

Supplementary tables:

Table S1: Characteristics of participants. The non-parametric Mann-Whitney test or the parametric t-test was used for quantitative variables and the chi-squared (χ^2) test for qualitative variables with GraphPad Prism, v.8.0 (GraphPad Software, San Diego, CA, USA). Differences were considered significant at p-value < 0.05.

		Control group n = 20	EO group n = 19	V group n = 22	p-value
Age (years)		35.6 ± 6.4	33.5 ± 6.4	41.8 ± 6.4	C vs EO : 0.32 C vs V : 0.003 EO vs V : 0.0002
Smoking status	Non smoker	7	13	0	C vs EO : 0.1
	Smoker	7	4	0	
	Information missing	6	2	22	
Sperm concentration (10 ⁶ / ml)		383 ± 220.3	0.3 ± 0.3	0 ± 0	The 3 groups < 0.0001
Genetic	Klinefelter	0	2	0	C vs EO : 0.18
	AZF deletion	0	1	0	
	None	20	16	0	
	Information missing	0	0	22	
Urological history	Cryptorchidism	0	6	0	C vs EO < 0.0001
	Hypospadias	0	1	0	
	Testicular hypotrophy	0	13	0	
	Other	0	3	0	
	None	20	6	0	
	Information missing	0	0	22	

Table S3: The relevant metabolites characterizing the multivariate signature of the three groups compared two by two. Molecules were sorted by decreasing VIP value. For each metabolite, the table shows the family, the $p(\text{corr})$ value, and the VIP value.

C versus V (increased or decreased in V)				EO versus V (increased or decreased in EO)				EO versus C (increased or decreased in EO)			
Identification		Multivariate analysis		Identification		Multivariate analysis		Identification		Multivariate analysis	
Molecules	Family	P(corr) value	VIP value	Molecules	Family	P(corr) value	VIP value	Molecules	Family	P(corr) value	VIP value
SM C18:1	Sphingolipids	-0.899	1.656	SM (OH) C22:1	Sphingolipids	-0.795	1.825	Lysine	Amino acids	-0.825	1.707
SM (OH) C22:1	Sphingolipids	-0.840	1.518	SM C24:1	Sphingolipids	-0.739	1.749	Aspartate	Amino acids	-0.822	1.694
SM C16:1	Sphingolipids	-0.800	1.492	SM (OH) C24:1	Sphingolipids	-0.747	1.742	Arginine	Amino acids	-0.831	1.678
Lysine	Amino acids	-0.811	1.487	PC aa C36:1	Glycerophospholipids	-0.731	1.738	Glutamate	Amino acids	-0.804	1.653
PC aa C32:0	Glycerophospholipids	-0.787	1.485	SM C24:0	Sphingolipids	-0.745	1.707	Glycine	Amino acids	-0.792	1.651
Aspartate	Amino acids	-0.787	1.463	SM (OH) C22:2	Sphingolipids	-0.690	1.652	Ac-Ornithine	Biogenic amines	-0.785	1.634
SM (OH) C22:2	Sphingolipids	-0.797	1.449	PC aa C32:0	Glycerophospholipids	-0.660	1.616	Threonine	Amino acids	-0.789	1.624

Glutamate	Amino acids	-0.778	1.43 4	SM C26:1	Sphingolipids	-0.695	1.61 0	Serine	Amino acids	-0.778	1.62 1
PC aa C38:6	Glycerophospholipids	-0.736	1.43 1	C0	Acylcarnitines	-0.694	1.59 7	PC aa C38:6	Glycerophospholipids	-0.773	1.59 5
SM C18:0	Sphingolipids	-0.700	1.37 6	SM C18:0	Sphingolipids	-0.624	1.54 8	Alanine	Amino acids	-0.710	1.54 4
Ac-Ornithine	Biogenic amines	-0.721	1.35 1	SM (OH) C16:1	Sphingolipids	-0.606	1.53 4	Methionine	Amino acids	-0.665	1.50 4
Glycine	Amino acids	-0.708	1.34 2	SM C18:1	Sphingolipids	-0.606	1.48 2	Asparagine	Amino acids	-0.717	1.48 4
Arginine	Amino acids	-0.728	1.33 9	PC ae C36:1	Glycerophospholipids	-0.557	1.46 8	Glutamine	Amino acids	-0.684	1.47 5
Alanine	Amino acids	-0.693	1.32 9	PC aa C30:0	Glycerophospholipids	-0.547	1.43 7	PC aa C40:6	Glycerophospholipids	-0.706	1.46 4
PC aa C40:6	Glycerophospholipids	-0.657	1.32 9	PC aa C38:3	Glycerophospholipids	-0.548	1.42 5	Tryptophan	Amino acids	-0.641	1.45 5
PC ae C40:6	Glycerophospholipids	-0.694	1.30 0	SM C16:1	Sphingolipids	-0.532	1.36 2	PC ae C40:6	Glycerophospholipids	-0.670	1.42 2
C5:1	Acylcarnitines	-0.693	1.29 2	PC ae C34:0	Glycerophospholipids	-0.519	1.35 4	Proline	Amino acids	-0.634	1.37 0
Proline	Amino acids	-0.681	1.29 2	PC ae C34:1	Glycerophospholipids	-0.479	1.34 9	lysoPC a C16:1	Glycerophospholipids	0.646	1.36 7
PC aa C38:3	Glycerophospholipids	-0.638	1.28 8	PC ae C32:1	Glycerophospholipids	-0.529	1.31 4	PC aa C36:1	Glycerophospholipids	0.659	1.35 1

SM C24:0	Sphingolipids	-0.711	1.28 3	PC aa C40:4	Glycerophospholipids	-0.530	1.28 6	PC ae C38:6	Glycerophospholipids	-0.660	1.34 6
SM (OH) C16:1	Sphingolipids	-0.623	1.26 9	SM C16:0	Sphingolipids	-0.433	1.26 0	Histidine	Amino acids	-0.591	1.33 4
Methionine	Amino acids	-0.626	1.26 2	PC aa C38:4	Glycerophospholipids	-0.478	1.24 6	SM C24:1	Sphingolipids	0.660	1.33 4
C0	Acylcarnitines	-0.691	1.26 1	SM (OH) C14:1	Sphingolipids	-0.399	1.19 7	lysoPC a C18:1	Glycerophospholipids	0.576	1.33 1
PC ae C38:6	Glycerophospholipids	-0.608	1.24 7	SM C26:0	Sphingolipids	-0.512	1.18 4	lysoPC a C17:0	Glycerophospholipids	0.548	1.31 6
Asparagine	Amino acids	-0.674	1.24 4	PC aa C36:2	Glycerophospholipids	-0.354	1.18 0	C5:1	Acylcarnitines	-0.615	1.31 2
PC aa C36:1	Glycerophospholipids	-0.631	1.24 2	lysoPC a C18:2	Glycerophospholipids	-0.470	1.16 9	lysoPC a C16:0	Glycerophospholipids	0.528	1.29 7
Tryptophan	Amino acids	-0.608	1.23 8	PC aa C36:4	Glycerophospholipids	-0.414	1.16 4	PC aa C34:1	Glycerophospholipids	0.506	1.28 1
PC aa C36:6	Glycerophospholipids	-0.643	1.23 1	PC aa C34:1	Glycerophospholipids	-0.346	1.15 8	lysoPC a C18:0	Glycerophospholipids	0.499	1.27 9
Tyrosine	Amino acids	-0.618	1.21 6	Ac- Ornithine	Biogenic amines	0.366	1.15 7	PC aa C36:6	Glycerophospholipids	-0.620	1.27 9
PC aa C42:4	Glycerophospholipids	-0.659	1.21 2	Isoleucine	Amino acids	0.324	1.12 4	SM C18:1	Sphingolipids	-0.553	1.27 7
SM C26:1	Sphingolipids	-0.646	1.20 8	PC aa C36:3	Glycerophospholipids	-0.350	1.10 6	Leucine	Amino acids	-0.518	1.26 4

PC aa C40:5	Glycerophospholipids	-0.604	1.201	PC aa C38:6	Glycerophospholipids	-0.433	1.100	PC ae C36:1	Glycerophospholipids	0.533	1.244
PC aa C30:0	Glycerophospholipids	-0.538	1.183	PC aa C34:2	Glycerophospholipids	-0.260	1.070	alpha-AAA	Biogenic amines	-0.591	1.214
PC aa C38:5	Glycerophospholipids	-0.553	1.166	PC ae C40:2	Glycerophospholipids	-0.410	1.065	PC aa C28:1	Glycerophospholipids	0.468	1.207
PC aa C36:3	Glycerophospholipids	-0.512	1.164	PC ae C34:2	Glycerophospholipids	-0.304	1.052	PC ae C34:0	Glycerophospholipids	0.458	1.196
PC aa C40:3	Glycerophospholipids	-0.625	1.162	Leucine	Amino acids	0.256	1.052	SM C16:0	Sphingolipids	0.437	1.179
PC aa C38:4	Glycerophospholipids	-0.518	1.158	lysoPC a C16:1	Glycerophospholipids	-0.339	1.050	PC aa C36:3	Glycerophospholipids	-0.484	1.120
Serine	Amino acids	-0.574	1.153	Glutamine	Amino acids	0.253	1.048	PC aa C38:3	Glycerophospholipids	-0.495	1.115
Threonine	Amino acids	-0.596	1.151	PC aa C28:1	Glycerophospholipids	-0.289	1.042	PC aa C40:5	Glycerophospholipids	-0.481	1.113
PC aa C40:4	Glycerophospholipids	-0.590	1.140	SM C20:2	Sphingolipids	-0.387	1.033	PC aa C38:5	Glycerophospholipids	-0.459	1.113
Ornithine	Amino acids	-0.610	1.140	Serine	Amino acids	0.234	1.021	SM (OH) C14:1	Sphingolipids	0.354	1.107
SM (OH) C24:1	Sphingolipids	-0.613	1.136	C5-DC (C6-OH)	Acylcarnitines	0.354	1.006	SM C24:0	Sphingolipids	0.481	1.056
PC aa C34:2	Glycerophospholipids	-0.518	1.136					PC aa C36:2	Glycerophospholipids	0.265	1.041

Histidine	Amino acids	-0.567	1.13 1
Spermidine	Biogenic amines	-0.556	1.11 3
SM C24:1	Sphingolipids	-0.575	1.07 3
lysoPC a C18:1	Glycerophospholipids	0.333	1.07 0
lysoPC a C16:0	Glycerophospholipids	0.346	1.05 3
PC ae C32:1	Glycerophospholipids	-0.512	1.04 9
SM (OH) C14:1	Sphingolipids	-0.368	1.04 4
PC aa C36:4	Glycerophospholipids	-0.421	1.04 0
PC aa C36:2	Glycerophospholipids	-0.354	1.03 5
PC ae C34:1	Glycerophospholipids	-0.467	1.02 6
SM C26:0	Sphingolipids	-0.563	1.02 3
Valine	Amino acids	-0.433	1.02 0

PC aa C30:0	Glycerophospholipids	0.342	1.02 5
SM (OH) C16:1	Sphingolipids	0.328	1.02 4
Valine	Amino acids	-0.358	1.02 1
Isoleucine	Amino acids	-0.375	1.01 3

lysoPC a C18:0	Glycerophospholipids	0.245	1.004
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Table S4: Metabolites of the Venn diagram

	Common to all three comparisons	C versus (V-EO)	V versus (C-EO)	EO versus (C-V)	C versus V	EO versus V	EO versus C
Class of metabolites	13 metabolites	23 metabolites	15 metabolites	9 metabolites	5 metabolites	5 metabolites	2 metabolites
Amino acids	Ser	Lys Met Asp Asn Glu Trp Gly Thr Arg His Ala Val Pro		Gln Ile Leu	Orn Tyr		
Biogenic amines	Ac-Orn				Spermidine		alpha-AAA
Acylcarnitines		C5:1	C0			C5-DC (C6-OH)	
Glycerophospholipids	PC aa C30:0	PC aa C36:6	PC aa C32:0	PC aa C28:1	PC aa C40:3	PC ae C34:2	lysoPC a C17:0

	PC aa C36:1 PC aa C36:2 PC aa C36:3 PC aa C38:3 PC aa C38:6	PC aa C40:5 PC aa C38:5 PC ae C38:6 PC aa C40:6 PC ae C40:6 lysoPC a C18:1 lysoPC a C16:0 lysoPC a C18:0	PC aa C34:2 PC aa C36:4 PC aa C38:4 PC aa C40:4 PC ae C32:1 PC ae C34:1	PC aa C34:1 PC ae C34:0 PC ae C36:1 lysoPC a C16:1	PC aa C42:4	PC ae C40:2 lysoPC a C18:2	
Sphingomyelins	SM (OH) C14:1 SM (OH) C16:1 SM C18:1 SM C24:0 SM C24:1		SM (OH) C22:1 SM (OH) C22:2 SM (OH) C24:1 SM C16:1 SM C18:0 SM C26:0 SM C26:1	SM C16:0		SM C20:2	

