



Supplemental Figure 1. Flow chart of sample selection and inclusion of participants into final analytical sample

Supplemental Table 1. Twenty-six metabolites were significantly associated with EDIP at the raw P -value <0.05 , and none at FDR-adjusted $P < 0.10$, among normal weight women in the discovery dataset (Hormone Therapy trial: $n=317$)^{1,2,3}

Metabolite	HMDB ID	Association with EDIP score			Association with CRP		
		Beta estimate (95%CI)	Raw P -value	FDR P -value	Beta estimate (95%CI)	Raw P -value	FDR P -value
Trigonelline	HMDB0000875	-0.97 (-1.51, -0.43)	0.0004	0.194	-0.01 (-0.12, 0.11)	0.920	0.920
5-acetylamino-6-amino-3-methyluracil	HMDB0004400	-0.72 (-1.25, -0.19)	0.008	0.694	-0.0004 (-0.11, 0.11)	0.995	0.995
Glycine	HMDB0000123	-0.60 (-1.16, -0.05)	0.034	0.723	-0.11 (-0.22, 0.01)	0.070	0.315
Caffeine	HMDB0001847	-0.59 (1.15, 0.03)	0.038	0.723	0.03 (-0.08, 0.15)	0.571	0.681
C18:3 CE	HMDB0010370	-0.72 (-1.26, -0.18)	0.009	0.694	-0.03 (-0.14, 0.08)	0.582	0.685
C20:5 CE	HMDB0006731	-0.68 (-1.23, -0.13)	0.016	0.723	-0.02 (-0.13, 0.09)	0.740	0.740
C36:4 PE	HMDB0008937	-0.67 (-1.19, -0.14)	0.013	0.723	0.02 (-0.09, 0.14)	0.670	0.719
C20:1 LPE	HMDB0011512	0.78 (0.22, 1.33)	0.006	0.694	-0.08 (-0.19, 0.03)	0.161	0.438
C12 carnitine	HMDB0002250	0.64 (0.06, 1.22)	0.031	0.723	0.12 (0.01, 0.24)	0.037	0.221
C12:1 carnitine	HMDB0013326	0.66 (0.10, 1.23)	0.022	0.723	0.14 (0.03, 0.26)	0.014	0.165
C14:1 carnitine	HMDB0002014	0.68 (0.09, 1.26)	0.023	0.723	0.14 (0.02, 0.26)	0.019	0.176
C14:2 carnitine	HMDB0013331	0.65 (0.07, 1.23)	0.027	0.723	0.13 (0.02, 0.25)	0.023	0.186
C18:1 carnitine	HMDB0005065	0.56 (0.04, 1.09)	0.035	0.723	0.03 (-0.07, 0.14)	0.522	0.680
C34:0 PS	HMDB0012356	-0.61 (-1.17, -0.06)	0.029	0.723	-0.01 (-0.12, 0.10)	0.861	0.861
C36:5 PC	HMDB0007890	-0.62 (-1.16, -0.08)	0.024	0.723	-0.03 (-0.14, 0.08)	0.636	0.709
C38:1 PC	HMDB0008268	0.64 (0.08, 1.20)	0.024	0.723	-0.06 (-0.18, 0.05)	0.280	0.550
C38:4 PC plasmalogen-A	HMDB0011252	0.59 (0.05, 1.13)	0.033	0.723	0.03 (-0.08, 0.14)	0.544	0.680
C36:0 DAG	HMDB0007158	-0.84 (-1.61, -0.07)	0.033	0.723	-0.03 (-0.19, 0.13)	0.714	0.723
C51:3 TAG	HMDB0043062	0.68 (0.11, 1.24)	0.019	0.723	0.04 (-0.07, 0.16)	0.474	0.654
C54:2 TAG	HMDB0005403	0.55 (0.02, 1.07)	0.041	0.753	0.07 (-0.04, 0.17)	0.219	0.497
C54:3 TAG	HMDB0005405	0.63 (0.05, 1.20)	0.033	0.723	0.03 (-0.09, 0.14)	0.648	0.711
C54:4 TAG	HMDB0005370	0.61 (0.01, 1.22)	0.046	0.753	0.02 (-0.10, 0.15)	0.689	0.719
C56:3 TAG	HMDB0005410	0.55 (0.03, 1.07)	0.037	0.723	0.04 (-0.07, 0.14)	0.455	0.641
Myristoleic acid	HMDB0002000	0.83 (0.28, 1.38)	0.003	0.694	0.01 (-0.11, 0.12)	0.922	0.922

Linoleate	HMDB0000673	0.87 (0.24, 1.49)	0.007	0.694	0.17 (0.06, 0.31)	0.004	0.09
Urate	HMDB0000289	-0.63 (1.25, 0.02)	0.044	0.753	0.07 (-0.05, 0.20)	0.267	0.539

¹All values are beta estimates obtained from multivariable-adjusted linear regression modeling 5-SD increments in EDIP or 5-unit increments in CRP as the main predictor of interest and metabolite as the main response variable of interest.

²Models were adjusted for body mass index (continuous) age, physical activity, educational level, race/ethnicity, aspirin/NSAIDs use, smoking status, WHI Hormone Therapy trial arm, CHD case-control status.

³Statistical significance was defined as false-discovery rate adjusted $p < 0.10$.

Supplemental Table 2. Forty-five metabolites were significantly associated with EDIP at an FDR-adjusted $P < 0.10$, among overweight or obese women in the discovery dataset (Hormone Therapy trial: $n = 792$)^{1,2,3}

Metabolite	HMDB ID	Association with EDIP score		Association with CRP	
		Beta estimate (95%CI)	FDR <i>P</i> -value	Beta estimate (95%CI)	FDR <i>P</i> -value
Trigonelline	HMDB0000875	-1.43 (-1.74, -1.12)	2.48 E-16	-0.08 (-0.13, -0.03)	0.016
5-acetylamino-6-amino-3-methyluracil	HMDB0004400	-0.73 (-1.03, -0.43)	1.89 E-04	-0.03 (-0.08, 0.02)	0.249
1,7-dimethyluric acid	HMDB0011103	-0.59 (-0.90, -0.28)	0.014	-0.02 (-0.07, 0.03)	0.413
Caffeine	HMDB0001847	-0.41 (-0.71, -0.12)	0.074	-0.04 (-0.08, 0.01)	0.204
3-methylxanthine	HMDB0001886	-0.58 (-0.91, -0.26)	0.019	-0.03 (-0.08, 0.02)	0.349
7-methylxanthine	HMDB0001991	-0.56 (-0.89, -0.24)	0.026	-0.02 (-0.08, 0.03)	0.393
C20:1 LPC	HMDB0010391	-0.62 (-0.99, -0.25)	0.026	-0.11 (-0.17, -0.05)	0.002
C24:0 LPC	HMDB0008038	-0.50 (-0.83, -0.16)	0.060	-0.12 (-0.17, -0.07)	1.93 E-04
C18:3 LPC	HMDB0010387	-0.54 (-0.91, -0.17)	0.066	-0.15 (-0.21, -0.09)	3.22 E-05
C18:2 LPC	HMDB0010386	-0.42 (-0.75, -0.09)	0.086	-0.18 (-0.23, -0.13)	2.43 E-09
C20:5 LPC	HMDB0010397	-0.40 (-0.74, -0.07)	0.086	-0.18 (-0.23, -0.13)	2.34 E-09
C36:0 PC	HMDB0008036	-0.44 (-0.77, -0.10)	0.081	-0.05 (-0.11, 0.001)	0.115
C37:4 PC	HMDB0008625	-0.41 (-0.75, -0.07)	0.086	-0.07 (-0.13, -0.02)	0.032
C38:2 PE	HMDB0008942	-0.43 (-0.77, -0.10)	0.081	-0.09 (-0.14, -0.04)	0.007
C18:1 LPE	HMDB0011506	-0.43 (-0.79, -0.07)	0.094	-0.13 (-0.19, -0.07)	1.87 E-04
Uracil	HMDB0000300	-0.57 (-0.92, -0.23)	0.026	-0.02 (-0.07, 0.04)	0.493
Uridine	HMDB0000296	-0.48 (-0.80, -0.16)	0.060	0.04 (-0.02, 0.09)	0.243
Glycine	HMDB0000123	-0.38 (-0.70, -0.60)	0.090	-0.14 (-0.19, -0.09)	1.74 E-06
Cortisol	HMDB0000063	-0.56 (-0.90, -0.23)	0.026	0.003 (-0.05, 0.06)	0.917
C14:0 SM	HMDB0012097	-0.45 (-0.79, -0.11)	0.081	0.01 (-0.05, 0.06)	0.843
C20:0 SM	HMDB0012102	-0.51 (-0.87, -0.15)	0.074	0.01 (-0.05, 0.06)	0.857
C22:1 SM	HMDB0012104	-0.45 (-0.80, -0.10)	0.081	-0.01 (-0.07, 0.04)	0.610
C24:0 SM	HMDB0011697	-0.43 (-0.78, -0.08)	0.086	-0.003 (-0.06, 0.05)	0.913
C24:1 SM	HMDB0012107	-0.44 (-0.77, -0.11)	0.081	0.05 (0.001, 0.11)	0.104
Sebacate	HMDB0000792	-0.47 (-0.84, -0.10)	0.081	-0.08 (-0.14, -0.02)	0.032

C18:3 CE	HMDB0010370	-0.50 (-0.84, -0.17)	0.060	-0.06 (-0.11, -0.002)	0.099
C20:1 CE	HMDB0005193	-0.44 (-0.78, -0.09)	0.081	-0.08 (-0.14, -0.02)	0.019
C24H38O5	NA	0.42 (0.08, 0.77)	0.086	-0.06 (-0.11, -0.002)	0.100
Linoleate	HMDB0000673	0.50 (0.14, 0.85)	0.074	0.04 (-0.01, 0.10)	0.206
Isoleucine	HMDB0000172	0.43 (0.12, 0.73)	0.074	0.08 (0.03, 0.13)	0.007
C12:1 carnitine	HMDB0013326	0.47 (0.14, 0.80)	0.074	0.04 (-0.01, 0.10)	0.206
C56:8 TAG	HMDB0005392	0.61 (0.27, 0.95)	0.019	0.003 (-0.05, 0.06)	0.920
C52:3 TAG	HMDB0005384	0.47 (0.13, 0.81)	0.074	0.01 (-0.05, 0.06)	0.817
C50:1 TAG	HMDB0044109	0.43 (0.12, 0.74)	0.074	0.05 (-0.003, 0.10)	0.133
C52:2 TAG	HMDB0005369	0.44 (0.12, 0.76)	0.074	0.03 (-0.02, 0.08)	0.356
C50:2 TAG	HMDB0005377	0.41 (0.09, 0.72)	0.081	0.04 (-0.01, 0.09)	0.243
C56:5 TAG	HMDB0005406	0.47 (0.10, 0.84)	0.081	-0.07 (-0.13, -0.01)	0.062
C34:0 DAG	HMDB0007100	0.42 (0.11, 0.73)	0.080	0.01 (-0.04, 0.06)	0.650
C34:2 DAG	HMDB0007103	0.39 (0.07, 0.71)	0.086	0.02 (-0.03, 0.07)	0.440
C36:0 DAG	HMDB0007158	0.43 (0.08, 0.78)	0.086	-0.02 (-0.08, 0.04)	0.484
Proline	HMDB0000162	0.41 (0.08, 0.74)	0.086	-0.002 (-0.05, 0.05)	0.934
Piperine	HMDB0029377	0.41 (0.08, 0.78)	0.086	-0.01 (-0.06, 0.04)	0.730
Cholate isomer	NA	0.42 (0.08, 0.76)	0.086	0.04 (-0.02, 0.09)	0.248
Indoxylsulfate	HMDB0000682	0.41 (0.07, 0.75)	0.086	-0.04 (-0.09, 0.01)	0.229

¹All values are beta estimates obtained from multivariable-adjusted linear regression modeling 5-SD increments in EDIP or 5-unit increments in CRP as the main predictor of interest and metabolite as the main response variable of interest. Metabolite associations in **bold face** are those that were also significantly associated with CRP at FDR-adjusted $P < 0.10$.

²Models were adjusted for body mass index (continuous) age, physical activity, educational level, race/ethnicity, aspirin/NSAIDs use, smoking status, WHI Hormone Therapy trial arm, CHD case-control status.

³Statistical significance was defined as false-discovery rate adjusted $p < 0.10$.

Supplemental Table 3. Sixteen of the forty-five metabolites discovered (FDR-adjusted $P < 0.10$) among overweight or obese women in the Hormone Therapy trial, were replicated at FDR-adjusted $P < 0.05$ in the Observational Study ($n=497$)^{1,2,3}

Metabolite	HMDB ID	Association with EDIP score		Association with CRP	
		Beta estimate (95%CI)	FDR <i>P</i> -value	Beta estimate (95%CI)	FDR <i>P</i> -value
Trigonelline	HMDB0000875	-1.31 (-1.72, -0.90)	1.22 E-08	0.01 (-0.05, 0.06)	0.795
1,7-dimethyluric acid	HMDB0011103	-0.77 (-1.23, -0.31)	0.003	0.07 (0.01, 0.13)	0.052
7-methylxanthine	HMDB0001991	-0.68 (-1.11, -0.24)	0.004	-0.02 (-0.07, 0.03)	0.622
3-methylxanthine	HMDB0001886	-0.64 (-1.07, -0.20)	0.006	0.01 (-0.04, 0.07)	0.716
5-acetylamino-6-amino-3-methyluracil	HMDB0004400	-0.65 (-1.10, -0.21)	0.006	-0.03 (-0.08, 0.03)	0.511
Caffeine	HMDB0001847	-0.54 (-0.99, -0.10)	0.017	0.10 (0.05, 0.16)	0.001
Glycine	HMDB0000123	-0.43 (-0.84, -0.01)	0.043	-0.13 (-0.18, -0.09)	4.96 E-06
C18:3 CE	HMDB0010370	-0.53 (-0.97, -0.09)	0.017	-0.01 (-0.06, 0.04)	0.773
C20:1 CE	HMDB0005193	0.01 (-0.39, 0.42)	0.946	-0.06 (-0.11, -0.01)	0.052
C14:0 SM	HMDB0012097	-0.48 (-0.90, -0.06)	0.025	-0.01 (-0.04, 0.06)	0.773
C20:0 SM	HMDB0012102	-0.04 (-0.46, 0.37)	0.834	0.02 (-0.03, 0.07)	0.575
C22:0 SM	HMDB0012103	-0.08 (-0.51, 0.34)	0.703	0.04 (-0.02, 0.09)	0.318
C22:1 SM	HMDB0012104	-0.07 (-0.50, 0.36)	0.746	-0.01 (-0.06, 0.04)	0.773
C24:0 SM	HMDB0011697	-0.32 (-0.76, 0.12)	0.152	-0.01 (-0.06, 0.04)	0.773
C24:1 SM	HMDB0012107	-0.13 (-0.58, 0.33)	0.576	0.04 (-0.02, 0.09)	0.318
C18:2 LPC	HMDB0010386	-0.41 (-0.84, 0.02)	0.061	-0.12 (-0.17, -0.07)	6.61 E-05
C18:3 LPC	HMDB0010387	-0.34 (-0.75, 0.07)	0.106	-0.06 (-0.11, -0.01)	0.087
C20:1 LPC	HMDB0010391	-0.35 (-0.72, 0.03)	0.073	-0.07 (-0.11, -0.02)	0.019
C20:5 LPC	HMDB0010397	-0.41 (-0.84, 0.01)	0.058	-0.11 (-0.17, -0.06)	1.15 E-04
C24:0 LPC	HMDB0008038	-0.26 (-0.67, 0.15)	0.218	-0.12 (-0.17, -0.07)	3.79 E-05
C36:0 PC	HMDB0008036	-0.15 (-0.60, 0.31)	0.527	0.02 (-0.02, 0.07)	0.455
C37:4 PC	HMDB0008625	0.15 (-0.27, 0.58)	0.482	0.02 (-0.03, 0.07)	0.622
C18:1 LPE	HMDB0011506	-0.18 (-0.58, 0.23)	0.388	-0.02 (-0.07, 0.03)	0.622

C38:2 PE	HMDB0008942	-0.04 (-0.46, 0.38)	0.836	-0.04 (-0.08, 0.02)	0.318
Uracil	HMDB0000296	-0.36 (-0.78, 0.07)	0.097	-0.04 (-0.09, 0.01)	0.281
C24H38O5	NA	-0.29 (-0.72, 0.15)	0.195	0.03 (-0.03, 0.08)	0.481
Uridine	HMDB0000300	-0.25 (-0.68, 0.18)	0.251	-0.05 (-0.11, -0.002)	0.110
Cortisol	HMDB0000063	-0.24 (-0.68, 0.19)	0.277	-0.02 (-0.08, 0.03)	0.524
Proline	HMDB0000162	-0.14 (-0.60, 0.31)	0.539	0.01 (-0.04, 0.07)	0.773
Indoxylsulfate	HMDB0000682	-0.13 (-0.58, 0.33)	0.587	-0.05 (-0.11, 0.003)	0.162
Linoleate	HMDB0000673	0.55 (0.10, 0.99)	0.017	0.04 (-0.01, 0.10)	0.270
Sebacate	HMDB0000792	0.25 (-0.17, 0.68)	0.241	0.04 (-0.01, 0.09)	0.281
C34:0 DAG	HMDB0007100	0.58 (0.08, 1.08)	0.024	0.07 (0.01, 0.13)	0.093
C34:2 DAG	HMDB0007103	0.69 (0.25, 1.13)	0.004	0.08 (0.02, 0.13)	0.019
C36:0 DAG	HMDB0007158	0.12 (-0.25, 0.49)	0.523	0.02 (-0.02, 0.07)	0.455
C50:1 TAG	HMDB0044109	0.72 (0.28, 1.16)	0.003	0.11 (0.05, 0.16)	7.75 E-04
C50:2 TAG	HMDB0005377	0.63 (0.18, 1.09)	0.008	0.11 (0.05, 0.16)	0.001
C52:2 TAG	HMDB0005369	0.76 (0.34, 1.19)	0.003	0.09 (0.04, 0.14)	0.002
C52:3 TAG	HMDB0005384	0.69 (0.27, 1.10)	0.003	0.11 (0.05, 0.16)	0.006
C56:5 TAG	HMDB0005406	0.38 (-0.06, 0.07)	0.093	-0.03 (-0.08, 0.02)	0.430
C56:8 TAG	HMDB0005392	0.10 (-0.28, 0.47)	0.614	-0.03 (-0.08, 0.01)	0.281
Isoleucine	HMDB0000172	0.10 (-0.32, 0.52)	0.628	0.06 (0.01, 0.11)	0.092
Cholate isomer	NA	0.37 (-0.05, 0.79)	0.082	-0.01 (-0.07, 0.04)	0.709
C12:1 carnitine	HMDB0013326	0.05 (-0.39, 0.50)	0.811	0.04 (-0.01, 0.09)	0.318
Piperine	HMDB0029377	-0.02 (-0.44, 0.40)	0.931	0.03 (-0.02, 0.08)	0.408

¹All values are beta estimates obtained from multivariable-adjusted linear regression modeling 5-SD increments in EDIP or 5-unit increments in CRP as the main predictor of interest and metabolite as the main response variable of interest. Metabolite associations in **bold face** are the EDIP replicated associations (FDR-adjusted $P < 0.10$) that were also significantly associated with CRP at FDR-adjusted $P < 0.10$.

²Models were adjusted for body mass index (continuous) age, physical activity, educational level, race/ethnicity, aspirin/NSAIDs use, smoking status, WHI Hormone Therapy trial arm, CHD case-control status.

³Statistical significance was defined as false-discovery rate adjusted $p < 0.10$.