4-OH carnitine	Fatty Acyls	0.169		0.085	0.093
HMDB0005356	C48:0 TAG	Glycerolipids	0.03		0.070	0.015
HMDB0005357	C50:0 TAG	Glycerolipids	-0.042	-0.027	-0.168	-0.109
HMDB0005359	C48:1 TAG	Glycerolipids			-0.185	-0.192
HMDB0005360	C50:1 TAG	Glycerolipids	0.126		0.171	0.092
HMDB0005362	C51:2 TAG	Glycerolipids	0.072	0	0.013	0.124
HMDB0005363	C52:4 TAG	Glycerolipids	-0.073	0.054	-0.054	-0.207
HMDB0005367	C52:1 TAG	Glycerolipids		0.198	0.084	0.172
HMDB0005369	C52:2 TAG	Glycerolipids	-0.005		-0.01	0.050
HMDB0005376	C48:2 TAG	Glycerolipids	-0.069		-0.088	
HMDB0005377	C50:2 TAG	Glycerolipids			0.004	0.006
HMDB0005385	C54:5 TAG	Glycerolipids	0.049	0.005	0.062	0.067
HMDB0005403	C54:2 TAG	Glycerolipids	0.109		0.143	0.073
HMDB0005410	C56:3 TAG	Glycerolipids	-0.167		-0.184	-0.105
HMDB0005432	C48:3 TAG	Glycerolipids			-0.040	
HMDB0005433	C50:3 TAG	Glycerolipids	0.074		0.129	0.102

Table 2.3 (continued). Coefficients for probit-transformed metabolites in predictive models for each adiposity measure

HMDB0005436	C52:6 TAG	Glycerolipids	-0.07	-0.001	-0.123	-0.162
HMDB0007098	C32:0 DAG	Glycerolipids	-0.111	-0.033	-0.179	
HMDB0007099	C32:1 DAG	Glycerolipids	-0.086	-0.067	-0.051	-0.131
HMDB0007100	C34:0 DAG	Glycerolipids	-0.057	-0.063		-0.135
HMDB0007102	C34:1 DAG	Glycerolipids	0.067		0.125	
HMDB0007199	C38:5 DAG	Glycerolipids	0.014	-0.084	-0.012	-0.054
HMDB0007216	C36:1 DAG	Glycerolipids	0.086			0.159
HMDB0007218	C36:2 DAG	Glycerolipids	-0.089		-0.215	-0.373
HMDB0010411	C46:0 TAG	Glycerolipids			0.05	0.102
HMDB0010412	C46:1 TAG	Glycerolipids			0.03	
HMDB0010419	C46:2 TAG	Glycerolipids			0.09	
HMDB0011706	C49:2 TAG	Glycerolipids	-0.027			
HMDB0010471	C50:5 TAG	Glycerolipids		-0.007		-0.037
HMDB0010497	C50:6 TAG	Glycerolipids		-0.017	0.011	-0.02
HMDB0011701	C51:3 TAG	Glycerolipids			-0.015	
HMDB0042076	C47:2 TAG	Glycerolipids		-0.011		0.117
HMDB0042103	C49:3 TAG	Glycerolipids		-0.001		
HMDB0031106	C51:0 TAG	Glycerolipids			-0.005	
HMDB0042076	C47:2 TAG	Glycerolipids			-0.072	
HMDB0011701	C51:3 TAG	Glycerolipids				0.079
HMDB0011706	C49:2 TAG	Glycerolipids				-0.16
HMDB0031106	C51:0 TAG	Glycerolipids				0.03
HMDB0042103	C49:3 TAG	Glycerolipids			0.134	0.004
HMDB0042104	C51:1 TAG	Glycerolipids	0.016	0.019	0.089	0.086
HMDB0042196	C53:2 TAG	Glycerolipids	0.078	0.085	-0.046	0.053
HMDB0042226	C55:2 TAG	Glycerolipids			0.022	
HMDB0002815	C18:1 LPC	Glycerophospholipids	0.175	-0.035	0.195	0.228
HMDB0007870	C30:1 PC	Glycerophospholipids	0.004	0.047	-0.042	

Table 2.3 (continued). Coefficients for probit-transformed metabolites in predictive models for each adiposity measure

HMDB0007873	C32:1 PC	Glycerophospholipids	0.015		0.065	0.069
HMDB0007874	C32:2 PC	Glycerophospholipids			0.029	
HMDB0007883	C34:4 PC	Glycerophospholipids	-0.047			-0.005
HMDB0008047	C38:3 PC	Glycerophospholipids	0.269	0.151	0.23	0.369
HMDB0008138	C36:4 PC-B	Glycerophospholipids	-0.071		-0.085	-0.112
HMDB0008942	C38:2 PE	Glycerophospholipids	-0.181	-0.161	-0.088	-0.145
HMDB0009003	C38:4 PE	Glycerophospholipids		-0.039		-0.093
HMDB0008993	C36:1 PE	Glycerophospholipids	0	0.13	0.037	
HMDB0009003	C38:4 PE	Glycerophospholipids	-0.111		-0.113	
HMDB0009016	C36:1 PE plasmalogen	Glycerophospholipids	0.065		0.108	0.127
HMDB0010386	C18:2 LPC	Glycerophospholipids	-0.089	-0.064	-0.256	-0.092
HMDB0010391	C20:1 LPC	Glycerophospholipids	-0.059	-0.05	0.007	-0.055
HMDB0010397	C20:5 LPC	Glycerophospholipids	0.007		0.137	0.048
HMDB0010404	C22:6 LPC	Glycerophospholipids	-0.109		-0.081	-0.175
HMDB0011208	C34:1 PC plasmalogen	Glycerophospholipids	-0.026	-0.041		-0.052
HMDB0011210	C34:2 PC plasmalogen	Glycerophospholipids		-0.068	-0.038	0.052
HMDB0011211	C34:3 PC plasmalogen	Glycerophospholipids	0.151	0.114	0.081	0.178

Table 2.3 (continued). Coefficients for probit-transformed metabolites in predictive models for each adiposity measure

HMDB0011239	C34:1 PC plasmalogen-B	Glycerophospholipids	-0.078		-0.110	-0.036
HMDB0011243	C36:2 PC plasmalogen	Glycerophospholipids			-0.004	0.006
HMDB0011244	C36:3 PC plasmalogen	Glycerophospholipids	-0.197	-0.17	-0.046	-0.309
HMDB0011310	C36:4 PC plasmalogen	Glycerophospholipids		0.014	-0.049	0
HMDB0011520	C22:0 LPE	Glycerophospholipids	-0.127	-0.045	-0.167	-0.163
HMDB0000289	urate	Imidazopyrimidines	0.093	0.064	0.083	0.07
HMDB0000875	trigonelline	NA			-0.014	
HMDB0000767	pseudouridine	Nucleoside and nucleotide analogues	-0.053	-0.03	-0.049	-0.064
HMDB0000062	carnitine	Organonitrogen compounds	0.021			
HMDB0001563	1-methylguanosine	Purine nucleosides	0.01	-0.001	0.016	
HMDB0004824	N2,N2-dimethylguanosine	Purine nucleosides	0.098	0.093	0.06	0.101
HMDB0001431	pyridoxamine	Pyridines and derivatives	0.027		0.006	0.036
HMDB0005923	N4-acetylcytidine	Pyrimidine nucleosides	0.054	0.057	0.023	0.083
HMDB0004952	C22:0 Ceramide (d18:1)	Sphingolipids		0.089	0.135	0.041
HMDB0004956	C24:0 Ceramide (d18:1)	Sphingolipids			-0.086	
HMDB0004949	C16:0 Ceramide (d18:1)	Sphingolipids	-0.002			

Table 2.3 (continued). Coefficients for probit-transformed metabolites in predictive models for each adiposity measure

HMDB0012097	C14:0 SM	Sphingolipids	0.248			
HMDB0000067	cholesterol	Steroids and steroid derivatives	0.047		0.158	
HMDB0000610	C18:2 CE	Steroids and steroid derivatives	0.056	0.029	0.027	0.037
HMDB0000885	C16:0 CE	Steroids and steroid derivatives	-0.006		-0.031	0
HMDB0000918	C18:1 CE	Steroids and steroid derivatives	-0.009		-0.033	-0.02
HMDB0006725	C14:0 CE	Steroids and steroid derivatives	-0.202	-0.102	-0.139	-0.134
HMDB0006726	C20:4 CE	Steroids and steroid derivatives	0.161	0.209	0.234	0.278
HMDB0006731	C20:5 CE	Steroids and steroid derivatives			0.148	
HMDB0006733	C22:6 CE	Steroids and steroid derivatives	-0.008	-0.057	-0.042	0.038
HMDB0010370	C18:3 CE	Steroids and steroid derivatives		-0.001	-0.027	-0.039
HMDB0010375	C22:5 CE	Steroids and steroid derivatives	-0.117	-0.082	-0.159	-0.126

*Metabolites were selected via LASSO regression. Sorted by absolute value of coefficient.

Some minor differences were noted in metabolite correlations when examining premenopausal and postmenopausal women separately (**Supplemental Table 2.1**). Among premenopausal participants, 113 metabolites were correlated with BMI (r>|0.15|); among postmenopausal participants, 87 metabolites were correlated with BMI. However, 80 metabolites overlapped between both groups, and had similar correlation strengths with BMI, with the average difference in correlations between pre- and postmenopausal groups equal to 0.05 (range for difference=0.003-0.14) for overlapping metabolites. The direction of correlation between each metabolite and BMI was the same among premenopausal and postmenopausal women, with one exception (sphingolipid C22:1 SM (HMDB0012104) r=0.22 for premenopausal women, r=-0.02 for postmenopausal women).

For those metabolites with strong correlations with BMI in premenopausal women, but not in postmenopausal women, the absolute value of the difference between correlations ranged from 0.03-0.24. Those with the largest differences in BMI correlations between groups (>0.15) included sphingolipids C22:1 SM (difference=0.24) and C14:0 SM (difference=0.23), as well as several glycerophospholipids. For metabolites strongly correlated with BMI in postmenopausal women but not in premenopausal women, the absolute value of the difference between correlations was smaller (range=0.05-0.18). Metabolites with differences above 0.15 in correlation coefficients were all glycerophospholipids: C38:6 PC, and C40:10 PC. Despite these noted differences, the impact of these uniquely selected metabolites to the prediction of BMI was minimal. For example, with respect to BMI, the correlations with derived scores separately by menopausal status vs. all women combined were 0.96 for premenopausal and 0.94 for postmenopausal women.

Sensitivity analysis – Including metabolites with high CVs

Several metabolites with high CVs (≥25%) were identified as being correlated with adiposity scores, though these metabolites were highly correlated with metabolites identified in the original set with low CVs. For example, C54:1 TAG and C52:0 TAG correlated with BMI (r=0.27 & r=0.25); these metabolites are highly correlated with TAGs with few double bonds, several of which were identified in the original correlation analysis. The metabolomic score derived using the larger set of metabolites, including those with CVs ≥25%, was strongly correlated with the score created when excluding these

metabolites (e.g.: for BMI, r=0.86). Due to the similar nature of findings, all analyses reported exclude metabolites with high CVs.

Sensitivity analysis – Comparing selection algorithms

The correlation between the LASSO regression metabolomic score and the ridge regression metabolomic score for BMI was >0.99. Because of this, we determined that either regression technique would produce a similar finding with respect to the metabolomic score.

We performed stepwise selection to obtain metabolomic scores for adiposity measures as well. Stepwise selection resulted in a model with fewer metabolites selected for each adiposity measure (e.g.: for BMI, stepwise selection chose 49 metabolites as opposed to LASSO's 75) (**Supplemental Table 2.2**). Only one metabolite (C48:1 TAG) was selected in stepwise but not selected in LASSO. Further, the correlation between metabolomic score for BMI using stepwise regression vs. LASSO was >0.99. Overall, results did not alter based on the selection algorithm used to produce the metabolomic score. Here we present results given for the LASSO-derived models.

Association of metabolomic scores with breast cancer risk

Premenopausal women

Quartile cutpoints were defined in the overall population and are given in **Supplemental Table 2.3**. Among women premenopausal at blood draw (N cases for BMI=820, waist circumference=504, weight change=817, FM=494), self-reported adiposity measures were generally inversely, though non-significantly, associated with breast cancer risk. For example, comparing quartile 4 with quartile 1, the BMI OR=0.94 (95% CI=0.67-1.33), and weight change OR=0.87 (95% CI=0.64-1.18). Metabolomic scores for each adiposity measure were more strongly inversely associated with breast cancer risk compared to self-reported measures (**Table 2.4)**. A significant inverse association was observed with increasing metabolomic weight change score (OR Q4 v. Q1=0.72, 95% CI=0.53-0.96, p-trend=0.05). Metabolomic scores for BMI and fat mass were also inversely associated with risk, though with non-significant trends. The inverse trends remained for ER+ breast cancers, though no significant trends were noted for ER- breast cancer (**Supplemental Table 2.4a & 2.4b**).

Table 2.4. Association between true and metabolomic-predicted adiposity scores & breast cancer incidence for women premenopausal at blood draw.†

Premenopausal at blood draw									
Adiposity Measures	Quartile 1*		Quartile 2*		Quartile 3*		Quartile 4*		
Self-reported	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	p-trend^
BMI (kg/m2)	268/262	1.0 (ref)	226/195	1.19 (0.92-1.56)	176/175	1.08 (0.81- 1.44)	150/181	0.94 (0.67- 1.33)	0.60
Waist circumference (cm)	132/140	1.0 (ref)	183/152	1.28 (0.92-1.78)	110/120	0.94 (0.65- 1.37)	79/82	1.03 (0.66- 1.61)	0.78
Weight change (kg)	219/210	1.0 (ref)	251/253	0.91 (0.69-1.18)	192/185	0.95 (0.71- 1.27)	155/168	0.87 (0.64- 1.18)	0.46
Fat mass	174/171	1.0 (ref)	142/108	1.31 (0.94-1.84)	82/102	0.79 (0.53- 1.15)	96/99	0.96 (0.63- 1.46)	0.38
Metabolomic score									
BMI (kg/m2)	262/225	1.0 (ref)	217/212	0.86 (0.66-1.12)	174/188	0.83 (0.63-1.10)	167/188	0.80 (0.59-1.08)	0.13
Waist circumference (cm)	143/135	1.0 (ref)	148/127	1.08 (0.77-1.53)	107/124	0.80 (0.56-1.14)	106/108	0.95 (0.65- 1.39)	0.47
Weight change (kg)	258/216	1.0 (ref)	213/221	0.80 (0.62-1.05)	185/184	0.86 (0.65- 1.14)	161/195	0.72 (0.53- 0.96)	0.05
Fat mass	149/125	1.0 (ref)	137/130	0.9 (0.63- 1.27)	103/118	0.74 (0.51-1.06)	105/107	0.84 (0.58 -1.23)	0.24
Premenopausal at blood draw & at diagnosis									
Adiposity Measures	Quartile 1*		Quartile 2*		Quartile 3*		Quartile 4*		
Self-reported	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	p-trend^
BMI (kg/m2)	156/148	1.0 (ref)	120/109	1.04 (0.73-1.49)	95/93	0.96 (0.65-1.42)	70/91	0.67 (0.41-1.08)	0.1

Table 2.4 (continued). Association between true and metabolomic-predicted adiposity scores & breast cancer, premenopausal at blood draw

Waist circumference (cm)	77/78	1.0 (ref)	100/74	1.32 (0.84-2.08)	61/61	0.92 (0.56- 1.51)	38/45	0.74 (0.40-1.35)	0.2
Weight change (kg)	125/122	1.0 (ref)	141/140	0.94 (0.66-1.34)	101/96	0.99 (0.67- 1.46)	71/82	0.77 (0.51-1.18)	0.28
Fat mass	110/85	1.0 (ref)	70/59	0.85 (0.53-1.34)	44/50	0.57 (0.33- 0.97)	46/54	0.53 (0.30- 0.94)	0.05
Metabolomic Score									
BMI (kg/m2)	147/134	1.0 (ref)	114/116	0.87 (0.61- 1.24)	100/100	0.91 (0.63-1.33)	80/91	0.78 (0.52-1.17)	0.28
Waist circumference (cm)	83/78	1.0 (ref)	87/69	1.08 (0.69-1.71)	59/54	0.95 (0.58-1.56)	47/57	0.72 (0.42-1.20)	0.2
Weight change (kg)	147/126	1.0 (ref)	115/131	0.76 (0.53-1.07)	98/89	0.95 (0.65-1.40)	78/94	0.70 (0.46-1.04)	0.17
Fat mass	82/74	1.0 (ref)	81/64	1.11 (0.70-1.77)	58/57	0.87 (0.53-1.42)	49/53	0.80 (0.47-1.36)	0.31

† Multivariable logistic regression models adjusted for: age at menarche, age at first birth and parity combined, breastfeeding history, history of benign breast disease, BMI at age 18 (kg/m2), hormone use at blood draw (any v. none), alcohol use (g/day) at blood draw, and activity level (MET-hrs/week) at blood draw

*Quartile values were determined from the full cohort (pre-and postmenopausal at blood draw) for each measure. See Supplemental Table 3 for values.

^ p-trend calculated using median of quartiles (defined by the overall cohort)

Associations were more strongly inverse for all adiposity measures, both self-reported and metabolomic, when considering women who were premenopausal at diagnosis (Table 2.4). Trends for this group were not significant, apart from derived fat mass (p-trend=0.05). Associations were more strongly inverse for metabolomic weight change score (Q4 vs. Q1 OR=0.70, 95% CI=0.46-1.04) compared with the self-reported weight change (OR=0.77, 95% CI=0.51-1.18). This pattern was also observed in ER+ breast cancers, though associations were not significant (Supplemental Table 4a).

Among women premenopausal at blood draw but postmenopausal at diagnosis (N cases BMI=287), there were no significant associations with breast cancer, though ORs tended to be >1 for self-reported adiposity and <1 for metabolomic scores, with the exception of self-reported weight change and waist circumference metabolomic score (**Supplemental Table 2.5**).

Postmenopausal women

For women postmenopausal at blood draw, higher self-reported adiposity measures were associated with increased breast cancer risk (**Table 2.5**). In particular, self-reported BMI was associated with significantly increased breast cancer risk (Q4 v. Q1 OR=1.34, 95% CI=0.95-1.89, p-trend=0.01), as was self-reported weight change (OR=1.47, 95% CI=1.05-2.05, p-trend=0.03). All metabolomic scores for adiposity were positively associated with breast cancer risk, with significant trends observed for waist circumference (OR=1.55, 95% CI=1.08-2.22, p-trend=0.01), weight change (OR=1.37, 95% CI=0.99-1.90, p-trend=0.04), and fat mass (OR=1.57, 95% CI=1.09-2.28, p-trend=0.01). Metabolomic scores for BMI, waist circumference and fat mass had stronger positive associations with breast cancer than self-reported measures. Similarly, among ER+ cases, all metabolomic measures were more strongly associated with breast cancer than self-reported measures. ORs comparing tertiles of metabolomic scores for adiposity and risk of ER- breast cancer were mostly less than 1, but no trends were apparent (Supplemental Table 2.4b).

Table 2.5. Association between true and metabolomic-predicted adiposity scores & breast cancer incidence for women postmenopausal at blood draw and diagnosis.†

Adiposity Measures	Quartile 1*		Quartile 2*		Quartile 3*		Quartile 4*		
Self-reported	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	p-trend^
BMI (kg/m2)	118/119	1.0 (ref)	154/181	0.84 (0.60-1.19)	196/205	1.02 (0.73- 1.43)	219/200	1.34 (0.95-1.89)	0.01
Waist circumference (cm)	41/49	1.0 (ref)	119/104	1.42 (0.86-2.37)	142/165	1.07 (0.65- 1.75)	226/228	1.34 (0.83-2.18)	0.44
Weight change (kg)	109/142	1.0 (ref)	148/147	1.20 (0.85-1.71)	184/197	1.13 (0.81- 1.59)	223/189	1.47 (1.05- 2.05)	0.03
Fat mass	78/78	1.0 (ref)	110/138	0.77 (0.51-1.16)	148/169	0.85 (0.57- 1.27)	162/146	1.28 (0.85- 1.93)	0.66
Metabolomic Score									
BMI (kg/m2)	130/158	1.0 (ref)	159/168	1.17 (0.85-1.62)	203/197	1.31 (0.96-1.79)	195/182	1.42 (1.03- 1.97)	0.03
Waist circumference (cm)	111/136	1.0 (ref)	116/130	1.11 (0.77-1.60)	138/143	1.25 (0.88-1.79)	163/137	1.55 (1.08- 2.22)	0.01
Weight change (kg)	129/156	1.0 (ref)	152/167	1.08 (0.78-1.50)	193/177	1.36 (0.99-1.87)	190/175	1.37 (0.99-1.90)	0.03
Fat mass	99/128	1.0 (ref)	111/130	1.13 (0.78-1.65)	137/138	1.32 (0.92-1.91)	151/135	1.57 (1.09-2.28)	0.01

† Multivariable logistic regression models adjusted for: age at menarche, age at first birth and parity combined, breastfeeding history, history of benign breast disease, BMI at age 18 (kg/m2), hormone use at blood draw (any v. none), alcohol use (g/day) at blood draw, and activity level (MET-hrs/week) at blood draw

*Quartile values were determined from the full cohort (pre-and postmenopausal at blood draw) for each measure. See Supplemental Table 3 for values.

^ p-trend calculated using median of quartiles (defined by the overall cohort)

Cross-classified self-reported values & metabolomic scores

We examined the association with breast cancer with cross-classified self-reported and metabolomic scores adiposity measures (**Supplemental Table 2.6**). Compared to individuals with self-reported and metabolomic scores both below the median value, postmenopausal women with high metabolomic scores but low self-reported measures for weight change had a 42% increased risk of breast cancer (OR=1.42, 95% CI=0.97-2.08), which was similar to women who had concordant high self-reported and metabolomic scores (OR=1.35, 95% CI=1.03-1.77). However, this result was not consistent across adiposity measures. In contrast, among premenopausal women discordant for self-reported and metabolomic scores, there were no consistent associations with breast cancer for any of the adiposity measures. Premenopausal women above the median in both measures had suggestively lower risk of breast cancer, which was significant for fat mass for women premenopausal at diagnosis (OR=0.59, 95% CI=0.38-0.93)).

DISCUSSION

We generated metabolomic scores for adiposity measures including BMI, waist circumference, weight change since age 18, and fat mass, to gain insight into the relationship between adiposity and pre- and postmenopausal breast cancer. With a panel of nearly 250 metabolites, representing lipids and amino acids and derivatives, we identified many metabolites associated with adiposity measures. Metabolomic scores for BMI, waist circumference, weight change, and fat mass were generally associated with lower risk of breast cancer among premenopausal women, and higher risk among postmenopausal women. Classes of metabolites positively associated with adiposity included branched chain amino acids (BCAAs), TAGs and DAGs with a low number of double bonds, and glycerophosphocholines. The individual metabolites selected for adiposity scores are reflective of metabolic dysregulation, providing insights into the complex relations between adiposity and breast cancer risk among premenopausal and postmenopausal women.

A large proportion of the 248 metabolites measured were significantly associated with adiposity measures. It is notable that the composition of metabolites for each metabolomic score was largely

overlapping. This provides evidence that self-reported measures we typically use, whether it be BMI, waist circumference, fat mass, or weight change, are similar in their underlying biology with respect to metabolomics. Most metabolites included in the metabolomic score for each adiposity measure did not have a strong individual influence on adiposity, but together, models derived from these measures explained as much as 50% of the variation in each adiposity measure.

One metabolite group with particularly strong positive associations with adiposity measures was branched-chain amino acids (BCAAs), which have been associated with BMI in prior literature,[19,26] A study within the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Cohort (PLCO), the Navy Adenoma Study, and the Shanghai Physical Activity study, that assessed pre-diagnostic serum metabolites, also found significant positive associations between valine and isoleucine and BMI.[18] It is worth noting that we observed potential interactions among adiposity-related metabolites, as reflected by the positive weighting of valine and isoleucine, but inverse weighting of leucine, in LASSO regressions, even though each BCAA was individually positively correlated with adiposity measures. The relationship between BCAAs and adiposity may be driven in part through insulin resistance, a key marker of metabolic dysregulation.[27,28]

Lipids, including triacylglycerols (TAGs) and diacylglycerols (DAGs) with low numbers of double bonds were strongly associated with adiposity measures. Our finding of TAGs and DAGs as key contributors to adiposity measures is consistent in the literature.[18] In diabetes literature, the structure of TAGs appears important for determining influence on insulin action;[19] TAGs with fewer double bonds are associated with insulin resistance. Thus, as with BCAAs, TAGs and DAGs with few double bonds may represent metabolic dysregulation.

Glycerophosphocholine metabolites, notably C38:3 PC, were strongly associated with adiposity measures in our study and may reflect metabolic dysregulation. A recent study compared metabolic profiles in individuals who were classified as metabolically healthy vs. unhealthy, with unhealthy defined as having one or more abnormal metabolic indexes: hyperglycemia, hypertension, dyslipidemia. Metabolite profiles were distinct between groups; notably featuring glycerophosphocholine, BCAAs, and metabolites involved in phenylalanine metabolism and fatty acid biosynthesis.[30]

Consistent with prior literature,[17,18,19,26,31] we observed that uric acid was positively associated with adiposity. Uric acid is also related to metabolic syndrome and hypertension.[32,33]

Carnitines, essential for fatty acid β-oxidation and therefore energy production,[34] were also positively and relatively strongly associated with adiposity measures, a finding consistent with other literature.[18,31] Chen's study of metabolically healthy vs. unhealthy individuals demonstrated a different acylcarnitine profile between the two groups;[30] moreover, acylcarnitine metabolism has been linked to obesity and insulin resistance.[32]

Given that many selected metabolites are associated with metabolic dysregulation, the stronger associations with breast cancer risk we observed for some metabolomic adiposity scores compared to self-reported measures suggests that metabolic dysregulation may be an important underlying contributor to adiposity as a breast cancer risk factor. Further supporting this idea, evidence suggests metabolic syndrome (MetS), defined as a combination of factors including obesity (waist circumference or BMI), triglyceride levels, high density lipoprotein (HDL) levels, hypertension, and hyperglycemia,[35] contributes more than adiposity alone to risk of disease and disease progression. For example, in the National Institute of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, MetS increased breast cancer risk in postmenopausal women by 13%, and women with more components of MetS had a higher risk of breast cancer compared to those with only one component (HR=1.45, 95% CI=0.99-2.13).[36]

Notably, we observed similar metabolites associated with adiposity in premenopausal and postmenopausal women. Thus, the different association between adiposity and breast cancer risk in premenopausal and postmenopausal women is not due to different metabolite profiles themselves, but perhaps to the distinct roles these metabolites, and more broadly, metabolic dysregulation, play at different stages in a woman's life.

BCAAs, which, as noted, are closely linked to insulin resistance, have been associated with breast cancer risk. Within PLCO, an increased risk for postmenopausal breast cancer was observed with higher postmenopausal levels of isoleucine and valine.[17] This finding was replicated in the NHS, with the same participants as in the present study, with a 63% increased risk of breast cancer for top vs. bottom

quartile of isoleucine (p-trend=0.01) among women postmenopausal at blood draw.[37] On the other hand, among women who were premenopausal at blood draw, BCAA levels were associated with lower risk of breast cancer, demonstrating that the same metabolites may have differential effects pre- vs. post-menopause. There is some discrepancy in the literature, as BCAAs in the Women's Health Study (WHS) were not associated with risk, with the exception of leucine.[37,38] C-peptide, a byproduct of insulin processing, and therefore closely linked to BCAAs, is also associated with breast cancer risk.[39] This relationship may differ by menopausal status. Within the European Investigation into Cancer and Nutrition (EPIC), investigators found that serum C-peptide levels were suggestively inversely associated with breast cancer before age 50 (OR=0.70, 95% CI=0.39-1.24, p-trend=0.05), but positively associated with breast cancer for women above age 60 (OR=2.03, 95% CI=1.20-3.43, p-trend=0.01).[40] Similarly, in the NHSII we observed C-peptide was suggestively inversely associated with risk for premenopausal women with fasting blood samples.[41]

Glycerophosphocholines have also been associated with breast cancer risk, though it is unclear whether the risk differs between pre- and postmenopausal women. For example, C32:1 PC was associated with increased breast cancer risk in the Cancer Prevention Study II, a cohort consisting entirely of postmenopausal women.[16] However, within EPIC, a cohort including approximately 25% premenopausal women at blood draw, glycerophosphocholines C38:3 PC and C18:2 LPC were both associated with decreased breast cancer risk (e.g.: OR C18:2 LPC=0.89, 95% CI=0.81-0.96).[42]

Carnitines have been implicated in breast cancer risk as well. In EPIC, acylcarnitine levels, measured in both premenopausal and postmenopausal women, were associated with elevated breast cancer risk.[42] Thus, while some metabolites may have a differential impact on breast cancer risk depending on measurement pre- or postmenopause, evidence suggests that carnitines are not driving the differential relationship between pre- and postmenopausal breast cancer risk.

More broadly, the differential associations observed between levels of adiposity-related metabolites and pre vs. postmenopausal breast cancer risk may be explained in part by the role of oxidative stress associated with MetS. Oxidative stress is related to metabolic disorders, such as cardiovascular disease development and obesity.[43,44] Thus, it is posited that adiposity-related metabolite

profiles contributing to metabolic syndrome (MetS) may also be informative of overall oxidative stress levels. In premenopausal women, some effects of oxidative stress have been shown to prevent cancer,[45] and higher oxidative stress has been suggestively associated with lower breast cancer risk in premenopausal women in prospective studies.[46-48] In contrast, levels of oxidative stress have been associated with increased breast cancer risk in postmenopausal women.[49] Thus, different functions of oxidative stress in pre- vs. postmenopausal breast cancer development may contribute to the observed differences of these metabolites on breast cancer risk before and after menopause.

It is possible that the relationship between adiposity and breast cancer, and the differential associations among pre-and postmenopausal women, may be due, in part, to hormonal influence. Adiposity in postmenopausal breast cancer is associated with higher levels of circulating estrogens.[50] Aromatase, active in adipose tissue, contributes to breast cancer development through conversion of androgens to estrogens in postmenopausal women,[51,52] and changes in aromatase expression in breast tissue are related to metabolic dysregulation markers such as insulin resistance.[53] Thus, higher adiposity may increase risk of breast cancer for postmenopausal women through higher aromatase levels. In premenopausal women, the relationship between adiposity and estrogen is less clear. At the extreme, adiposity may cause anovulatory cycles and lower hormone exposure. In fact, BMI as low as 24 kg/m^2 has been associated with ovulatory disruption.[54] There is further evidence that BMI is inversely related to estrogen levels in premenopausal women, even in normally ovulating individuals, suggesting another potential mechanism of risk reduction.[55,56] This may be related to the correlation between current BMI and BMI in young adulthood. Body fatness at younger ages, measured up to age 20, is associated with lower levels of urinary parent estrogens.[57] It is possible that the impact of early life adiposity on circulating estrogens may have longevity that allows for continued lower estrogen levels in premenopausal women with higher BMI overall. Given that associations we found in pre- and postmenopausal women are stronger in ER+ cases compared with ER- cases, the metabolomic scores may represent the correlation between adiposity and estrogen levels. This makes it difficult to tell if mechanisms driving adiposity-related associations are metabolic or estrogenic. Exploring how to parse these elements would allow us to better understand the importance of metabolomic adiposity.

In the NIH-AARP study mentioned above, women with MetS but normal BMI had worse survival than women without MetS.[58] Thus, it is important to understand the potential impact of discordant adiposity and metabolic health. We observed that postmenopausal women with high metabolomic scores but low self-reported weight change and waist circumference were generally at higher risk of breast cancer, compared to women with low metabolomic and self-reported measures. These women were at similar risk compared to women with concordant high scores for metabolomic and self-reported measures. While this indicates potential importance of considering the contribution of both adiposity and metabolomic profiling to risk, our results using BMI and fat mass as adiposity measures did not echo this finding. Further research is required to better understand the relationship between discordant adiposity and metabolic health.

Previously, we established metabolomic scores for fat mass, BMI, and waist circumference among men in the Health Professionals Follow-Up Study (HPFS).[31] While fewer adiposity-related metabolites were identified compared to our study, there was high overlap between metabolites identified for each adiposity measure, consistent with our findings among women. Classes of metabolites associated with adiposity measures did not differ between men and women. For example, TAGs were positively associated with all measures in HPFS; glycerophosphocholine C38:3 PC was also positively associated with adiposity measures (e.g., correlation with BMI=0.20, p=0.01); and C22:5 CE was inversely related to BMI (r=-0.21).

This study has several strengths. Use of both the NHS and NHSII allowed us to thoroughly investigate adiposity and metabolomics in both premenopausal and postmenopausal women, particularly important given the complicated relationship between adiposity and breast cancer risk by menopausal status. We leveraged metabolomics to understand how metabolic health may affect breast cancer risk and had large numbers of breast cancer cases to evaluate these associations. Despite the advantages of this study, there are also limitations. We did not have a large subset of women who were premenopausal at blood collection and postmenopausal at diagnosis, and ER- cases were limited, making analysis of these subgroups more difficult.

In this study of 3,302 premenopausal and postmenopausal breast cancer cases and controls, we identified many metabolites associated with adiposity measures of BMI, waist circumference, weight change since age 18, and derived fat mass, the majority of which overlapped significantly between adiposity measures. Some metabolomic scores for adiposity were more predictive of breast cancer than self-reported measures, suggesting metabolomics may better capture metabolic dysregulation and improve our understanding of breast cancer risk. Further, we found that metabolic composition of adiposity did not differ between premenopausal and postmenopausal women. This suggests that the opposing associations for adiposity and breast cancer risk by menopausal status reflect the differential impact of metabolic dysregulation on breast cancer risk over the life course. Further exploration of how metabolic dysregulation intersects with menopausal status to differentially impact breast cancer is warranted.

REFERENCES

1. van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol*. 2000;152(6):514-527.

2. White KK, Park S-Y, Kolonel LN, Henderson BE, Wilkens LR. Body size and breast cancer risk: the Multiethnic Cohort. *Int J Cancer*. 2012;131(5):E705-716.

3. Harris HR, Willett WC, Terry KL, Michels KB. Body fat distribution and risk of premenopausal breast cancer in the Nurses' Health Study II. *J Natl Cancer Inst*. 2011;103(3):273-278.

4. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007;335(7630):1134.

5. Ahn J, Schatzkin A, Lacey JV, et al. Adiposity, adult weight change, and postmenopausal breast cancer risk. *Arch Intern Med*. 2007;167(19):2091-2102.

6. Palmer JR, Adams-Campbell LL, Boggs DA, Wise LA, Rosenberg L. A prospective study of body size and breast cancer in black women. *Cancer Epidemiol Biomarkers Prev*. 2007;16(9):1795-1802.

7. Lahmann PH, Hoffmann K, Allen N, et al. Body size and breast cancer risk: findings from the European Prospective Investigation into Cancer And Nutrition (EPIC). *Int J Cancer*. 2004;111(5):762-771.

8. Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). *Cancer Causes Control*. 2002;13(8):741-751.

9. Matthews SB, Thompson HJ. The Obesity-Breast Cancer Conundrum: An Analysis of the Issues. *Int J Mol Sci*. 2016;17(6).

10. Cheraghi Z, Poorolajal J, Hashem T, Esmailnasab N, Doosti Irani A. Effect of body mass index on breast cancer during premenopausal and postmenopausal periods: a meta-analysis. *PLoS One*. 2012;7(12):e51446.

11. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612):569-578.

12. Premenopausal Breast Cancer Collaborative Group, Schoemaker MJ, Nichols HB, et al. Association of Body Mass Index and Age with Subsequent Breast Cancer Risk in Premenopausal Women. *JAMA Oncol*. 2018;4(11):e181771.

13. Luo J, Chen X, Manson JE, et al. Birth weight, weight over the adult life course and risk of breast cancer. *Int J Cancer*. 2020;147(1):65-75.

14. Hartz A, He T, Rimm A. Comparison of adiposity measures as risk factors in postmenopausal women. *J Clin Endocrinol Metab*. 2012;97(1):227-233.

15. Lee DH, Keum N, Hu FB, et al. Development and validation of anthropometric prediction equations for lean body mass, fat mass and percent fat in adults using the National Health and Nutrition Examination Survey (NHANES) 1999-2006. *Br J Nutr*. 2017;118(10):858-866.

16. Moore SC, Mazzilli KM, Sampson JN, et al. A Metabolomics Analysis of Postmenopausal Breast Cancer Risk in the Cancer Prevention Study II. *Metabolites*. 2021;11(2).

17. Moore SC, Playdon MC, Sampson JN, et al. A Metabolomics Analysis of Body Mass Index and Postmenopausal Breast Cancer Risk. *J Natl Cancer Inst*. 2018;110(6):588-597.

18. Moore SC, Matthews CE, Sampson JN, et al. Human metabolic correlates of body mass index. *Metabolomics*. 2014;10(2):259-269.

19. Cheng S, Rhee EP, Larson MG, et al. Metabolite profiling identifies pathways associated with metabolic risk in humans. *Circulation*. 2012;125(18):2222-2231.

20. Gaudet MM, Falk RT, Stevens RD, et al. Analysis of serum metabolic profiles in women with endometrial cancer and controls in a population-based case-control study. *J Clin Endocrinol Metab*. 2012;97(9):3216-3223.

21. Mascanfroni ID, Takenaka MC, Yeste A, et al. Metabolic control of type 1 regulatory T cell differentiation by AHR and HIF1-α. *Nat Med*. 2015;21(6):638-646. doi:10.1038/nm.3868

22. O'Sullivan JF, Morningstar JE, Yang Q, et al. Dimethylguanidino valeric acid is a marker of liver fat and predicts diabetes. *J Clin Invest*. 2017;127(12):4394-4402.

23. Paynter NP, Balasubramanian R, Giulianini F, et al. Metabolic Predictors of Incident Coronary Heart Disease in Women. *Circulation*. 2018;137(8):841-853.

24. Townsend MK, Clish CB, Kraft P, et al. Reproducibility of metabolomic profiles among men and women in 2 large cohort studies. *Clin Chem*. 2013;59(11):1657-1667.

25. Benjamini Y, Krieger AM, Yekutieli D. Adaptive linear step-up procedures that control the false discovery rate. Biometrika. 2006;93(3):491–507

26. Ho JE, Larson MG, Ghorbani A, et al. Metabolomic Profiles of Body Mass Index in the Framingham Heart Study Reveal Distinct Cardiometabolic Phenotypes. *PLoS One*. 2016;11(2):e0148361.

27. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. *Cell Metab*. 2009;9(4):311-326.

28. Wang Q, Holmes MV, Davey Smith G, Ala-Korpela M. Genetic Support for a Causal Role of Insulin Resistance on Circulating Branched-Chain Amino Acids and Inflammation. Diabetes Care. 2017;40(12):1779-1786.

29. Rhee EP, Cheng S, Larson MG, et al. Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. *J Clin Invest*. 2011;121(4):1402-1411.

30. Chen H-H, Tseng YJ, Wang S-Y, et al. The metabolome profiling and pathway analysis in metabolic healthy and abnormal obesity. *Int J Obes (Lond)*. 2015;39(8):1241-1248.

31. Dickerman BA, Ebot EM, Healy BC, et al. A Metabolomics Analysis of Adiposity and Advanced Prostate Cancer Risk in the Health Professionals Follow-Up Study. *Metabolites*. 2020;10(3).

32. Choi HK, Liu S, Curhan G. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2005;52(1):283-289.

33. Coutinho T de A, Turner ST, Peyser PA, Bielak LF, Sheedy PF, Kullo IJ. Associations of serum uric acid with markers of inflammation, metabolic syndrome, and subclinical coronary atherosclerosis. *Am J Hypertens*. 2007;20(1):83-89.

34. Rebouche CJ. Kinetics, pharmacokinetics, and regulation of L-carnitine and acetyl-L-carnitine metabolism. *Ann N Y Acad Sci*. 2004;1033:30-41. doi:10.1196/annals.1320.003

35. Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic Review of Metabolic Syndrome Biomarkers: A Panel for Early Detection, Management, and Risk Stratification in the West Virginian Population. *Int J Med Sci*. 2016;13(1):25-38.

36. Dibaba DT, Braithwaite D, Akinyemiju T. Metabolic Syndrome and the Risk of Breast Cancer and Subtypes by Race, Menopause and BMI. *Cancers (Basel)*. 2018;10(9).

37. Zeleznik OA, Balasubramanian R, Ren Y, et al. Branched chain amino acids and risk of breast cancer. *medRxiv*. Published online January 1, 2020:2020.08.31.20185470.

38. Tobias DK, Hazra A, Lawler PR, et al. Circulating branched-chain amino acids and long-term risk of obesity-related cancers in women. *Sci Rep*. 2020;10(1):16534.

39. Li M, Song L, Yuan J, et al. Association Between Serum Insulin and C-Peptide Levels and Breast Cancer: An Updated Systematic Review and Meta-Analysis. *Front Oncol*. 2020;10:553332.

40. Verheus M, Peeters PHM, Rinaldi S, et al. Serum C-peptide levels and breast cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*. 2006;119(3):659-667.

41. Eliassen AH, Tworoger SS, Mantzoros CS, Pollak MN, Hankinson SE. Circulating insulin and c-peptide levels and risk of breast cancer among predominately premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2007;16(1):161-164.

42. His M, Viallon V, Dossus L, et al. Prospective analysis of circulating metabolites and breast cancer in EPIC. *BMC Med*. 2019;17(1):178.

43. Davies SS, Roberts LJ. F2-isoprostanes as an indicator and risk factor for coronary heart disease. Free Radic Biol Med. 2011;50(5):559-566.

44. Il'yasova D, Wang F, Spasojevic I, Base K, D'Agostino RB, Wagenknecht LE. Urinary F2-isoprostanes, obesity, and weight gain in the IRAS cohort. Obesity (Silver Spring). 2012;20(9):1915-1921.

45. Nemoto S, Finkel T. Ageing and the mystery at Arles. *Nature*. 2004;429(6988):149-152.

46. Dai Q, Gao Y-T, Shu X-O, et al. Oxidative stress, obesity, and breast cancer risk: results from the Shanghai Women's Health Study. *J Clin Oncol*. 2009;27(15):2482-2488.

47. Sisti JS, Lindström S, Kraft P, et al. Premenopausal plasma carotenoids, fluorescent oxidation products, and subsequent breast cancer risk in the nurses' health studies. *Breast Cancer Res Treat*. 2015;151(2):415-425.

48. Nichols HB, Anderson C, White AJ, Milne GL, Sandler DP. Oxidative Stress and Breast Cancer Risk in Premenopausal Women. *Epidemiology*. 2017;28(5):667-674.

49. Fortner RT, Katzke V, Kühn T, Kaaks R. Obesity and Breast Cancer. *Recent Results Cancer Res*. 2016;208:43-65.

50. Simpson ER. Sources of estrogen and their importance. *J Steroid Biochem Mol Biol*. 2003;86(3-5):225-230.

51. Zhou C, Zhou D, Esteban J, et al. Aromatase gene expression and its exon I usage in human breast tumors. Detection of aromatase messenger RNA by reverse transcription-polymerase chain reaction. *J Steroid Biochem Mol Biol*. 1996;59(2):163-171.

52. Sasano H, Nagura H, Harada N, Goukon Y, Kimura M. Immunolocalization of aromatase and other steroidogenic enzymes in human breast disorders. *Hum Pathol*. 1994;25(5):530-535.

53. Brown KA, Iyengar NM, Zhou XK, et al. Menopause Is a Determinant of Breast Aromatase Expression and Its Associations With BMI, Inflammation, and Systemic Markers. *J Clin Endocrinol Metab*. 2017;102(5):1692-1701.

54. Rich-Edwards JW, Spiegelman D, Garland M, et al. Physical activity, body mass index, and ovulatory disorder infertility. *Epidemiology*. 2002;13(2):184-190.

55. Tworoger SS, Eliassen AH, Missmer SA, et al. Birthweight and body size throughout life in relation to sex hormones and prolactin concentrations in premenopausal women. *Cancer Epidemiol Biomarkers Prev*. 2006;15(12):2494-2501.

56. Potischman N, Swanson CA, Siiteri P, Hoover RN. Reversal of relation between body mass and endogenous estrogen concentrations with menopausal status. *J Natl Cancer Inst*. 1996;88(11):756-758.

57. Houghton LC, Sisti JS, Hankinson SE, et al. Estrogen Metabolism in Premenopausal Women Is Related to Early Life Body Fatness. *Cancer Epidemiol Biomarkers Prev*. 2018;27(5):585-593.

58. Dibaba DT, Ogunsina K, Braithwaite D, Akinyemiju T. Metabolic syndrome and risk of breast cancer mortality by menopause, obesity, and subtype. *Breast Cancer Res Treat*. 2019;174(1):209-218.

CHAPTER 3

Premenopausal breast cancer risk prediction in four large prospective cohorts

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ABSTRACT

Breast cancer is the leading cancer diagnosis among premenopausal women worldwide. Younger age at diagnosis of breast cancer is associated with poorer prognosis compared to diagnosis in postmenopausal years. While risk factors and risk prediction models have been determined for overall breast cancer risk, most are driven by postmenopausal cases given the limited number of premenopausal cases in individual cohorts. Given that some risk factors differ in their associations with pre- versus postmenopausal breast cancer, it is important to understand risk prediction in premenopausal women specifically.

We developed a risk prediction model for premenopausal breast cancer based on the 2017-updated Rosner-Colditz risk model. Data from four cohorts in the United States and the United Kingdom were combined for this analysis, including the Nurses' Health Study (NHS), the Nurses' Health Study II (NHSII), Generations Study (GS), and the Sister Study (SS), totaling 289,704 women and 5,165 premenopausal breast cancer cases. We focused analysis on a dataset with complete covariate information (N=211,242, Cases=3,524). We used Cox proportional hazards regression to test risk factors included in the Rosner-Colditz 2017 model on premenopausal breast cancer risk: 1) age at menarche 2) time between menarche and first birth 3) parous (yes/no) 4) parity 5) current BMI (kg/m^2) 6) BMI in young adulthood (kg/m^2) 7) height (cm) 8) family history of breast cancer 9) history of benign breast disease, (biopsy confirmed and unconfirmed combined), 10) current alcohol intake (drinks/week), and 11) premenopausal duration (years). Model selection was completed by removing risk factors with $p<0.05$ from the model one at a time. Three candidate risk factors were added and removed one at a time depending on p-values: ever oral contraceptive use, breastfeeding duration (months), and recent weight change (kg). Variables removed in step 1 were added back to the final model and checked for significance. Gonen and Heller's concordance index was calculated to determine model discrimination and we used the Hosmer-Lemeshow goodness of fit test to determine calibration. We completed sensitivity analyses in a subset with complete information on birth index, and in a group with polygenic risk score (PRS) information to assess the potential usefulness of these variables in a prediction model. A sensitivity

analysis in the full cohort, using the missing indicator method to account for missing variables, was completed.

We found several similarities in the risk factors selected for the premenopausal risk prediction model compared to those included in the Rosner Colditz 2017 model, and some notable differences. Premenopausal duration, time from menarche to first birth, height, alcohol intake, family history of breast cancer, and history of benign breast disease were all included in our risk prediction model and were predictive of increased premenopausal breast cancer risk. Young adulthood BMI was associated with a decreased risk of premenopausal breast cancer (HR pre 1 kg/m^2=0.96, 95% CI=0.94-0.97). An indicator for parous (yes/no) was strongly predictive of reduced premenopausal breast cancer risk (HR=0.49, 95% CI=0.40-0.59). While recent weight change and breastfeeding duration did not influence risk prediction, ever oral contraceptive use was included and represented a reduced risk of premenopausal breast cancer compared with never use (HR=0.88, 95% CI=0.78-0.98). Addition of the birth index variable or parity as opposed to the parous indicator did not improve the model AUC (AUC parous=0.626, AUC birth index=0.621, AUC parity=0.623). Addition of the PRS to the model improved model discrimination, with an AUC increase up to 0.032.

Many variables that predict breast cancer risk among primarily postmenopausal breast cancer cases are also key to predicting premenopausal breast cancer risk. Uniquely in premenopausal women, ever use of oral contraceptives added to the prediction of breast cancer risk and was associated with a decreased risk of premenopausal breast cancer. However, this should be interpreted with caution given that measurement of ever/never use fails to capture details of recency, formulation, and duration of use, all of which have been associated with breast cancer risk. Finer details on birth, such as parity and birth index, are not needed to predict premenopausal breast cancer risk. Addition of the PRS improves premenopausal breast cancer risk prediction.

INTRODUCTION

Breast cancer is the leading cancer diagnosis for premenopausal women.[1] Diagnosis before menopause, compared to after menopause, generally involves a more aggressive form of disease

associated with worse prognosis.[2] Identification of risk factors for premenopausal breast cancer is important to better understand etiologic mechanisms and prevention strategies.

Risk factors and risk prediction models for overall breast cancer are well-established, though models are usually based on primarily postmenopausal women, and therefore are most useful for the prediction of postmenopausal breast cancer. The most prominent risk models are the Gail model[3] and the Rosner-Colditz model.[4,5] The original Rosner-Colditz log-incidence risk model was developed in the Nurses' Health Study (NHS) in 1996 with 2,249 incident cases, 89,312 women, and up to 24 years of follow up.[4] Initially this model included several reproductive risk factors: age at menarche, age at first birth, age at subsequent births (incorporating spacing between births), and age at menopause. Conceptually, reproductive factors are thought to alter the rate of cell proliferation, thus influencing DNA damage accumulation.[6] Spacing of births was included because women with shorter periods from first birth to subsequent births had a reduced risk of breast cancer.[7] Further, the time between menarche and first birth was included, which accounts for an initial increase in breast cancer risk following the first pregnancy.[4] The model was expanded in 2000 to include risk factors identified in epidemiologic studies: type of menopause,[8] duration of postmenopausal hormone (PMH) use,[9] history of benign breast disease, adiposity, height, alcohol use, and family history. Birth index was also incorporated to represent both the number and spacing of pregnancies. It is estimated as the sum of the total years from each birth to a woman's current age, with nulliparous women having a birth index of zero.

While this model works well for overall breast cancer risk prediction, it remains unclear if these risk factors adequately represent premenopausal breast cancer risk, especially as research has identified risk factors that have different associations with pre- and postmenopausal breast cancers.[10,11] Notably, current adiposity shows opposite associations with pre- vs. postmenopausal breast cancer risk.[12] Despite this evidence, the development of a premenopausal risk prediction model has been elusive based on the small number of cases in individual cohorts resulting in inadequate statistical power to develop models.

Here, we combine data from four large prospective cohorts: The Nurses' Health Study (NHS), the Nurses' Health Study II (NHSII), the Generations Study (GS), and the Sister Study (SS), to investigate risk factors for premenopausal breast cancer. We sought to develop a risk prediction model that would be

pertinent to premenopausal women specifically, predicting 5-year risk of breast cancer based on risk factors measured at the start of the 5-year period.

METHODS

Cohort Descriptions

We included four prospective cohorts based in the United States (NHS, NHSII, SS) and the United Kingdom (GS). NHS and NHSII are prospective cohorts of female nurses. NHS was established in 1976, with 121,700 women aged 30-55 years at baseline. NHSII was established in 1989 with 116,429 women aged 25-42 years at baseline.[13] Participants in NHS and NHSII complete detailed biennial questionnaires to record information on risk factors and disease status. Follow up is consistent; cumulative response rates of at least 90% have been achieved for both cohorts. Breast cancer cases are identified by self-report and confirmed by medical record review. Deaths are captured by next of kin, postal service, or by annual linkage to the National Death Index.

The Sister Study was established in 2003, with enrollment continuing until 2009, reaching a baseline enrollment of 50,884 women. Volunteers were women aged 35-74, residing in the United States and Puerto Rico, who had a sister with breast cancer, and had no personal history of cancer. Baseline data collection included questions on breast cancer risk factors across the life course, anthropometric, and socioeconomic factors. A brief update on health status and contact information is completed annually. Every two to three years a detailed follow up questionnaire is mailed to participants, tracking changes in health and risk factors. Medical records, pathology reports, and physician verification are used to complement self-reported breast cancer or other incident cancer information.[14] Information on causes of death is sought from next of kin and death certificates are requested. Additionally, linkage to the National Death Index is used to obtain vital status and cause of death for participants lost to follow-up.

The Generations Study was established in the United Kingdom in 2004 to investigate lifestyle, hormonal, and genetic risk factors for breast cancer. Over 113,700 women aged 16 years or older were enrolled in GS. Participants complete a baseline questionnaire on lifestyle factors that may be associated with breast cancer risk. Detailed follow-up questionnaires were completed 2 ½ years, 6 years, and 9 ½

years following recruitment, by 99%, 96%, and 94% of eligible participants, respectively.[15] Data on cancer incidence, disease status, and mortality are obtained from multiple sources including reports from cohort members or relatives. Annual newsletters are sent to participants; when returned as undeliverable women are traced via email, telephone, and/or by the National Health Service Central Registers (NHSCRs). Data on cancers, deaths, and emigrations can be obtained from the NHSCR. Copies of death certificates are collected to ascertain cause of death and diagnostic confirmation and details of cancer incidence is collected from cancer registry data or through contacting physicians directly.

Data from all cohorts has been harmonized within the Premenopausal Breast Cancer Collaboration to create consistent variables across cohorts.[16]

Identification of breast cancer cases

Breast cancer cases were identified in NHS and NHSII by self-report by participants or next of kin on follow-up questionnaires and confirmed by medical record review. Cases in the Sister Study were similarly identified by self-report; medical records, pathology reports, and physician verification were used to confirm the diagnoses. The GS obtained incident breast cancer information from self-reported data and through the NHSCR, which records incident cancers. Incident cancers for this analysis are identified as in situ or invasive breast cancer diagnoses.

Risk Prediction

Risk Factors from the Rosner-Colditz 2017 Model

We began by considering risk factors included in the most recent update to the Rosner-Colditz model, based on the NHS and NHSII.[17] The final fitted exponential breast cancer model included: duration of premenopause, duration of menopause, type of menopause, age at first birth minus age at menarche, birth index (summarizing number and spacing of births), history of benign breast disease, postmenopausal hormone use (with type and duration), BMI, height, alcohol intake in cumulative grams before and after menopause, adolescent body fatness, mammographic density, and family history of breast cancer. This resulted in a model with an age-adjusted AUC of 0.64, demonstrating an increase in AUC of 0.02 from the 2000 model (Rice 2017).

Candidate Risk Factors

We tested additional risk factors that may be specifically useful to prediction of premenopausal risk: recent weight change, oral contraceptive (OC) use, and breastfeeding duration. Though BMI overall is associated with decreased risk of premenopausal breast cancer, short term weight gain was associated with increased breast cancer risk in pre- and postmenopausal women in the NHS, with a stronger association among premenopausal women.[18] To test short-term weight change, we created a weight calendar using linear interpolation to determine weights throughout the life-course for individual participants in the study. The interpolation relied on measures of weight in young adulthood (age 18-24), and recorded weight and corresponding age at each questionnaire cycle. Use of OCs, especially current use, has been associated with increased breast cancer risk, and has been linked to increased risk among women under 50 years of age.[9,19] Given the limited data on duration and type of formulation in all participating cohorts, we tested the addition of ever/never use of OCs among women to our prediction model. Breastfeeding is associated with decreased risk of both pre- and postmenopausal breast cancer.[20] This variable was tested in the 2017 Rosner-Colditz model but was not significant. Here we reexamined whether breastfeeding duration adds information to the prediction of premenopausal breast cancer. This variable was collected as cumulative months of breast feeding determined at each questionnaire cycle.

Statistical Methods

Modeling Details

As noted, we started with the framework of the 2017-updated Rosner-Colditz model for breast cancer incidence to develop our prediction model for premenopausal breast cancer. STCOX in STATA was used to model 5-year risk using a Cox proportional hazards model. Risk factors were evaluated at the start of the five-year period for individuals and were updated for subsequent 5-year risk periods if participants remained in the study. Due to likelihood of different baseline hazards for distinct cohorts, we stratified by cohort.

We started with the following risk factors: 1) age at menarche 2) time between menarche and first birth (years) 3) parous (yes/no) 4) parity 5) current BMI (kg/m^2) 6) BMI in young adulthood (ages 18-24) (kg/m^2) 7) height (cm) 8) family history of breast cancer 9) history of benign breast disease, (biopsy confirmed and unconfirmed combined), 10) current alcohol intake (drinks/week), and 11)

premenopausal duration (years). Time from menarche to first birth was set to zero for nulliparous women. Based on significance in the 2017 model, an interaction term was also included for benign breast disease and age at menarche. A sensitivity analysis evaluated the model using only those with complete data on birth index and substituting birth index or parity for parous (yes/no). Birth index was derived based on parity and age at each birth, by the following equation: Birth index = (n*current age) – (age birth 1) – (age birth 2) – … – (age birth n), where n represents parity. All analyses were conducted using STATA 17.

Missingness

Most variables had <20% missingness. Because birth index ranged from 21-58% missingness across cohorts, this factor was only considered in a subgroup of participants. Primary analyses were completed in individuals with complete data for all covariates of interest. In a sensitivity analysis using all individuals regardless of missing status, we used the missing indicator method to account for missing variables. Missing values for dichotomous variables were set to zero; missing values for time from menarche to first birth and age at first birth were set to median values for parous individuals. Breastfeeding duration was set to the mean value if parous. Values for missing drinks per week, BMI, and height were set to the median values.

Assumptions

Before beginning with variable selection, we ran the Cox model with all covariates and checked model assumptions of proportional hazards and linearity. Proportional hazards assumption was checked by using a statistical test based on assessment of Schoenfeld residuals, and by evaluating plots of Schoenfeld residuals for each variable vs. analysis time. Schoenfeld residuals are defined by $r_{ik} = x_{ik} - \bar{x}_{w_i k}$, where x_{ik} is the kth covariate for individual i if that subject has an event, and $\bar{x}_{w_i k}$, is the weighted mean of x_{ik} for all subjects in the risk set at the same time. A positive value of r_{ik} indicates a covariate value that is higher than expected. The plot of the residuals should be symmetric about zero. Variables were considered to violate proportional hazards if they had both a significant statistical test for proportional hazards ($p<0.05$), and a skewed Schoenfeld residual plot. For categorical variables, log-

negative-log survivor plots were examined; if lines were roughly parallel, we maintained the assumption of proportional hazards. The proportional hazards assumptions held for all variables in our model.

Linearity of the covariates was checked by plotting martingale residuals against time for each variable and examining patterns. Martingale residuals represent values [1, -∞] for uncensored observations and [0, -∞] for censored observations. Residuals were plotted against time and a locally weighted scatterplot smoothing line (LOWESS) was added to the plots to better visualize the data. This technique requires first running a regression of y on x using only (x_i, y_i) and variables close to this point. The central point is weighted more heavily, while points farther away abased on $|x_j - x_i|$ receive less weight. The regression line predicts the smoothed value of y_i for each point. Therefore, if the LOWESS line is parallel to zero on the y-axis, the assumption of linearity was assumed to hold. No variables had notable patterns in martingale residuals, though additional function forms were tested for continuous variables. Outliers were checked using deviance residuals, a transformation of martingale residuals mean-centered around zero.

Selection of variables

After checking modeling assumptions of proportional hazards and linearity, we performed model selection. To begin this process, we used a backwards selection method. Starting with the full model including relevant Rosner-Colditz variables, any variables that were not significantly associated with the outcome ($p>0.05$) were removed from the model one at a time. After all variables remaining were significantly associated with risk, variables that were removed were retested. If a variable became significant when re-added to the model, it was kept in the model. After all variables were tested and were significant, Model 1 was complete.

Next, additional risk factors were considered. Short term weight change (kg), ever oral contraceptive use (yes/no), and breastfeeding duration (months) were added to Model 1 simultaneously. They were removed one at a time if significance at $p<0.05$ was not reached. After all variables in the model were significant, if any changes were made to Model 1, we again revisited any variables that were eliminated in the original selection of Model 1. This was done to ensure inclusion of new risk factors did

not warrant re-inclusion of previously excluded variables in the model. Model 2, the final model, included variables with significant associations with risk ($p<0.05$).

Assessing Model Performance

Model discrimination, or the ability to separate cases from non-cases, was assessed by Gonen and Heller's Concordance Index for Cox proportional hazards models, a derivative of Harrell's c-index that is an asymptomatically unbiased estimate of concordance.[21] The concordance index is representative of the area under the curve (AUC) for the data, which is based on plotting the sensitivity vs. 1-specificity. Values of the AUC close to 1.00 are favorable and represent perfect discriminatory power of the model. These statistics were compared for the derivation and validation data.

Model calibration, measuring the agreement between observed and predicted risk, was evaluated by categorizing individuals by decile of breast cancer risk and comparing expected and observed risks across categories. The Hosmer-Lemeshow goodness of fit test statistic with 8 degrees of freedom was calculated by the following equation:

$$X_{HL}^2 = \sum_{d=1}^{10} \frac{|O^{(d)} - E^{(d)}|^2}{E^{(d)}}$$

Large p-values, with a threshold >0.05, demonstrated decent calibration of the model.

RESULTS

Participant Characteristics

The Sister Study did not collect information on weight in young adulthood; no participants from this study were included in the dataset for our primary analysis which required complete covariate information. Participant characteristics at baseline are given in **Table 3.1**, separated by derivation and validation datasets. A total of 3,524 breast cancer cases were included in our main dataset. The derivation data contained 140,896 participants and 2,366 cases. Many of the differences seen between the cohorts were expected given the different birth cohorts and age of study entry for each group. Mean age at baseline questionnaire ranged from 34-41 years with the highest mean age at entry in the NHS (40.5, SD=6.1 years), and the lowest age of entry in the NHSII (34.8, SD=4.6 years). Age at menarche

was consistent across cohorts, ranging from 12.4-12.7 years. Parous women was most prevalent in NHS (95%), and least in GS (65%). Mean age at first birth was lowest in NHS (24.8, SD=3.1 years) and highest in GS (27.8, SD=4.7 years). BMI at baseline questionnaire was similar across the three cohorts (range 23.6-24.9 kg/m^2). Patterns seen in the derivation data were similar in the validation dataset (N=70,346, cases=1,291).

Table 3.1. Participant Characteristics at study entry, derivation & validation data^ (N=211,242; Total cases=3,524)

	Derivation Data (N=140,896, cases=2,366)			Validation data (N=70,346, Cases=1,291)		
	GS	NHS	NHSII	GS	NHS	NHSII
N	32369	46410	62117	16,144	23,149	31,053
N cases (full study)	247	915	1204	125	461	572
Age (years)	38.1 (8.0)	40.5 (6.1)	34.8 (4.6)	38.2 (8.0)	40.5 (6.2)	34.9 (4.6)
Age at menarche (years)	12.7 (1.4)	12.5 (1.4)	12.4 (1.4)	12.7 (1.4)	12.5 (1.4)	12.4 (1.4)
Premenopausal duration	25.4 (8.1)	28.0 (6.2)	22.5 (4.9)	25.6 (8.1)	28.0 (6.2)	22.5 (4.9)
Parous (yes)	21058 (65%)	43930 (95%)	44438 (72%)	10,720 (66%)	21,894 (95%)	22,131 (72%)
Parity*	2.0 (0.8)	3.0 (1.5)	2.0 (0.9)	2.00 (0.8)	3.01 (1.5)	2.0 (0.9)
Age at first birth (years)*	27.8 (4.7)	24.8 (3.1)	25.6 (4.1)	27.7 (4.8)	24.9 (3.1)	25.6 (4.1)
Time from menarche to first birth (years)*	15.1 (4.8)	12.3 (3.4)	13.2 (4.3)	15.0 (4.9)	12.4 (3.4)	13.2 (4.3)
Birth index*	19.3 (15.1)	20.3 (12.6)	13.2 (10.5)	19.4 (15.2)	20.0 (12.6)	13.3 (10.5)
Missing birth index* (%)	4430 (14%)	25562 (55%)	11386 (18%)	2340 (14%)	12767 (55%)	5658 (18%)
Breastfeeding duration, months*	12.7 (13.4)	16.6 (11.2)	18.9 (10.8)	12.6 (13.1)	16.4 (11.2)	18.9 (10.7)
Ever oral contraceptive use (%)	30482 (94%)	25,702 (55%)	51,898 (84%)	15,200 (94%)	12,821 (55%)	25,997 (84%)
Height (cm)	165.2 (6.6)	163.9 (6.1)	164.9 (6.5)	165.2 (6.5)	164.0 (6.1)	164.8 (6.5)
BMI (kg/m2)	24.9 (4.7)	23.6 (4.0)	24.1 (4.9)	24.9 (4.7)	23.6 (4.0)	24.1 (4.9)
BMI in young adulthood, age 18-24 (kg/m2)	22.0 (3.2)	21.4 (2.9)	21.3 (3.3)	22.0 (3.2)	21.4 (3.0)	21.3 (3.3)
Weight change in last 4 years (kg)	0.62 (2.32)	0.13 (0.33)	0.50 (2.30)	0.61 (2328)	0.12 (0.34)	0.50 (2.28)
Alcohol use (drinks/week)	5.9 (6.7)	3.6 (5.8)	1.8 (3.6)	5.8 (6.6)	3.6 (5.8)	1.8 (3.5)
Family history of breast cancer (%)	4757 (15%)	2646 (5.7%)	9,970 (16%)	2,402 (15%)	1,323 (5.7%)	4,856 (16%)
History of benign breast disease (%)	4943 (15%)	20,392 (43%)	34,067 (55%)	2,472 (15%)	10,297 (45%)	16,922 (55%)

^Continuous variables given in mean (SD). Categorical variables with N (%).
*Among parous women

Fitted Model

The fitted premenopausal breast cancer risk model among participants with complete covariate information is given in **Table 3.2**. Variables from the original Rosner-Colditz model that were selected into the model included premenopausal duration (here, representative of age), time from menarche to first birth, height, BMI in young adulthood (18-24 years), alcohol use, family history of breast cancer, and history of benign breast disease. Parity was selected into the model in the form of our parous yes/no indicator. Consideration of OC use, breastfeeding duration, and 4-y weight change resulted in OC use being selected into the model. No variables initially removed needed to be reincluded in the model after the addition of OC use. Thus, the final variables in the model included premenopausal duration, time from menarche to first birth, parous (yes/no), height (cm), history of benign breast disease, family history of breast cancer, alcohol use in drinks/week, BMI in young adulthood, and ever oral contraceptive use. The concordance statistic (equivalent to the AUC) was 0.620 in the training data and 0.611 in the testing dataset. The model fit was acceptable; the difference between observed and expected values was not statistically significant (Hosmer-Lemeshow χ_8^2=9.61, p=0.29) (**Table 3.3**).

A longer period from menarche to first birth was associated with a 3% increase in breast cancer risk per additional year. Current BMI was not selected, though BMI in young adulthood was associated with a decrease in breast cancer risk of approximately 4.5% per BMI unit increase. Family history and history of benign breast disease were the two largest risk factors in our model for premenopausal breast cancer, with family history increasing risk by 73% and history of benign breast disease increasing risk by 67% within the five-year risk period. Notably, women who were parous had a 51% reduced risk of premenopausal breast cancer. Having ever used oral contraceptives was significantly inversely associated with premenopausal breast cancer, with a 12% reduction in risk. Breast feeding duration and 4-year weight change were not selected into the risk prediction model.

Table 3.2. Fitted incidence model for breast cancer in complete data cohort, stratified by cohort (N cases=2,366)*

	HR	95% CI		parameter	SE	P>|z|
Premenopausal duration	1.019	1.010	1.029	0.019	0.005	<0.0001
Parous (yes)	0.486	0.402	0.586	-0.723	0.047	<0.0001
Time from menarche to first birth	1.035	1.024	1.045	0.034	0.005	<0.0001
Ever oral contraceptive use	0.876	0.781	0.984	-0.132	0.052	0.025
Height (cm)	1.012	1.006	1.018	0.012	0.003	<0.0001
BMI age 18-24 (kg/m^2)	0.955	0.941	0.969	-0.046	0.007	<0.0001
Alcohol (drinks/week)	1.011	1.003	1.019	0.011	0.004	0.007
Family history of breast cancer (yes)	1.737	1.574	1.917	0.552	0.087	<0.0001
History of benign breast disease (yes)	1.669	1.531	1.820	0.512	0.074	<0.0001

*AUC derivation=0.620; AUC validation= 0.611
Observations=386,269; Time at risk=1,612,072. LR p-value <0.0001

Table 3.3. Observed and expected cases by decile of risk score*

	Risk decile									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Observed Cases	115	131	144	177	217	224	278	312	320	448
Expected cases	113	145	162	177	199	228	257	289	332	464
Hosmer-Lemeshow X^2 , df=8	9.61									
P-value	0.29									

*Within derivation data

Birth Index Subset

The subset of women with non-missing information on birth index (N=149,099, cases=2,402) was used to assess whether the model using birth index or parity (number of births) added information to prediction compared to the model using the parous yes/no indicator. Baseline characteristics of this subset of women and patterns across cohorts were similar to those of the main dataset, with the exception of parity, which only represented up to 2 births based on data collection for this group (**Supplemental Table 3.1**).

Within this subset of women, the model derived using parous (yes/no) included all factors selected in the original dataset, and hazard ratios for selected variables were similar to those seen in the cohort with incomplete birth index information (**Table 3.4**). The AUC of this model was 0.626 in the derivation data, and 0.620 in the validation data. When considering birth index in place of parous (yes/no) in derivation of the model, terms incorporating birth information, including birth index and time from menarche to first birth, were not selected in the final model. Breastfeeding duration was selected into the model, with a slight reduction in risk seen for increased breastfeeding duration (per additional month, HR=0.995, 95% CI=0.991-1.00) (**Table 3.5**). The model derived using parity as opposed to parous yes/no included time from menarche to first birth in the model, though the hazard ratio was smaller than that seen for the parous yes/no derived model (HR parity model=1.02 vs. HR parous model=1.04). Parity was selected as significant in this model, with approximately 20% reduction in risk of premenopausal breast cancer with each additional birth. Other coefficients remained similar to those in the parous indicator derived model (Table 5). The AUC for the birth index model was 0.621 in the derivation data and 0.613 in the validation data; the AUC was higher for the parity model (AUC derivation=0.623, AUC validation=0.616). Both models had worse discrimination than the model including parous yes/no as the birth variable of interest. The Hosmer-Lemeshow X^2 statistic demonstrated non-significant variation comparing observed vs. expected cases per risk decile for all models (**Table 3.6).**

Table 3.4. Fitted incidence model for breast cancer in subset with full birth index information, stratified by cohort (N cases=1,610, N subjects=131,716)*

	HR	95% CI		Parameter	SE	P>|z|
Premenopausal duration	1.034	1.023	1.046	0.034	0.006	<0.0001
Time from menarche to first birth	1.036	1.023	1.049	0.035	0.007	<0.0001
Parous (yes/no)	0.457	0.365	0.572	-0.784	0.053	<0.0001
Oral contraceptive use (ever)	0.843	0.727	0.979	-0.170	0.064	0.025
Height	1.013	1.006	1.021	0.013	0.004	0.001
BMI age 18-24 (kg/m2)	0.957	0.941	0.974	-0.044	0.008	<0.0001
Alcohol, drinks per week	1.010	1.001	1.020	0.010	0.005	0.029
History of benign breast disease (yes)	1.612	1.449	1.792	0.477	0.087	<0.0001
Family history of breast cancer	1.708	1.519	1.919	0.535	0.102	<0.0001

*AUC derivation=0.626; AUC validation=0.620
Observations=264,124; time at risk=1,113,266 person-yrs; LR p<0.0001

Table 3.5. Fitted incidence models for breast cancer in subset with full birth index information (N cases=1,610, N subjects=131,716)

	Consideration of birth index*†						Consideration of parity^					
	HR	95% CI		Parameter	SE	P>|z|	HR	95% CI		Parameter	SE	P>|z|
Premenopausal duration (years)	1.036	1.025	1.048	0.036	0.006	<0.0001	1.036	1.024	1.047	0.035	0.006	<0.0001
Time from menarche to first birth (yrs)							1.015	1.006	1.023	0.014	0.004	0.001
Parity							0.808	0.748	0.873	-0.213	0.032	<0.0001
Breastfeeding duration, months	0.995	0.991	1.000	-0.005	0.002	0.033						
Ever oral contraceptive use	0.817	0.704	0.947	-0.202	0.062	0.007	0.834	0.719	0.968	-0.181	0.063	0.017
Height (cm)	1.014	1.006	1.022	0.014	0.004	<0.0001	1.014	1.006	1.021	0.014	0.004	<0.0001
BMI age 18-24 (kg/m2)	0.959	0.943	0.976	-0.041	0.008	<0.0001	0.958	0.942	0.975	-0.043	0.008	<0.0001
Alcohol, drinks/week	1.012	1.003	1.022	0.012	0.005	0.010	1.011	1.002	1.021	0.011	0.005	0.019
History of benign breast disease	1.600	1.439	1.779	0.470	0.087	<0.0001	1.600	1.439	1.779	0.470	0.087	<0.0001
Family history of breast cancer	1.712	1.523	1.924	0.538	0.102	<0.0001	1.711	1.522	1.923	0.537	0.102	<0.0001

*AUC derivation=0.621; AUC validation=0.613

^AUC derivation=0.623; AUC validation=0.616

†Birth index not selected for inclusion in risk model

Table 3.6. Observed and expected cases by decile of risk score for birth index complete data subset*

Parous (yes/no) model									
		Risk decile							
	1	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**10**
Observed Cases	69	81	104	128	154	149	192	226	313
Expected cases	71	93	108	123	139	155	197	230	320
Hosmer-Lemeshow X^2, df=8	6.46								
P-value	0.6								
Birth index model									
		Risk decile							
	1	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**10**
Observed Cases	74	94	108	129	152	156	204	227	294
Expected cases	75	99	112	126	142	160	194	224	302
Hosmer-Lemeshow X^2, df=8	2.14								
P-value	0.97								
Parity model									
		Risk decile							
	1	**2**	**3**	**4**	**5**	**6**	**8**	**9**	**10**
Observed Cases	80	90	109	114	165	153	215	216	309
Expected cases	77	97	111	125	141	156	194	227	309
Hosmer-Lemeshow X^2, df=8	9.71								
P-value	0.29								

*Within derivation data

Polygenic Risk Score

Participants with available PRS scores were only from a subset of NHS and NHSII cohorts (**Supplemental Table 3.2**), though within these cohorts the distribution of covariates was similar to that of the original dataset. Addition of the PRS to the model developed in Table 2 improved premenopausal breast cancer risk prediction. The AUC derived in the subset of women with a polygenic risk score available (NHS and NHS2 participants, training data N=7,216, events=689) was 0.587 for the model developed in Table 2 (**Table 3.7a**). Addition of the PRS to this group improved the AUC by 0.032 points (AUC with PRS, derivation data=0.619). This improvement in the AUC with the addition of the PRS remained in the validation dataset (change in AUC=0.02). Model calibration was acceptable (Hosmer-Lemeshow χ_8^2 = 7.76, p=0.46 (**Table 3.7b**). A one-unit standard deviation increase in PRS was associated with a 55% increased risk of premenopausal breast cancer. After adding the PRS score, alcohol use and OC use were no longer significant in the prediction model. Main effects of parous (yes/no), time from menarche to first birth, and height had similar magnitudes compared to the model in Table 2. Addition of the PRS resulted in a slight reduction in the influence of family history of breast cancer on risk (HR PRS model=1.19, 95% CI=0.99-1.42 vs. HR non-PRS=1.24, 95% CI=1.04-1.48).

Missing data sensitivity analysis

The prediction model developed in all participants (N=289,704, N cases=5,165), including those with missing data via the missing indicator approach, resulted in a similar AUC compared with the model developed in the complete data group (AUC derivation=0.620, AUC validation=0.613) (**Table 3.8a**) but less-robust calibration (Hosmer-Lemeshow χ_8^2 = 11.68, p=0.17 (**Table 3.8b**)). Characteristics of participants were similar to the complete covariate subjects (**Supplemental Table 3.3**). As with the complete data set, this model selected oral contraceptive use into the model, with a decreased risk in premenopausal breast cancer with ever use of OCs (HR=0.88, 95% CI=0.80-0.97). The hazard ratios for selected variables were similar to those seen in the subset with complete covariate information. For example, having a child decreased risk of premenopausal breast cancer by about 52%, family history of breast cancer increased risk by 75%, history of benign breast disease increased risk by 71%, and BMI in young adulthood was associated with a decreased risk of breast cancer (HR 1 kg/m^2 increase=0.96, 95%

CI=0.94-0.97). Overall, the missing indicator model demonstrated similar directions and magnitudes of included risk factors when compared with the complete data model, though the interpretation of significant missing indicators makes the model less useful in practice.

Table 3.7a. Fitted incidence model for breast cancer with v. without PRS, stratified by cohort (N=7,216, Events=689)

	Without PRS^						With PRS†					
	HR	95% CI		Coef.	SE	P>|z|	HR	95% CI		Coef.	SE	P>|z|
Premenopausal duration (yrs)	0.927	0.909	0.945	-0.076	0.010	<0.0001	0.929	0.911	0.947	-0.074	0.010	<0.0001
Parous (yes/no)	0.487	0.346	0.685	-0.719	0.174	<0.0001	0.485	0.344	0.682	-0.724	0.174	<0.0001
Time from menarche to first birth (yrs)	1.036	1.016	1.055	0.035	0.010	<0.0001	1.038	1.019	1.058	0.037	0.010	<0.0001
OC use (ever)	0.911	0.712	1.167	-0.093	0.126	0.462	0.907	0.708	1.162	-0.098	0.126	0.438
Height (cm)	1.002	0.990	1.014	0.002	0.006	0.774	1.001	0.989	1.013	0.001	0.006	0.864
BMI age 18-24 (kg/m^2)	0.979	0.952	1.008	-0.021	0.015	0.149	0.978	0.950	1.006	-0.023	0.015	0.124
Alcohol drinks/week	1.015	0.997	1.032	0.015	0.009	0.097	1.017	1.000	1.034	0.017	0.009	0.055
Family history of breast cancer	1.241	1.040	1.482	0.216	0.090	0.017	1.187	0.993	1.417	0.171	0.091	0.059
History of benign breast disease (yes)	1.374	1.171	1.612	0.318	0.082	<0.0001	1.347	1.148	1.581	0.298	0.082	<0.0001
Polygenic Risk Score*							**1.547**	**1.373**	**1.743**	**0.436**	**0.061**	**<0.0001**

^AUC derivation=0.587; AUC validation=0.622
†AUC derivation=0.619; AUC validation=0.640
*Z-score standardized, includes 313 SNPs

Table 3.7b. Observed and expected cases by decile of risk score for PRS model*

	Risk decile									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Observed Cases	24	45	49	64	69	72	78	89	81	118
Expected cases	27	38	47	58	67	76	86	86	98	106
Hosmer-Lemeshow X2 , df=8	7.76									
P-value	0.46									

*Within derivation data

Table 3.8a. Fitted incidence model for breast cancer in full data (w/missing values), stratified by cohort (N cases=3,463; N subjects=261,942)*

	HR	95% CI		parameter	SE	P>|z|
Premenopausal duration (per year)	1.014	1.006	1.021	0.014	0.004	0.000
Parous (yes/no)	0.483	0.415	0.562	-0.729	0.037	0.000
Time from menarche to first birth (per year)	1.035	1.026	1.044	0.035	0.004	0.000
Missing time from menarche to first birth	1.621	1.213	2.167	0.483	0.240	0.001
Oral contraceptive use (ever)	0.877	0.795	0.968	-0.131	0.044	0.009
Missing oral contraceptive use	0.806	0.686	0.945	-0.216	0.066	0.008
Height (cm)	1.005	1.001	1.009	0.005	0.002	0.018
BMI in young adulthood, ages 18-24 (kg/m2)	0.955	0.943	0.968	-0.046	0.006	0.000
Missing BMI in young adulthood	0.968	0.818	1.146	-0.032	0.083	0.706
Alcohol, drinks/week	1.011	1.004	1.018	0.011	0.004	0.003
Missing alcohol use	0.793	0.704	0.893	-0.232	0.048	0.000
Family history of breast cancer	1.746	1.604	1.900	0.538	0.076	0.000
History of benign breast disease	1.712	1.592	1.842	0.557	0.235	0.000
Missing history of benign breast disease	0.754	0.409	1.389	-0.282	0.064	0.365

*AUC derivation=0.620; AUC validation=0.613
Coefficient values for derivation data; Observations=566,843, Time at risk=2,335,477

Table 3.8b. Observed and expected cases by decile of risk score for birth index model*

	Risk decile									
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Observed Cases	171	205	216	258	304	317	391	492	456	653
Expected cases	162	206	233	260	294	337	393	436	478	664
Hosmer-Lemeshow X2 , df=8	11.68									
P-value	0.17									

*Within derivation data

DISCUSSION

We developed a risk prediction model for premenopausal breast cancer using harmonized data from four large prospective cohorts. Several components of the Rosner-Colditz 2017 model remained significant for premenopausal women, including premenopausal duration, time from menarche to first birth, ever giving birth, height, alcohol use, weight in young adulthood (ages 18-24), history of benign breast disease, and family history of breast cancer. We found that ever use of oral contraceptive use was significant for premenopausal breast cancer risk prediction, while recent weight change and breastfeeding duration did not influence the risk prediction model. Testing the addition of birth index or parity to our model, we found that neither variable improved predictive ability of the model above that seen with the parous indicator alone. Addition of the PRS to the model did improve discrimination (AUC increase=0.02-0.032) and model calibration.

Several risk factors selected in our risk prediction model for premenopausal breast cancer are also included in the general breast cancer risk models which have been developed within majority postmenopausal women. For instance, time from menarche to first birth was positively associated with premenopausal breast cancer in our model. This "bump" variable, demonstrating an increase in breast cancer risk following first pregnancy, has been important in prior risk factor models with primarily postmenopausal women involved.[5] An additional year of premenopausal time was associated with increased risk of overall breast cancer of approximately 10% in the Rosner-Colditz 2017 model; we found that premenopausal duration was associated with a 2% increase in 5-year risk for premenopausal breast cancer. Because this study only includes premenopausal time, the duration variable is more accurately reflecting current age, whereas the variable captures the duration of premenopause, and not the age of participant, in the model developed in primarily postmenopausal women. We found high risks for benign breast disease history and family history of breast cancer in premenopausal women; these were notably higher than those reported previously for postmenopausal women, illustrating the additional importance of disease history in influencing premenopausal breast cancer risk. Alcohol use was associated with a small increase in risk among premenopausal women, as was height, which is consistent with findings in

postmenopausal women. Though significant, the relative strength of these risk factors remained quite small.

Several notable differences were also identified in our model. First, we found that parous (yes/no) was strongly associated with lower risk of premenopausal breast cancer in all models, with a reduction of approximately 51% in the main risk model. This simplified birth term was not originally examined in the 2017 model. When testing the use of birth index or parity (continuous) as the birth variable of interest, we found no improvement in model prediction, demonstrating that finer detail in birth information is not necessary to obtain adequate premenopausal breast cancer prediction. Notably, testing the addition of birth index resulted in a final model without birth index or time from menarche to first birth, but did include the addition of breastfeeding duration as a protective term. Our model derived using parity in place of parous showed a decreased risk in premenopausal breast cancer for every additional birth, though the magnitude of this decrease was much smaller than the magnitude for the protective effect of parous alone. With a single indicator, all births are wrapped into one variable, thus enhancing the magnitude of the effect. In future work, it would be worthwhile to model the parity term as current age- age at first birth instead, essentially incorporating a portion of the birth index term. In this way, parity will be able to accumulate its effect over time, instead of acting all at once, and the high missingness of birth index will not inhibit a more nuanced measure of parity.

Oral contraceptive use was associated with a reduced risk of premenopausal breast cancer in our risk prediction model; this is in opposition to findings from breast cancer literature.[19,22] Our assessment was of ever vs. never OC use; while the majority of participants were ever users (derivation data: 54% in NHS, 84% in NHSII, and 94% in GS), participants did not differ in other risk factors dependent on OC use. The timing, formulation, and duration of hormone use may all be important components to better capture this risk factor. For instance, some evidence suggests that use of oral contraceptives early in life (e.g., in teenage years) is associated with increased risk of premenopausal breast cancer, whereas later use of OCs is not associated with premenopausal breast cancer.[23] On the other hand, recent OC use was associated with increased risk of breast cancer among women under 50 years of age in a nested case-control study of 1,102 cases and 22,100 matched controls within a large US integrated health care

delivery system.[19] Difference in formulation may influence results; women on low-dose estrogen formulations were not at an increased risk of breast cancer.[19] Moreover, increased risk with current OC use may differ by progestin formulations, as previously observed in NHSII.[24] Another recent study demonstrated that this risk may be further dependent on breast cancer subtype, with recent use of OCs being associated with lower risk of HER2- overexpressing breast tumors and higher risk of luminal A breast cancers.[25] A study among Norwegian women comparing progestin-only and combined oral contraceptives (estrogen + progestin) found combined OC use was not associated with common subtypes of breast cancer (ER+/PR+) but was associated with increased risk of ER- breast cancers, while progestin-only use was associated with ER+ but not ER- breast cancers in premenopausal women.[26] Together, the evidence suggests that a much more detailed measurement of oral contraceptive use, with respect to formulation, duration, and recent vs. former use, needs to be incorporated in future risk prediction models to better capture the role of this risk factor. Stratification of risk prediction by ER/PR subtypes may also be necessary to distinguish risk profiles for premenopausal women.

As noted above, recent weight change and breastfeeding duration were not predictive of premenopausal breast cancer risk. Within the NHS, we observed an increased risk of both pre- and postmenopausal breast cancer with short-term (4-year) weight change.[18] In the Premenopausal Breast Cancer Collaborative Group, an inverse association was observed for BMI and breast cancer risk at all ages.[27] Though weight change in recent years was not evaluated in the consortium, the inverse relationship flattened out over time, with high BMIs at older ages less strongly associated with lower risk than high BMIs at younger ages. This supports the possibility that increases in weight over time may contribute to increased premenopausal breast cancer risk. If this is the case, it is possible that a short-term gain in weight may not be enough to override the general protective effect that higher BMI has on premenopausal breast cancer risk. Overall, the evidence suggests weight change, like BMI, may have a differential effect on pre- and postmenopausal breast cancers, though it does not appear important for premenopausal breast cancer risk prediction.

The evidence for breastfeeding thus far suggests that increased duration of breastfeeding is suggestively, though non-significantly, associated with decreased risk of premenopausal breast cancer;[28,29] we found that breastfeeding was not predictive of premenopausal breast cancer.

The addition of the PRS improved premenopausal breast cancer risk prediction, which aligns with previous findings with addition of a PRS to the Rosner-Colditz overall breast cancer model, developed in NHS and NHSII.[30] Addition of polygenic risk scores with varying numbers of SNPs to risk prediction models have shown benefit to discrimination of risk models in other cohorts as well. For example, addition of an 83-SNP PRS to lifestyle factors increased model discrimination by 0.03 in the Breast Cancer Surveillance Cohort (AUC with PRS=0.65 v. 0.62 without PRS).[31] A one-standard deviation increase in PRS was associated with a 55% increased risk of premenopausal breast cancer in our model. This is similar to the magnitude found when the same 313-SNP PRS was added to an overall breast cancer prediction model developed among 79 studies within the Breast Cancer Association Consortium (BCAC) (OR for PRS=1.61, 95% CI=1.57-1.65).[32] We found here that the addition of the PRS to our model decreased the HR for family history, aligning with previous literature. Attenuation of family history upon the addition of a 77-SNP PRS within BCAC ranged from 5% to 13% depending on age range.[33] For example, for women <40 years of age, the HR for family history without adjustment for PRS was 2.90 (95% CI=2.07-4.07), and 2.76 (95% CI=1.96-3.89) with adjustment for the PRS.[33]

This study's strengths lie in its combination of harmonized data from four separate prospective cohorts for an analysis of premenopausal breast cancer risk prediction. We were able to leverage the large number of premenopausal cases from the combined data to develop the prediction model in a statistically robust manner. Even after limiting our main analysis to individuals with complete covariate data, we had 3,524 cases in total.

We were limited in our ability to adequately assess certain risk factors of interest, such as OC use, as all cohorts included did not have information on duration, timing, and formulation of dose, limiting exploration of these factors. Missing data was a limitation here as well. We restricted our main analysis to individuals with complete covariate information. While our case numbers remained high, we did lose an entire cohort, the Sister Study, as information was not collected for young adulthood weight

in this study. Though analysis of all cohorts using the missing indicator method produced similar results to our complete covariate dataset, several missing indicators were significant in the model, making interpretation difficult. It is worth exploring whether the missing indicator method is introducing bias. As we move forward and extend this project into additional cohorts, it will be important to test other missing data methods, including multiple imputation, to determine if we can maintain the full dataset for analysis. Because some cohorts will be completely missing a variable of interest, imputation will need to be based on a reference dataset.

In conclusion, we developed a prediction model for premenopausal breast cancer with adequate discrimination. The final model included: premenopausal duration, parous (yes/no), time from menarche to first birth, ever OC use, height, BMI in young adulthood (age 18-24), alcohol use, family history of breast cancer, and history of benign breast disease. In subset analyses we observed that the addition of birth index or parity in place of the parous indicator did not improve the model fit, while addition of a PRS improved model discrimination. Our study confirms that several factors identified in earlier overall risk prediction models are also important in premenopausal risk prediction, though some factors were not included here. Current BMI, and detailed description of births via birth index, were not found to be important for premenopausal breast cancer prediction. Moreover, the relative increase in risk of premenopausal breast cancer differed for some risk factors as compared to overall breast cancer; family history and history of benign breast disease were more strongly predictive of premenopausal breast cancer. This study will be expanded to 16 additional cohorts from the Breast Cancer Collaborative Cohort to confirm findings, and missing data methods will be explored to best capture all cohorts.

REFERENCES

1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer*. 2013;49(6):1374-1403.

2. Rosenberg SM, Partridge AH. Management of breast cancer in very young women. *Breast*. 2015;24 Suppl 2:S154-158.

3. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81(24):1879-1886.

4. Rosner B, Colditz GA. Nurses' health study: log-incidence mathematical model of breast cancer incidence. *J Natl Cancer Inst*. 1996;88(6):359-364. doi:10.1093/jnci/88.6.359

5. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol*. 2000;152(10):950-964.

6. Pike MC. Krailo MD. Henderson BE, Casagrande JT, Hoel DC. Hormonal' risk factors, breast tissue age and the age-incidence of breast cancer. Nature. 983;303:767-70.

7. Rosner B, Colditz GA, Willett WC. Reproductive risk factors in a prospective study of breast cancer: the Nurses' Health Study. *Am J Epidemiol*. 1994;139(8):819-835.

8. Stuewing JP, Watson P, Easton DF, et al. Prophylactic oophorectomy in inherited breast/ovarian cancer families. J Natl Cancer Inst Monogr 1995;17:33–5.

9. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet. 1996;347(9017):1713-1727.

10. Schedin P. Pregnancy-associated breast cancer and metastasis. *Nat Rev Cancer*. 2006;6(4):281-291. doi:10.1038/nrc1839

11. Johnson KC, Miller AB, Collishaw NE, et al. Active smoking and secondhand smoke increase breast cancer risk: the report of the Canadian Expert Panel on Tobacco Smoke and Breast Cancer Risk (2009). *Tob Control*. 2011;20(1):e2.

12. Amadou A, Ferrari P, Muwonge R, et al. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. *Obes Rev*. 2013;14(8):665-678.

13. Bao Y, Bertoia ML, Lenart EB, et al. Origin, Methods, and Evolution of the Three Nurses' Health Studies. *Am J Public Health*. 2016;106(9):1573-1581.

14. Sandler DP, Hodgson ME, Deming-Halverson SL, et al. The Sister Study Cohort: Baseline Methods and Participant Characteristics. *Environ Health Perspect*. 2017;125(12):127003. doi:10.1289/EHP1923

15. Swerdlow AJ, Jones ME, Schoemaker MJ, et al. The Breakthrough Generations Study: design of a long-term UK cohort study to investigate breast cancer aetiology. *Br J Cancer*. 2011;105(7):911-917. doi:10.1038/bjc.2011.337

16. Nichols HB, Schoemaker MJ, Wright LB, et al. The Premenopausal Breast Cancer Collaboration: A Pooling Project of Studies Participating in the National Cancer Institute Cohort Consortium. *Cancer Epidemiol Biomarkers Prev*. 2017;26(9):1360-1369.

17. Rice MS, Tworoger SS, Hankinson SE, et al. Breast cancer risk prediction: an update to the Rosner-Colditz breast cancer incidence model. *Breast Cancer Res Treat*. 2017;166(1):227-240. doi:10.1007/s10549-017-4391-5

18. Rosner B, Eliassen AH, Toriola AT, et al. Short-term weight gain and breast cancer risk by hormone receptor classification among pre- and postmenopausal women. *Breast Cancer Res Treat*. 2015;150(3):643-653. doi:10.1007/s10549-015-3344-0

19. Beaber EF, Buist DSM, Barlow WE, Malone KE, Reed SD, Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. *Cancer Res*. 2014;74(15):4078-4089.

20. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert report 2018. Diet, nutrition, physical activity and breast cancer. Available at dietandcancerreport.org.

21. Gönen M, Heller G. Concordance probability and discriminatory power in proportional hazards regression. *Biometrika*. 2005;92(4):965-970.

22. Kahlenborn C, Modugno F, Potter DM, Severs WB. Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. *Mayo Clin Proc*. 2006;81(10):1290-1302.

23. Olsson H, Borg A, Fernö M, Möller TR, Ranstam J. Early oral contraceptive use and premenopausal breast cancer--a review of studies performed in southern Sweden. *Cancer Detect Prev*. 1991;15(4):265-271.

24. Hunter DJ, Colditz GA, Hankinson SE, et al. Oral contraceptive use and breast cancer: a prospective study of young women. *Cancer Epidemiol Biomarkers Prev*. 2010;19(10):2496-2502.

25. Lorona NC, Cook LS, Tang M-TC, Hill DA, Wiggins CL, Li CI. Recent Use of Oral Contraceptives and Risk of Luminal B, Triple-Negative, and HER2-Overexpressing Breast Cancer. *Horm Cancer*. 2019;10(2-3):71-76.

26. Busund M, Bugge NS, Braaten T, Waaseth M, Rylander C, Lund E. Progestin-only and combined oral contraceptives and receptor-defined premenopausal breast cancer risk: The Norwegian Women and Cancer Study. *Int J Cancer*. 2018;142(11):2293-2302.

27. Schoemaker MJ, Nichols HB, Wright LB, et al. Adult weight change and premenopausal breast cancer risk: A prospective pooled analysis of data from 628,463 women. *Int J Cancer*. 2020;147(5):1306-1314.

28. Warner ET, Colditz GA, Palmer JR, Partridge AH, Rosner BA, Tamimi RM. Reproductive factors and risk of premenopausal breast cancer by age at diagnosis: are there differences before and after age 40? *Breast Cancer Res Treat*. 2013;142(1):165-175.

29. Nichols HB, Schoemaker MJ, Cai J, et al. Breast Cancer Risk After Recent Childbirth: A Pooled Analysis of 15 Prospective Studies. *Ann Intern Med*. 2019;170(1):22-30.

30. Zhang X, Rice M, Tworoger SS, et al. Addition of a polygenic risk score, mammographic density, and endogenous hormones to existing breast cancer risk prediction models: A nested case-control study. PLoS Med. 2018;15(9):e1002644.

31. Shieh Y, Hu D, Ma L, et al. Breast cancer risk prediction using a clinical risk model and polygenic risk score. *Breast Cancer Res Treat*. 2016;159(3):513-525.

32. Mavaddat N, Michailidou K, Dennis J, et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *Am J Hum Genet*. 2019;104(1):21-34.

33. Mavaddat N, Pharoah PDP, Michailidou K, et al. Prediction of breast cancer risk based on profiling with common genetic variants. *J Natl Cancer Inst*. 2015;107(5).

DISCUSSION

In this dissertation I aimed to uncover potential etiologic mechanisms for breast cancer and to explore differences in risk profiles for pre- and postmenopausal breast cancers, through both metabolomics and risk prediction modeling.

In **Chapter 1**, I used a nested case-control study within the Nurses' Health Study (NHS) and took an agnostic approach to identify metabolites involved in breast cancer. This work revealed several classes of metabolite groups associated with breast cancer risk. It also provided evidence that associations between metabolites and breast cancer differed based on measurement time. I found that the class of cholesteryl esters were significantly inversely associated with breast cancer risk, especially >10 years prior to breast cancer diagnosis (normalized enrichment score (NES)=-2.26, p_{adj}=0.02). I also found the association between triacylglycerols (TAGs) and breast cancer differed based on number of carbon atoms and double bonds. For example, TAGs with ≥3 double bonds were significantly inversely associated with breast cancer closer to diagnosis (NES=-2.91, p_{adj} =0.03), and TAGS with <3 double bonds were significantly positively associated with breast cancer further from diagnosis (NES=2.57, p=0.02). This finding suggests importance of metabolic dysregulation in breast cancer disease development, as TAGs are also differentially associated with insulin resistance based on number of carbon atoms and double bond status.[1] Moreover, due to the differences seen in metabolite associations based on timing of measurement, I hypothesized that metabolic actions may change across the life-course, thereby altering breast cancer risk over time. These findings led me to explore metabolic dysregulation more closely as an etiologic explanation for breast cancer, and to examine potential metabolic differences based on menopausal status.

In **Chapter 2**, I delved into the specific risk factor of adiposity to gain insights into metabolic dysregulation. Adiposity is known to act differentially in pre- vs. postmenopausal breast cancer; therefore, this provided a unique opportunity to explore how metabolite profiles or actions may change over time. In this analysis, I found glycerophosphocholines, TAGs with low numbers of double bonds,

branched-chain amino acids (BCAAs), and carnitines, were positively associated with adiposity measures. I created a metabolomic score for adiposity measures based on metabolites highly correlated with each adiposity measure. The metabolomic scores for adiposity predicted breast cancer risk better than self-reported measures in some cases, indicating importance of the metabolomic basis of adiposity factors in breast cancer risk. For example, the metabolic score for BMI had a stronger association with breast cancer than self-reported BMI in postmenopausal women (OR metabolomic score=1.42, 95% CI=1.03-1.97 vs. OR self-report=1.34, 95% CI=0.95-1.89). As expected, we observed inverse associations between adiposity measures and premenopausal breast cancer risk, but positive associations between adiposity measures and postmenopausal risk. However, the metabolomic score describing each adiposity measure was very similar when derived in premenopausal or derived in postmenopausal women, with a correlation between scores of 0.94-0.96. This suggests that altered metabolite action over the life-course, and not the metabolite composition itself, influences the differences in pre- vs. postmenopausal breast cancer risk. Closer examination of specific metabolite groups revealed several that may account for the difference in association between adiposity and breast cancer risk for pre- and postmenopausal women. For example, there is evidence that BCAAs are inversely related to premenopausal breast cancer risk,[2] but positively associated with postmenopausal risk.[2-4] BCAAs are also closely linked to insulin resistance,[5] further indicating the importance of metabolic dysregulation in breast cancer development that was noted in Chapter 1, especially given that markers of insulin resistance have also been associated with opposing associations for pre- and postmenopausal breast cancer.[6] I hypothesized that the different effects of adiposity on pre- vs. postmenopausal breast cancer risk may be related to the impact of metabolic-related oxidative stress on cancer development, as oxidative stress has been shown to act differently on pre- and post-menopausal cancers.[7-9]

Taken together, Chapters 1 and 2 identified groups of metabolites associated with breast cancer risk and applied metabolomics knowledge to explain the differences between pre- and postmenopausal risk. Given the finding that metabolites can act differentially depending on stage of a woman's life, it became apparent that risk factors for premenopausal cancer may not be the same as those known for

postmenopausal breast cancer. Because of this, there was a need to broadly explore premenopausal breast cancer risk factors

Thus, in **Chapter 3**, I focused solely on premenopausal breast cancer, and developed a risk prediction model using information from four large prospective cohorts. To develop this prediction model, I started from risk models previously created in primarily postmenopausal cohorts.[10-12] Candidate risk factors of oral contraceptive use, breastfeeding duration, and recent weight change were tested. Several factors identified in primarily postmenopausal risk prediction models were also predictive of risk of premenopausal breast cancer, while some factors that were important in models for primarily postmenopausal breast cancer were not essential to the risk prediction of premenopausal breast cancer, including BMI. This is interesting to note given the earlier finding that underlying mechanisms of metabolic dysregulation, perhaps not measured well enough by BMI itself, may be causing the differential associations seen between BMI and pre- vs. postmenopausal breast cancer. The model identified ever oral contraceptive as a protective factor unique to premenopausal risk prediction. This contrasts with expected associations based on previous epidemiologic literature and should be interpreted with caution based on the evaluation of ever vs. never use here, which does not capture finer details of recency, duration, and formulation.[13-15] It is possible that past users make up more of the ever users than current users, suggesting that latency of oral contraceptive use may be important for determining risk. The risk factor of family history was stronger in premenopausal women compared with previous risk models (HR premenopausal= 1.74, 95% CI=1.57-1.92 vs. HR primarily postmenopausal[16]= 1.53, 95% CI=1.43-1.64), indicating potential increased importance in inherited genetic factors for premenopausal breast cancer risk. Moreover, addition of the polygenic risk score (PRS) to our model improved discrimination (AUC increase 0.020-0.032). This information can inform exploration of metabolites and biologic pathways. It seems pertinent to focus on determining how metabolites are affected based on inherited genetic alterations within premenopausal women to expose areas for possible prevention mechanisms.

The major strength of this dissertation lies in the large datasets available for use in each of the studies. Over 300 metabolites were measured for agnostic evaluation of metabolites associated with

breast cancer for a total of 939 cases and controls. Metabolites were also measured at two different time points, allowing the unique ability to examine changes in metabolite associations with breast cancer over time. To evaluate metabolomics of adiposity measures and relation to breast cancer, a study of 1,652 cases and controls was used. Over half of participants were premenopausal at blood draw, and one-fourth were premenopausal at diagnosis, allowing the robust examination of differences by pre- vs. postmenopausal status at blood draw and at diagnosis. Finally, a total of 5,165 premenopausal breast cancer cases were available for risk prediction modeling, which is comparable to the dataset that was used to develop the most recent (2017) Rosner-Colditz prediction model in primarily postmenopausal breast cancer, a truly remarkable feat for the study of premenopausal breast cancer.

Despite these strengths, this dissertation has several limitations that should be addressed in future studies. While I was able to assess metabolites over time for many postmenopausal women using two blood collections within NHS, this was not possible for women diagnosed with premenopausal breast cancer given limited cases. This will be important data to gather in the future to enhance understanding of how metabolomic changes in pre-menopause influence premenopausal breast cancer risk. The inability to explore relationships in ER- breast cancer with robust statistical power due to limited cases is a limitation across all studies in this dissertation. Further work in consortium projects will be needed to reveal intricacies of metabolomic relationships for breast cancer by molecular subtype. Missing data posed threats to internal validity throughout this work. Missing data was perhaps the biggest barrier to the premenopausal risk prediction model. Ideally, imputation would be performed within individual cohorts to gather this missing data; however, because some of the cohorts used for this analysis were completely missing a variable of interest, missingness for that variable could not be imputed in such a manner. With that in mind, the difficulties of imputation led me to use complete data, which eliminated use of an entire cohort. Trial of the missing indicator method revealed difficulties in interpretation due to significant missing indicator variables. Future work will need to focus on how to combine cohort data while incorporating missing data in a statistically sound manner.

Overall, these studies increase understanding of breast cancer etiology by identifying potential metabolomic groups associated with breast cancer risk, examining how these metabolites act

differentially in pre- and postmenopausal breast cancer risk, and seeking out risk factors relevant to premenopausal breast cancer risk prediction to serve as a basis for further exploration. Future research will focus on continuing to uncover the mechanisms that underlie the action of breast cancer risk factors and evaluating how these mechanisms differ for pre- and postmenopausal breast cancer.

REFERENCES

1. Rhee EP, Cheng S, Larson MG, et al. Lipid profiling identifies a triacylglycerol signature of insulin resistance and improves diabetes prediction in humans. *J Clin Invest*. 2011;121(4):1402-1411.

2. Zeleznik OA, Balasubramanian R, Ren Y, et al. Branched chain amino acids and risk of breast cancer. *medRxiv*. Published online January 1, 2020:2020.08.31.20185470.

3. Tobias DK, Hazra A, Lawler PR, et al. Circulating branched-chain amino acids and long-term risk of obesity-related cancers in women. *Sci Rep*. 2020;10(1):16534.

4. Moore SC, Playdon MC, Sampson JN, et al. A Metabolomics Analysis of Body Mass Index and Postmenopausal Breast Cancer Risk. *J Natl Cancer Inst*. 2018;110(6):588-597.

5. Wang Q, Holmes MV, Davey Smith G, Ala-Korpela M. Genetic Support for a Causal Role of Insulin Resistance on Circulating Branched-Chain Amino Acids and Inflammation. Diabetes Care. 2017;40(12):1779-1786.

6. Verheus M, Peeters PHM, Rinaldi S, et al. Serum C-peptide levels and breast cancer risk: results from the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*. 2006;119(3):659-667.

7. Davies SS, Roberts LJ. F2-isoprostanes as an indicator and risk factor for coronary heart disease. *Free Radic Biol Med*. 2011;50(5):559-566.

8. Nemoto S, Finkel T. Ageing and the mystery at Arles. *Nature*. 2004;429(6988):149-152. doi:10.1038/429149a

9. Dai Q, Gao Y-T, Shu X-O, et al. Oxidative stress, obesity, and breast cancer risk: results from the Shanghai Women's Health Study. *J Clin Oncol*. 2009;27(15):2482-2488. doi:10.1200/JCO.2008.19.7970

10. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst*. 1989;81(24):1879-1886.

11. Rosner B, Colditz GA. Nurses' health study: log-incidence mathematical model of breast cancer incidence. *J Natl Cancer Inst*. 1996;88(6):359-364.

12. Colditz GA, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol*. 2000;152(10):950-964.

13. Kahlenborn C, Modugno F, Potter DM, Severs WB. Oral contraceptive use as a risk factor for premenopausal breast cancer: a meta-analysis. *Mayo Clin Proc*. 2006;81(10):1290-1302.

14. Beaber EF, Buist DSM, Barlow WE, Malone KE, Reed SD, Li CI. Recent oral contraceptive use by formulation and breast cancer risk among women 20 to 49 years of age. *Cancer Res*. 2014;74(15):4078-4089.

15. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Lancet. 1996;347(9017):1713-1727.

16. Rice MS, Tworoger SS, Hankinson SE, et al. Breast cancer risk prediction: an update to the Rosner-Colditz breast cancer incidence model. *Breast Cancer Res Treat*. 2017;166(1):227-240.

APPENDIX 1: Supplementary Materials Chapter 1

Supplemental Table 1.1. Odds ratios for breast cancer risk comparing 90th to 10th percentiles of metabolite levels, measured at distant blood.**

				Unadjusted model		Multivariable adjusted^	
Metabolite Name	**HMDB ID**	**Class**	**Subclass**	**OR (95% CI)**	**p value**	**OR (95% CI)**	**p value**
allantoin	HMDB0000462	Azoles	Imidazoles	1.16 (0.91-1.48)	0.235	1.06 (0.82-1.36)	0.660
urocanic acid	HMDB0000301	Azoles	Imidazoles	0.99 (0.74-1.33)	0.956	0.99 (0.74-1.34)	0.969
metronidazole	HMDB0015052	Azoles	Imidazoles	1.15 (0.81-1.63)	0.428	0.89 (0.61-1.31)	0.563
sulfamethoxazole	HMDB0015150	Benzene and substituted derivatives	Benzenesulfonamides	1.28 (0.89-1.82)	0.181	1.35 (0.94-1.95)	0.107
2-aminohippuric acid	HMDB0001867	Benzene and substituted derivatives	Benzoic acids and derivatives	0.86 (0.68-1.09)	0.219	0.8 (0.62-1.02)	0.075
4-hydroxyhippurate	HMDB0013678	Benzene and substituted derivatives	Benzoic acids and derivatives	0.88 (0.69-1.11)	0.273	0.88 (0.69-1.11)	0.278
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	0.84 (0.66-1.06)	0.148	0.9 (0.71-1.16)	0.423
N-acetylputrescine	HMDB0002064	Carboximidic acids and derivatives	Carboximidic acids	1.28 (1.01-1.63)	0.042	1.22 (0.95-1.56)	0.120
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	1.23 (0.98-1.54)	0.072	1.2 (0.95-1.52)	0.121
palmitoylethanol-amide	HMDB0002100	Carboximidic acids and derivatives	Carboximidic acids	0.88 (0.68-1.13)	0.315	0.84 (0.64-1.09)	0.186
N1-acetylspermidine	HMDB0001276	Carboximidic acids and derivatives	Carboximidic acids	0.83 (0.65-1.07)	0.157	0.84 (0.65-1.08)	0.178
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.5 (1.17-1.94)	0.002	1.41 (1.08-1.85)	0.012

Supplemental Table 1.1 (continued).

homoarginine	HMDB0000670*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.41 (1.11-1.8)	0.005	1.3 (1.01-1.68)	0.039
lysine	HMDB0000182	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.38 (1.08-1.77)	0.011	1.31 (1.01-1.69)	0.040
citrulline	HMDB0000904	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.74 (0.58-0.94)	0.015	0.78 (0.61-1)	0.051
alanine	HMDB0000161	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.37 (1.07-1.75)	0.013	1.25 (0.96-1.61)	0.094
proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.37 (1.07-1.75)	0.012	1.33 (1.03-1.72)	0.032
histidine	HMDB0000177	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.28 (0.99-1.66)	0.061	1.22 (0.94-1.6)	0.138
N-acetylhistidine	HMDB0032055	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.78 (0.61-0.99)	0.041	0.82 (0.64-1.05)	0.115
oleoyl glycine	HMDB0013631	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.81 (0.64-1.04)	0.093	0.79 (0.61-1.01)	0.065
methionine	HMDB0000696	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.22 (0.96-1.54)	0.104	1.19 (0.93-1.52)	0.160
asparagine	HMDB0000168	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.12 (0.87-1.44)	0.377	1.18 (0.91-1.53)	0.224
threonine	HMDB0000167	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.17 (0.92-1.49)	0.209	1.2 (0.93-1.54)	0.162

Supplemental Table 1.1 (continued).

phenylacetylglutamine	HMDB0006344	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.82 (0.65-1.04)	0.096	0.84 (0.66-1.07)	0.152
tyrosine	HMDB0000158	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.27 (1-1.61)	0.054	1.11 (0.86-1.43)	0.428
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.3 (1.03-1.65)	0.028	1.17 (0.9-1.51)	0.236
ADMA/SDMA	HMDB0001539	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.2 (0.93-1.54)	0.153	1.13 (0.87-1.46)	0.351
leucine	HMDB0000687	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.3 (1.03-1.65)	0.029	1.17 (0.9-1.51)	0.244
N6,N6,N6-trimethyllysine	HMDB0001325	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.89 (0.7-1.13)	0.337	0.82 (0.64-1.05)	0.112
serine	HMDB0000187	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.09 (0.85-1.4)	0.500	1.22 (0.94-1.58)	0.134
N-acetyltryptophan	HMDB0013713	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.87 (0.69-1.09)	0.228	0.83 (0.65-1.05)	0.123
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.86 (0.69-1.09)	0.207	0.84 (0.66-1.06)	0.137
glycine	HMDB0000123	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.82 (0.64-1.04)	0.102	0.89 (0.69-1.14)	0.356
NMMA	HMDB0029416	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.19 (0.93-1.51)	0.162	1.09 (0.85-1.41)	0.482

Supplemental Table 1.1 (continued).

pipecolic acid	HMDB0000716	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.09 (0.86-1.39)	0.474	1.05 (0.82-1.35)	0.683
hydroxyproline	HMDB0000725	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.9 (0.71-1.14)	0.387	0.9 (0.71-1.14)	0.387
4-acetamidobutanoate	HMDB0003681	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.9 (0.71-1.15)	0.419	0.87 (0.68-1.12)	0.279
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.9 (0.71-1.14)	0.388	0.89 (0.69-1.13)	0.333
N6,N6-dimethyllysine	HMDB0013287	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.14 (0.9-1.44)	0.289	1.07 (0.84-1.37)	0.565
N-lauroylglycine	HMDB0013272	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.13 (0.88-1.46)	0.326	1.08 (0.83-1.4)	0.562
pantothenate	HMDB0000210	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.93 (0.73-1.19)	0.568	0.88 (0.68-1.12)	0.297
creatinine	HMDB0000562	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.73-1.17)	0.506	0.92 (0.72-1.17)	0.483
aminoisobutyric acid	HMDB0001906*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.84-1.37)	0.582	1.07 (0.83-1.38)	0.593
N6-acetyllysine	HMDB0000206*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.06 (0.84-1.34)	0.615	1.02 (0.8-1.3)	0.888
guanidinoacetic acid	HMDB0000128	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.97 (0.77-1.22)	0.792	1.08 (0.84-1.39)	0.536

Supplemental Table 1.1 (continued).

GABA	HMDB0000112	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.84-1.36)	0.575	0.99 (0.77-1.26)	0.919
valine	HMDB0000883	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.19 (0.94-1.5)	0.145	1.05 (0.82-1.36)	0.687
2-aminooctanoic acid	HMDB0000991*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95 (0.76-1.19)	0.645	0.97 (0.77-1.23)	0.828
betaine	HMDB0000043	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.91 (0.7-1.18)	0.475	0.97 (0.74-1.28)	0.851
1-methylhistidine	HMDB0000001	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95 (0.75-1.21)	0.673	0.94 (0.73-1.21)	0.645
glutamine	HMDB0000641	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.96 (0.76-1.22)	0.749	1.06 (0.83-1.35)	0.662
proline betaine	HMDB0004827	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.98 (0.77-1.24)	0.863	1.06 (0.83-1.35)	0.660
creatine	HMDB0000064	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.02 (0.8-1.28)	0.897	0.98 (0.77-1.24)	0.848
dimethylglycine	HMDB0000092	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.02 (0.8-1.3)	0.891	1.04 (0.81-1.33)	0.773
5-hydroxymethyl-4-methyluracil	HMDB0000544	Diazines	Pyrimidines and pyrimidine derivatives	0.88 (0.67-1.16)	0.354	0.8 (0.6-1.06)	0.118
cytosine	HMDB0000630	Diazines	Pyrimidines and pyrimidine derivatives	0.95 (0.74-1.23)	0.703	0.94 (0.72-1.22)	0.652
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.72 (0.57-0.92)	0.007	0.73 (0.57-0.93)	0.012
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	0.8 (0.64-1.01)	0.064	0.73 (0.57-0.93)	0.010
C4 carnitine	HMDB0002013	Fatty Acyls	Fatty acid esters	0.89 (0.71-1.13)	0.348	0.86 (0.67-1.09)	0.208
C14 carnitine	HMDB0005066	Fatty Acyls	Fatty acid esters	1.18 (0.93-1.5)	0.169	1.08 (0.85-1.39)	0.522

Supplemental Table 1.1 (continued).

C4-OH carnitine	HMDB0013127	Fatty Acyls	Fatty acid esters	1.2 (0.95-1.52)	0.131	1.1 (0.85-1.41)	0.468
C14:2 carnitine	HMDB0013331	Fatty Acyls	Fatty acid esters	0.86 (0.68-1.1)	0.234	0.86 (0.67-1.1)	0.221
C12:1 carnitine	HMDB0013326	Fatty Acyls	Fatty acid esters	0.91 (0.71-1.15)	0.416	0.87 (0.68-1.12)	0.275
C3 carnitine	HMDB0000824	Fatty Acyls	Fatty acid esters	0.96 (0.76-1.22)	0.739	0.89 (0.69-1.14)	0.344
C10:2 carnitine	HMDB0013325	Fatty Acyls	Fatty acid esters	0.91 (0.73-1.15)	0.441	0.88 (0.69-1.11)	0.285
C12 carnitine	HMDB0002250	Fatty Acyls	Fatty acid esters	0.9 (0.71-1.14)	0.373	0.86 (0.68-1.1)	0.241
C10 carnitine	HMDB0000651	Fatty Acyls	Fatty acid esters	0.9 (0.71-1.14)	0.393	0.89 (0.7-1.14)	0.351
C8 carnitine	HMDB0000791	Fatty Acyls	Fatty acid esters	0.92 (0.72-1.16)	0.484	0.9 (0.7-1.14)	0.382
C9 carnitine	HMDB0013288	Fatty Acyls	Fatty acid esters	1.06 (0.85-1.33)	0.605	1.06 (0.84-1.33)	0.644
C14:1 carnitine	HMDB0002014	Fatty Acyls	Fatty acid esters	0.93 (0.73-1.18)	0.542	0.9 (0.7-1.15)	0.411
C26 carnitine	HMDB0006347	Fatty Acyls	Fatty acid esters	0.97 (0.77-1.23)	0.811	0.94 (0.73-1.2)	0.606
C5 carnitine	HMDB0000688	Fatty Acyls	Fatty acid esters	1.12 (0.89-1.41)	0.326	1.02 (0.8-1.31)	0.850
C7 carnitine	HMDB0013238	Fatty Acyls	Fatty acid esters	1.05 (0.83-1.33)	0.689	1.01 (0.79-1.29)	0.956
C6 carnitine	HMDB0000705	Fatty Acyls	Fatty acid esters	1.03 (0.81-1.3)	0.813	0.95 (0.74-1.21)	0.672
C2 carnitine	HMDB0000201	Fatty Acyls	Fatty acid esters	1.03 (0.81-1.3)	0.835	0.95 (0.74-1.23)	0.717
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	1.03 (0.8-1.31)	0.829	1.04 (0.8-1.34)	0.776
3-dehydroxycarnitine	HMDB0006831	Fatty Acyls	Fatty acids and conjugates	0.99 (0.78-1.27)	0.967	1 (0.78-1.29)	0.996
C34:2 DAG	HMDB0007103*	Fatty Acyls	Lineolic acids and derivatives	1.36 (1.08-1.72)	0.009	1.23 (0.96-1.59)	0.104
C34:3 DAG	HMDB0007132*	Fatty Acyls	Lineolic acids and derivatives	1.23 (0.99-1.54)	0.066	1.12 (0.88-1.42)	0.364
C36:3 DAG	HMDB0007219*	Fatty Acyls	Lineolic acids and derivatives	1.16 (0.93-1.45)	0.197	1.11 (0.87-1.42)	0.385
C36:4 DAG	HMDB0007248*	Fatty Acyls	Lineolic acids and derivatives	1.05 (0.84-1.32)	0.643	1.05 (0.83-1.33)	0.685
C32:0 DAG	HMDB0007098*	Glycerolipids	Diacylglycerols	1.46 (1.14-1.85)	0.002	1.26 (0.96-1.63)	0.091
C34:0 DAG	HMDB0007100*	Glycerolipids	Diacylglycerols	1.38 (1.09-1.76)	0.008	1.17 (0.9-1.52)	0.246
C34:1 DAG	HMDB0007102*	Glycerolipids	Diacylglycerols	1.33 (1.06-1.69)	0.016	1.17 (0.9-1.52)	0.232
C32:1 DAG	HMDB0007099*	Glycerolipids	Diacylglycerols	1.29 (1.02-1.63)	0.032	1.13 (0.88-1.47)	0.337

Supplemental Table 1.1 (continued).

C36:1 DAG	HMDB0007216*	Glycerolipids	Diacylglycerols	1.28 (1.01-1.62)	0.040	1.09 (0.85-1.41)	0.491
C36:2 DAG	HMDB0007218*	Glycerolipids	Diacylglycerols	1.22 (0.97-1.54)	0.092	1.1 (0.85-1.41)	0.470
C38:5 DAG	HMDB0007199*	Glycerolipids	Diacylglycerols	1.1 (0.87-1.39)	0.411	1 (0.78-1.28)	0.987
C51:0 TAG	HMDB0031106*	Glycerolipids	Triacylglycerols	1.46 (1.15-1.86)	0.002	1.3 (1.01-1.68)	0.044
C43:0 TAG	HMDB0042062*	Glycerolipids	Triacylglycerols	1.39 (1.09-1.77)	0.009	1.28 (0.99-1.65)	0.059
C43:2 TAG	HMDB0043169*	Glycerolipids	Triacylglycerols	1.41 (1.11-1.79)	0.005	1.24 (0.96-1.6)	0.096
C55:2 TAG	HMDB0042226*	Glycerolipids	Triacylglycerols	1.41 (1.11-1.79)	0.005	1.29 (1-1.66)	0.054
C43:1 TAG	HMDB0042098*	Glycerolipids	Triacylglycerols	1.4 (1.1-1.78)	0.006	1.25 (0.97-1.6)	0.088
C48:0 TAG	HMDB0005356*	Glycerolipids	Triacylglycerols	1.38 (1.09-1.76)	0.007	1.17 (0.91-1.52)	0.225
C50:0 TAG	HMDB0005357*	Glycerolipids	Triacylglycerols	1.4 (1.1-1.78)	0.006	1.18 (0.9-1.53)	0.226
C50:1 TAG	HMDB0005360*	Glycerolipids	Triacylglycerols	1.41 (1.11-1.79)	0.004	1.2 (0.92-1.57)	0.173
C51:1 TAG	HMDB0042104*	Glycerolipids	Triacylglycerols	1.39 (1.09-1.75)	0.007	1.26 (0.97-1.62)	0.082
C52:0 TAG	HMDB0005365*	Glycerolipids	Triacylglycerols	1.37 (1.08-1.74)	0.009	1.17 (0.9-1.52)	0.231
C50:2 TAG	HMDB0005377*	Glycerolipids	Triacylglycerols	1.39 (1.1-1.76)	0.006	1.2 (0.93-1.57)	0.166
C45:2 TAG	HMDB0043170*	Glycerolipids	Triacylglycerols	1.35 (1.06-1.71)	0.014	1.19 (0.92-1.53)	0.183
C56:1 TAG	HMDB0005396*	Glycerolipids	Triacylglycerols	1.34 (1.05-1.71)	0.021	1.17 (0.9-1.52)	0.241
C56:2 TAG	HMDB0005404*	Glycerolipids	Triacylglycerols	1.31 (1.03-1.67)	0.029	1.16 (0.9-1.5)	0.243
C52:1 TAG	HMDB0005367*	Glycerolipids	Triacylglycerols	1.34 (1.06-1.7)	0.014	1.13 (0.87-1.47)	0.358
C56:3 TAG	HMDB0005410*	Glycerolipids	Triacylglycerols	1.27 (1-1.61)	0.053	1.2 (0.93-1.53)	0.160
C46:0 TAG	HMDB0010411*	Glycerolipids	Triacylglycerols	1.29 (1.02-1.64)	0.034	1.11 (0.86-1.43)	0.416
C44:0 TAG	HMDB0042063*	Glycerolipids	Triacylglycerols	1.3 (1.02-1.65)	0.031	1.15 (0.89-1.48)	0.295
C45:1 TAG	HMDB0042099*	Glycerolipids	Triacylglycerols	1.29 (1.02-1.64)	0.034	1.17 (0.91-1.5)	0.217
C54:1 TAG	HMDB0005395*	Glycerolipids	Triacylglycerols	1.31 (1.03-1.66)	0.029	1.13 (0.87-1.46)	0.353
C48:1 TAG	HMDB0005359*	Glycerolipids	Triacylglycerols	1.3 (1.03-1.65)	0.026	1.11 (0.86-1.44)	0.408
C49:2 TAG	HMDB0011706*	Glycerolipids	Triacylglycerols	1.26 (1-1.58)	0.054	1.17 (0.92-1.49)	0.202
C47:1 TAG	HMDB0042100*	Glycerolipids	Triacylglycerols	1.23 (0.98-1.56)	0.079	1.14 (0.89-1.45)	0.302
C49:1 TAG	HMDB0011705*	Glycerolipids	Triacylglycerols	1.23 (0.99-1.53)	0.065	1.12 (0.89-1.41)	0.332
C52:2 TAG	HMDB0005369*	Glycerolipids	Triacylglycerols	1.3 (1.03-1.65)	0.027	1.16 (0.89-1.51)	0.277
C54:2 TAG	HMDB0005403*	Glycerolipids	Triacylglycerols	1.28 (1.01-1.62)	0.044	1.13 (0.88-1.46)	0.343
C58:8 TAG	HMDB0005413*	Glycerolipids	Triacylglycerols	1.12 (0.89-1.41)	0.332	1.11 (0.88-1.41)	0.380

Supplemental Table 1.1 (continued).

C50:3 TAG	HMDB0005433*	Glycerolipids	Triacylglycerols	1.27 (1.01-1.61)	0.044	1.14 (0.88-1.47)	0.326
C47:2 TAG	HMDB0042076*	Glycerolipids	Triacylglycerols	1.23 (0.97-1.56)	0.082	1.12 (0.87-1.43)	0.373
C56:6 TAG	HMDB0005456*	Glycerolipids	Triacylglycerols	0.92 (0.73-1.16)	0.502	0.88 (0.69-1.11)	0.278
C51:2 TAG	HMDB0005362*	Glycerolipids	Triacylglycerols	1.22 (0.97-1.54)	0.091	1.14 (0.89-1.46)	0.300
C56:5 TAG	HMDB0005406*	Glycerolipids	Triacylglycerols	0.91 (0.72-1.15)	0.443	0.87 (0.68-1.11)	0.251
C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	1.04 (0.82-1.32)	0.733	1.09 (0.85-1.4)	0.493
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.88 (0.7-1.12)	0.311	0.88 (0.68-1.13)	0.307
C46:1 TAG	HMDB0010412*	Glycerolipids	Triacylglycerols	1.21 (0.96-1.53)	0.105	1.06 (0.82-1.36)	0.655
C52:4 TAG	HMDB0005363*	Glycerolipids	Triacylglycerols	1.16 (0.93-1.45)	0.195	1.15 (0.9-1.45)	0.267
C60:12 TAG	HMDB0005478*	Glycerolipids	Triacylglycerols	1.05 (0.83-1.34)	0.675	1.04 (0.81-1.33)	0.755
C56:7 TAG	HMDB0005462*	Glycerolipids	Triacylglycerols	1.13 (0.9-1.43)	0.295	1.08 (0.85-1.38)	0.524
C51:3 TAG	HMDB0011701*	Glycerolipids	Triacylglycerols	1.18 (0.94-1.49)	0.154	1.19 (0.92-1.53)	0.181
C49:3 TAG	HMDB0042103*	Glycerolipids	Triacylglycerols	1.17 (0.93-1.48)	0.182	1.15 (0.89-1.47)	0.286
C46:2 TAG	HMDB0010419*	Glycerolipids	Triacylglycerols	1.21 (0.96-1.53)	0.112	1.06 (0.82-1.36)	0.659
C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	1.01 (0.8-1.27)	0.959	0.93 (0.72-1.18)	0.539
C56:4 TAG	HMDB0005398*	Glycerolipids	Triacylglycerols	1.06 (0.84-1.34)	0.630	1.08 (0.85-1.38)	0.536
C48:2 TAG	HMDB0005376*	Glycerolipids	Triacylglycerols	1.19 (0.94-1.5)	0.151	1.03 (0.8-1.32)	0.846
C54:5 TAG	HMDB0005385*	Glycerolipids	Triacylglycerols	1.08 (0.86-1.36)	0.504	1.11 (0.87-1.41)	0.405
C55:3 TAG	HMDB0042466*	Glycerolipids	Triacylglycerols	1.02 (0.81-1.29)	0.851	1.13 (0.88-1.44)	0.335
C58:6 TAG	HMDB0005458*	Glycerolipids	Triacylglycerols	0.96 (0.74-1.23)	0.735	0.93 (0.72-1.21)	0.589
C53:2 TAG	HMDB0042196*	Glycerolipids	Triacylglycerols	1.14 (0.9-1.44)	0.282	1.11 (0.86-1.43)	0.413
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	1.01 (0.8-1.28)	0.924	0.94 (0.73-1.2)	0.604
C52:6 TAG	HMDB0005436*	Glycerolipids	Triacylglycerols	1.08 (0.86-1.36)	0.523	1 (0.78-1.28)	0.987
C56:8 TAG	HMDB0005392*	Glycerolipids	Triacylglycerols	1.01 (0.8-1.27)	0.937	1.02 (0.8-1.3)	0.872
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	1.04 (0.82-1.32)	0.758	0.97 (0.76-1.25)	0.836
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	0.95 (0.75-1.21)	0.698	0.97 (0.76-1.24)	0.806
C54:3 TAG	HMDB0005405*	Glycerolipids	Triacylglycerols	1.07 (0.84-1.35)	0.593	1.06 (0.83-1.35)	0.661
C54:4 TAG	HMDB0005370*	Glycerolipids	Triacylglycerols	0.99 (0.79-1.25)	0.957	1.04 (0.82-1.32)	0.755
C54:7 TAG	HMDB0005447*	Glycerolipids	Triacylglycerols	1.02 (0.81-1.29)	0.839	0.99 (0.78-1.26)	0.953
C50:6 TAG	HMDB0010497*	Glycerolipids	Triacylglycerols	1.11 (0.88-1.4)	0.371	0.99 (0.77-1.27)	0.948

Supplemental Table 1.1 (continued).

C50:5 TAG	HMDB0010471*	Glycerolipids	Triacylglycerols	1.14 (0.9-1.43)	0.283	1.03 (0.8-1.33)	0.811
C52:7 TAG	HMDB0010517*	Glycerolipids	Triacylglycerols	1.1 (0.87-1.39)	0.415	1 (0.78-1.28)	0.990
C53:3 TAG	HMDB0043058*	Glycerolipids	Triacylglycerols	1.04 (0.83-1.3)	0.735	1.1 (0.86-1.4)	0.459
C48:3 TAG	HMDB0005432*	Glycerolipids	Triacylglycerols	1.13 (0.9-1.43)	0.297	1 (0.78-1.29)	0.995
C56:9 TAG	HMDB0005448*	Glycerolipids	Triacylglycerols	1.03 (0.81-1.3)	0.835	0.98 (0.77-1.25)	0.862
C54:8 TAG	HMDB0010518*	Glycerolipids	Triacylglycerols	1.07 (0.85-1.35)	0.560	0.99 (0.78-1.26)	0.932
C54:6 TAG	HMDB0005391*	Glycerolipids	Triacylglycerols	1 (0.79-1.25)	0.986	1.04 (0.82-1.32)	0.763
C22:5 LPC	HMDB0010403*	Glycero-phospholipids	Glycerophosphocholines	0.78 (0.61-0.99)	0.041	0.78 (0.6-1)	0.047
C18:0 LPC	HMDB0010384	Glycero-phospholipids	Glycerophosphocholines	0.8 (0.62-1.03)	0.082	0.78 (0.6-1.01)	0.060
C32:1 PC	HMDB0007873*	Glycero-phospholipids	Glycerophosphocholines	1.33 (1.05-1.7)	0.020	1.15 (0.89-1.5)	0.280
C32:0 PC	HMDB0007871*	Glycero-phospholipids	Glycerophosphocholines	1.22 (0.96-1.55)	0.108	1.13 (0.88-1.45)	0.338
C36:5 PC plasmalogen-B	HMDB0011220*	Glycero-phospholipids	Glycerophosphocholines	0.85 (0.68-1.07)	0.158	0.82 (0.65-1.04)	0.104
C18:2 LPC	HMDB0010386*	Glycero-phospholipids	Glycerophosphocholines	0.77 (0.6-0.99)	0.039	0.81 (0.62-1.05)	0.114
C34:1 PC	HMDB0007972*	Glycero-phospholipids	Glycerophosphocholines	1.23 (0.97-1.55)	0.090	1.09 (0.85-1.39)	0.519
C38:6 PC	HMDB0007991*	Glycero-phospholipids	Glycerophosphocholines	1.16 (0.9-1.49)	0.250	1.15 (0.89-1.49)	0.288
C34:3 PC plasmalogen	HMDB0011211*	Glycero-phospholipids	Glycerophosphocholines	0.81 (0.64-1.01)	0.065	0.84 (0.66-1.08)	0.172
C18:1 LPC	HMDB0002815*	Glycero-phospholipids	Glycerophosphocholines	0.81 (0.64-1.04)	0.094	0.83 (0.64-1.07)	0.152
C34:1 PC plasmalogen-B	HMDB0011239*	Glycero-phospholipids	Glycerophosphocholines	1.06 (0.84-1.33)	0.630	1.13 (0.89-1.44)	0.313
C20:5 LPC	HMDB0010397	Glycero-phospholipids	Glycerophosphocholines	0.8 (0.62-1.03)	0.080	0.83 (0.64-1.08)	0.170

Supplemental Table 1.1 (continued).

C30:1 PC	HMDB0007870*	Glycero-phospholipids	Glycerophosphocholines	1.21 (0.95-1.53)	0.122	1.07 (0.83-1.38)	0.591
C36:5 PC plasmalogen-A	HMDB0011221*	Glycero-phospholipids	Glycerophosphocholines	0.9 (0.71-1.14)	0.379	0.84 (0.66-1.07)	0.161
C30:0 PC	HMDB0007869*	Glycero-phospholipids	Glycerophosphocholines	1.16 (0.91-1.47)	0.219	1.03 (0.8-1.32)	0.830
C40:9 PC	HMDB0008731*	Glycero-phospholipids	Glycerophosphocholines	1.09 (0.85-1.4)	0.498	1.1 (0.85-1.42)	0.470
C32:2 PC	HMDB0007874*	Glycero-phospholipids	Glycerophosphocholines	1.19 (0.93-1.52)	0.160	1.05 (0.81-1.36)	0.698
C40:10 PC	HMDB0008511*	Glycero-phospholipids	Glycerophosphocholines	1.12 (0.87-1.43)	0.379	1.08 (0.84-1.39)	0.551
C38:4 PC plasmalogen	HMDB0011252*	Glycero-phospholipids	Glycerophosphocholines	0.92 (0.73-1.16)	0.498	0.95 (0.75-1.2)	0.646
C14:0 LPC	HMDB0010379	Glycerophospholipids	Glycerophosphocholines	1.16 (0.93-1.46)	0.194	1.02 (0.8-1.29)	0.876
C16:1 LPC	HMDB0010383*	Glycero-phospholipids	Glycerophosphocholines	1.12 (0.89-1.4)	0.347	1.04 (0.82-1.32)	0.755
C22:6 LPC	HMDB0010404	Glycero-phospholipids	Glycerophosphocholines	1 (0.79-1.28)	0.977	1.05 (0.81-1.35)	0.714
C34:1 PC plasmalogen	HMDB0011208*	Glycero-phospholipids	Glycerophosphocholines	0.98 (0.78-1.23)	0.860	1.07 (0.84-1.36)	0.594
C40:6 PC	HMDB0008057*	Glycero-phospholipids	Glycerophosphocholines	1.09 (0.85-1.39)	0.500	1.08 (0.84-1.38)	0.557
C38:7 PC plasmalogen	HMDB0011229*	Glycero-phospholipids	Glycerophosphocholines	0.94 (0.75-1.18)	0.592	0.94 (0.74-1.19)	0.586
C38:3 PC	HMDB0008047*	Glycero-phospholipids	Glycerophosphocholines	1.1 (0.87-1.4)	0.424	0.94 (0.73-1.22)	0.655
C36:2 PC plasmalogen	HMDB0011243*	Glycero-phospholipids	Glycerophosphocholines	0.9 (0.71-1.14)	0.396	1 (0.78-1.29)	0.972
C36:4 PC plasmalogen	HMDB0011310*	Glycero-phospholipids	Glycerophosphocholines	0.91 (0.72-1.16)	0.454	0.99 (0.77-1.27)	0.958

Supplemental Table 1.1 (continued).

C16:0 LPC	HMDB0010382	Glycero-phospholipids	Glycerophosphocholines	1.01 (0.8-1.27)	0.927	0.95 (0.75-1.21)	0.682
C36:1 PC	HMDB0008038*	Glycero-phospholipids	Glycerophosphocholines	1.04 (0.83-1.31)	0.711	0.94 (0.74-1.19)	0.610
C36:4 PC-B	HMDB0008138*	Glycero-phospholipids	Glycerophosphocholines	1.07 (0.83-1.37)	0.614	0.98 (0.76-1.27)	0.890
C18:3 LPC	HMDB0010387*	Glycero-phospholipids	Glycerophosphocholines	1 (0.79-1.26)	0.978	0.94 (0.74-1.2)	0.627
C22:0 LPE	HMDB0011520	Glycero-phospholipids	Glycerophospho-ethanolamines	0.69 (0.54-0.89)	0.004	0.75 (0.58-0.98)	0.035
C38:6 PE plasmalogen	HMDB0011387*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.82 (0.65-1.03)	0.088	0.78 (0.61-0.99)	0.039
C36:5 PE plasmalogen	HMDB0011410*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.84 (0.66-1.06)	0.134	0.8 (0.63-1.01)	0.063
C36:4 PE plasmalogen	HMDB0011442*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.79 (0.63-1)	0.050	0.81 (0.63-1.02)	0.078
C34:3 PE plasmalogen	HMDB0011343*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.81 (0.64-1.02)	0.072	0.82 (0.64-1.03)	0.092
C36:1 PE plasmalogen	HMDB0009016*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.09 (0.86-1.37)	0.477	1.19 (0.93-1.52)	0.172
C38:5 PE	HMDB0009069*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.89 (0.7-1.15)	0.374	0.86 (0.66-1.1)	0.233
C22:6 LPE	HMDB0011526	Glycero-phospholipids	Glycerophospho-ethanolamines	1.15 (0.91-1.46)	0.246	1.14 (0.89-1.46)	0.287
C38:5 PE plasmalogen	HMDB0011386*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.88 (0.7-1.11)	0.280	0.84 (0.66-1.06)	0.147
C34:0 PE	HMDB0008925*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.17 (0.93-1.47)	0.191	1.15 (0.9-1.45)	0.260
C36:3 PE plasmalogen	HMDB0011441*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.88 (0.7-1.11)	0.272	0.88 (0.69-1.11)	0.280
C16:0 LPE	HMDB0011503	Glycero-phospholipids	Glycerophospho-ethanolamines	1.08 (0.85-1.36)	0.521	1.07 (0.84-1.37)	0.560

Supplemental Table 1.1 (continued).

C36:0 PE	HMDB0008991*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.1 (0.87-1.38)	0.431	1.11 (0.88-1.4)	0.389
C36:2 PE	HMDB0008994*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.19 (0.94-1.51)	0.158	1.07 (0.83-1.37)	0.618
C34:2 PE	HMDB0008928*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.18 (0.92-1.5)	0.186	1.08 (0.84-1.38)	0.567
C32:0 PE	HMDB0008923*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.12 (0.89-1.41)	0.351	1.07 (0.85-1.36)	0.559
C38:2 PE	HMDB0008942*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.89 (0.71-1.11)	0.303	0.99 (0.78-1.25)	0.932
C38:4 PE	HMDB0009003*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.02 (0.8-1.3)	0.890	0.91 (0.71-1.18)	0.483
C36:1 PE	HMDB0008993*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.19 (0.93-1.51)	0.170	1.04 (0.8-1.35)	0.774
C40:6 PE	HMDB0009012*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.15 (0.9-1.48)	0.265	1.03 (0.79-1.34)	0.815
C18:2 LPE	HMDB0011507*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.01 (0.79-1.29)	0.916	1.02 (0.79-1.31)	0.882
C36:2 PE plasmalogen	HMDB0009082*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.96 (0.76-1.2)	0.718	0.91 (0.72-1.16)	0.460
C20:4 LPE	HMDB0011517	Glycero-phospholipids	Glycerophospho-ethanolamines	0.97 (0.76-1.22)	0.771	0.95 (0.75-1.21)	0.691
C38:7 PE plasmalogen	HMDB0011420*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.03 (0.81-1.31)	0.785	0.97 (0.76-1.25)	0.831
C18:1 LPE	HMDB0011506*	Glycero-phospholipids	Glycerophospho-ethanolamines	1 (0.79-1.27)	0.994	0.99 (0.78-1.27)	0.943
C40:7 PE plasmalogen	HMDB0011394*	Glycero-phospholipids	Glycerophospho-ethanolamines	0.96 (0.76-1.21)	0.724	0.96 (0.76-1.22)	0.740
C34:2 PE plasmalogen	HMDB0008952*	Glycero-phospholipids	Glycerophospho-ethanolamines	1 (0.8-1.26)	0.980	0.96 (0.76-1.22)	0.747
C36:3 PE	HMDB0009060*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.03 (0.81-1.31)	0.809	0.99 (0.77-1.27)	0.935

Supplemental Table 1.1 (continued).

C18:0 LPE	HMDB0011130	Glycero-phospholipids	Glycerophospho-ethanolamines	0.98 (0.78-1.24)	0.890	0.94 (0.74-1.2)	0.641
C38:6 PE	HMDB0009102*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.04 (0.8-1.35)	0.758	0.98 (0.75-1.27)	0.861
C36:4 PE	HMDB0008937*	Glycero-phospholipids	Glycerophospho-ethanolamines	1.06 (0.82-1.35)	0.664	0.96 (0.75-1.25)	0.785
C38:4 PI	HMDB0009815*	Glycero-phospholipids	Glycerophosphoinositols	0.95 (0.75-1.22)	0.708	0.9 (0.7-1.16)	0.412
C34:0 PS	HMDB0012356*	Glycero-phospholipids	Glycerophosphoserines	1.09 (0.86-1.38)	0.497	0.95 (0.74-1.21)	0.662
1-methylguanine	HMDB0003282	Imidazo-pyrimidines	Purines and purine derivatives	1.2 (0.95-1.53)	0.129	1.13 (0.88-1.45)	0.333
7-methylguanine	HMDB0000897	Imidazo-pyrimidines	Purines and purine derivatives	1.12 (0.88-1.43)	0.347	1.02 (0.79-1.32)	0.880
caffeine	HMDB0001847	Imidazo-pyrimidines	Purines and purine derivatives	1.1 (0.87-1.39)	0.441	1.02 (0.79-1.3)	0.901
uric acid	HMDB0000289	Imidazo-pyrimidines	Purines and purine derivatives	1.07 (0.84-1.36)	0.592	0.87 (0.67-1.14)	0.325
1,7-dimethyluric acid	HMDB0011103	Imidazo-pyrimidines	Purines and purine derivatives	0.97 (0.77-1.22)	0.799	0.92 (0.73-1.17)	0.507
3-methylxanthine	HMDB0001886	Imidazo-pyrimidines	Purines and purine derivatives	1 (0.8-1.26)	0.967	0.98 (0.78-1.24)	0.871
7-methylxanthine	HMDB0001991	Imidazo-pyrimidines	Purines and purine derivatives	1 (0.8-1.25)	0.988	0.99 (0.78-1.24)	0.918
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	1.11 (0.88-1.41)	0.373	1.08 (0.85-1.38)	0.510
serotonin	HMDB0000259	Indoles and derivatives	Tryptamines and derivatives	1.16 (0.91-1.47)	0.230	1.26 (0.99-1.62)	0.065
thyroxine	HMDB0000248	NA	NA	1.5 (1.16-1.95)	0.002	1.56 (1.19-2.05)	0.001
2-methyl-4,5-benzoxazole	HMDB0032390	NA	NA	0.82 (0.65-1.03)	0.084	0.79 (0.63-1)	0.051
methyl N-methylanthranilate	HMDB0034169	NA	NA	1.21 (0.96-1.52)	0.116	1.15 (0.91-1.47)	0.239

Supplemental Table 1.1 (continued).

C20:4 LPC	HMDB0010395	NA	NA	0.82 (0.65-1.04)	0.107	0.82 (0.64-1.05)	0.116
trigonelline	HMDB0000875	NA	NA	0.83 (0.66-1.04)	0.109	0.82 (0.64-1.04)	0.099
C20:1 LPE	HMDB0011512*	NA	NA	0.86 (0.67-1.09)	0.214	0.87 (0.68-1.11)	0.260
piperine	HMDB0029377	NA	NA	0.94 (0.74-1.18)	0.574	0.85 (0.67-1.09)	0.202
C36:3 PC plasmalogen	HMDB0011244*	NA	NA	0.83 (0.66-1.04)	0.104	0.9 (0.7-1.15)	0.393
coenzyme Q10	HMDB0001072	NA	NA	0.89 (0.7-1.12)	0.307	0.88 (0.69-1.12)	0.295
C34:2 PC plasmalogen	HMDB0011210*	NA	NA	0.96 (0.76-1.21)	0.734	1.01 (0.79-1.3)	0.930
DMGV	HMDB0240212	NA	NA	1.07 (0.84-1.36)	0.595	0.92 (0.7-1.21)	0.549
C34:5 PC plasmalogen	HMDB0011214*	NA	NA	0.95 (0.75-1.2)	0.681	0.92 (0.72-1.17)	0.484
C20:1 LPC	HMDB0010391*	NA	NA	1 (0.78-1.28)	0.999	0.94 (0.72-1.22)	0.634
cerulenin	HMDB0015168	NA	NA	0.98 (0.78-1.23)	0.868	0.91 (0.72-1.15)	0.449
valsartan	HMDB0014323	NA	NA	1.03 (0.76-1.41)	0.837	1.09 (0.79-1.5)	0.595
C18:3 LPE	HMDB0011478*	NA	NA	1.02 (0.8-1.3)	0.854	0.98 (0.76-1.25)	0.865
C34:4 PC	HMDB0007883*	NA	NA	1.12 (0.87-1.43)	0.389	0.98 (0.75-1.27)	0.875
deoxyguanosine	HMDB0000085	NA	NA	0.99 (0.77-1.27)	0.934	0.99 (0.76-1.28)	0.923
pseudouridine	HMDB0000767	Nucleoside and nucleotide analogues	NA	0.93 (0.72-1.21)	0.598	0.81 (0.62-1.07)	0.137
N-carbamoyl-beta-alanine	HMDB0000026	Organic carbonic acids and derivatives	Ureas	0.98 (0.77-1.25)	0.869	0.9 (0.7-1.15)	0.391
1-methylhistamine	HMDB0000898	Organonitrogen compounds	Amines	1.23 (0.97-1.56)	0.085	1.15 (0.9-1.47)	0.256
trimethylamine-N-oxide	HMDB0000925	Organonitrogen compounds	Aminoxides	1.03 (0.82-1.3)	0.785	0.96 (0.75-1.21)	0.711
metformin	HMDB0001921	Organonitrogen compounds	Guanidines	1.1 (0.64-1.89)	0.738	1.27 (0.72-2.22)	0.407

Supplemental Table 1.1 (continued).

carnitine	HMDB0000062	Organonitrogen compounds	Quaternary ammonium salts	0.98 (0.77-1.25)	0.862	0.9 (0.69-1.16)	0.400
phosphocholine	HMDB0001565	Organonitrogen compounds	Quaternary ammonium salts	1.04 (0.81-1.32)	0.771	1.02 (0.8-1.31)	0.863
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	1.42 (1.1-1.84)	0.008	1.35 (1.02-1.77)	0.035
4-hydroxy-3-methylacetophenone	HMDB0059824	Organooxygen compounds	Carbonyl compounds	1.08 (0.82-1.42)	0.583	1.05 (0.79-1.39)	0.760
acetaminophen	HMDB0001859	Phenols	1-hydroxy-2-unsubstituted benzenoids	1.03 (0.8-1.34)	0.810	1.02 (0.78-1.32)	0.911
guanosine	HMDB0000133	Purine nucleosides	NA	0.77 (0.61-0.97)	0.027	0.78 (0.61-0.99)	0.041
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	1.38 (1.07-1.77)	0.014	1.32 (1.01-1.72)	0.039
1-methylguanosine	HMDB0001563	Purine nucleosides	NA	1.34 (1.05-1.71)	0.018	1.2 (0.92-1.55)	0.172
N2,N2-dimethylguanosine	HMDB0004824	Purine nucleosides	NA	1.07 (0.82-1.39)	0.642	0.92 (0.69-1.23)	0.574
N1-methyl-2-pyridone-5-carboxamide	HMDB0004193	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.92 (0.73-1.16)	0.462	0.91 (0.72-1.16)	0.443
1-methylnicotinamide	HMDB0000699	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.9 (0.71-1.14)	0.397	0.91 (0.71-1.16)	0.429
pyridoxamine	HMDB0001431	Pyridines and derivatives	Pyridoxamines	1.25 (0.97-1.62)	0.083	1.16 (0.89-1.52)	0.262
cotinine	HMDB0001046	Pyridines and derivatives	Pyrrolidinylpyridines	1.13 (0.89-1.44)	0.302	1.12 (0.87-1.43)	0.392
N4-acetylcytidine	HMDB0005923	Pyrimidine nucleosides	NA	1.24 (0.97-1.59)	0.080	1.1 (0.85-1.43)	0.458

Supplemental Table 1.1 (continued).

ribothymidine	HMDB0000884	Pyrimidine nucleosides	NA	0.94 (0.74-1.2)	0.630	0.94 (0.73-1.21)	0.629
kynurenic acid	HMDB0000715	Quinolines and derivatives	Quinoline carboxylic acids	0.94 (0.74-1.21)	0.648	0.83 (0.64-1.07)	0.149
C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	Ceramides	1.28 (1.01-1.63)	0.040	1.17 (0.92-1.5)	0.205
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	Ceramides	1.22 (0.96-1.56)	0.096	1.17 (0.91-1.5)	0.211
C24:0 Ceramide (d18:1)	HMDB0004956	Sphingolipids	Ceramides	1.02 (0.81-1.3)	0.844	0.92 (0.72-1.18)	0.514
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	Ceramides	1.12 (0.88-1.43)	0.347	1.01 (0.78-1.3)	0.942
C14:0 SM	HMDB0012097	Sphingolipids	Phosphosphingolipids	1.24 (0.97-1.57)	0.082	1.1 (0.86-1.41)	0.452
C22:1 SM	HMDB0012104*	Sphingolipids	Phosphosphingolipids	1 (0.79-1.26)	0.972	0.97 (0.76-1.24)	0.835
glycodeoxycholate/glycochenodeoxycholate	HMDB0000631*	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.3 (1.02-1.66)	0.034	1.24 (0.96-1.59)	0.098
glycocholate	HMDB0000138	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.25 (0.98-1.59)	0.070	1.19 (0.93-1.53)	0.168
cholesterol	HMDB0000067	Steroids and steroid derivatives	Cholestane steroids	1.06 (0.84-1.34)	0.644	0.98 (0.77-1.25)	0.884
campesterol	HMDB0002869	Steroids and steroid derivatives	Ergostane steroids	1.03 (0.81-1.31)	0.792	0.97 (0.76-1.24)	0.798
cortisone	HMDB0002802	Steroids and steroid derivatives	Hydroxysteroids	0.85 (0.66-1.09)	0.195	0.87 (0.67-1.13)	0.287
cortisol	HMDB0000063	Steroids and steroid derivatives	Hydroxysteroids	0.86 (0.67-1.11)	0.253	0.88 (0.68-1.14)	0.341

Supplemental Table 1.1 (continued).

21-deoxycortisol	HMDB0004030	Steroids and steroid derivatives	Pregnane steroids	0.95 (0.75-1.21)	0.668	1.01 (0.78-1.3)	0.950
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesterol esters	0.61 (0.48-0.77)	0.000	0.67 (0.52-0.86)	0.002
C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesterol esters	0.7 (0.55-0.88)	0.003	0.69 (0.54-0.89)	0.004
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesterol esters	0.72 (0.57-0.92)	0.008	0.78 (0.6-1)	0.051
C20:4 CE	HMDB0006726	Steroids and steroid derivatives	Cholesterol esters	0.73 (0.58-0.93)	0.009	0.81 (0.63-1.03)	0.085
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesterol esters	0.75 (0.6-0.95)	0.016	0.74 (0.58-0.95)	0.017
C18:2 CE	HMDB0000610*	Steroids and steroid derivatives	Cholesterol esters	0.74 (0.58-0.94)	0.014	0.82 (0.63-1.07)	0.151
C18:1 CE	HMDB0000918*	Steroids and steroid derivatives	Cholesterol esters	0.76 (0.6-0.96)	0.023	0.83 (0.64-1.07)	0.146
C20:3 CE	HMDB0006736*	Steroids and steroid derivatives	Cholesterol esters	0.81 (0.64-1.01)	0.066	0.84 (0.66-1.06)	0.142
C16:0 CE	HMDB0000885	Steroids and steroid derivatives	Cholesterol esters	0.78 (0.61-0.98)	0.035	0.85 (0.66-1.1)	0.208
C16:1 CE	HMDB0000658*	Steroids and steroid derivatives	Cholesterol esters	1.1 (0.88-1.39)	0.408	0.99 (0.77-1.28)	0.965

Supplemental Table 1.1 (continued).

C22:6 CE	HMDB0006733	Steroids and steroid derivatives	Cholesterol esters	0.83 (0.66-1.05)	0.116	0.95 (0.74-1.22)	0.691
C14:0 CE	HMDB0006725	Steroids and steroid derivatives	Cholesterol esters	0.9 (0.72-1.13)	0.354	0.87 (0.69-1.11)	0.275
bilirubin	HMDB0000054	Tetrapyrroles and derivatives	Bilirubins	0.81 (0.64-1.03)	0.085	0.81 (0.63-1.03)	0.088
biliverdin	HMDB0001008	Tetrapyrroles and derivatives	Bilirubins	1.02 (0.8-1.31)	0.857	1.02 (0.79-1.32)	0.872

**Includes metabolites with <10% missingness. Missing values were imputed with 1/2 the minimum value. Results are sorted by class, subclass, and p-value for fully adjusted models. CLR includes matched factors: age at blood draw, month of blood draw, fasting status at blood draw, menopausal status at blood draw, hormone use at blood draw.
^Multivariable adjusted includes BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).
*Representative HMDBID

Supplemental Table 1.1b. Odds ratios for breast cancer risk comparing 90th to 10th percentiles of metabolite levels, measured at proximate blood.**

				Unadjusted Model		Multivariable Adjusted^	
Metabolite Name	**HMDB ID**	**Class**	**Subclass**	OR (95% CI)	p value	OR (95% CI)	p value
urocanic acid	HMDB0000301	Azoles	Imidazoles	1.18 (0.81-1.72)	0.392	1.17 (0.79-1.73)	0.445
allantoin	HMDB0000462	Azoles	Imidazoles	1.09 (0.81-1.47)	0.549	1.07 (0.78-1.46)	0.685
metronidazole	HMDB0015052	Azoles	Imidazoles	1.04 (0.67-1.6)	0.872	0.99 (0.63-1.56)	0.972
sulfamethoxazole	HMDB0015150	Benzene and substituted derivatives	Benzenesulfonamide	0.76 (0.5-1.17)	0.212	0.83 (0.53-1.3)	0.425
2-aminohippuric acid	HMDB0001867	Benzene and substituted derivatives	Benzoic acids and derivatives	1.39 (1.01-1.93)	0.046	1.45 (1.02-2.06)	0.038
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	0.69 (0.52-0.92)	0.013	0.75 (0.55-1.02)	0.065
4-hydroxyhippurate	HMDB0013678	Benzene and substituted derivatives	Benzoic acids and derivatives	0.95 (0.71-1.27)	0.722	0.97 (0.72-1.31)	0.859
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	1.38 (1.02-1.85)	0.034	1.41 (1.03-1.94)	0.032
N1-acetylspermidine	HMDB0001276	Carboximidic acids and derivatives	Carboximidic acids	1.19 (0.87-1.64)	0.283	1.3 (0.93-1.81)	0.128
palmitoylethanolamide	HMDB0002100	Carboximidic acids and derivatives	Carboximidic acids	0.88 (0.65-1.2)	0.425	0.88 (0.63-1.21)	0.418
N-acetylputrescine	HMDB0002064	Carboximidic acids and derivatives	Carboximidic acids	0.92 (0.68-1.25)	0.596	0.95 (0.7-1.3)	0.767
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.77 (1.29-2.42)	0.000	1.76 (1.25-2.48)	0.001

Supplemental Table 1.1b (continued).

proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.52 (1.12-2.07)	0.007	1.59 (1.13-2.22)	0.007
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.55 (1.15-2.08)	0.004	1.56 (1.12-2.17)	0.009
leucine	HMDB0000687	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.5 (1.12-2.02)	0.007	1.48 (1.06-2.06)	0.020
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.39 (1.03-1.89)	0.033	1.45 (1.06-2)	0.022
serine	HMDB0000187	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.35 (0.99-1.85)	0.058	1.46 (1.05-2.02)	0.023
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.78 (0.58-1.03)	0.081	0.71 (0.53-0.96)	0.026
betaine	HMDB0000043	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.27 (0.91-1.79)	0.164	1.47 (1.03-2.12)	0.035
Guanidino-acetic acid	HMDB0000128	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.22 (0.91-1.63)	0.186	1.35 (0.99-1.84)	0.059
valine	HMDB0000883	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.42 (1.06-1.89)	0.018	1.36 (0.98-1.87)	0.062
N6,N6,N6-trimethyllysine	HMDB0001325	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.31 (0.97-1.77)	0.083	1.36 (0.99-1.87)	0.062
tyrosine	HMDB0000158	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.46 (1.07-1.98)	0.016	1.35 (0.98-1.88)	0.068

Supplemental Table 1.1b (continued).

ADMA/SDMA	HMDB0001539	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.39 (1.01-1.91)	0.045	1.33 (0.95-1.86)	0.095
lysine	HMDB0000182	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.31 (0.97-1.78)	0.078	1.28 (0.93-1.75)	0.131
N6-acetyllysine	HMDB0000206*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.23 (0.91-1.67)	0.185	1.28 (0.93-1.77)	0.135
2-aminooctanoic acid	HMDB0000991*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.8 (0.6-1.07)	0.130	0.79 (0.59-1.08)	0.137
alanine	HMDB0000161	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.34 (1-1.81)	0.053	1.27 (0.92-1.75)	0.154
Aminoiso-butyric acid	HMDB0001906*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.76 (0.56-1.04)	0.083	0.79 (0.57-1.1)	0.164
pipecolic acid	HMDB0000716	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.83 (0.61-1.13)	0.239	0.8 (0.57-1.1)	0.168
N6,N6-dimethyllysine	HMDB0013287	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.28 (0.95-1.73)	0.110	1.22 (0.89-1.68)	0.209
creatinine	HMDB0000562	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.14 (0.84-1.54)	0.393	1.21 (0.88-1.67)	0.233
methionine	HMDB0000696	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.22 (0.9-1.64)	0.204	1.21 (0.88-1.65)	0.239
1-methylhistidine	HMDB0000001	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.17 (0.87-1.58)	0.303	1.18 (0.86-1.62)	0.304

Supplemental Table 1.1b (continued).

glycine	HMDB0000123	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.78-1.48)	0.674	1.18 (0.84-1.66)	0.334
histidine	HMDB0000177	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.21 (0.88-1.66)	0.242	1.17 (0.84-1.63)	0.359
dimethylglycine	HMDB0000092	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.79-1.46)	0.660	1.17 (0.84-1.62)	0.367
pantothenate	HMDB0000210	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.93 (0.68-1.25)	0.622	0.87 (0.63-1.19)	0.381
asparagine	HMDB0000168	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.12 (0.81-1.54)	0.499	1.11 (0.79-1.57)	0.533
oleoyl glycine	HMDB0013631	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.9 (0.67-1.22)	0.503	0.91 (0.67-1.25)	0.556
creatine	HMDB0000064	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.93 (0.7-1.24)	0.624	0.92 (0.68-1.24)	0.598
GABA	HMDB0000112	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.08 (0.8-1.46)	0.617	1.08 (0.79-1.47)	0.645
N-acetylhistidine	HMDB0032055	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.05 (0.77-1.44)	0.736	1.08 (0.78-1.49)	0.656
proline betaine	HMDB0004827	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.11 (0.82-1.49)	0.499	1.07 (0.78-1.46)	0.675
threonine	HMDB0000167	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.04 (0.77-1.41)	0.800	1.05 (0.76-1.44)	0.767

Supplemental Table 1.1b (continued).

N-lauroylglycine	HMDB0013272	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.97 (0.69-1.36)	0.838	1.05 (0.74-1.5)	0.790
4-acetamidobutanoate	HMDB0003681	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.9 (0.65-1.23)	0.498	0.97 (0.69-1.34)	0.840
hydroxyproline	HMDB0000725	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.97 (0.73-1.3)	0.862	0.98 (0.72-1.32)	0.878
citrulline	HMDB0000904	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1 (0.73-1.36)	0.987	1.02 (0.74-1.41)	0.899
NMMA	HMDB0029416	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.05 (0.78-1.43)	0.733	1.01 (0.73-1.39)	0.961
N-acetyltrypto-phan	HMDB0013713	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.04 (0.77-1.42)	0.790	1.01 (0.73-1.4)	0.966
homoarginine	HMDB0000670*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.02 (0.75-1.4)	0.889	0.99 (0.71-1.38)	0.974
phenylacetylglutamine	HMDB0006344	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.97 (0.72-1.3)	0.837	1 (0.73-1.36)	0.989
glutamine	HMDB0000641	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.93 (0.68-1.27)	0.662	1 (0.72-1.38)	0.990
cytosine	HMDB0000630	Diazines	Pyrimidines and pyrimidine derivatives	1.23 (0.9-1.69)	0.191	1.19 (0.85-1.65)	0.311
5-hydroxymethyl-4-methyluracil	HMDB0000544	Diazines	Pyrimidines and pyrimidine derivatives	1.06 (0.74-1.52)	0.753	1.15 (0.78-1.69)	0.481
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.67 (0.5-0.91)	0.010	0.71 (0.52-0.97)	0.030
C14 carnitine	HMDB0005066	Fatty Acyls	Fatty acid esters	1.42 (1.04-1.94)	0.027	1.29 (0.94-1.79)	0.119

Supplemental Table 1.1b (continued).

C5 carnitine	HMDB0000688	Fatty Acyls	Fatty acid esters	1.3 (0.96-1.75)	0.088	1.28 (0.92-1.78)	0.142
C3 carnitine	HMDB0000824	Fatty Acyls	Fatty acid esters	1.19 (0.9-1.58)	0.224	1.23 (0.91-1.67)	0.182
C4-OH carnitine	HMDB0013127	Fatty Acyls	Fatty acid esters	1.36 (1.01-1.85)	0.044	1.24 (0.89-1.71)	0.199
C2 carnitine	HMDB0000201	Fatty Acyls	Fatty acid esters	1.29 (0.95-1.75)	0.106	1.23 (0.89-1.69)	0.203
C10:2 carnitine	HMDB0013325	Fatty Acyls	Fatty acid esters	0.86 (0.64-1.16)	0.327	0.83 (0.61-1.14)	0.256
C7 carnitine	HMDB0013238	Fatty Acyls	Fatty acid esters	1.24 (0.92-1.67)	0.162	1.2 (0.88-1.64)	0.258
C6 carnitine	HMDB0000705	Fatty Acyls	Fatty acid esters	1.21 (0.9-1.63)	0.213	1.17 (0.86-1.6)	0.326
C26 carnitine	HMDB0006347	Fatty Acyls	Fatty acid esters	1.15 (0.86-1.53)	0.353	1.11 (0.82-1.5)	0.507
C4 carnitine	HMDB0002013	Fatty Acyls	Fatty acid esters	1.13 (0.84-1.52)	0.421	1.09 (0.8-1.49)	0.594
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	1.14 (0.84-1.55)	0.390	1.09 (0.79-1.5)	0.600
C12 carnitine	HMDB0002250	Fatty Acyls	Fatty acid esters	1.1 (0.81-1.49)	0.537	1.06 (0.78-1.46)	0.704
C12:1 carnitine	HMDB0013326	Fatty Acyls	Fatty acid esters	1.05 (0.78-1.42)	0.743	1.05 (0.77-1.43)	0.768
C14:2 carnitine	HMDB0013331	Fatty Acyls	Fatty acid esters	0.97 (0.71-1.32)	0.834	0.96 (0.69-1.32)	0.794
C9 carnitine	HMDB0013288	Fatty Acyls	Fatty acid esters	1.05 (0.79-1.41)	0.739	1.04 (0.77-1.4)	0.813
C14:1 carnitine	HMDB0002014	Fatty Acyls	Fatty acid esters	1.05 (0.78-1.42)	0.758	1.03 (0.75-1.42)	0.840
C10 carnitine	HMDB0000651	Fatty Acyls	Fatty acid esters	1.04 (0.78-1.4)	0.774	1.03 (0.76-1.4)	0.855
C8 carnitine	HMDB0000791	Fatty Acyls	Fatty acid esters	1.04 (0.78-1.4)	0.782	1.02 (0.75-1.39)	0.885
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	1.5 (1.07-2.1)	0.018	1.58 (1.11-2.24)	0.012
3-dehydroxycarnitine	HMDB0006831	Fatty Acyls	Fatty acids and conjugates	1.22 (0.89-1.67)	0.224	1.32 (0.94-1.84)	0.105
C36:4 DAG	HMDB0007248*	Fatty Acyls	Lineolic acids and derivatives	0.93 (0.7-1.24)	0.620	0.91 (0.66-1.25)	0.542
C34:2 DAG	HMDB0007103*	Fatty Acyls	Lineolic acids and derivatives	1.19 (0.89-1.58)	0.248	1.09 (0.79-1.5)	0.617
C36:3 DAG	HMDB0007219*	Fatty Acyls	Lineolic acids and derivatives	1.01 (0.76-1.33)	0.970	0.96 (0.71-1.31)	0.813
C34:3 DAG	HMDB0007132*	Fatty Acyls	Lineolic acids and derivatives	1.13 (0.85-1.5)	0.390	1.02 (0.74-1.41)	0.891
C34:0 DAG	HMDB0007100*	Glycerolipids	Diacylglycerols	1.48 (1.11-1.99)	0.008	1.35 (0.98-1.87)	0.063

Supplemental Table 1.1b (continued).

C36:1 DAG	HMDB0007216*	Glycerolipids	Diacylglycerols	1.41 (1.05-1.88)	0.021	1.32 (0.96-1.81)	0.090
C34:1 DAG	HMDB0007102*	Glycerolipids	Diacylglycerols	1.31 (0.98-1.76)	0.068	1.2 (0.87-1.66)	0.273
C32:0 DAG	HMDB0007098*	Glycerolipids	Diacylglycerols	1.37 (1.02-1.84)	0.038	1.2 (0.86-1.66)	0.279
C36:2 DAG	HMDB0007218*	Glycerolipids	Diacylglycerols	1.2 (0.91-1.6)	0.198	1.15 (0.84-1.57)	0.371
C32:1 DAG	HMDB0007099*	Glycerolipids	Diacylglycerols	1.28 (0.95-1.72)	0.107	1.16 (0.83-1.61)	0.380
C38:5 DAG	HMDB0007199*	Glycerolipids	Diacylglycerols	0.93 (0.7-1.24)	0.625	0.87 (0.64-1.2)	0.401
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.6 (0.44-0.82)	0.001	0.59 (0.42-0.82)	0.002
C56:9 TAG	HMDB0005448*	Glycerolipids	Triacylglycerols	0.68 (0.51-0.91)	0.010	0.64 (0.46-0.87)	0.004
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	0.69 (0.52-0.93)	0.013	0.63 (0.46-0.86)	0.004
C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	0.7 (0.52-0.94)	0.017	0.64 (0.47-0.87)	0.005
C54:8 TAG	HMDB0010518*	Glycerolipids	Triacylglycerols	0.7 (0.52-0.94)	0.017	0.65 (0.47-0.88)	0.006
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	0.7 (0.52-0.94)	0.017	0.64 (0.47-0.88)	0.006
C56:8 TAG	HMDB0005392*	Glycerolipids	Triacylglycerols	0.69 (0.51-0.93)	0.015	0.66 (0.48-0.9)	0.008
C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	0.67 (0.5-0.91)	0.010	0.66 (0.47-0.9)	0.010
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	0.69 (0.51-0.93)	0.014	0.66 (0.48-0.9)	0.010
C56:7 TAG	HMDB0005462*	Glycerolipids	Triacylglycerols	0.74 (0.55-0.99)	0.044	0.68 (0.5-0.94)	0.017
C58:6 TAG	HMDB0005458*	Glycerolipids	Triacylglycerols	0.68 (0.49-0.92)	0.013	0.68 (0.49-0.94)	0.018
C52:7 TAG	HMDB0010517*	Glycerolipids	Triacylglycerols	0.76 (0.57-1.02)	0.065	0.69 (0.5-0.94)	0.019
C54:7 TAG	HMDB0005447*	Glycerolipids	Triacylglycerols	0.73 (0.54-0.97)	0.031	0.7 (0.51-0.95)	0.021
C60:12 TAG	HMDB0005478*	Glycerolipids	Triacylglycerols	0.76 (0.56-1.02)	0.071	0.71 (0.51-0.98)	0.035
C52:6 TAG	HMDB0005436*	Glycerolipids	Triacylglycerols	0.79 (0.59-1.06)	0.114	0.73 (0.53-0.99)	0.046
C52:0 TAG	HMDB0005365*	Glycerolipids	Triacylglycerols	1.48 (1.11-1.98)	0.007	1.36 (1-1.86)	0.052
C58:8 TAG	HMDB0005413*	Glycerolipids	Triacylglycerols	0.75 (0.55-1.02)	0.065	0.73 (0.53-1.02)	0.064
C50:6 TAG	HMDB0010497*	Glycerolipids	Triacylglycerols	0.84 (0.63-1.13)	0.251	0.75 (0.55-1.03)	0.076
C54:1 TAG	HMDB0005395*	Glycerolipids	Triacylglycerols	1.39 (1.05-1.85)	0.024	1.3 (0.95-1.78)	0.096
C50:0 TAG	HMDB0005357*	Glycerolipids	Triacylglycerols	1.44 (1.08-1.93)	0.013	1.27 (0.93-1.75)	0.134
C52:1 TAG	HMDB0005367*	Glycerolipids	Triacylglycerols	1.4 (1.05-1.87)	0.021	1.27 (0.93-1.75)	0.135
C51:0 TAG	HMDB0031106*	Glycerolipids	Triacylglycerols	1.4 (1.05-1.88)	0.023	1.26 (0.93-1.72)	0.142
C56:6 TAG	HMDB0005456*	Glycerolipids	Triacylglycerols	0.8 (0.6-1.07)	0.140	0.8 (0.59-1.09)	0.152
C50:5 TAG	HMDB0010471*	Glycerolipids	Triacylglycerols	0.89 (0.67-1.19)	0.437	0.81 (0.59-1.11)	0.192
C54:2 TAG	HMDB0005403*	Glycerolipids	Triacylglycerols	1.27 (0.96-1.69)	0.096	1.22 (0.9-1.66)	0.207
C43:0 TAG	HMDB0042062*	Glycerolipids	Triacylglycerols	1.32 (0.98-1.77)	0.065	1.22 (0.89-1.66)	0.214
C48:0 TAG	HMDB0005356*	Glycerolipids	Triacylglycerols	1.4 (1.04-1.88)	0.025	1.22 (0.88-1.68)	0.230
C46:0 TAG	HMDB0010411*	Glycerolipids	Triacylglycerols	1.35 (1.01-1.81)	0.043	1.19 (0.87-1.63)	0.276
C53:2 TAG	HMDB0042196*	Glycerolipids	Triacylglycerols	1.15 (0.86-1.54)	0.348	1.19 (0.87-1.63)	0.284

Supplemental Table 1.1b (continued).

C54:6 TAG	HMDB0005391*	Glycerolipids	Triacylglycerols	0.82 (0.61-1.11)	0.206	0.84 (0.61-1.16)	0.295
C56:5 TAG	HMDB0005406*	Glycerolipids	Triacylglycerols	0.86 (0.64-1.15)	0.299	0.86 (0.63-1.17)	0.329
C50:1 TAG	HMDB0005360*	Glycerolipids	Triacylglycerols	1.35 (1.01-1.81)	0.043	1.17 (0.85-1.63)	0.332
C44:0 TAG	HMDB0042063*	Glycerolipids	Triacylglycerols	1.32 (0.98-1.76)	0.065	1.16 (0.85-1.59)	0.338
C52:2 TAG	HMDB0005369*	Glycerolipids	Triacylglycerols	1.24 (0.93-1.67)	0.146	1.16 (0.84-1.61)	0.367
C51:1 TAG	HMDB0042104*	Glycerolipids	Triacylglycerols	1.29 (0.96-1.73)	0.093	1.16 (0.84-1.6)	0.369
C46:1 TAG	HMDB0010412*	Glycerolipids	Triacylglycerols	1.27 (0.95-1.71)	0.105	1.15 (0.84-1.57)	0.385
C47:1 TAG	HMDB0042100*	Glycerolipids	Triacylglycerols	1.24 (0.92-1.66)	0.155	1.14 (0.84-1.55)	0.397
C43:2 TAG	HMDB0043169*	Glycerolipids	Triacylglycerols	1 (0.75-1.35)	0.975	0.88 (0.64-1.21)	0.425
C56:4 TAG	HMDB0005398*	Glycerolipids	Triacylglycerols	0.83 (0.62-1.11)	0.219	0.89 (0.65-1.2)	0.435
C54:5 TAG	HMDB0005385*	Glycerolipids	Triacylglycerols	0.87 (0.65-1.16)	0.339	0.88 (0.64-1.21)	0.438
C51:2 TAG	HMDB0005362*	Glycerolipids	Triacylglycerols	1.2 (0.89-1.62)	0.226	1.13 (0.82-1.55)	0.450
C49:1 TAG	HMDB0011705*	Glycerolipids	Triacylglycerols	1.22 (0.91-1.63)	0.177	1.11 (0.82-1.5)	0.506
C48:1 TAG	HMDB0005359*	Glycerolipids	Triacylglycerols	1.27 (0.95-1.71)	0.108	1.11 (0.81-1.53)	0.508
C48:2 TAG	HMDB0005376*	Glycerolipids	Triacylglycerols	1.23 (0.91-1.66)	0.173	1.11 (0.81-1.53)	0.516
C45:1 TAG	HMDB0042099*	Glycerolipids	Triacylglycerols	1.22 (0.91-1.65)	0.182	1.11 (0.81-1.51)	0.531
C55:2 TAG	HMDB0042226*	Glycerolipids	Triacylglycerols	1.16 (0.87-1.55)	0.301	1.1 (0.81-1.49)	0.534
C52:4 TAG	HMDB0005363*	Glycerolipids	Triacylglycerols	0.96 (0.73-1.27)	0.765	0.91 (0.67-1.23)	0.538
C56:1 TAG	HMDB0005396*	Glycerolipids	Triacylglycerols	1.2 (0.9-1.61)	0.208	1.1 (0.81-1.5)	0.544
C54:3 TAG	HMDB0005405*	Glycerolipids	Triacylglycerols	1.05 (0.78-1.4)	0.763	1.1 (0.8-1.5)	0.551
C56:2 TAG	HMDB0005404*	Glycerolipids	Triacylglycerols	1.15 (0.87-1.54)	0.322	1.09 (0.8-1.47)	0.595
C54:4 TAG	HMDB0005370*	Glycerolipids	Triacylglycerols	0.89 (0.67-1.19)	0.440	0.92 (0.68-1.26)	0.616
C43:1 TAG	HMDB0042098*	Glycerolipids	Triacylglycerols	1.22 (0.9-1.64)	0.202	1.08 (0.79-1.49)	0.621
C49:2 TAG	HMDB0011706*	Glycerolipids	Triacylglycerols	1.16 (0.86-1.56)	0.318	1.07 (0.78-1.46)	0.679
C53:3 TAG	HMDB0043058*	Glycerolipids	Triacylglycerols	0.91 (0.68-1.21)	0.520	0.94 (0.68-1.29)	0.695
C50:2 TAG	HMDB0005377*	Glycerolipids	Triacylglycerols	1.22 (0.91-1.63)	0.189	1.07 (0.77-1.47)	0.698
C55:3 TAG	HMDB0042466*	Glycerolipids	Triacylglycerols	0.86 (0.65-1.14)	0.303	0.94 (0.69-1.28)	0.698
C50:3 TAG	HMDB0005433*	Glycerolipids	Triacylglycerols	1.17 (0.87-1.56)	0.304	1.06 (0.77-1.46)	0.726
C46:2 TAG	HMDB0010419*	Glycerolipids	Triacylglycerols	1.17 (0.87-1.57)	0.292	1.05 (0.77-1.44)	0.762
C47:2 TAG	HMDB0042076*	Glycerolipids	Triacylglycerols	1.14 (0.84-1.54)	0.396	1.05 (0.76-1.44)	0.771
C56:3 TAG	HMDB0005410*	Glycerolipids	Triacylglycerols	1.04 (0.79-1.38)	0.773	1.04 (0.78-1.4)	0.785
C48:3 TAG	HMDB0005432*	Glycerolipids	Triacylglycerols	1.07 (0.8-1.44)	0.652	0.97 (0.71-1.34)	0.868
C49:3 TAG	HMDB0042103*	Glycerolipids	Triacylglycerols	1.03 (0.76-1.38)	0.861	1 (0.73-1.37)	0.982
C45:2 TAG	HMDB0043170*	Glycerolipids	Triacylglycerols	1.13 (0.84-1.52)	0.432	1 (0.72-1.37)	0.989

Supplemental Table 1.1b (continued).

C51:3 TAG	HMDB0011701*	Glycerolipids	Triacylglycerols	1.01 (0.76-1.35)	0.929	1 (0.72-1.38)	0.993
C18:3 LPC	HMDB0010387*	Glycerophospho-lipids	Glycerophospho-cholines	1.4 (1.04-1.9)	0.026	1.4 (1.02-1.93)	0.035
C16:1 LPC	HMDB0010383*	Glycerophospho-lipids	Glycerophospho-cholines	1.39 (1.04-1.87)	0.028	1.39 (1.02-1.89)	0.038
C16:0 LPC	HMDB0010382	Glycerophospho-lipids	Glycerophospho-cholines	1.4 (1.04-1.89)	0.026	1.38 (1.01-1.89)	0.042
C18:1 LPC	HMDB0002815*	Glycerophospho-lipids	Glycerophospho-cholines	1.32 (0.97-1.79)	0.072	1.39 (1.01-1.93)	0.046
C40:9 PC	HMDB0008731*	Glycerophospho-lipids	Glycerophospho-cholines	0.76 (0.56-1.04)	0.087	0.72 (0.51-1.01)	0.060
C18:0 LPC	HMDB0010384	Glycerophospho-lipids	Glycerophospho-cholines	1.36 (0.99-1.87)	0.060	1.36 (0.97-1.89)	0.074
C40:10 PC	HMDB0008511*	Glycerophospho-lipids	Glycerophospho-cholines	0.78 (0.58-1.06)	0.108	0.75 (0.54-1.04)	0.083
C38:6 PC	HMDB0007991*	Glycerophospho-lipids	Glycerophospho-cholines	0.79 (0.58-1.09)	0.152	0.75 (0.53-1.05)	0.090
C40:6 PC	HMDB0008057*	Glycerophospho-lipids	Glycerophospho-cholines	0.82 (0.6-1.11)	0.199	0.78 (0.56-1.07)	0.123
C38:7 PC plasmalogen	HMDB0011229*	Glycerophospho-lipids	Glycerophospho-cholines	0.86 (0.64-1.15)	0.299	0.79 (0.58-1.08)	0.146
C36:5 PC plasmalogen-A	HMDB0011221*	Glycerophospho-lipids	Glycerophospho-cholines	0.86 (0.64-1.16)	0.323	0.79 (0.58-1.09)	0.152
C34:1 PC plasmalogen-B	HMDB0011239*	Glycerophospho-lipids	Glycerophospho-cholines	1.17 (0.88-1.57)	0.279	1.24 (0.91-1.69)	0.168
C20:5 LPC	HMDB0010397	Glycerophospho-lipids	Glycerophospho-cholines	1.23 (0.91-1.67)	0.174	1.26 (0.91-1.74)	0.170
C18:2 LPC	HMDB0010386*	Glycerophospho-lipids	Glycerophospho-cholines	1.22 (0.9-1.65)	0.207	1.25 (0.9-1.74)	0.182
C22:5 LPC	HMDB0010403*	Glycerophospho-lipids	Glycerophospho-cholines	1.19 (0.89-1.59)	0.242	1.2 (0.88-1.64)	0.239
C14:0 LPC	HMDB0010379	Glycerophospho-lipids	Glycerophospho-cholines	1.28 (0.95-1.72)	0.105	1.2 (0.88-1.64)	0.252
C32:2 PC	HMDB0007874*	Glycerophospho-lipids	Glycerophospho-cholines	0.91 (0.67-1.23)	0.540	0.83 (0.6-1.15)	0.259

Supplemental Table 1.1b (continued).

C34:1 PC plasmalogen	HMDB0011208*	Glycerophospho-lipids	Glycerophospho-cholines	1.09 (0.81-1.46)	0.586	1.18 (0.86-1.63)	0.308
C34:3 PC plasmalogen	HMDB0011211*	Glycerophospho-lipids	Glycerophospho-cholines	0.89 (0.67-1.2)	0.448	0.88 (0.63-1.21)	0.417
C38:4 PC plasmalogen	HMDB0011252*	Glycerophospho-lipids	Glycerophospho-cholines	1.06 (0.79-1.42)	0.698	1.13 (0.84-1.53)	0.426
C38:3 PC	HMDB0008047*	Glycerophospho-lipids	Glycerophospho-cholines	1.18 (0.89-1.57)	0.245	1.13 (0.84-1.52)	0.427
C36:4 PC plasmalogen	HMDB0011310*	Glycerophospho-lipids	Glycerophospho-cholines	1.02 (0.76-1.38)	0.891	1.13 (0.81-1.57)	0.467
C36:1 PC	HMDB0008038*	Glycerophospho-lipids	Glycerophospho-cholines	1.17 (0.88-1.55)	0.289	1.11 (0.82-1.49)	0.509
C32:0 PC	HMDB0007871*	Glycerophospho-lipids	Glycerophospho-cholines	1.18 (0.86-1.62)	0.293	1.1 (0.79-1.53)	0.574
C36:2 PC plasmalogen	HMDB0011243*	Glycerophospho-lipids	Glycerophospho-cholines	1.01 (0.75-1.36)	0.962	1.1 (0.8-1.51)	0.576
C36:4 PC-B	HMDB0008138*	Glycerophospho-lipids	Glycerophospho-cholines	0.92 (0.68-1.25)	0.589	0.92 (0.67-1.26)	0.588
C34:1 PC	HMDB0007972*	Glycerophospho-lipids	Glycerophospho-cholines	1.15 (0.86-1.54)	0.338	1.07 (0.79-1.46)	0.647
C22:6 LPC	HMDB0010404	Glycerophospho-lipids	Glycerophospho-cholines	1.01 (0.75-1.36)	0.938	0.97 (0.71-1.33)	0.839
C30:1 PC	HMDB0007870*	Glycerophospho-lipids	Glycerophospho-cholines	1.04 (0.77-1.41)	0.783	0.97 (0.7-1.33)	0.850
C32:1 PC	HMDB0007873*	Glycerophospho-lipids	Glycerophospho-cholines	1.09 (0.81-1.48)	0.558	0.98 (0.71-1.35)	0.904
C30:0 PC	HMDB0007869*	Glycerophospho-lipids	Glycerophospho-cholines	1.12 (0.82-1.52)	0.484	1.01 (0.73-1.4)	0.931
C36:5 PC plasmalogen-B	HMDB0011220*	Glycerophospho-lipids	Glycerophospho-cholines	1 (0.75-1.34)	0.982	1.01 (0.74-1.36)	0.961
C38:6 PE	HMDB0009102*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.76 (0.55-1.05)	0.091	0.69 (0.49-0.97)	0.035
C18:0 LPE	HMDB0011130	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.38 (1.02-1.87)	0.035	1.34 (0.98-1.83)	0.071
C22:6 LPE	HMDB0011526	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.86 (0.63-1.16)	0.319	0.76 (0.55-1.06)	0.105

Supplemental Table 1.1b (continued).

C36:1 PE plasmalogen	HMDB0009016*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.22 (0.91-1.64)	0.193	1.27 (0.93-1.75)	0.137
C38:5 PE	HMDB0009069*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.81 (0.6-1.09)	0.167	0.8 (0.59-1.1)	0.168
C36:2 PE plasmalogen	HMDB0009082*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.19 (0.9-1.59)	0.226	1.24 (0.91-1.67)	0.168
C18:1 LPE	HMDB0011506*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.23 (0.92-1.65)	0.170	1.24 (0.91-1.68)	0.178
C36:3 PE	HMDB0009060*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.85 (0.64-1.14)	0.278	0.81 (0.6-1.1)	0.186
C40:6 PE	HMDB0009012*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.9 (0.66-1.23)	0.510	0.8 (0.57-1.12)	0.187
C36:4 PE	HMDB0008937*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.86 (0.63-1.16)	0.326	0.81 (0.59-1.11)	0.195
C38:5 PE plasmalogen	HMDB0011386*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.17 (0.88-1.55)	0.275	1.21 (0.9-1.62)	0.205
C22:0 LPE	HMDB0011520	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.13 (0.83-1.53)	0.442	1.22 (0.88-1.71)	0.234
C34:2 PE	HMDB0008928*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.91 (0.68-1.22)	0.517	0.83 (0.61-1.13)	0.240
C38:7 PE plasmalogen	HMDB0011420*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.91 (0.68-1.23)	0.550	0.85 (0.62-1.17)	0.321
C36:3 PE plasmalogen	HMDB0011441*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.12 (0.84-1.51)	0.432	1.17 (0.85-1.59)	0.333
C36:5 PE plasmalogen	HMDB0011410*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.09 (0.82-1.45)	0.560	1.15 (0.85-1.55)	0.361
C38:4 PE	HMDB0009003*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.95 (0.71-1.28)	0.728	0.9 (0.65-1.23)	0.495
C16:0 LPE	HMDB0011503	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.14 (0.85-1.54)	0.374	1.11 (0.81-1.52)	0.505
C34:3 PE plasmalogen	HMDB0011343*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.05 (0.78-1.41)	0.756	1.11 (0.81-1.52)	0.519
C36:4 PE plasmalogen	HMDB0011442*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.02 (0.75-1.37)	0.912	1.11 (0.81-1.52)	0.519

Supplemental Table 1.1b (continued).

C36:2 PE	HMDB0008994*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.01 (0.76-1.35)	0.923	0.91 (0.67-1.24)	0.563
C18:2 LPE	HMDB0011507*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.14 (0.85-1.54)	0.378	1.09 (0.8-1.5)	0.573
C34:2 PE plasmalogen	HMDB0008952*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.05 (0.79-1.4)	0.755	1.09 (0.81-1.48)	0.575
C20:4 LPE	HMDB0011517	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.08 (0.81-1.44)	0.593	1.07 (0.79-1.45)	0.666
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1 (0.76-1.33)	0.986	1.05 (0.78-1.41)	0.740
C36:0 PE	HMDB0008991*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.06 (0.78-1.43)	0.704	1.04 (0.76-1.43)	0.790
C40:7 PE plasmalogen	HMDB0011394*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.99 (0.75-1.33)	0.972	0.97 (0.72-1.31)	0.850
C32:0 PE	HMDB0008923*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.02 (0.75-1.38)	0.889	0.98 (0.71-1.34)	0.893
C34:0 PE	HMDB0008925*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.06 (0.78-1.44)	0.697	1.02 (0.74-1.4)	0.917
C38:2 PE	HMDB0008942*	Glycerophospho-lipids	Glycerophospho-ethanolamines	0.94 (0.7-1.26)	0.685	1 (0.73-1.37)	0.985
C36:1 PE	HMDB0008993*	Glycerophospho-lipids	Glycerophospho-ethanolamines	1.1 (0.82-1.47)	0.543	1 (0.73-1.37)	0.986
C38:4 PI	HMDB0009815*	Glycerophospho-lipids	Glycerophospho-inositols	1.08 (0.8-1.46)	0.601	1.09 (0.8-1.49)	0.577
C34:0 PS	HMDB0012356*	Glycerophospho-lipids	Glycerophospho-serines	0.85 (0.63-1.14)	0.283	0.77 (0.56-1.06)	0.114
7-methylguanine	HMDB0000897	Imidazo-pyrimidines	Purines and purine derivatives	1.02 (0.74-1.4)	0.921	0.87 (0.62-1.24)	0.449
caffeine	HMDB0001847	Imidazo-pyrimidines	Purines and purine derivatives	1.16 (0.86-1.56)	0.336	1.12 (0.81-1.54)	0.494
uric acid	HMDB0000289	Imidazo-pyrimidines	Purines and purine derivatives	1.21 (0.89-1.65)	0.221	1.13 (0.8-1.59)	0.503

Supplemental Table 1.1b (continued).

3-methylxanthine	HMDB0001886	Imidazo-pyrimidines	Purines and purine derivatives	1.05 (0.78-1.4)	0.752	1.06 (0.78-1.43)	0.705
7-methylxanthine	HMDB0001991	Imidazo-pyrimidines	Purines and purine derivatives	0.99 (0.74-1.32)	0.926	1.02 (0.75-1.38)	0.906
1-methylguanine	HMDB0003282	Imidazo-pyrimidines	Purines and purine derivatives	1.08 (0.78-1.48)	0.650	1.01 (0.73-1.42)	0.934
1,7-dimethyluric acid	HMDB0011103	Imidazo-pyrimidines	Purines and purine derivatives	1 (0.75-1.35)	0.978	0.99 (0.72-1.35)	0.942
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	1.39 (1.04-1.87)	0.028	1.4 (1.03-1.9)	0.030
serotonin	HMDB0000259	Indoles and derivatives	Tryptamines and derivatives	0.86 (0.63-1.16)	0.319	0.9 (0.66-1.24)	0.529
C20:1 LPE	HMDB0011512*	NA	NA	1.27 (0.94-1.72)	0.118	1.32 (0.96-1.82)	0.085
C34:5 PC plasmalogen	HMDB0011214*	NA	NA	1.28 (0.96-1.71)	0.094	1.3 (0.96-1.75)	0.092
C34:4 PC	HMDB0007883*	NA	NA	0.83 (0.61-1.13)	0.232	0.78 (0.56-1.08)	0.140
C20:4 LPC	HMDB0010395	NA	NA	1.17 (0.88-1.57)	0.279	1.2 (0.88-1.63)	0.239
C20:1 LPC	HMDB0010391*	NA	NA	0.82 (0.6-1.12)	0.218	0.83 (0.6-1.16)	0.275
2-methyl-4,5-benzoxazole	HMDB0032390	NA	NA	1.08 (0.81-1.43)	0.617	1.15 (0.85-1.55)	0.358
trigonelline	HMDB0000875	NA	NA	0.87 (0.65-1.17)	0.361	0.88 (0.65-1.2)	0.434
DMGV	HMDB0240212	NA	NA	1.16 (0.86-1.57)	0.328	1.13 (0.8-1.61)	0.493
coenzyme Q10	HMDB0001072	NA	NA	1.06 (0.8-1.41)	0.677	1.06 (0.79-1.43)	0.688
piperine	HMDB0029377	NA	NA	0.98 (0.74-1.31)	0.904	0.94 (0.69-1.28)	0.699
cerulenin	HMDB0015168	NA	NA	0.99 (0.74-1.32)	0.949	0.95 (0.7-1.28)	0.734
C18:3 LPE	HMDB0011478*	NA	NA	1.02 (0.76-1.37)	0.914	0.95 (0.7-1.29)	0.740
methyl N-methylanthranilate	HMDB0034169	NA	NA	1.11 (0.84-1.48)	0.456	1.05 (0.78-1.41)	0.761
deoxyguanosine	HMDB0000085	NA	NA	0.92 (0.66-1.27)	0.612	0.96 (0.68-1.35)	0.808
thyroxine	HMDB0000248	NA	NA	1 (0.74-1.36)	0.985	1.03 (0.75-1.42)	0.837

Supplemental Table 1.1b (continued).

C34:2 PC plasmalogen	HMDB0011210*	NA	NA	0.96 (0.72-1.29)	0.799	0.97 (0.7-1.35)	0.861
C36:3 PC plasmalogen	HMDB0011244*	NA	NA	0.94 (0.71-1.26)	0.693	0.99 (0.72-1.35)	0.943
pseudouridine	HMDB0000767	Nucleoside and nucleotide analogues	NA	1.13 (0.81-1.58)	0.458	1.15 (0.8-1.64)	0.457
N-carbamoyl-beta-alanine	HMDB0000026	Organic carbonic acids and derivatives	Ureas	1.2 (0.88-1.65)	0.248	1.14 (0.82-1.6)	0.431
1-methylhistamine	HMDB0000898	Organonitrogen compounds	Amines	1.09 (0.82-1.46)	0.556	1.03 (0.76-1.4)	0.850
trimethylamine-N-oxide	HMDB0000925	Organonitrogen compounds	Aminoxides	0.93 (0.7-1.22)	0.583	0.93 (0.69-1.24)	0.612
metformin	HMDB0001921	Organonitrogen compounds	Guanidines	1.26 (0.76-2.09)	0.378	1.25 (0.74-2.13)	0.409
carnitine	HMDB0000062	Organonitrogen compounds	Quaternary ammonium salts	1.2 (0.88-1.63)	0.245	1.27 (0.91-1.75)	0.157
phosphocholine	HMDB0001565	Organonitrogen compounds	Quaternary ammonium salts	1.13 (0.84-1.52)	0.417	1.14 (0.83-1.57)	0.403
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	1.34 (0.96-1.88)	0.084	1.31 (0.91-1.88)	0.153
4-hydroxy-3-methylacetophenone	HMDB0059824	Organooxygen compounds	Carbonyl compounds	0.78 (0.56-1.08)	0.132	0.75 (0.53-1.06)	0.101
acetaminophen	HMDB0001859	Phenols	1-hydroxy-2-unsubstituted benzenoids	0.88 (0.65-1.19)	0.396	0.87 (0.64-1.19)	0.375
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	1.25 (0.9-1.72)	0.181	1.22 (0.87-1.71)	0.257
1-methylguanosine	HMDB0001563	Purine nucleosides	NA	1.09 (0.8-1.49)	0.584	1.05 (0.75-1.45)	0.794

Supplemental Table 1.1b (continued).

N2,N2-dimethylguanosine	HMDB0004824	Purine nucleosides	NA	1.06 (0.75-1.49)	0.742	0.97 (0.67-1.42)	0.888
guanosine	HMDB0000133	Purine nucleosides	NA	0.98 (0.73-1.31)	0.868	1 (0.74-1.36)	0.985
1-methylnicotinamide	HMDB0000699	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.8 (0.59-1.08)	0.145	0.75 (0.55-1.03)	0.078
N1-methyl-2-pyridone-5-carboxamide	HMDB0004193	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.92 (0.69-1.25)	0.607	0.85 (0.62-1.17)	0.320
pyridoxamine	HMDB0001431	Pyridines and derivatives	Pyridoxamines	1.44 (1.05-1.99)	0.025	1.4 (1-1.95)	0.051
cotinine	HMDB0001046	Pyridines and derivatives	Pyrrolidinylpyridines	1.03 (0.74-1.43)	0.855	1.05 (0.75-1.48)	0.763
ribothymidine	HMDB0000884	Pyrimidine nucleosides	NA	1.19 (0.86-1.65)	0.283	1.21 (0.86-1.71)	0.266
N4-acetylcytidine	HMDB0005923	Pyrimidine nucleosides	NA	1.12 (0.82-1.51)	0.479	1.04 (0.74-1.44)	0.836
kynurenic acid	HMDB0000715	Quinolines and derivatives	Quinoline carboxylic acids	1.25 (0.9-1.73)	0.181	1.15 (0.81-1.63)	0.441
Ceramide (d18:1) C16:0	HMDB0004949	Sphingolipids	Ceramides	1.62 (1.18-2.22)	0.003	1.72 (1.23-2.4)	0.002
Ceramide (d18:1) C24:1	HMDB0004953*	Sphingolipids	Ceramides	1.46 (1.08-1.98)	0.014	1.42 (1.04-1.94)	0.028
Ceramide (d18:1) C22:0	HMDB0004952	Sphingolipids	Ceramides	1.43 (1.06-1.94)	0.020	1.39 (1.01-1.92)	0.044
Ceramide (d18:1) C24:0	HMDB0004956	Sphingolipids	Ceramides	1.33 (0.99-1.78)	0.060	1.24 (0.91-1.7)	0.169
C14:0 SM	HMDB0012097	Sphingolipids	Phosphosphingo-lipids	1.14 (0.85-1.53)	0.379	1.1 (0.8-1.49)	0.561

Supplemental Table 1.1b (continued).

C22:1 SM	HMDB0012104*	Sphingolipids	Phosphosphingo-lipids	1 (0.75-1.35)	0.988	1.02 (0.75-1.39)	0.908
glycodeoxycholate/glycochenodeoxycholate	HMDB0000631*	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.31 (0.99-1.75)	0.063	1.35 (0.99-1.84)	0.057
glycocholate	HMDB0000138	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.17 (0.88-1.54)	0.275	1.16 (0.86-1.56)	0.324
cholesterol	HMDB0000067	Steroids and steroid derivatives	Cholestane steroids	1.07 (0.8-1.42)	0.658	1.06 (0.79-1.43)	0.696
campesterol	HMDB0002869	Steroids and steroid derivatives	Ergostane steroids	1.06 (0.8-1.42)	0.672	1.07 (0.8-1.45)	0.642
cortisone	HMDB0002802	Steroids and steroid derivatives	Hydroxysteroids	1.16 (0.85-1.57)	0.348	1.18 (0.85-1.63)	0.325
cortisol	HMDB0000063	Steroids and steroid derivatives	Hydroxysteroids	1.03 (0.75-1.4)	0.868	1.03 (0.75-1.43)	0.842
21-deoxycortisol	HMDB0004030	Steroids and steroid derivatives	Pregnane steroids	0.95 (0.7-1.28)	0.741	1.01 (0.73-1.38)	0.965
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesterol esters	1.14 (0.84-1.53)	0.405	1.25 (0.91-1.7)	0.168
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesterol esters	0.83 (0.62-1.11)	0.214	0.84 (0.61-1.14)	0.265
C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesterol esters	1.04 (0.78-1.39)	0.782	1.11 (0.82-1.52)	0.499
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesterol esters	0.8 (0.6-1.05)	0.111	0.9 (0.67-1.23)	0.517
C16:1 CE	HMDB0000658*	Steroids and steroid derivatives	Cholesterol esters	1.14 (0.85-1.51)	0.389	1.08 (0.79-1.48)	0.624
C22:6 CE	HMDB0006733	Steroids and steroid derivatives	Cholesterol esters	0.88 (0.66-1.17)	0.367	0.94 (0.69-1.29)	0.709
C20:3 CE	HMDB0006736*	Steroids and steroid derivatives	Cholesterol esters	0.97 (0.73-1.3)	0.857	1.06 (0.78-1.44)	0.727
C16:0 CE	HMDB0000885	Steroids and steroid derivatives	Cholesterol esters	0.86 (0.64-1.15)	0.320	0.95 (0.69-1.3)	0.740

Supplemental Table 1.1b (continued).

C20:4 CE	HMDB0006726	Steroids and steroid derivatives	Cholesterol esters	0.92 (0.69-1.22)	0.561	1.05 (0.77-1.41)	0.774
C18:1 CE	HMDB0000918*	Steroids and steroid derivatives	Cholesterol esters	0.94 (0.71-1.26)	0.686	1.03 (0.75-1.43)	0.846
C18:2 CE	HMDB0000610*	Steroids and steroid derivatives	Cholesterol esters	0.9 (0.67-1.2)	0.465	0.99 (0.71-1.36)	0.933
C14:0 CE	HMDB0006725	Steroids and steroid derivatives	Cholesterol esters	1.03 (0.78-1.36)	0.851	1.01 (0.75-1.38)	0.934
biliverdin	HMDB0001008	Tetrapyrroles and derivatives	Bilirubins	1.3 (0.96-1.75)	0.092	1.29 (0.94-1.77)	0.115
bilirubin	HMDB0000054	Tetrapyrroles and derivatives	Bilirubins	0.98 (0.73-1.32)	0.894	0.99 (0.73-1.36)	0.964

**Includes metabolites with <10% missingness. Missing values were imputed with 1/2 the minimum value. Results sorted by class, subclass, and p-value for fully adjusted model. CLR includes matched factors: age at blood draw, month of blood draw, fasting status at blood draw, menopausal status at blood draw, hormone use at blood draw

^Multivariable adjusted model includes BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).

*Representative HMDBID

Supplemental Table 1.2a. Odds ratio for breast cancer risk by presence or absence of metabolite, and by continuous measure (90th - 10th percentile comparison), for metabolites with >10% missingness, Distant blood.**

				Multivariable Adjusted^				
HMDB ID	**Metabolite Name**	**Class**	**Subclass**	OR (95% CI) (present v absent)		p value	OR 95% CI (continuous)	p value
HMDB0000033	carnosine	Peptidomimetics	Hybrid peptides	1.10	(0.61, 1.96)	0.760	1.16 (0.89-1.5)	0.270
HMDB0000895	acetylcholine	Organonitrogen compounds	Quaternary ammonium salts	1.55	(0.78, 3.05)	0.208	1.12 (0.86-1.46)	0.385
HMDB0001390	hydroxycotinine	Pyridines and derivatives	Pyrrolidinyl-pyridines	1.12	(0.61, 2.07)	0.720	1.02 (0.78-1.33)	0.870
HMDB0001850	verapamil	Benzene and substituted derivatives	Phenylbutyl-amines	0.97	(0.32, 2.92)	0.960	2.34 (0.78-7.04)	0.122
HMDB0001924	atenolol	Benzene and substituted derivatives	Phenylacetamides	1.55	(0.53, 4.54)	0.427	1.03 (0.35-3.04)	0.953
HMDB0001932	metoprolol	Phenols	Tyrosols and derivatives	0.81	(0.38, 1.75)	0.597	1.29 (0.95-1.74)	0.106
HMDB0001935	warfarin	Coumarins and derivatives	Hydroxy-coumarins	0.27	(0.08, 0.94)	0.040	1.78 (0.52-6.09)	0.352
HMDB0003464	4-guanidinobutanoic acid	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92	(0.55, 1.56)	0.766	1.14 (0.82-1.58)	0.428
HMDB0004158	D-urobilinogen	NA	NA	0.99	(0.51, 1.94)	0.980	0.93 (0.7-1.23)	0.609
HMDB0005015	gabapentin	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	2.07	(0.75, 5.72)	0.162	0.99 (0.71-1.38)	0.963
HMDB0007011*	C30:0 DAG	Glycerolipids	Diacylglycerols	1.23	(0.68, 2.22)	0.490	1.09 (0.82-1.45)	0.559

Supplemental Table 1.2a (continued).

HMDB0010316	4-acetamidophenylglucuronide	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	0.65	(0.37, 1.13)	0.125	1.03 (0.63-1.69)	0.903
HMDB0014611	quinine	NA	NA	1.11	(0.59, 2.09)	0.746	1.12 (0.65-1.94)	0.677
HMDB0015028	sulfapyridine	NA	NA	1.26	(0.43, 3.64)	0.675	2.1 (0.66-6.68)	0.203
HMDB0042093*	C45:0 TAG	Glycerolipids	Triacylglycerols	0.98	(0.45, 2.14)	0.964	1.13 (0.87-1.46)	0.356

**Continuous results are presented only including those with a continuous measure for the metabolite available. Results sorted by class, subclass, and p-value for fully adjusted model.
^Multivariable model includes BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).
*Representative HMDBID

Supplemental Table 1.2b. Odds ratios for breast cancer risk by presence or absence of metabolite, and by continuous measure (90th - 10th percentile comparison), for metabolites with >10% missingness, Proximate blood.**

				Multivariable Adjusted^				
HMDB ID	**Metabolite Name**	**Class**	**Subclass**	OR (95% CI) (present v absent)		p value	OR (95% CI) (continuous)	p value
HMDB0001924	atenolol	Benzene and substituted derivatives	Phenylacetamides	0.97	(0.38, 2.49)	0.947	1.79 (0.68-4.74)	0.235
HMDB0001850	verapamil	Benzene and substituted derivatives	Phenylbutylamines	1.64	(0.38, 7.07)	0.505	4.4 (0.82-23.5)	0.072
HMDB0005015	gabapentin	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.58	(0.15, 2.26)	0.430	1.24 (0.77-2)	0.368
HMDB0003464	4-guanidinobutanoic acid	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95	(0.48, 1.89)	0.879	1.28 (0.84-1.94)	0.244
HMDB0001935	warfarin	Coumarins and derivatives	Hydroxycoumarins	1.36	(0.41, 4.50)	0.618	1.65 (0.47-5.71)	0.430
HMDB0007011*	C30:0 DAG	Glycerolipids	Diacylglycerols	1.03	(0.48, 2.23)	0.934	1.25 (0.85-1.84)	0.250
HMDB0042093*	C45:0 TAG	Glycerolipids	Triacylglycerols	2.26	(0.84, 6.12)	0.108	1.17 (0.85-1.6)	0.340

Supplemental Table 1.2b (continued).

HMDB0015028	sulfapyridine	NA	NA	0.51	(0.16, 1.64)	0.257	1.21 (0.4-3.69)	0.738
HMDB0014323	valsartan	NA	NA	1.4	(0.53, 3.71)	0.503	1.5 (0.96-2.34)	0.071
HMDB0014611	quinine	NA	NA	0.77	(0.35, 1.72)	0.522	1.23 (0.62-2.44)	0.551
HMDB0004158	D-urobilinogen	NA	NA	1.3	(0.57, 2.97)	0.525	0.96 (0.67-1.36)	0.799
HMDB0000895	acetylcholine	Organonitrogen compounds	Quaternary ammonium salts	0.3	(0.10, 0.92)	0.035	1.07 (0.78-1.47)	0.681
HMDB0010316	4-acetamidophenylglucuronide	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	0.81	(0.43, 1.53)	0.521	1.11 (0.66-1.85)	0.700
HMDB0000033	carnosine	Peptidomimetics	Hybrid peptides	0.62	(0.25, 1.53)	0.301	0.93 (0.66-1.3)	0.659
HMDB0001932	metoprolol	Phenols	Tyrosols and derivatives	1.32	(0.56, 3.12)	0.522	0.93 (0.64-1.34)	0.685
HMDB0001390	hydroxycotinine	Pyridines and derivatives	Pyrrolidinylpyridines	0.79	(0.34, 1.85)	0.593	1.03 (0.71-1.48)	0.888

**Continuous results are presented only including those with a continuous measure for the metabolite available. Results are sorted by class, subclass, and p-value for fully adjusted models (present v. absent analysis).
*Representative HMDBID
^Multivariable model includes BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).

Supplemental Table 1.3a. Odds ratios for ER+ breast cancer risk comparing 90th to 10th percentiles of metabolite levels, measured at distant blood.**

				Multivariable adjusted^	
Metabolite Name	**HMDB ID**	**Class**	**Subclass**	**OR (95% CI)**	**p value**
metronidazole	HMDB0015052	Azoles	Imidazoles	0.90 (0.67-1.19)	0.456
urocanic acid	HMDB0000301	Azoles	Imidazoles	1.05 (0.80-1.38)	0.732
allantoin	HMDB0000462	Azoles	Imidazoles	0.95 (0.70-1.29)	0.751
sulfamethoxazole	HMDB0015150	Benzene and substituted derivatives	Benzenesulfonamides	1.03 (0.79-1.34)	0.833
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	0.67 (0.50-0.90)	0.007
4-hydroxyhippurate	HMDB0013678	Benzene and substituted derivatives	Benzoic acids and derivatives	0.75 (0.57-1.00)	0.05
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	1.28 (0.97-1.70)	0.081
N-acetylputrescine	HMDB0002064	Carboximidic acids and derivatives	Carboximidic acids	1.27 (0.95-1.69)	0.101
Palmitoylethanol-amide	HMDB0002100	Carboximidic acids and derivatives	Carboximidic acids	0.80 (0.61-1.06)	0.126
N1-acetylspermidine	HMDB0001276	Carboximidic acids and derivatives	Carboximidic acids	0.96 (0.71-1.30)	0.807
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.70 (0.53-0.94)	0.016
citrulline	HMDB0000904	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.74 (0.55-0.99)	0.045
hydroxyproline	HMDB0000725	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.79 (0.59-1.04)	0.099

Supplemental Table 1.3a (continued).

proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.28 (0.95-1.72)	0.111
lysine	HMDB0000182	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.25 (0.95-1.67)	0.115
alanine	HMDB0000161	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.26 (0.94-1.7)	0.124
N-acetylhistidine	HMDB0032055	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.80 (0.60-1.07)	0.131
homoarginine	HMDB0000670*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.24 (0.93-1.66)	0.136
creatine	HMDB0000064	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.81 (0.61-1.07)	0.139
betaine	HMDB0000043	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.79 (0.57-1.08)	0.143
4-acetamidobutan-oate	HMDB0003681	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.82 (0.61-1.10)	0.186
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.22 (0.90-1.64)	0.195
N-acetyltryptophan	HMDB0013713	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.83 (0.63-1.11)	0.217
oleoyl glycine	HMDB0013631	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.83 (0.62-1.12)	0.224
phenylacetylglutamine	HMDB0006344	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.84 (0.63-1.12)	0.246

Supplemental Table 1.3a (continued).

N-lauroylglycine	HMDB0013272	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.16 (0.88-1.54)	0.282
N6,N6,N6-trimethyllysine	HMDB0001325	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.86 (0.65-1.14)	0.302
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.87 (0.66-1.15)	0.32
ADMA/SDMA	HMDB0001539	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.14 (0.86-1.51)	0.363
glycine	HMDB0000123	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.87 (0.65-1.17)	0.367
histidine	HMDB0000177	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.13 (0.86-1.5)	0.375
1-methylhistidine	HMDB0000001	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.88 (0.67-1.16)	0.376
aminoisobutyric acid	HMDB0001906*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.12 (0.85-1.48)	0.412
GABA	HMDB0000112	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.89 (0.67-1.18)	0.413
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.13 (0.84-1.52)	0.42
glutamine	HMDB0000641	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.9 (0.67-1.19)	0.448

Supplemental Table 1.3a (continued).

leucine	HMDB0000687	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.12 (0.83-1.50)	0.453
methionine	HMDB0000696	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.11 (0.84-1.47)	0.462
N6-acetyllysine	HMDB0000206*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.91 (0.68-1.20)	0.489
2-aminooctanoic acid	HMDB0000991*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.09 (0.83-1.43)	0.553
dimethylglycine	HMDB0000092	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.09 (0.81-1.47)	0.564
creatinine	HMDB0000562	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.70-1.21)	0.572
NMMA	HMDB0029416	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.08 (0.82-1.43)	0.592
N6,N6-dimethyllysine	HMDB0013287	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.81-1.41)	0.647
tyrosine	HMDB0000158	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.79-1.44)	0.658
asparagine	HMDB0000168	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.94 (0.70-1.26)	0.666
pantothenate	HMDB0000210	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.94 (0.70-1.25)	0.673

Supplemental Table 1.3a (continued).

guanidinoacetic acid	HMDB0000128	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95 (0.70-1.27)	0.707
proline betaine	HMDB0004827	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95 (0.71-1.27)	0.727
threonine	HMDB0000167	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.96 (0.72-1.28)	0.785
pipecolic acid	HMDB0000716	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.04 (0.77-1.40)	0.8
valine	HMDB0000883	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.98 (0.73-1.32)	0.892
serine	HMDB0000187	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.98 (0.74-1.32)	0.916
cytosine	HMDB0000630	Diazines	Pyrimidines and pyrimidine derivatives	0.94 (0.72-1.24)	0.665
5-hydroxymethyl-4-methyluracil	HMDB0000544	Diazines	Pyrimidines and pyrimidine derivatives	0.95 (0.72-1.26)	0.73
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	0.59 (0.44-0.79)	0
C4 carnitine	HMDB0002013	Fatty Acyls	Fatty acid esters	0.69 (0.52-0.92)	0.012
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.70 (0.53-0.93)	0.015
C3 carnitine	HMDB0000824	Fatty Acyls	Fatty acid esters	0.72 (0.54-0.97)	0.029
C9 carnitine	HMDB0013288	Fatty Acyls	Fatty acid esters	1.13 (0.86-1.50)	0.368
C12 carnitine	HMDB0002250	Fatty Acyls	Fatty acid esters	0.89 (0.66-1.19)	0.414
C26 carnitine	HMDB0006347	Fatty Acyls	Fatty acid esters	0.89 (0.67-1.18)	0.419
C4-OH carnitine	HMDB0013127	Fatty Acyls	Fatty acid esters	1.10 (0.82-1.48)	0.508
C14:1 carnitine	HMDB0002014	Fatty Acyls	Fatty acid esters	0.91 (0.68-1.22)	0.538
C2 carnitine	HMDB0000201	Fatty Acyls	Fatty acid esters	0.92 (0.68-1.23)	0.568
C14:2 carnitine	HMDB0013331	Fatty Acyls	Fatty acid esters	0.92 (0.68-1.24)	0.585

Supplemental Table 1.3a (continued).

C12:1 carnitine	HMDB0013326	Fatty Acyls	Fatty acid esters	0.92 (0.69-1.24)	0.600
C5 carnitine	HMDB0000688	Fatty Acyls	Fatty acid esters	0.93 (0.69-1.24)	0.602
C10:2 carnitine	HMDB0013325	Fatty Acyls	Fatty acid esters	0.94 (0.71-1.24)	0.657
C14 carnitine	HMDB0005066	Fatty Acyls	Fatty acid esters	1.04 (0.78-1.39)	0.792
C6 carnitine	HMDB0000705	Fatty Acyls	Fatty acid esters	1.04 (0.77-1.39)	0.81
C8 carnitine	HMDB0000791	Fatty Acyls	Fatty acid esters	1.02 (0.76-1.37)	0.883
C10 carnitine	HMDB0000651	Fatty Acyls	Fatty acid esters	0.98 (0.73-1.32)	0.889
C7 carnitine	HMDB0013238	Fatty Acyls	Fatty acid esters	1.01 (0.76-1.35)	0.919
3-dehydroxycarnitine	HMDB0006831	Fatty Acyls	Fatty acids and conjugates	0.87 (0.64-1.17)	0.344
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	0.96 (0.72-1.28)	0.801
C34:2 DAG	HMDB0007103*	Fatty Acyls	Lineolic acids and derivatives	1.50 (1.12-2.02)	0.007
C36:3 DAG	HMDB0007219*	Fatty Acyls	Lineolic acids and derivatives	1.35 (1.01-1.80)	0.04
C34:3 DAG	HMDB0007132*	Fatty Acyls	Lineolic acids and derivatives	1.31 (0.99-1.74)	0.06
C36:4 DAG	HMDB0007248*	Fatty Acyls	Lineolic acids and derivatives	1.25 (0.94-1.66)	0.121
C32:0 DAG	HMDB0007098*	Glycerolipids	Diacylglycerols	1.44 (1.06-1.94)	0.018
C34:1 DAG	HMDB0007102*	Glycerolipids	Diacylglycerols	1.38 (1.03-1.87)	0.034
C32:1 DAG	HMDB0007099*	Glycerolipids	Diacylglycerols	1.32 (0.98-1.77)	0.067
C34:0 DAG	HMDB0007100*	Glycerolipids	Diacylglycerols	1.30 (0.96-1.75)	0.089
C36:2 DAG	HMDB0007218*	Glycerolipids	Diacylglycerols	1.28 (0.95-1.72)	0.101
C36:1 DAG	HMDB0007216*	Glycerolipids	Diacylglycerols	1.23 (0.91-1.66)	0.176
C38:5 DAG	HMDB0007199*	Glycerolipids	Diacylglycerols	1.16 (0.86-1.56)	0.326
C52:4 TAG	HMDB0005363*	Glycerolipids	Triacylglycerols	1.43 (1.07-1.90)	0.015
C50:2 TAG	HMDB0005377*	Glycerolipids	Triacylglycerols	1.44 (1.06-1.96)	0.021
C50:1 TAG	HMDB0005360*	Glycerolipids	Triacylglycerols	1.42 (1.04-1.93)	0.027
C50:3 TAG	HMDB0005433*	Glycerolipids	Triacylglycerols	1.38 (1.02-1.87)	0.035
C52:2 TAG	HMDB0005369*	Glycerolipids	Triacylglycerols	1.39 (1.02-1.88)	0.035
C51:1 TAG	HMDB0042104*	Glycerolipids	Triacylglycerols	1.38 (1.02-1.86)	0.036
C43:2 TAG	HMDB0043169*	Glycerolipids	Triacylglycerols	1.37 (1.01-1.85)	0.041
C55:2 TAG	HMDB0042226*	Glycerolipids	Triacylglycerols	1.35 (1.00-1.82)	0.047

Supplemental Table 1.3a (continued).

C51:0 TAG	HMDB0031106*	Glycerolipids	Triacylglycerols	1.34 (0.99-1.80)	0.055
C43:1 TAG	HMDB0042098*	Glycerolipids	Triacylglycerols	1.33 (0.99-1.80)	0.061
C50:0 TAG	HMDB0005357*	Glycerolipids	Triacylglycerols	1.31 (0.97-1.78)	0.082
C45:2 TAG	HMDB0043170*	Glycerolipids	Triacylglycerols	1.29 (0.96-1.75)	0.091
C43:0 TAG	HMDB0042062*	Glycerolipids	Triacylglycerols	1.28 (0.96-1.72)	0.094
C52:1 TAG	HMDB0005367*	Glycerolipids	Triacylglycerols	1.29 (0.95-1.76)	0.099
C54:5 TAG	HMDB0005385*	Glycerolipids	Triacylglycerols	1.27 (0.95-1.69)	0.103
C56:3 TAG	HMDB0005410*	Glycerolipids	Triacylglycerols	1.26 (0.94-1.69)	0.118
C48:0 TAG	HMDB0005356*	Glycerolipids	Triacylglycerols	1.27 (0.94-1.72)	0.125
C48:1 TAG	HMDB0005359*	Glycerolipids	Triacylglycerols	1.26 (0.94-1.70)	0.127
C44:0 TAG	HMDB0042063*	Glycerolipids	Triacylglycerols	1.25 (0.93-1.68)	0.142
C54:2 TAG	HMDB0005403*	Glycerolipids	Triacylglycerols	1.24 (0.92-1.68)	0.154
C52:0 TAG	HMDB0005365*	Glycerolipids	Triacylglycerols	1.24 (0.92-1.69)	0.161
C51:3 TAG	HMDB0011701*	Glycerolipids	Triacylglycerols	1.23 (0.92-1.65)	0.168
C45:1 TAG	HMDB0042099*	Glycerolipids	Triacylglycerols	1.23 (0.91-1.65)	0.175
C56:4 TAG	HMDB0005398*	Glycerolipids	Triacylglycerols	1.21 (0.91-1.62)	0.186
C50:5 TAG	HMDB0010471*	Glycerolipids	Triacylglycerols	1.22 (0.91-1.65)	0.19
C56:7 TAG	HMDB0005462*	Glycerolipids	Triacylglycerols	1.21 (0.91-1.61)	0.201
C56:2 TAG	HMDB0005404*	Glycerolipids	Triacylglycerols	1.20 (0.90-1.62)	0.22
C46:0 TAG	HMDB0010411*	Glycerolipids	Triacylglycerols	1.20 (0.89-1.62)	0.225
C52:6 TAG	HMDB0005436*	Glycerolipids	Triacylglycerols	1.20 (0.89-1.62)	0.225
C46:2 TAG	HMDB0010419*	Glycerolipids	Triacylglycerols	1.19 (0.89-1.60)	0.25
C46:1 TAG	HMDB0010412*	Glycerolipids	Triacylglycerols	1.18 (0.88-1.59)	0.268
C54:1 TAG	HMDB0005395*	Glycerolipids	Triacylglycerols	1.19 (0.88-1.61)	0.268
C56:1 TAG	HMDB0005396*	Glycerolipids	Triacylglycerols	1.18 (0.88-1.60)	0.268
C54:6 TAG	HMDB0005391*	Glycerolipids	Triacylglycerols	1.17 (0.88-1.56)	0.269
C52:7 TAG	HMDB0010517*	Glycerolipids	Triacylglycerols	1.18 (0.87-1.59)	0.282
C48:2 TAG	HMDB0005376*	Glycerolipids	Triacylglycerols	1.17 (0.87-1.58)	0.291
C55:3 TAG	HMDB0042466*	Glycerolipids	Triacylglycerols	1.17 (0.88-1.55)	0.292
C48:3 TAG	HMDB0005432*	Glycerolipids	Triacylglycerols	1.17 (0.87-1.58)	0.298
C49:3 TAG	HMDB0042103*	Glycerolipids	Triacylglycerols	1.17 (0.87-1.56)	0.300
C54:3 TAG	HMDB0005405*	Glycerolipids	Triacylglycerols	1.17 (0.87-1.56)	0.300
C53:3 TAG	HMDB0043058*	Glycerolipids	Triacylglycerols	1.16 (0.87-1.55)	0.312
C50:6 TAG	HMDB0010497*	Glycerolipids	Triacylglycerols	1.16 (0.86-1.57)	0.329
C49:2 TAG	HMDB0011706*	Glycerolipids	Triacylglycerols	1.15 (0.87-1.53)	0.333

Supplemental Table 1.3a (continued).

C47:2 TAG	HMDB0042076*	Glycerolipids	Triacylglycerols	1.16 (0.86-1.55)	0.335
C53:2 TAG	HMDB0042196*	Glycerolipids	Triacylglycerols	1.15 (0.86-1.54)	0.348
C47:1 TAG	HMDB0042100*	Glycerolipids	Triacylglycerols	1.14 (0.86-1.52)	0.372
C54:4 TAG	HMDB0005370*	Glycerolipids	Triacylglycerols	1.13 (0.85-1.51)	0.397
C49:1 TAG	HMDB0011705*	Glycerolipids	Triacylglycerols	1.12 (0.86-1.47)	0.399
C54:7 TAG	HMDB0005447*	Glycerolipids	Triacylglycerols	1.12 (0.84-1.48)	0.442
C54:8 TAG	HMDB0010518*	Glycerolipids	Triacylglycerols	1.12 (0.84-1.50)	0.456
C51:2 TAG	HMDB0005362*	Glycerolipids	Triacylglycerols	1.11 (0.83-1.49)	0.464
C56:6 TAG	HMDB0005456*	Glycerolipids	Triacylglycerols	0.91 (0.68-1.21)	0.518
C56:8 TAG	HMDB0005392*	Glycerolipids	Triacylglycerols	1.09 (0.82-1.45)	0.547
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.92 (0.69-1.23)	0.593
C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	1.08 (0.81-1.44)	0.616
C56:5 TAG	HMDB0005406*	Glycerolipids	Triacylglycerols	0.93 (0.70-1.25)	0.640
C56:9 TAG	HMDB0005448*	Glycerolipids	Triacylglycerols	1.05 (0.78-1.40)	0.746
C58:8 TAG	HMDB0005413*	Glycerolipids	Triacylglycerols	1.05 (0.79-1.38)	0.747
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	0.96 (0.72-1.29)	0.802
C58:6 TAG	HMDB0005458*	Glycerolipids	Triacylglycerols	1.03 (0.76-1.40)	0.853
C60:12 TAG	HMDB0005478*	Glycerolipids	Triacylglycerols	1.02 (0.76-1.36)	0.888
C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	1.02 (0.76-1.36)	0.908
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	0.99 (0.74-1.33)	0.946
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	1.01 (0.75-1.35)	0.956
C22:5 LPC	HMDB0010403*	Glycerophospholipids	Glycerophosphocholines	0.58 (0.43-0.77)	0
C18:2 LPC	HMDB0010386*	Glycerophospholipids	Glycerophosphocholines	0.64 (0.47-0.87)	0.005
C20:5 LPC	HMDB0010397	Glycerophospholipids	Glycerophosphocholines	0.65 (0.48-0.88)	0.006
C18:1 LPC	HMDB0002815*	Glycerophospholipids	Glycerophosphocholines	0.68 (0.51-0.91)	0.011
C18:0 LPC	HMDB0010384	Glycerophospholipids	Glycerophosphocholines	0.69 (0.51-0.93)	0.014
C36:5 PC plasmalogen-B	HMDB0011220*	Glycerophospholipids	Glycerophosphocholines	0.75 (0.57-0.99)	0.043

Supplemental Table 1.3a (continued).

C22:6 LPC	HMDB0010404	Glycerophospholipids	Glycerophosphocholines	0.75 (0.56-1.00)	0.052
C32:1 PC	HMDB0007873*	Glycerophospholipids	Glycerophosphocholines	1.34 (0.98-1.84)	0.067
C32:2 PC	HMDB0007874*	Glycerophospholipids	Glycerophosphocholines	1.29 (0.96-1.74)	0.092
C36:5 PC plasmalogen-A	HMDB0011221*	Glycerophospholipids	Glycerophosphocholines	0.79 (0.60-1.04)	0.092
C34:3 PC plasmalogen	HMDB0011211*	Glycerophospholipids	Glycerophosphocholines	0.80 (0.60-1.07)	0.13
C38:7 PC plasmalogen	HMDB0011229*	Glycerophospholipids	Glycerophosphocholines	0.82 (0.62-1.09)	0.173
C30:1 PC	HMDB0007870*	Glycerophospholipids	Glycerophosphocholines	1.22 (0.9-1.65)	0.194
C18:3 LPC	HMDB0010387*	Glycerophospholipids	Glycerophosphocholines	0.83 (0.63-1.11)	0.206
C32:0 PC	HMDB0007871*	Glycerophospholipids	Glycerophosphocholines	1.21 (0.9-1.63)	0.207
C16:0 LPC	HMDB0010382	Glycerophospholipids	Glycerophosphocholines	0.84 (0.63-1.11)	0.218
C34:1 PC	HMDB0007972*	Glycerophospholipids	Glycerophosphocholines	1.15 (0.85-1.55)	0.363
C30:0 PC	HMDB0007869*	Glycerophospholipids	Glycerophosphocholines	1.14 (0.85-1.54)	0.389
C36:1 PC	HMDB0008038*	Glycerophospholipids	Glycerophosphocholines	0.93 (0.70-1.23)	0.612
C38:3 PC	HMDB0008047*	Glycerophospholipids	Glycerophosphocholines	1.08 (0.79-1.46)	0.631
C38:6 PC	HMDB0007991*	Glycerophospholipids	Glycerophosphocholines	1.07 (0.79-1.46)	0.651
C34:1 PC plasmalogen-B	HMDB0011239*	Glycerophospholipids	Glycerophosphocholines	1.07 (0.81-1.41)	0.653
C38:4 PC plasmalogen	HMDB0011252*	Glycerophospholipids	Glycerophosphocholines	0.94 (0.71-1.24)	0.655

Supplemental Table 1.3a (continued).

C16:1 LPC	HMDB0010383*	Glycerophospholipids	Glycerophosphocholines	0.95 (0.71-1.25)	0.703
C34:1 PC plasmalogen	HMDB0011208*	Glycerophospholipids	Glycerophosphocholines	1.05 (0.79-1.39)	0.729
C36:4 PC plasmalogen	HMDB0011310*	Glycerophospholipids	Glycerophosphocholines	0.95 (0.72-1.26)	0.738
C14:0 LPC	HMDB0010379	Glycerophospholipids	Glycerophosphocholines	1.04 (0.78-1.39)	0.794
C36:4 PC-B	HMDB0008138*	Glycerophospholipids	Glycerophosphocholines	1.04 (0.76-1.42)	0.811
C36:2 PC plasmalogen	HMDB0011243*	Glycerophospholipids	Glycerophosphocholines	1.03 (0.78-1.37)	0.831
C40:10 PC	HMDB0008511*	Glycerophospholipids	Glycerophosphocholines	1.02 (0.75-1.38)	0.898
C40:6 PC	HMDB0008057*	Glycerophospholipids	Glycerophosphocholines	0.98 (0.73-1.32)	0.915
C40:9 PC	HMDB0008731*	Glycerophospholipids	Glycerophosphocholines	1.01 (0.75-1.36)	0.962
C22:0 LPE	HMDB0011520	Glycerophospholipids	Glycerophospho-ethanolamines	0.65 (0.48-0.88)	0.005
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospholipids	Glycerophospho-ethanolamines	0.72 (0.54-0.95)	0.022
C36:5 PE plasmalogen	HMDB0011410*	Glycerophospholipids	Glycerophospho-ethanolamines	0.73 (0.55-0.97)	0.028
C34:3 PE plasmalogen	HMDB0011343*	Glycerophospholipids	Glycerophospho-ethanolamines	0.76 (0.57-1.00)	0.05
C36:4 PE plasmalogen	HMDB0011442*	Glycerophospholipids	Glycerophospho-ethanolamines	0.76 (0.58-1.00)	0.054
C36:2 PE	HMDB0008994*	Glycerophospholipids	Glycerophospho-ethanolamines	1.27 (0.94-1.72)	0.121
C34:2 PE	HMDB0008928*	Glycerophospholipids	Glycerophospho-ethanolamines	1.26 (0.94-1.71)	0.123
C18:1 LPE	HMDB0011506*	Glycerophospholipids	Glycerophospho-ethanolamines	0.81 (0.61-1.08)	0.149

Supplemental Table 1.3a (continued).

C40:6 PE	HMDB0009012*	Glycerophospholipids	Glycerophospho-ethanolamines	1.25 (0.92-1.71)	0.151
C38:5 PE plasmalogen	HMDB0011386*	Glycerophospholipids	Glycerophospho-ethanolamines	0.82 (0.62-1.08)	0.157
C36:2 PE plasmalogen	HMDB0009082*	Glycerophospholipids	Glycerophospho-ethanolamines	0.82 (0.62-1.08)	0.163
C20:4 LPE	HMDB0011517	Glycerophospholipids	Glycerophospho-ethanolamines	0.82 (0.62-1.09)	0.177
C34:2 PE plasmalogen	HMDB0008952*	Glycerophospholipids	Glycerophospho-ethanolamines	0.83 (0.62-1.1)	0.192
C36:3 PE plasmalogen	HMDB0011441*	Glycerophospholipids	Glycerophospho-ethanolamines	0.85 (0.64-1.12)	0.255
C18:0 LPE	HMDB0011130	Glycerophospholipids	Glycerophospho-ethanolamines	0.88 (0.66-1.16)	0.353
C34:0 PE	HMDB0008925*	Glycerophospholipids	Glycerophospho-ethanolamines	1.13 (0.86-1.50)	0.38
C18:2 LPE	HMDB0011507*	Glycerophospholipids	Glycerophospho-ethanolamines	0.88 (0.65-1.18)	0.381
C36:1 PE	HMDB0008993*	Glycerophospholipids	Glycerophospho-ethanolamines	1.14 (0.84-1.55)	0.386
C38:7 PE plasmalogen	HMDB0011420*	Glycerophospholipids	Glycerophospho-ethanolamines	0.88 (0.66-1.18)	0.399
C38:6 PE	HMDB0009102*	Glycerophospholipids	Glycerophospho-ethanolamines	1.13 (0.82-1.56)	0.445
C36:3 PE	HMDB0009060*	Glycerophospholipids	Glycerophospho-ethanolamines	1.12 (0.83-1.51)	0.447
C40:7 PE plasmalogen	HMDB0011394*	Glycerophospholipids	Glycerophospho-ethanolamines	0.90 (0.68-1.19)	0.448
C36:4 PE	HMDB0008937*	Glycerophospholipids	Glycerophospho-ethanolamines	1.12 (0.83-1.53)	0.457
C38:4 PE	HMDB0009003*	Glycerophospholipids	Glycerophospho-ethanolamines	1.11 (0.82-1.51)	0.493
C32:0 PE	HMDB0008923*	Glycerophospholipids	Glycerophospho-ethanolamines	1.10 (0.83-1.46)	0.51

Supplemental Table 1.3a (continued).

C36:1 PE plasmalogen	HMDB0009016*	Glycerophospholipids	Glycerophospho-ethanolamines	1.08 (0.81-1.43)	0.603
C36:0 PE	HMDB0008991*	Glycerophospholipids	Glycerophospho-ethanolamines	1.06 (0.81-1.4)	0.664
C38:2 PE	HMDB0008942*	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.73-1.27)	0.777
C16:0 LPE	HMDB0011503	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.72-1.28)	0.784
C38:5 PE	HMDB0009069*	Glycerophospholipids	Glycerophospho-ethanolamines	1.01 (0.75-1.37)	0.931
C22:6 LPE	HMDB0011526	Glycerophospholipids	Glycerophospho-ethanolamines	1.00 (0.74-1.35)	0.99
C38:4 PI	HMDB0009815*	Glycerophospholipids	Glycerophosphoinositols	0.89 (0.67-1.18)	0.407
C34:0 PS	HMDB0012356*	Glycerophospholipids	Glycerophosphoserines	0.96 (0.71-1.29)	0.784
uric acid	HMDB0000289	Imidazopyrimidines	Purines and purine derivatives	0.84 (0.62-1.13)	0.25
1,7-dimethyluric acid	HMDB0011103	Imidazopyrimidines	Purines and purine derivatives	0.91 (0.69-1.20)	0.515
caffeine	HMDB0001847	Imidazopyrimidines	Purines and purine derivatives	0.93 (0.70-1.25)	0.636
3-methylxanthine	HMDB0001886	Imidazopyrimidines	Purines and purine derivatives	0.95 (0.72-1.26)	0.744
7-methylxanthine	HMDB0001991	Imidazopyrimidines	Purines and purine derivatives	0.98 (0.74-1.30)	0.877
7-methylguanine	HMDB0000897	Imidazopyrimidines	Purines and purine derivatives	0.99 (0.75-1.32)	0.969
1-methylguanine	HMDB0003282	Imidazopyrimidines	Purines and purine derivatives	1.00 (0.76-1.33)	0.973
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	0.99 (0.74-1.33)	0.973
serotonin	HMDB0000259	Indoles and derivatives	Tryptamines and derivatives	1.37 (1.04-1.81)	0.025

Supplemental Table 1.3a (continued).

C20:4 LPC	HMDB0010395	NA	NA	0.66 (0.50-0.88)	0.004
thyroxine	HMDB0000248	NA	NA	1.50 (1.11-2.04)	0.009
C20:1 LPE	HMDB0011512*	NA	NA	0.69 (0.52-0.92)	0.011
trigonelline	HMDB0000875	NA	NA	0.71 (0.53-0.95)	0.021
2-methyl-4,5-benzoxazole	HMDB0032390	NA	NA	0.78 (0.59-1.03)	0.084
methyl N-methylanthranilate	HMDB0034169	NA	NA	1.21 (0.92-1.59)	0.183
coenzyme Q10	HMDB0001072	NA	NA	0.84 (0.63-1.11)	0.216
C18:3 LPE	HMDB0011478*	NA	NA	0.87 (0.65-1.16)	0.338
C34:5 PC plasmalogen	HMDB0011214*	NA	NA	0.87 (0.66-1.16)	0.345
C20:1 LPC	HMDB0010391*	NA	NA	0.88 (0.67-1.17)	0.396
C34:4 PC	HMDB0007883*	NA	NA	1.13 (0.83-1.54)	0.439
piperine	HMDB0029377	NA	NA	0.89 (0.67-1.19)	0.443
C36:3 PC plasmalogen	HMDB0011244*	NA	NA	0.90 (0.68-1.20)	0.488
cerulenin	HMDB0015168	NA	NA	1.10 (0.83-1.46)	0.505
C34:2 PC plasmalogen	HMDB0011210*	NA	NA	0.96 (0.72-1.28)	0.779
deoxyguanosine	HMDB0000085	NA	NA	1.04 (0.79-1.37)	0.804
DMGV	HMDB0240212	NA	NA	0.96 (0.70-1.32)	0.808
valsartan	HMDB0014323	NA	NA	1.01 (0.77-1.31)	0.962
pseudouridine	HMDB0000767	Nucleoside and nucleotide analogues	NA	0.89 (0.66-1.20)	0.452
N-carbamoyl-beta-alanine	HMDB0000026	Organic carbonic acids and derivatives	Ureas	0.76 (0.57-1.02)	0.065
1-methylhistamine	HMDB0000898	Organonitrogen compounds	Amines	1.14 (0.87-1.49)	0.36
trimethylamine-N-oxide	HMDB0000925	Organonitrogen compounds	Aminoxides	1.03 (0.78-1.36)	0.843

Supplemental Table 1.3a (continued).

metformin	HMDB0001921	Organonitrogen compounds	Guanidines	1.03 (0.78-1.36)	0.834
carnitine	HMDB0000062	Organonitrogen compounds	Quaternary ammonium salts	0.73 (0.54-0.99)	0.041
phosphocholine	HMDB0001565	Organonitrogen compounds	Quaternary ammonium salts	1.02 (0.77-1.35)	0.896
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	1.26 (0.95-1.69)	0.114
4-hydroxy-3-methylacetophenone	HMDB0059824	Organooxygen compounds	Carbonyl compounds	0.93 (0.71-1.22)	0.599
acetaminophen	HMDB0001859	Phenols	1-hydroxy-2-unsubstituted benzenoids	1.12 (0.85-1.47)	0.424
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	1.34 (1.00-1.80)	0.05
guanosine	HMDB0000133	Purine nucleosides	NA	0.81 (0.62-1.07)	0.139
1-methylguanosine	HMDB0001563	Purine nucleosides	NA	1.13 (0.85-1.51)	0.413
N2,N2-dimethylguanosine	HMDB0004824	Purine nucleosides	NA	0.94 (0.70-1.26)	0.674
1-methylnicotinamide	HMDB0000699	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	1.11 (0.83-1.49)	0.47
N1-methyl-2-pyridone-5-carboxamide	HMDB0004193	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.93 (0.70-1.24)	0.638
pyridoxamine	HMDB0001431	Pyridines and derivatives	Pyridoxamines	1.16 (0.88-1.53)	0.298
cotinine	HMDB0001046	Pyridines and derivatives	Pyrrolidinylpyridines	1.11 (0.84-1.48)	0.466
N4-acetylcytidine	HMDB0005923	Pyrimidine nucleosides	NA	1.17 (0.87-1.57)	0.306
ribothymidine	HMDB0000884	Pyrimidine nucleosides	NA	0.91 (0.69-1.2)	0.513

Supplemental Table 1.3a (continued).

kynurenic acid	HMDB0000715	Quinolines and derivatives	Quinoline carboxylic acids	0.76 (0.57-1.02)	0.068
C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	Ceramides	1.17 (0.88-1.56)	0.277
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	Ceramides	1.17 (0.87-1.56)	0.293
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	Ceramides	1.08 (0.80-1.45)	0.608
C24:0 Ceramide (d18:1)	HMDB0004956	Sphingolipids	Ceramides	0.96 (0.72-1.29)	0.799
C14:0 SM	HMDB0012097	Sphingolipids	Phosphosphingolipids	1.10 (0.82-1.47)	0.515
C22:1 SM	HMDB0012104*	Sphingolipids	Phosphosphingolipids	0.94 (0.71-1.25)	0.667
glycodeoxycholate/ glycochenodeoxycholate	HMDB0000631*	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.16 (0.86-1.57)	0.321
glycocholate	HMDB0000138	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.00 (0.75-1.34)	0.999
cholesterol	HMDB0000067	Steroids and steroid derivatives	Cholestane steroids	1.01 (0.76-1.35)	0.933
campesterol	HMDB0002869	Steroids and steroid derivatives	Ergostane steroids	0.99 (0.74-1.32)	0.926
cortisone	HMDB0002802	Steroids and steroid derivatives	Hydroxysteroids	0.91 (0.68-1.21)	0.516
cortisol	HMDB0000063	Steroids and steroid derivatives	Hydroxysteroids	0.91 (0.66-1.24)	0.542
21-deoxycortisol	HMDB0004030	Steroids and steroid derivatives	Pregnane steroids	0.95 (0.70-1.29)	0.738
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesteryl esters	0.52 (0.39-0.70)	0
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesteryl esters	0.61 (0.46-0.82)	0.001

Supplemental Table 1.3a (continued).

C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesteryl esters	0.65 (0.49-0.86)	0.003
C20:4 CE	HMDB0006726	Steroids and steroid derivatives	Cholesteryl esters	0.67 (0.50-0.89)	0.006
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesteryl esters	0.68 (0.51-0.91)	0.01
C20:3 CE	HMDB0006736*	Steroids and steroid derivatives	Cholesteryl esters	0.73 (0.55-0.96)	0.026
C18:1 CE	HMDB0000918*	Steroids and steroid derivatives	Cholesteryl esters	0.72 (0.54-0.97)	0.03
C22:6 CE	HMDB0006733	Steroids and steroid derivatives	Cholesteryl esters	0.75 (0.56-1.01)	0.058
C16:0 CE	HMDB0000885	Steroids and steroid derivatives	Cholesteryl esters	0.76 (0.57-1.01)	0.063
C14:0 CE	HMDB0006725	Steroids and steroid derivatives	Cholesteryl esters	0.76 (0.57-1.01)	0.064
C18:2 CE	HMDB0000610*	Steroids and steroid derivatives	Cholesteryl esters	0.76 (0.56-1.02)	0.072
C16:1 CE	HMDB0000658*	Steroids and steroid derivatives	Cholesteryl esters	1.02 (0.76-1.37)	0.889
bilirubin	HMDB0000054	Tetrapyrroles and derivatives	Bilirubins	0.85 (0.64-1.12)	0.252
biliverdin	HMDB0001008	Tetrapyrroles and derivatives	Bilirubins	1.12 (0.85-1.48)	0.421

** Includes metabolites with <10% missingness. Missing values were imputed with 1/2 the minimum value. Results sorted by class, subclass, and p-value for fully adjusted models.
^Multivariable adjusted includes BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).
*Representative HMDBID

Supplemental Table 1.3b. Odds ratios for ER+ breast cancer risk comparing 90th to 10th percentiles of metabolite levels, measured at proximate blood.

				Multivariable Adjusted^	
Metabolite Name	**HMDB ID**	**Class**	**Subclass**	**OR (95% CI)**	**p value**
metronidazole	HMDB0015052	Azoles	Imidazoles	0.93 (0.66-1.3)	0.66
allantoin	HMDB0000462	Azoles	Imidazoles	0.94 (0.65-1.35)	0.722
urocanic acid	HMDB0000301	Azoles	Imidazoles	1.04 (0.74-1.46)	0.839
sulfamethoxazole	HMDB0015150	Benzene and substituted derivatives	Benzenesulfonamides	0.91 (0.65-1.28)	0.592
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	0.64 (0.45-0.91)	0.014
4-hydroxyhippurate	HMDB0013678	Benzene and substituted derivatives	Benzoic acids and derivatives	0.82 (0.59-1.16)	0.268
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	1.46 (1.02-2.08)	0.038
N1-acetylspermidine	HMDB0001276	Carboximidic acids and derivatives	Carboximidic acids	1.26 (0.87-1.84)	0.225
Palmitoylethanol-amide	HMDB0002100	Carboximidic acids and derivatives	Carboximidic acids	0.85 (0.6-1.2)	0.358
N-acetylputrescine	HMDB0002064	Carboximidic acids and derivatives	Carboximidic acids	1.16 (0.81-1.67)	0.423
proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.52 (1.04-2.21)	0.029
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.48 (1.03-2.14)	0.035
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.47 (1-2.16)	0.049
leucine	HMDB0000687	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.45 (0.99-2.12)	0.054

Supplemental Table 1.3b (continued).

N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.76 (0.54-1.07)	0.118
valine	HMDB0000883	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.34 (0.92-1.97)	0.13
2-aminooctanoic acid	HMDB0000991*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.77 (0.54-1.09)	0.136
hydroxyproline	HMDB0000725	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.77 (0.54-1.1)	0.157
tyrosine	HMDB0000158	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.24 (0.86-1.79)	0.243
threonine	HMDB0000167	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.82 (0.57-1.16)	0.26
aminoisobutyric acid	HMDB0001906*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.83 (0.58-1.18)	0.29
alanine	HMDB0000161	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.21 (0.85-1.72)	0.296
pipecolic acid	HMDB0000716	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.82 (0.57-1.19)	0.297
lysine	HMDB0000182	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.2 (0.85-1.70)	0.303
ADMA/SDMA	HMDB0001539	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.19 (0.84-1.69)	0.329

Supplemental Table 1.3b (continued).

glycine	HMDB0000123	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.19 (0.82-1.73)	0.353
guanidinoacetic acid	HMDB0000128	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.17 (0.82-1.67)	0.389
homoarginine	HMDB0000670*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.85 (0.59-1.23)	0.396
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.16 (0.81-1.64)	0.419
betaine	HMDB0000043	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.17 (0.78-1.77)	0.448
Phenylacetyl-glutamine	HMDB0006344	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.14 (0.8-1.63)	0.458
1-methylhistidine	HMDB0000001	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.13 (0.8-1.62)	0.484
pantothenate	HMDB0000210	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.88 (0.62-1.25)	0.485
methionine	HMDB0000696	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.12 (0.79-1.58)	0.517
asparagine	HMDB0000168	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.89 (0.62-1.28)	0.536
creatinine	HMDB0000562	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.11 (0.79-1.58)	0.542
creatine	HMDB0000064	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.9 (0.64-1.27)	0.55

Supplemental Table 1.3b (continued).

citrulline	HMDB0000904	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.91 (0.63-1.31)	0.603
histidine	HMDB0000177	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.09 (0.77-1.55)	0.609
N6,N6-dimethyllysine	HMDB0013287	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.09 (0.77-1.55)	0.622
N-acetyltryptophan	HMDB0013713	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.64-1.32)	0.632
NMMA	HMDB0029416	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.65-1.3)	0.634
N6,N6,N6-trimethyllysine	HMDB0001325	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.09 (0.76-1.55)	0.646
4-acetamidobutanoate	HMDB0003681	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.93 (0.64-1.34)	0.684
glutamine	HMDB0000641	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.75-1.53)	0.708
dimethylglycine	HMDB0000092	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.74-1.55)	0.724
GABA	HMDB0000112	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.94 (0.67-1.33)	0.728
serine	HMDB0000187	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.74-1.53)	0.732
N6-acetyllysine	HMDB0000206*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.06 (0.74-1.51)	0.75

Supplemental Table 1.3b (continued).

N-acetylhistidine	HMDB0032055	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.94 (0.65-1.36)	0.755
oleoyl glycine	HMDB0013631	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95 (0.67-1.36)	0.787
proline betaine	HMDB0004827	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.05 (0.74-1.5)	0.788
N-lauroylglycine	HMDB0013272	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.99 (0.70-1.40)	0.968
cytosine	HMDB0000630	Diazines	Pyrimidines and pyrimidine derivatives	1.19 (0.84-1.69)	0.328
5-hydroxymethyl-4-methyluracil	HMDB0000544	Diazines	Pyrimidines and pyrimidine derivatives	0.98 (0.68-1.42)	0.918
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.60 (0.42-0.86)	0.004
C4-OH carnitine	HMDB0013127	Fatty Acyls	Fatty acid esters	1.33 (0.92-1.93)	0.132
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	0.80 (0.55-1.14)	0.218
C2 carnitine	HMDB0000201	Fatty Acyls	Fatty acid esters	1.19 (0.82-1.73)	0.356
C6 carnitine	HMDB0000705	Fatty Acyls	Fatty acid esters	1.15 (0.81-1.65)	0.435
C10:2 carnitine	HMDB0013325	Fatty Acyls	Fatty acid esters	0.87 (0.62-1.23)	0.436
C7 carnitine	HMDB0013238	Fatty Acyls	Fatty acid esters	1.13 (0.80-1.61)	0.492
C8 carnitine	HMDB0000791	Fatty Acyls	Fatty acid esters	1.10 (0.77-1.58)	0.601
C10 carnitine	HMDB0000651	Fatty Acyls	Fatty acid esters	1.09 (0.76-1.56)	0.636
C12:1 carnitine	HMDB0013326	Fatty Acyls	Fatty acid esters	1.09 (0.76-1.57)	0.645
C14 carnitine	HMDB0005066	Fatty Acyls	Fatty acid esters	1.08 (0.75-1.57)	0.672
C3 carnitine	HMDB0000824	Fatty Acyls	Fatty acid esters	1.06 (0.73-1.52)	0.766
C12 carnitine	HMDB0002250	Fatty Acyls	Fatty acid esters	1.05 (0.73-1.51)	0.805
C5 carnitine	HMDB0000688	Fatty Acyls	Fatty acid esters	0.96 (0.66-1.39)	0.817
C26 carnitine	HMDB0006347	Fatty Acyls	Fatty acid esters	1.03 (0.72-1.46)	0.882
C14:1 carnitine	HMDB0002014	Fatty Acyls	Fatty acid esters	1.03 (0.71-1.49)	0.887
C14:2 carnitine	HMDB0013331	Fatty Acyls	Fatty acid esters	1.02 (0.71-1.47)	0.912
C9 carnitine	HMDB0013288	Fatty Acyls	Fatty acid esters	0.99 (0.71-1.38)	0.943

Supplemental Table 1.3b (continued).

C4 carnitine	HMDB0002013	Fatty Acyls	Fatty acid esters	0.99 (0.70-1.40)	0.953
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	1.37 (0.96-1.94)	0.08
3-dehydroxycarnitine	HMDB0006831	Fatty Acyls	Fatty acids and conjugates	1.07 (0.74-1.55)	0.722
C34:2 DAG	HMDB0007103*	Fatty Acyls	Lineolic acids and derivatives	1.22 (0.85-1.76)	0.275
C36:3 DAG	HMDB0007219*	Fatty Acyls	Lineolic acids and derivatives	1.13 (0.79-1.61)	0.499
C34:3 DAG	HMDB0007132*	Fatty Acyls	Lineolic acids and derivatives	1.09 (0.77-1.56)	0.624
C36:4 DAG	HMDB0007248*	Fatty Acyls	Lineolic acids and derivatives	0.99 (0.69-1.43)	0.970
C34:0 DAG	HMDB0007100*	Glycerolipids	Diacylglycerols	1.42 (1.00-2.04)	0.053
C36:1 DAG	HMDB0007216*	Glycerolipids	Diacylglycerols	1.43 (0.99-2.05)	0.055
C36:2 DAG	HMDB0007218*	Glycerolipids	Diacylglycerols	1.33 (0.93-1.91)	0.118
C32:0 DAG	HMDB0007098*	Glycerolipids	Diacylglycerols	1.27 (0.88-1.83)	0.197
C34:1 DAG	HMDB0007102*	Glycerolipids	Diacylglycerols	1.27 (0.88-1.83)	0.201
C32:1 DAG	HMDB0007099*	Glycerolipids	Diacylglycerols	1.17 (0.82-1.67)	0.400
C38:5 DAG	HMDB0007199*	Glycerolipids	Diacylglycerols	0.90 (0.62-1.29)	0.553
C52:0 TAG	HMDB0005365*	Glycerolipids	Triacylglycerols	1.49 (1.04-2.15)	0.030
C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	0.68 (0.48-0.98)	0.037
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	0.69 (0.48-0.98)	0.038
C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	0.69 (0.48-0.99)	0.043
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.68 (0.47-0.99)	0.044
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	0.69 (0.49-0.99)	0.045
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	0.70 (0.49-0.99)	0.046
C52:1 TAG	HMDB0005367*	Glycerolipids	Triacylglycerols	1.45 (1.01-2.09)	0.047
C53:2 TAG	HMDB0042196*	Glycerolipids	Triacylglycerols	1.42 (0.99-2.05)	0.054
C56:9 TAG	HMDB0005448*	Glycerolipids	Triacylglycerols	0.71 (0.49-1.01)	0.057
C52:2 TAG	HMDB0005369*	Glycerolipids	Triacylglycerols	1.42 (0.99-2.04)	0.059
C54:2 TAG	HMDB0005403*	Glycerolipids	Triacylglycerols	1.40 (0.97-2.02)	0.069
C50:0 TAG	HMDB0005357*	Glycerolipids	Triacylglycerols	1.39 (0.97-2.01)	0.071
C54:1 TAG	HMDB0005395*	Glycerolipids	Triacylglycerols	1.38 (0.96-1.99)	0.084
C51:0 TAG	HMDB0031106*	Glycerolipids	Triacylglycerols	1.36 (0.96-1.94)	0.084

Supplemental Table 1.3b (continued).

C54:8 TAG	HMDB0010518*	Glycerolipids	Triacylglycerols	0.73 (0.51-1.05)	0.090
C50:1 TAG	HMDB0005360*	Glycerolipids	Triacylglycerols	1.35 (0.93-1.96)	0.11
C51:1 TAG	HMDB0042104*	Glycerolipids	Triacylglycerols	1.33 (0.92-1.92)	0.124
C60:12 TAG	HMDB0005478*	Glycerolipids	Triacylglycerols	0.75 (0.52-1.08)	0.127
C56:8 TAG	HMDB0005392*	Glycerolipids	Triacylglycerols	0.77 (0.54-1.10)	0.153
C54:3 TAG	HMDB0005405*	Glycerolipids	Triacylglycerols	1.28 (0.89-1.85)	0.179
C50:3 TAG	HMDB0005433*	Glycerolipids	Triacylglycerols	1.26 (0.88-1.79)	0.206
C43:0 TAG	HMDB0042062*	Glycerolipids	Triacylglycerols	1.25 (0.88-1.77)	0.215
C52:7 TAG	HMDB0010517*	Glycerolipids	Triacylglycerols	0.80 (0.56-1.14)	0.217
C54:7 TAG	HMDB0005447*	Glycerolipids	Triacylglycerols	0.80 (0.56-1.14)	0.223
C58:6 TAG	HMDB0005458*	Glycerolipids	Triacylglycerols	0.80 (0.54-1.16)	0.236
C56:7 TAG	HMDB0005462*	Glycerolipids	Triacylglycerols	0.81 (0.56-1.15)	0.237
C48:0 TAG	HMDB0005356*	Glycerolipids	Triacylglycerols	1.23 (0.86-1.76)	0.264
C50:2 TAG	HMDB0005377*	Glycerolipids	Triacylglycerols	1.22 (0.85-1.76)	0.282
C51:3 TAG	HMDB0011701*	Glycerolipids	Triacylglycerols	1.22 (0.85-1.75)	0.29
C50:6 TAG	HMDB0010497*	Glycerolipids	Triacylglycerols	0.83 (0.58-1.18)	0.294
C58:8 TAG	HMDB0005413*	Glycerolipids	Triacylglycerols	0.83 (0.58-1.18)	0.303
C53:3 TAG	HMDB0043058*	Glycerolipids	Triacylglycerols	1.19 (0.83-1.72)	0.34
C51:2 TAG	HMDB0005362*	Glycerolipids	Triacylglycerols	1.17 (0.82-1.67)	0.381
C48:1 TAG	HMDB0005359*	Glycerolipids	Triacylglycerols	1.17 (0.82-1.67)	0.385
C52:4 TAG	HMDB0005363*	Glycerolipids	Triacylglycerols	1.17 (0.82-1.67)	0.392
C46:0 TAG	HMDB0010411*	Glycerolipids	Triacylglycerols	1.17 (0.82-1.66)	0.392
C55:2 TAG	HMDB0042226*	Glycerolipids	Triacylglycerols	1.17 (0.82-1.66)	0.393
C56:6 TAG	HMDB0005456*	Glycerolipids	Triacylglycerols	0.85 (0.59-1.23)	0.394
C44:0 TAG	HMDB0042063*	Glycerolipids	Triacylglycerols	1.15 (0.81-1.65)	0.427
C56:3 TAG	HMDB0005410*	Glycerolipids	Triacylglycerols	1.14 (0.81-1.61)	0.466
C48:2 TAG	HMDB0005376*	Glycerolipids	Triacylglycerols	1.14 (0.80-1.62)	0.48
C43:1 TAG	HMDB0042098*	Glycerolipids	Triacylglycerols	1.13 (0.79-1.60)	0.507
C45:1 TAG	HMDB0042099*	Glycerolipids	Triacylglycerols	1.12 (0.79-1.59)	0.512
C46:1 TAG	HMDB0010412*	Glycerolipids	Triacylglycerols	1.12 (0.79-1.60)	0.526
C52:6 TAG	HMDB0005436*	Glycerolipids	Triacylglycerols	0.89 (0.63-1.27)	0.534
C56:1 TAG	HMDB0005396*	Glycerolipids	Triacylglycerols	1.10 (0.77-1.57)	0.6
C47:1 TAG	HMDB0042100*	Glycerolipids	Triacylglycerols	1.09 (0.77-1.54)	0.62
C56:2 TAG	HMDB0005404*	Glycerolipids	Triacylglycerols	1.09 (0.77-1.55)	0.627
C49:2 TAG	HMDB0011706*	Glycerolipids	Triacylglycerols	1.08 (0.76-1.53)	0.674

Supplemental Table 1.3b (continued).

C50:5 TAG	HMDB0010471*	Glycerolipids	Triacylglycerols	0.94 (0.66-1.33)	0.711
C49:3 TAG	HMDB0042103*	Glycerolipids	Triacylglycerols	1.07 (0.75-1.52)	0.72
C46:2 TAG	HMDB0010419*	Glycerolipids	Triacylglycerols	1.07 (0.75-1.52)	0.722
C47:2 TAG	HMDB0042076*	Glycerolipids	Triacylglycerols	1.06 (0.75-1.50)	0.74
C54:4 TAG	HMDB0005370*	Glycerolipids	Triacylglycerols	1.06 (0.74-1.52)	0.747
C56:4 TAG	HMDB0005398*	Glycerolipids	Triacylglycerols	1.06 (0.74-1.51)	0.761
C43:2 TAG	HMDB0043169*	Glycerolipids	Triacylglycerols	0.95 (0.67-1.35)	0.769
C45:2 TAG	HMDB0043170*	Glycerolipids	Triacylglycerols	1.05 (0.74-1.49)	0.785
C49:1 TAG	HMDB0011705*	Glycerolipids	Triacylglycerols	1.05 (0.74-1.48)	0.788
C54:5 TAG	HMDB0005385*	Glycerolipids	Triacylglycerols	1.05 (0.73-1.50)	0.799
C56:5 TAG	HMDB0005406*	Glycerolipids	Triacylglycerols	0.96 (0.67-1.37)	0.808
C55:3 TAG	HMDB0042466*	Glycerolipids	Triacylglycerols	1.04 (0.73-1.47)	0.837
C48:3 TAG	HMDB0005432*	Glycerolipids	Triacylglycerols	1.03 (0.72-1.46)	0.878
C54:6 TAG	HMDB0005391*	Glycerolipids	Triacylglycerols	0.99 (0.69-1.41)	0.951
C38:3 PC	HMDB0008047*	Glycerophospholipids	Glycerophosphocholines	1.32 (0.93-1.89)	0.123
C22:6 LPC	HMDB0010404	Glycerophospholipids	Glycerophosphocholines	0.76 (0.53-1.08)	0.13
C34:1 PC plasmalogen-B	HMDB0011239*	Glycerophospholipids	Glycerophosphocholines	1.30 (0.92-1.85)	0.142
C40:10 PC	HMDB0008511*	Glycerophospholipids	Glycerophosphocholines	0.77 (0.54-1.12)	0.172
C36:5 PC plasmalogen-A	HMDB0011221*	Glycerophospholipids	Glycerophosphocholines	0.79 (0.55-1.13)	0.193
C40:9 PC	HMDB0008731*	Glycerophospholipids	Glycerophosphocholines	0.79 (0.55-1.15)	0.217
C38:7 PC plasmalogen	HMDB0011229*	Glycerophospholipids	Glycerophosphocholines	0.81 (0.57-1.15)	0.231
C38:6 PC	HMDB0007991*	Glycerophospholipids	Glycerophosphocholines	0.81 (0.55-1.17)	0.258
C34:3 PC plasmalogen	HMDB0011211*	Glycerophospholipids	Glycerophosphocholines	0.83 (0.58-1.18)	0.304
C36:1 PC	HMDB0008038*	Glycerophospholipids	Glycerophosphocholines	1.19 (0.84-1.69)	0.319

Supplemental Table 1.3b (continued).

C34:1 PC	HMDB0007972*	Glycerophospholipids	Glycerophosphocholines	1.19 (0.83-1.72)	0.338
C40:6 PC	HMDB0008057*	Glycerophospholipids	Glycerophosphocholines	0.84 (0.59-1.20)	0.342
C34:1 PC plasmalogen	HMDB0011208*	Glycerophospholipids	Glycerophosphocholines	1.18 (0.83-1.68)	0.354
C16:1 LPC	HMDB0010383*	Glycerophospholipids	Glycerophosphocholines	1.18 (0.83-1.67)	0.362
C18:3 LPC	HMDB0010387*	Glycerophospholipids	Glycerophosphocholines	1.13 (0.79-1.61)	0.497
C32:1 PC	HMDB0007873*	Glycerophospholipids	Glycerophosphocholines	1.11 (0.77-1.61)	0.563
C16:0 LPC	HMDB0010382	Glycerophospholipids	Glycerophosphocholines	1.11 (0.78-1.57)	0.565
C36:2 PC plasmalogen	HMDB0011243*	Glycerophospholipids	Glycerophosphocholines	1.11 (0.78-1.57)	0.567
C36:4 PC-B	HMDB0008138*	Glycerophospholipids	Glycerophosphocholines	0.90 (0.62-1.31)	0.589
C36:5 PC plasmalogen-B	HMDB0011220*	Glycerophospholipids	Glycerophosphocholines	0.91 (0.65-1.28)	0.595
C38:4 PC plasmalogen	HMDB0011252*	Glycerophospholipids	Glycerophosphocholines	1.10 (0.78-1.55)	0.596
C22:5 LPC	HMDB0010403*	Glycerophospholipids	Glycerophosphocholines	0.91 (0.64-1.30)	0.615
C18:1 LPC	HMDB0002815*	Glycerophospholipids	Glycerophosphocholines	1.09 (0.75-1.59)	0.645
C18:0 LPC	HMDB0010384	Glycerophospholipids	Glycerophosphocholines	1.09 (0.75-1.59)	0.649
C32:2 PC	HMDB0007874*	Glycerophospholipids	Glycerophosphocholines	0.93 (0.64-1.33)	0.675
C32:0 PC	HMDB0007871*	Glycerophospholipids	Glycerophosphocholines	1.05 (0.73-1.52)	0.774
C20:5 LPC	HMDB0010397	Glycerophospholipids	Glycerophosphocholines	0.96 (0.65-1.40)	0.821

Supplemental Table 1.3b (continued).

C18:2 LPC	HMDB0010386*	Glycerophospholipids	Glycerophosphocholines	0.96 (0.66-1.40)	0.829
C36:4 PC plasmalogen	HMDB0011310*	Glycerophospholipids	Glycerophosphocholines	1.03 (0.72-1.48)	0.861
C30:1 PC	HMDB0007870*	Glycerophospholipids	Glycerophosphocholines	1.00 (0.70-1.43)	0.992
C30:0 PC	HMDB0007869*	Glycerophospholipids	Glycerophosphocholines	1.00 (0.69-1.44)	0.994
C14:0 LPC	HMDB0010379	Glycerophospholipids	Glycerophosphocholines	1.00 (0.7-1.42)	0.995
C38:7 PE plasmalogen	HMDB0011420*	Glycerophospholipids	Glycerophospho-ethanolamines	0.80 (0.55-1.15)	0.226
C22:6 LPE	HMDB0011526	Glycerophospholipids	Glycerophospho-ethanolamines	0.81 (0.56-1.17)	0.253
C34:2 PE plasmalogen	HMDB0008952*	Glycerophospholipids	Glycerophospho-ethanolamines	0.83 (0.59-1.18)	0.308
C18:0 LPE	HMDB0011130	Glycerophospholipids	Glycerophospho-ethanolamines	1.16 (0.82-1.63)	0.412
C36:1 PE plasmalogen	HMDB0009016*	Glycerophospholipids	Glycerophospho-ethanolamines	1.16 (0.81-1.66)	0.418
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospholipids	Glycerophospho-ethanolamines	0.89 (0.63-1.26)	0.519
C34:3 PE plasmalogen	HMDB0011343*	Glycerophospholipids	Glycerophospho-ethanolamines	0.90 (0.63-1.26)	0.529
C38:6 PE	HMDB0009102*	Glycerophospholipids	Glycerophospho-ethanolamines	0.89 (0.61-1.3)	0.542
C36:5 PE plasmalogen	HMDB0011410*	Glycerophospholipids	Glycerophospho-ethanolamines	0.90 (0.63-1.27)	0.548
C36:2 PE	HMDB0008994*	Glycerophospholipids	Glycerophospho-ethanolamines	1.10 (0.77-1.57)	0.607
C36:3 PE	HMDB0009060*	Glycerophospholipids	Glycerophospho-ethanolamines	0.91 (0.64-1.30)	0.615
C40:7 PE plasmalogen	HMDB0011394*	Glycerophospholipids	Glycerophospho-ethanolamines	0.92 (0.64-1.31)	0.637

Supplemental Table 1.3b (continued).

C36:1 PE	HMDB0008993*	Glycerophospholipids	Glycerophospho-ethanolamines	1.08 (0.75-1.55)	0.677
C36:4 PE plasmalogen	HMDB0011442*	Glycerophospholipids	Glycerophospho-ethanolamines	0.93 (0.66-1.32)	0.7
C36:4 PE	HMDB0008937*	Glycerophospholipids	Glycerophospho-ethanolamines	0.93 (0.65-1.34)	0.711
C38:5 PE plasmalogen	HMDB0011386*	Glycerophospholipids	Glycerophospho-ethanolamines	1.06 (0.75-1.49)	0.76
C38:5 PE	HMDB0009069*	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.67-1.37)	0.818
C22:0 LPE	HMDB0011520	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.66-1.39)	0.818
C36:2 PE plasmalogen	HMDB0009082*	Glycerophospholipids	Glycerophospho-ethanolamines	1.04 (0.74-1.47)	0.82
C38:4 PE	HMDB0009003*	Glycerophospholipids	Glycerophospho-ethanolamines	1.04 (0.73-1.50)	0.824
C34:0 PE	HMDB0008925*	Glycerophospholipids	Glycerophospho-ethanolamines	1.04 (0.72-1.48)	0.848
C20:4 LPE	HMDB0011517	Glycerophospholipids	Glycerophospho-ethanolamines	0.97 (0.68-1.37)	0.861
C16:0 LPE	HMDB0011503	Glycerophospholipids	Glycerophospho-ethanolamines	1.03 (0.73-1.46)	0.868
C36:0 PE	HMDB0008991*	Glycerophospholipids	Glycerophospho-ethanolamines	1.03 (0.72-1.47)	0.874
C36:3 PE plasmalogen	HMDB0011441*	Glycerophospholipids	Glycerophospho-ethanolamines	1.03 (0.73-1.45)	0.884
C32:0 PE	HMDB0008923*	Glycerophospholipids	Glycerophospho-ethanolamines	0.98 (0.68-1.39)	0.895
C38:2 PE	HMDB0008942*	Glycerophospholipids	Glycerophospho-ethanolamines	1.02 (0.72-1.45)	0.901
C18:1 LPE	HMDB0011506*	Glycerophospholipids	Glycerophospho-ethanolamines	0.98 (0.69-1.40)	0.91
C18:2 LPE	HMDB0011507*	Glycerophospholipids	Glycerophospho-ethanolamines	1.01 (0.70-1.44)	0.968

Supplemental Table 1.3b (continued).

C34:2 PE	HMDB0008928*	Glycerophospholipids	Glycerophospho-ethanolamines	1.01 (0.71-1.43)	0.976
C40:6 PE	HMDB0009012*	Glycerophospholipids	Glycerophospho-ethanolamines	1.00 (0.69-1.44)	0.983
C38:4 PI	HMDB0009815*	Glycerophospholipids	Glycerophosphoinositols	1.00 (0.71-1.42)	0.983
C34:0 PS	HMDB0012356*	Glycerophospholipids	Glycerophosphoserines	0.82 (0.57-1.18)	0.282
uric acid	HMDB0000289	Imidazopyrimidines	Purines and purine derivatives	1.09 (0.75-1.57)	0.665
caffeine	HMDB0001847	Imidazopyrimidines	Purines and purine derivatives	1.07 (0.75-1.54)	0.704
7-methylxanthine	HMDB0001991	Imidazopyrimidines	Purines and purine derivatives	0.94 (0.67-1.32)	0.731
1-methylguanine	HMDB0003282	Imidazopyrimidines	Purines and purine derivatives	1.02 (0.72-1.44)	0.919
1,7-dimethyluric acid	HMDB0011103	Imidazopyrimidines	Purines and purine derivatives	1.01 (0.71-1.43)	0.948
3-methylxanthine	HMDB0001886	Imidazopyrimidines	Purines and purine derivatives	0.99 (0.71-1.40)	0.974
7-methylguanine	HMDB0000897	Imidazopyrimidines	Purines and purine derivatives	1.00 (0.70-1.43)	0.988
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	1.56 (1.09-2.23)	0.015
serotonin	HMDB0000259	Indoles and derivatives	Tryptamines and derivatives	1.13 (0.80-1.60)	0.474
C34:4 PC	HMDB0007883*	NA	NA	0.83 (0.57-1.20)	0.315
DMGV	HMDB0240212	NA	NA	1.23 (0.82-1.85)	0.321
deoxyguanosine	HMDB0000085	NA	NA	1.18 (0.83-1.68)	0.346
C20:1 LPC	HMDB0010391*	NA	NA	0.86 (0.61-1.21)	0.383
thyroxine	HMDB0000248	NA	NA	1.13 (0.79-1.62)	0.512
C34:5 PC plasmalogen	HMDB0011214*	NA	NA	1.12 (0.79-1.58)	0.531
methyl N-methylanthranilate	HMDB0034169	NA	NA	1.10 (0.78-1.55)	0.58

Supplemental Table 1.3b (continued).

trigonelline	HMDB0000875	NA	NA	0.91 (0.64-1.29)	0.588
C20:4 LPC	HMDB0010395	NA	NA	0.92 (0.64-1.31)	0.63
C18:3 LPE	HMDB0011478*	NA	NA	0.92 (0.65-1.31)	0.659
cerulenin	HMDB0015168	NA	NA	0.94 (0.66-1.33)	0.724
piperine	HMDB0029377	NA	NA	0.95 (0.66-1.35)	0.765
2-methyl-4,5-benzoxazole	HMDB0032390	NA	NA	1.05 (0.74-1.50)	0.767
C20:1 LPE	HMDB0011512*	NA	NA	1.05 (0.73-1.49)	0.803
C36:3 PC plasmalogen	HMDB0011244*	NA	NA	1.03 (0.72-1.47)	0.862
C34:2 PC plasmalogen	HMDB0011210*	NA	NA	1.00 (0.69-1.45)	0.991
coenzyme Q10	HMDB0001072	NA	NA	1.00 (0.70-1.42)	0.997
pseudouridine	HMDB0000767	Nucleoside and nucleotide analogues	NA	1.15 (0.78-1.68)	0.477
N-carbamoyl-beta-alanine	HMDB0000026	Organic carbonic acids and derivatives	Ureas	1.05 (0.73-1.53)	0.782
1-methylhistamine	HMDB0000898	Organonitrogen compounds	Amines	1.07 (0.76-1.50)	0.708
trimethylamine-N-oxide	HMDB0000925	Organonitrogen compounds	Aminoxides	0.91 (0.64-1.31)	0.622
metformin	HMDB0001921	Organonitrogen compounds	Guanidines	1.15 (0.81-1.64)	0.437
phosphocholine	HMDB0001565	Organonitrogen compounds	Quaternary ammonium salts	1.11 (0.78-1.59)	0.557
carnitine	HMDB0000062	Organonitrogen compounds	Quaternary ammonium salts	1.00 (0.69-1.44)	0.998
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	1.16 (0.82-1.66)	0.399

Supplemental Table 1.3b (continued).

4-hydroxy-3-methylacetophenone	HMDB0059824	Organooxygen compounds	Carbonyl compounds	0.88 (0.62-1.23)	0.444
acetaminophen	HMDB0001859	Phenols	1-hydroxy-2-unsubstituted benzenoids	0.91 (0.64-1.29)	0.599
guanosine	HMDB0000133	Purine nucleosides	NA	1.45 (1.02-2.06)	0.039
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	1.27 (0.88-1.82)	0.198
1-methylguanosine	HMDB0001563	Purine nucleosides	NA	1.13 (0.79-1.62)	0.511
N2,N2-dimethylguanosine	HMDB0004824	Purine nucleosides	NA	1.07 (0.73-1.57)	0.736
N1-methyl-2-pyridone-5-carboxamide	HMDB0004193	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.82 (0.57-1.17)	0.269
1-methylnicotinamide	HMDB0000699	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.83 (0.58-1.19)	0.319
pyridoxamine	HMDB0001431	Pyridines and derivatives	Pyridoxamines	1.31 (0.93-1.85)	0.121
cotinine	HMDB0001046	Pyridines and derivatives	Pyrrolidinylpyridines	1.08 (0.77-1.52)	0.662
ribothymidine	HMDB0000884	Pyrimidine nucleosides	NA	1.28 (0.89-1.86)	0.183
N4-acetylcytidine	HMDB0005923	Pyrimidine nucleosides	NA	1.01 (0.69-1.47)	0.965
kynurenic acid	HMDB0000715	Quinolines and derivatives	Quinoline carboxylic acids	0.97 (0.67-1.41)	0.888
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	Ceramides	1.50 (1.05-2.16)	0.027
C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	Ceramides	1.48 (1.03-2.13)	0.035
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	Ceramides	1.48 (1.02-2.15)	0.037
C24:0 Ceramide (d18:1)	HMDB0004956	Sphingolipids	Ceramides	1.28 (0.90-1.82)	0.168
C14:0 SM	HMDB0012097	Sphingolipids	Phosphosphingolipids	1.07 (0.75-1.52)	0.722

Supplemental Table 1.3b (continued).

C22:1 SM	HMDB0012104*	Sphingolipids	Phosphosphingolipids	1.06 (0.75-1.49)	0.754
glycodeoxycholate/ glycochenodeoxycholate	HMDB0000631*	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.28 (0.90-1.82)	0.177
glycocholate	HMDB0000138	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	0.93 (0.66-1.33)	0.705
cholesterol	HMDB0000067	Steroids and steroid derivatives	Cholestane steroids	1.14 (0.81-1.60)	0.466
campesterol	HMDB0002869	Steroids and steroid derivatives	Ergostane steroids	1.11 (0.79-1.57)	0.543
cortisone	HMDB0002802	Steroids and steroid derivatives	Hydroxysteroids	1.32 (0.92-1.90)	0.133
cortisol	HMDB0000063	Steroids and steroid derivatives	Hydroxysteroids	1.19 (0.82-1.73)	0.36
21-deoxycortisol	HMDB0004030	Steroids and steroid derivatives	Pregnane steroids	1.09 (0.76-1.57)	0.641
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesteryl esters	0.69 (0.49-0.98)	0.04
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesteryl esters	0.78 (0.55-1.10)	0.157
C16:0 CE	HMDB0000885	Steroids and steroid derivatives	Cholesteryl esters	0.80 (0.56-1.14)	0.225
C20:4 CE	HMDB0006726	Steroids and steroid derivatives	Cholesteryl esters	0.82 (0.58-1.15)	0.254
C22:6 CE	HMDB0006733	Steroids and steroid derivatives	Cholesteryl esters	0.82 (0.58-1.16)	0.256
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesteryl esters	1.19 (0.83-1.69)	0.346
C18:2 CE	HMDB0000610*	Steroids and steroid derivatives	Cholesteryl esters	0.85 (0.59-1.22)	0.378
C18:1 CE	HMDB0000918*	Steroids and steroid derivatives	Cholesteryl esters	0.87 (0.60-1.25)	0.44
C14:0 CE	HMDB0006725	Steroids and steroid derivatives	Cholesteryl esters	0.87 (0.60-1.26)	0.466

Supplemental Table 1.3b (continued).

C20:3 CE	HMDB0006736*	Steroids and steroid derivatives	Cholesteryl esters	0.88 (0.62-1.25)	0.468
C16:1 CE	HMDB0000658*	Steroids and steroid derivatives	Cholesteryl esters	1.06 (0.74-1.53)	0.752
C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesteryl esters	1.02 (0.72-1.46)	0.898
biliverdin	HMDB0001008	Tetrapyrroles and derivatives	Bilirubins	1.30 (0.92-1.85)	0.138
bilirubin	HMDB0000054	Tetrapyrroles and derivatives	Bilirubins	0.97 (0.69-1.37)	0.866

**Includes metabolites with <10% missingness. Missing values were imputed with 1/2 the minimum value. Results sorted by class, subclass, and p-value for fully adjusted models.
^Multivariable model includes: BMI age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).
*Representative HMDBID

Supplemental Table 1.4a. Odds ratios for ER- breast cancer risk comparing 90th to 10th percentiles of metabolite levels, measured at distant blood.**

				Multivariable adjusted^	
Metabolite Name	**HMDB ID**	**Class**	**Subclass**	**OR (95% CI)**	**p value**
metronidazole	HMDB0015052	Azoles	Imidazoles	0.62 (0.34-1.11)	0.112
allantoin	HMDB0000462	Azoles	Imidazoles	0.71 (0.37-1.37)	0.307
urocanic acid	HMDB0000301	Azoles	Imidazoles	0.87 (0.49-1.56)	0.641
sulfamethoxazole	HMDB0015150	Benzene and substituted derivatives	Benzenesulfonamides	1.02 (0.59-1.77)	0.952
4-hydroxyhippurate	HMDB0013678	Benzene and substituted derivatives	Benzoic acids and derivatives	1.12 (0.62-2.03)	0.715
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	1.02 (0.57-1.82)	0.952
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	1.51 (0.86-2.66)	0.153
palmitoylethanolamide	HMDB0002100	Carboximidic acids and derivatives	Carboximidic acids	0.74 (0.41-1.33)	0.318
N-acetylputrescine	HMDB0002064	Carboximidic acids and derivatives	Carboximidic acids	0.85 (0.47-1.54)	0.59
N1-acetylspermidine	HMDB0001276	Carboximidic acids and derivatives	Carboximidic acids	0.91 (0.50-1.67)	0.768
homoarginine	HMDB0000670*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.69 (0.94-3.08)	0.082
GABA	HMDB0000112	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.57 (0.89-2.77)	0.121
N-acetyltryptophan	HMDB0013713	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.66 (0.37-1.18)	0.163

Supplemental Table 1.4a (continued).

aminoisobutyric acid	HMDB0001906*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.48 (0.84-2.62)	0.172
oleoyl glycine	HMDB0013631	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.66 (0.36-1.20)	0.179
glycine	HMDB0000123	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.66 (0.35-1.24)	0.199
betaine	HMDB0000043	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.65 (0.33-1.27)	0.213
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.69 (0.39-1.23)	0.214
guanidinoacetic acid	HMDB0000128	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.69 (0.38-1.26)	0.224
creatine	HMDB0000064	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.71 (0.39-1.26)	0.243
tyrosine	HMDB0000158	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.71 (0.39-1.32)	0.279
1-methylhistidine	HMDB0000001	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.34 (0.76-2.36)	0.307
methionine	HMDB0000696	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.76 (0.43-1.33)	0.34
proline betaine	HMDB0004827	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.76 (0.43-1.34)	0.341
ADMA/SDMA	HMDB0001539	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.31 (0.75-2.29)	0.347

Supplemental Table 1.4a (continued).

threonine	HMDB0000167	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.29 (0.72-2.32)	0.388
N6,N6,N6-trimethyllysine	HMDB0001325	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.78 (0.44-1.39)	0.398
pantothenate	HMDB0000210	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.79 (0.43-1.43)	0.433
dimethylglycine	HMDB0000092	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.79 (0.43-1.44)	0.443
N-lauroylglycine	HMDB0013272	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.81 (0.46-1.42)	0.461
pipecolic acid	HMDB0000716	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.81 (0.44-1.46)	0.48
citrulline	HMDB0000904	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.82 (0.46-1.46)	0.496
creatinine	HMDB0000562	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.21 (0.68-2.17)	0.52
hydroxyproline	HMDB0000725	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.18 (0.67-2.07)	0.573
leucine	HMDB0000687	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.85 (0.47-1.54)	0.596
4-acetamidobutanoate	HMDB0003681	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.85 (0.47-1.55)	0.6

Supplemental Table 1.4a (continued).

alanine	HMDB0000161	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.86 (0.46-1.59)	0.626
glutamine	HMDB0000641	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.86 (0.48-1.55)	0.626
NMMA	HMDB0029416	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.14 (0.64-2.03)	0.659
N-acetylhistidine	HMDB0032055	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.88 (0.50-1.56)	0.664
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.88 (0.48-1.60)	0.673
proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.88 (0.47-1.65)	0.694
lysine	HMDB0000182	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.12 (0.63-1.99)	0.701
N6,N6-dimethyllysine	HMDB0013287	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.11 (0.63-1.96)	0.722
serine	HMDB0000187	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.90 (0.49-1.64)	0.734
2-aminooctanoic acid	HMDB0000991*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.51-1.65)	0.783
N6-acetyllysine	HMDB0000206*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.52-1.65)	0.791

Supplemental Table 1.4a (continued).

asparagine	HMDB0000168	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.93 (0.51-1.69)	0.807
histidine	HMDB0000177	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95 (0.53-1.73)	0.873
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95 (0.54-1.69)	0.874
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.96 (0.52-1.79)	0.907
phenylacetylglutamine	HMDB0006344	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.97 (0.54-1.74)	0.926
valine	HMDB0000883	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.00 (0.55-1.84)	0.988
5-hydroxymethyl-4-methyluracil	HMDB0000544	Diazines	Pyrimidines and pyrimidine derivatives	0.84 (0.47-1.50)	0.549
cytosine	HMDB0000630	Diazines	Pyrimidines and pyrimidine derivatives	1.02 (0.58-1.78)	0.956
C26 carnitine	HMDB0006347	Fatty Acyls	Fatty acid esters	1.34 (0.76-2.40)	0.316
C2 carnitine	HMDB0000201	Fatty Acyls	Fatty acid esters	0.81 (0.45-1.47)	0.489
C7 carnitine	HMDB0013238	Fatty Acyls	Fatty acid esters	1.23 (0.67-2.24)	0.507
C14 carnitine	HMDB0005066	Fatty Acyls	Fatty acid esters	1.20 (0.65-2.19)	0.562
C5 carnitine	HMDB0000688	Fatty Acyls	Fatty acid esters	1.17 (0.65-2.11)	0.601
C10:2 carnitine	HMDB0013325	Fatty Acyls	Fatty acid esters	0.86 (0.47-1.56)	0.616
C3 carnitine	HMDB0000824	Fatty Acyls	Fatty acid esters	1.16 (0.64-2.10)	0.621
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	1.12 (0.61-2.06)	0.715
C10 carnitine	HMDB0000651	Fatty Acyls	Fatty acid esters	1.12 (0.61-2.05)	0.716

Supplemental Table 1.4a (continued).

C4 carnitine	HMDB0002013	Fatty Acyls	Fatty acid esters	0.91 (0.50-1.64)	0.748
C4-OH carnitine	HMDB0013127	Fatty Acyls	Fatty acid esters	1.10 (0.60-2.04)	0.759
C14:1 carnitine	HMDB0002014	Fatty Acyls	Fatty acid esters	0.93 (0.51-1.71)	0.823
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.94 (0.52-1.68)	0.823
C9 carnitine	HMDB0013288	Fatty Acyls	Fatty acid esters	0.94 (0.52-1.69)	0.838
C12:1 carnitine	HMDB0013326	Fatty Acyls	Fatty acid esters	1.04 (0.57-1.91)	0.897
C6 carnitine	HMDB0000705	Fatty Acyls	Fatty acid esters	1.02 (0.55-1.88)	0.942
C12 carnitine	HMDB0002250	Fatty Acyls	Fatty acid esters	1.01 (0.55-1.86)	0.963
C8 carnitine	HMDB0000791	Fatty Acyls	Fatty acid esters	1.01 (0.55-1.86)	0.965
C14:2 carnitine	HMDB0013331	Fatty Acyls	Fatty acid esters	1.00 (0.54-1.83)	0.992
3-dehydroxycarnitine	HMDB0006831	Fatty Acyls	Fatty acids and conjugates	1.12 (0.62-2.03)	0.705
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	1.01 (0.56-1.81)	0.962
C34:2 DAG	HMDB0007103*	Fatty Acyls	Lineolic acids and derivatives	1.49 (0.81-2.78)	0.203
C34:3 DAG	HMDB0007132*	Fatty Acyls	Lineolic acids and derivatives	1.36 (0.77-2.44)	0.291
C36:3 DAG	HMDB0007219*	Fatty Acyls	Lineolic acids and derivatives	1.29 (0.70-2.39)	0.419
C36:4 DAG	HMDB0007248*	Fatty Acyls	Lineolic acids and derivatives	1.15 (0.63-2.10)	0.65
C32:1 DAG	HMDB0007099*	Glycerolipids	Diacylglycerols	1.57 (0.85-2.91)	0.149
C34:0 DAG	HMDB0007100*	Glycerolipids	Diacylglycerols	1.52 (0.82-2.85)	0.185
C32:0 DAG	HMDB0007098*	Glycerolipids	Diacylglycerols	1.49 (0.80-2.77)	0.209
C34:1 DAG	HMDB0007102*	Glycerolipids	Diacylglycerols	1.41 (0.75-2.66)	0.284
C36:1 DAG	HMDB0007216*	Glycerolipids	Diacylglycerols	1.25 (0.67-2.34)	0.489
C36:2 DAG	HMDB0007218*	Glycerolipids	Diacylglycerols	1.25 (0.66-2.36)	0.49
C38:5 DAG	HMDB0007199*	Glycerolipids	Diacylglycerols	0.96 (0.53-1.76)	0.896
C43:0 TAG	HMDB0042062*	Glycerolipids	Triacylglycerols	1.55 (0.86-2.84)	0.151
C51:0 TAG	HMDB0031106*	Glycerolipids	Triacylglycerols	1.55 (0.85-2.84)	0.154

Supplemental Table 1.4a (continued).

C49:1 TAG	HMDB0011705*	Glycerolipids	Triacylglycerols	1.47 (0.84-2.58)	0.177
C45:1 TAG	HMDB0042099*	Glycerolipids	Triacylglycerols	1.49 (0.83-2.72)	0.186
C49:2 TAG	HMDB0011706*	Glycerolipids	Triacylglycerols	1.49 (0.82-2.69)	0.189
C43:1 TAG	HMDB0042098*	Glycerolipids	Triacylglycerols	1.49 (0.82-2.73)	0.191
C44:0 TAG	HMDB0042063*	Glycerolipids	Triacylglycerols	1.48 (0.81-2.71)	0.199
C47:1 TAG	HMDB0042100*	Glycerolipids	Triacylglycerols	1.47 (0.82-2.68)	0.201
C54:6 TAG	HMDB0005391*	Glycerolipids	Triacylglycerols	0.69 (0.38-1.25)	0.22
C43:2 TAG	HMDB0043169*	Glycerolipids	Triacylglycerols	1.46 (0.80-2.67)	0.22
C51:1 TAG	HMDB0042104*	Glycerolipids	Triacylglycerols	1.46 (0.79-2.68)	0.227
C49:3 TAG	HMDB0042103*	Glycerolipids	Triacylglycerols	1.44 (0.80-2.61)	0.228
C50:3 TAG	HMDB0005433*	Glycerolipids	Triacylglycerols	1.45 (0.78-2.73)	0.245
C45:2 TAG	HMDB0043170*	Glycerolipids	Triacylglycerols	1.41 (0.77-2.57)	0.264
C46:1 TAG	HMDB0010412*	Glycerolipids	Triacylglycerols	1.37 (0.75-2.51)	0.299
C47:2 TAG	HMDB0042076*	Glycerolipids	Triacylglycerols	1.36 (0.75-2.47)	0.309
C48:1 TAG	HMDB0005359*	Glycerolipids	Triacylglycerols	1.36 (0.73-2.52)	0.331
C56:6 TAG	HMDB0005456*	Glycerolipids	Triacylglycerols	0.74 (0.40-1.37)	0.337
C46:0 TAG	HMDB0010411*	Glycerolipids	Triacylglycerols	1.35 (0.72-2.51)	0.347
C51:2 TAG	HMDB0005362*	Glycerolipids	Triacylglycerols	1.33 (0.73-2.42)	0.348
C46:2 TAG	HMDB0010419*	Glycerolipids	Triacylglycerols	1.32 (0.73-2.39)	0.358
C56:5 TAG	HMDB0005406*	Glycerolipids	Triacylglycerols	0.75 (0.41-1.39)	0.362
C51:3 TAG	HMDB0011701*	Glycerolipids	Triacylglycerols	1.32 (0.72-2.42)	0.373
C54:3 TAG	HMDB0005405*	Glycerolipids	Triacylglycerols	0.77 (0.41-1.43)	0.413
C54:7 TAG	HMDB0005447*	Glycerolipids	Triacylglycerols	0.80 (0.45-1.42)	0.439
C52:0 TAG	HMDB0005365*	Glycerolipids	Triacylglycerols	1.27 (0.68-2.36)	0.454
C48:0 TAG	HMDB0005356*	Glycerolipids	Triacylglycerols	1.27 (0.68-2.39)	0.457
C50:0 TAG	HMDB0005357*	Glycerolipids	Triacylglycerols	1.25 (0.67-2.34)	0.476
C50:2 TAG	HMDB0005377*	Glycerolipids	Triacylglycerols	1.26 (0.67-2.38)	0.476
C52:2 TAG	HMDB0005369*	Glycerolipids	Triacylglycerols	1.25 (0.67-2.36)	0.479
C48:2 TAG	HMDB0005376*	Glycerolipids	Triacylglycerols	1.24 (0.68-2.28)	0.489
C50:1 TAG	HMDB0005360*	Glycerolipids	Triacylglycerols	1.24 (0.66-2.33)	0.508

Supplemental Table 1.4a (continued).

C52:4 TAG	HMDB0005363*	Glycerolipids	Triacylglycerols	1.22 (0.67-2.25)	0.518
C48:3 TAG	HMDB0005432*	Glycerolipids	Triacylglycerols	1.20 (0.66-2.20)	0.545
C54:5 TAG	HMDB0005385*	Glycerolipids	Triacylglycerols	0.83 (0.45-1.53)	0.551
C54:4 TAG	HMDB0005370*	Glycerolipids	Triacylglycerols	0.84 (0.45-1.56)	0.581
C55:2 TAG	HMDB0042226*	Glycerolipids	Triacylglycerols	1.18 (0.64-2.19)	0.591
C58:8 TAG	HMDB0005413*	Glycerolipids	Triacylglycerols	1.13 (0.64-2.02)	0.668
C56:7 TAG	HMDB0005462*	Glycerolipids	Triacylglycerols	1.13 (0.61-2.09)	0.704
C56:3 TAG	HMDB0005410*	Glycerolipids	Triacylglycerols	1.11 (0.60-2.06)	0.746
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.91 (0.49-1.70)	0.76
C54:2 TAG	HMDB0005403*	Glycerolipids	Triacylglycerols	0.91 (0.49-1.71)	0.777
C56:9 TAG	HMDB0005448*	Glycerolipids	Triacylglycerols	0.92 (0.50-1.69)	0.781
C50:5 TAG	HMDB0010471*	Glycerolipids	Triacylglycerols	1.09 (0.59-2.02)	0.782
C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	1.08 (0.59-1.99)	0.796
C55:3 TAG	HMDB0042466*	Glycerolipids	Triacylglycerols	0.92 (0.50-1.70)	0.797
C56:2 TAG	HMDB0005404*	Glycerolipids	Triacylglycerols	1.08 (0.58-2.01)	0.802
C53:2 TAG	HMDB0042196*	Glycerolipids	Triacylglycerols	1.08 (0.58-1.97)	0.815
C54:8 TAG	HMDB0010518*	Glycerolipids	Triacylglycerols	0.94 (0.52-1.70)	0.837
C52:1 TAG	HMDB0005367*	Glycerolipids	Triacylglycerols	1.07 (0.57-2.00)	0.839
C60:12 TAG	HMDB0005478*	Glycerolipids	Triacylglycerols	1.06 (0.56-2.00)	0.853
C50:6 TAG	HMDB0010497*	Glycerolipids	Triacylglycerols	1.06 (0.58-1.93)	0.853
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	0.95 (0.52-1.74)	0.868
C58:6 TAG	HMDB0005458*	Glycerolipids	Triacylglycerols	0.95 (0.50-1.80)	0.874
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	0.95 (0.51-1.77)	0.876
C56:8 TAG	HMDB0005392*	Glycerolipids	Triacylglycerols	0.96 (0.52-1.76)	0.889
C56:4 TAG	HMDB0005398*	Glycerolipids	Triacylglycerols	1.04 (0.56-1.91)	0.901
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	1.04 (0.56-1.92)	0.903
C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	0.97 (0.53-1.77)	0.917
C52:6 TAG	HMDB0005436*	Glycerolipids	Triacylglycerols	0.97 (0.53-1.79)	0.922
C53:3 TAG	HMDB0043058*	Glycerolipids	Triacylglycerols	0.97 (0.52-1.82)	0.935
C52:7 TAG	HMDB0010517*	Glycerolipids	Triacylglycerols	1.02 (0.55-1.88)	0.953

Supplemental Table 1.4a (continued).

C54:1 TAG	HMDB0005395*	Glycerolipids	Triacylglycerols	1.01 (0.54-1.89)	0.969
C56:1 TAG	HMDB0005396*	Glycerolipids	Triacylglycerols	0.99 (0.54-1.84)	0.984
C14:0 LPC	HMDB0010379	Glycerophospholipids	Glycerophosphocholines	1.43 (0.79-2.58)	0.231
C30:0 PC	HMDB0007869*	Glycerophospholipids	Glycerophosphocholines	1.45 (0.79-2.67)	0.235
C38:6 PC	HMDB0007991*	Glycerophospholipids	Glycerophosphocholines	1.47 (0.78-2.78)	0.239
C22:5 LPC	HMDB0010403*	Glycerophospholipids	Glycerophosphocholines	0.71 (0.39-1.27)	0.248
C32:2 PC	HMDB0007874*	Glycerophospholipids	Glycerophosphocholines	1.39 (0.76-2.55)	0.289
C40:9 PC	HMDB0008731*	Glycerophospholipids	Glycerophosphocholines	1.36 (0.73-2.53)	0.334
C40:6 PC	HMDB0008057*	Glycerophospholipids	Glycerophosphocholines	1.32 (0.72-2.43)	0.376
C36:5 PC plasmalogen-A	HMDB0011221*	Glycerophospholipids	Glycerophosphocholines	0.77 (0.43-1.38)	0.383
C30:1 PC	HMDB0007870*	Glycerophospholipids	Glycerophosphocholines	1.31 (0.71-2.42)	0.386
C40:10 PC	HMDB0008511*	Glycerophospholipids	Glycerophosphocholines	1.29 (0.69-2.43)	0.428
C32:0 PC	HMDB0007871*	Glycerophospholipids	Glycerophosphocholines	1.28 (0.69-2.40)	0.435
C16:0 LPC	HMDB0010382	Glycerophospholipids	Glycerophosphocholines	1.25 (0.70-2.24)	0.452
C18:2 LPC	HMDB0010386*	Glycerophospholipids	Glycerophosphocholines	0.78 (0.41-1.49)	0.453
C32:1 PC	HMDB0007873*	Glycerophospholipids	Glycerophosphocholines	1.25 (0.66-2.39)	0.499
C22:6 LPC	HMDB0010404	Glycerophospholipids	Glycerophosphocholines	1.22 (0.67-2.24)	0.518

Supplemental Table 1.4a (continued).

C36:5 PC plasmalogen-B	HMDB0011220*	Glycerophospholipids	Glycerophosphocholines	0.84 (0.47-1.47)	0.534
C20:5 LPC	HMDB0010397	Glycerophospholipids	Glycerophosphocholines	0.82 (0.43-1.54)	0.535
C34:3 PC plasmalogen	HMDB0011211*	Glycerophospholipids	Glycerophosphocholines	0.84 (0.47-1.49)	0.549
C36:4 PC plasmalogen	HMDB0011310*	Glycerophospholipids	Glycerophosphocholines	0.85 (0.48-1.50)	0.572
C36:4 PC-B	HMDB0008138*	Glycerophospholipids	Glycerophosphocholines	1.17 (0.62-2.22)	0.629
C16:1 LPC	HMDB0010383*	Glycerophospholipids	Glycerophosphocholines	1.12 (0.62-2.01)	0.711
C34:1 PC	HMDB0007972*	Glycerophospholipids	Glycerophosphocholines	1.11 (0.61-2.04)	0.727
C18:3 LPC	HMDB0010387*	Glycerophospholipids	Glycerophosphocholines	1.11 (0.61-1.99)	0.737
C38:3 PC	HMDB0008047*	Glycerophospholipids	Glycerophosphocholines	0.90 (0.48-1.69)	0.742
C18:0 LPC	HMDB0010384	Glycerophospholipids	Glycerophosphocholines	1.09 (0.58-2.03)	0.789
C34:1 PC plasmalogen-B	HMDB0011239*	Glycerophospholipids	Glycerophosphocholines	1.08 (0.61-1.90)	0.797
C18:1 LPC	HMDB0002815*	Glycerophospholipids	Glycerophosphocholines	0.96 (0.52-1.74)	0.889
C38:4 PC plasmalogen	HMDB0011252*	Glycerophospholipids	Glycerophosphocholines	0.96 (0.55-1.70)	0.901
C36:1 PC	HMDB0008038*	Glycerophospholipids	Glycerophosphocholines	0.97 (0.54-1.73)	0.911
C36:2 PC plasmalogen	HMDB0011243*	Glycerophospholipids	Glycerophosphocholines	0.98 (0.55-1.75)	0.951
C38:7 PC plasmalogen	HMDB0011229*	Glycerophospholipids	Glycerophosphocholines	1.00 (0.56-1.81)	0.987

Supplemental Table 1.4a (continued).

C34:1 PC plasmalogen	HMDB0011208*	Glycerophospholipids	Glycerophosphocholines	1.00 (0.57-1.75)	0.991
C22:6 LPE	HMDB0011526	Glycerophospholipids	Glycerophospho-ethanolamines	1.50 (0.81-2.78)	0.199
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospholipids	Glycerophospho-ethanolamines	0.72 (0.41-1.27)	0.254
C32:0 PE	HMDB0008923*	Glycerophospholipids	Glycerophospho-ethanolamines	1.40 (0.78-2.51)	0.263
C34:0 PE	HMDB0008925*	Glycerophospholipids	Glycerophospho-ethanolamines	1.37 (0.76-2.50)	0.298
C38:5 PE	HMDB0009069*	Glycerophospholipids	Glycerophospho-ethanolamines	0.73 (0.39-1.35)	0.31
C38:5 PE plasmalogen	HMDB0011386*	Glycerophospholipids	Glycerophospho-ethanolamines	0.76 (0.43-1.34)	0.338
C36:3 PE	HMDB0009060*	Glycerophospholipids	Glycerophospho-ethanolamines	0.75 (0.40-1.41)	0.376
C36:0 PE	HMDB0008991*	Glycerophospholipids	Glycerophospho-ethanolamines	1.26 (0.70-2.28)	0.44
C18:2 LPE	HMDB0011507*	Glycerophospholipids	Glycerophospho-ethanolamines	0.8 (0.43-1.46)	0.463
C16:0 LPE	HMDB0011503	Glycerophospholipids	Glycerophospho-ethanolamines	1.22 (0.68-2.22)	0.504
C38:4 PE	HMDB0009003*	Glycerophospholipids	Glycerophospho-ethanolamines	0.81 (0.44-1.52)	0.516
C36:5 PE plasmalogen	HMDB0011410*	Glycerophospholipids	Glycerophospho-ethanolamines	0.84 (0.48-1.47)	0.542
C18:1 LPE	HMDB0011506*	Glycerophospholipids	Glycerophospho-ethanolamines	0.83 (0.46-1.51)	0.55
C36:1 PE	HMDB0008993*	Glycerophospholipids	Glycerophospho-ethanolamines	0.83 (0.44-1.57)	0.568
C38:2 PE	HMDB0008942*	Glycerophospholipids	Glycerophospho-ethanolamines	0.87 (0.47-1.58)	0.637

Supplemental Table 1.4a (continued).

C34:3 PE plasmalogen	HMDB0011343*	Glycerophospholipids	Glycerophospho-ethanolamines	0.88 (0.49-1.57)	0.656
C36:2 PE	HMDB0008994*	Glycerophospholipids	Glycerophospho-ethanolamines	0.88 (0.46-1.66)	0.692
C40:6 PE	HMDB0009012*	Glycerophospholipids	Glycerophospho-ethanolamines	1.13 (0.59-2.15)	0.717
C20:4 LPE	HMDB0011517	Glycerophospholipids	Glycerophospho-ethanolamines	0.90 (0.51-1.60)	0.718
C36:1 PE plasmalogen	HMDB0009016*	Glycerophospholipids	Glycerophospho-ethanolamines	0.90 (0.50-1.64)	0.738
C34:2 PE plasmalogen	HMDB0008952*	Glycerophospholipids	Glycerophospho-ethanolamines	1.10 (0.62-1.95)	0.754
C36:4 PE plasmalogen	HMDB0011442*	Glycerophospholipids	Glycerophospho-ethanolamines	0.92 (0.51-1.64)	0.776
C36:4 PE	HMDB0008937*	Glycerophospholipids	Glycerophospho-ethanolamines	0.93 (0.49-1.76)	0.814
C36:3 PE plasmalogen	HMDB0011441*	Glycerophospholipids	Glycerophospho-ethanolamines	0.94 (0.52-1.68)	0.825
C18:0 LPE	HMDB0011130	Glycerophospholipids	Glycerophospho-ethanolamines	0.95 (0.52-1.71)	0.854
C38:7 PE plasmalogen	HMDB0011420*	Glycerophospholipids	Glycerophospho-ethanolamines	1.06 (0.58-1.91)	0.854
C34:2 PE	HMDB0008928*	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.51-1.80)	0.887
C36:2 PE plasmalogen	HMDB0009082*	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.54-1.72)	0.895
C22:0 LPE	HMDB0011520	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.51-1.80)	0.9
C40:7 PE plasmalogen	HMDB0011394*	Glycerophospholipids	Glycerophospho-ethanolamines	1.02 (0.57-1.82)	0.956
C38:6 PE	HMDB0009102*	Glycerophospholipids	Glycerophospho-ethanolamines	1.01 (0.53-1.96)	0.966

Supplemental Table 1.4a (continued).

C38:4 PI	HMDB0009815*	Glycerophospholipids	Glycerophosphoinositols	0.94 (0.51-1.72)	0.832
C34:0 PS	HMDB0012356*	Glycerophospholipids	Glycerophosphoserines	0.86 (0.47-1.59)	0.632
7-methylxanthine	HMDB0001991	Imidazopyrimidines	Purines and purine derivatives	1.32 (0.74-2.37)	0.354
7-methylguanine	HMDB0000897	Imidazopyrimidines	Purines and purine derivatives	1.28 (0.72-2.27)	0.404
caffeine	HMDB0001847	Imidazopyrimidines	Purines and purine derivatives	0.88 (0.49-1.59)	0.67
uric acid	HMDB0000289	Imidazopyrimidines	Purines and purine derivatives	1.09 (0.58-2.06)	0.781
1-methylguanine	HMDB0003282	Imidazopyrimidines	Purines and purine derivatives	0.94 (0.54-1.65)	0.828
1,7-dimethyluric acid	HMDB0011103	Imidazopyrimidines	Purines and purine derivatives	1.05 (0.59-1.85)	0.864
3-methylxanthine	HMDB0001886	Imidazopyrimidines	Purines and purine derivatives	1.04 (0.58-1.86)	0.89
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	0.66 (0.36-1.19)	0.166
serotonin	HMDB0000259	Indoles and derivatives	Tryptamines and derivatives	1.03 (0.59-1.80)	0.925
thyroxine	HMDB0000248	NA	NA	2.16 (1.15-4.13)	0.018
C34:5 PC plasmalogen	HMDB0011214*	NA	NA	0.63 (0.35-1.14)	0.127
C20:1 LPC	HMDB0010391*	NA	NA	0.63 (0.35-1.15)	0.135
trigonelline	HMDB0000875	NA	NA	0.66 (0.37-1.18)	0.161
C20:1 LPE	HMDB0011512*	NA	NA	0.71 (0.39-1.30)	0.27
cerulenin	HMDB0015168	NA	NA	0.74 (0.41-1.33)	0.316
C36:3 PC plasmalogen	HMDB0011244*	NA	NA	0.76 (0.43-1.35)	0.352
C34:4 PC	HMDB0007883*	NA	NA	1.31 (0.70-2.47)	0.407

Supplemental Table 1.4a (continued).

deoxyguanosine	HMDB0000085	NA	NA	0.80 (0.45-1.42)	0.450
valsartan	HMDB0014323	NA	NA	0.84 (0.49-1.44)	0.523
DMGV	HMDB0240212	NA	NA	0.81 (0.41-1.61)	0.554
C34:2 PC plasmalogen	HMDB0011210*	NA	NA	0.84 (0.47-1.51)	0.56
2-methyl-4,5-benzoxazole	HMDB0032390	NA	NA	1.11 (0.62-2.00)	0.721
coenzyme Q10	HMDB0001072	NA	NA	1.10 (0.62-1.97)	0.742
piperine	HMDB0029377	NA	NA	0.92 (0.51-1.65)	0.786
C18:3 LPE	HMDB0011478*	NA	NA	0.93 (0.52-1.68)	0.821
C20:4 LPC	HMDB0010395	NA	NA	0.94 (0.52-1.67)	0.823
methyl N-methylanthra-nilate	HMDB0034169	NA	NA	1.03 (0.58-1.82)	0.93
pseudouridine	HMDB0000767	Nucleoside and nucleotide analogues	NA	1.11 (0.60-2.03)	0.742
N-carbamoyl-beta-alanine	HMDB0000026	Organic carbonic acids and derivatives	Ureas	0.97 (0.53-1.77)	0.913
1-methylhistamine	HMDB0000898	Organonitrogen compounds	Amines	1.13 (0.64-1.99)	0.681
trimethylamine-N-oxide	HMDB0000925	Organonitrogen compounds	Aminoxides	0.78 (0.44-1.36)	0.379
metformin	HMDB0001921	Organonitrogen compounds	Guanidines	0.90 (0.50-1.60)	0.711
phosphocholine	HMDB0001565	Organonitrogen compounds	Quaternary ammonium salts	0.87 (0.49-1.56)	0.651
carnitine	HMDB0000062	Organonitrogen compounds	Quaternary ammonium salts	1.12 (0.60-2.07)	0.729

Supplemental Table 1.4a (continued).

acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	1.85 (1.04-3.33)	0.037
4-hydroxy-3-methylacetophenone	HMDB0059824	Organooxygen compounds	Carbonyl compounds	1.29 (0.74-2.25)	0.377
acetaminophen	HMDB0001859	Phenols	1-hydroxy-2-unsubstituted benzenoids	0.80 (0.45-1.41)	0.446
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	2.02 (1.13-3.64)	0.019
1-methylguanosine	HMDB0001563	Purine nucleosides	NA	1.58 (0.88-2.88)	0.129
guanosine	HMDB0000133	Purine nucleosides	NA	0.83 (0.47-1.46)	0.51
N2,N2-dimethylguanosine	HMDB0004824	Purine nucleosides	NA	1.11 (0.61-2.03)	0.721
N1-methyl-2-pyridone-5-carboxamide	HMDB0004193	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	1.10 (0.62-1.95)	0.754
1-methylnicotinamide	HMDB0000699	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.91 (0.50-1.65)	0.758
pyridoxamine	HMDB0001431	Pyridines and derivatives	Pyridoxamines	1.18 (0.66-2.08)	0.577
cotinine	HMDB0001046	Pyridines and derivatives	Pyrrolidinylpyridines	0.98 (0.53-1.80)	0.936
N4-acetylcytidine	HMDB0005923	Pyrimidine nucleosides	NA	1.35 (0.74-2.49)	0.329
ribothymidine	HMDB0000884	Pyrimidine nucleosides	NA	0.93 (0.53-1.65)	0.814
kynurenic acid	HMDB0000715	Quinolines and derivatives	Quinoline carboxylic acids	0.73 (0.40-1.34)	0.308

Supplemental Table 1.4a (continued).

C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	Ceramides	1.58 (0.86-2.91)	0.141
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	Ceramides	1.32 (0.71-2.46)	0.386
C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	Ceramides	1.26 (0.68-2.33)	0.465
C24:0 Ceramide (d18:1)	HMDB0004956	Sphingolipids	Ceramides	1.25 (0.69-2.28)	0.466
C14:0 SM	HMDB0012097	Sphingolipids	Phosphosphingolipids	0.78 (0.43-1.42)	0.417
C22:1 SM	HMDB0012104*	Sphingolipids	Phosphosphingolipids	0.88 (0.49-1.58)	0.676
glycodeoxycholate/glycochenodeoxycholate	HMDB0000631*	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	0.84 (0.45-1.59)	0.597
glycocholate	HMDB0000138	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	0.98 (0.54-1.79)	0.949
cholesterol	HMDB0000067	Steroids and steroid derivatives	Cholestane steroids	1.11 (0.61-2.02)	0.731
campesterol	HMDB0002869	Steroids and steroid derivatives	Ergostane steroids	1.05 (0.58-1.91)	0.871
cortisol	HMDB0000063	Steroids and steroid derivatives	Hydroxysteroids	1.38 (0.70-2.71)	0.354
cortisone	HMDB0002802	Steroids and steroid derivatives	Hydroxysteroids	1.13 (0.61-2.10)	0.687
21-deoxycortisol	HMDB0004030	Steroids and steroid derivatives	Pregnane steroids	1.90 (1.00-3.64)	0.051
C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesteryl esters	0.55 (0.30-1.01)	0.054
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesteryl esters	0.60 (0.33-1.10)	0.103

Supplemental Table 1.4a (continued).

C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesteryl esters	0.65 (0.35-1.18)	0.16
C20:3 CE	HMDB0006736*	Steroids and steroid derivatives	Cholesteryl esters	0.69 (0.38-1.25)	0.225
C18:2 CE	HMDB0000610*	Steroids and steroid derivatives	Cholesteryl esters	0.73 (0.39-1.36)	0.324
C20:4 CE	HMDB0006726	Steroids and steroid derivatives	Cholesteryl esters	0.77 (0.42-1.38)	0.374
C18:1 CE	HMDB0000918*	Steroids and steroid derivatives	Cholesteryl esters	0.77 (0.41-1.42)	0.404
C16:1 CE	HMDB0000658*	Steroids and steroid derivatives	Cholesteryl esters	0.82 (0.44-1.54)	0.532
C16:0 CE	HMDB0000885	Steroids and steroid derivatives	Cholesteryl esters	0.90 (0.48-1.66)	0.728
C22:6 CE	HMDB0006733	Steroids and steroid derivatives	Cholesteryl esters	1.03 (0.56-1.89)	0.931
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesteryl esters	0.99 (0.53-1.83)	0.965
C14:0 CE	HMDB0006725	Steroids and steroid derivatives	Cholesteryl esters	1.00 (0.54-1.84)	0.988
bilirubin	HMDB0000054	Tetrapyrroles and derivatives	Bilirubins	0.97 (0.55-1.71)	0.916
biliverdin	HMDB0001008	Tetrapyrroles and derivatives	Bilirubins	0.99 (0.56-1.72)	0.96

** Includes metabolites with <10% missingness. Missing values were imputed with 1/2 the minimum value. Results sorted by class, subclass, and p-value for fully adjusted models.
^Multivariable model includes BMI at age 18, weight change since age 18, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).
*Representative HMDBID

Supplemental Table 1.4b. Odds ratios for ER- breast cancer risk comparing 90th to 10th percentiles of metabolite levels, measured at proximate blood.**

				Multivariable Adjusted^	
Metabolite Name	**HMDB ID**	**Class**	**Subclass**	**OR (95% CI)**	**p value**
allantoin	HMDB0000462	Azoles	Imidazoles	1.3 (0.62-2.79)	0.488
urocanic acid	HMDB0000301	Azoles	Imidazoles	0.84 (0.42-1.69)	0.627
metronidazole	HMDB0015052	Azoles	Imidazoles	0.87 (0.43-1.73)	0.686
sulfamethoxazole	HMDB0015150	Benzene and substituted derivatives	Benzenesulfon-amides	1.05 (0.53-2.09)	0.882
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	0.52 (0.26-1.03)	0.062
4-hydroxyhippurate	HMDB0013678	Benzene and substituted derivatives	Benzoic acids and derivatives	0.78 (0.39-1.56)	0.49
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	2.33 (1.14-4.81)	0.02
N1-acetylspermidine	HMDB0001276	Carboximidic acids and derivatives	Carboximidic acids	1.64 (0.8-3.39)	0.177
N-acetylputrescine	HMDB0002064	Carboximidic acids and derivatives	Carboximidic acids	0.64 (0.31-1.33)	0.235
palmitoylethanolamide	HMDB0002100	Carboximidic acids and derivatives	Carboximidic acids	0.82 (0.42-1.6)	0.566
hydroxyproline	HMDB0000725	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	2.03 (1.01-4.15)	0.048
creatinine	HMDB0000562	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.88 (0.92-3.93)	0.085

Supplemental Table 1.4b (continued).

N6,N6,N6-trimethyllysine	HMDB0001325	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.85 (0.92-3.74)	0.085
N-acetylhistidine	HMDB0032055	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.82 (0.91-3.73)	0.092
N6,N6-dimethyllysine	HMDB0013287	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.76 (0.87-3.59)	0.116
citrulline	HMDB0000904	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.75 (0.87-3.59)	0.12
GABA	HMDB0000112	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.67 (0.84-3.34)	0.146
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.67 (0.8-3.5)	0.171
ADMA/SDMA	HMDB0001539	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.56 (0.78-3.17)	0.211
threonine	HMDB0000167	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.55 (0.76-3.21)	0.233
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.53 (0.76-3.12)	0.235
pipecolic acid	HMDB0000716	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.67 (0.32-1.38)	0.278
betaine	HMDB0000043	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.44 (0.72-2.9)	0.306
valine	HMDB0000883	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.45 (0.68-3.11)	0.337

Supplemental Table 1.4b (continued).

homoarginine	HMDB0000670*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.4 (0.69-2.86)	0.351
N6-acetyllysine	HMDB0000206*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.38 (0.65-2.93)	0.399
1-methylhistidine	HMDB0000001	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.33 (0.65-2.7)	0.432
creatine	HMDB0000064	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.75 (0.37-1.53)	0.434
pantothenate	HMDB0000210	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.32 (0.65-2.7)	0.44
aminoisobutyric acid	HMDB0001906*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.32 (0.62-2.8)	0.47
asparagine	HMDB0000168	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.3 (0.63-2.72)	0.476
NMMA	HMDB0029416	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.29 (0.64-2.61)	0.476
isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.31 (0.62-2.79)	0.487
serine	HMDB0000187	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.29 (0.63-2.66)	0.489
alanine	HMDB0000161	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.78 (0.37-1.63)	0.506

Supplemental Table 1.4b (continued).

lysine	HMDB0000182	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.25 (0.63-2.51)	0.529
leucine	HMDB0000687	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.26 (0.61-2.63)	0.537
N-lauroylglycine	HMDB0013272	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.81 (0.41-1.6)	0.542
N-acetyltryptophan	HMDB0013713	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.81 (0.4-1.64)	0.555
phenylacetylglutamine	HMDB0006344	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.84 (0.42-1.68)	0.616
dimethylglycine	HMDB0000092	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.19 (0.58-2.41)	0.636
histidine	HMDB0000177	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.16 (0.57-2.35)	0.687
proline betaine	HMDB0004827	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.89 (0.44-1.8)	0.743
guanidinoacetic acid	HMDB0000128	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.11 (0.57-2.18)	0.753
proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.89 (0.41-1.91)	0.76
glycine	HMDB0000123	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.1 (0.55-2.17)	0.791

Supplemental Table 1.4b (continued).

2-aminooctanoic acid	HMDB0000991*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.44-1.88)	0.812
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.44-1.92)	0.826
oleoyl glycine	HMDB0013631	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.92 (0.45-1.86)	0.827
tyrosine	HMDB0000158	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.05 (0.5-2.19)	0.897
methionine	HMDB0000696	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.04 (0.51-2.1)	0.918
4-acetamidobutanoate	HMDB0003681	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.02 (0.48-2.15)	0.967
glutamine	HMDB0000641	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.01 (0.49-2.08)	0.989
cytosine	HMDB0000630	Diazines	Pyrimidines and pyrimidine derivatives	1.7 (0.87-3.35)	0.124
5-hydroxymethyl-4-methyluracil	HMDB0000544	Diazines	Pyrimidines and pyrimidine derivatives	1.31 (0.64-2.68)	0.466
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	2.44 (1.19-5.07)	0.015
C26 carnitine	HMDB0006347	Fatty Acyls	Fatty acid esters	1.57 (0.77-3.25)	0.216
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	1.46 (0.72-2.97)	0.289
C14 carnitine	HMDB0005066	Fatty Acyls	Fatty acid esters	1.42 (0.7-2.89)	0.326

Supplemental Table 1.4b (continued).

C9 carnitine	HMDB0013288	Fatty Acyls	Fatty acid esters	1.39 (0.69-2.84)	0.357
C12 carnitine	HMDB0002250	Fatty Acyls	Fatty acid esters	1.33 (0.67-2.66)	0.418
C2 carnitine	HMDB0000201	Fatty Acyls	Fatty acid esters	1.33 (0.65-2.71)	0.433
C5 carnitine	HMDB0000688	Fatty Acyls	Fatty acid esters	1.32 (0.64-2.72)	0.447
C14:1 carnitine	HMDB0002014	Fatty Acyls	Fatty acid esters	1.27 (0.63-2.57)	0.504
C14:2 carnitine	HMDB0013331	Fatty Acyls	Fatty acid esters	1.27 (0.63-2.55)	0.507
C10 carnitine	HMDB0000651	Fatty Acyls	Fatty acid esters	1.23 (0.61-2.5)	0.558
C12:1 carnitine	HMDB0013326	Fatty Acyls	Fatty acid esters	1.2 (0.6-2.41)	0.611
C7 carnitine	HMDB0013238	Fatty Acyls	Fatty acid esters	1.16 (0.57-2.35)	0.681
C8 carnitine	HMDB0000791	Fatty Acyls	Fatty acid esters	1.15 (0.56-2.32)	0.705
C10:2 carnitine	HMDB0013325	Fatty Acyls	Fatty acid esters	0.9 (0.45-1.79)	0.772
C3 carnitine	HMDB0000824	Fatty Acyls	Fatty acid esters	1.1 (0.53-2.26)	0.793
C6 carnitine	HMDB0000705	Fatty Acyls	Fatty acid esters	0.92 (0.45-1.88)	0.827
C4 carnitine	HMDB0002013	Fatty Acyls	Fatty acid esters	1.02 (0.5-2.1)	0.948
C4-OH carnitine	HMDB0013127	Fatty Acyls	Fatty acid esters	1.02 (0.49-2.1)	0.952
3-dehydroxycarnitine	HMDB0006831	Fatty Acyls	Fatty acids and conjugates	1.76 (0.89-3.5)	0.105
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	1.39 (0.69-2.83)	0.356
C36:3 DAG	HMDB0007219*	Fatty Acyls	Lineolic acids and derivatives	1.24 (0.6-2.56)	0.557
C36:4 DAG	HMDB0007248*	Fatty Acyls	Lineolic acids and derivatives	1.08 (0.52-2.22)	0.84

Supplemental Table 1.4b (continued).

C34:2 DAG	HMDB0007103*	Fatty Acyls	Lineolic acids and derivatives	1.06 (0.51-2.19)	0.873
C34:3 DAG	HMDB0007132*	Fatty Acyls	Lineolic acids and derivatives	1.06 (0.52-2.13)	0.879
C32:1 DAG	HMDB0007099*	Glycerolipids	Diacylglycerols	1.17 (0.56-2.41)	0.675
C36:2 DAG	HMDB0007218*	Glycerolipids	Diacylglycerols	1.16 (0.57-2.37)	0.675
C34:1 DAG	HMDB0007102*	Glycerolipids	Diacylglycerols	1.16 (0.56-2.38)	0.689
C32:0 DAG	HMDB0007098*	Glycerolipids	Diacylglycerols	1.14 (0.56-2.33)	0.714
C34:0 DAG	HMDB0007100*	Glycerolipids	Diacylglycerols	1.13 (0.56-2.29)	0.734
C38:5 DAG	HMDB0007199*	Glycerolipids	Diacylglycerols	0.91 (0.44-1.88)	0.799
C36:1 DAG	HMDB0007216*	Glycerolipids	Diacylglycerols	1.07 (0.54-2.15)	0.839
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.55 (0.27-1.1)	0.093
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	0.55 (0.26-1.15)	0.113
C58:6 TAG	HMDB0005458*	Glycerolipids	Triacylglycerols	0.59 (0.29-1.16)	0.128
C56:9 TAG	HMDB0005448*	Glycerolipids	Triacylglycerols	0.59 (0.28-1.21)	0.15
C56:6 TAG	HMDB0005456*	Glycerolipids	Triacylglycerols	0.6 (0.29-1.22)	0.16
C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	0.6 (0.29-1.23)	0.16
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	0.61 (0.29-1.27)	0.189
C54:8 TAG	HMDB0010518*	Glycerolipids	Triacylglycerols	0.63 (0.31-1.29)	0.207
C56:7 TAG	HMDB0005462*	Glycerolipids	Triacylglycerols	0.66 (0.32-1.36)	0.255

Supplemental Table 1.4b (continued).

C56:8 TAG	HMDB0005392*	Glycerolipids	Triacylglycerols	0.67 (0.32-1.37)	0.267
C52:7 TAG	HMDB0010517*	Glycerolipids	Triacylglycerols	0.67 (0.33-1.37)	0.269
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	0.67 (0.32-1.37)	0.272
C54:7 TAG	HMDB0005447*	Glycerolipids	Triacylglycerols	0.69 (0.34-1.41)	0.312
C52:6 TAG	HMDB0005436*	Glycerolipids	Triacylglycerols	0.7 (0.34-1.44)	0.336
C56:5 TAG	HMDB0005406*	Glycerolipids	Triacylglycerols	0.71 (0.36-1.43)	0.34
C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	0.7 (0.34-1.46)	0.345
C58:8 TAG	HMDB0005413*	Glycerolipids	Triacylglycerols	0.73 (0.36-1.51)	0.397
C60:12 TAG	HMDB0005478*	Glycerolipids	Triacylglycerols	0.75 (0.36-1.54)	0.431
C50:6 TAG	HMDB0010497*	Glycerolipids	Triacylglycerols	0.76 (0.38-1.52)	0.433
C54:6 TAG	HMDB0005391*	Glycerolipids	Triacylglycerols	0.8 (0.4-1.61)	0.528
C50:0 TAG	HMDB0005357*	Glycerolipids	Triacylglycerols	0.82 (0.4-1.69)	0.594
C50:5 TAG	HMDB0010471*	Glycerolipids	Triacylglycerols	0.83 (0.41-1.67)	0.594
C52:1 TAG	HMDB0005367*	Glycerolipids	Triacylglycerols	0.83 (0.41-1.7)	0.614
C54:3 TAG	HMDB0005405*	Glycerolipids	Triacylglycerols	1.21 (0.58-2.49)	0.614
C55:2 TAG	HMDB0042226*	Glycerolipids	Triacylglycerols	1.19 (0.6-2.38)	0.62
C50:2 TAG	HMDB0005377*	Glycerolipids	Triacylglycerols	0.84 (0.41-1.7)	0.627
C55:3 TAG	HMDB0042466*	Glycerolipids	Triacylglycerols	1.18 (0.57-2.43)	0.649
C52:0 TAG	HMDB0005365*	Glycerolipids	Triacylglycerols	0.86 (0.42-1.74)	0.668
C56:3 TAG	HMDB0005410*	Glycerolipids	Triacylglycerols	1.15 (0.58-2.28)	0.677

Supplemental Table 1.4b (continued).

C43:2 TAG	HMDB0043169*	Glycerolipids	Triacylglycerols	0.87 (0.43-1.73)	0.683
C56:2 TAG	HMDB0005404*	Glycerolipids	Triacylglycerols	1.14 (0.58-2.23)	0.7
C51:0 TAG	HMDB0031106*	Glycerolipids	Triacylglycerols	0.88 (0.44-1.78)	0.717
C54:5 TAG	HMDB0005385*	Glycerolipids	Triacylglycerols	0.88 (0.43-1.79)	0.721
C56:4 TAG	HMDB0005398*	Glycerolipids	Triacylglycerols	0.88 (0.44-1.79)	0.733
C52:2 TAG	HMDB0005369*	Glycerolipids	Triacylglycerols	0.9 (0.43-1.84)	0.769
C50:1 TAG	HMDB0005360*	Glycerolipids	Triacylglycerols	0.9 (0.44-1.84)	0.778
C46:1 TAG	HMDB0010412*	Glycerolipids	Triacylglycerols	1.1 (0.55-2.21)	0.781
C47:1 TAG	HMDB0042100*	Glycerolipids	Triacylglycerols	1.1 (0.55-2.2)	0.788
C51:1 TAG	HMDB0042104*	Glycerolipids	Triacylglycerols	0.91 (0.44-1.86)	0.79
C54:4 TAG	HMDB0005370*	Glycerolipids	Triacylglycerols	1.08 (0.53-2.2)	0.823
C48:2 TAG	HMDB0005376*	Glycerolipids	Triacylglycerols	1.08 (0.53-2.18)	0.836
C49:1 TAG	HMDB0011705*	Glycerolipids	Triacylglycerols	1.07 (0.54-2.12)	0.841
C48:0 TAG	HMDB0005356*	Glycerolipids	Triacylglycerols	0.94 (0.46-1.91)	0.855
C53:3 TAG	HMDB0043058*	Glycerolipids	Triacylglycerols	0.94 (0.46-1.92)	0.871
C54:1 TAG	HMDB0005395*	Glycerolipids	Triacylglycerols	0.95 (0.47-1.89)	0.875
C43:1 TAG	HMDB0042098*	Glycerolipids	Triacylglycerols	0.95 (0.48-1.89)	0.884
C51:3 TAG	HMDB0011701*	Glycerolipids	Triacylglycerols	1.05 (0.51-2.17)	0.886

Supplemental Table 1.4b (continued).

C45:2 TAG	HMDB0043170*	Glycerolipids	Triacylglycerols	0.96 (0.48-1.89)	0.896
C48:3 TAG	HMDB0005432*	Glycerolipids	Triacylglycerols	1.04 (0.52-2.09)	0.902
C47:2 TAG	HMDB0042076*	Glycerolipids	Triacylglycerols	1.04 (0.52-2.08)	0.906
C45:1 TAG	HMDB0042099*	Glycerolipids	Triacylglycerols	0.97 (0.49-1.93)	0.936
C46:2 TAG	HMDB0010419*	Glycerolipids	Triacylglycerols	1.03 (0.52-2.03)	0.94
C52:4 TAG	HMDB0005363*	Glycerolipids	Triacylglycerols	1.02 (0.5-2.06)	0.959
C50:3 TAG	HMDB0005433*	Glycerolipids	Triacylglycerols	1.02 (0.5-2.07)	0.959
C49:2 TAG	HMDB0011706*	Glycerolipids	Triacylglycerols	1.02 (0.5-2.05)	0.961
C54:2 TAG	HMDB0005403*	Glycerolipids	Triacylglycerols	0.98 (0.49-1.98)	0.964
C44:0 TAG	HMDB0042063*	Glycerolipids	Triacylglycerols	1.02 (0.51-2.03)	0.964
C49:3 TAG	HMDB0042103*	Glycerolipids	Triacylglycerols	1.01 (0.5-2.06)	0.971
C51:2 TAG	HMDB0005362*	Glycerolipids	Triacylglycerols	0.99 (0.49-2.01)	0.976
C53:2 TAG	HMDB0042196*	Glycerolipids	Triacylglycerols	1.01 (0.48-2.1)	0.983
C43:0 TAG	HMDB0042062*	Glycerolipids	Triacylglycerols	1.01 (0.5-2.02)	0.989
C56:1 TAG	HMDB0005396*	Glycerolipids	Triacylglycerols	1 (0.5-1.99)	0.991
C46:0 TAG	HMDB0010411*	Glycerolipids	Triacylglycerols	1 (0.5-2.02)	0.998
C48:1 TAG	HMDB0005359*	Glycerolipids	Triacylglycerols	1 (0.5-2.01)	0.999
C22:5 LPC	HMDB0010403*	Glycerophospholipids	Glycerophospho-cholines	1.82 (0.89-3.74)	0.1
C18:1 LPC	HMDB0002815*	Glycerophospholipids	Glycerophospho-cholines	1.76 (0.88-3.54)	0.108
C22:6 LPC	HMDB0010404	Glycerophospholipids	Glycerophospho-cholines	1.72 (0.84-3.53)	0.137

Supplemental Table 1.4b (continued).

C18:0 LPC	HMDB0010384	Glycerophospholipids	Glycerophospho-cholines	1.66 (0.83-3.32)	0.15
C18:2 LPC	HMDB0010386*	Glycerophospholipids	Glycerophospho-cholines	1.66 (0.82-3.41)	0.158
C20:5 LPC	HMDB0010397	Glycerophospholipids	Glycerophospho-cholines	1.65 (0.82-3.38)	0.162
C16:0 LPC	HMDB0010382	Glycerophospholipids	Glycerophospho-cholines	1.58 (0.79-3.18)	0.199
C36:2 PC plasmalogen	HMDB0011243*	Glycerophospholipids	Glycerophospho-cholines	1.56 (0.77-3.21)	0.221
C34:1 PC plasmalogen	HMDB0011208*	Glycerophospholipids	Glycerophospho-cholines	1.49 (0.74-3.05)	0.269
C34:1 PC plasmalogen-B	HMDB0011239*	Glycerophospholipids	Glycerophospho-cholines	1.45 (0.71-2.97)	0.307
C18:3 LPC	HMDB0010387*	Glycerophospholipids	Glycerophospho-cholines	1.39 (0.7-2.79)	0.35
C36:4 PC plasmalogen	HMDB0011310*	Glycerophospholipids	Glycerophospho-cholines	1.4 (0.69-2.89)	0.354
C38:3 PC	HMDB0008047*	Glycerophospholipids	Glycerophospho-cholines	0.74 (0.36-1.52)	0.411
C32:1 PC	HMDB0007873*	Glycerophospholipids	Glycerophospho-cholines	0.76 (0.38-1.51)	0.442
C14:0 LPC	HMDB0010379	Glycerophospholipids	Glycerophospho-cholines	1.31 (0.65-2.66)	0.448
C38:4 PC plasmalogen	HMDB0011252*	Glycerophospholipids	Glycerophospho-cholines	1.29 (0.64-2.58)	0.474
C38:7 PC plasmalogen	HMDB0011229*	Glycerophospholipids	Glycerophospho-cholines	1.28 (0.65-2.56)	0.476
C16:1 LPC	HMDB0010383*	Glycerophospholipids	Glycerophospho-cholines	1.27 (0.63-2.57)	0.497
C32:0 PC	HMDB0007871*	Glycerophospholipids	Glycerophospho-cholines	1.26 (0.64-2.49)	0.509

Supplemental Table 1.4b (continued).

C36:4 PC-B	HMDB0008138*	Glycerophospholipids	Glycerophospho-cholines	0.8 (0.4-1.57)	0.512
C34:3 PC plasmalogen	HMDB0011211*	Glycerophospholipids	Glycerophospho-cholines	1.27 (0.61-2.63)	0.523
C34:1 PC	HMDB0007972*	Glycerophospholipids	Glycerophospho-cholines	0.89 (0.45-1.72)	0.72
C40:9 PC	HMDB0008731*	Glycerophospholipids	Glycerophospho-cholines	0.88 (0.44-1.77)	0.722
C30:0 PC	HMDB0007869*	Glycerophospholipids	Glycerophospho-cholines	1.12 (0.57-2.22)	0.74
C36:1 PC	HMDB0008038*	Glycerophospholipids	Glycerophospho-cholines	0.9 (0.46-1.77)	0.76
C36:5 PC plasmalogen-B	HMDB0011220*	Glycerophospholipids	Glycerophospho-cholines	1.1 (0.55-2.2)	0.793
C40:10 PC	HMDB0008511*	Glycerophospholipids	Glycerophospho-cholines	1.09 (0.54-2.23)	0.807
C36:5 PC plasmalogen-A	HMDB0011221*	Glycerophospholipids	Glycerophospho-cholines	0.93 (0.45-1.9)	0.835
C30:1 PC	HMDB0007870*	Glycerophospholipids	Glycerophospho-cholines	0.95 (0.48-1.89)	0.88
C32:2 PC	HMDB0007874*	Glycerophospholipids	Glycerophosphocho lines	0.97 (0.48-1.95)	0.924
C38:6 PC	HMDB0007991*	Glycerophospholipids	Glycerophosphocho lines	1.02 (0.51-2.05)	0.958
C40:6 PC	HMDB0008057*	Glycerophospholipids	Glycerophosphocho lines	1.01 (0.51-2.02)	0.97
C22:0 LPE	HMDB0011520	Glycerophospholipids	Glycerophospho-ethanolamines	2.39 (1.16-5.01)	0.018
C36:4 PE	HMDB0008937*	Glycerophospholipids	Glycerophospho-ethanolamines	0.56 (0.28-1.1)	0.093
C38:4 PE	HMDB0009003*	Glycerophospholipids	Glycerophospho-ethanolamines	0.57 (0.28-1.11)	0.1

Supplemental Table 1.4b (continued).

C38:5 PE	HMDB0009069*	Glycerophospholipids	Glycerophospho-ethanolamines	0.6 (0.3-1.19)	0.144
C38:6 PE	HMDB0009102*	Glycerophospholipids	Glycerophospho-ethanolamines	0.61 (0.31-1.21)	0.162
C40:6 PE	HMDB0009012*	Glycerophospholipids	Glycerophospho-ethanolamines	0.64 (0.32-1.26)	0.195
C40:7 PE plasmalogen	HMDB0011394*	Glycerophospholipids	Glycerophospho-ethanolamines	1.59 (0.79-3.24)	0.195
C36:4 PE plasmalogen	HMDB0011442*	Glycerophospholipids	Glycerophospho-ethanolamines	1.56 (0.76-3.23)	0.228
C36:2 PE plasmalogen	HMDB0009082*	Glycerophospholipids	Glycerophospho-ethanolamines	1.56 (0.75-3.25)	0.231
C38:2 PE	HMDB0008942*	Glycerophospholipids	Glycerophospho-ethanolamines	1.56 (0.75-3.26)	0.234
C34:2 PE	HMDB0008928*	Glycerophospholipids	Glycerophospho-ethanolamines	0.66 (0.33-1.32)	0.242
C18:1 LPE	HMDB0011506*	Glycerophospholipids	Glycerophospho-ethanolamines	1.49 (0.76-2.94)	0.246
C36:3 PE plasmalogen	HMDB0011441*	Glycerophospholipids	Glycerophospho-ethanolamines	1.43 (0.7-2.94)	0.333
C34:2 PE plasmalogen	HMDB0008952*	Glycerophospholipids	Glycerophospho-ethanolamines	1.42 (0.7-2.9)	0.336
C36:2 PE	HMDB0008994*	Glycerophospholipids	Glycerophospho-ethanolamines	0.72 (0.36-1.44)	0.348
C34:3 PE plasmalogen	HMDB0011343*	Glycerophospholipids	Glycerophospho-ethanolamines	1.4 (0.69-2.87)	0.351
C36:5 PE plasmalogen	HMDB0011410*	Glycerophospholipids	Glycerophospho-ethanolamines	1.33 (0.66-2.73)	0.427
C38:5 PE plasmalogen	HMDB0011386*	Glycerophospholipids	Glycerophospho-ethanolamines	1.32 (0.65-2.7)	0.445
C36:3 PE	HMDB0009060*	Glycerophospholipids	Glycerophospho-ethanolamines	0.76 (0.38-1.55)	0.455

Supplemental Table 1.4b (continued).

C38:6 PE plasmalogen	HMDB0011387*	Glycerophospholipids	Glycerophospho-ethanolamines	1.31 (0.64-2.7)	0.455
C38:7 PE plasmalogen	HMDB0011420*	Glycerophospholipids	Glycerophospho-ethanolamines	1.25 (0.62-2.55)	0.532
C18:0 LPE	HMDB0011130	Glycerophospholipids	Glycerophospho-ethanolamines	1.15 (0.57-2.28)	0.699
C36:1 PE plasmalogen	HMDB0009016*	Glycerophospholipids	Glycerophospho-ethanolamines	1.14 (0.55-2.35)	0.722
C36:0 PE	HMDB0008991*	Glycerophospholipids	Glycerophospho-ethanolamines	1.13 (0.57-2.23)	0.725
C18:2 LPE	HMDB0011507*	Glycerophospholipids	Glycerophospho-ethanolamines	1.1 (0.54-2.22)	0.799
C36:1 PE	HMDB0008993*	Glycerophospholipids	Glycerophospho-ethanolamines	0.92 (0.46-1.85)	0.807
C16:0 LPE	HMDB0011503	Glycerophospholipids	Glycerophospho-ethanolamines	1.09 (0.55-2.18)	0.807
C34:0 PE	HMDB0008925*	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.49-1.88)	0.906
C20:4 LPE	HMDB0011517	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.48-1.92)	0.915
C32:0 PE	HMDB0008923*	Glycerophospholipids	Glycerophospho-ethanolamines	1.04 (0.52-2.06)	0.917
C22:6 LPE	HMDB0011526	Glycerophospholipids	Glycerophospho-ethanolamines	0.99 (0.48-2.05)	0.983
C38:4 PI	HMDB0009815*	Glycerophospholipids	Glycerophospho-inositols	1.21 (0.59-2.48)	0.607
C34:0 PS	HMDB0012356*	Glycerophospholipids	Glycerophospho-serines	0.7 (0.34-1.43)	0.331
1,7-dimethyluric acid	HMDB0011103	Imidazopyrimidines	Purines and purine derivatives	0.76 (0.37-1.55)	0.445
1-methylguanine	HMDB0003282	Imidazopyrimidines	Purines and purine derivatives	0.77 (0.38-1.58)	0.48

Supplemental Table 1.4b (continued).

uric acid	HMDB0000289	Imidazopyrimidines	Purines and purine derivatives	0.78 (0.36-1.68)	0.523
caffeine	HMDB0001847	Imidazopyrimidines	Purines and purine derivatives	0.84 (0.4-1.75)	0.64
7-methylguanine	HMDB0000897	Imidazopyrimidines	Purines and purine derivatives	1.18 (0.57-2.42)	0.657
7-methylxanthine	HMDB0001991	Imidazopyrimidines	Purines and purine derivatives	1.07 (0.54-2.15)	0.841
3-methylxanthine	HMDB0001886	Imidazopyrimidines	Purines and purine derivatives	0.94 (0.47-1.88)	0.855
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	0.98 (0.49-1.97)	0.956
serotonin	HMDB0000259	Indoles and derivatives	Tryptamines and derivatives	0.79 (0.4-1.57)	0.503
deoxyguanosine	HMDB0000085	NA	NA	0.47 (0.23-0.98)	0.043
methyl N-methylanthranilate	HMDB0034169	NA	NA	0.5 (0.25-0.98)	0.045
trigonelline	HMDB0000875	NA	NA	0.57 (0.28-1.14)	0.113
piperine	HMDB0029377	NA	NA	1.71 (0.82-3.58)	0.154
C20:1 LPC	HMDB0010391*	NA	NA	0.64 (0.31-1.29)	0.212
C20:1 LPE	HMDB0011512*	NA	NA	1.53 (0.76-3.1)	0.235
C18:3 LPE	HMDB0011478*	NA	NA	0.67 (0.33-1.36)	0.27
coenzyme Q10	HMDB0001072	NA	NA	1.42 (0.72-2.8)	0.308
C34:5 PC plasmalogen	HMDB0011214*	NA	NA	1.37 (0.65-2.9)	0.406
C34:4 PC	HMDB0007883*	NA	NA	0.75 (0.37-1.52)	0.431

Supplemental Table 1.4b (continued).

C20:4 LPC	HMDB0010395	NA	NA	1.32 (0.66-2.62)	0.434
DMGV	HMDB0240212	NA	NA	0.73 (0.32-1.65)	0.446
C36:3 PC plasmalogen	HMDB0011244*	NA	NA	1.25 (0.6-2.6)	0.55
thyroxine	HMDB0000248	NA	NA	1.17 (0.58-2.35)	0.665
cerulenin	HMDB0015168	NA	NA	1.17 (0.57-2.41)	0.669
C34:2 PC plasmalogen	HMDB0011210*	NA	NA	1.04 (0.5-2.17)	0.91
2-methyl-4,5-benzoxazole	HMDB0032390	NA	NA	1.01 (0.51-1.98)	0.981
pseudouridine	HMDB0000767	Nucleoside and nucleotide analogues	NA	1.34 (0.64-2.84)	0.44
N-carbamoyl-beta-alanine	HMDB0000026	Organic carbonic acids and derivatives	Ureas	1.06 (0.52-2.19)	0.866
1-methylhistamine	HMDB0000898	Organonitrogen compounds	Amines	0.77 (0.39-1.51)	0.451
trimethylamine-N-oxide	HMDB0000925	Organonitrogen compounds	Aminoxides	1.18 (0.59-2.33)	0.637
metformin	HMDB0001921	Organonitrogen compounds	Guanidines	0.83 (0.41-1.66)	0.599
carnitine	HMDB0000062	Organonitrogen compounds	Quaternary ammonium salts	1.42 (0.71-2.87)	0.323
phosphocholine	HMDB0001565	Organonitrogen compounds	Quaternary ammonium salts	0.84 (0.4-1.73)	0.628
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	1.86 (0.89-3.92)	0.099

Supplemental Table 1.4b (continued).

4-hydroxy-3-methylacetophenone	HMDB0059824	Organooxygen compounds	Carbonyl compounds	0.87 (0.44-1.74)	0.697
acetaminophen	HMDB0001859	Phenols	1-hydroxy-2-unsubstituted benzenoids	0.62 (0.31-1.24)	0.179
guanosine	HMDB0000133	Purine nucleosides	NA	0.71 (0.35-1.42)	0.332
N2,N2-dimethylguanosine	HMDB0004824	Purine nucleosides	NA	1.31 (0.61-2.82)	0.487
1-methylguanosine	HMDB0001563	Purine nucleosides	NA	0.84 (0.4-1.75)	0.65
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	1.03 (0.5-2.12)	0.938
N1-methyl-2-pyridone-5-carboxamide	HMDB0004193	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	1.18 (0.56-2.49)	0.667
1-methylnicotinamide	HMDB0000699	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	1.04 (0.5-2.15)	0.912
pyridoxamine	HMDB0001431	Pyridines and derivatives	Pyridoxamines	1.51 (0.74-3.11)	0.256
cotinine	HMDB0001046	Pyridines and derivatives	Pyrrolidinylpyridines	1.09 (0.53-2.22)	0.821
ribothymidine	HMDB0000884	Pyrimidine nucleosides	NA	1.39 (0.7-2.79)	0.349
N4-acetylcytidine	HMDB0005923	Pyrimidine nucleosides	NA	0.99 (0.48-2.03)	0.975
kynurenic acid	HMDB0000715	Quinolines and derivatives	Quinoline carboxylic acids	2.14 (1.03-4.5)	0.041
C16:0 Ceramide (d18:1)	HMDB0004949	Sphingolipids	Ceramides	1.89 (0.95-3.82)	0.071
C24:0 Ceramide (d18:1)	HMDB0004956	Sphingolipids	Ceramides	1.62 (0.8-3.26)	0.177

Supplemental Table 1.4b (continued).

C22:0 Ceramide (d18:1)	HMDB0004952	Sphingolipids	Ceramides	1.28 (0.63-2.59)	0.488
C24:1 Ceramide (d18:1)	HMDB0004953*	Sphingolipids	Ceramides	1.26 (0.61-2.6)	0.533
C22:1 SM	HMDB0012104*	Sphingolipids	Phosphosphingo-lipids	1.11 (0.55-2.26)	0.775
C14:0 SM	HMDB0012097	Sphingolipids	Phosphosphingo-lipids	1.04 (0.52-2.11)	0.903
glycocholate	HMDB0000138	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.73 (0.86-3.53)	0.126
glycodeoxycholate/glycochenodeoxycholate	HMDB0000631*	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.69 (0.83-3.49)	0.15
cholesterol	HMDB0000067	Steroids and steroid derivatives	Cholestane steroids	1.28 (0.65-2.53)	0.472
campesterol	HMDB0002869	Steroids and steroid derivatives	Ergostane steroids	1.46 (0.74-2.92)	0.277
cortisol	HMDB0000063	Steroids and steroid derivatives	Hydroxysteroids	1.27 (0.6-2.69)	0.537
cortisone	HMDB0002802	Steroids and steroid derivatives	Hydroxysteroids	0.94 (0.45-1.95)	0.874
21-deoxycortisol	HMDB0004030	Steroids and steroid derivatives	Pregnane steroids	1.54 (0.74-3.21)	0.246
C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesteryl esters	1.91 (0.93-3.99)	0.077
C16:1 CE	HMDB0000658*	Steroids and steroid derivatives	Cholesteryl esters	0.71 (0.35-1.4)	0.323
C14:0 CE	HMDB0006725	Steroids and steroid derivatives	Cholesteryl esters	1.44 (0.68-3.11)	0.34
C22:6 CE	HMDB0006733	Steroids and steroid derivatives	Cholesteryl esters	1.31 (0.66-2.61)	0.441
C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesteryl esters	0.78 (0.39-1.59)	0.498

Supplemental Table 1.4b (continued).

C18:2 CE	HMDB0000610*	Steroids and steroid derivatives	Cholesteryl esters	1.21 (0.6-2.46)	0.598
C18:1 CE	HMDB0000918*	Steroids and steroid derivatives	Cholesteryl esters	1.17 (0.57-2.45)	0.671
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesteryl esters	0.87 (0.44-1.7)	0.675
C20:3 CE	HMDB0006736*	Steroids and steroid derivatives	Cholesteryl esters	0.89 (0.45-1.76)	0.743
C16:0 CE	HMDB0000885	Steroids and steroid derivatives	Cholesteryl esters	1.1 (0.55-2.25)	0.784
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesteryl esters	1.08 (0.56-2.1)	0.814
C20:4 CE	HMDB0006726	Steroids and steroid derivatives	Cholesteryl esters	0.99 (0.5-1.96)	0.974
bilirubin	HMDB0000054	Tetrapyrroles and derivatives	Bilirubins	0.81 (0.4-1.62)	0.548
biliverdin	HMDB0001008	Tetrapyrroles and derivatives	Bilirubins	0.9 (0.44-1.81)	0.759

**Includes metabolites with <10% missingness. Missing values were imputed with 1/2 the minimum value. Results sorted by class, subclass, and p-value for fully adjusted models.
^Multivariable model includes BMI at age 18, weight change from 18 to blood draw, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).
*Representative HMDBID

Supplemental Table 1.5a. Metabolite set enrichment analysis for subclasses of metabolites, distant blood.

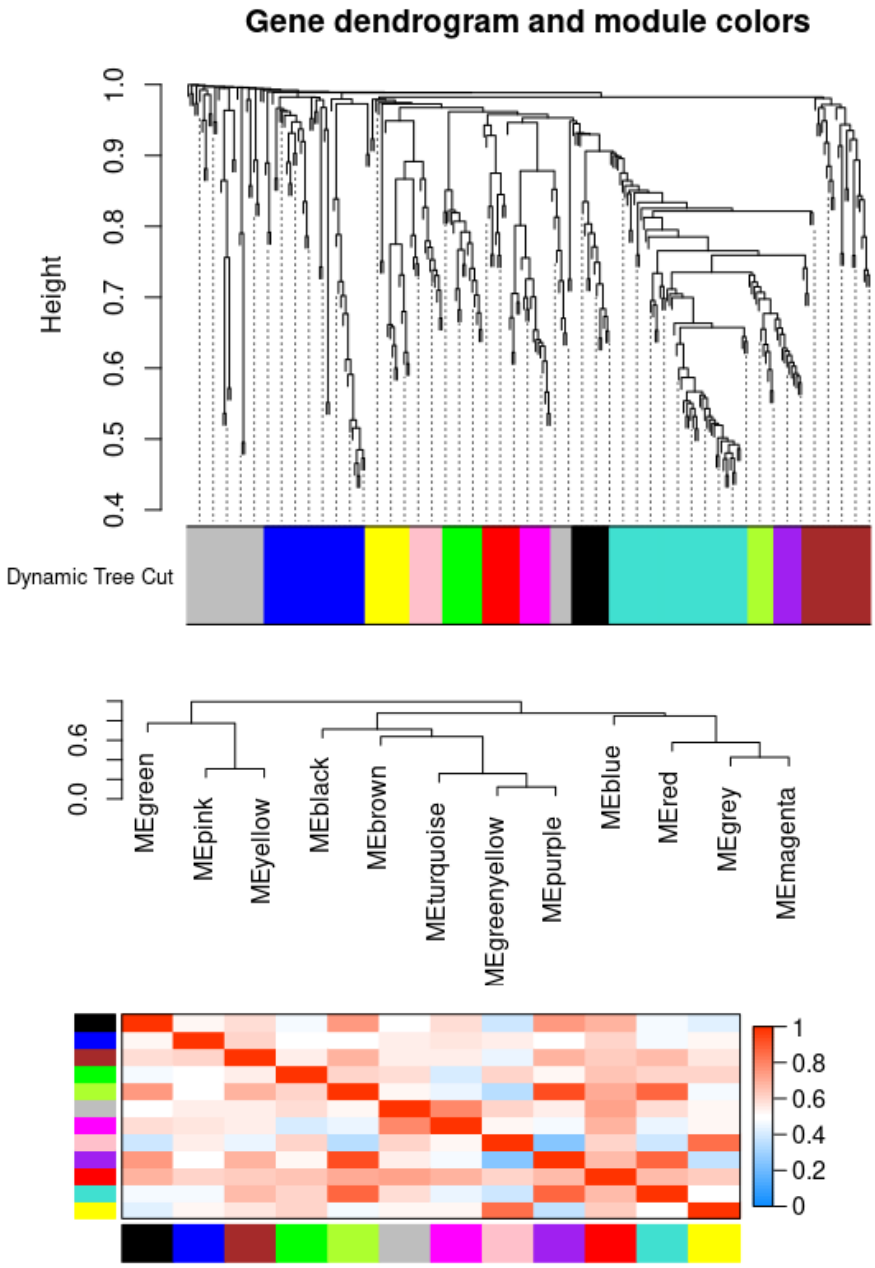
Pathway	Enrichment Score	Normalized enrichment score	P value adj.*	Size of pathway
Cholesteryl esters	-0.83	-2.26	0.02	12
Triacylglycerols (<3 DB)	0.76	2.57	0.02	32
Fatty acid esters	-0.59	-1.86	0.03	19
Glycerophosphocholines	-0.39	-1.43	0.17	32
Diacylglycerols	0.68	1.60	0.17	8
Glycerophospho-ethanolamines	-0.38	-1.40	0.17	33
Glycerophospholipids	-0.64	-1.45	0.22	6
Amino acids, peptides, and analogues	0.29	1.07	0.56	45
Ceramides	0.64	1.18	0.56	4
Lineolic acids and derivatives	0.62	1.15	0.56	4
Purine nucleosides	0.48	0.90	0.84	4
Imidazoles	-0.43	-0.77	0.84	3
Carboximidic acids	0.43	0.79	0.84	4
Triacylglycerols (>=3 DB)	0.24	0.82	0.84	33
Quaternary ammonium salts	-0.26	-0.46	1.00	3
Purines and purine derivatives	-0.25	-0.59	1.00	7

*FDR corrected p-value based on number of pathways. Models fully adjusted for covariates included in conditional logistic regression models.

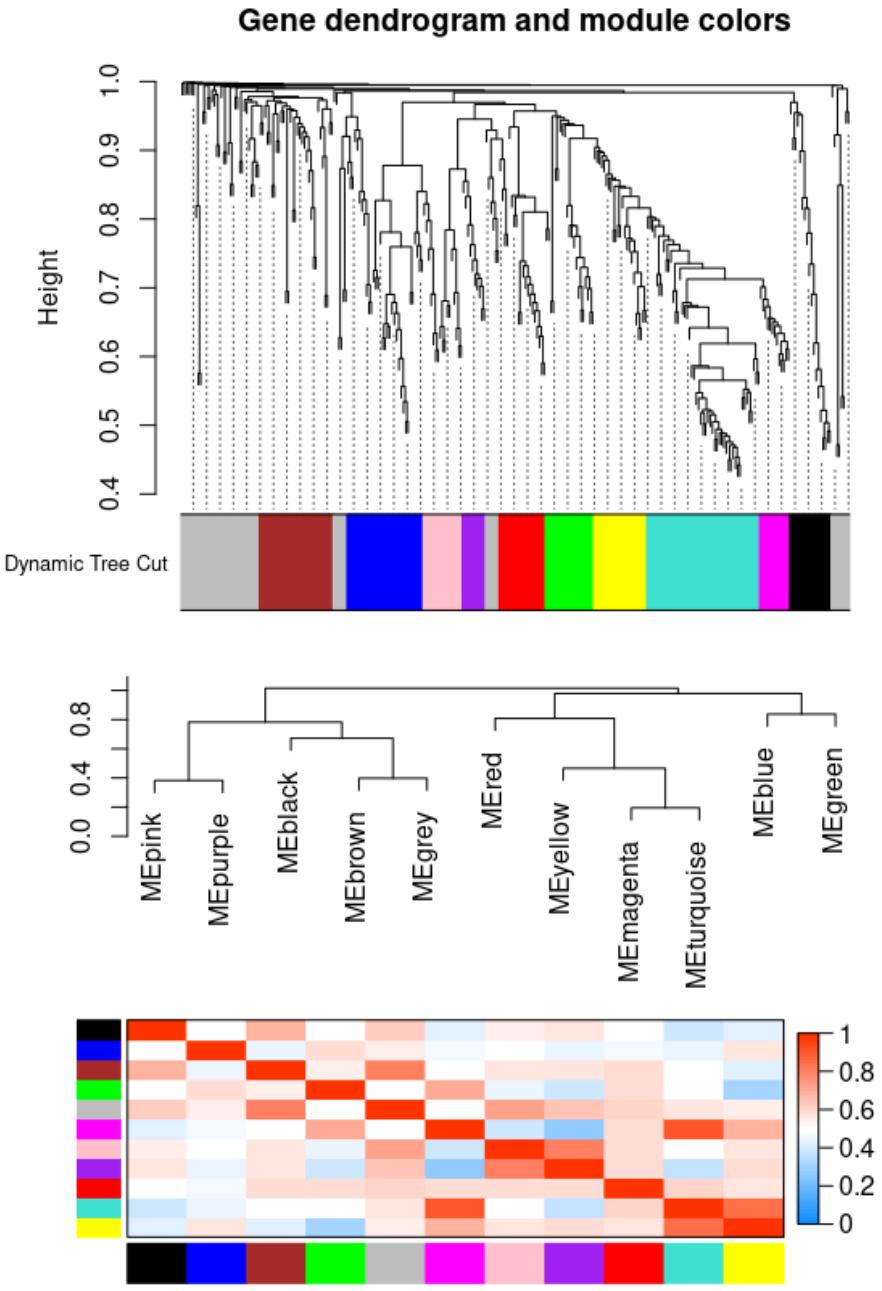
Supplemental Table 1.5b. Metabolite set enrichment analysis for subclasses of metabolites, proximate blood.

Pathway	Enrichment Score	Normalized enrichment score	P value adj.*	Size of pathway
Amino acids	0.51	1.78	0.02	45
Triacylglycerols (>=3 DB)	-0.80	-2.91	0.03	33
Ceramides	0.82	1.50	0.11	4
Triacylglycerols (<3 DB)	0.49	1.59	0.11	32
Diacylglycerols	0.60	1.36	0.38	8
Carboximidic acids	0.65	1.18	0.69	4
Quaternary ammonium salts	0.51	0.86	0.91	3
Purine nucleosides	0.50	0.91	0.91	4
Fatty acid esters	0.29	0.81	0.91	19
Purines and purine derivatives	-0.39	-0.93	0.91	7
Imidazoles	0.47	0.78	0.91	3
Lineolic acids and derivatives	-0.47	-0.92	0.91	4
Glycerophospholipids	-0.33	-0.74	0.91	6
Glycerophospho-ethanolamines	-0.24	-0.86	0.91	33
Glycerophosphocholines	0.22	0.72	0.92	32
Cholesteryl esters	-0.19	-0.52	0.99	12

*FDR corrected p-value based on number of pathways. Models fully adjusted for covariates included in conditional logistic regression models.



Supplemental Figure 1.1a. WGCNA dendogram (a) and eigengene network correlations (b) for distant blood



Supplemental Figure 1.1b. WGCNA dendogram (a) and eigengene network correlations (b) for proximate blood

Supplemental Table 1.6. Assigned modules for metabolites at distant and proximate blood, assessed via WGCNA.

Time 1			Time 2		
Metabolite Name	**Subclass**	**Module**	**Metabolite Name**	**Subclass**	**Module**
cortisol	Hydroxysteroids	M1	1-methylhistidine	Amino acids, peptides, and analogues	M1
deoxyguanosine	NA	M1	carnitine	Quaternary ammonium salts	M1
guanosine	NA	M1	cortisol	Hydroxysteroids	M1
glycocholate	Bile acids, alcohol and derivatives	M1	creatine	Amino acids, peptides, and analogues	M1
serotonin	Tryptamines and derivatives	M1	cholesterol	Cholestane steroids	M1
urocanic acid	Imidazoles	M1	deoxyguanosine	NA	M1
glycodeoxycholate/glycochenodeoxycholate	Bile acids, alcohol and derivatives	M1	guanosine	NA	M1
hippurate	Benzoic acids and derivatives	M1	lysine	Amino acids, peptides, and analogues	M1
trigonelline	NA	M1	pantothenate	Amino acids, peptides, and analogues	M1
1-methylhistamine	Amines	M1	thyroxine	NA	M1
trimethylamine-N-oxide	Aminoxides	M1	serotonin	Tryptamines and derivatives	M1
cotinine	Pyrrolidinylpyridines	M1	urocanic acid	Imidazoles	M1
phosphocholine	Quaternary ammonium salts	M1	homoarginine	Amino acids, peptides, and analogues	M1
caffeine	Purines and purine derivatives	M1	C5 carnitine	Fatty acid esters	M1
acetaminophen	1-hydroxy-2-unsubstituted benzenoids	M1	1-methylnicotinamide	Pyridinecarboxylic acids and derivatives	M1

Supplemental Table 1.6 (continued).

3-methylxanthine	Purines and purine derivatives	M1	hippurate	Benzoic acids and derivatives	M1
metformin	Guanidines	M1	hydroxyproline	Amino acids, peptides, and analogues	M1
7-methylxanthine	Purines and purine derivatives	M1	C3 carnitine	Fatty acid esters	M1
myristoleic acid	Fatty acids and conjugates	M1	trigonelline	NA	M1
palmitoylethanolamide	Carboximidic acids	M1	1-methylhistamine	Amines	M1
cortisone	Hydroxysteroids	M1	2-aminooctanoic acid	Amino acids, peptides, and analogues	M1
N-acetylornithine	Amino acids, peptides, and analogues	M1	cotinine	Pyrrolidinylpyridines	M1
21-deoxycortisol	Pregnane steroids	M1	pyridoxamine	Pyridoxamines	M1
proline betaine	Amino acids, peptides, and analogues	M1	phosphocholine	Quaternary ammonium salts	M1
phenylacetylglutamine	Amino acids, peptides, and analogues	M1	caffeine	Purines and purine derivatives	M1
C38:6 PC	Glycerophosphocholines	M1	acetaminophen	1-hydroxy-2-unsubstituted benzenoids	M1
C40:6 PC	Glycerophosphocholines	M1	3-methylxanthine	Purines and purine derivatives	M1
C40:10 PC	Glycerophosphocholines	M1	metformin	Guanidines	M1
C40:9 PC	Glycerophosphocholines	M1	7-methylxanthine	Purines and purine derivatives	M1
C22:6 LPC	Glycerophosphocholines	M1	myristoleic acid	Fatty acids and conjugates	M1
1,7-dimethyluric acid	Purines and purine derivatives	M1	C4 carnitine	Fatty acid esters	M1
C22:6 LPE	Glycerophospho-ethanolamines	M1	palmitoylethanolamide	Carboximidic acids	M1
C34:0 PS	Glycerophosphoserines	M1	C5:1 carnitine	Fatty acid esters	M1
N-lauroylglycine	Amino acids, peptides, and analogues	M1	cortisone	Hydroxysteroids	M1

Supplemental Table 1.6 (continued).

4-hydroxyhippurate	Benzoic acids and derivatives	M1	campesterol	Ergostane steroids	M1
valsartan	NA	M1	N-acetylornithine	Amino acids, peptides, and analogues	M1
metronidazole	Imidazoles	M1	21-deoxycortisol	Pregnane steroids	M1
sulfamethoxazole	Benzenesulfonamides	M1	N1-methyl-2-pyridone-5-carboxamide	Pyridinecarboxylic acids and derivatives	M1
piperine	NA	M1	proline betaine	Amino acids, peptides, and analogues	M1
2-methyl-4,5-benzoxazole	NA	M1	phenylacetylglutamine	Amino acids, peptides, and analogues	M1
methyl N-methylanthranilate	NA	M1	C26 carnitine	Fatty acid esters	M1
4-hydroxy-3-methylacetophenone	Carbonyl compounds	M1	C20:1 LPC	NA	M1
betaine	Amino acids, peptides, and analogues	M2	1,7-dimethyluric acid	Purines and purine derivatives	M1
alanine	Amino acids, peptides, and analogues	M2	C14:0 SM	Phosphosphingolipids	M1
proline	Amino acids, peptides, and analogues	M2	C22:1 SM	Phosphosphingolipids	M1
serine	Amino acids, peptides, and analogues	M2	N-lauroylglycine	Amino acids, peptides, and analogues	M1
coenzyme Q10	NA	M2	4-hydroxyhippurate	Benzoic acids and derivatives	M1
C24:1 Ceramide (d18:1)	Ceramides	M2	metronidazole	Imidazoles	M1
C48:0 TAG	Triacylglycerols	M2	sulfamethoxazole	Benzenesulfonamides	M1
C50:0 TAG	Triacylglycerols	M2	piperine	NA	M1
C48:1 TAG	Triacylglycerols	M2	NMMA	Amino acids, peptides, and analogues	M1

Supplemental Table 1.6 (continued).

C50:1 TAG	Triacylglycerols	M2	2-methyl-4,5-benzoxazole	NA	M1
C51:2 TAG	Triacylglycerols	M2	methyl N-methylanthranilate	NA	M1
C52:0 TAG	Triacylglycerols	M2	4-hydroxy-3-methylacetophenone	Carbonyl compounds	M1
C52:1 TAG	Triacylglycerols	M2	C48:0 TAG	Triacylglycerols	M2
C48:2 TAG	Triacylglycerols	M2	C50:0 TAG	Triacylglycerols	M2
C50:2 TAG	Triacylglycerols	M2	C48:1 TAG	Triacylglycerols	M2
C48:3 TAG	Triacylglycerols	M2	C50:1 TAG	Triacylglycerols	M2
C32:0 DAG	Diacylglycerols	M2	C51:2 TAG	Triacylglycerols	M2
C34:0 DAG	Diacylglycerols	M2	C52:0 TAG	Triacylglycerols	M2
C30:0 PC	Glycerophosphocholines	M2	C52:1 TAG	Triacylglycerols	M2
C30:1 PC	Glycerophosphocholines	M2	C48:2 TAG	Triacylglycerols	M2
C32:0 PC	Glycerophosphocholines	M2	C50:2 TAG	Triacylglycerols	M2
C32:1 PC	Glycerophosphocholines	M2	C54:1 TAG	Triacylglycerols	M2
C32:2 PC	Glycerophosphocholines	M2	C56:1 TAG	Triacylglycerols	M2
C34:4 PC	NA	M2	C56:2 TAG	Triacylglycerols	M2
C34:1 PC	Glycerophosphocholines	M2	C56:3 TAG	Triacylglycerols	M2
C36:1 PC	Glycerophosphocholines	M2	C48:3 TAG	Triacylglycerols	M2
C38:3 PC	Glycerophosphocholines	M2	C22:6 CE	Cholesteryl esters	M2
C36:4 PC-B	Glycerophosphocholines	M2	C32:0 DAG	Diacylglycerols	M2
C32:0 PE	Glycerophospho-ethanolamines	M2	C34:0 DAG	Diacylglycerols	M2
C34:0 PE	Glycerophospho-ethanolamines	M2	C38:5 DAG	Diacylglycerols	M2
C34:2 PE	Glycerophospho-ethanolamines	M2	C36:1 DAG	Diacylglycerols	M2
C36:4 PE	Glycerophospho-ethanolamines	M2	C38:3 PC	Glycerophosphocholines	M2
C36:0 PE	Glycerophospho-ethanolamines	M2	C34:2 PE	Glycerophospho-ethanolamines	M2

Supplemental Table 1.6 (continued).

C36:1 PE	Glycerophospho-ethanolamines	M2	C36:4 PE	Glycerophospho-ethanolamines	M2
C36:2 PE	Glycerophospho-ethanolamines	M2	C36:1 PE	Glycerophospho-ethanolamines	M2
C38:4 PE	Glycerophospho-ethanolamines	M2	C36:2 PE	Glycerophospho-ethanolamines	M2
C40:6 PE	Glycerophospho-ethanolamines	M2	C38:4 PE	Glycerophospho-ethanolamines	M2
C36:3 PE	Glycerophospho-ethanolamines	M2	C36:3 PE	Glycerophospho-ethanolamines	M2
C38:5 PE	Glycerophospho-ethanolamines	M2	C38:5 PE	Glycerophospho-ethanolamines	M2
C38:6 PE	Glycerophospho-ethanolamines	M2	C14:0 LPC	Glycerophosphocholines	M2
C18:0 CE	Cholesteryl esters	M2	C46:0 TAG	Triacylglycerols	M2
C14:0 LPC	Glycerophosphocholines	M2	C46:1 TAG	Triacylglycerols	M2
C46:0 TAG	Triacylglycerols	M2	C46:2 TAG	Triacylglycerols	M2
C46:1 TAG	Triacylglycerols	M2	C50:5 TAG	Triacylglycerols	M2
C46:2 TAG	Triacylglycerols	M2	C50:6 TAG	Triacylglycerols	M2
C49:1 TAG	Triacylglycerols	M2	C51:3 TAG	Triacylglycerols	M2
C49:2 TAG	Triacylglycerols	M2	C49:1 TAG	Triacylglycerols	M2
C51:0 TAG	Triacylglycerols	M2	C49:2 TAG	Triacylglycerols	M2
C43:0 TAG	Triacylglycerols	M2	C51:0 TAG	Triacylglycerols	M2
C44:0 TAG	Triacylglycerols	M2	C43:0 TAG	Triacylglycerols	M2
C47:2 TAG	Triacylglycerols	M2	C44:0 TAG	Triacylglycerols	M2
C43:1 TAG	Triacylglycerols	M2	C47:2 TAG	Triacylglycerols	M2
C45:1 TAG	Triacylglycerols	M2	C43:1 TAG	Triacylglycerols	M2
C47:1 TAG	Triacylglycerols	M2	C45:1 TAG	Triacylglycerols	M2
C49:3 TAG	Triacylglycerols	M2	C47:1 TAG	Triacylglycerols	M2
C51:1 TAG	Triacylglycerols	M2	C49:3 TAG	Triacylglycerols	M2
C43:2 TAG	Triacylglycerols	M2	C51:1 TAG	Triacylglycerols	M2
C45:2 TAG	Triacylglycerols	M2	C53:2 TAG	Triacylglycerols	M2
DMGV	NA	M2	C55:2 TAG	Triacylglycerols	M2
N-carbamoyl-beta-alanine	Ureas	M3	C43:2 TAG	Triacylglycerols	M2

Supplemental Table 1.6 (continued).

C2 carnitine	Fatty acid esters	M3	C45:2 TAG	Triacylglycerols	M2
N6-acetyllysine	Amino acids, peptides, and analogues	M3	tyrosine	Amino acids, peptides, and analogues	M3
pantothenate	Amino acids, peptides, and analogues	M3	phenylalanine	Amino acids, peptides, and analogues	M3
acetyl-galactosamine	Carbohydrates and carbohydrate conjugates	M3	proline	Amino acids, peptides, and analogues	M3
uric acid	Purines and purine derivatives	M3	threonine	Amino acids, peptides, and analogues	M3
5-hydroxymethyl-4-methyluracil	Pyrimidines and pyrimidine derivatives	M3	asparagine	Amino acids, peptides, and analogues	M3
creatinine	Amino acids, peptides, and analogues	M3	isoleucine	Amino acids, peptides, and analogues	M3
cytosine	Pyrimidines and pyrimidine derivatives	M3	histidine	Amino acids, peptides, and analogues	M3
glutamine	Amino acids, peptides, and analogues	M3	leucine	Amino acids, peptides, and analogues	M3
C10 carnitine	Fatty acid esters	M3	methionine	Amino acids, peptides, and analogues	M3
1-methylnicotinamide	Pyridinecarboxylic acids and derivatives	M3	valine	Amino acids, peptides, and analogues	M3
C6 carnitine	Fatty acid esters	M3	tryptophan	Indolyl carboxylic acids and derivatives	M3
pseudouridine	NA	M3	C56:8 TAG	Triacylglycerols	M3
C8 carnitine	Fatty acid esters	M3	C56:5 TAG	Triacylglycerols	M3
ribothymidine	NA	M3	C58:8 TAG	Triacylglycerols	M3
7-methylguanine	Purines and purine derivatives	M3	C52:6 TAG	Triacylglycerols	M3
citrulline	Amino acids, peptides, and analogues	M3	C54:7 TAG	Triacylglycerols	M3
ADMA/SDMA	Amino acids, peptides, and analogues	M3	C56:9 TAG	Triacylglycerols	M3

Supplemental Table 1.6 (continued).

1-methylguanosine	NA	M3	C56:6 TAG	Triacylglycerols	M3
C14:1 carnitine	Fatty acid esters	M3	C58:6 TAG	Triacylglycerols	M3
N-acetylputrescine	Carboximidic acids	M3	C56:7 TAG	Triacylglycerols	M3
C12 carnitine	Fatty acid esters	M3	C58:9 TAG	Triacylglycerols	M3
1-methylguanine	Purines and purine derivatives	M3	C58:7 TAG	Triacylglycerols	M3
4-acetamidobutanoate	Amino acids, peptides, and analogues	M3	C58:10 TAG	Triacylglycerols	M3
N1-methyl-2-pyridone-5-carboxamide	Pyridinecarboxylic acids and derivatives	M3	C60:12 TAG	Triacylglycerols	M3
N-alpha-acetylarginine	Amino acids, peptides, and analogues	M3	C54:9 TAG	Triacylglycerols	M3
N2,N2-dimethylguanosine	NA	M3	C56:10 TAG	Triacylglycerols	M3
C14 carnitine	Fatty acid esters	M3	C52:7 TAG	Triacylglycerols	M3
2-methylguanosine	NA	M3	C54:8 TAG	Triacylglycerols	M3
N4-acetylcytidine	NA	M3	C58:11 TAG	Triacylglycerols	M3
3-dehydroxycarnitine	Fatty acids and conjugates	M3	C36:5 PC plasmalogen-A	Glycerophosphocholines	M3
C4-OH carnitine	Fatty acid esters	M3	C38:7 PC plasmalogen	Glycerophosphocholines	M3
C5-DC carnitine	Fatty acid esters	M3	C40:7 PE plasmalogen	Glycerophospho-ethanolamines	M3
C7 carnitine	Fatty acid esters	M3	C38:7 PE plasmalogen	Glycerophospho-ethanolamines	M3
N6,N6-dimethyllysine	Amino acids, peptides, and analogues	M3	N-carbamoyl-beta-alanine	Ureas	M4

Supplemental Table 1.6 (continued).

C9 carnitine	Fatty acid esters	M3	dimethylglycine	Amino acids, peptides, and analogues	M4
C10:2 carnitine	Fatty acid esters	M3	N6-acetyllysine	Amino acids, peptides, and analogues	M4
C12:1 carnitine	Fatty acid esters	M3	acetyl-galactosamine	Carbohydrates and carbohydrate conjugates	M4
C14:2 carnitine	Fatty acid esters	M3	uric acid	Purines and purine derivatives	M4
oleoyl glycine	Amino acids, peptides, and analogues	M3	allantoin	Imidazoles	M4
N-acetyltryptophan	Amino acids, peptides, and analogues	M3	5-hydroxymethyl-4-methyluracil	Pyrimidines and pyrimidine derivatives	M4
N-acetylhistidine	Amino acids, peptides, and analogues	M3	creatinine	Amino acids, peptides, and analogues	M4
1-methylhistidine	Amino acids, peptides, and analogues	M4	cytosine	Pyrimidines and pyrimidine derivatives	M4
carnitine	Quaternary ammonium salts	M4	glutamine	Amino acids, peptides, and analogues	M4
creatine	Amino acids, peptides, and analogues	M4	kynurenic acid	Quinoline carboxylic acids	M4
dimethylglycine	Amino acids, peptides, and analogues	M4	pseudouridine	NA	M4
tyrosine	Amino acids, peptides, and analogues	M4	ribothymidine	NA	M4
phenylalanine	Amino acids, peptides, and analogues	M4	7-methylguanine	Purines and purine derivatives	M4
threonine	Amino acids, peptides, and analogues	M4	citrulline	Amino acids, peptides, and analogues	M4
asparagine	Amino acids, peptides, and analogues	M4	trimethylamine-N-oxide	Aminoxides	M4
isoleucine	Amino acids, peptides, and analogues	M4	N1-acetylspermidine	Carboximidic acids	M4
histidine	Amino acids, peptides, and analogues	M4	N6,N6,N6-trimethyllysine	Amino acids, peptides, and analogues	M4

Supplemental Table 1.6 (continued).

lysine	Amino acids, peptides, and analogues	M4	ADMA/SDMA	Amino acids, peptides, and analogues	M4
homoarginine	Amino acids, peptides, and analogues	M4	1-methylguanosine	NA	M4
leucine	Amino acids, peptides, and analogues	M4	N-acetylputrescine	Carboximidic acids	M4
C5 carnitine	Fatty acid esters	M4	N1,N12-diacetylspermine	Carboximidic acids	M4
methionine	Amino acids, peptides, and analogues	M4	1-methylguanine	Purines and purine derivatives	M4
kynurenic acid	Quinoline carboxylic acids	M4	4-acetamidobutanoate	Amino acids, peptides, and analogues	M4
C3 carnitine	Fatty acid esters	M4	N-alpha-acetylarginine	Amino acids, peptides, and analogues	M4
valine	Amino acids, peptides, and analogues	M4	N2,N2-dimethylguanosine	NA	M4
tryptophan	Indolyl carboxylic acids and derivatives	M4	2-methylguanosine	NA	M4
N6,N6,N6-trimethyllysine		M4	N4-acetylcytidine	NA	M4
pyridoxamine	Pyridoxamines	M4	3-dehydroxycarnitine	Fatty acids and conjugates	M4
C4 carnitine	Fatty acid esters	M4	N6,N6-dimethyllysine	Amino acids, peptides, and analogues	M4
C5:1 carnitine	Fatty acid esters	M4	N-acetyltryptophan		M4
C20:5 CE	Cholesteryl esters	M4	N-acetylhistidine	Amino acids, peptides, and analogues	M4
C38:5 DAG	Diacylglycerols	M4	betaine	Amino acids, peptides, and analogues	M5
C18:3 CE	Cholesteryl esters	M4	alanine	Amino acids, peptides, and analogues	M5
C50:5 TAG	Triacylglycerols	M4	serine	Amino acids, peptides, and analogues	M5

Supplemental Table 1.6 (continued).

C50:6 TAG	Triacylglycerols	M4	coenzyme Q10	NA	M5
NMMA	Amino acids, peptides, and analogues	M4	C20:5 CE	Cholesteryl esters	M5
bilirubin	Bilirubins	M5	C20:3 CE	Cholesteryl esters	M5
GABA	Amino acids, peptides, and analogues	M5	C30:0 PC	Glycerophosphocholines	M5
thyroxine	NA	M5	C30:1 PC	Glycerophosphocholines	M5
allantoin	Imidazoles	M5	C32:0 PC	Glycerophosphocholines	M5
hydroxyproline	Amino acids, peptides, and analogues	M5	C32:1 PC	Glycerophosphocholines	M5
biliverdin	Bilirubins	M5	C32:2 PC	Glycerophosphocholines	M5
N1-acetylspermidine	Carboximidic acids	M5	C34:4 PC	NA	M5
aminoisobutyric acid	Amino acids, peptides, and analogues	M5	C34:1 PC	Glycerophosphocholines	M5
N1,N12-diacetylspermine	Carboximidic acids	M5	C36:1 PC	Glycerophosphocholines	M5
C34:2 PE plasmalogen	Glycerophospho-ethanolamines	M5	C36:4 PC-B	Glycerophosphocholines	M5
C36:2 PE plasmalogen	Glycerophospho-ethanolamines	M5	C32:0 PE	Glycerophospho-ethanolamines	M5
C34:5 PC plasmalogen	NA	M5	C34:0 PE	Glycerophospho-ethanolamines	M5
C36:5 PC plasmalogen-B	Glycerophosphocholines	M5	C36:0 PE	Glycerophospho-ethanolamines	M5
C34:3 PE plasmalogen	Glycerophospho-ethanolamines	M5	C40:6 PE	Glycerophospho-ethanolamines	M5
C38:5 PE plasmalogen	Glycerophospho-ethanolamines	M5	C38:6 PE	Glycerophospho-ethanolamines	M5
C38:6 PE plasmalogen	Glycerophospho-ethanolamines	M5	C18:0 CE	Cholesteryl esters	M5
C36:5 PE plasmalogen	Glycerophospho-ethanolamines	M5	C18:3 CE	Cholesteryl esters	M5

Supplemental Table 1.6 (continued).

C36:3 PE plasmalogen	Glycerophospho-ethanolamines	M5	DMGV	NA	M5
C36:4 PE plasmalogen	Glycerophospho-ethanolamines	M5	bilirubin	Bilirubins	M6
C18:1 LPC	Glycerophosphocholines	M6	glycine	Amino acids, peptides, and analogues	M6
C16:0 LPC	Glycerophosphocholines	M6	guanidinoacetic acid	Amino acids, peptides, and analogues	M6
C16:1 LPC	Glycerophosphocholines	M6	glycocholate	Bile acids	M6
C18:0 LPC	Glycerophosphocholines	M6	glycodeoxycholate/glycochenodeoxycholate	Bile acids	M6
C18:2 LPC	Glycerophosphocholines	M6	C16:1 CE	Cholesteryl esters	M6
C18:3 LPC	Glycerophosphocholines	M6	pipecolic acid	Amino acids, peptides, and analogues	M6
C20:4 LPC	NA	M6	biliverdin	Bilirubins	M6
C20:5 LPC	Glycerophosphocholines	M6	C52:4 TAG	Triacylglycerols	M6
C22:5 LPC	Glycerophosphocholines	M6	C54:4 TAG	Triacylglycerols	M6
C18:0 LPE	Glycerophospho-ethanolamines	M6	C54:5 TAG	Triacylglycerols	M6
C18:3 LPE	NA	M6	C54:6 TAG	Triacylglycerols	M6
C16:0 LPE	Glycerophospho-ethanolamines	M6	C56:4 TAG	Triacylglycerols	M6
C18:1 LPE	Glycerophospho-ethanolamines	M6	C54:3 TAG	Triacylglycerols	M6
C18:2 LPE	Glycerophospho-ethanolamines	M6	C14:0 CE	Cholesteryl esters	M6
C20:1 LPE	NA	M6	C36:3 DAG	Lineolic acids and derivatives	M6
C20:4 LPE	Glycerophospho-ethanolamines	M6	C36:4 DAG	Lineolic acids and derivatives	M6
C22:0 LPE	Glycerophospho-ethanolamines	M6	C18:1 LPE	Glycerophospho-ethanolamines	M6
cholesterol	Cholestane steroids	M7	C18:2 LPE	Glycerophospho-ethanolamines	M6

Supplemental Table 1.6 (continued).

campesterol	Ergostane steroids	M7	C55:3 TAG	Triacylglycerols	M6
C16:0 Ceramide (d18:1)	Ceramides	M7	C53:3 TAG	Triacylglycerols	M6
C22:0 Ceramide (d18:1)	Ceramides	M7	C18:1 LPC	Glycerophosphocholines	M7
C24:0 Ceramide (d18:1)	Ceramides	M7	C16:0 Ceramide (d18:1)	Ceramides	M7
C52:6 TAG	Triacylglycerols	M7	C22:0 Ceramide (d18:1)	Ceramides	M7
C54:7 TAG	Triacylglycerols	M7	C24:1 Ceramide (d18:1)	Ceramides	M7
C26 carnitine	Fatty acid esters	M7	C24:0 Ceramide (d18:1)	Ceramides	M7
C38:4 PI	Glycerophosphoinositols	M7	C38:4 PI	Glycerophosphoinositols	M7
C20:1 LPC	NA	M7	C16:0 LPC	Glycerophosphocholines	M7
C54:9 TAG	Triacylglycerols	M7	C16:1 LPC	Glycerophosphocholines	M7
C52:7 TAG	Triacylglycerols	M7	C18:0 LPC	Glycerophosphocholines	M7
C54:8 TAG	Triacylglycerols	M7	C18:2 LPC	Glycerophosphocholines	M7
C14:0 SM	Phosphosphingolipids	M7	C18:3 LPC	Glycerophosphocholines	M7
C22:1 SM	Phosphosphingolipids	M7	C20:4 LPC	NA	M7
cerulenin	NA	M7	C20:5 LPC	Glycerophosphocholines	M7
glycine	Amino acids, peptides, and analogues	M8	C22:5 LPC	Glycerophosphocholines	M7
guanidinoacetic acid	Amino acids, peptides, and analogues	M8	C18:0 LPE	Glycerophospho-ethanolamines	M7
C16:1 CE	Cholesteryl esters	M8	C18:3 LPE	NA	M7
pipecolic acid	Amino acids, peptides, and analogues	M8	C16:0 LPE	Glycerophospho-ethanolamines	M7
2-aminooctanoic acid	Amino acids, peptides, and analogues	M8	C20:1 LPE	NA	M7
C52:4 TAG	Triacylglycerols	M8	C20:4 LPE	Glycerophospho-ethanolamines	M7
C54:4 TAG	Triacylglycerols	M8	C22:0 LPE	Glycerophospho-ethanolamines	M7
C54:5 TAG	Triacylglycerols	M8	GABA	Amino acids	M8

Supplemental Table 1.6 (continued).

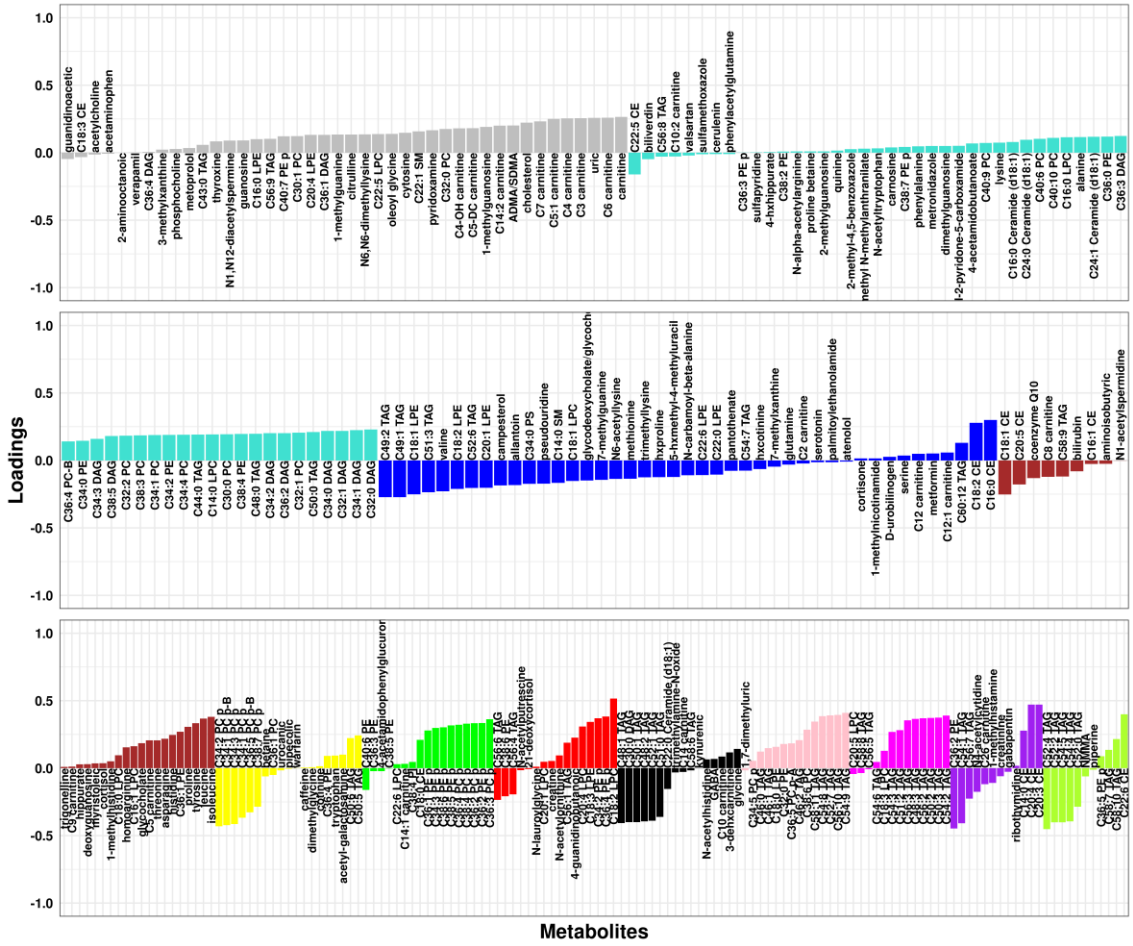
C54:6 TAG	Triacylglycerols	M8	C2 carnitine	Fatty acid esters	M8
C56:4 TAG	Triacylglycerols	M8	C10 carnitine	Fatty acid esters	M8
C54:3 TAG	Triacylglycerols	M8	C6 carnitine	Fatty acid esters	M8
C14:0 CE	Cholesteryl esters	M8	C8 carnitine	Fatty acid esters	M8
C36:3 DAG	Lineolic acids and derivatives	M8	aminoisobutyric acid	Amino acids	M8
C36:4 DAG	Lineolic acids and derivatives	M8	C14:1 carnitine	Fatty acid esters	M8
C55:3 TAG	Triacylglycerols	M8	C12 carnitine	Fatty acid esters	M8
C53:3 TAG	Triacylglycerols	M8	C14 carnitine	Fatty acid esters	M8
C38:2 PE	Glycerophospho-ethanolamines	M9	C4-OH carnitine	Fatty acid esters	M8
C36:1 PE plasmalogen	Glycerophospho-ethanolamines	M9	C5-DC carnitine	Fatty acid esters	M8
C34:1 PC plasmalogen	Glycerophosphocholines	M9	C7 carnitine	Fatty acid esters	M8
C34:2 PC plasmalogen	NA	M9	C9 carnitine	Fatty acid esters	M8
C34:3 PC plasmalogen	Glycerophosphocholines	M9	C10:2 carnitine	Fatty acid esters	M8
C36:5 PC plasmalogen-A	Glycerophosphocholines	M9	C12:1 carnitine	Fatty acid esters	M8
C38:7 PC plasmalogen	Glycerophosphocholines	M9	C14:2 carnitine	Fatty acid esters	M8
C34:1 PC plasmalogen-B	Glycerophosphocholines	M9	oleoyl glycine	Amino acids, peptides, and analogues	
C36:2 PC plasmalogen	Glycerophosphocholines	M9	cerulenin	NA	M8
C36:3 PC plasmalogen	NA	M9	C38:6 PC	Glycerophosphocholines	M9
C38:4 PC plasmalogen	Glycerophosphocholines	M9	C40:6 PC	Glycerophosphocholines	M9
C36:4 PC plasmalogen	Glycerophosphocholines	M9	C40:10 PC	Glycerophosphocholines	M9

Supplemental Table 1.6 (continued).

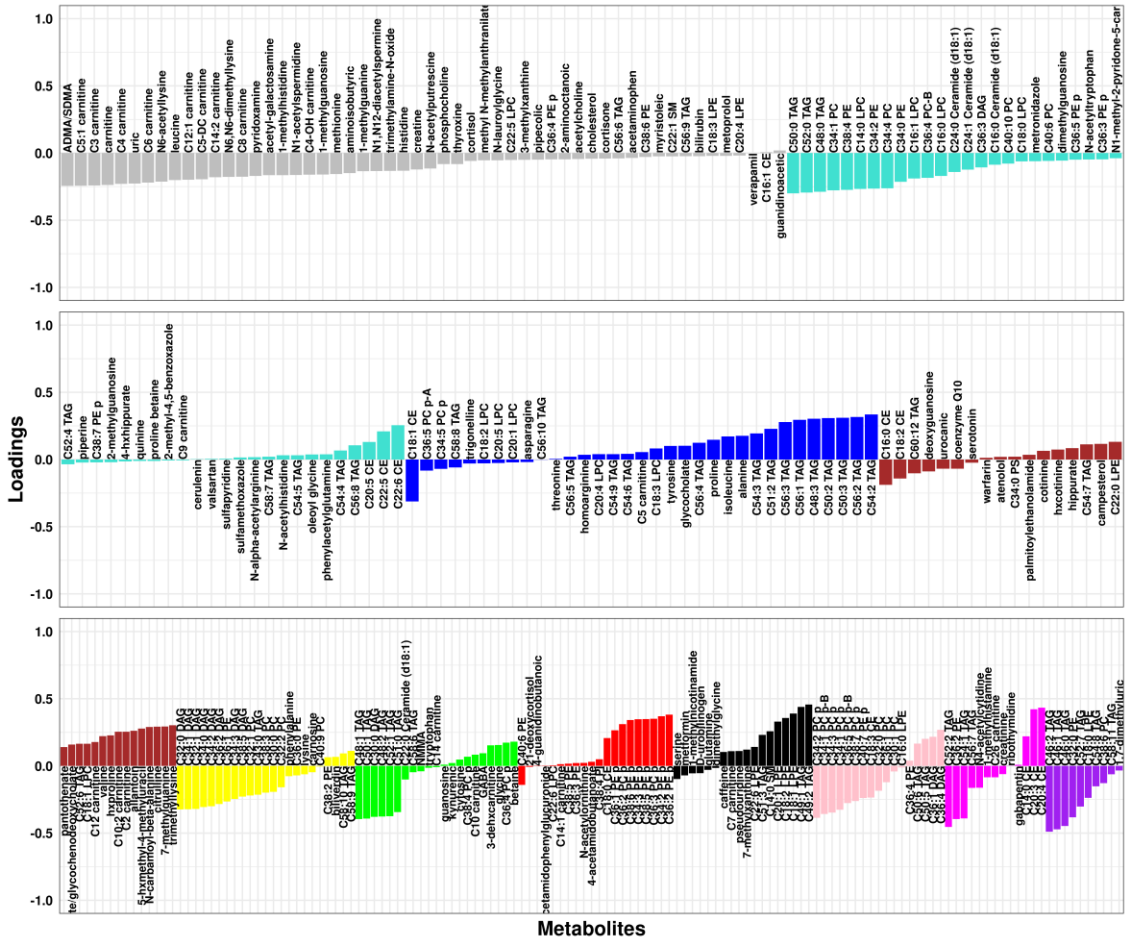
C40:7 PE plasmalogen	Glycerophospho-ethanolamines	M9	C40:9 PC	Glycerophosphocholines	M9
C38:7 PE plasmalogen	Glycerophospho-ethanolamines	M9	C34:2 PE plasmalogen	Glycerophospho-ethanolamines	M9
C56:8 TAG	Triacylglycerols	M10	C36:2 PE plasmalogen	Glycerophospho-ethanolamines	M9
C56:5 TAG	Triacylglycerols	M10	C22:6 LPC	Glycerophosphocholines	M9
C58:8 TAG	Triacylglycerols	M10	C34:5 PC plasmalogen	NA	M9
C56:9 TAG	Triacylglycerols	M10	C36:5 PC plasmalogen-B	Glycerophosphocholines	M9
C56:6 TAG	Triacylglycerols	M10	C34:3 PE plasmalogen	Glycerophospho-ethanolamines	M9
C58:6 TAG	Triacylglycerols	M10	C38:5 PE plasmalogen	Glycerophospho-ethanolamines	M9
C56:7 TAG	Triacylglycerols	M10	C38:6 PE plasmalogen	Glycerophospho-ethanolamines	M9
C58:9 TAG	Triacylglycerols	M10	C36:5 PE plasmalogen	Glycerophospho-ethanolamines	M9
C58:7 TAG	Triacylglycerols	M10	C36:3 PE plasmalogen	Glycerophospho-ethanolamines	M9
C58:10 TAG	Triacylglycerols	M10	C36:4 PE plasmalogen	Glycerophospho-ethanolamines	M9
C60:12 TAG	Triacylglycerols	M10	C22:6 LPE	Glycerophospho-ethanolamines	M9
C56:10 TAG	Triacylglycerols	M10	C34:0 PS	Glycerophosphoserines	M9
C58:11 TAG	Triacylglycerols	M10	C18:2 CE	Cholesteryl esters	M10
C18:2 CE	Cholesteryl esters	M11	C16:0 CE	Cholesteryl esters	M10
C16:0 CE	Cholesteryl esters	M11	C18:1 CE	Cholesteryl esters	M10
C18:1 CE	Cholesteryl esters	M11	C52:2 TAG	Triacylglycerols	M10
C52:2 TAG	Triacylglycerols	M11	C54:2 TAG	Triacylglycerols	M10
C50:3 TAG	Triacylglycerols	M11	C50:3 TAG	Triacylglycerols	M10
C20:4 CE	Cholesteryl esters	M11	C20:4 CE	Cholesteryl esters	M10
C32:1 DAG	Diacylglycerols	M11	C32:1 DAG	Diacylglycerols	M10
C34:1 DAG	Diacylglycerols	M11	C34:1 DAG	Diacylglycerols	M10

Supplemental Table 1.6 (continued).

C34:2 DAG	Lineolic acids and derivatives	M11	C34:2 DAG	Lineolic acids and derivatives	M10
C34:3 DAG	Lineolic acids and derivatives	M11	C34:3 DAG	Lineolic acids and derivatives	M10
C36:2 DAG	Diacylglycerols	M11	C36:2 DAG	Diacylglycerols	M10
C22:5 CE	Cholesteryl esters	M11	C22:5 CE	Cholesteryl esters	M10
C54:1 TAG	Triacylglycerols	M12	C38:2 PE	Glycerophospho-ethanolamines	M11
C56:1 TAG	Triacylglycerols	M12	C36:1 PE plasmalogen	Glycerophospho-ethanolamines	M11
C54:2 TAG	Triacylglycerols	M12	C34:1 PC plasmalogen	Glycerophosphocholines	M11
C56:2 TAG	Triacylglycerols	M12	C34:2 PC plasmalogen	NA	M11
C56:3 TAG	Triacylglycerols	M12	C34:3 PC plasmalogen	Glycerophosphocholines	M11
C22:6 CE	Cholesteryl esters	M12	C34:1 PC plasmalogen-B	Glycerophosphocholines	M11
C20:3 CE	Cholesteryl esters	M12	C36:2 PC plasmalogen	Glycerophosphocholines	M11
C36:1 DAG	Diacylglycerols	M12	C36:3 PC plasmalogen	NA	M11
C51:3 TAG	Triacylglycerols	M12	C38:4 PC plasmalogen	Glycerophosphocholines	M11
C53:2 TAG	Triacylglycerols	M12	C36:4 PC plasmalogen	Glycerophosphocholines	M11
C55:2 TAG	Triacylglycerols	M12			



Supplemental Figure 1.2a. Breast cancer WGCNA loadings on first principal component for each metabolite by identified metabolite module at distant blood time point. 12 modules are visualized here, defined by their colors: M1 grey, M2 turquoise, M3 blue, M4 brown, M5 yellow, M6 green, M7 red, M8 black, M9 pink, M10 magenta, M11 purple, and M12 green-yellow. Bars below 0 represent negative loading of the metabolite in a given module, while bars above 0 represent positive loading of a metabolite in a given module.



Supplemental Figure 1.2b. Breast cancer WGCNA loadings on first principal component for each metabolite by identified metabolite module at proximate blood time point. 11 modules are visualized here, defined by their colors: M1 grey, M2 turquoise, M3 blue, M4 brown, M5 yellow, M6 green, M7 red, M8 black, M9 pink, M10 magenta, M11 purple. Bars below 0 represent negative loading of the metabolite in a given module, while bars above 0 represent positive loading of a metabolite in a given module.

Supplemental Table 1.7a. Association between metabolite modules and breast cancer risk at distant blood draw.

	Overall BC			ER+ BC*			ER- BC*		
Metabolite module	OR (95% CI)	p-value	FDR adjusted p-value	OR (95% CI)	p-value	FDR adjusted p-value	OR (95% CI)	p-value	FDR adjusted p-value
M1 grey	0.89 (0.67-1.17)	0.40	0.53	0.80 (0.59-1.09)	0.15	0.26	1.14 (0.62-2.12)	0.67	0.92
M2 turquoise	1.15 (0.88-1.49)	0.30	0.47	1.33 (0.98-1.81)	0.06	0.16	1.25 (0.68-2.29)	0.47	0.92
M3 blue	0.95 (0.74-1.22)	0.69	0.76	1.02 (0.76-1.38)	0.87	0.87	1.05 (0.57-1.91)	0.88	0.92
M4 brown	1.27 (0.98-1.65)	0.07	0.47	1.18 (0.88-1.60)	0.27	0.33	0.95 (0.53-1.72)	0.86	0.92
M5 yellow	1.06 (0.83-1.35)	0.65	0.76	1.18 (0.88-1.57)	0.27	0.33	0.92 (0.51-1.65)	0.78	0.92
M6 green	0.88 (0.69-1.12)	0.31	0.47	0.83 (0.62-1.09)	0.18	0.27	0.85 (0.48-1.50)	0.57	0.92
M7 red	0.86 (0.67-1.11)	0.24	0.47	0.66 (0.49-0.89)	0.01	0.08	1.09 (0.61-1.95)	0.76	0.92
M8 black	0.86 (0.67-1.12)	0.27	0.47	0.75 (0.55-1.02)	0.06	0.16	0.81 (0.44-1.47)	0.49	0.92
M9 pink	0.98 (0.77-1.26)	0.90	0.90	1.06 (0.79-1.43)	0.69	0.75	1.03 (0.57-1.86)	0.92	0.92
M10 magenta	1.16 (0.90-1.5)	0.27	0.47	1.30 (0.97-1.76)	0.08	0.17	0.93 (0.50-1.71)	0.82	0.92
M11 purple	0.84 (0.65-1.07)	0.16	0.47	0.70 (0.52-0.93)	0.02	0.09	0.84 (0.46-1.53)	0.58	0.92
M12 green-yellow	0.86 (0.67-1.11)	0.25	0.47	0.71 (0.53-0.95)	0.02	0.09	1.05 (0.57-1.92)	0.88	0.92

* Note that metabolite loadings differ by subtype, causing overall, ER+, and ER- to have distinct ORs that are not directly comparable.

Supplemental Table 1.7b. Association between metabolite modules and breast cancer risk at proximate blood.

	Overall BC			ER+ BC*			ER- BC*		
Metabolite module	OR (95% CI)	p-value	FDR adjusted p-value	OR (95% CI)	p-value	FDR adjusted p-value	OR (95% CI)	p-value	FDR adjusted p-value
M1 grey	0.75 (0.53-1.07)	0.11	0.66	0.87 (0.61-1.26)	0.47	0.86	0.64 (0.30-1.34)	0.24	0.88
M2 turquoise	0.84 (0.61-1.14)	0.26	0.97	0.78 (0.55-1.11)	0.18	0.54	1.02 (0.51-2.03)	0.95	0.96
M3 blue	1.17 (0.85-1.61)	0.34	0.98	1.27 (0.89-1.83)	0.19	0.54	1.05 (0.51-2.15)	0.90	0.96
M4 brown	1.16 (0.81-1.66)	0.42	0.66	0.98 (0.66-1.45)	0.93	0.97	0.48 (0.22-1.03)	0.06	0.69
M5 yellow	0.86 (0.62-1.19)	0.37	0.66	0.79 (0.55-1.14)	0.21	0.54	0.93 (0.46-1.87)	0.83	0.96
M6 green	0.89 (0.65-1.24)	0.50	0.66	0.81 (0.56-1.16)	0.25	0.54	1.21 (0.60-2.45)	0.60	0.96
M7 red	1.17 (0.86-1.59)	0.32	0.66	0.98 (0.70-1.39)	0.93	0.97	1.56 (0.77-3.18)	0.22	0.88
M8 black	1.18 (0.87-1.61)	0.30	0.69	1.07 (0.76-1.51)	0.71	0.97	1.34 (0.67-2.69)	0.41	0.96
M9 pink	0.95 (0.68-1.31)	0.74	0.66	1.01 (0.70-1.45)	0.97	0.97	0.77 (0.37-1.58)	0.48	0.96
M10 magenta	0.98 (0.71-1.34)	0.88	0.66	0.77 (0.54-1.10)	0.16	0.54	1.14 (0.56-2.32)	0.71	0.96
M11 purple	1.00 (0.73-1.38)	0.98	0.90	0.97 (0.69-1.38)	0.88	0.97	1.02 (0.51-2.02)	0.96	0.96

* Note that metabolite loadings differ by subtype, causing overall, ER+, and ER- to have distinct ORs that are not directly comparable.

Supplemental Table 1.8. Spearman correlations for distant and proximate metabolite measures.

HMDBID	Metabolite Name	Model 1	Model 2	Model 3	Model 4
HMDB0000001	1-methylhistidine	0.227	0.227	0.229	0.228
HMDB0000026	N-carbamoyl-beta-alanine	0.459	0.455	0.423	0.424
HMDB0000033	carnosine	0.335	0.334	0.341	0.343
HMDB0000043	betaine	0.468	0.467	0.474	0.472
HMDB0000054	bilirubin	0.433	0.435	0.435	0.431
HMDB0000062	carnitine	0.499	0.499	0.488	0.480
HMDB0000063	cortisol	0.239	0.220	0.222	0.216
HMDB0000064	creatine	0.497	0.498	0.498	0.497
HMDB0000067	cholesterol	0.358	0.355	0.372	0.371
HMDB0000085	deoxyguanosine	0.425	0.425	0.420	0.421
HMDB0000092	dimethylglycine	0.547	0.548	0.534	0.529
HMDB0000112	GABA	0.456	0.455	0.452	0.453
HMDB0000123	glycine	0.664	0.664	0.669	0.659
HMDB0000128	guanidinoacetic acid	0.540	0.538	0.538	0.522
HMDB0000133	guanosine	0.198	0.189	0.191	0.190
HMDB0000138	glycocholate	0.297	0.287	0.287	0.284
HMDB0000158	tyrosine	0.402	0.401	0.403	0.379
HMDB0000159	phenylalanine	0.350	0.346	0.355	0.332
HMDB0000161	alanine	0.389	0.391	0.392	0.369
HMDB0000162	proline	0.487	0.486	0.486	0.458
HMDB0000167	threonine	0.364	0.362	0.350	0.351
HMDB0000168	asparagine	0.390	0.387	0.393	0.377
HMDB0000172	isoleucine	0.412	0.410	0.422	0.370
HMDB0000177	histidine	0.416	0.416	0.428	0.428
HMDB0000182	lysine	0.439	0.439	0.446	0.442

Supplemental Table 1.8 (continued).

HMDB0000187	serine	0.434	0.428	0.422	0.423
HMDB0000201	C2 carnitine	0.388	0.389	0.363	0.363
HMDB0000206	N6-acetyllysine	0.571	0.573	0.561	0.561
HMDB0000210	pantothenate	0.413	0.413	0.379	0.379
HMDB0000212	acetyl-galactosamine	0.444	0.444	0.439	0.429
HMDB0000248	thyroxine	0.404	0.405	0.413	0.413
HMDB0000259	serotonin	0.249	0.249	0.251	0.245
HMDB0000289	uric acid	0.608	0.608	0.591	0.560
HMDB0000301	urocanic acid	0.394	0.393	0.391	0.391
HMDB0000462	allantoin	0.196	0.171	0.177	0.162
HMDB0000544	5-hydroxymethyl-4-methyluracil	0.520	0.520	0.507	0.499
HMDB0000562	creatinine	0.595	0.595	0.596	0.597
HMDB0000610	C18:2 CE	0.574	0.576	0.569	0.533
HMDB0000630	cytosine	0.452	0.451	0.452	0.452
HMDB0000631	glycodeoxycholate/glycochenodeoxycholate	0.263	0.253	0.259	0.255
HMDB0000641	glutamine	0.467	0.466	0.462	0.454
HMDB0000651	C10 carnitine	0.326	0.321	0.313	0.310
HMDB0000658	C16:1 CE	0.547	0.547	0.555	0.557
HMDB0000670	homoarginine	0.529	0.527	0.527	0.517
HMDB0000687	leucine	0.408	0.407	0.426	0.374
HMDB0000688	C5 carnitine	0.347	0.346	0.348	0.320
HMDB0000696	methionine	0.250	0.251	0.258	0.259
HMDB0000699	1-methylnicotinamide	0.293	0.290	0.296	0.288
HMDB0000705	C6 carnitine	0.419	0.417	0.394	0.391
HMDB0000714	hippurate	0.316	0.314	0.300	0.291
HMDB0000715	kynurenic acid	0.466	0.467	0.465	0.450
HMDB0000716	pipecolic acid	0.278	0.278	0.290	0.291

Supplemental Table 1.8 (continued).

HMDB0000725	hydroxyproline	0.173	0.173	0.174	0.174
HMDB0000767	pseudouridine	0.594	0.593	0.547	0.535
HMDB0000791	C8 carnitine	0.372	0.367	0.353	0.353
HMDB0000824	C3 carnitine	0.443	0.442	0.437	0.418
HMDB0000875	trigonelline	0.506	0.498	0.499	0.493
HMDB0000883	valine	0.446	0.445	0.459	0.398
HMDB0000884	ribothymidine	0.547	0.546	0.552	0.548
HMDB0000885	C16:0 CE	0.522	0.526	0.521	0.487
HMDB0000895	acetylcholine	0.231	0.224	0.219	0.216
HMDB0000897	7-methylguanine	0.447	0.447	0.449	0.444
HMDB0000898	1-methylhistamine	0.638	0.637	0.636	0.636
HMDB0000904	citrulline	0.588	0.588	0.556	0.553
HMDB0000918	C18:1 CE	0.551	0.555	0.548	0.508
HMDB0000925	trimethylamine-N-oxide	0.188	0.188	0.160	0.156
HMDB0000929	tryptophan	0.404	0.403	0.395	0.395
HMDB0000991	2-aminooctanoic acid	0.455	0.454	0.458	0.461
HMDB0001008	biliverdin	0.457	0.460	0.456	0.455
HMDB0001046	cotinine	0.444	0.445	0.438	0.437
HMDB0001072	coenzyme Q10	0.368	0.367	0.373	0.372
HMDB0001276	N1-acetylspermidine	0.434	0.434	0.440	0.444
HMDB0001325	N6,N6,N6-trimethyllysine	0.334	0.336	0.343	0.337
HMDB0001390	hydroxycotinine	0.452	0.453	0.460	0.457
HMDB0001431	pyridoxamine	0.436	0.436	0.442	0.439
HMDB0001539	ADMA/SDMA	0.679	0.680	0.672	0.672
HMDB0001563	1-methylguanosine	0.348	0.348	0.340	0.322
HMDB0001565	phosphocholine	0.386	0.386	0.390	0.384
HMDB0001847	caffeine	0.432	0.422	0.422	0.421
HMDB0001850	verapamil	0.600	0.504	0.900	0.795

Supplemental Table 1.8 (continued).

HMDB0001859	acetaminophen	0.237	0.237	0.233	0.233
HMDB0001867	4-aminohippuric acid	0.489	0.489	0.429	0.413
HMDB0001886	3-methylxanthine	0.353	0.350	0.349	0.350
HMDB0001906	aminoisobutyric acid	0.508	0.507	0.502	0.502
HMDB0001921	metformin	0.784	0.784	0.782	0.782
HMDB0001924	atenolol	0.695	0.683	0.684	0.649
HMDB0001932	metoprolol	0.294	0.293	0.292	0.291
HMDB0001935	warfarin	0.705	0.684	0.683	0.697
HMDB0001991	7-methylxanthine	0.284	0.283	0.284	0.286
HMDB0002000	myristoleic acid	0.518	0.518	0.513	0.505
HMDB0002013	C4 carnitine	0.594	0.594	0.586	0.585
HMDB0002014	C14:1 carnitine	0.271	0.266	0.242	0.242
HMDB0002064	N-acetylputrescine	0.577	0.581	0.560	0.560
HMDB0002100	palmitoylethanolamide	0.042	0.041	0.040	0.040
HMDB0002172	N1,N12-diacetylspermine	0.485	0.487	0.493	0.494
HMDB0002250	C12 carnitine	0.299	0.296	0.289	0.288
HMDB0002366	C5:1 carnitine	0.464	0.463	0.457	0.456
HMDB0002802	cortisone	0.268	0.261	0.268	0.262
HMDB0002815	C18:1 LPC	0.384	0.382	0.390	0.380
HMDB0002869	campesterol	0.357	0.355	0.368	0.368
HMDB0003282	1-methylguanine	0.348	0.346	0.359	0.350
HMDB0003357	N-acetylornithine	0.735	0.736	0.730	0.729
HMDB0003464	4-guanidinobutanoic acid	0.339	0.330	0.328	0.331
HMDB0003681	4-acetamidobutanoate	0.589	0.594	0.536	0.535
HMDB0004030	21-deoxycortisol	0.244	0.226	0.221	0.207
HMDB0004158	D-urobilinogen	0.331	0.328	0.332	0.335
HMDB0004193	N1-methyl-2-pyridone-5-carboxamide	0.350	0.351	0.322	0.322
HMDB0004620	N-alpha-acetylarginine	0.659	0.660	0.655	0.655
HMDB0004824	N2,N2-dimethylguanosine	0.532	0.531	0.506	0.487

Supplemental Table 1.8 (continued).

HMDB0004827	proline betaine	0.394	0.393	0.370	0.365
HMDB0004949	C16:0 Ceramide (d18:1)	0.428	0.428	0.417	0.412
HMDB0004952	C22:0 Ceramide (d18:1)	0.508	0.507	0.509	0.495
HMDB0004953	C24:1 Ceramide (d18:1)	0.495	0.494	0.463	0.463
HMDB0004956	C24:0 Ceramide (d18:1)	0.465	0.463	0.466	0.464
HMDB0005015	gabapentin	0.291	0.291	0.280	0.279
HMDB0005066	C14 carnitine	0.299	0.302	0.286	0.284
HMDB0005356	C48:0 TAG	0.371	0.375	0.389	0.362
HMDB0005357	C50:0 TAG	0.383	0.386	0.402	0.369
HMDB0005359	C48:1 TAG	0.411	0.414	0.428	0.388
HMDB0005360	C50:1 TAG	0.506	0.510	0.524	0.474
HMDB0005362	C51:2 TAG	0.418	0.418	0.426	0.393
HMDB0005363	C52:4 TAG	0.496	0.496	0.492	0.477
HMDB0005365	C52:0 TAG	0.369	0.370	0.380	0.342
HMDB0005367	C52:1 TAG	0.485	0.490	0.500	0.448
HMDB0005369	C52:2 TAG	0.552	0.552	0.553	0.502
HMDB0005370	C54:4 TAG	0.403	0.407	0.403	0.402
HMDB0005376	C48:2 TAG	0.403	0.406	0.418	0.380
HMDB0005377	C50:2 TAG	0.516	0.519	0.529	0.482
HMDB0005385	C54:5 TAG	0.429	0.433	0.429	0.426
HMDB0005391	C54:6 TAG	0.377	0.378	0.379	0.378
HMDB0005392	C56:8 TAG	0.432	0.427	0.426	0.426
HMDB0005395	C54:1 TAG	0.430	0.432	0.438	0.393
HMDB0005396	C56:1 TAG	0.363	0.368	0.375	0.341
HMDB0005398	C56:4 TAG	0.405	0.403	0.391	0.392
HMDB0005403	C54:2 TAG	0.491	0.496	0.486	0.443
HMDB0005404	C56:2 TAG	0.414	0.419	0.418	0.391
HMDB0005405	C54:3 TAG	0.382	0.386	0.369	0.361

Supplemental Table 1.8 (continued).

HMDB0005406	C56:5 TAG	0.504	0.502	0.497	0.497
HMDB0005410	C56:3 TAG	0.438	0.443	0.426	0.418
HMDB0005413	C58:8 TAG	0.453	0.452	0.459	0.457
HMDB0005432	C48:3 TAG	0.416	0.418	0.426	0.383
HMDB0005433	C50:3 TAG	0.525	0.526	0.530	0.489
HMDB0005436	C52:6 TAG	0.500	0.498	0.490	0.467
HMDB0005447	C54:7 TAG	0.394	0.392	0.388	0.383
HMDB0005448	C56:9 TAG	0.489	0.485	0.489	0.490
HMDB0005456	C56:6 TAG	0.564	0.562	0.561	0.561
HMDB0005458	C58:6 TAG	0.427	0.423	0.434	0.434
HMDB0005462	C56:7 TAG	0.512	0.509	0.500	0.499
HMDB0005463	C58:9 TAG	0.473	0.472	0.475	0.467
HMDB0005471	C58:7 TAG	0.426	0.419	0.423	0.420
HMDB0005476	C58:10 TAG	0.481	0.480	0.488	0.487
HMDB0005478	C60:12 TAG	0.496	0.495	0.504	0.502
HMDB0005862	2-methylguanosine	0.260	0.258	0.250	0.237
HMDB0005923	N4-acetylcytidine	0.665	0.666	0.646	0.635
HMDB0006344	phenylacetylglutamine	0.351	0.351	0.338	0.338
HMDB0006347	C26 carnitine	0.552	0.552	0.556	0.556
HMDB0006725	C14:0 CE	0.449	0.449	0.444	0.431
HMDB0006726	C20:4 CE	0.532	0.536	0.532	0.517
HMDB0006731	C20:5 CE	0.488	0.491	0.494	0.483
HMDB0006733	C22:6 CE	0.517	0.521	0.526	0.491
HMDB0006736	C20:3 CE	0.530	0.532	0.529	0.523
HMDB0006831	3-dehydroxycarnitine	0.508	0.507	0.514	0.514
HMDB0007011	C30:0 DAG	0.340	0.345	0.356	0.336
HMDB0007098	C32:0 DAG	0.484	0.487	0.502	0.461
HMDB0007099	C32:1 DAG	0.516	0.517	0.526	0.473
HMDB0007100	C34:0 DAG	0.434	0.435	0.445	0.406
HMDB0007102	C34:1 DAG	0.545	0.546	0.554	0.504

Supplemental Table 1.8 (continued).

HMDB0007103	C34:2 DAG	0.544	0.544	0.547	0.502
HMDB0007132	C34:3 DAG	0.540	0.540	0.540	0.492
HMDB0007199	C38:5 DAG	0.595	0.595	0.603	0.583
HMDB0007216	C36:1 DAG	0.512	0.515	0.519	0.468
HMDB0007218	C36:2 DAG	0.548	0.549	0.542	0.502
HMDB0007219	C36:3 DAG	0.551	0.551	0.546	0.524
HMDB0007248	C36:4 DAG	0.519	0.519	0.519	0.504
HMDB0007869	C30:0 PC	0.341	0.342	0.359	0.360
HMDB0007870	C30:1 PC	0.362	0.363	0.385	0.382
HMDB0007871	C32:0 PC	0.468	0.468	0.477	0.477
HMDB0007873	C32:1 PC	0.458	0.459	0.478	0.473
HMDB0007874	C32:2 PC	0.353	0.352	0.373	0.373
HMDB0007883	C34:4 PC	0.436	0.435	0.461	0.456
HMDB0007972	C34:1 PC	0.437	0.438	0.448	0.453
HMDB0007991	C38:6 PC	0.537	0.536	0.547	0.545
HMDB0008038	C36:1 PC	0.339	0.340	0.342	0.344
HMDB0008047	C38:3 PC	0.469	0.468	0.481	0.445
HMDB0008057	C40:6 PC	0.530	0.529	0.529	0.530
HMDB0008138	C36:4 PC-B	0.590	0.589	0.613	0.609
HMDB0008511	C40:10 PC	0.454	0.453	0.459	0.461
HMDB0008731	C40:9 PC	0.541	0.540	0.552	0.548
HMDB0008923	C32:0 PE	0.314	0.314	0.322	0.325
HMDB0008925	C34:0 PE	0.373	0.373	0.378	0.380
HMDB0008928	C34:2 PE	0.503	0.506	0.514	0.509
HMDB0008937	C36:4 PE	0.509	0.509	0.519	0.517
HMDB0008942	C38:2 PE	0.486	0.486	0.486	0.471
HMDB0008952	C34:2 PE plasmalogen	0.440	0.440	0.441	0.440
HMDB0008991	C36:0 PE	0.417	0.417	0.422	0.423
HMDB0008993	C36:1 PE	0.423	0.430	0.444	0.427
HMDB0008994	C36:2 PE	0.478	0.484	0.496	0.486

Supplemental Table 1.8 (continued).

HMDB0009003	C38:4 PE	0.564	0.564	0.573	0.565
HMDB0009012	C40:6 PE	0.551	0.550	0.562	0.557
HMDB0009016	C36:1 PE plasmalogen	0.630	0.629	0.623	0.608
HMDB0009060	C36:3 PE	0.465	0.473	0.482	0.480
HMDB0009069	C38:5 PE	0.557	0.556	0.564	0.564
HMDB0009082	C36:2 PE plasmalogen	0.422	0.422	0.421	0.420
HMDB0009102	C38:6 PE	0.537	0.535	0.549	0.549
HMDB0009815	C38:4 PI	0.556	0.555	0.568	0.566
HMDB0010316	4-acetamidophenylglucuronide	0.113	0.117	0.113	0.114
HMDB0010368	C18:0 CE	0.400	0.405	0.403	0.403
HMDB0010370	C18:3 CE	0.506	0.506	0.495	0.487
HMDB0010375	C22:5 CE	0.493	0.495	0.498	0.467
HMDB0010379	C14:0 LPC	0.255	0.252	0.271	0.263
HMDB0010382	C16:0 LPC	0.290	0.290	0.298	0.298
HMDB0010383	C16:1 LPC	0.378	0.376	0.378	0.376
HMDB0010384	C18:0 LPC	0.347	0.347	0.351	0.351
HMDB0010386	C18:2 LPC	0.373	0.370	0.365	0.346
HMDB0010387	C18:3 LPC	0.294	0.291	0.301	0.301
HMDB0010391	C20:1 LPC	0.551	0.549	0.563	0.565
HMDB0010395	C20:4 LPC	0.458	0.459	0.459	0.459
HMDB0010397	C20:5 LPC	0.368	0.365	0.361	0.343
HMDB0010403	C22:5 LPC	0.402	0.401	0.404	0.403
HMDB0010404	C22:6 LPC	0.438	0.440	0.437	0.432
HMDB0010411	C46:0 TAG	0.320	0.323	0.332	0.307
HMDB0010412	C46:1 TAG	0.342	0.344	0.353	0.315
HMDB0010419	C46:2 TAG	0.361	0.363	0.371	0.328
HMDB0010471	C50:5 TAG	0.492	0.495	0.497	0.463
HMDB0010497	C50:6 TAG	0.450	0.453	0.454	0.425
HMDB0010498	C54:9 TAG	0.469	0.465	0.469	0.467
HMDB0010513	C56:10 TAG	0.490	0.486	0.493	0.493

Supplemental Table 1.8 (continued).

HMDB0010517	C52:7 TAG	0.478	0.477	0.473	0.455
HMDB0010518	C54:8 TAG	0.443	0.441	0.438	0.433
HMDB0010531	C58:11 TAG	0.510	0.508	0.520	0.522
HMDB0011103	1,7-dimethyluric acid	0.477	0.474	0.475	0.474
HMDB0011130	C18:0 LPE	0.359	0.357	0.365	0.366
HMDB0011208	C34:1 PC plasmalogen	0.563	0.564	0.569	0.548
HMDB0011210	C34:2 PC plasmalogen	0.654	0.654	0.654	0.626
HMDB0011211	C34:3 PC plasmalogen	0.518	0.518	0.507	0.483
HMDB0011214	C34:5 PC plasmalogen	0.362	0.363	0.360	0.360
HMDB0011220	C36:5 PC plasmalogen-B	0.527	0.528	0.531	0.531
HMDB0011221	C36:5 PC plasmalogen-A	0.388	0.386	0.386	0.385
HMDB0011229	C38:7 PC plasmalogen	0.536	0.536	0.541	0.538
HMDB0011239	C34:1 PC plasmalogen-B	0.559	0.559	0.557	0.541
HMDB0011243	C36:2 PC plasmalogen	0.553	0.553	0.563	0.545
HMDB0011244	C36:3 PC plasmalogen	0.572	0.572	0.566	0.539
HMDB0011252	C38:4 PC plasmalogen	0.545	0.545	0.543	0.543
HMDB0011310	C36:4 PC plasmalogen	0.576	0.576	0.581	0.555
HMDB0011343	C34:3 PE plasmalogen	0.377	0.377	0.372	0.371
HMDB0011386	C38:5 PE plasmalogen	0.390	0.391	0.392	0.391
HMDB0011387	C38:6 PE plasmalogen	0.398	0.397	0.400	0.400
HMDB0011394	C40:7 PE plasmalogen	0.477	0.477	0.479	0.476
HMDB0011410	C36:5 PE plasmalogen	0.399	0.399	0.406	0.400
HMDB0011420	C38:7 PE plasmalogen	0.519	0.518	0.532	0.532
HMDB0011441	C36:3 PE plasmalogen	0.408	0.408	0.409	0.406
HMDB0011442	C36:4 PE plasmalogen	0.405	0.405	0.404	0.401
HMDB0011478	C18:3 LPE	0.316	0.316	0.321	0.320
HMDB0011503	C16:0 LPE	0.387	0.385	0.393	0.386
HMDB0011506	C18:1 LPE	0.335	0.327	0.336	0.336
HMDB0011507	C18:2 LPE	0.341	0.343	0.349	0.346

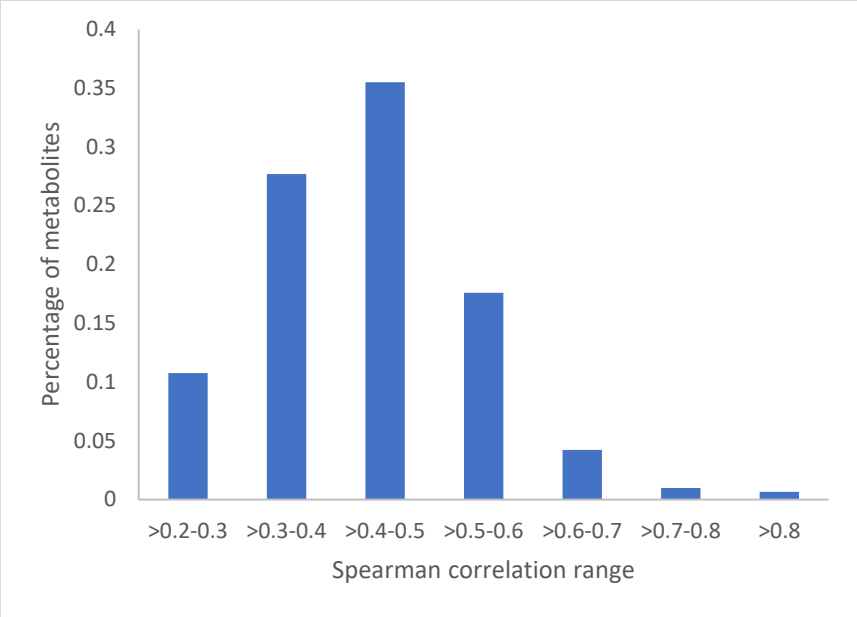
Supplemental Table 1.8 (continued).

HMDB0011512	C20:1 LPE	0.372	0.371	0.375	0.374
HMDB0011517	C20:4 LPE	0.455	0.457	0.464	0.464
HMDB0011520	C22:0 LPE	0.434	0.437	0.438	0.416
HMDB0011526	C22:6 LPE	0.442	0.441	0.434	0.432
HMDB0011701	C51:3 TAG	0.502	0.501	0.501	0.479
HMDB0011705	C49:1 TAG	0.343	0.342	0.351	0.327
HMDB0011706	C49:2 TAG	0.380	0.380	0.388	0.365
HMDB0012097	C14:0 SM	0.493	0.493	0.503	0.503
HMDB0012104	C22:1 SM	0.437	0.436	0.461	0.463
HMDB0012356	C34:0 PS	0.438	0.437	0.445	0.450
HMDB0013127	C4-OH carnitine	0.338	0.339	0.326	0.309
HMDB0013130	C5-DC carnitine	0.640	0.637	0.630	0.630
HMDB0013238	C7 carnitine	0.392	0.391	0.385	0.384
HMDB0013272	N-lauroylglycine	0.287	0.285	0.280	0.280
HMDB0013287	N6,N6-dimethyllysine	0.872	0.872	0.870	0.870
HMDB0013288	C9 carnitine	0.496	0.496	0.500	0.499
HMDB0013325	C10:2 carnitine	0.314	0.309	0.299	0.299
HMDB0013326	C12:1 carnitine	0.291	0.284	0.267	0.267
HMDB0013331	C14:2 carnitine	0.281	0.272	0.253	0.251
HMDB0013631	oleoyl glycine	0.343	0.338	0.328	0.327
HMDB0013678	4-hydroxyhippurate	0.210	0.201	0.198	0.198
HMDB0013713	N-acetyltryptophan	0.458	0.460	0.452	0.453
HMDB0014323	valsartan	0.615	0.616	0.610	0.610
HMDB0014611	quinine	0.383	0.384	0.389	0.385
HMDB0015028	sulfapyridine	0.086	0.153	0.766	0.428
HMDB0015052	metronidazole	0.840	0.840	0.844	0.841
HMDB0015150	sulfamethoxazole	0.593	0.593	0.594	0.594
HMDB0015168	cerulenin	0.281	0.281	0.281	0.273
HMDB0029377	piperine	0.460	0.459	0.462	0.458
HMDB0029416	NMMA	0.478	0.478	0.487	0.481

Supplemental Table 1.8 (continued).

HMDB0031106	C51:0 TAG	0.321	0.321	0.330	0.309
HMDB0032055	N-acetylhistidine	0.561	0.562	0.533	0.530
HMDB0032390	2-methyl-4,5-benzoxazole	0.354	0.352	0.348	0.345
HMDB0034169	methyl N-methylanthranilate	0.163	0.163	0.159	0.160
HMDB0042062	C43:0 TAG	0.248	0.243	0.242	0.228
HMDB0042063	C44:0 TAG	0.286	0.288	0.294	0.263
HMDB0042076	C47:2 TAG	0.354	0.354	0.363	0.334
HMDB0042093	C45:0 TAG	0.219	0.213	0.208	0.206
HMDB0042098	C43:1 TAG	0.302	0.303	0.309	0.283
HMDB0042099	C45:1 TAG	0.296	0.297	0.304	0.278
HMDB0042100	C47:1 TAG	0.315	0.313	0.317	0.300
HMDB0042103	C49:3 TAG	0.427	0.427	0.433	0.407
HMDB0042104	C51:1 TAG	0.448	0.450	0.463	0.414
HMDB0042196	C53:2 TAG	0.464	0.463	0.455	0.434
HMDB0042226	C55:2 TAG	0.472	0.476	0.474	0.451
HMDB0042466	C55:3 TAG	0.408	0.406	0.397	0.397
HMDB0043058	C53:3 TAG	0.476	0.475	0.471	0.468
HMDB0043169	C43:2 TAG	0.345	0.347	0.356	0.329
HMDB0043170	C45:2 TAG	0.360	0.362	0.370	0.339
HMDB0059824	4-hydroxy-3-methylacetophenone	0.358	0.358	0.361	0.359
HMDB0240212	DMGV	0.732	0.733	0.716	0.675

Model 1 is unadjusted; Model 2 is adjusted for fasting status (combined distant & proximate blood); Model 3 is adjusted for fasting status and age at blood draw; Model 4 is adjusted for fasting status, age at blood draw, and weight change from age 18 to blood draw.



Supplemental Figure 1.3. Spearman correlations for metabolites comparing distant to proximate measures, by percentage of metabolites within the range.

Supplemental Table 1.9. Odds ratios for breast cancer risk comparing 90th to 10th percentile of metabolite levels, taken as an average as distant and proximate blood.**

				Multivariable Adjusted^	
	HMDB ID	**Class**	**Subclass**	**OR (95% CI)**	**p value**
metronidazole	HMDB0015052	Azoles	Imidazoles	0.88 (0.64-1.21)	0.446
allantoin	HMDB0000462	Azoles	Imidazoles	1.07 (0.7-1.63)	0.755
urocanic acid	HMDB0000301	Azoles	Imidazoles	1.01 (0.72-1.44)	0.942
sulfamethoxazole	HMDB0015150	Benzene and substituted derivatives	Benzenesulfonamides	1.03 (0.74-1.45)	0.845
hippurate	HMDB0000714	Benzene and substituted derivatives	Benzoic acids and derivatives	0.65 (0.45-0.95)	0.026
4-hydroxyhippurate	HMDB0013678	Benzene and substituted derivatives	Benzoic acids and derivatives	0.72 (0.49-1.05)	0.091
N1,N12-diacetylspermine	HMDB0002172	Carboximidic acids and derivatives	Carboximidic acids	1.6 (1.13-2.29)	0.009
N1-acetylspermidine	HMDB0001276	Carboximidic acids and derivatives	Carboximidic acids	1.19 (0.83-1.72)	0.346
N-acetylputrescine	HMDB0002064	Carboximidic acids and derivatives	Carboximidic acids	1.12 (0.79-1.59)	0.51
palmitoylethanolamide	HMDB0002100	Carboximidic acids and derivatives	Carboximidic acids	0.91 (0.61-1.36)	0.634
phenylalanine	HMDB0000159	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.89 (1.27-2.81)	0.002

Supplemental Table 1.9 (continued).

isoleucine	HMDB0000172	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.71 (1.15-2.55)	0.008
leucine	HMDB0000687	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.63 (1.09-2.44)	0.016
proline	HMDB0000162	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.51 (1.04-2.2)	0.03
serine	HMDB0000187	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.49 (1.03-2.16)	0.037
ADMA/SDMA	HMDB0001539	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.39 (1.02-1.91)	0.04
N-acetylornithine	HMDB0003357	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.74 (0.53-1.03)	0.075
valine	HMDB0000883	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.42 (0.96-2.11)	0.083
lysine	HMDB0000182	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.34 (0.93-1.93)	0.113
N6,N6-dimethyllysine	HMDB0013287	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.28 (0.94-1.75)	0.122

Supplemental Table 1.9 (continued).

alanine	HMDB0000161	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.34 (0.92-1.95)	0.128
methionine	HMDB0000696	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.32 (0.9-1.93)	0.15
tyrosine	HMDB0000158	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.25 (0.85-1.82)	0.257
N6,N6,N6-trimethyllysine	HMDB0001325	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.23 (0.85-1.78)	0.278
guanidinoacetic acid	HMDB0000128	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.18 (0.83-1.67)	0.358
asparagine	HMDB0000168	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.18 (0.82-1.7)	0.371
N6-acetyllysine	HMDB0000206*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.16 (0.82-1.64)	0.389
phenylacetylglutamine	HMDB0006344	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.85 (0.58-1.25)	0.413
GABA	HMDB0000112	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.15 (0.81-1.62)	0.434

Supplemental Table 1.9 (continued).

hydroxyproline	HMDB0000725	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.86 (0.58-1.28)	0.451
pipecolic acid	HMDB0000716	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.87 (0.6-1.26)	0.46
glycine	HMDB0000123	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.13 (0.81-1.59)	0.469
pantothenate	HMDB0000210	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.88 (0.6-1.27)	0.484
betaine	HMDB0000043	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.13 (0.79-1.63)	0.492
N-alpha-acetylarginine	HMDB0004620*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.12 (0.8-1.58)	0.496
N-acetyltryptophan	HMDB0013713	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.89 (0.62-1.26)	0.508
NMMA	HMDB0029416	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.1 (0.79-1.54)	0.583
histidine	HMDB0000177	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.1 (0.77-1.57)	0.589

Supplemental Table 1.9 (continued).

creatine	HMDB0000064	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.91 (0.64-1.29)	0.59
threonine	HMDB0000167	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.09 (0.75-1.57)	0.647
creatinine	HMDB0000562	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.07 (0.77-1.5)	0.678
4-acetamidobutanoate	HMDB0003681	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.93 (0.64-1.34)	0.684
2-aminooctanoic acid	HMDB0000991*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.93 (0.65-1.34)	0.705
citrulline	HMDB0000904	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.94 (0.66-1.33)	0.713
1-methylhistidine	HMDB0000001	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.05 (0.73-1.52)	0.784
oleoyl glycine	HMDB0013631	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.95 (0.65-1.39)	0.806
homoarginine	HMDB0000670*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.05 (0.73-1.5)	0.807

Supplemental Table 1.9 (continued).

proline betaine	HMDB0004827	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.05 (0.72-1.52)	0.808
N-acetylhistidine	HMDB0032055	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.97 (0.68-1.38)	0.87
glutamine	HMDB0000641	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	0.98 (0.69-1.4)	0.903
dimethylglycine	HMDB0000092	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.02 (0.71-1.45)	0.929
aminoisobutyric acid	HMDB0001906*	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.01 (0.72-1.42)	0.944
N-lauroylglycine	HMDB0013272	Carboxylic acids and derivatives	Amino acids, peptides, and analogues	1.01 (0.7-1.45)	0.972
cytosine	HMDB0000630	Diazines	Pyrimidines and pyrimidine derivatives	1.22 (0.87-1.71)	0.257
5-hydroxymethyl-4-methyluracil	HMDB0000544	Diazines	Pyrimidines and pyrimidine derivatives	0.89 (0.63-1.27)	0.535
C5-DC carnitine	HMDB0013130	Fatty Acyls	Fatty acid esters	0.7 (0.5-0.98)	0.036
C4-OH carnitine	HMDB0013127	Fatty Acyls	Fatty acid esters	1.43 (0.98-2.09)	0.064
C14 carnitine	HMDB0005066	Fatty Acyls	Fatty acid esters	1.42 (0.97-2.08)	0.073
C7 carnitine	HMDB0013238	Fatty Acyls	Fatty acid esters	1.27 (0.88-1.82)	0.196
C5:1 carnitine	HMDB0002366	Fatty Acyls	Fatty acid esters	0.8 (0.56-1.15)	0.232
C6 carnitine	HMDB0000705	Fatty Acyls	Fatty acid esters	1.22 (0.84-1.77)	0.289

Supplemental Table 1.9 (continued).

C2 carnitine	HMDB0000201	Fatty Acyls	Fatty acid esters	1.21 (0.84-1.75)	0.307
C9 carnitine	HMDB0013288	Fatty Acyls	Fatty acid esters	1.18 (0.84-1.67)	0.345
C14:1 carnitine	HMDB0002014	Fatty Acyls	Fatty acid esters	1.13 (0.77-1.67)	0.526
C10:2 carnitine	HMDB0013325	Fatty Acyls	Fatty acid esters	0.89 (0.6-1.31)	0.56
C12 carnitine	HMDB0002250	Fatty Acyls	Fatty acid esters	1.12 (0.77-1.63)	0.56
C8 carnitine	HMDB0000791	Fatty Acyls	Fatty acid esters	1.11 (0.77-1.61)	0.577
C12:1 carnitine	HMDB0013326	Fatty Acyls	Fatty acid esters	1.11 (0.76-1.64)	0.58
C5 carnitine	HMDB0000688	Fatty Acyls	Fatty acid esters	1.12 (0.75-1.66)	0.589
C10 carnitine	HMDB0000651	Fatty Acyls	Fatty acid esters	1.11 (0.76-1.61)	0.598
C4 carnitine	HMDB0002013	Fatty Acyls	Fatty acid esters	0.92 (0.65-1.29)	0.621
C26 carnitine	HMDB0006347	Fatty Acyls	Fatty acid esters	1.04 (0.74-1.47)	0.832
C3 carnitine	HMDB0000824	Fatty Acyls	Fatty acid esters	1.03 (0.71-1.5)	0.869
C14:2 carnitine	HMDB0013331	Fatty Acyls	Fatty acid esters	1.03 (0.7-1.51)	0.889
myristoleic acid	HMDB0002000	Fatty Acyls	Fatty acids and conjugates	1.32 (0.92-1.89)	0.136
3-dehydroxycarnitine	HMDB0006831	Fatty Acyls	Fatty acids and conjugates	1.09 (0.77-1.54)	0.622
C34:2 DAG	HMDB0007103*	Fatty Acyls	Lineolic acids and derivatives	1.21 (0.84-1.75)	0.303
C36:3 DAG	HMDB0007219*	Fatty Acyls	Lineolic acids and derivatives	1.09 (0.76-1.57)	0.621
C34:3 DAG	HMDB0007132*	Fatty Acyls	Lineolic acids and derivatives	1.07 (0.74-1.54)	0.727
C36:4 DAG	HMDB0007248*	Fatty Acyls	Lineolic acids and derivatives	0.96 (0.66-1.38)	0.807
C34:0 DAG	HMDB0007100*	Glycerolipids	Diacylglycerols	1.34 (0.91-1.98)	0.137
C36:1 DAG	HMDB0007216*	Glycerolipids	Diacylglycerols	1.3 (0.9-1.9)	0.167
C32:0 DAG	HMDB0007098*	Glycerolipids	Diacylglycerols	1.27 (0.88-1.85)	0.205
C34:1 DAG	HMDB0007102*	Glycerolipids	Diacylglycerols	1.25 (0.86-1.82)	0.236

Supplemental Table 1.9 (continued).

C36:2 DAG	HMDB0007218*	Glycerolipids	Diacylglycerols	1.22 (0.85-1.77)	0.287
C32:1 DAG	HMDB0007099*	Glycerolipids	Diacylglycerols	1.16 (0.8-1.69)	0.434
C38:5 DAG	HMDB0007199*	Glycerolipids	Diacylglycerols	0.91 (0.64-1.29)	0.604
C58:7 TAG	HMDB0005471*	Glycerolipids	Triacylglycerols	0.68 (0.47-0.99)	0.047
C54:9 TAG	HMDB0010498*	Glycerolipids	Triacylglycerols	0.71 (0.49-1.01)	0.059
C54:8 TAG	HMDB0010518*	Glycerolipids	Triacylglycerols	0.71 (0.5-1.03)	0.069
C56:10 TAG	HMDB0010513*	Glycerolipids	Triacylglycerols	0.72 (0.51-1.03)	0.072
C58:6 TAG	HMDB0005458*	Glycerolipids	Triacylglycerols	0.71 (0.49-1.04)	0.077
C52:0 TAG	HMDB0005365*	Glycerolipids	Triacylglycerols	1.42 (0.96-2.11)	0.083
C51:0 TAG	HMDB0031106*	Glycerolipids	Triacylglycerols	1.41 (0.95-2.09)	0.086
C58:10 TAG	HMDB0005476*	Glycerolipids	Triacylglycerols	0.74 (0.52-1.06)	0.102
C54:7 TAG	HMDB0005447*	Glycerolipids	Triacylglycerols	0.74 (0.51-1.07)	0.112
C56:9 TAG	HMDB0005448*	Glycerolipids	Triacylglycerols	0.75 (0.53-1.07)	0.113
C58:11 TAG	HMDB0010531*	Glycerolipids	Triacylglycerols	0.76 (0.53-1.08)	0.122
C55:2 TAG	HMDB0042226*	Glycerolipids	Triacylglycerols	1.34 (0.91-1.96)	0.135
C43:0 TAG	HMDB0042062*	Glycerolipids	Triacylglycerols	1.35 (0.91-2.01)	0.137
C54:1 TAG	HMDB0005395*	Glycerolipids	Triacylglycerols	1.33 (0.9-1.96)	0.15
C54:2 TAG	HMDB0005403*	Glycerolipids	Triacylglycerols	1.31 (0.9-1.92)	0.156
C52:1 TAG	HMDB0005367*	Glycerolipids	Triacylglycerols	1.3 (0.89-1.88)	0.174
C52:7 TAG	HMDB0010517*	Glycerolipids	Triacylglycerols	0.78 (0.54-1.12)	0.175
C50:0 TAG	HMDB0005357*	Glycerolipids	Triacylglycerols	1.31 (0.89-1.93)	0.178
C52:6 TAG	HMDB0005436*	Glycerolipids	Triacylglycerols	0.78 (0.54-1.13)	0.19
C52:2 TAG	HMDB0005369*	Glycerolipids	Triacylglycerols	1.28 (0.88-1.84)	0.195
C56:3 TAG	HMDB0005410*	Glycerolipids	Triacylglycerols	1.27 (0.87-1.85)	0.213
C50:1 TAG	HMDB0005360*	Glycerolipids	Triacylglycerols	1.26 (0.87-1.84)	0.225
C53:2 TAG	HMDB0042196*	Glycerolipids	Triacylglycerols	1.25 (0.86-1.82)	0.239
C48:0 TAG	HMDB0005356*	Glycerolipids	Triacylglycerols	1.26 (0.85-1.85)	0.251
C44:0 TAG	HMDB0042063*	Glycerolipids	Triacylglycerols	1.25 (0.85-1.86)	0.259
C56:6 TAG	HMDB0005456*	Glycerolipids	Triacylglycerols	0.82 (0.58-1.16)	0.259
C51:1 TAG	HMDB0042104*	Glycerolipids	Triacylglycerols	1.24 (0.85-1.81)	0.267

Supplemental Table 1.9 (continued).

C56:8 TAG	HMDB0005392*	Glycerolipids	Triacylglycerols	0.82 (0.57-1.17)	0.271
C46:0 TAG	HMDB0010411*	Glycerolipids	Triacylglycerols	1.23 (0.83-1.83)	0.293
C56:2 TAG	HMDB0005404*	Glycerolipids	Triacylglycerols	1.23 (0.83-1.81)	0.298
C50:6 TAG	HMDB0010497*	Glycerolipids	Triacylglycerols	0.82 (0.56-1.19)	0.299
C56:5 TAG	HMDB0005406*	Glycerolipids	Triacylglycerols	0.83 (0.58-1.18)	0.3
C58:9 TAG	HMDB0005463*	Glycerolipids	Triacylglycerols	0.83 (0.57-1.19)	0.304
C54:3 TAG	HMDB0005405*	Glycerolipids	Triacylglycerols	1.2 (0.83-1.74)	0.336
C47:1 TAG	HMDB0042100*	Glycerolipids	Triacylglycerols	1.2 (0.82-1.76)	0.338
C43:1 TAG	HMDB0042098*	Glycerolipids	Triacylglycerols	1.2 (0.82-1.76)	0.349
C56:1 TAG	HMDB0005396*	Glycerolipids	Triacylglycerols	1.2 (0.81-1.78)	0.357
C50:2 TAG	HMDB0005377*	Glycerolipids	Triacylglycerols	1.19 (0.82-1.73)	0.364
C51:2 TAG	HMDB0005362*	Glycerolipids	Triacylglycerols	1.18 (0.82-1.72)	0.375
C45:1 TAG	HMDB0042099*	Glycerolipids	Triacylglycerols	1.19 (0.81-1.73)	0.376
C49:1 TAG	HMDB0011705*	Glycerolipids	Triacylglycerols	1.17 (0.81-1.69)	0.409
C48:1 TAG	HMDB0005359*	Glycerolipids	Triacylglycerols	1.17 (0.8-1.71)	0.41
C55:3 TAG	HMDB0042466*	Glycerolipids	Triacylglycerols	1.17 (0.8-1.71)	0.412
C50:5 TAG	HMDB0010471*	Glycerolipids	Triacylglycerols	0.86 (0.59-1.25)	0.428
C60:12 TAG	HMDB0005478*	Glycerolipids	Triacylglycerols	0.87 (0.61-1.24)	0.432
C51:3 TAG	HMDB0011701*	Glycerolipids	Triacylglycerols	1.15 (0.79-1.68)	0.463
C56:7 TAG	HMDB0005462*	Glycerolipids	Triacylglycerols	0.88 (0.61-1.25)	0.465
C50:3 TAG	HMDB0005433*	Glycerolipids	Triacylglycerols	1.14 (0.8-1.64)	0.468
C46:1 TAG	HMDB0010412*	Glycerolipids	Triacylglycerols	1.14 (0.78-1.68)	0.492
C49:2 TAG	HMDB0011706*	Glycerolipids	Triacylglycerols	1.13 (0.78-1.64)	0.513
C45:2 TAG	HMDB0043170*	Glycerolipids	Triacylglycerols	1.12 (0.77-1.64)	0.542
C47:2 TAG	HMDB0042076*	Glycerolipids	Triacylglycerols	1.09 (0.75-1.59)	0.634
C48:2 TAG	HMDB0005376*	Glycerolipids	Triacylglycerols	1.09 (0.75-1.59)	0.648
C54:6 TAG	HMDB0005391*	Glycerolipids	Triacylglycerols	0.92 (0.64-1.33)	0.671
C46:2 TAG	HMDB0010419*	Glycerolipids	Triacylglycerols	1.08 (0.74-1.59)	0.681
C53:3 TAG	HMDB0043058*	Glycerolipids	Triacylglycerols	1.06 (0.73-1.54)	0.764
C49:3 TAG	HMDB0042103*	Glycerolipids	Triacylglycerols	1.04 (0.72-1.5)	0.844

Supplemental Table 1.9 (continued).

C52:4 TAG	HMDB0005363*	Glycerolipids	Triacylglycerols	1.03 (0.72-1.48)	0.859
C58:8 TAG	HMDB0005413*	Glycerolipids	Triacylglycerols	0.98 (0.68-1.39)	0.89
C56:4 TAG	HMDB0005398*	Glycerolipids	Triacylglycerols	1.02 (0.7-1.49)	0.914
C54:4 TAG	HMDB0005370*	Glycerolipids	Triacylglycerols	1.02 (0.7-1.47)	0.935
C48:3 TAG	HMDB0005432*	Glycerolipids	Triacylglycerols	0.99 (0.68-1.44)	0.942
C54:5 TAG	HMDB0005385*	Glycerolipids	Triacylglycerols	1.01 (0.7-1.47)	0.946
C43:2 TAG	HMDB0043169*	Glycerolipids	Triacylglycerols	1 (0.69-1.46)	0.999
C34:1 PC plasmalogen-B	HMDB0011239*	Glycerophospholipids	Glycerophosphocholines	1.33 (0.94-1.9)	0.108
C34:3 PC plasmalogen	HMDB0011211*	Glycerophospholipids	Glycerophosphocholines	0.78 (0.54-1.11)	0.171
C16:1 LPC	HMDB0010383*	Glycerophospholipids	Glycerophosphocholines	1.25 (0.87-1.8)	0.232
C36:5 PC plasmalogen-A	HMDB0011221*	Glycerophospholipids	Glycerophosphocholines	0.81 (0.56-1.17)	0.271
C34:1 PC plasmalogen	HMDB0011208*	Glycerophospholipids	Glycerophosphocholines	1.21 (0.85-1.72)	0.287
C38:7 PC plasmalogen	HMDB0011229*	Glycerophospholipids	Glycerophosphocholines	0.84 (0.59-1.19)	0.325
C40:6 PC	HMDB0008057*	Glycerophospholipids	Glycerophosphocholines	0.85 (0.6-1.21)	0.377
C32:0 PC	HMDB0007871*	Glycerophospholipids	Glycerophosphocholines	1.16 (0.81-1.66)	0.417
C40:9 PC	HMDB0008731*	Glycerophospholipids	Glycerophosphocholines	0.87 (0.62-1.22)	0.426
C34:1 PC	HMDB0007972*	Glycerophospholipids	Glycerophosphocholines	1.16 (0.8-1.67)	0.439
C40:10 PC	HMDB0008511*	Glycerophospholipids	Glycerophosphocholines	0.87 (0.6-1.25)	0.45

Supplemental Table 1.9 (continued).

C36:5 PC plasmalogen-B	HMDB0011220*	Glycerophospholipids	Glycerophosphocholines	0.89 (0.63-1.25)	0.494
C16:0 LPC	HMDB0010382	Glycerophospholipids	Glycerophosphocholines	1.14 (0.78-1.66)	0.496
C18:3 LPC	HMDB0010387*	Glycerophospholipids	Glycerophosphocholines	1.14 (0.78-1.66)	0.501
C22:5 LPC	HMDB0010403*	Glycerophospholipids	Glycerophosphocholines	0.9 (0.63-1.28)	0.552
C18:1 LPC	HMDB0002815*	Glycerophospholipids	Glycerophosphocholines	1.12 (0.77-1.61)	0.56
C32:1 PC	HMDB0007873*	Glycerophospholipids	Glycerophosphocholines	1.1 (0.76-1.6)	0.6
C38:6 PC	HMDB0007991*	Glycerophospholipids	Glycerophosphocholines	0.91 (0.64-1.3)	0.612
C14:0 LPC	HMDB0010379	Glycerophospholipids	Glycerophosphocholines	1.1 (0.75-1.61)	0.64
C36:4 PC plasmalogen	HMDB0011310*	Glycerophospholipids	Glycerophosphocholines	1.08 (0.76-1.54)	0.659
C36:2 PC plasmalogen	HMDB0011243*	Glycerophospholipids	Glycerophosphocholines	1.06 (0.75-1.51)	0.733
C36:4 PC-B	HMDB0008138*	Glycerophospholipids	Glycerophosphocholines	0.94 (0.67-1.33)	0.739
C38:4 PC plasmalogen	HMDB0011252*	Glycerophospholipids	Glycerophosphocholines	1.06 (0.75-1.48)	0.758
C32:2 PC	HMDB0007874*	Glycerophospholipids	Glycerophosphocholines	0.95 (0.65-1.37)	0.767
C20:5 LPC	HMDB0010397	Glycerophospholipids	Glycerophosphocholines	1.04 (0.71-1.53)	0.839

Supplemental Table 1.9 (continued).

C22:6 LPC	HMDB0010404	Glycerophospholipids	Glycerophosphocholines	0.97 (0.68-1.38)	0.852
C30:1 PC	HMDB0007870*	Glycerophospholipids	Glycerophosphocholines	1.03 (0.71-1.5)	0.857
C30:0 PC	HMDB0007869*	Glycerophospholipids	Glycerophosphocholines	1.03 (0.71-1.5)	0.859
C36:1 PC	HMDB0008038*	Glycerophospholipids	Glycerophosphocholines	1.03 (0.71-1.49)	0.865
C38:3 PC	HMDB0008047*	Glycerophospholipids	Glycerophosphocholines	1.03 (0.71-1.49)	0.894
C18:0 LPC	HMDB0010384	Glycerophospholipids	Glycerophosphocholines	0.99 (0.68-1.43)	0.938
C18:2 LPC	HMDB0010386*	Glycerophospholipids	Glycerophosphocholines	1 (0.68-1.47)	0.996
C36:1 PE plasmalogen	HMDB0009016*	Glycerophospholipids	Glycerophospho-ethanolamines	1.28 (0.9-1.81)	0.168
C18:0 LPE	HMDB0011130	Glycerophospholipids	Glycerophospho-ethanolamines	1.18 (0.82-1.71)	0.368
C38:6 PE	HMDB0009102*	Glycerophospholipids	Glycerophospho-ethanolamines	0.86 (0.61-1.22)	0.4
C38:5 PE	HMDB0009069*	Glycerophospholipids	Glycerophospho-ethanolamines	0.88 (0.63-1.24)	0.466
C34:3 PE plasmalogen	HMDB0011343*	Glycerophospholipids	Glycerophospho-ethanolamines	0.88 (0.61-1.26)	0.471
C38:6 PE plasmalogen	HMDB0011387*	Glycerophospholipids	Glycerophospho-ethanolamines	0.88 (0.62-1.26)	0.496
C18:1 LPE	HMDB0011506*	Glycerophospholipids	Glycerophospho-ethanolamines	1.13 (0.79-1.64)	0.501

Supplemental Table 1.9 (continued).

C36:0 PE	HMDB0008991*	Glycerophospholipids	Glycerophospho-ethanolamines	1.12 (0.79-1.61)	0.52
C36:3 PE	HMDB0009060*	Glycerophospholipids	Glycerophospho-ethanolamines	0.9 (0.63-1.28)	0.544
C36:5 PE plasmalogen	HMDB0011410*	Glycerophospholipids	Glycerophospho-ethanolamines	0.9 (0.63-1.28)	0.553
C36:4 PE	HMDB0008937*	Glycerophospholipids	Glycerophospho-ethanolamines	0.9 (0.64-1.28)	0.564
C36:2 PE plasmalogen	HMDB0009082*	Glycerophospholipids	Glycerophospho-ethanolamines	1.11 (0.78-1.58)	0.569
C34:0 PE	HMDB0008925*	Glycerophospholipids	Glycerophospho-ethanolamines	1.11 (0.77-1.59)	0.585
C16:0 LPE	HMDB0011503	Glycerophospholipids	Glycerophospho-ethanolamines	1.1 (0.77-1.59)	0.593
C40:6 PE	HMDB0009012*	Glycerophospholipids	Glycerophospho-ethanolamines	0.92 (0.65-1.3)	0.634
C22:0 LPE	HMDB0011520	Glycerophospholipids	Glycerophospho-ethanolamines	0.92 (0.64-1.33)	0.653
C36:4 PE plasmalogen	HMDB0011442*	Glycerophospholipids	Glycerophospho-ethanolamines	0.92 (0.64-1.32)	0.655
C38:7 PE plasmalogen	HMDB0011420*	Glycerophospholipids	Glycerophospho-ethanolamines	0.92 (0.65-1.31)	0.659
C38:4 PE	HMDB0009003*	Glycerophospholipids	Glycerophospho-ethanolamines	0.93 (0.65-1.32)	0.674
C22:6 LPE	HMDB0011526	Glycerophospholipids	Glycerophospho-ethanolamines	0.95 (0.66-1.36)	0.76
C34:2 PE	HMDB0008928*	Glycerophospholipids	Glycerophospho-ethanolamines	0.95 (0.68-1.35)	0.79

Supplemental Table 1.9 (continued).

C18:2 LPE	HMDB0011507*	Glycerophospholipids	Glycerophospho-ethanolamines	1.04 (0.72-1.52)	0.819
C40:7 PE plasmalogen	HMDB0011394*	Glycerophospholipids	Glycerophospho-ethanolamines	0.96 (0.67-1.37)	0.832
C34:2 PE plasmalogen	HMDB0008952*	Glycerophospholipids	Glycerophospho-ethanolamines	1.04 (0.73-1.47)	0.84
C32:0 PE	HMDB0008923*	Glycerophospholipids	Glycerophospho-ethanolamines	1.03 (0.71-1.49)	0.883
C20:4 LPE	HMDB0011517	Glycerophospholipids	Glycerophospho-ethanolamines	1.02 (0.72-1.45)	0.915
C36:1 PE	HMDB0008993*	Glycerophospholipids	Glycerophospho-ethanolamines	1.02 (0.71-1.45)	0.932
C36:2 PE	HMDB0008994*	Glycerophospholipids	Glycerophospho-ethanolamines	1.01 (0.7-1.44)	0.962
C36:3 PE plasmalogen	HMDB0011441*	Glycerophospholipids	Glycerophospho-ethanolamines	1.01 (0.7-1.44)	0.97
C38:5 PE plasmalogen	HMDB0011386*	Glycerophospholipids	Glycerophospho-ethanolamines	1.01 (0.7-1.44)	0.97
C38:2 PE	HMDB0008942*	Glycerophospholipids	Glycerophospho-ethanolamines	1 (0.7-1.43)	0.985
C38:4 PI	HMDB0009815*	Glycerophospholipids	Glycerophosphoinositols	0.97 (0.69-1.36)	0.862
C34:0 PS	HMDB0012356*	Glycerophospholipids	Glycerophosphoserines	0.88 (0.61-1.27)	0.502
1,7-dimethyluric acid	HMDB0011103	Imidazopyrimidines	Purines and purine derivatives	0.93 (0.65-1.33)	0.689

Supplemental Table 1.9 (continued).

7-methylguanine	HMDB0000897	Imidazopyrimidines	Purines and purine derivatives	1.07 (0.75-1.52)	0.718
3-methylxanthine	HMDB0001886	Imidazopyrimidines	Purines and purine derivatives	1.07 (0.74-1.54)	0.73
1-methylguanine	HMDB0003282	Imidazopyrimidines	Purines and purine derivatives	1.06 (0.74-1.54)	0.742
caffeine	HMDB0001847	Imidazopyrimidines	Purines and purine derivatives	0.96 (0.66-1.4)	0.821
7-methylxanthine	HMDB0001991	Imidazopyrimidines	Purines and purine derivatives	1.04 (0.71-1.51)	0.846
uric acid	HMDB0000289	Imidazopyrimidines	Purines and purine derivatives	1.01 (0.7-1.47)	0.937
tryptophan	HMDB0000929	Indoles and derivatives	Indolyl carboxylic acids and derivatives	1.33 (0.92-1.91)	0.125
serotonin	HMDB0000259	Indoles and derivatives	Tryptamines and derivatives	1.1 (0.75-1.61)	0.619
trigonelline	HMDB0000875	NA	NA	0.66 (0.46-0.95)	0.024
thyroxine	HMDB0000248	NA	NA	1.48 (1.02-2.15)	0.039
piperine	HMDB0029377	NA	NA	0.78 (0.54-1.12)	0.181
C34:4 PC	HMDB0007883*	NA	NA	0.84 (0.59-1.21)	0.35
C34:5 PC plasmalogen	HMDB0011214*	NA	NA	1.18 (0.83-1.7)	0.359

Supplemental Table 1.9 (continued).

cerulenin	HMDB0015168	NA	NA	0.85 (0.58-1.24)	0.399
methyl N-methylanthranilate	HMDB0034169	NA	NA	1.17 (0.8-1.72)	0.413
coenzyme Q10	HMDB0001072	NA	NA	0.86 (0.59-1.25)	0.416
C20:1 LPC	HMDB0010391*	NA	NA	0.89 (0.64-1.25)	0.504
2-methyl-4,5-benzoxazole	HMDB0032390	NA	NA	0.89 (0.62-1.29)	0.539
DMGV	HMDB0240212	NA	NA	1.09 (0.75-1.58)	0.652
C20:1 LPE	HMDB0011512*	NA	NA	1.05 (0.73-1.51)	0.781
C36:3 PC plasmalogen	HMDB0011244*	NA	NA	0.95 (0.67-1.36)	0.793
deoxyguanosine	HMDB0000085	NA	NA	0.95 (0.67-1.36)	0.796
C18:3 LPE	HMDB0011478*	NA	NA	0.96 (0.66-1.39)	0.825
C20:4 LPC	HMDB0010395	NA	NA	0.97 (0.69-1.38)	0.882
C34:2 PC plasmalogen	HMDB0011210*	NA	NA	1 (0.7-1.43)	0.994
pseudouridine	HMDB0000767	Nucleoside and nucleotide analogues	NA	1.1 (0.76-1.59)	0.621
N-carbamoyl-beta-alanine	HMDB0000026	Organic carbonic acids and derivatives	Ureas	1.05 (0.73-1.52)	0.775
1-methylhistamine	HMDB0000898	Organonitrogen compounds	Amines	1.1 (0.79-1.53)	0.562
trimethylamine-N-oxide	HMDB0000925	Organonitrogen compounds	Aminoxides	0.97 (0.65-1.45)	0.881
metformin	HMDB0001921	Organonitrogen compounds	Guanidines	0.95 (0.67-1.36)	0.795
phosphocholine	HMDB0001565	Organonitrogen compounds	Quaternary ammonium salts	1.16 (0.81-1.65)	0.417

Supplemental Table 1.9 (continued).

carnitine	HMDB0000062	Organonitrogen compounds	Quaternary ammonium salts	0.97 (0.67-1.38)	0.847
acetyl-galactosamine	HMDB0000212	Organooxygen compounds	Carbohydrates and carbohydrate conjugates	1.48 (1.03-2.12)	0.034
4-hydroxy-3-methylacetophenone	HMDB0059824	Organooxygen compounds	Carbonyl compounds	0.89 (0.61-1.29)	0.531
acetaminophen	HMDB0001859	Phenols	1-hydroxy-2-unsubstituted benzenoids	0.85 (0.59-1.23)	0.393
2-methylguanosine	HMDB0005862	Purine nucleosides	NA	1.73 (1.16-2.59)	0.008
1-methylguanosine	HMDB0001563	Purine nucleosides	NA	1.41 (0.97-2.06)	0.073
N2,N2-dimethylguanosine	HMDB0004824	Purine nucleosides	NA	1.15 (0.79-1.67)	0.463
guanosine	HMDB0000133	Purine nucleosides	NA	0.88 (0.59-1.3)	0.512
1-methylnicotinamide	HMDB0000699	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.72 (0.48-1.06)	0.094
N1-methyl-2-pyridone-5-carboxamide	HMDB0004193	Pyridines and derivatives	Pyridinecarboxylic acids and derivatives	0.76 (0.52-1.11)	0.16
pyridoxamine	HMDB0001431	Pyridines and derivatives	Pyridoxamines	1.41 (0.97-2.04)	0.071
cotinine	HMDB0001046	Pyridines and derivatives	Pyrrolidinylpyridines	1.09 (0.76-1.56)	0.629

Supplemental Table 1.9 (continued).

ribothymidine	HMDB0000884	Pyrimidine nucleosides	NA	1.14 (0.81-1.61)	0.437
N4-acetylcytidine	HMDB0005923	Pyrimidine nucleosides	NA	1.09 (0.77-1.55)	0.609
kynurenic acid	HMDB0000715	Quinolines and derivatives	Quinoline carboxylic acids	0.9 (0.63-1.28)	0.551
Ceramide (d18:1) C16:0	HMDB0004949	Sphingolipids	Ceramides	1.58 (1.1-2.29)	0.014
Ceramide (d18:1) C24:1	HMDB0004953*	Sphingolipids	Ceramides	1.47 (1.02-2.12)	0.037
Ceramide (d18:1) C22:0	HMDB0004952	Sphingolipids	Ceramides	1.28 (0.9-1.82)	0.174
Ceramide (d18:1) C24:0	HMDB0004956	Sphingolipids	Ceramides	1.12 (0.79-1.59)	0.527
C14:0 SM	HMDB0012097	Sphingolipids	Phosphosphingolipids	1.14 (0.8-1.63)	0.464
C22:1 SM	HMDB0012104*	Sphingolipids	Phosphosphingolipids	0.99 (0.69-1.41)	0.949
glycodeoxycholate/glycochenodeoxycholate	HMDB0000631*	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.53 (1.04-2.27)	0.032
glycocholate	HMDB0000138	Steroids and steroid derivatives	Bile acids, alcohols and derivatives	1.36 (0.93-2)	0.117
cholesterol	HMDB0000067	Steroids and steroid derivatives	Cholestane steroids	1.08 (0.75-1.55)	0.69
campesterol	HMDB0002869	Steroids and steroid derivatives	Ergostane steroids	1.1 (0.77-1.59)	0.6

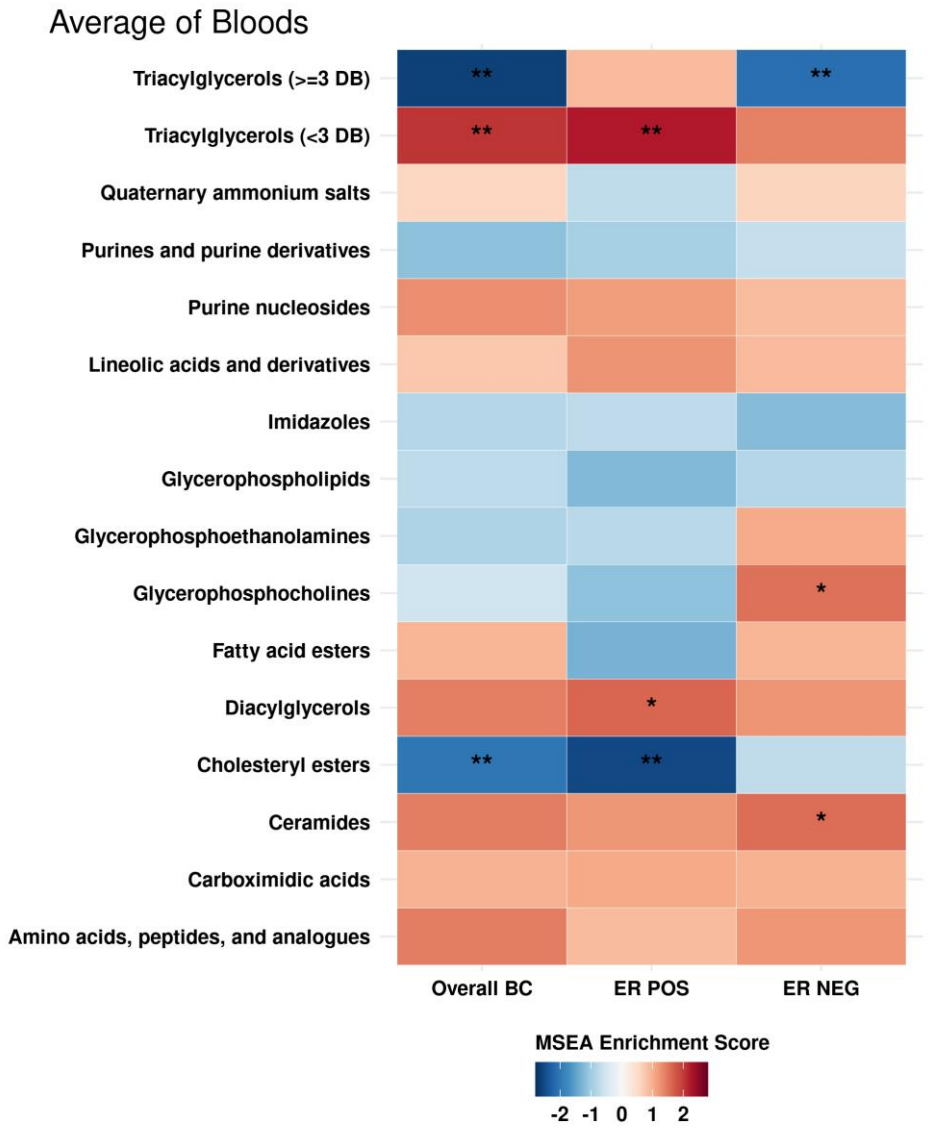
Supplemental Table 1.9 (continued).

cortisol	HMDB0000063	Steroids and steroid derivatives	Hydroxysteroids	1.16 (0.77-1.73)	0.477
cortisone	HMDB0002802	Steroids and steroid derivatives	Hydroxysteroids	1.09 (0.74-1.61)	0.654
21-deoxycortisol	HMDB0004030	Steroids and steroid derivatives	Pregnane steroids	1.18 (0.79-1.76)	0.43
C22:5 CE	HMDB0010375*	Steroids and steroid derivatives	Cholesteryl esters	0.67 (0.46-0.97)	0.035
C20:5 CE	HMDB0006731	Steroids and steroid derivatives	Cholesteryl esters	0.75 (0.52-1.08)	0.12
C18:3 CE	HMDB0010370*	Steroids and steroid derivatives	Cholesteryl esters	0.81 (0.57-1.17)	0.262
C16:0 CE	HMDB0000885	Steroids and steroid derivatives	Cholesteryl esters	0.85 (0.58-1.22)	0.377
C14:0 CE	HMDB0006725	Steroids and steroid derivatives	Cholesteryl esters	0.86 (0.59-1.26)	0.433
C20:3 CE	HMDB0006736*	Steroids and steroid derivatives	Cholesteryl esters	0.88 (0.62-1.25)	0.468
C18:1 CE	HMDB0000918*	Steroids and steroid derivatives	Cholesteryl esters	0.87 (0.6-1.27)	0.47
C18:2 CE	HMDB0000610*	Steroids and steroid derivatives	Cholesteryl esters	0.88 (0.61-1.26)	0.492
C20:4 CE	HMDB0006726	Steroids and steroid derivatives	Cholesteryl esters	0.9 (0.63-1.28)	0.567
C22:6 CE	HMDB0006733	Steroids and steroid derivatives	Cholesteryl esters	0.94 (0.65-1.36)	0.752
C16:1 CE	HMDB0000658*	Steroids and steroid derivatives	Cholesteryl esters	1.04 (0.72-1.49)	0.832

Supplemental Table 1.9 (continued).

C18:0 CE	HMDB0010368	Steroids and steroid derivatives	Cholesteryl esters	0.96 (0.67-1.4)	0.847
bilirubin	HMDB0000054	Tetrapyrroles and derivatives	Bilirubins	0.81 (0.57-1.15)	0.24
biliverdin	HMDB0001008	Tetrapyrroles and derivatives	Bilirubins	1.22 (0.85-1.73)	0.281

**Metabolites with <10% missingness. Missing values imputed with 1/2 minimum value. Results sorted by class, subclass, and p-value for fully adjusted models.
^Multivariable model includes: BMI age 18, weight change from 18 to blood draw, age at menarche, combined age at first birth and parity, breastfeeding history, history of benign breast disease, family history of breast cancer, alcohol use (g/day), activity level (met hrs/week).
*Representative HMDBID



Supplemental Figure 1.3. MSEA results for average of distant and proximate bloods.

APPENDIX 2: Supplementary Materials Chapter 2

Supplemental Table 2.1. Metabolites correlated with BMI with r>|0.15|detected uniquely in premenopausal or postmenopausal-only participant groups.[†]

HMDBID	Metabolite name	Metabolite class	Spearman correlation*	
			Premenopausal women	Postmenopausal women
Uniquely selected in premenopausal women				
HMDB0000064	creatine	Carboxylic acids and derivatives	0.18	0.03
HMDB0000112	GABA	Carboxylic acids and derivatives	0.16	0.09
HMDB0000182	lysine	Carboxylic acids and derivatives	0.21	0.06
HMDB0029416	NMMA	Carboxylic acids and derivatives	0.20	0.10
HMDB0000705	C6 carnitine	Fatty Acyls	0.19	0.14
HMDB0005385	C54:5 TAG	Glycerolipids	0.29	0.12
HMDB0005410	C56:3 TAG	Glycerolipids	0.19	0.10
HMDB0010517	C52:7 TAG	Glycerolipids	0.25	0.13
HMDB0002815	C18:1 LPC	Glycerophospholipids	-0.25	-0.14
HMDB0007870	C30:1 PC	Glycerophospholipids	0.20	0.06
HMDB0007873	C32:1 PC	Glycerophospholipids	0.24	0.09
HMDB0007874	C32:2 PC	Glycerophospholipids	0.20	0.01
HMDB0007883	C34:4 PC	Glycerophospholipids	0.24	0.06
HMDB0008138	C36:4 PC-B	Glycerophospholipids	0.22	0.09
HMDB0009003	C38:4 PE	Glycerophospholipids	0.18	0.14
HMDB0010379	C14:0 LPC	Glycerophospholipids	0.17	0.07
HMDB0010391	C20:1 LPC	Glycerophospholipids	-0.30	-0.10
HMDB0011503	C16:0 LPE	Glycerophospholipids	-0.16	-0.13
HMDB0001431	pyridoxamine	Pyridines and derivatives	0.22	0.11
HMDB0004949	C16:0 Ceramide (d18:1)	Sphingolipids	0.20	0.09
HMDB0004956	C24:0 Ceramide (d18:1)	Sphingolipids	0.21	0.02
HMDB0012097	C14:0 SM	Sphingolipids	0.23	0.01
HMDB0012104	C22:1 SM	Sphingolipids	0.22	-0.02

Supplemental Table 2.1 (continued).

HMDB0000067	cholesterol	Steroids and steroid derivatives	0.25	0.04
HMDB0002869	campesterol	Steroids and steroid derivatives	0.21	0.02
HMDB0010370	C18:3 CE	Steroids and steroid derivatives	-0.20	-0.14
HMDB0000054	bilirubin	Tetrapyrroles and derivatives	-0.16	-0.09
HMDB0001008	biliverdin	Tetrapyrroles and derivatives	-0.17	-0.07
Uniquely selected in postmenopausal women				
HMDB0000462	allantoin	Azoles	0.07	0.16
HMDB0007991	C38:6 PC	Glycerophospholipids	-0.02	-0.17
HMDB0008511	C40:10 PC	Glycerophospholipids	-0.01	-0.19
HMDB0008731	C40:9 PC	Glycerophospholipids	-0.03	-0.17
HMDB0008942	C38:2 PE	Glycerophospholipids	-0.14	-0.23
HMDB0008993	C36:1 PE	Glycerophospholipids	0.15	0.16
HMDB0000897	7-methylguanine	Imidazopyrimidines	0.04	0.16
HMDB0006731	C20:5 CE	Steroids and steroid derivatives	-0.12	-0.17

† Does not include 80 metabolites that overlapped between pre-and postmenopausal groups.
*Spearman correlations with BMI, adjusted for age at blood draw.

Supplemental Table 2.2. Comparison of selected metabolites & coefficients using LASSO, Ridge, and Stepwise regression.*

RIDGE^			LASSO^	STEPWISE^
HMDBID	Metabolite Name	coefficient	coefficient	coefficient
	Intercept	25.98202087	25.99	26.00
HMDB0000062	carnitine	0.106147338	0.11	0.18
HMDB0000067	cholesterol	0.304588118	0.25	0.45
HMDB0000123	glycine	-0.144932927	-0.10	-0.12
HMDB0000128	guanidinoacetic acid	-0.347399399	-0.31	-0.25
HMDB0000158	tyrosine	0.423924003	0.42	0.48
HMDB0000159	phenylalanine	-0.067707381	-0.04	0.18
HMDB0000161	alanine	0.115781243	0.08	
HMDB0000162	proline	0.19004368	0.17	
HMDB0000172	isoleucine	0.053466025	0.05	
HMDB0000182	lysine	-0.42334201	-0.44	-0.36
HMDB0000201	C2 carnitine	-0.475298989	-0.53	-0.59
HMDB0000289	urate	0.496583223	0.50	0.48
HMDB0000610	C18:2 CE	0.360647212	0.30	
HMDB0000687	leucine	-0.583394966	-0.71	-0.78
HMDB0000688	C5 carnitine	0.04480631	0.01	
HMDB0000705	C6 carnitine	**0.010208859**		
HMDB0000767	pseudouridine	-0.284301997	-0.28	
HMDB0000824	C3 carnitine	0.057393976	0.07	0.90
HMDB0000883	valine	0.711388316	0.82	
HMDB0000885	C16:0 CE	-0.019795215	-0.03	1.29
HMDB0000918	C18:1 CE	-0.111788835	-0.05	
HMDB0001431	pyridoxamine	0.15923255	0.15	
HMDB0001563	1-methylguanosine	0.069687865	0.05	
HMDB0002815	C18:1 LPC	0.628221491	0.94	0.51
HMDB0004824	N2,N2-dimethylguanosine	0.510699619	0.53	
HMDB0004949	C16:0 Ceramide (d18:1)	0.015035744	-0.01	
HMDB0004952	C22:0 Ceramide (d18:1)	**0.027635701**		
HMDB0005356	C48:0 TAG	0.178525936	0.16	
HMDB0005357	C50:0 TAG	-0.3534856	-0.22	
HMDB0005359	C48:1 TAG	**-0.241278644**		**-0.44**
HMDB0005360	C50:1 TAG	0.370956461	0.67	1.22
HMDB0005362	C51:2 TAG	0.345780338	0.39	0.36
HMDB0005363	C52:4 TAG	-0.278114934	-0.39	-0.81
HMDB0005367	C52:1 TAG	**0.256205433**		
HMDB0005369	C52:2 TAG	-0.053368442	-0.03	
HMDB0005376	C48:2 TAG	-0.306917631	-0.37	
HMDB0005377	C50:2 TAG	**0.146623013**		

Supplemental Table 2.2 (continued)

HMDB0005385	C54:5 TAG	0.252782035	0.26	0.36
HMDB0005403	C54:2 TAG	0.413031716	0.59	0.89
HMDB0005410	C56:3 TAG	-0.763104443	-0.90	-0.97
HMDB0005432	C48:3 TAG	**-0.047307183**		
HMDB0005433	C50:3 TAG	0.348607776	0.40	0.63
HMDB0005436	C52:6 TAG	-0.306822888	-0.38	-0.63
HMDB0005923	N4-acetylcytidine	0.31046602	0.29	
HMDB0006725	C14:0 CE	-0.976890955	-1.08	-1.13
HMDB0006726	C20:4 CE	0.763483701	0.87	1.05
HMDB0006733	C22:6 CE	-0.155431829	-0.04	
HMDB0007098	C32:0 DAG	-0.482528308	-0.59	-1.28
HMDB0007099	C32:1 DAG	-0.303180041	-0.46	-1.18
HMDB0007100	C34:0 DAG	-0.317971606	-0.31	
HMDB0007102	C34:1 DAG	0.350669709	0.36	1.42
HMDB0007103	C34:2 DAG	**-0.08986484**		
HMDB0007132	C34:3 DAG	0.401514173	0.41	0.69
HMDB0007199	C38:5 DAG	0.076399787	0.08	
HMDB0007216	C36:1 DAG	0.391857334	0.46	
HMDB0007218	C36:2 DAG	-0.172890317	-0.48	-1.28
HMDB0007219	C36:3 DAG	**-0.122206603**		1.27
HMDB0007248	C36:4 DAG	0.503809501	0.70	
HMDB0007870	C30:1 PC	0.106568938	0.02	
HMDB0007873	C32:1 PC	0.031910606	0.08	
HMDB0007883	C34:4 PC	-0.348927632	-0.25	
HMDB0008047	C38:3 PC	1.223053435	1.45	1.50
HMDB0008138	C36:4 PC-B	-0.304165142	-0.38	-0.67
HMDB0008942	C38:2 PE	-0.891646454	-0.97	-0.93
HMDB0008993	C36:1 PE	0.063665073	0.00	
HMDB0008994	C36:2 PE	**-0.052797588**		
HMDB0009003	C38:4 PE	-0.585272323	-0.60	-0.59
HMDB0009016	C36:1 PE plasmalogen	0.299672558	0.35	0.36
HMDB0010370	C18:3 CE	**0.065061851**		
HMDB0010375	C22:5 CE	-0.578697171	-0.63	-0.68
HMDB0010386	C18:2 LPC	-0.42683284	-0.48	-2.50
HMDB0010391	C20:1 LPC	-0.301687655	-0.32	-0.34
HMDB0010397	C20:5 LPC	0.076654402	0.04	1.94
HMDB0010404	C22:6 LPC	-0.486530215	-0.59	-0.68
HMDB0010411	C46:0 TAG	**0.098556369**		
HMDB0010412	C46:1 TAG	**0.019159901**		
HMDB0010419	C46:2 TAG	**0.080380515**		
HMDB0010471	C50:5 TAG	**-0.088392325**		
HMDB0010497	C50:6 TAG	**-0.002549172**		

Supplemental Table 2.2 (continued)

HMDB0010517	C52:7 TAG	**0.030071205**		
HMDB0011208	C34:1 PC plasmalogen	-0.138887605	-0.14	-0.15
HMDB0011210	C34:2 PC plasmalogen	**0.013612643**		
HMDB0011211	C34:3 PC plasmalogen	0.582000349	0.81	0.94
HMDB0011239	C34:1 PC plasmalogen-B	-0.423042446	-0.42	-0.42
HMDB0011243	C36:2 PC plasmalogen	**-0.021762429**		
HMDB0011244	C36:3 PC plasmalogen	-0.778343614	-1.06	-1.16
HMDB0011310	C36:4 PC plasmalogen	**-0.032532688**		
HMDB0011520	C22:0 LPE	-0.564067651	-0.68	-0.89
HMDB0011701	C51:3 TAG	**0.007257966**		
HMDB0011706	C49:2 TAG	-0.253317864	-0.14	
HMDB0012097	C14:0 SM	1.223244269	1.33	1.29
HMDB0013127	C4-OH carnitine	0.818012156	0.91	0.96
HMDB0029416	NMMA	0.220684438	0.24	0.26
HMDB0031106	C51:0 TAG	**-0.047851562**		
HMDB0042076	C47:2 TAG	**-0.140263825**		
HMDB0042103	C49:3 TAG	**0.173861546**		
HMDB0042104	C51:1 TAG	0.278092722	0.08	
HMDB0042196	C53:2 TAG	0.305789122	0.42	0.47
HMDB0042226	C55:2 TAG	**-0.025664489**		

*Metabolites unique to Ridge or to Stepwise regression (i.e. not included in LASSO equation) are in bold.

^ LASSO regression uses a penalty (λ=0.003, α=1). Ridge regression using a penalty equivalent to square of the magnitude of the coefficients (λ=0.20, α=0). Lasso and ridge regression perfomed using glmnet function in R, with cross-validation. Stepwise selection performed in both directions, using OLSRR package in R.

Supplemental Table 2.3. Quartile values for adiposity measures, true and predicted, in entire cohort (pre- and post-menopausal combined).

Adiposity Measures	*Quartile 1*	*Quartile 2*	*Quartile 3*
Self-reported			
BMI (kg/m2)	22.16	24.74	28.35
Waist circumference (cm)	71.12	78.74	88.9
Weight change (kg)	4.55	10.91	19.55
Fat mass	20.61	24.78	30.88
Metabolomic Score			
BMI (kg/m2)	23.26	25.56	28.3
Waist circumference (cm)	76.61	81.4	86.61
Weight change (kg)	6.94	12.32	18.50
Fat mass	22.55	26.39	30.44

Supplemental Table 2.4a. Association between true and metabolomic-predicted adiposity scores & ER+ breast cancer incidence for women by menopausal status at blood draw and/or diagnosis.†

Adiposity Measures	Quartile 1*		Quartile 2*			Quartile 3*			Quartile 4*			
Premenopausal at blood draw												
Self-reported measures	N ca/co	OR (95% CI)	N cases/ controls	OR	95 % CI	N cases/ controls	OR	95% CI	N cases/ controls	OR	95% CI	p-trend^
BMI (kg/m2)	139/62	1.0 (ref)	132/195	1.33	(0.97-1.82)	90/175	1.03	(0.72-1.46)	80/181	0.95	(0.63-1.44)	0.54
Waist circumference (cm)	76/140	1.0 (ref)	96/152	1.18	(0.80-1.74)	60/120	0.86	(0.56-1.34)	37/82	0.87	(0.50- 1.51)	0.41
Weight change (kg)	118/210	1.0 (ref)	133/253	0.86	(0.63-1.18)	99/185	0.86	(0.61-1.21)	88/168	0.89	(0.62-1.27)	0.57
Fat mass	98/171	1.0 (ref)	82/108	1.32	(0.89-1.95)	36/102	0.59	(0.36-0.94)	48/98	0.85	(0.51-1.42)	0.07
Metabolomic Score												
BMI (kg/m2)	154/225	1.0 (ref)	108/212	0.73	(0.53-1.00)	82/188	0.65	(0.46-0.91)	97/188	0.78	(0.55-1.11)	0.1
Waist circumference (cm)	78/135	1.0 (ref)	85/127	1.15	(0.77-1.72)	54/124	0.72	(0.47-1.12)	52/108	0.85	(0.54-1.35)	0.22
Weight change (kg)	149/216	1.0 (ref)	105/221	0.69	(0.50-0.94)	94/184	0.73	(0.52-1.02)	90/195	0.67	(0.48-0.95)	0.04
Fat mass	89/125	1.0 (ref)	75/130	0.79	(0.53-1.19)	45/118	0.53	(0.33-0.82)	55/107	0.73	(0.47-1.15)	0.06

Supplemental Table 2.4a (continued).

Premenopausal at blood draw & diagnosis												
Self-reported measures	N cases/ controls	OR (95% CI)	N cases/ controls	OR	95% CI	N cases/ controls	OR	95% CI	N cases/ controls	OR	95% CI	p-trend^
BMI (kg/m2)	80/148	1.0 (ref)	64/109	1.08	(0.70-1.66)	46/93	0.86	(0.54-1.39)	36/91	0.63	(0.34-1.13)	0.10
Waist circumference (cm)	36/78	1.0 (ref)	53/74	1.49	(0.86-2.60)	35/61	1.07	(0.59-1.96)	17/45	0.67	(0.30-1.46)	0.25
Weight change (kg)	64/122	1.0 (ref)	72/140	0.91	(0.59-1.39)	46/96	0.85	(0.52-1.37)	41/82	0.86	(0.52-1.41)	0.53
Fat mass	58/85	1.0 (ref)	38/59	0.85	(0.49-1.46)	20/50	0.46	(0.23-0.90)	21/54	0.45	(0.21-0.91)	0.03
Metabolomic Score												
BMI (kg/m2)	75/134	1.0 (ref)	59/116	0.88	(0.57-1.36)	45/100	0.81	(0.51-1.28)	47/91	0.89	(0.55-1.46)	0.56
Waist circumference (cm)	40/78	1.0 (ref)	50/69	1.41	(0.81-2.45)	28/54	1.01	(0.55-1.87)	23/57	0.77	(0.39-1.49)	0.33
Weight change (kg)	77/126	1.0 (ref)	54/131	0.68	(0.44-1.05)	51/89	0.95	(0.60-1.51)	41/94	0.69	(0.42-1.12)	0.27
Fat mass	43/74	1.0 (ref)	47/64	1.26	(0.72-2.21)	22/57	0.64	(0.34-1.22)	25/53	0.80	(0.41-1.53)	0.22
Postmenopausal at blood draw												
Self-reported measures	N cases/ controls	OR (95% CI)	N cases/ controls	OR	95% CI	N cases/ controls	OR	95% CI	N cases/ controls	OR	95% CI	p-trend
BMI (kg/m2)	65/119	1.0 (ref)	89/181	0.88	(0.59-1.32)	133/205	1.27	(0.86-1.87)	138/200	1.55	(1.04-2.34)	0.003
Waist circumference (cm)	26/49	1.0 (ref)	69/104	1.22	(0.68-2.21)	90/165	1.01	(0.58-1.79)	149/228	1.3	(0.76-2.28)	0.21

Supplemental Table 2.4a (continued).

Weight change (kg)	67/142	1.0 (ref)	89/147	1.19	(0.79-1.80)	116/197	1.21	(0.82-1.80)	139/189	1.56	(1.06-2.31)	0.02
Fat mass	43/78	1.0 (ref)	70/138	0.85	(0.53-1.38)	93/169	0.98	(0.62-1.57)	109/146	1.57	(0.98-2.56)	0.83
Metabolomic Score												
BMI (kg/m2)	64/158	1.0 (ref)	99/168	1.53	(1.04-2.27)	141/197	1.92	(1.32-2.81)	121/182	1.93	(1.30-2.86)	0.001
Waist circumference (cm)	60/136	1.0 (ref)	70/130	1.27	(0.83-1.96)	93/143	1.62	(1.07-2.48)	111/137	2.11	(1.39-3.24)	<0.0001
Weight change (kg)	71/156	1.0 (ref)	92/167	1.23	(0.83-1.81)	128/177	1.7	(1.17-2.47)	120/175	1.66	(1.14-2.45)	0.004
Fat mass	53/128	1.0 (ref)	71/130	1.43	(0.92-2.25)	91/138	1.76	(1.15-2.73)	100/135	2.15	(1.39-3.37)	0.001

† Multivariable logistic regression models adjusted for: age at menarche, age at first birth and parity combined, breastfeeding history, history of benign breast disease, BMI at age 18 (kg/m2), hormone use at blood draw (any v. none), alcohol use (g/day) at blood draw, and activity level (MET-hrs/week) at blood draw

*Quartile values were determined from the full cohort (pre-and postmenopausal at blood draw) for each measure. See Supplemental Table 3 for values.

^ p-trend calculated using median of quartiles (defined by the overall cohort)

Supplemental Table 2.4b. Association between true and metabolomic-predicted adiposity scores & ER- breast cancer incidence for women by menopausal status at blood draw.†

Adiposity Measures	Tertile 1*		Tertile 2*			Tertile 3*			
Premenopausal at blood draw									
Self-reported measures	N cases/ controls	OR (95% CI)	N cases/controls	OR	95% CI	N cases/ controls	OR	95% CI	p-trend
BMI (kg/m2)	42/311	1.0 (ref)	26/265	0.77	(0.44 , 1.31)	26/237	0.99	(0.52 , 1.85)	1
Waist circumference (cm)	25/195	1.0 (ref)	21/191	0.86	(0.45 , 1.64)	17/108	1.35	(0.62 , 2.88)	0.46
Weight change (kg)	40/339	1.0 (ref)	31/256	1.01	(0.60 , 1.67)	23/221	0.94	(0.53 , 1.64)	0.84
Fat mass	21/212	1.0 (ref)	23/139	1.66	(0.85 , 3.24)	16/129	1.42	(0.62 , 3.20)	0.42
Metabolomic Score									
BMI (kg/m2)	38/285	1.0 (ref)	32/276	0.89	(0.53 , 1.47)	24/252	0.78	(0.43 , 1.37)	0.38
Waist circumference (cm)	17/173	1.0 (ref)	25/169	1.52	(0.79 , 2.99)	21/152	1.53	(0.75 , 3.15)	0.25
Weight change (kg)	34/295	1.0 (ref)	35/265	1.2	(0.72 , 1.99)	25/256	0.93	(0.52 , 1.63)	0.82
Fat mass	23/159	1.0 (ref)	16/169	0.64	(0.32 , 1.27)	21/152	0.99	(0.50 , 1.93)	0.96
Premenopausal at blood draw & diagnosis									
Self-reported measures	N cases/controls	OR (95% CI)	N cases/controls	OR	95% CI	N cases/controls	OR	95% CI	
BMI (kg/m2)	24/175	1.0 (ref)	12/149	0.61	(0.28 , 1.29)	18/117	1.21	(0.53 , 2.69)	0.58
Waist circumference (cm)	14/102	1.0 (ref)	11/101	0.65	(0.26 , 1.59)	10/55	1	(0.34 , 2.84)	0.98
Weight change (kg)	22/192	1.0 (ref)	19/137	1.17	(0.59 , 2.29)	13/111	0.95	(0.44 , 1.99)	0.92
Fat mass	12/109	1.0 (ref)	11/72	1.22	(0.48 , 3.08)	10/67	1.25	(0.40 , 3.72)	0.7
Metabolomic Score									
BMI (kg/m2)	21/172	1.0 (ref)	19/147	1.08	(0.55 , 2.12)	14/122	0.88	(0.40 , 1.89)	0.77
Waist circumference (cm)	8/101	1.0 (ref)	14/81	2.19	(0.86 , 5.87)	13/76	2.18	(0.82 , 6.09)	0.12
Weight change (kg)	19/170	1.0 (ref)	19/149	1.19	(0.60 , 2.36)	16/121	1.17	(0.55 , 2.49)	0.67
Fat mass	12/89	1.0 (ref)	8/86	0.65	(0.24 , 1.71)	13/73	1.35	(0.53 , 3.47)	0.53

Supplemental Table 2.4b (continued).

	Postmenopausal at blood draw								
Self-reported measures	N cases/controls	OR (95% CI)	N cases/controls	OR	95% CI	N cases/controls	OR	95% CI	
BMI (kg/m2)	19/174	1.0 (ref)	32/250	1.1	(0.60 , 2.08)	21/281	0.68	(0.34 , 1.39)	0.2
Waist circumference (cm)	6/79	1.0 (ref)	28/199	2.09	(0.85 , 5.96)	21/268	1.11	(0.43 , 3.28)	0.4
Weight change (kg)	19/211	1.0 (ref)	27/215	1.16	(0.61 , 2.25)	24/249	0.85	(0.44 , 1.67)	0.51
Fat mass	14/110	1.0 (ref)	18/215	0.64	(0.30 , 1.38)	21/206	0.85	(0.40 , 1.84)	0.93
Metabolomic Score									
BMI (kg/m2)	31/205	1.0 (ref)	16/240	0.37	(0.18 , 0.70)	25/260	0.56	(0.30 , 1.01)	0.08
Waist circumference (cm)	23/177	1.0 (ref)	14/173	0.53	(0.25 , 1.08)	18/196	0.62	(0.31 , 1.22)	0.18
Weight change (kg)	26/203	1.0 (ref)	21/224	0.63	(0.33 , 1.18)	23/248	0.61	(0.32 , 1.14)	0.14
Fat mass	22/166	1.0 (ref)	11/176	0.43	(0.19 , 0.91)	20/189	0.71	(0.35 , 1.40)	0.36

† Multivariable logistic regression models adjusted for: age at menarche, age at first birth and parity combined, breastfeeding history, history of benign breast disease, BMI at age 18 (kg/m2), hormone use at blood draw (any v. none), alcohol use (g/day) at blood draw, and activity level (MET-hrs/week) at blood draw

*Tertile values were determined from the full cohort (pre-and postmenopausal at blood draw) for each measure.

^ p-trend calculated using median of tertiles (defined by the overall cohort)

Supplemental Table 2.5. Association between true and metabolomic-predicted adiposity scores & breast cancer incidence for women premenopausal at blood draw and postmenopausal at diagnosis.†

Adiposity Measures	Quartile 1*		Quartile 2*		Quartile 3*		Quartile 4*		
Self-reported	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	p-trend ^
BMI (kg/m2)	84/85	1.0 (ref)	79/67	1.39 (0.87-2.24)	58/70	1.05 (0.63-1.75)	66/69	1.35 (0.76-2.41)	0.51
Waist circumference (cm)	40/48	1.0 (ref)	63/61	1.33 (0.76-2.35)	40/46	1.18 (0.62-2.24)	36/29	1.74 (0.81-3.76)	0.22
Weight change (kg)	76/68	1.0 (ref)	83/83	0.88 (0.55-1.41)	59/75	0.68 (0.41-1.12)	67/69	0.86 (0.52-1.42)	0.49
Fat mass	50/66	1.0 (ref)	56/38	2.33 (1.30-4.24)	28/42	1.12 (0.58-2.16)	44/36	2.18 (1.07-4.52)	0.67
Metabolomic Score									
BMI (kg/m2)	97/68	1.0 (ref)	65/73	0.64 (0.40-1.02)	56/75	0.59 (0.36-0.96)	69/75	0.68 (0.41-1.12)	0.11
Waist circumference (cm)	51/44	1.0 (ref)	47/41	1.09 (0.59-2.01)	29/57	0.46 (0.24-0.87)	52/42	1.19 (0.64-2.21)	0.98
Weight change (kg)	90/68	1.0 (ref)	62/68	0.66 (0.41-1.07)	69/79	0.68 (0.42-1.08)	66/80	0.62 (0.38-1.02)	0.07
Fat mass	55/37	1.0 (ref)	41/51	0.56 (0.30-1.01)	32/50	0.47 (0.25-0.88)	50/44	0.82 (0.44-1.54)	0.47

† Multivariable logistic regression models adjusted for: age at menarche, age at first birth and parity combined, breastfeeding history, history of benign breast disease, BMI at age 18 (kg/m2), hormone use at blood draw (any v. none), alcohol use (g/day) at blood draw, and activity level (MET-hrs/week) at blood draw

*Quartile values were determined from the full cohort (pre-and postmenopausal at blood draw) for each measure. See Supplemental Table 3 for values.

^ p-trend calculated using median of quartiles (defined by the overall cohort)

Supplemental Table 2.6. Odds ratio (95% confidence interval) for self-reported adiposity measures and adiposity metabolomic scores, cross-classified as above or below the median, with breast cancer, by menopausal status at blood draw and diagnosis.[†]

	Below median in both		Above median true, Below median predicted		Below median true, Above median predicted		Above median in both	
	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)	N cases/ controls	OR (95% CI)
BMI								
Premenopausal	396/355	1.0 (ref)	83/82	0.98 (0.69-1.40)	98/102	0.85 (0.62-1.17)	243/274	0.88 (0.69-1.14)
Pre-Pre*	218/203	1.0 (ref)	43/47	0.85 (0.52-1.37)	58/54	1.00 (0.65-1.53)	122/137	0.82 (0.58-1.17)
Postmenopausal	197/213	1.0 (ref)	92/113	0.97 (0.68-1.37)	75/87	0.89 (0.61-1.30)	323/292	1.35 (1.04-1.77)
Weight change								
Premenopausal	374/364	1.0 (ref)	97/73	1.23 (0.87-1.74)	96/99	0.99 (0.72-1.37)	250/280	0.89 (0.70-1.12)
Pre-Pre	217/214	1.0 (ref)	45/43	0.98 (0.62-1.57)	49/48	1.03 (0.66-1.62)	127/135	0.91 (0.66-1.26)
Postmenopausal	175/213	1.0 (ref)	106/110	1.12 (0.79-1.59)	82/76	1.42 (0.97-2.08)	301/276	1.35 (1.03-1.77)
Waist circumference								
Premenopausal	232/205	1.0 (ref)	59/57	0.88 (0.58-1.35)	83/87	0.85 (0.59-1.23)	130/145	0.78 (0.56-1.08)
Pre-Pre	137/111	1.0 (ref)	33/36	0.68 (0.39-1.19)	41/40	0.79 (0.47-1.33)	66/70	0.70 (0.44-1.10)
Postmenopausal	119/122	1.0 (ref)	108/144	0.76 (0.52-1.10)	41/31	1.26 (0.73-2.18)	260/249	1.13 (0.82-1.56)
FM								
Premenopausal	239/207	1.0 (ref)	47/48	0.78 (0.49-1.26)	77/72	0.90 (0.62-1.32)	131/153	0.72 (0.52-1.01)
Pre-Pre	140/116	1.0 (ref)	23/22	0.67 (0.33-1.33)	40/28	1.11 (0.64-1.95)	67/82	0.59 (0.38-0.93)
Postmenopausal	136/163	1.0 (ref)	74/95	0.97 (0.65-1.44)	52/53	1.15 (0.73-1.82)	236/220	1.38 (1.02-1.88)

† Multivariable logistic regression models adjusted for: age at menarche, age at first birth and parity combined, breastfeeding history, history of benign breast disease, BMI at age 18 (kg/m2), hormone use at blood draw (any v. none), alcohol consumption (g/day) at blood draw, and physical activity level (MET-hrs/week) at blood draw.
*Premenopausal at blood draw and at diagnosis

APPENDIX 3: Supplementary Materials Chapter 3

Supplemental Table 3.1. Participant Characteristics at study entry, for subset with full birth index information, derivation & validation data (N=149,099 N cases=2,402)^

	Derivation Data (N=99,518)			Validation data (N=49,581)		
	GS	NHS	NHSII	GS	NHS	NHSII
N	27,939	20,848	50,731	13,804	10,382	25,395
N cases (full study)	208	453	949	110	227	455
Premenopausal duration	24.6 (8.1)	26.2 (6.3)	22.0 (5.0)	24.7 (8.1)	26.1 (6.4)	22.0 (5.0)
Age (years)	37.3 (8.1)	38.6 (6.2)	34.4 (4.7))	37.4 (8.0)	38.5 (6.3)	34.4 (4.7)
Age at menarche (years)	12.7 (1.4)	12.4 (1.4)	12.4 (1.4)	12.7 (1.4)	12.4 (1.4)	12.4 (1.4)
Parous (yes)	16628 (60%)	18368 (88%)	33052 (65%)	8,380 (61%)	9,127 (88%)	16,473 (65%)
Parity*	1.7 (0.5)	1.7 (0.5)	1.6 (0.5)	1.7 (0.5)	1.7 (0.5)	1.6 (0.5)
Age from menarche to first birth*	15.7 (4.8)	13.3 (3.8)	13.8 (4.3)	15.6 (4.9)	13.3 (3.8)	13.7 (4.3)
Age at first birth (years)*	28.3 (4.7)	25.8 (3.6)	26.2 (4.1)	28.2 (4.8)	25.8 (3.6)	26.1 (4.1)
Birth index*	19.3 (15.1)	20.3 (12.6)	13.2 (10.5)	19.4 (15.2)	20.0 (12.6)	13.3 (10.5)
Breastfeeding duration, months*	10.6 (10.9)	17.1 (10.8)	17.3 (9.5)	10.4 (10.7)	17.1 (10.8)	17.4 (9.5)
Oral contraceptive use (%)	26,336 (94%)	12,327 (59%)	42,393 (84%)	12,990 (94%)	6,201 (60%)	21,222 (84%)
Height (cm)	165.3 (6.6)	164.1 (6.2)	164.9 (6.5)	165.3 (6.5)	164.2 (6.1)	164.9 (6.5)
BMI (kg/m2)	24.9 (4.6)	23.3 (4.0)	24.0 (4.9)	24.9 (4.7)	23.3 (4.1)	24.0 (4.9)
BMI in young adulthood (kg/m2)	22.1 (3.2)	21.4 (3.1)	21.4 (3.4)	22.0 (3.2)	21.5 (3.1)	21.3 (3.3)
Weight Change last 4 yrs (kg)	0.65 (2.47)	0.12 (0.34)	0.54 (2.50)	0.64 (2.49)	0.11 (0.35)	0.54 (2.48)
Alcohol (drinks/week)	5.9 (6.7)	3.5 (5.7)	1.9 (3.7)	5.8 (6.6)	3.5 (5.8)	1.9 (3.6)
Family history of BC (%)	4,071 (15%)	1,119 (5.4%)	8,025 (16%)	2,044 (15%)	557 (5.4%)	3,985 (16%)
BBD (yes) (%)	4,040 (14%)	10,430 (50%)	27,984 (55%)	2,032 (15%)	5,192 (50%)	13,903 (55%)

^Continuous variables given in mean (SD). Categorical variables with N (%).
*Among parous women

Supplemental Table 3.2. Participant Characteristics at study entry, for subset with PRS, derivation & validation data.^

	Derivation		Validation	
	NHS	NHSII	NHS	NHSII
N	3207	2483	1509	1086
N cases (full study)	161	537	72	245
Premenopausal duration	28.6 (5.9)	24.3 (4.5)	28.4 (5.9)	24.2 (4.6)
Age (years)	41.1 (5.9)	36.7 (4.2)	40.9 (5.8)	36.5 (4.3)
Age at menarche (years)	12.5 (1.3)	12.4 (1.4)	12.5 (1.3)	12.4 (1.4)
Parous (yes)	2871 (95%)	575 (75%)	1430 (95%)	820 (76%)
Parity*	3.1 (1.5)	2.0 (0.9)	3.1 (1.5)	2.1 (1.0)
Age from menarche to first birth*	12.3 (3.2)	13.6 (4.4)	12.5 (3.5)	13.4 (4.3)
Age at first birth (years)*	24.8 (3.0)	26.0 (4.2)	25.0 (3.2)	25.8 (4.1)
Birth index*	24.4 (8.3)	18.3 (10.5)	23.8 (8.2)	18.5 (10.3)
Breastfeeding duration, months*	15.2 (11.3)	19.0 (10.7)	14.9 (11.3)	20.0 (11.0)
Breastfeeding duration*				
>0-52 weeks	2293 (76%)	1125 (49%)	1172 (78%)	478 (44%)
52-104 weeks	391 (13%)	370 (16%)	169 (11%)	207 (19%)
104-156 weeks	115 (3.8%)	167 (7.2%)	62 (4.1%)	92 (8.5%)
156 + weeks	72 (2.4%)	71 (3.1%)	27 (1.8%)	43 (4.0%)
Oral contraceptive use (%)	1655 (55%)	1971 (85%)	825 (55%)	907 (84%)
Height (cm)	164.2 (6.0)	165.3 (6.4)	164.3 (6.1)	165.4 (6.5)
BMI (kg/m2)	23.3 (3.7)	23.7 (4.4)	23.3 (3.7)	23.5 (4.3)
BMI in young adulthood (kg/m^2)	21.2 (2.8)	21.0 (2.9)	21.3 (2.9)	20.9 (2.8)
Weight Change last 4 yrs (kg)	0.11 (0.30)	0.27 (1.34)	0.11 (0.29)	0.34 (1.71)
Alcohol (drinks/week)	3.8 (5.8)	2.1 (3.8)	3.6 (5.6)	2.0 (3.9)
Family history of BC (%)	206 (6.8%)	471 (20.4%)	101 (6.7%)	185 (17%)
BBD (yes) (%)	1505 (50%)	1457 (63%)	792 (52%)	703 (65%)
PRS (std)	0.09 (1.02)	0.10 (1.03)	0.06 (0.99)	0.10 (1.01)

^Continuous variables given in mean (SD). Categorical variables with N (%).
*Among parous women

Supplemental Table 3.3. Participant Characteristics at study entry for full data, derivation & validation data (Total cases=5,165).^

	Derivation Data (N=193,088, cases=3,463)				Validation data (N=96,616, Cases=1,712)			
	GS	NHS	NHSII	Sister Study	GS	NHS	NHSII	Sister Study
N	41,018	63,461	77,360	11,249	20,576	31,730	38,680	5,630
N cases (full study)	311	1,275	1,633	244	148	666	768	130
Premenopausal duration	24.6 (8.8)	28.3 (6.3)	22.4 (4.9)	33.7 (5.1)	24.6 (8.8)	28.2 (6.4)	22.4 (4.9)	33.6 (5.1)
Age (years)	37.2 (8.8)	40.8 (6.3)	34.8 (4.7)	46.4 (4.8)	37.3 (8.7)	40.7 (6.3)	34.8 (4.7)	46.4 (4.8)
Age at menarche (years)	12.7 (1.4)	12.5 (1.4)	12.4 (1.4)	12.7 (1.5)	12.7 (1.4)	12.5 (1.4)	12.4 (1.4)	12.7 (1.5)
Missing age at menarche	4636 (11%)	486 (0.7%)	248 (0.3%)	7 (<0.1%)	2315 (11%)	255 (0.4%)	137 (0.3%)	8 (0.1%)
Parous (yes)	25,150 (62%)	58,564 (94%)	55,248 (71%)	8,870 (79%)	12,822 (63%)	29,210 (94%)	27,562 (71%)	29,210 (94%)
Missing parous yes/no	607 (1.5%)	1,396 (2.3%)	11 (<0.1%)	22 (<0.1%)	329 (1.6)	723 (2.3)	5 (<1%)	8 (<1%)
Parity*	2.0 (0.8)	3.0 (1.5)	2.0 (0.9)	2.2 (0.9)	2.0 (0.8)	3.0 (1.5)	2.0 (0.9)	2.2 (0.9)
Age from menarche to first birth*								
Age at first birth (years)*	27.8 (4.8)	24.9 (3.2)	25.6 (4.1)	26.3 (5.6)	27.7 (4.8)	24.9 (3.2)	25.5 (4.1)	26.3 (5.7)
Birth index*	19.1 (15.1)	20.7 (12.9)	13.1 (10.5)	30.2 (15.9)	19.2 (15.2)	20.5 (12.9)	13.1 (10.5)	30.2 (16.0)
Missing birth index*	5296 (21%)	34256 (58%)	14176 (25%)	2,699 (30%)	2,770 (22%)	17,061 (58%)	7,053 (26%)	1,374 (31%)
Breastfeeding duration, months*	12.7 (13.4)	17.4 (11.1)	19.3 (10.6)	18.4 (15.9)				
Oral contraceptive use (%)	38,226 (93%)	34,125 (54%)	64,430 (84%)	9,937 (88%)	19,189 (93%)	16,988 (54%)	32,282 (84%)	4,980 (89%)
Missing OC use	22 (<0.1%)	0	90 (0.1%)	4 (<0.1%)	7 (<0.1%)	0	52 (0.1%)	3 (<0.1%)
Height (cm)	164.5 (13.1)	163.6 (9.5)	164.2 (11.7)	165.2 (6.6)	164.5 (13.2)	163.6 (9.2)	164.2 (12.0)	165.2 (6.8)
BMI (kg/m2)	24.9 (4.7)	23.7 (4.1)	24.1 (4.9)	27.2 (6.0)	24.9 (4.7)	23.7 (4.1)	24.1 (4.9)	27.0 (5.9)

Supplemental Table 3.3 (continued).

Missing BMI	749 (1.8%)	318 (0.5%)	494 (0.6%)	88 (0.8%)	377 (1.8%)	148 (0.5%)	255 (0.7%)	54 (1.0%)
BMI in young adulthood (kg/m2)	22.1 (3.3)	21.4 (3.0)	21.3 (3.3)	0	22.1 (3.3)	21.4 (3.0)	21.3 (3.2)	0
Missing BMI in young adulthood	2,097 (5.1%)	12,462 (20%)	1,110 (1.4%)	11,249 (100%)	1,040 (5.1%)	6,179 (19%)	570 (1.5%)	5,630 (100%)
Weight Change last 4 yrs (kg)								
Alcohol (drinks/week)	5.8 (6.7)	3.6 (5.8)	1.8 (3.6)	2.8 (4.6)	5.7 (6.6)	3.5 (5.8)	1.8 (3.5)	2.8 (4.6)
Missing drinks/week	760 (1.8%)	15,450 (24%)	14,081 (18%)	8 (<0.1%)	420 (2.0%)	7,727 (24%)	7,028 (18%)	7 (0.1%)
Family history of BC (%)	5,894 (14%)	3,626 (5.7)	12,353 (16%)	10,783 (96%)	2,980 (14%)	1,807 (5.7%)	6,024 (16%)	5,391 (96%)
BBD (yes) (%)	5,933 (14%)	26,296 (41%)	41,222 (53%)	407 (3.8%)	2,927 (14%)	13,256 (42%)	20,516 (53%)	207 (3.9%)
Missing BBD	0	0	0	584 (5.2%)	0	0	0	317 (5.6%)

^Continuous variables given in mean (SD). Categorical variables with N (%).
*Among parous women