

Evidence for Stress-like Alterations in the HPA-Axis in Women Taking Oral Contraceptives

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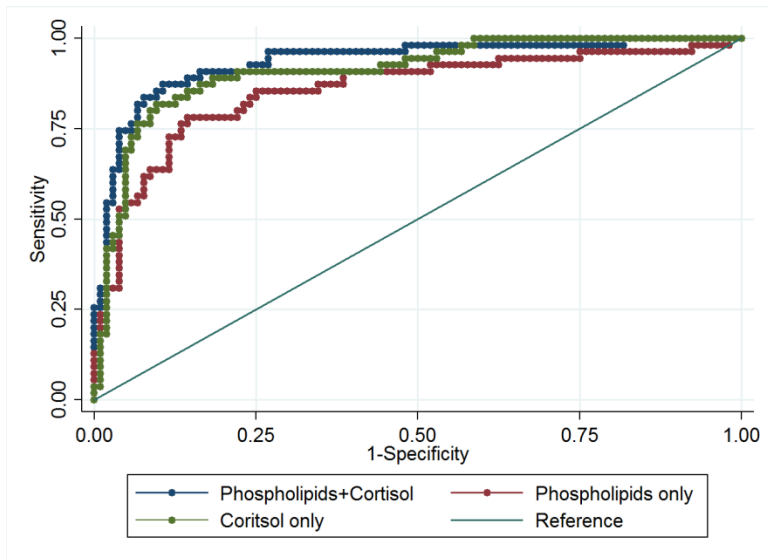


Figure S1: ROC curves for phospholipid classification of OC usage (red, area under the curve (AUC)=0.86), cortisol (green, AUC=0.91) and cortisol combined with phospholipids (blue, AUC=0.94). ROC curves are statistically different ($p < 0.01$).

Table S1: Eigenvalues of the principle components of phospholipids

Principle Component	Eigenvalue
1	2.58
2	2.14
3	0.90
4	0.70
5	0.61
6	0.54
7	0.40
8	0.13

Table S2: Loadings of phospholipids on the first two principle components

	Principle Component 1	Principle Component 2
1-linoleoylglycerophosphocholine	0.49	0.36
1-palmitoylglycerophosphate	-0.33	0.26
2-linoleoylglycerophosphocholine	0.45	0.31
1-palmitoylglycerophosphoinositol	-0.31	0.36
1-palmitoylglycerophosphoethanolamine	-0.23	0.48
1-oleoylglycerophosphoinositol	-0.30	0.27
1-docosapentaenoylglycerophosphocholine	-0.43	0.30
1-docosahexaenoylglycerophosphoethanolamine	-0.15	0.43

Table S3: Association of phospholipid species and total triglycerides with OC usage. Sensitivity analyses

Compound	Mis., %	Model 1^a b(95%-CI) for OC usage	p	N	Model 2^b b(95%-CI) for OC usage	p
Cortisol	0.0	0.89 (0.73;1.06)	6.366e-21	197	0.95 (0.77,1.14)	4.881e-20
Triglycerides	0.0	0.37 (0.19; 0.56)	0.0001	200	0.41 (0.20;0.62)	0.0002
1-linoleoylglycerophosphocholine (18:2n6)	0.0	-0.24 (-0.38;-0.10)	0.0007	197	-0.24 (-0.39;-0.09)	0.0019
1-palmitoylglycerophosphate	8.3	0.35 (0.15;0.55)	0.0006	181	0.36 (0.14;0.58)	0.0017
2-linoleoylglycerophosphocholine	0.0	-0.24 (-0.39;-0.09)	0.0018	197	-0.26 (-0.42;-0.09)	0.0028
1-palmitoylglycerophosphoinositol	17.0	0.45 (0.30;0.59)	4.18e-09	161	0.43 (0.26;0.59)	6.215e-07
1-palmitoylglycerophosphoethanolamine	0.0	0.32 (0.19;0.45)	1.81e-06	197	0.37 (0.23;0.50)	1.578e-07
2-palmitoylglycerophosphoethanolamine	20.9	0.30 (0.14;0.47)	0.0004	156	0.34 (0.16;0.51)	0.0002
1-oleoylglycerophosphoinositol	9.6	0.35 (0.16;0.54)	0.0003	178	0.30 (0.10;0.51)	0.0044
1-docosapentaenoylglycerophosphocholine (22:5n3)	1.3	-0.42 (-0.61;-0.23)	2.58e-05	195	-0.43 (-0.64;-0.22)	8.40e-05
1-docosahexaenoylglycerophosphoethanolamine	0.0	0.22 (0.11;0.34)	0.0002	197	0.23 (0.11;0.35)	0.0003

^aModel 1: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling and BDI-II-score

^bModel 2: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling and BDI-II-score, MDD lifetime and CTQ score

Table S4: Top-Hits of the Transcriptome Wide Association Study (TWAS) on Circulating Cortisol Levels

Gene	beta	Standard Error	t	p ^a	Mean Intensity	Detection Rate	FDR ^b
<i>DDIT4</i>	0.30999	0.01978457	15.66828	0	8.525642395	1	0
<i>FKBP5</i>	0.19543	0.021948732	8.903933	2.98E-18	9.026628494	1	7.27E-14
<i>CEBPD</i>	0.121855	0.014438373	8.439684	1.28E-16	11.52982616	1	2.08E-12
<i>TSC22D3</i>	0.148345	0.019576032	7.577876	8.81E-14	10.81162262	1	1.06E-09
<i>ECHDC3</i>	0.141087	0.018700032	7.544766	1.12E-13	7.401368141	0.996742666	1.06E-09
<i>DUSP1</i>	0.178655	0.023745332	7.523806	1.3E-13	11.75978661	0.998914242	1.06E-09
<i>IRS2</i>	0.153778	0.021141438	7.27376	7.67E-13	8.539684296	1	5.34E-09
<i>KLF9</i>	0.132867	0.019235406	6.907442	9.39E-12	8.529838562	1	5.73E-08
<i>FBXO32</i>	0.080941	0.01340034	6.040214	2.26E-09	7.693478584	1	1E-05
<i>CCND3</i>	0.079452	0.013562377	5.858269	6.58E-09	12.50660133	1	2.6E-05
<i>ZBTB16</i>	0.120713	0.02063573	5.849691	6.91E-09	7.488571644	0.997828424	2.6E-05
<i>TSC22D3</i>	0.108573	0.018637262	5.82561	7.95E-09	7.473699093	0.992399573	2.63E-05
<i>IL18R1</i>	0.115021	0.019755004	5.822386	8.1E-09	8.12012291	1	2.63E-05
<i>ZBTB16</i>	0.098722	0.01703673	5.794641	9.5E-09	6.809102058	0.85233444	2.9E-05
<i>CXCR4</i>	0.097555	0.017459987	5.587322	3.06E-08	8.861386299	1	8.8E-05
<i>RNF144B</i>	0.088643	0.016143128	5.49104	5.21E-08	8.186312675	1	0.000141
<i>ID3</i>	-0.08677	0.016014749	-5.41837	7.75E-08	7.780823708	0.998914242	0.000199
<i>SOCS1</i>	0.075597	0.014539026	5.199621	2.48E-07	6.695757389	0.845819771	0.000576
<i>IL7R</i>	0.092921	0.018605242	4.994351	7.1E-07	10.64928913	1	0.001576
<i>IL1B</i>	-0.09457	0.019148158	-4.93899	9.38E-07	9.05814743	1	0.00199
<i>CDKN1B</i>	-0.06413	0.013474356	-4.75958	2.26E-06	9.012987137	1	0.004602
<i>TLR10</i>	-0.06783	0.014507816	-4.67511	3.39E-06	7.260742664	0.992399573	0.006368
<i>ILIR2</i>	0.096261	0.021317955	4.515485	7.17E-06	8.580068588	0.997828424	0.012491
<i>HCAR2</i>	-0.07182	0.016090393	-4.4634	9.1E-06	6.866519928	0.887079239	0.015317
<i>GPR18</i>	-0.06704	0.01511117	-4.43601	1.03E-05	7.56951189	0.996742666	0.016233
<i>P2RY13</i>	-0.06719	0.015176388	-4.42699	1.07E-05	10.27272224	1	0.016313
<i>TSC22D3</i>	0.09939	0.022480585	4.421144	1.1E-05	10.58773518	1	0.016313
<i>TLR10</i>	-0.07021	0.016108844	-4.35868	1.46E-05	7.028824329	0.952225864	0.020798
<i>CDK5R1</i>	0.084563	0.019539991	4.327712	1.68E-05	8.054044724	0.998914242	0.02274

<i>BID</i>	-0.05978	0.013950498	-4.28547	2.02E-05	8.100402832	1	0.026674
<i>PASK</i>	-0.08577	0.020225292	-4.24088	2.46E-05	7.918303967	0.997828424	0.030774
<i>TLR2</i>	0.061194	0.01460359	4.190306	3.06E-05	6.981621742	0.937024951	0.037378
<i>HVCN1</i>	-0.06801	0.016264427	-4.18122	3.19E-05	7.28487587	0.976112902	0.037925
<i>SLA</i>	0.067773	0.016288623	4.160729	3.48E-05	7.309864521	0.986970663	0.040323
<i>ETSI</i>	0.068334	0.016442554	4.1559	3.55E-05	11.27615261	1	0.040323
<i>NFKBIA</i>	0.069396	0.016787166	4.133865	3.9E-05	10.59403896	1	0.043305
<i>SESNI</i>	0.071551	0.017355151	4.122779	4.09E-05	7.553817749	0.997828424	0.044393

^auncorrected p-value

^bFDR=false discovery rate

Table S5: Associations of *FKBP5* and *DDIT4* whole-blood transcript levels with OC usage. Sensitivity analyses.

Transcript	Mis., %	Model 1 ^a b(95%-CI)	p	N	Model 2 ^b b(95%-CI)	P
		Main Effect (OC usage)			Main Effect (OC usage)	
<i>FKBP5</i>	3.0%	0.10 (-0.01;0.20)	0.0660	195	0.12 (0.00;0.23)	0.049
<i>DDIT4</i>	3.0%	0.18 (0.08;0.28)	0.0004	195	0.19 (0.09;0.28)	0.0003
		Interaction term (rs1360780xOC usage)			Interaction term (rs1360780xOC usage)	
<i>FKBP5</i>	3.0%	-0.34 (-0.59;-0.09)	0.008	195	-0.31 (-0.60;-0.02)	0.038
<i>DDIT4</i>	3.0%	-0.01 (-0.25;0.23)	0.966	195	-0.01 (-0.27;0.26)	0.961

^aModel 1: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling and BDI-II-score

^bModel 2: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling and BDI-II-score, MDD lifetime and CTQ score

Table S6: Interaction effects of the rs1360780 genotype (CC/CT vs TT) and OC intake on DNA Methylation Levels in FKBP5 Intron 7. Sensitivity analyses.

Model	N	Interaction term (rs1360780xOC usage)	
		OR(95%-CI)	p
^a Model 1	229	1.22 (0.98;1.51)	0.069
^b Model 2	233	1.24 (1.00;1.53)	0.048
^c Model 3	200	1.20 (0.95;1.53)	0.130

^aModel 1: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling and cortisol

^bModel 2: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling and BDI-II-score

^cModel 3: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling and BDI-II-score, MDD lifetime and CTQ score; note that Model 3 is **misspecified** as the CTQ score interacts itself with OC intake, Model 3 is only given for completeness.

Table S7: Descriptive Statistics for 303 pre-menopausal women of SHIP-2

	no OC usage	OC usage	p-Value
N	229	74	
Age (years)	42.8 (5.9)	40.8 (5.6)	0.007 ^c
Waist Circumference (cm)	81.4 (11.9)	76.3 (7.5)	<0.001 ^c
Triglycerides (mmol/l)	1.3 (0.9)	1.3 (0.6)	0.409 ^c
rs1360780 (TT carrier, %)	7.86	10.81	0.474 ^d
CTQ ^a	33.2 (12.8)	31.2 (8.0)	0.098 ^c
BDI-II ^b	6.0 (6.5)	4.2 (5.9)	0.031 ^c
Lifetime depression (%)	24.12	16.22	0.198 ^d

^aCTQ = Childhood Trauma Questionnaire

^bBDI-II = Beck Depression Inventory II

^cp-values from Welch t-test

^dp-values from Fisher's exact test

Table S8: Interaction Effect between Childhood Trauma Questionnaire Scores and Intake of OCs. Sensitivity Analyses.

Model	SHIP-Trend-0		SHIP-2		Combined	
	Interaction term (CTQxOC usage) OR(95%-CI)	p	Interaction term (CTQxOC usage) OR(95%-CI)	p	Interaction term (CTQxOC usage) OR(95%-CI)	p
Model 1 ^a	1.01 (1.00;1.02)	0.002	1.01 (0.99; 1.01)	0.117	1.01 (1.00; 1.01)	0.003
Model 2 ^b	1.01 (1.00;1.02)	0.003	1.01 (1.00; 1.02)	0.030	1.01 (1.00;1.01)	0.001

CTQ=Childhood trauma questionnaire; combined modelling included cohort as covariate

Model 1^a: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling

Model 2^b: adjusted for age, waist circumference, blood cell counts, fasting time, time of blood sampling, MDD lifetime and current depressive symptoms

Table S9: Associations of the hippocampal volume with OC intake. Sensitivity Analyses.

Model	SHIP-Trend-0		SHIP-2		combined	
	b(95%-CI) for OC usage	p	b(95%-CI) for OC usage	p	b(95%-CI) for OC usage	p
Model 1 ^a	-75.61 (-157.58; 6.36)	0.070	-42.41 (-142.11; 57.29)	0.402	-61.52 (-124.45; 1.41)	0.055
Model 2 ^b	-84.07 (-166.57; -1.56)	0.046	-44.36 (-142.93; 54.20)	0.375	-67.36 (-130.07; -4.64)	0.035
Model 3 ^c	-99.31 (-182.36; -16.26)	0.019	-48.00 (-148.21; 52.22)	0.345	-78.15 (-141.43; -14.88)	0.016
Model 4 ^d	-179.47 (-285.74; -73.19)	0.001	-----	-----	-----	-----
Model 5 ^e	-71.82 (-155.45; 11.82)	0.092	-44.15 (-143.57; 55.27)	0.381	-63.24 (-125.78; -0.70)	0.048
Model 6 ^f	-98.19 (-180.80; -15.59)	0.020	-41.71 (-142.54; 59.12)	0.415	-78.10 (-141.56; -14.63)	0.016
Model 7 ^g	-99.79 (-183.37; -16.21)	0.020	-46.39 (-146.64; 53.85)	0.362	-78.14 (-141.33; -14.96)	0.016
Model 8 ^h	Interaction (SNP×OC) -69.22 (-298.09; 159.65)	0.551	Interaction (SNP×OC) 104.05 (-170.59; 378.70)	0.455	Interaction (SNP×OC) 17.08 (-174.79; 208.95)	0.861

^aModel 1: adjusted for age, intracranial volume, waist circumference and education

^bModel 2: adjusted for age, intracranial volume, waist circumference, education and CTQ scores

^cModel 3: adjusted for age, intracranial volume, waist circumference, education, CTQ scores and BDI-II scores

^dModel 4: adjusted for age, intracranial volume, waist circumference, education, CTQ scores, BDI-II scores and circulating cortisol

^eModel 5: adjusted for age, intracranial volume, waist circumference, education, CTQ scores, BDI-II scores and triglycerides

^fModel 6: adjusted for age, intracranial volume, waist circumference, education, CTQ scores, BDI-II scores and SNP rs1360780

^gModel 8: adjusted for age, intracranial volume, waist circumference, education, CTQ scores and BDI-II scores and MDD lifetime

^hModel 7: interaction effect of SNP and OC intake, adjusted for adjusted for age, intracranial volume, waist circumference, education, CTQ scores, BDI-II scores

Table S10: Genotype distribution and Hardy-Weinberg Equilibrium for rs1360780 for subjects with MRI. The corresponding total genotype-sample (genotype distribution for SHIP-2 and SHIP-TREND, respectively) is given in brackets.

	CC	CT	TT	HWE (p-value)
SHIP-2	310 (1988)	278 (1742)	41 (334)	0.05 (0.08)
SHIP-TREND (Illumine HumanOmni)	326 (467)	296 (422)	64 (92)	0.86 (0.88)

Table S11. Sequences of PCR tagged primers used for EpiTYPER methylation analysis

Amplicon	Primer	Sequence	Product size (bp)	Total No. of CpG sites in amplicon
<i>FKBP5</i>	forward	aggaagagagTTGTTTTGGAATTTAAGGTAATTGA	341	5
	revers	cagtaatacgactcactataggagaaggctAAATCCAAAACCTTATCCCTTATTTA		