

Supplementary Table 1. Completeness and exclusions of the different metabolites, with limits of detection (LOD) and limits of quantification (LOQ)

Metabolites ¹	Non-quantifiable results ²			CV ⁴ , %
	Missing ³ data, %	Results outside the measurable range		
		Samples, %	Criteria	
Acylcarnitines				
C0	0	0	<LOD	4.0
C2	0	0	<LOD	4.1
C3	0	0	<LOD	5.0
C3-DC (C4-OH)	0	39.04	<LOD	-
C4	0	0.06	<LOD	5.4
C5	0	0.77	<LOD	5.4
C5-DC (C6-OH)	0	90.21	<LOD	-
C8	0	92.43	<LOD	-
C10	0	52.99	<LOD	-
C10:1	0	93.1	<LOD	-
C12	0	85.01	<LOD	-
C12:1	0	56.34	<LOD	-
C14:1	0	6.13	<LOD	9.2
C14:2	0	63.02	<LOD	-
C16	0	0.15	<LOD	5.4
C16:1	0	90.73	<LOD	-
C18	0	23.52	<LOD	-
C18:1	0	0.28	<LOD	4.8
C18:2	0	22.11	<LOD	-
Amino acids				
Alanine	0	0	<LOQ (< 20 µmol/L)	4.2
Arginine	0	0	<LOQ (< 5 µmol/L)	5.4
Asparagine	0	0	<LOQ (< 5 µmol/L)	4.0
Aspartate	0	34.33	<LOQ (< 5 µmol/L)	-
Citrulline	0	0	<LOQ (< 5 µmol/L)	5.9
Glutamine	0	0	<LOQ (< 20 µmol/L)	6.3
Glutamate	0	0.22	<LOQ (< 10 µmol/L)	4.7
Glycine	0	0	<LOQ (< 25 µmol/L)	6.2
Histidine	0	0	<LOQ (< 5 µmol/L)	5.7
Isoleucine	0	0	<LOQ (< 5 µmol/L)	6.8
Leucine	0	0.03	<LOQ (< 50 µmol/L)	6.2
Lysine	0	0	<LOQ (< 10 µmol/L)	8.5
Methionine	0	0	<LOQ (< 5 µmol/L)	8.4
Ornithine	0	0	<LOQ (< 5 µmol/L)	8.2
Phenylalanine	0	0	<LOQ (< 5 µmol/L)	6.0
Proline	0	0	<LOQ (< 10 µmol/L)	5.5
Serine	0	0	<LOQ (< 5 µmol/L)	5.6
Threonine	0	0	<LOQ (< 5 µmol/L)	4.2
Tryptophane	0	0	<LOQ (< 5 µmol/L)	6.2
Tyrosine	0	0	<LOQ (< 5 µmol/L)	5.6
Valine	0	0	<LOQ (< 10 µmol/L)	5.5
Biogenic amines				
ADMA	0	2.19	<LOQ (< 0.25 µmol/L)	8.3
Creatinine	0	0	<LOQ (< 10 µmol/L)	3.2
Kynurenine	0	0.95	<LOQ (< 1 µmol/L)	6.5
Nitro-Tyr	0	98.83	<LOQ (< 1 µmol/L)	-
Putrescine	0	72.78	<LOQ (< 0.1 µmol/L)	-
SDMA	0	0	<LOQ (< 0.1 µmol/L)	7.7
Sarcosine	0	29.65	<LOQ (< 1 µmol/L)	-
Serotonin	0	76.29	<LOQ (< 0.1 µmol/L)	-
Spermidine	0	91.72	<LOQ (< 0.25 µmol/L)	-
Spermine	0	95.72	<LOQ (< 0.25 µmol/L)	-

Metabolites ¹	Non-quantifiable results ²			CV ⁴ , %
	Missing ³ data, %	Results outside the measurable range		
		Samples, %	Criteria	
Taurine	0	0	<LOQ (< 2.5 µmol/L)	3.1
alpha-AAA	0	80.23	<LOQ (< 1 µmol/L)	-
t4-OH-Pro	0	0	<LOQ (< 2 µmol/L)	5.0
Glycerophospholipids				
PC aa C28:1	0	0	<LOD	4.5
PC aa C30:0	0	0	<LOD	4.7
PC aa C32:0	0	0	<LOD	5.1
PC aa C32:1	0	0	<LOD	5.5
PC aa C32:2	0	0	<LOD	6.0
PC aa C32:3	0	0	<LOD	5.5
PC aa C34:1	0	0	<LOD	5.3
PC aa C34:2	0	0	<LOD	6.3
PC aa C34:3	0	0	<LOD	5.1
PC aa C34:4	0	0	<LOD	5.4
PC aa C36:0	0	0.06	<LOD	6.6
PC aa C36:1	0	0	<LOD	4.6
PC aa C36:2	0	0	<LOD	4.5
PC aa C36:3	0	0	<LOD	4.4
PC aa C36:4	0	0	<LOD	4.4
PC aa C36:5	0	0	<LOD	4.7
PC aa C36:6	0	0	<LOD	5.3
PC aa C38:0	0	0	<LOD	4.5
PC aa C38:3	0	0	<LOD	3.9
PC aa C38:4	0	0	<LOD	4.0
PC aa C38:5	0	0	<LOD	4.1
PC aa C38:6	0	0	<LOD	4.0
PC aa C40:1	0	69.77	<LOD	-
PC aa C40:2	0	0	<LOD	7.2
PC aa C40:3	0	0	<LOD	5.6
PC aa C40:4	0	0	<LOD	4.1
PC aa C40:5	0	0	<LOD	4.3
PC aa C40:6	0	0	<LOD	4.0
PC aa C42:0	0	0	<LOD	5.3
PC aa C42:1	0	0	<LOD	5.7
PC aa C42:2	0	0.03	<LOD	4.5
PC aa C42:4	0	0	<LOD	6.7
PC aa C42:5	0	0	<LOD	5.7
PC aa C42:6	0	0	<LOD	5.3
PC ae C30:0	0	0	<LOD	5.8
PC ae C30:2	0	0	<LOD	7.9
PC ae C32:1	0	0	<LOD	5.3
PC ae C32:2	0	0	<LOD	5.5
PC ae C34:0	0	0	<LOD	5.6
PC ae C34:1	0	0	<LOD	5.1
PC ae C34:2	0	0	<LOD	5.3
PC ae C34:3	0	0	<LOD	5.1
PC ae C36:0	0	0	<LOD	6.2
PC ae C36:1	0	0	<LOD	4.7
PC ae C36:2	0	0	<LOD	4.8
PC ae C36:3	0	0	<LOD	4.7
PC ae C36:4	0	0	<LOD	5.0
PC ae C36:5	0	0	<LOD	4.9
PC ae C38:0	0	0	<LOD	4.4
PC ae C38:2	0	0	<LOD	6.4
PC ae C38:3	0	0	<LOD	4.3
PC ae C38:4	0	0	<LOD	4.3

Metabolites ¹	Non-quantifiable results ²			CV ⁴ , %
	Missing ³ data, %	Results outside the measurable range		
		Samples, %	Criteria	
PC ae C38:5	0	0	<LOD	5.1
PC ae C38:6	0	0	<LOD	4.7
PC ae C40:1	0	0	<LOD	5.5
PC ae C40:2	0	0	<LOD	4.2
PC ae C40:3	0	0	<LOD	4.1
PC ae C40:4	0	0	<LOD	4.4
PC ae C40:5	0	0	<LOD	4.2
PC ae C40:6	0	0	<LOD	4.3
PC ae C42:1	0	0.09	<LOD	6.0
PC ae C42:2	0	0	<LOD	5.5
PC ae C42:3	0	0	<LOD	5.7
PC ae C42:4	0	0	<LOD	5.3
PC ae C42:5	0	0	<LOD	3.6
PC ae C44:3	0	0	<LOD	9.5
PC ae C44:4	0	0.03	<LOD	7.3
PC ae C44:5	0	0	<LOD	4.8
PC ae C44:6	0	0	<LOD	4.9
lysoPC a C16:0	0	0	<LOD	6.4
lysoPC a C16:1	0	0	<LOD	6.4
lysoPC a C17:0	0	0	<LOD	6.7
lysoPC a C18:0	0	0	<LOD	6.4
lysoPC a C18:1	0	0	<LOD	6.5
lysoPC a C18:2	0	0	<LOD	6.3
lysoPC a C20:3	0	0	<LOD	6.0
lysoPC a C20:4	0	0	<LOD	5.8
lysoPC a C24:0	0	0	<LOD	13.5
lysoPC a C28:1	0	0	<LOD	11.7
Sphingolipids				
SM C16:0	0	0	<LOD	5.2
SM C16:1	0	0	<LOD	5.3
SM C18:0	0	0	<LOD	5.1
SM C18:1	0	0	<LOD	5.0
SM C20:2	0	0	<LOD	8.0
SM C24:0	0	0	<LOD	5.5
SM C24:1	0	0	<LOD	4.8
SM C26:0	0	0	<LOD	9.8
SM C26:1	0	0	<LOD	7.9
SM (OH) C14:1	0	0	<LOD	5.8
SM (OH) C16:1	0	0	<LOD	5.1
SM (OH) C22:1	0	0	<LOD	5.0
SM (OH) C22:2	0	0	<LOD	4.9
SM (OH) C24:1	0	0	<LOD	6.0
Hexose				
Hexose	0	2.03	<LOQ (< 1500 µmol/L)	3.7

¹Metabolites in gray were excluded from the statistical analysis because more than 20% or the measures were outside the measurable range.

²Limit of detection (LOD) is applicable to acylcarnitines, glycerophospholipids, sphingolipids. Limit of quantification (LOQ) is applicable to amino acids, biogenic amines and hexose. No results was reported to be higher than the upper limit of quantification.

³Missing values were defined as unmeasured metabolite in samples because of technical problems.

⁴Mean intra- and inter-batch coefficients of variation (CVs) based on two quality control samples measured in duplicate in each batch.

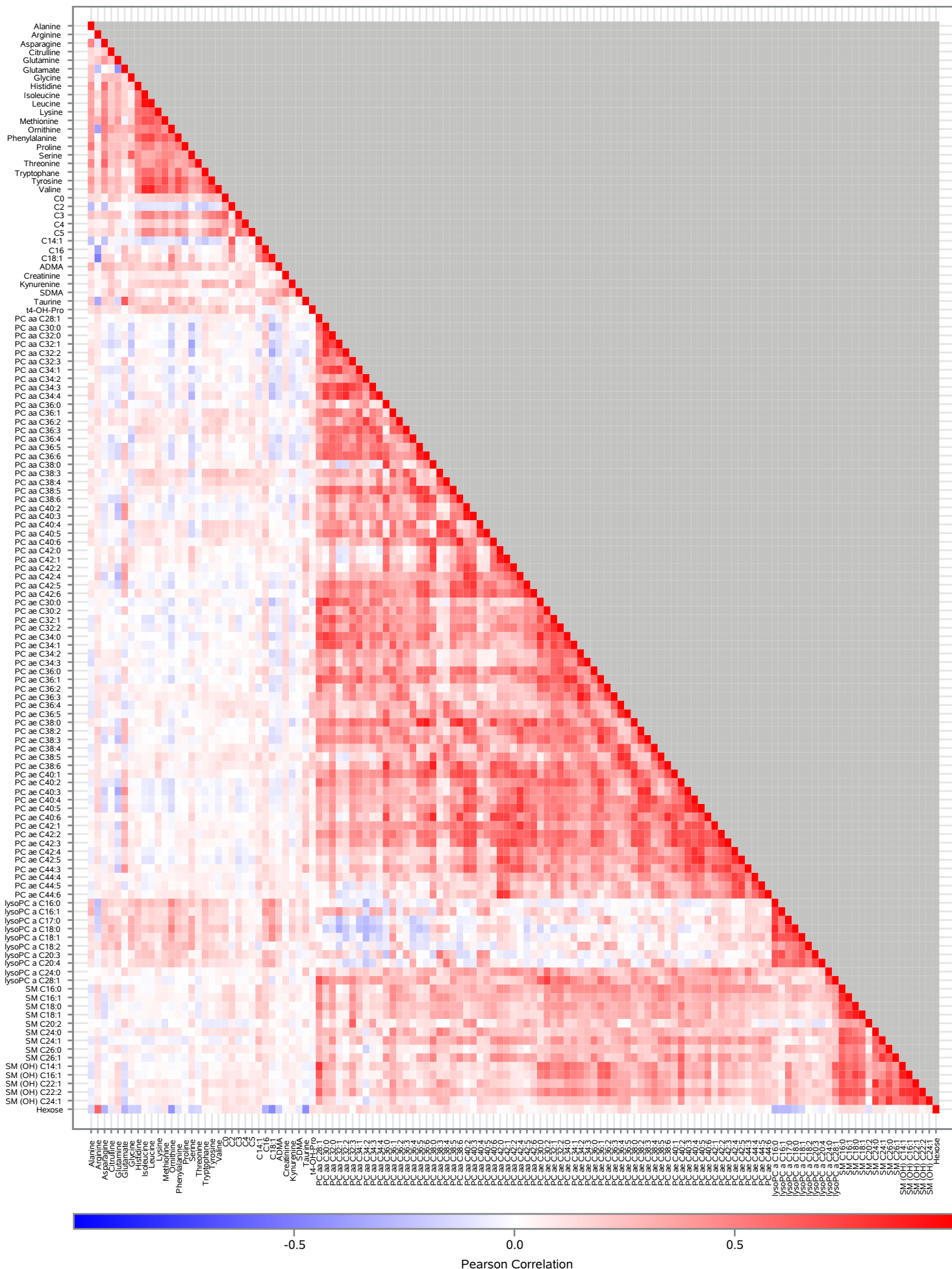
Supplementary Table 2. Description of metabolites concentrations by case-control status

Metabolites	Cases	Controls
	N=1624	N=1624
	Geometric mean (95% CI) - μmol/L	Geometric mean (95% CI) - μmol/L
Acylcarnitines		
C0	28.75 (28.43-29.07)	28.65 (28.33-28.97)
C2	4.57 (4.48-4.65)	4.38 (4.30-4.46)
C3	0.27 (0.26-0.27)	0.27 (0.26-0.27)
C4	0.15 (0.14-0.15)	0.15 (0.14-0.15)
C5	0.10 (0.09-0.10)	0.10 (0.09-0.10)
C14:1	0.06 (0.06-0.06)	0.06 (0.06-0.06)
C16	0.10 (0.09-0.10)	0.09 (0.09-0.10)
C18:1	0.10 (0.10-0.11)	0.10 (0.10-0.10)
Amino acids		
Alanine	308.30 (304.61-312.03)	311.99 (308.20-315.82)
Arginine	54.87 (53.59-56.19)	56.16 (54.88-57.47)
Asparagine	39.11 (38.65-39.58)	39.97 (39.50-40.44)
Citrulline	26.17 (25.82-26.52)	26.59 (26.23-26.95)
Glutamine	478.89 (474.29-483.53)	485.02 (480.38-489.70)
Glutamate	45.60 (44.07-47.19)	45.80 (44.26-47.39)
Glycine	201.74 (198.65-204.88)	207.59 (204.35-210.87)
Histidine	71.95 (71.39-72.52)	72.80 (72.20-73.40)
Isoleucine	58.50 (57.67-59.35)	58.76 (57.90-59.63)
Leucine	108.31 (106.94-109.70)	108.61 (107.19-110.04)
Lysine	180.44 (178.34-182.56)	183.83 (181.74-185.94)
Methionine	19.36 (19.12-19.61)	19.54 (19.28-19.80)
Ornithine	73.26 (71.96-74.58)	74.17 (72.84-75.53)
Phenylalanine	54.72 (54.21-55.23)	54.86 (54.34-55.38)
Proline	155.81 (153.43-158.23)	158.62 (156.10-161.19)
Serine	91.38 (90.34-92.43)	92.31 (91.25-93.39)
Threonine	106.52 (105.20-107.86)	108.38 (107.05-109.73)
Tryptophane	51.50 (51.02-51.99)	51.75 (51.28-52.23)
Tyrosine	58.99 (58.22-59.78)	58.91 (58.12-59.70)
Valine	184.04 (182.12-185.97)	184.01 (182.10-185.93)
Biogenic amines		
ADMA	0.38 (0.38-0.38)	0.38 (0.38-0.39)
Creatinine	54.07 (53.63-54.51)	54.25 (53.78-54.73)
Kynurenine	1.89 (1.87-1.92)	1.91 (1.88-1.93)
SDMA	0.35 (0.35-0.35)	0.35 (0.35-0.35)
Taurine	49.48 (48.59-50.39)	49.42 (48.51-50.35)
t4-OH-Pro	7.76 (7.59-7.92)	7.71 (7.55-7.88)
Glycerophospholipids		
PC aa C28:1	2.34 (2.31-2.37)	2.34 (2.31-2.37)
PC aa C30:0	3.22 (3.16-3.27)	3.24 (3.19-3.29)
PC aa C32:0	13.48 (13.34-13.61)	13.55 (13.41-13.68)
PC aa C32:1	15.06 (14.69-15.44)	14.96 (14.58-15.34)
PC aa C32:2	4.24 (4.16-4.32)	4.33 (4.24-4.41)
PC aa C32:3	0.59 (0.58-0.59)	0.59 (0.59-0.60)
PC aa C34:1	178.36 (176.52-180.22)	178.42 (176.57-180.28)
PC aa C34:2	269.59 (266.86-272.35)	271.29 (268.59-274.01)
PC aa C34:3	15.27 (15.03-15.52)	15.52 (15.27-15.77)
PC aa C34:4	1.78 (1.75-1.81)	1.81 (1.78-1.84)
PC aa C36:0	1.86 (1.82-1.89)	1.85 (1.81-1.88)
PC aa C36:1	42.48 (41.96-43.01)	42.99 (42.46-43.52)
PC aa C36:2	189.43 (187.79-191.09)	191.91 (190.28-193.57)
PC aa C36:3	117.37 (116.26-118.49)	119.62 (118.53-120.72)
PC aa C36:4	151.52 (149.99-153.07)	151.57 (149.99-153.17)

Metabolites	Cases	Controls
	N=1624	N=1624
	Geometric mean (95% CI) - µmol/L	Geometric mean (95% CI) - µmol/L
PC aa C36:5	20.44 (19.92-20.98)	20.09 (19.58-20.61)
PC aa C36:6	0.99 (0.97-1.01)	0.99 (0.97-1.01)
PC aa C38:0	2.17 (2.14-2.20)	2.19 (2.16-2.22)
PC aa C38:3	36.80 (36.34-37.27)	37.43 (36.97-37.89)
PC aa C38:4	76.85 (75.95-77.76)	77.43 (76.54-78.33)
PC aa C38:5	40.20 (39.70-40.70)	40.34 (39.84-40.84)
PC aa C38:6	68.00 (66.97-69.06)	67.24 (66.20-68.31)
PC aa C40:2	0.20 (0.20-0.20)	0.20 (0.20-0.21)
PC aa C40:3	0.36 (0.36-0.37)	0.37 (0.36-0.37)
PC aa C40:4	2.13 (2.10-2.16)	2.16 (2.14-2.19)
PC aa C40:5	5.47 (5.40-5.55)	5.53 (5.46-5.61)
PC aa C40:6	19.53 (19.22-19.85)	19.44 (19.13-19.77)
PC aa C42:0	0.34 (0.34-0.35)	0.35 (0.34-0.35)
PC aa C42:1	0.16 (0.16-0.17)	0.17 (0.16-0.17)
PC aa C42:2	0.14 (0.14-0.14)	0.14 (0.14-0.14)
PC aa C42:4	0.10 (0.10-0.10)	0.10 (0.10-0.10)
PC aa C42:5	0.20 (0.20-0.20)	0.20 (0.20-0.20)
PC aa C42:6	0.30 (0.29-0.30)	0.30 (0.29-0.30)
PC ae C30:0	0.27 (0.27-0.28)	0.28 (0.27-0.28)
PC ae C30:2	0.08 (0.08-0.08)	0.08 (0.08-0.08)
PC ae C32:1	2.61 (2.58-2.64)	2.60 (2.57-2.63)
PC ae C32:2	0.75 (0.74-0.76)	0.75 (0.74-0.76)
PC ae C34:0	1.51 (1.49-1.53)	1.53 (1.51-1.55)
PC ae C34:1	9.61 (9.51-9.71)	9.67 (9.57-9.77)
PC ae C34:2	11.32 (11.20-11.45)	11.56 (11.43-11.70)
PC ae C34:3	7.50 (7.40-7.60)	7.62 (7.52-7.72)
PC ae C36:0	0.73 (0.72-0.74)	0.73 (0.73-0.74)
PC ae C36:1	7.82 (7.72-7.92)	7.87 (7.77-7.97)
PC ae C36:2	14.01 (13.85-14.17)	14.29 (14.13-14.45)
PC ae C36:3	7.12 (7.05-7.19)	7.30 (7.22-7.37)
PC ae C36:4	14.00 (13.85-14.15)	14.20 (14.04-14.35)
PC ae C36:5	9.42 (9.31-9.53)	9.43 (9.32-9.54)
PC ae C38:0	1.82 (1.79-1.84)	1.82 (1.79-1.85)
PC ae C38:2	1.68 (1.66-1.71)	1.73 (1.70-1.75)
PC ae C38:3	3.73 (3.68-3.78)	3.80 (3.75-3.85)
PC ae C38:4	10.31 (10.21-10.41)	10.43 (10.34-10.54)
PC ae C38:5	12.80 (12.67-12.93)	12.97 (12.84-13.10)
PC ae C38:6	6.00 (5.93-6.07)	6.03 (5.95-6.10)
PC ae C40:1	0.90 (0.89-0.91)	0.91 (0.90-0.93)
PC ae C40:2	1.37 (1.35-1.39)	1.37 (1.36-1.39)
PC ae C40:3	0.79 (0.78-0.80)	0.80 (0.79-0.81)
PC ae C40:4	1.59 (1.57-1.61)	1.62 (1.60-1.63)
PC ae C40:5	2.55 (2.52-2.59)	2.57 (2.54-2.60)
PC ae C40:6	3.56 (3.52-3.61)	3.59 (3.54-3.63)
PC ae C42:1	0.23 (0.23-0.23)	0.23 (0.23-0.24)
PC ae C42:2	0.35 (0.34-0.35)	0.35 (0.35-0.36)
PC ae C42:3	0.51 (0.50-0.52)	0.52 (0.51-0.52)
PC ae C42:4	0.49 (0.49-0.50)	0.50 (0.49-0.50)
PC ae C42:5	1.31 (1.30-1.33)	1.32 (1.31-1.33)
PC ae C44:3	0.08 (0.08-0.08)	0.08 (0.08-0.08)
PC ae C44:4	0.20 (0.20-0.20)	0.20 (0.20-0.20)
PC ae C44:5	0.81 (0.80-0.82)	0.80 (0.79-0.81)
PC ae C44:6	0.62 (0.61-0.63)	0.62 (0.61-0.63)
lysoPC a C16:0	76.32 (75.34-77.32)	76.90 (75.92-77.89)
lysoPC a C16:1	2.28 (2.25-2.32)	2.29 (2.25-2.32)

Metabolites	Cases	Controls
	N=1624	N=1624
	Geometric mean (95% CI) - µmol/L	Geometric mean (95% CI) - µmol/L
lysoPC a C17:0	1.55 (1.52-1.57)	1.57 (1.54-1.60)
lysoPC a C18:0	22.89 (22.52-23.27)	23.35 (22.97-23.74)
lysoPC a C18:1	15.67 (15.42-15.91)	15.88 (15.63-16.13)
lysoPC a C18:2	21.75 (21.37-22.14)	22.41 (22.02-22.80)
lysoPC a C20:3	1.64 (1.61-1.66)	1.67 (1.65-1.70)
lysoPC a C20:4	4.30 (4.24-4.36)	4.32 (4.25-4.38)
lysoPC a C24:0	0.11 (0.11-0.11)	0.11 (0.11-0.11)
lysoPC a C28:1	0.31 (0.30-0.31)	0.31 (0.31-0.32)
Sphingolipids		
SM C16:0	84.24 (83.56-84.93)	84.72 (84.03-85.41)
SM C16:1	12.30 (12.18-12.42)	12.33 (12.21-12.46)
SM C18:0	17.01 (16.83-17.20)	17.08 (16.89-17.26)
SM C18:1	8.54 (8.44-8.63)	8.58 (8.49-8.68)
SM C20:2	0.39 (0.39-0.40)	0.41 (0.40-0.42)
SM C24:0	11.22 (11.10-11.34)	11.37 (11.25-11.49)
SM C24:1	25.41 (25.14-25.67)	25.31 (25.05-25.57)
SM C26:0	0.09 (0.08-0.09)	0.09 (0.09-0.09)
SM C26:1	0.18 (0.18-0.19)	0.18 (0.18-0.19)
SM (OH) C14:1	5.03 (4.97-5.09)	5.04 (4.98-5.11)
SM (OH) C16:1	2.73 (2.70-2.77)	2.75 (2.71-2.78)
SM (OH) C22:1	8.58 (8.49-8.68)	8.74 (8.65-8.84)
SM (OH) C22:2	7.07 (6.99-7.14)	7.15 (7.07-7.22)
SM (OH) C24:1	0.71 (0.70-0.72)	0.72 (0.71-0.73)
Sugars		
Hexose	3978.9 (3918.2-4040.6)	3915.1 (3852.0-3979.2)
Abbreviations: CI, confidence interval; PC, phosphatidylcholine; SM, sphingomyelin.		

Supplementary Figure 1. Age-adjusted partial correlations between metabolites among controls (N=1624)



Supplementary Figure 2. Permutation-based stepdown minP adjusted P-values for association between metabolites and risk of breast cancer, by subtype

