Chapter 4

Genetic variation in ethinylestradiol metabolism and venous thrombosis

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Abstract

Background: Use of ethinylestradiol, one of the active ingredients in combined oral contraceptives, affects the incidence of venous thrombosis. To explain why some women develop thrombosis when using oral contraceptives and others do not, we hypothesized a role for the first-pass metabolism of ethinylestradiol in the liver.
Objectives: To determine the association between genetic variation in the first-pass metabolism of ethinylestradiol, venous thrombosis risk and the effect on SHBG levels, a marker for venous thrombosis risk in oral contraceptive users.
Methods: Premenopausal women with venous thrombosis and control subjects were included from two large case-control studies, i.e., the LETS and the MEGA study. Women exposed to acquired risk factors other than combined oral contraceptives were excluded. Haplotype-tagging SNPs were selected in 11 candidate genes; *COMT*, *CYP1A2*, *CYP2C9*, *CYP3A4*, *CYP3A5*, *SULT1A1*, *SULT1E1*, *UGT1A1*, *UGT1A3*, *UGT1A9*, and *UGT2B7*. Venous thrombosis risk was expressed as odds ratios (OR) with 95% confidence intervals (CI). For SHBG levels, mean differences with 95%CI were estimated in combined oral contraceptive-using control subjects from the MEGA study.
Results: 262 premenopausal women (103 cases; 159 controls) were included from the LETS and 1193 (397 cases; 796 controls) from the MEGA study. 74 SNPs in the 11 genes were determined. Two copies of haplotype D in the *UGT2B7* gene increased venous thrombosis risk (OR~3) as well as SHBG levels (mean difference 27.6 nmol/L, 95%CI: -61.7 to 116.9 compared with no copies) in oral contraceptive users and not in non-users. In oral contraceptive users, haplotype A and B in the *CYP3A4* gene were associated with the risk of venous thrombosis, but not in non-users; however, the effect on SHBG levels was not directional with the risk. None of the other haplotypes were associated with venous thrombosis.

Conclusion: Genetic variation in the *UGT2B7* gene can at least in part explain the risk of venous thrombosis in combined oral contraceptive users.

Introduction

Combined oral contraceptive use, containing an estrogen (i.e., ethinylestradiol) and a progestagen, increase venous thrombosis risk[1–4]. Over time the dose of ethinylestradiol was stepwise reduced from ≥100 µg to 50 µg and 30/20 µg, which resulted in the intended lowering in the risk of venous thrombosis[1,5,6]. The risk of venous thrombosis is the highest in the first three months of combined oral contraceptive use, i.e., about twelve-fold increased compared with non-users[7–9]. With extended use the risk remains approximately five-fold increased[9]. While some high-risk groups have been identified, i.e., women with prothrombotic genetic defects and women who are obese, it is largely unknown why oral contraceptive use leads to thrombosis in some women, and not in others.

Because they are taken orally, combined oral contraceptives are metabolised in the liver through the so-called first-pass metabolism. In the liver many coagulation factors are produced; therefore, we hypothesized that the first-pass metabolism of oral contraceptives, in particular of ethinylestradiol (Figure 4.1), influences the risk of venous thrombosis, and that genetic variation in involved genes explains the different susceptibility between women. In general, the first-pass metabolism of drugs mainly involves conjugation and hydroxylation. Sulfonation and glucuronidation are both conjugation steps leading to inactive and water-soluble compounds which are excreted by the kidneys or the intestinal tract (via bile). The genes *SULT1A1* and *SULT1E1* code for sulfotransferases that are involved in sulfonation of ethinylestradiol[10–15] and the genes *UGT1A1*, *UGT1A3* and *UGT1A9* code for UDP-glucuronosyltransferases involved in the glucuronidation of ethinylestradiol[15–18]. Hydroxylation and subsequent methylation of the hydroxyl group lead to hydroxy-ethinylestradiol and methoxy-ethinylestradiol, respectively. The genes *CYP1A2*, *CYP2C9*, *CYP3A4* and *CYP3A5* code for enzymes involved in the hydroxylation step[15,19–21] and the *COMT*

gene codes for catechol O-methyltransferase involved in the methylation step[22]. To inactivate hydroxyl-ethinylestradiol and methoxy-ethinylestradiol, the aforementioned conjugation steps are used.

Sex hormone binding globulin (SHBG) is a marker for the hormonal effects of combined oral contraceptives on venous thrombosis risk. SHBG is a hepatic plasma glycoprotein that binds the sex steroid hormones testosterone and 17β -estradiol, but not ethinylestradiol. Estrogens such as ethinylestradiol increase the synthesis of SHBG[23], while progestagens induce a decrease in SHBG levels depending on the type and dose[24,25]. The effect of a combined oral contraceptive on SHBG levels may be seen as the result of the stimulating effect of ethinylestradiol and the inhibiting effect of the progestagen in a contraceptive[25].

The aim of this study was to explain differences in susceptibility to the prothrombotic effect of oral contraceptives by assessing genetic variation in the first-pass metabolism of ethinylestradiol in premenopausal women. Because the investigated enzymes are also involved in other metabolic pathways, results from non-users were evaluated to assess the specificity of the association with risk. Any risk associations with venous thrombosis observed in non-users, in whom the first-pass metabolism of ethinylestradiol is not activated, will be a reflection of genetic variation in the other pathways. Furthermore, genetic variation in the first-pass metabolism of ethinylestradiol was linked to an intermediate variable, SHBG levels, in combined oral contraceptive users. A priori, three criteria were established to determine whether a haplotype was associated with venous thrombosis through changes in the first-pass metabolism of ethinylestradiol, i.e., a similar association with venous thrombosis in combined oral contraceptive users in two independent studies (LETS and MEGA study), no association in non-users, and a direction of the effect on SHBG levels in accordance with the association with venous thrombosis risk.

Methods

Participants Participants were selected from two case-control studies on venous thrombosis, i.e., the LETS (Leiden Thrombophilia Study) and the MEGA (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis) study. In the LETS, participants with a first, symptomatic, objectively confirmed episode of deep venous thrombosis in the leg, younger than 70 years and without a known malignant disorder were enrolled between 1 January 1988 and 31 December 1992. As controls, acquaintances and partners of the patients were invited to participate[26]. In the MEGA study, participants with a first symptomatic deep venous thrombosis in the leg or arm or pulmonary embolism were recruited between 1 March 1999 and 31 August 2004. Controls were either the partners of the patients or recruited through random digit dialling (RDD). Details of the study have been described elsewhere[27]. Participants of both studies were asked to fill in a questionnaire and to provide a blood or buccal swab sample. The LETS and the MEGA study differed slightly in their in- and exclusion criteria. To increase homogeneity in the present analysis, only patients with a deep venous thrombosis of the leg were studied.

The population of interest consisted of premenopausal women younger than 50 years (N_{LETS}=347; N_{MEGA}=2657). Women who had any type of cancer (N_{MEGA}=63), were hospitalized (N_{LETS}=22; N_{MEGA}=357), had undergone surgery (N_{LETS}=29; N_{MEGA}=277), suffered bone fractures (N_{LETS}=2; N_{MEGA}=81) or had soft-tissue injuries (N_{LETS}=0; N_{MEGA}=529) in the twelve months before the index date were excluded. We also excluded women who were pregnant (N_{LETS}=11; N_{MEGA}=65), were within four weeks postpartum (N_{LETS}=4; N_{MEGA}=17) or were using hormone replacement therapy (N_{MEGA}=14) at the index date or had experienced a miscarriage (N_{LETS}=1; N_{MEGA}=10) in the twelve months before the index date. Oral contraceptive users were defined as users of a combined oral contraceptive at the

index date (i.e., a contraceptive containing ethinylestradiol and a progestagen). Hence, in both studies women using a contraceptive without ethinylestradiol, e.g., progestagen-only pills, were excluded (N_{LETS}=2; N_{MEGA}=26). Women without a blood or buccal samples were also excluded (N_{MEGA}=366). 500 patients and 955 controls were included in the current analysis (LETS: 103 cases and 159 controls; MEGA: 397 cases and 796 controls). In both studies, the sum of all exclusions does not add up to the total number of excluded participants because women could be exposed to one or more risk factors.

DNA preparation and SNP typing Collection and processing of blood samples and buccal swabs and subsequent DNA isolation have been described previously[26,27]. To determine the haplotypes in the selected genes, the Genome Variation Server (GWS)[28] was used. GVS incorporates information from HapMap and other sources and is sponsored by SeattleSNPs. Only SNPs with a minor allele frequency of 5% or more in Caucasians were considered.

A total of 11 genes involved in ethinylestradiol metabolism were selected prior to genotyping, i.e., *COMT*, *CYP1A2*, *CYP2C9*, *CYP3A4*, *CYP3A5*, *SULT1A1*, *SULT1E1*, *UGT1A1*, *UGT1A3*, *UGT1A9*, and *UGT2B7* in which a total of 74 SNPs were selected (Supplementary table 4.1). Care was taken to select SNPs from each haplotype that enabled a clear distinction between highly related genes. The SNPs were either determined with the MassARRAY platform (Sequenom, San Diego, California, USA) according to manufacturer's protocols (Sequenom) or determined with the 5' nuclease/Taqman assay (Assay-by-Design, Applied Biosystems, Foster City, California, USA). SNP rs28946889 was determined via restriction digest of the PCR product (details available on request). Genotyping determination was done blinded to the case/control status and study number. Five percent of the samples were repeated for allele-calling consistency, no discrepancies were found.

Laboratory measurements SHBG levels (nmol/L) were measured with an immunometric assay (Immulite 2000 XPi; Siemens Healthcare Diagnostics, Tarrytown, NY, USA) in combined oral contraceptive users of the control group of the MEGA (plasma of the LETS subjects was no longer available). The sensitivity of the assay is 0.2 nmol/L and the assay has a log-term variation of 6% at levels of 5 nmol/L and 80 nmol/L. The within-assay variation is 3-4% and the between-assay variation 3.5- 6%. The samples were analysed in a single series in random order. SHBG levels were measured without knowledge of any other of the participant's characteristics.

Statistical analysis Hardy-Weinberg Equilibrium was assessed with a Chi-squared test in controls from the LETS and MEGA study. Due to the large number of SNPs tested we used a Bonferroni correction for the Hardy-Weinberg Equilibrium tests. The posterior probabilities of correct haplotype assignment as estimated by PLINK (version 1.07) [29] were used as weights in all statistical analyses. Because women could be assigned two possible combinations of haplotypes, no number of women per copies of a haplotype was given in the tables. Odds ratios (OR) were calculated to determine the risk of venous thrombosis associated with the number of copies of a specific haplotype. To account for multiple testing, the False Discovery Rate q-value was calculated. First, the p-value of the association was derived from the univariate unconditional logistic regression analysis between a haplotype and venous thrombosis risk while assuming an additive model for the genetic relationship with venous thrombosis. Second, the p-values were ranked from smallest till largest, where rank order 1 was given to the smallest p-value. Third, the q-values were calculated as follows; the p-values were multiplied by the number of tests performed and then divided by the rank order of each p-value. For each test, the q-value is then defined as the minimum among tests with equal or higher rank. The threshold was set at 0.20 and can be interpreted as follows: among tests

with a q-value of 0.20 or lower, at most 20% or lower of the tests might be a false discovery. The analyses were restricted to combined oral contraceptives users or non-users. Linear regression analysis was used to determine the effect of a haplotype on SHBG levels in controls using combined oral contraceptives from the MEGA study. In this analysis, combined oral contraceptive use was defined at venipuncture and not at the index date. To determine whether a haplotype was associated with venous thrombosis, we used several criteria. An association with venous thrombosis in the same direction had to be present in the LETS and MEGA study, no association in non-users and a same directional effect on SHBG levels as expected based on the risk association with venous thrombosis. Statistical analyses were performed with STATA, version 12.0 (Statacorp LP, College Station, Texas, USA).

Results

General description of the population Baseline characteristics of the studies are given in Table 4.1. In the LETS, the mean age in cases and controls was 35 years (range cases: 16 to 49 and controls: 15 to 48). In the MEGA study, the mean age in the cases was 37 years (range: 18 to 49) and in the controls 38 years (range: 18 to 49). No information about ancestry was available in the LETS. In the MEGA study, about 90% of cases and controls reported to be from Western European ancestry. The majority of the cases (80% and 87%, respectively in the LETS and the MEGA study) were using combined oral contraceptives at the time of the event.

Hardy-Weinberg Equilibrium Hardy-Weinberg Equilibrium was assessed in the controls from the LETS and MEGA study. To control for multiple testing, we performed a Bonferroni correction. All SNPs were in Hardy-Weinberg Equilibrium ($p>0.0007$), except for SNP rs12445705 in the *SULT1A1* gene in the MEGA

Table 4.1: Baseline characteristics of the selected population from the LETS and the MEGA study

	LETS		MEGA study	
Variables	**Cases (N=103)**	**Controls (N=159)**	**Cases (N=397)**	**Controls (N=796)**
Mean age (SD)	35 (10)	35 (9)	37 (9)	38 (8)
Caucasian[a](%)	-	-	347 (90)	695 (89)
Pill use (%)	78 (80)	62 (42)	343 (87)	335 (42)

[a] No information about race was available in the LETS study

study. To exclude a measurement error, we confirmed this SNP with a Taqman assay. The results did not materially differ between the Sequenom and Taqman assay. Consensus among controls from the LETS was 95.7% and 97.1% in the MEGA study.

Results per gene family The results were grouped per gene family. In nine genes, no associations in the same direction were observed between the LETS and MEGA study (Supplementary tables 4.2-9). In *CYP3A4*, two of the five haplotypes were associated with the risk of venous thrombosis, i.e., the similar results were observed in both studies (Table 4.2 & 4.3), and in *UGT2B7*, two of the eight haplotypes were associated with venous thrombosis (Table 4.4 & 4.5).

Gene family *CYP* In combined oral contraceptive users, two haplotypes in *CYP3A4* were associated with venous thrombosis in both studies (Table 4.2). Carrying one copy of haplotype A was associated with a decreased risk of venous thrombosis (OR_{LETS}: 0.29, 95%CI: 0.11-0.76 and OR_{MEGA}: 0.57, 95%CI: 0.37-0.89). Similar results were observed for carriers of two copies of haplotype A (OR_{LETS}: 0.40, 95%CI: 0.14-1.13 and OR_{MEGA}: 0.59, 95%CI: 0.37-0.94). With an additive model, each copy of

Table 4.2: Results from carriers of haplotypes in the *CYP3A4* gene among oral contraceptive users

Haplotype		LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
A									
	0	1			1			125.5 (105.7-145.4)	Reference
	1	0.29 (0.11-0.76)			0.57 (0.37-0.89)			141.3 (126.0-156.7)	15.8 (-8.5 to 40.1)
	2	0.40 (0.14-1.13)			0.59 (0.37-0.94)			152.1 (134.2-170.1)	26.6 (-0.3 to 53.5)
	Additive	0.72 (0.45-1.17)	0.18	0.88	0.83 (0.66-1.03)	0.09	0.98		
B									
	0	1			1			145.5 (134.2-156.8)	Reference
	1	2.14 (0.76-6.05)			1.86 (1.17-2.94)			116.2 (89.4-142.9)	-29.4 (-58.0 to -0.7)
	2	-			0.34 (0.04-3.31)			161.9 (135.4-188.3)	16.3 (-12.6 to 45.3)
	Additive	1.41 (0.52-3.83)	0.50	0.88	1.49 (0.95-2.33)	0.79	0.98		
C									
	0	1			1			142.1 (131.5-152.7)	Reference
	1	0.42 (0.10-1.78)			1.46 (0.65-3.30)			177.7 (109.1-246.3)	35.6 (-34.0 to 105.3)
	2	-			-			-	-
	Additive	0.42 (0.10-1.78)	0.24	0.88	1.46 (0.65-3.30)	0.36	0.98		
D									
	0	1			1			149.3 (134.8-163.9)	Reference
	1	0.92 (0.45-1.90)			1.06 (0.78-1.46)			137.3 (121.4-153.2)	-12.1 (-33.4 to 9.3)
	2	3.81 (0.75-19.29)			0.75 (0.32-1.75)			115.8 (85.4-146.2)	-33.5 (-67.4 to 0.4)
	Additive	1.36 (0.80-2.29)	0.26	0.88	0.99 (0.76-1.29)	0.93	0.98		
E									
	0	1			1			144.1 (133.4-154.9)	Reference
	1	-			1.46 (0.65-3.31)			128.1 (74.2-181.9)	-16.1 (-71.2 to 39.0)
	2	-			-			-	-
	Additive	-	-	-	1.46 (0.65-3.31)	0.36	0.98		

the allele reduced the risk by 20-30% (OR_{LETS}: 0.72, 95%CI: 0.45-1.17 and OR_{MEGA}: 0.83, 95%CI: 0.66-1.03). Carrying one copy of haplotype B increased venous thrombosis risk (OR_{LETS}: 2.14, 95%CI: 0.76-6.05; OR_{MEGA}: 1.86, 95%CI: 1.17-2.94). None of the cases in the LETS study were carriers of two copies of haplotype B, whereas only one case in the MEGA study carried two copies of haplotype B. With an additive model, a ~1.5 fold increase in risk was observed per extra allele (OR_{LETS}: 1.41, 95%CI: 0.52-3.83 and OR_{MEGA}: 1.49, 95%CI: 0.95-2.33). None of the other haplotypes in *CYP3A4* were associated with venous thrombosis risk, i.e., associations in the same direction in both the LETS and MEGA study were not observed.

Both haplotypes A and B in *CYP3A4* were associated with changes in SHBG levels in combined oral contraceptive users among the controls of the MEGA study. Carrying haplotype A increased SHBG levels in controls of the MEGA study (mean difference one copy versus no copies: 15.8 nmol/L, 95%CI: -8.5 to 40.1 and mean difference two copies versus no copies: 26.6 nmol/L, 95%CI: -0.3 to 53.5). We observed a decrease in SHBG levels among controls of the MEGA study carrying one copy of haplotype B (mean difference: -29.4 nmol/L, 95%CI: -58.0 to -0.7). For both haplotyoes, the effect on SHBG levels was in the opposite direction as expected based on the effect on the risk of venous thrombosis; the protective haplotype A is associated with increased SHBG levels, whereas the reverse was true for the pro-thrombotic haplotype B.

In table 4.3, the effect of haplotypes in *CYP3A4* on risk of venous thrombosis in non-users is given. None of the haplotypes were associated with venous thrombosis in non-users, i.e., no associations in the same direction were observed.

Gene family *UGT* Carrying one copy of haplotype D of *UGT2B7* was not associated with venous thrombosis (OR_{LETS}: 1.02, 96%CI: 0.49-2.12 and OR_{MEGA}: 0.93, 95%CI: 0.67-1.30). Carriers of two copies of haplotype D in *UGT2B7* had an in-

Table 4.3: Results from carriers of haplotypes in the emphCYP3A4 gene among non-users

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513) OR (95%CI)	p	FDR q
A						
0	1			1		
1	0.94 (0.23-3.89)			0.71 (0.33-1.52)		
2	1.13 (0.25-5.07)			0.90 (0.40-2.02)		
Additive	1.10 (0.52-2.32)	0.80	0.98	1.00 (0.64-1.55)	0.99	0.99
B						
0	1			1		
1	0.83 (0.17-4.14)			1.33 (0.60-2.95)		
2	-			-		
Additive	0.83 (0.17-4.14)	0.82	0.98	1.11 (0.55-2.23)	0.77	0.94
C						
0	1			1		
1	4.75 (0.87-25.93)			1.18 (0.26-5.31)		
2	-			-		
Additive	4.75 (0.87-25.93)	0.07	0.98	1.18 (0.26-5.31)	0.83	0.95
D						
0	1			1		
1	0.59 (0.20-1.68)			1.45 (0.81-2.60)		
2	1.16 (0.11-12.23)			0.93 (0.21-4.21)		
Additive	0.74 (0.28-1.94)	0.54	0.98	1.22 (0.78-1.91)	0.38	0.91
E						
0	1			1		
1	2.14 (0.18-25.22)			0.54 (0.07-4.16)		
2	-			-		
Additive	2.14 (0.18-25.22)	0.55	0.98	0.54 (0.07-4.16)	0.55	0.94

creased risk of venous thrombosis in both LETS and MEGA study (OR_{LETS}: 3.78, 95%CI: 0.40-35.84 and OR_{MEGA}: 2.61, 95%CI: 1.07-6.34) (Table 4.4). Because the effect seemed clearly recessive, we did not interpret the results from an additive model. None of the other haplotypes in *UGT2B7* were consistently associated with venous thrombosis in both studies. Fully in line with the effect of this haplotype on the risk of venous thrombosis, no effect on SHBG levels in controls of the MEGA study was observed in carriers of one copy of haplotype D in *UGT2B7* (mean difference one copy versus no copies: -5.5 nmol/L, 95%CI:

-28.5 to 17.6), and an increase in SHBG levels was observed with carriers of two copies of haplotype D (mean difference two copies versus no copies of haplotype D: 27.6 nmol/L, 95%CI: -61.7 to 116.9).

In table 4.5, the results for the *UGT2B7* gene are given in non-users. Carriership of one copy of haplotype E was associated with an increase in risk of venous thrombosis (OR_{LETS}: 1.58, 95%CI: 0.15-16.42 and OR_{MEGA}: 1.47, 95%CI: 0.32-6.77). Carriers of two copies of haplotype E were not present in either the LETS or MEGA study and therefore the odds ratio assuming an additive model did not change.

Multiple testing Overall, eight tests of a total of 321 tests were significant at a 0.05 level. Given the large number of tests, we calculated FDR q-values which were all above 0.20.

Discussion

In a search of explanations for ethinylestradiol-associated venous thrombosis, we studied haplotypes of 11 genes involved in ethinylestradiol metabolism in two case-control studies on venous thrombosis with a total of 500 patients and 955 control women. For nine genes we found no association of the haplotypes with risk, while two genes (*CYP3A4* and *UGT2B7*) were associated with venous thrombosis risk. Haplotpe D in the *UGT2B7* gene showed a consistent effect on SHBG levels as well. Homozygous carriers of haplotype D in *UGT2B7* had a three-fold increased risk of thrombosis and a substantial increase in SHBG levels. For all genotypes the FDR was above the threshold of 0.20. However, the likelihood that the association is the result of chance variation is unlikely given the large odds ratios in two separate studies (3.87 and 2.61) in combined oral contraceptive users, the absence of an effect in non-users meaning the result is specific for the first-pass metabolism of ethinylestradiol and the substantial chance in SHBG levels in combined oral contraceptive users

Table 4.4: Results from carriers of haplotypes in the *UGT2B7* gene among non-users

Haplotype		LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513) OR (95%CI)	p	FDR q
A							
	0	1			1		
	1	1.58 (0.15-16.42)			-		
	2	-			-		
	Additive	1.58 (0.15-16.42)	0.70	0.98	-	-	-
B							
	0	1			1		
	1	1.21 (0.38-3.88)			0.49 (0.21-1.13)		
	2	-			0.84 (0.10-6.83)		
	Additive	1.07 (0.37-3.09)	0.90	0.98	0.59 (0.28-1.26)	0.17	0.89
C							
	0	1			1		
	1	0.92 (0.27-3.20)			1.46 (0.76-2.79)		
	2	-			1.07 (0.13-8.71)		
	Additive	0.72 (0.26-1.98)	0.53	0.98	1.31 (0.77-2.25)	0.32	0.91
D							
	0	1			1		
	1	2.10 (0.71-6.15)			0.90 (0.48-1.71)		
	2	-			2.06 (0.65-6.53)		
	Additive	1.25 (0.59-2.66)	0.56	0.98	1.14 (0.67-1.93)	0.63	0.94
E							
	0	1			1		
	1	1.58 (0.15-16.42)			1.47 (0.32-6.77)		
	2	-			-		
	Additive	1.58 (0.15-16.42)	0.70	0.98	1.47 (0.32-6.77)	0.62	0.94
F							
	0	1			1		
	1	2.91 (0.98-8.71)			1.19 (0.64-2.20)		
	2	-			-		
	Additive	1.96 (0.78-4.92)	0.15	0.98	0.87 (0.55-1.40)	0.58	0.94
G							
	0	1			1		
	1	0.43 (0.09-2.08)			0.97 (0.49-1.89)		
	2	-			0.96 (0.12-7.79)		
	Additive	0.38 (0.09-1.49)	0.17	0.98	0.97 (0.54-1.74)	0.92	0.99
H							
	0	1			1		
	1	0.98 (0.25-3.90)			1.43 (0.74-2.76)		
	2	-			-		
	Additive	0.86 (0.25-2.96)	0.81	0.98	1.24 (0.69-2.22)	0.48	0.94

Table 4.5: Results from carriers of haplotypes in the *UGT2B7* gene among combined oral contraceptive users

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
A								
0	1			1			144.3 (133.3-155.2)	Reference
1	-			2.62 (0.69-10.05)			108.7	-35.6 (-46.5 to -24.6)
2	-			-			-	-
Additive	-	-	-	2.91 (0.88-9.66)	0.08	0.98		
B								
0	1			1			140.6 (127.6-153.7)	Reference
1	1.14 (0.50-2.58)			0.74 (0.52-1.06)			150.4 (130.8-170.0)	9.8 (-13.9 to 33.5)
2	-			0.65 (0.22-1.91)			185.0 (81.2-288.7)	44.3 (-60.9 to 149.5)
Additive	1.27 (0.59-2.73)	0.53	0.88	0.76 (0.56-1.03)	0.08	0.98		
C								
0	1			1			145.3 (132.2-158.5)	Reference
1	1.25 (0.56-2.75)			1.07 (0.74-1.55)			141.4 (122.1-160.7)	-3.9 (-27.5 to 19.6)
2	-			2.28 (0.58-8.92)			113.2	-32.1 (-45.4 to -18.9)
Additive	1.07 (0.50-2.27)	0.86	0.97	1.16 (0.84-1.61)	0.37	0.98		
D								
0	1			1			145.1 (131.7-158.4)	Reference
1	1.02 (0.49-2.12)			0.93 (0.67-1.30)			139.6 (120.9-158.2)	-5.5 (-28.5 to 17.6)
2	3.78 (0.40-35.84)			2.61 (1.07-6.34)			172.7 (84.9-260.4)	27.6 (-61.7 to 116.9)
Additive	1.26 (0.69-2.30)	0.46	0.88	1.15 (0.87-1.50)	0.33	0.98		
E								
0	1			1			143.5 (132.3-154.7)	Reference
1	-			0.59 (0.32-1.12)			151.9 (107.8-196.1)	8.4 (-37.3 to 54.1)
2	-			-			-	-
Additive	-	-	-	0.59 (0.32-1.12)	0.11	0.98		

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Table 4.5 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
F								
0	1			1			149.1 (135.2-163.1)	Reference
1	0.59 (0.26-1.34)			1.17 (0.83-1.65)			138.1 (119.9-156.4)	-11.0 (-34.1 to 12.1)
2	0.51 (0.08-3.21)			1.08 (0.48-2.42)			99.7 (86.6-112.7)	-49.5 (-68.7 to -30.3)
Additive	0.64 (0.33-1.24)	0.19	0.88	1.12 (0.84-1.48)	0.44	0.98		
G								
0	1			1			146.1 (132.8-159.3)	Reference
1	0.47 (0.20-1.12)			0.90 (0.62-1.31)			135.0 (118.8-151.1)	-11.1 (-32.3 to 10.1)
2	-			1.04 (0.40-2.75)			190.7 (50.5-330.8)	44.6 (-97.0 to 186.2)
Additive	0.41 (0.19-0.88)	0.02	0.88	0.94 (0.69-1.29)	0.71	0.98		
H								
0	1			1			141.0 (129.1-153.0)	Reference
1	1.21 (0.55-2.69)			0.90 (0.62-1.32)			150.0 (124.3-175.2)	8.7 (-19.7 to 37.2)
2	-			1.08 (0.36-3.27)			200.2 (129.7-270.8)	59.2 (-12.8 to 131.2)
Additive	1.34 (0.64-2.82)	0.44	0.88	0.94 (0.68-1.30)	0.72	0.98		

consistent with an increased risk. *UGT2B7* is therefore a strong candidate for futher investigation, and may prove clinically relevant given its high odds ratio specific for oral contraceptive use.

To bypass the first-pass metabolism of ethinylestradiol in the liver, other types of contraception with hormones were developed that deliver the hormones directly to the systemic circulation, i.e., the transdermal patch and the vaginal ring. Two case reports concerning mesenteric vein thrombosis[30] and cerebral venous sinus thrombosis[31] and two serious adverse event in two trials[32,33] were reported in users of the vaginal ring. This potential association with venous thrombosis was confirmed in a large cohort study showing that the use of vaginal ring increased the risk of venous thrombosis compared to non-users[34]. The risk of venous thrombosis in transdermal patch users has been assessed in two observational studies using health insurance databases. Transdermal patch users have about the same risk of venous thrombosis compared to third generation users or higher[35–38], i.e., a risk that is substantially higher than that conferred by the safest oral contraceptives (containing second generation progestagens). These results were confirmed by a large cohort study[34].

To our knowledge, no studies regarding the genetics of the first-pass metabolism of ethinylestradiol in association with venous thrombosis have been published before. Earlier studies of the first-pass metabolism of estrogens showed that genetic variation in this metabolism was associated with esophageal cancer[39] and prostate cancer[40]. However, either the *CYP3A4* or *UGT2B7* genes were not studied or no association was found with these genes.

A limitation of our study is that only common genetic variation (i.e., SNPs with a frequency above 5%) was taken into account. However, rare haplotypes were captured since these common SNPs could code for haplotypes with a frequency below 5%. A strength of our study is that a highly selected population was used to ensure that venous thrombosis events were only re-

lated to oral contraceptive use. Furthermore, haplotypes were used to look at the entire gene of interest in contrast to individual SNPs.

In conclusion, genetic variation in the *UGT2B7* gene explains part of the risk of venous thrombosis in combined oral contraceptive users.

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Supplementary data

Supplementary table 4.1 Overview of the selected SNPs in the 11 genes from ethinylestradiol metabolism

Gen	SNP	Allel change	MAF	Assay
COMT	rs4333017	C/T	0.175	Sequenom
COMT	rs9605030	C/T	0.117	Sequenom
COMT	rs9617850	G/A	0.169	Sequenom
COMT	rs5746846	G/C	0.500	Sequenom
COMT	rs174675	C/T	0.258	Sequenom
COMT	rs5746847	C/T	0.433	Sequenom
COMT	rs4680	G/A	0.483	Sequenom
COMT	rs887199	G/A	0.125	Sequenom
COMT	rs887204	A/G	0.292	Sequenom
COMT	rs165849	A/G	0.308	Taqman
COMT	rs2240713	G/A	0.068	Sequenom
CYP1A2	rs1378942	T/G	0.339	Sequenom
CYP1A2	rs762551	A/C	0.308	Sequenom
CYP1A2	rs8033381	A/G	0.263	Sequenom
CYP1A2	rs2071501	T/G	0.054	Sequenom
CYP2C9	rs9332174	A/G	0.225	Sequenom
CYP2C9	rs10509679	G/A	0.110	Sequenom
CYP2C9	rs2475377	G/A	0.059	Sequenom
CYP2C9	rs2253635	A/G	0.331	Sequenom
CYP2C9	rs4917636	A/G	0.158	Sequenom
CYP2C9	rs9332245	G/A	0.058	Taqman
CYP3A4	rs2242480	C/T	0.080	Sequenom
CYP3A4	rs6945984	T/C	0.117	Sequenom
CYP3A4	rs2246709	A/G	0.308	Sequenom
CYP3A4	rs4646437	C/T	0.133	Taqman
CYP3A5	rs4646450	C/T	0.175	Sequenom
CYP3A5	rs2740565	T/A	0.067	Sequenom
CYP3A5	rs11734	C/G	0.052	Sequenom
CYP3A5	rs7792939	T/C	0.125	Sequenom
CYP3A5	rs2687134	C/A	0.050	Taqman
SULT1A1	rs17707300	A/G	0.333	Taqman
SULT1A1	rs9924471	C/T	0.136	Sequenom
SULT1A1	rs12445705	G/A	0.121	Sequenom
SULT1A1	rs10521145	C/T	0.119	Taqman

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Supplementary table 4.1 – continued from previous page

Gen	SNP	Allel change	MAF	Assay
SULT1E1	rs1590128	A/G	0.292	Taqman
SULT1E1	rs13112570	G/A	0.360	Taqman
SULT1E1	rs12506209	C/T	0.350	Taqman
SULT1E1	rs1220833	G/A	0.017	Taqman
SULT1E1	rs3736599	G/A	0.110	Taqman
SULT1E1	rs4149526	G/T	0.292	Taqman
SULT1E1	rs3775770	G/A	0.283	Taqman
SULT1E1	rs1220724	C/T	0.142	Taqman
SULT1E1	rs1220702	C/G	0.167	Taqman
SULT1E1	rs3822173	C/T	0.108	Taqman
UGT1A	rs2602376	C/T	0.220	Sequenom
UGT1A	rs4553819	A/G	0.375	Sequenom
UGT1A	rs10179094	T/A	0.342	Sequenom
UGT1A	rs17864689	G/T	0.075	Sequenom
UGT1A	rs6761246	C/A	0.373	Sequenom
UGT1A	rs12466747	G/C	0.242	Sequenom
UGT1A	rs7583278	C/T	0.325	Sequenom
UGT1A	rs6744284	C/T	0.250	Sequenom
UGT1A	rs28898590	G/T	0.058	Sequenom
UGT1A	rs4663326	A/G	0.133	Taqman
UGT1A	rs904855	G/C	0.092	Sequenom
UGT1A	rs871514	A/G	0.424	Sequenom
UGT1A	rs10179091	T/C	0.451	Taqman
UGT1A	rs6742078	G/T	0.283	Sequenom
UGT1A	rs11891311	G/A	0.314	Sequenom
UGT1A	rs28898621	C/T	0.092	Sequenom
UGT1A	rs28946889	G/T	0.306	Restriction
UGT1A	rs4663972	T/C	0.225	Sequenom
UGT1A	rs10203853	T/A	0.492	Sequenom
UGT1A	rs12468017	T/C	0.150	Sequenom
UGT1A	rs17868346	A/G	0.258	Sequenom
UGT1A	rs6719561	C/T	0.383	Sequenom
UGT2B7	rs4587017	G/T	0.483	Sequenom
UGT2B7	rs3924194	C/G	0.169	Sequenom
UGT2B7	rs6600898	G/C	0.450	Sequenom
UGT2B7	rs10028494	A/C	0.133	Sequenom
UGT2B7	rs4385139	G/C	0.474	Sequenom
UGT2B7	rs6600894	G/A	0.217	Taqman
UGT2B7	rs7662029	G/A	0.500	Sequenom
UGT2B7	rs7680341	A/G	0.175	Sequenom

Supplementary table 4.2 Results from carriers of haplotypes in the *COMT* gene among OC users

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
COMT block 1								
A								
0	1			1			144.4 (131.1-157.7)	Reference
1	0.45 (0.20-1.02)			1.22 (0.84-1.76)			140.1 (119.9-160.3)	-4.3 (-28.7 to 20.1)
2	-			0.39 (0.08-2.05)			105.7 (40.3-171.2)	-38.6 (-105.9 to 28.6)
Additive	0.55 (0.24-1.24)	0.15	0.88	1.09 (0.77-1.53)	0.63	0.98		
B								
0	1			1			139.7 (127.8-151.6)	Reference
1	1.18 (0.45-3.07)			0.82 (0.54-1.24)			154.2 (125.1-183.3)	14.5 (-17.1 to 46.1)
2	-			1.38 (0.23-8.32)			162.2	22.5 (10.6 to 34.5)
Additive	1.36 (0.57-3.22)	0.49	0.88	0.87 (0.59-1.27)	0.47	0.98		
C								
0	1			1			146.4 (133.5-159.4)	Reference
1	0.92 (0.40-2.14)			0.93 (0.66-1.32)			134.9 (112.7-157.1)	-11.5 (-37.3 to 14.3)
2	0.54 (0.08-3.42)			2.05 (0.77-5.51)			102.1 (38.5-165.6)	-44.4 (-109.6 to 20.8)
Additive	0.83 (0.44-1.59)	0.58	0.88	1.08 (0.81-1.44)	0.62	0.98		
D								
0	1			1			143.4 (131.9-155.0)	Reference
1	1.54 (0.42-5.59)			1.33 (0.74-2.41)			126.8 (97.8-155.8)	-16.7 (-48.0 to 14.6)
2	-			-			-	-
Additive	1.54 (0.42-5.59)	0.51	0.88	1.41 (0.80-2.49)	0.23	0.98		
E								
0	1			1			145.4 (133.5-157.3)	Reference
1	0.81 (0.25-2.70)			1.15 (0.69-1.94)			115.4 (91.9-139.9)	-29.5 (-56.3 to -2.7)
2	-			-			-	-
Additive	0.64 (0.23-1.75)	0.39	0.88	1.22 (0.74-2.01)	0.44	0.98		

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Supplementary table 4.2 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
F								
0	1			1			138.3 (115.3-161.3)	Reference
1	1.40 (0.60-3.27)			0.97 (0.67-1.40)			142.9 (127.9-158.0)	4.6 (-23.0 to 32.3)
2	1.68 (0.63-4.49)			0.93 (0.60-1.43)			146.4 (123.4-169.5)	8.1 (-24.7 to 40.9)
Additive	1.30 (0.79-2.13)	0.30	0.88	0.96 (0.78-1.20)	0.73	0.98		
SNP rs4680								
GG	1			1			137.7 (117.4-157.9)	Reference
GA	1.62 (0.74-3.55)			1.20 (0.84-1.71)			153.9 (137.6-170.3)	16.3 (-8.2 to 40.7)
AA	1.71 (0.70-4.19)			1.18 (0.75-1.86)			127.4 (112.7-142.2)	-10.3 (-40.8 to 20.3)
Additive	1.37 (0.91-2.06)	0.14	0.88	1.10 (0.88-1.37)	0.42	0.98		
COMT block 2								
A								
0	1			1			118.2 (93.7-142.7)	Reference
1	0.71 (0.21-2.46)			0.97 (0.57-1.66)			151.6 (134.0-169.1)	33.3 (2.9 to 63.7)
2	0.54 (0.16-1.79)			0.87 (0.51-1.48)			141.5 (125.3-157.8)	23.3 (-6.4 to 52.9)
Additive	0.74 (0.44-1.25)	0.26	0.88	0.92 (0.73-1.16)	0.47	0.98		
B								
0	1			1			141.8 (130.9-152.6)	Reference
1	0.94 (0.13-6.95)			1.09 (0.48-2.47)			173.3 (102.5-244.0)	31.5 (-40.3 to 103.3)
2	-			-			-	-
Additive	0.94 (0.13-6.95)	0.95	0.98	1.09 (0.48-2.47)	0.84	0.98		
C								
0	1			1			144.0 (132.0 to 156.1)	Reference
1	2.03 (0.72-5.66)			1.13 (0.72-1.77)			148.1 (118.5-177.6)	4.0 (-28.0 to 36.1)
2	-			0.57 (0.13-2.39)			95.1 (25.6-164.6)	-48.9 (-119.9 to 22.0)
Additive	2.03 (0.73-5.66)	0.18	0.88	1.01 (0.69-1.48)	0.96	0.98		

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Supplementary table 4.2 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
D								
0	1			1			144.2 (130.2-158.3)	Reference
1	0.91 (0.41-2.01)			1.15 (0.81-1.64)			142.7 (123.4-161.9)	-1.6 (-25.6 to 22.4)
2	0.85 (0.05-14.09)			0.85 (0.30-2.37)			139.1 (100.3=177.9)	-5.2 (-46.7 to 36.4)
Additive	0.91 (0.45-1.86)	0.80	0.95	1.08 (0.80-1.46)	0.63	0.98		
E								
0	1			1			146.1 (134.3-157.9)	Reference
1	2.37 (0.70-8.04)			1.02 (0.58-1.80)			109.9 (84.6=135.3)	-36.1 (-64.3 to -8.0)
2	-			0.93 (0.06-15.04)			236.5	90.4 (78.6 to 102.3)
Additive	2.37 (0.70-8.04)	0.17	0.88	1.02 (0.60-1.72)	0.96	0.98		

Supplementary table 4.3 Results from carriers of haplotypes in the *COMT* gene among non-users

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513) OR (95%CI)	p	FDR q
COMT block 1						
A						
0	1			1		
1	0.95 (0.30-2.99)			1.12 (0.58-2.16)		
2	-			-		
Additive	0.95 (0.30-2.99)	0.93	0.98	0.92 (0.53-1.59)	0.76	0.94
B						
0	1			1		
1	2.25 (0.72-7.07)			1.31 (0.65-2.61)		
2	-			-		
Additive	2.83 (1.06-7.51)	0.04	0.98	1.13 (0.61-2.09)	0.70	0.94
C						
0	1			1		
1	0.98 (0.33-2.93)			0.51 (0.25-1.06)		
2	-			0.37 (0.05-2.85)		
Additive	0.70 (0.31-1.61)	0.40	0.98	0.54 (0.29-1.02)	0.06	0.86
D						
0	1			1		
1	0.34 (0.04-2.89)			1.82 (0.64-5.21)		
2	-			-		
Additive	0.34 (0.04-2.89)	0.33	0.98	1.59 (0.60-4.20)	0.35	0.91
E						
0	1			1		
1	1.57 (0.41-6.05)			0.78 (0.26-2.29)		
2	-			-		
Additive	1.57 (0.41-6.05)	0.51	0.98	0.68 (0.26-1.76)	0.43	0.92
F						
0	1			1		
1	0.68 (0.22-2.05)			1.77 (0.85-3.66)		
2	0.63 (0.14-2.75)			1.44 (0.59-3.54)		
Additive	0.76 (0.36-1.61)	0.48	0.98	1.22 (0.83-1.78)	0.31	0.91
SNP rs4680						
GG	1			1		
GA	2.06 (0.52-8.20)			0.66 (0.33-1.31)		
AA	4.04 (0.91-18.02)			1.09 (0.51-2.31)		
Additive	1.24 (0.80-1.93)	0.33	0.98	1.02 (0.68-1.53)	0.93	0.99

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Supplementary table 4.3 – continued from previous page

Haplotype		LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513)) OR (95%CI)	p	FDR q
COMT block 2							
A							
	0	1			1		
	1	0.35 (0.08-1.49)			0.47 (0.19-1.13)		
	2	0.44 (0.10-1.88)			0.63 (0.28-1.44)		
	Additive	0.77 (0.34-1.71)	0.52	0.98	0.90 (0.57-1.42)	0.65	0.94
B							
	0	1			1		
	1	-			1.51 (0.50-4.55)		
	2	-			-		
	Additive	-	-	-	1.51 (0.50-4.55)	0.46	0.94
C							
	0	1			1		
	1	1.42 (0.44-4.55)			1.05 (0.44-2.51)		
	2	-			1.25 (0.15-10.39)		
	Additive	1.42 (0.44-4.55)	0.55	0.98	1.07 (0.53-2.17)	0.84	0.95
D							
	0	1			1		
	1	1.20 (0.40-3.56)			0.90 (0.46-1.75)		
	2	-			1.12 (0.25-5.12)		
	Additive	1.64 (0.60-4.44)	0.34	0.98	0.96 (0.55-1.67)	0.88	0.97
E							
	0	1			1		
	1	0.36 (0.17-0.46)			1.26 (0.42-3.76)		
	2	-			-		
	Additive	0.36 (0.04-3.05)	0.35	0.98	1.26 (0.42-3.76)	0.68	0.94

Supplementary table 4.4 Results from carriers of haplotypes in the *CYP* genes among OC users

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
CYP1A2								
A								
0	1			1			138.1 (110.1-166.2)	Reference
1	0.94 (0.30-2.94)			1.00 (0.62-1.63)			140.6 (125.2-156.0)	2.5 (-29.8 to 34.7)
2	1.20 (0.37-3.85)			1.15 (0.70-1.89)			150.5 (132.2-168.8)	12.3 (-21.5 to 46.1)
Additive	1.15 (0.67-1.97)	0.62	0.88	1.09 (0.86-1.38)	0.47	0.98		
B								
0	1			1			144.4 (133.0-155.9)	Reference
1	0.98 (0.35-2.76)			1.43 (0.89-2.30)			144.2 (106.0-182.3)	-0.3 (-40.3 to 39.8)
2	-			2.53 (0.49-13.19)			106.3 (98.3-114.3)	-38.1 (-52.2 to -24.1)
Additive	1.40 (0.62-3.19)	0.42	0.88	1.47 (0.97-2.22)	0.07	0.98		
C								
0	1			1			144.4 (133.3-155.6)	Reference
1	1.94 (0.38-9.84)			1.35 (0.63-2.88)			133.2 (81.3-185.1)	-11.2 (-64.4 to 42.0)
2	-			-			-	-
Additive	1.94 (0.38-9.84)	0.43	0.88	1.13 (0.55-2.32)	0.73	0.98		
D								
0	1			1			144.3 (130.1-158.6)	Reference
1	0.45 (0.19-1.06)			0.79 (0.56-1.11)			144.7 (127.4-162.1)	0.4 (-22.1 to 23.0)
2	1.01 (0.21-4.83)			0.43 (0.17-1.09)			132.0 (66.1-197.9)	-12.3 (-80.1 to 55.5)
Additive	0.70 (0.37-1.32)	0.27	0.88	0.74 (0.55-0.99)	0.04	0.98		
E								
0	1			1			144.9 (133.2-156.5)	Reference
1	0.69 (0.15-3.23)			0.95 (0.54-1.65)			135.4 (107.2-163.7)	-9.4 (-40.1 to 21.2)
2	-			-			-	-
Additive	0.69 (0.15-3.23)	0.63	0.89	0.95 (0.54-1.65)	0.85	0.98		

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Supplementary table 4.4 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
CYP2C9								
A								
0	1			1			144.2 (129.5-159.0)	Reference
1	1.12 (0.51-2.45)			1.00 (0.72-1.40)			138.7 (123.7-153.8)	-5.5 (-26.8 to 15.8)
2	3.00 (0.57-15.83)			0.58 (0.24-1.44)			170.3 (110.0-230.5)	26.0 (-36.4 to 88.4)
Additive	1.39 (0.78-2.47)	0.26	0.88	0.92 (0.69-1.21)	0.53	0.98		
B								
0	1			1			146.4 (133.6-159.3)	Reference
1	2.26 (0.89-5.77)			0.92 (0.65-1.30)			142.1 (120.7-163.4)	-4.4 (-29.4 to 20.8)
2	1.07 (0.25-4.54)			0.65 (0.24-1.74)			84.4 (70.6-98.1)	-62.1 (-81.0 to -43.2)
Additive	1.39 (0.73-2.64)	0.31	0.88	0.88 (0.66-1.19)	0.41	0.98		
C								
0	1			1			141.6 (130.5 to 152.7)	Reference
1	0.24 (0.05-1.20)			1.01 (0.55-1.85)			166.3 (122.6 to 210.0)	24.7 (-20.5 to 70.0)
2	-			-			-	-
Additive	0.24 (0.05-1.20)	0.08	0.88	1.01 (0.55-1.85)	0.98	0.99		
D								
0	1			1			157.9 (139.0-176.9)	Reference
1	0.58 (0.27-1.24)			0.90 (0.64-1.26)			130.8 (116.8-144.9)	-27.1 (-50.8 to -3.4)
2	0.66 (0.22-1.96)			1.10 (0.68-1.76)			150.0 (120.5-179.4)	-8.0 (-43.2 to 27.2)
Additive	0.75 (0.44-1.25)	0.27	0.88	1.01 (0.81-1.27)	0.92	0.98		
E								
0	1			1			146.5 (133.6-159.4)	Reference
1	0.89 (0.37-2.11)			1.27 (0.87-1.85)			130.0 (112.0-148.1)	-16.5 (-38.8 to 5.9)
2	0.89 (0.05-14.74)			2.40 (0.61-9.40)			234.2 (105.9-362.4)	87.7 (-42.0 to 217.3)
Additive	0.90 (0.42-1.92)	0.79	0.95	1.33 (0.95-1.85)	0.09	0.98		

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Supplementary table 4.4 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
F								
0	1			1			138.0 (127.0-149.0)	Reference
1	0.82 (0.33-2.02)			0.88 (0.56-1.39)			174.6 (143.4-205.7)	36.6 (3.4 to 69.8)
2	-			1.90 (0.17-21.13)			390.9	252.9 (241.9 to 264.0)
Additive	0.98 (0.43-2.27)	0.97	0.98	0.94 (0.91-1.44)	0.76	0.98		
CYP3A5								
A								
0	1			1			138.8 (104.6-173.0)	Reference
1	2.25 (0.66-7.64)			0.66 (0.39-1.13)			138.3 (122.5-154.0)	-0.5 (-38.3 to 37.3)
2	3.37 (0.98-11.59)			0.67 (0.39-1.14)			151.0 (134.7-167.3)	12.2 (-26.0 to 50.3)
Additive	1.72 (1.00-2.95)	0.05	0.88	0.88 (0.70-1.11)	0.28	0.98		
B								
0	1			1			144.7 (133.4-156.1)	Reference
1	1.19 (0.30-4.71)			1.48 (0.86-2.55)			135.3 (101.3-169.4)	-9.4 (-45.4 to 26.6)
2	-			-			-	-
Additive	1.19 (0.30-4.71)	0.80	0.95	1.48 (0.86-2.55)	0.15	0.98		
C								
0	1			1			143.5 (132.5-154.5)	Reference
1	0.62 (0.10-3.86)			1.73 (0.75-3.97)			154.8 (92.6-217.1)	11.3 (-52.3 to 74.9)
2	-			-			180.8	37.3 (26.2 to 48.4)
Additive	0.62 (0.10-3.86)	0.61	0.88	1.37 (0.62-3.03)	0.43	0.98		
D								
0	1			1			144.8 (133.3-156.3)	Reference
1	0.33 (0.12-0.93)			0.99 (0.65-1.51)			139.5 (109.2-169.8)	-5.3 (-37.8 to 27.1)
2	-			1.91 (0.17-21.23)			-	-
Additive	0.31 (0.12-0.82)	0.18	0.88	1.03 (0.69-1.54)	0.90	0.98		

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Supplementary table 4.4 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
E								
0	1			1			144.0 (133.2-154.8)	Reference
1	-			6.92 (0.51-93.52)			-	-
2	-			-			-	-
Additive	-	-	-	6.92 (0.51-93.52)	0.15	0.98		
F								
0	1			1			142.5 (131.7-153.2)	Reference
1	0.93 (0.13-6.91)			1.30 (0.54-3.14)			190.5 (107.6-273.4)	48.0 (-35.8 to 131.8)
2	-			-			-	-
Additive	0.93 (0.13-6.91)	0.95	0.98	1.30 (0.54-3.14)	0.56	0.98		
G								
0	1			1			147.7 (134.5-160.9)	Reference
1	0.70 (0.30-1.62)			0.92 (0.63-1.33)			131.0 (113.6-148.4)	-16.7 (-38.7 to 5.3)
2	0.42 (0.04-4.84)			0.78 (0.23-2.58)			162.9 (86.5-239.2)	15.2 (-62.8 to 93.1)
Additive	0.68 (0.33-1.39)	0.29	0.88	0.91 (0.66-1.26)	0.56	0.98		

Supplementary table 4.5 Results from carriers of haplotypes in the *CYP* genes among non-users

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513) OR (95%CI)	p	FDR q
CYP1A2						
A						
0	1			1		
1	0.38 (0.05-2.81)			1.05 (0.46-2.40)		
2	0.77 (0.13-4.45)			0.90 (0.38-2.16)		
Additive	1.14 (0.44-2.97)	0.79	0.98	0.93 (0.62-1.41)	0.74	0.94
B						
0	1			1		
1	2.63 (0.57-12.08)			0.62 (0.25-1.57)		
2	-			-		
Additive	2.63 (0.57-12.08)	0.22	0.98	0.57 (0.24-1.33)	0.19	0.89
C						
0	1			1		
1	-			0.99 (0.26-3.80)		
2	-			-		
Additive	-	-		0.99 (0.26-3.80)	0.98	0.99
D						
0	1			1		
1	0.95 (0.23-3.85)			1.14 (0.61-2.14)		
2	-			0.51 (0.07-3.95)		
Additive	0.76 (0.24-2.41)	0.64	0.98	0.98 (0.59-1.62)	0.94	0.99
E						
0	1			1		
1	0.63 (0.07-5.64)			1.56 (0.65-3.79)		
2	-			4.50 (0.40-50.82)		
Additive	0.63 (0.07-5.64)	0.68	0.98	1.73 (0.82-3.65)	0.15	0.89
CYP2C9						
A						
0	1			1		
1	0.68 (0.22-2.14)			1.37 (0.74-2.52)		
2	1.42 (0.24-8.23)			2.79 (0.96-8.12)		
Additive	0.96 (0.41-2.22)	0.92	0.98	1.53 (0.95-2.46)	0.08	0.86
B						
0	1			1		
1	0.64 (0.19-2.16)			0.63 (0.30-1.29)		
2	-			0.60 (0.08-4.69)		
Additive	0.57 (0.19-1.66)	0.30	0.98	0.66 (0.35-1.26)	0.21	0.89
C						
0	1			1		
1	0.53 (0.06-4.60)			0.71 (0.21-2.40)		
2	-			-		
Additive	0.53 (0.06-4.60)	0.56	0.98	0.71 (0.21-2.40)	0.58	0.94

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Supplementary table 4.5 – continued from previous page

Haplotype		LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513)) OR (95%CI)	p	FDR q
D							
	0	1			1		
	1	1.16 (0.38-3.55)			0.54 (0.29-1.02)		
	2	1.30 (0.27-6.28)			0.72 (0.30-1.74)		
	Additive	1.14 (0.54-2.43)	0.73	0.98	0.74 (0.46-1.19)	0.21	0.89
E							
	0	1			1		
	1	0.84 (0.21-3.32)			1.77 (0.90-3.50)		
	2	-			-		
	Additive	1.43 (0.45-4.50)	0.55	0.98	1.33 (0.76-2.31)	0.32	0.91
F							
	0	1			1		
	1	1.18 (0.29-4.81)			1.32 (0.59-2.96)		
	2	-			-		
	Additive	1.18 (0.29-4.81)	0.82	0.98	1.21 (0.57-2.55)	0.62	0.94
CYP3A5							
A							
	0	1			1		
	1	0.92 (0.22-3.88)			1.14 (0.41-3.14)		
	2	0.57 (0.12-2.78)			1.28 (0.46-3.54)		
	Additive	0.68 (0.32-1.44)	0.32	0.98	1.13 (0.72-1.77)	0.60	0.94
B							
	0	1			1		
	1	1.03 (0.11-9.88)			0.82 (0.24-2.81)		
	2	-			-		
	Additive	1.03 (0.11-9.88)	0.98	0.99	0.69 (0.24-1.99)	0.50	0.94
C							
	0	1			1		
	1	0.02 (0.00-0.21)			2.01 (0.65-6.22)		
	2	-			-		
	Additive	0.02 (0.00-0.21)	0.00	0.08	1.71 (0.61-4.79)	0.31	0.91
D							
	0	1			1		
	1	1.09 (0.27-4.38)			1.03 (0.46-2.30)		
	2	-			-		
	Additive	0.92 (0.27-3.13)	0.90	0.98	0.95 (0.45-1.98)	0.88	0.97
E							
	0	1			1		
	1	0.95 (0.09-9.77)			-		
	2	-			-		
	Additive	0.95 (0.09-9.77)	0.96	0.99	-	-	-

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Supplementary table 4.5 – continued from previous page

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513)) OR (95%CI)	p	FDR q
F						
0	1			1		
1	-			0.78 (0.10-6.12)		
2	-			-		
Additive	-	-	-	0.69 (0.11-4.39)	0.69	94
G						
0	1			1		
1	0.94 (0.30-2.93)			1.04 (0.53-2.03)		
2	2.08 (0.17-24.94)			0.88 (0.11-7.07)		
Additive	1.14 (0.44-2.91)	0.79	0.98	1.01 (0.57-1.79)	0.98	0.99

Supplementary table 4.6 Results from carriers of haplotypes in the *SULT* genes among OC users

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
SULT1A1								
A								
0	1			1			145.4 (128.5-162.3)	Reference
1	0.75 (0.36-1.59)			0.93 (0.67-1.30)			145.2 (128.2-162.1)	-0.2 (-24.3 to 23.9)
2	0.91 (0.31-2.70)			1.40 (0.86-2.27)			129.3 (112.3-146.4)	-16.1 (-40.2 to 8.1)
Additive	0.90 (0.54-1.49)	0.68	0.91	1.11 (0.89-1.39)	0.35	0.98		
B								
0	1			1			137.9 (123.2-152.5)	Reference
1	0.82 (0.39-1.73)			1.07 (0.76-1.49)			149.9 (133.2-166.7)	12.1 (-10.3 to 34.4)
2	1.40 (0.48-4.08)			1.25 (0.77-2.01)			137.3 (102.3-172.3)	-0.6 (-38.8 to 37.6)
Additive	1.08 (0.67-1.74)	0.76	0.95	1.10 (0.88-1.38)	0.39	0.98		
C								
0	1			1			145.4 (134.0-156.7)	Reference
1	0.99 (0.28-3.43)			0.78 (0.45-1.38)			121.9 (93.9-150.0)	-23.4 (-53.8 to 7.0)
2	-			-			-	-
Additive	0.99 (0.28-3.43)	0.98	0.98	0.86 (0.50-1.48)	0.58	0.98		
D								
0	1			1			141.0 (129.5-152.4)	Reference
1	1.53 (0.66-3.58)			0.85 (0.58-1.27)			153.8 (126.9-180.8)	12.9 (-16.5 to 42.3)
2	-			3.77 (0.42-34.05)			59.4	-81.6 (-93.1 to -70.1)
Additive	1.67 (0.76-3.67)	0.20	0.88	0.96 (0.66-1.38)	0.82	0.98		
E								
0	1			1			142.5 (129.5-155.4)	Reference
1	0.47 (0.19-1.20)			0.71 (0.49-1.04)			147.4 (128.8-165.9)	4.9 (-17.9 to 27.7)
2	0.74 (0.04-12.24)			-			86.9 (55.6 to 118.1)	-55.6 (-89.6 to -21.6)
Additive	0.56 (0.24-1.29)	0.17	0.88	0.67 (0.46-0.95)	0.03	0.98		

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Supplementary table 4.6 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
SULT1E1 promoter region								
A								
0	1			1			148.8 (132.7-164.9)	Reference
1	0.81 (0.40-1.61)			1.09 (0.80-1.50)			137.4 (123.4-151.3)	-11.4 (-32.8 to 10.0)
2	0.98 (0.20-4.71)			1.57 (0.80-3.06)			140.3 (98.7-181.9)	-8.5 (-53.4 to 36.4)
Additive	0.88 (0.50-1.55)	0.66	0.91	1.17 (0.91-1.50)	0.23	0.98		
B								
0	1			1			141.7 (126.9-156.5)	Reference
1	1.25 (0.62-2.53)			0.94 (0.69-1.30)			139.8 (124.3-155.3)	-1.9 (-23.5 to 19.6)
2	0.30 (0.07-1.25)			0.60 (0.35-1.04)			161.9 (124.3-199.5)	20.2 (-20.4 to 60.8)
Additive	0.80 (0.47-1.37)	0.42	0.88	0.84 (0.66-1.06)	0.13	0.98		
C								
0	1			1			145.3 (128.9-161.7)	Reference
1	1.66 (0.79-3.47)			1.33 (0.96-1.84)			140.2 (124.8-155.7)	-5.1 (-27.7 to 17.6)
2	1.14 (0.41-3.15)			0.80 (0.49-1.32)			147.1 (118.3-175.9)	1.8 (-31.5 to 35.2)
Additive	1.18 (0.72-1.94)	0.51	0.88	1.00 (0.80-1.26)	0.99	0.99		
D								
0	1			1			143.0 (132.1-153.9)	Reference
1	1.45 (0.40-5.22)			0.75 (0.40-1.42)			153.6 (117.6-189.6)	10.6 (-27.1 to 48.3)
2	-			-			-	-
Additive	1.45 (0.40-5.22)	0.57	0.88	0.75 (0.40-1.42)	0.38	0.98		
SNP rs3736599								
GG	1			1			141.8 (130.1-153.4)	Reference
GA	1.02 (0.47-2.21)			1.08 (0.72-1.62)			148.3 (123.0-173.5)	6.5 (-21.5 to 34.5)
AA	1.64 (0.14-18.80)			0.99 (0.28-3.46)			248.3	106.5 (-35.9 to 248.9)
Additive	1.07 (0.55-2.08)	0.84	0.97	1.01 (0.88-1.16)	0.91	0.98		

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Supplementary table 4.6 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
SULT1E1 gene region								
A								
0	1			1			148.5 (133.3-163.7)	Reference
1	0.96 (0.47-1.95)			1.02 (0.74-1.41)			141.5 (124.1-158.9)	-7.0 (-30.3 to 16.2)
2	1.12 (0.32-3.88)			0.70 (0.41-1.20)			128.6 (104.1-153.1)	-19.9 (-48.9 to 9.1)
Additive	1.02 (0.61-1.71)	0.95	0.98	0.90 (0.72-1.14)	0.39	0.98		
B								
0	1			1			151.0 (136.3-165.8)	Reference
1	1.05 (0.51-2.15)			1.24 (0.90-1.71)			131.0 (116.4-145.7)	-20.0 (-40.9 to 0.9)
2	5.09 (1.05-24.63)			1.07 (0.57-2.01)			154.0 (99.9-208.1)	3.0 (-53.4 to 59.4)
Additive	1.56 (0.95-2.57)	0.08	0.88	1.13 (0.88-1.45)	0.33	0.98		
C								
0	1			1			141.1 (129.2-153.0)	Reference
1	1.06 (0.49-2.29)			1.07 (0.75-1.53)			148.3 (126.1-170.6)	7.2 (-18.3 to 32.7)
2	0.81 (0.19-3.44)			0.62 (0.20-1.91)			248.3	107.2 (95.2 to 119.2)
Additive	0.97 (0.55-1.71)	0.92	0.97	0.98 (0.72-1.34)	0.91	0.98		
D								
0	1			1			137.7 (125.7-149.8)	Reference
1	0.53 (0.24-1.18)			0.87 (0.61-1.25)			152.6 (131.1-174.2)	14.9 (-10.0 to 39.8)
2	0.34 (0.03-3.89)			0.67 (0.21-2.15)			200.1 (163.4-236.8)	62.4 (23.5 to 101.2)
Additive	0.54 (0.27-1.09)	0.09	0.88	0.86 (0.63-1.17)	0.34	0.98		
E								
0	1			1			143.7 (132.5-155.0)	Reference
1	1.08 (0.35-3.32)			1.11 (0.66-1.84)			145.8 (112.6-178.9)	2.1 (-33.1 to 37.3)
2	-			-			103.9 (71.3 to 136.5)	-39.8 (-74.5 to -5.2)
Additive	1.08 (0.35-3.32)	0.89	0.98	0.92 (0.58-1.47)	0.74	0.98		

Supplementary table 4.7 Results from carriers of haplotypes in the *SULT* genes among non-users

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513) OR (95%CI)	p	FDR q
SULT1A1						
A						
0	1			1		
1	2.30 (0.79-6.66)			0.92 (0.48-1.76)		
2	-			1.26 (0.52-3.05)		
Additive	1.05 (0.57-1.92)	0.89	0.98	1.08 (0.68-1.69)	0.75	0.94
B						
0	1			1		
1	1.83 (0.53-6.27)			0.80 (0.43-1.48)		
2	2.27 (0.48-10.71)			0.48 (0.16-1.44)		
Additive	1.52 (0.74-3.14)	0.26	0.98	0.73 (0.47-1.14)	0.16	0.89
C						
0	1			1		
1	0.50 (0.06-4.29)			2.53 (1.14-5.63)		
2	-			-		
Additive	0.50 (0.06-4.29)	0.53	0.98	2.08 (1.00-4.33)	0.05	0.86
D						
0	1			1		
1	0.57 (0.15-2.18)			0.83 (0.36-1.92)		
2	-			-		
Additive	0.57 (0.15-2.18)	0.42	0.98	0.73 (0.35-1.54)	0.41	0.91
E						
0	1			1		
1	1.04 (0.20-5.37)			1.46 (0.73-2.92)		
2	-			3.31 (0.34-32.78)		
Additive	0.85 (0.21-3.41)	0.82	0.98	1.53 (0.82-2.88)	0.18	0.89
SULT1E1 promoter region						
A						
0	1			1		
1	0.94 (0.35-2.53)			0.82 (0.45-1.50)		
2	-			1.09 (0.40-3.02)		
Additive	0.64 (0.31-1.33)	0.23	0.98	0.95 (0.59-1.52)	0.82	0.95
B						
0	1			1		
1	0.84 (0.29-2.41)			1.75 (0.94-3.27)		
2	0.85 (0.16-4.54)			1.46 (0.55-3.86)		
Additive	0.89 (0.42-1.88)	0.76	0.98	1.34 (0.90-1.97)	0.15	0.89
C						
0	1			1		
1	0.98 (0.32-2.98)			0.93 (0.52-1.68)		
2	2.71 (0.71-10.33)			0.55 (0.16-1.91)		
Additive	1.52 (0.74-3.13)	0.26	0.98	0.83 (0.54-1.29)	0.41	0.91

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Supplementary table 4.7 – continued from previous page

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513)) OR (95%CI)	p	FDR q
D						
0	1			1		
1	0.91 (0.18-4.64)			-		
2	-			-		
Additive	0.91 (0.18-4.64)	0.91	0.98	-	-	-
SNP rs3736599						
GG	1			1		
GA	0.92 (0.23-3.63)			1.47(0.75-2.89)		
AA	-			1.06 (0.13-8.58)		
Additive	0.70 (0.30-1.66)	0.42	0.98	0.96 (0.68-1.34)	0.80	0.94
SULT1E1 gene region						
A						
0	1			1		
1	0.67 (0.24-1.86)			1.17 (0.64-2.15)		
2	-			1.00 (0.36-2.77)		
Additive	0.51 (0.23-1.15)	0.11	0.98	1.06 (0.69-1.61)	0.80	0.94
B						
0	1			1		
1	2.32 (0.73-7.38)			1.02 (0.55-1.90)		
2	3.38 (0.75-15.28)			1.92 (0.73-5.05)		
Additive	1.89 (0.94-3.81)	0.07	0.98	1.24 (0.78-1.97)	0.37	0.91
C						
0	1			1		
1	0.94 (0.32-2.75)			0.89 (0.46-1.73)		
2	-			0.49 (0.06-377)		
Additive	0.76 (0.31-1.87)	0.56	0.98	0.82 (0.48-1.42)	0.49	0.94
D						
0	1			1		
1	0.25 (0.03-2.03)			0.82 (0.37-1.80)		
2	3.72 (0.22-63.33)			-		
Additive	0.73 (0.16-3.27)	0.69	0.98	0.71 (0.35-1.41)	0.33	0.91
E						
0	1			1		
1	1.29 (0.32-5.23)			0.73 (0.25-2.12)		
2	-			4.30 (0.38-48.42)		
Additive	1.29 (0.32-5.23)	0.72	0.98	1.03 (0.40-2.60)	0.96	0.99

Supplementary table 4.8 Results from carriers of haplotypes in the *UGT* genes among OC users

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
UGT1A Block 1								
A								
0	1			1			148.0 (132.5-163.5)	Reference
1	0.86 (0.40-1.86)			1.07 (0.77-1.48)			142.8 (124.8-160.7)	-5.2 (-29.1 to 18.6)
2	1.83 (0.54-6.19)			0.61 (0.34-1.07)			127.3 (101.4-153.2)	-20.7 (-51.1 to 9.7)
Additive	1.18 (0.69-2.02)	0.54	0.88	0.88 (0.70-1.12)	0.31	0.98		
B								
0	1			1			144.1 (133.0-155.3)	Reference
1	1.14 (0.24-5.37)			1.18 (0.59-2.38)			128.4 (93.7-163.0)	-15.8 (-52.3 to 20.7)
2	-			0.95 (0.13-6.80)			-	-
Additive	1.57 (0.47-5.29)	0.46	0.88	1.11 (0.62-1.98)	0.72	0.98		
C								
0	1			1			144.1 (132.9-155.2)	Reference
1	1.72 (0.30-9.81)			0.86 (0.37-1.97)			142.8 (97.4-188.1)	-1.3 (-48.3 to 45.7)
2	-			-			58.1	-85.9 (-97.2 to -74.7)
Additive	1.72 (0.30-9.81)	0.54	0.88	0.75 (0.35-1.60)	0.46	0.98		
D								
0	1			1			139.2 (128.2-150.2)	Reference
1	0.82 (0.25-2.72)			0.91 (0.55-1.49)			172.8 (132.5-213.2)	33.6 (-8.4 o 75.7)
2	-			0.93 (0.13-6.67)			225.6	86.4 (75.4 to 97.4)
Additive	0.82 (0.25-2.72)	0.75	0.95	0.92 (0.58-1.44)	0.71	0.98		
E								
0	1			1			147.4 (129.1-165.6)	Reference
1	0.69 (0.33-1.44)			1.27 (0.91-1.78)			135.8 (121.8-149.8)	-11.6 (-34.7 to 11.6)
2	0.69 (0.18-2.64)			1.21 (0.75-1.96)			157.9 (125.2-190.6)	10.5 (-27.2 to 48.2)
Additive	0.76 (0.43-1.34)	0.35	0.88	1.14 (0.91-1.43)	0.26	0.98		

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Supplementary table 4.8 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
F								
0	1			1			140.6 (127.3-153.9)	Reference
1	0.82 (0.38-1.76)			0.99 (0.71-1.39)			151.6 (131.9-171.3)	11.0 (-12.9 to 34.9)
2	-			1.12 (0.49-2.55)			112.8 (73.0-152.6)	-27.8 (-70.1 to 14.4)
Additive	1.12 (0.58-2.15)	0.74	0.95	1.02 (0.77-1.34)	0.91	0.98		
UGT1A Block 2								
A								
0	1			1			153.4 (130.2-176.7)	Reference
1	0.56 (0.24-1.31)			1.07 (0.72-1.59)			134.3 (118.1-150.6)	-19.1 (-47.6 to 9.5)
2	0.94 (0.32-2.72)			1.16 (0.75-1.78)			145.1 (128.0-162.3)	-8.3 (-37.4 to 20.8)
Additive	0.94 (0.56-1.56)	0.80	0.95	1.08 (0.87-1.33)	0.50	0.98		
B								
0	1			1			138.0 (127.3-148.7)	Reference
1	0.73 (0.22-2.43)			0.83 (0.50-1.38)			172.8 (132.5-213.2)	34.8 (-7.1 to 76.8)
2	-			0.91 (0.13-6.50)			225.6	87.6 (76.9 to 98.4)
Additive	0.73 (0.22-2.43)	0.61	0.88	0.85 (0.54-1.35)	0.49	0.98		
C								
0	1			1			142.2 (127.8-156.7)	Reference
1	0.98 (0.46-2.07)			1.13 (0.81-1.57)			143.6 (124.4-162.8)	1.4 (-22.8 to 25.6)
2	1.57 (0.50-4.91)			0.75 (0.43-1.30)			140.6 (114.1-167.1)	-1.7 (-32.0 to 28.7)
Additive	1.17 (0.70-1.94)	0.55	0.88	0.95 (0.75-1.21)	0.70	0.98		
D								
0	1			1			144.3 (133.1-155.4)	Reference
1	0.66 (0.19-2.28)			1.10 (0.56-2.19)			116.3 (85.2-147.4)	-28.0 (-61.1 to 5.2)
2	-			0.46 (0.04-5.16)			-	-
Additive	0.66 (0.19-2.28)	0.51	0.88	0.98 (0.54-1.76)	0.93	0.98		

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Supplementary table 4.8 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
E								
0	1			1			142.5 (131.5-153.6)	Reference
1	1.74 (0.56-5.43)			0.94 (0.61-1.46)			144.7 (109.8-179.5)	2.1 (-34.6 to 38.9)
2	-			1.84 (0.17-20.48)			81.5	-61.1 (-72.2 to -49.9)
Additive	1.74 (0.56-5.43)	0.34	0.88	0.98 (0.65-1.48)	0.93	0.98		
UGT1A Block 3								
A								
0	1			1			153.9 (128.5-179.3)	Reference
1	0.46 (0.19-1.12)			1.09 (0.72-1.64)			137.3 (121.4-153.1)	-16.7 (-46.8 to 13.4)
2	0.73 (0.25-2.08)			1.18 (0.76-1.82)			145.4 (128.0-162.8)	-8.5 (-39.5 to 22.4)
Additive	0.87 (0.53-1.44)	0.59	0.88	1.08 (0.88-1.34)	0.46	0.98		
B								
0	1			1			144.5 (133.4-155.5)	Reference
1	3.64 (0.39-33.73)			1.04 (0.61-1.79)			134.5 (93.5-175.4)	-10.0 (-52.5 to 32.5)
2	-			-		0.98	-	-
Additive	3.64 (0.39-33.73)	0.26	0.88	1.04 (0.61-1.79)	0.88			
C								
0	1			1			140.1 (124.4-155.8)	Reference
1	0.62 (0.27-1.43)			1.01 (0.72-1.42)			144.6 (126.5-162.6)	4.5 (-19.5 to 28.5)
2	1.19 (0.42-3.37)			0.79 (0.50-1.25)			148.9 (124.9-173.0)	8.9 (-20.0 to 37.8)
Additive	1.05 (0.64-1.73)	0.85	0.97	0.91 (0.73-1.14)	0.41	0.98		

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Supplementary table 4.8 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
UGT1A Block 4								
A								
0	1			1			137.9 (124.5-151.4)	Reference
1	0.68 (0.33-1.37)			1.30 (0.94-1.80)			153.1 (133.4-172.8)	15.2 (-8.7 to 39.1)
2	0.96 (0.15-6.18)			1.08 (0.61-1.93)			141.0 (109.0-173.1)	3.1 (-31.9 to 38.2)
Additive	0.77 (0.42-1.41)	0.40	0.88	1.14 (0.90-1.46)	0.28	0.98		
B								
0	1			1			144.0 (129.7-158.3)	Reference
1	1.00 (0.47-2.11)			1.06 (0.77-1.47)			147.9 (128.0-167.7)	3.9 (-20.7 to 28.5)
2	1.10 (0.35-3.39)			0.75 (0.42-1.33)			128.3 (105.5-151.1)	-15.7 (-42.8 to 11.4)
Additive	1.03 (0.61-1.74)	0.91	0.98	0.94 (0.74-1.19)	0.62	0.98		
C								
0	1			1			145.6 (134.4-156.8)	Reference
1	0.55 (0.12-2.59)			0.82 (0.43-1.57)			116.2 (87.7-144.7)	-29.4 (-60.2 to 1.3)
2	-			0.95 (0.06-15.37)			-	-
Additive	0.55 (0.12-2.59)	0.45	0.88	0.84 (0.46-1.53)	0.58	0.98		
D								
0	1			1			139.7 (129.0-150.5)	Reference
1	0.75 (0.21-2.73)			0.94 (0.57-1.55)			171.6 (129.2-213.9)	31.9 (-12.1 to 75.8)
2	-			0.48 (0.04-5.32)			225.6	85.9 (75.0 to 96.7)
Additive	0.75 (0.21-2.73)	0.67	0.91	0.90 (0.57-1.43)	0.65	0.98		
E								
0	1			1			144.1 (133.1-155.1)	Reference
1	4.00 (0.45-35.52)			1.08 (0.63-1.86)			139.1 (97.3-181.0)	-4.9 (-48.4 to 38.5)
2	-			-			-	-
Additive	4.00 (0.45-35.52)	0.21	0.88	1.08 (0.63-1.86)	0.78	0.98		

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Supplementary table 4.8 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
F								
0	1			1			151.9 (135.7-168.1)	Reference
1	1.26 (0.62-2.57)			0.98 (0.71-1.36)			134.6 (118.1-151.0)	-17.3 (-40.6 to 5.9)
2	1.12 (0.23-5.38)			0.88 (0.50-1.56)			142.8 (123.6-161.9)	-9.2 (-34.4 to 16.1)
Additive	1.17 (0.65-2.09)	0.61	0.88	0.96 (0.75-1.21)	0.71	0.98		
UGT1A Block 5								
A								
0	1			1			153.4 (130.2-176.7)	Reference
1	1.29 (0.62-2.71)			1.03 (0.73-1.46)			134.3 (118.1-150.6)	-19.1 (-47.6 to 9.5)
2	0.48 (0.04-5.57)			1.03 (0.48-2.19)			145.1 (128.0-162.3)	-8.3 (-37.4 to 20.8)
Additive	1.10 (0.57-2.12)	0.78	0.95	1.02 (0.78-1.34)	0.86	0.98		
B								
0	1			1			138.0 (127.3-148.7)	Reference
1	1.39 (0.65-2.97)			1.09 (0.78-1.51)			172.8 (132.5- 213.2)	34.8 (-7.1 to 76.8)
2	2.13 (0.68-6.74)			0.85 (0.50-1.47)			225.6	87.6 (76.9 to 98.4)
Additive	1.44 (0.85-2.44)	0.18	0.88	0.98 (0.77-1.24)	0.87	0.98		
C								
0	1			1			142.2 (127.8-156.7)	Reference
1	0.97 (0.39-2.41)			0.98 (0.67-1.44)			143.6 (124.4-162.8)	1.4 (-22.8 to 25.6)
2	-			1.27 (0.43-3.72)			140.6 (114.1-167.1)	-1.7 (-32.0 to 28.7)
Additive	0.97 (0.39-2.41)	0.95	0.98	1.03 (0.74-1.42)	0.87	0.98		
D								
0	1			1			144.3 (133.1-155.4)	Reference
1	0.71 (0.33-1.51)			0.98 (0.69-1.38)			116.3 (85.2-147.4)	-28.0 (-61.1 to 5.2)
2	1.63 (0.14-18.81)			0.78 (0.33-1.85)			-	-
Additive	0.83 (0.42-1.63)	0.59	0.88	0.94 (0.71-1.25)	0.67	0.98		

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Supplementary table 4.8 – continued from previous page

Haplotype	LETS (N=140) OR (95%CI)	p	FDR q	MEGA (N=678) OR (95%CI)	p	FDR q	SHBG levels (95%CI)	Mean difference (95%CI)
E								
0	1			1			142.5 (131.5-153.6)	Reference
1	0.39 (0.16-0.92)			1.05 (0.74-1.49)			144.7 (109.8-179.5)	2.1 (-34.6 to 38.9)
2	-			1.79 (0.65-4.94)			81.5	-61.1 (-72.2 to -49.9)
Additive	0.61 (0.27-1.37)	0.23	0.88	1.13 (0.84-1.52)	0.41	0.98		

Supplementary table 4.9 Results from carriers of haplotypes in the *UGT* genes among non-users

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513) OR (95%CI)	p	FDR q
UGT1A Block 1						
A						
0	1			1		
1	0.84 (0.26-2.68)			2.00 (1.08-3.70)		
2	1.58 (0.14-17.48)			0.89 (0.25-3.16)		
Additive	1.00 (0.36-2.74)	1.00	1.00	1.28 (0.87-1.89)	0.20	0.89
B						
0	1			1		
1	1.67 (0.16-17.44)			1.55 (0.51-4.68)		
2	-			-		
Additive	0.79 (0.18-3.51)	0.75	0.98	1.55 (0.51-4.68)	0.44	0.92
C						
0	1			1		
1	-			1.60 (0.53-4.85)		
2	-			-		
Additive	-	-	-	1.30 (0.50-3.39)	0.59	0.94
D						
0	1			1		
1	2.09 (0.48-9.11)			1.62 (0.64-4.07)		
2	-			-		
Additive	2.09 (0.48-9.11)	0.33	0.98	1.62 (0.64-4.07)	0.31	0.91
E						
0	1			1		
1	0.82 (0.24-2.80)			1.12 (0.59-2.13)		
2	1.31 (0.21-8.41)			1.20 (0.47-3.04)		
Additive	1.04 (0.39-2.75)	0.94	0.98	1.10 (0.71-1.70)	0.67	0.94
F						
0	1			1		
1	0.54 (0.15-1.90)			0.45 (0.22-0.93)		
2	2.10 (0.17-25.88)			0.40 (0.05-3.10)		
Additive	0.80 (0.25-2.55)	0.71	0.98	0.49 (0.26-0.95)	0.04	0.86
UGT1A Block 2						
A						
0	1			1		
1	0.87 (0.20-3.71)			1.17 (0.53-2.61)		
2	1.20 (0.24-6.01)			0.73 (0.29-1.84)		
Additive	1.13 (0.48-2.68)	0.78	0.98	0.84 (0.56-1.26)	0.40	0.91
B						
0	1			1		
1	1.41 (0.34-5.86)			1.24 (0.42-3.70)		
2	-			-		
Additive	1.41 (0.34-5.86)	0.63	0.98	1.24 (0.42-3.70)	0.70	0.94

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Supplementary table 4.9 – continued from previous page

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513)) OR (95%CI)	p	FDR q
C						
0	1			1		
1	0.83 (0.27-2.60)			2.06 (1.08-3.93)		
2	2.22 (0.35-14.20)			1.08 (0.30-3.89)		
Additive	1.17 (0.48-2.89)	0.73	0.98	1.37 (0.91-2.05)	0.13	0.89
D						
0	1			1		
1	0.89 (0.10-8.22)			0.82 (0.19-3.63)		
2	-			-		
Additive	0.89 (0.10-8.22)	0.92	0.98	0.82 (0.19-3.63)	0.80	0.94
E						
0	1			1		
1	0.30 (0.04-2.48)			0.66 (0.25-1.75)		
2	-			-		
Additive	0.28 (0.04-2.14)	0.22	0.98	0.64 (0.25-1.61)	0.34	0.91
UGT1A Block 3						
A						
0	1			1		
1	0.89 (0.21-3.79)			1.31 (0.58-2.99)		
2	0.46 (0.09-2.46)			0.78 (0.31-1.97)		
Additive	0.66 (0.31-1.40)	0.28	0.98	0.84 (0.57-1.23)	0.37	0.91
B						
0	1			1		
1	1.64 (0.29-9.25)			0.19 (0.03-1.40)		
2	-			-		
Additive	1.64 (0.29-9.25)	0.57	0.98	0.19 (0.03-1.33)	0.09	0.86
C						
0	1			1		
1	1.24 (0.41-3.74)			2.16 (1.10-4.26)		
2	2.07 (0.41-10.48)			1.74 (0.66-4.56)		
Additive	1.39 (0.62-3.09)	0.43	0.98	1.43 (0.98-2.10)	0.06	0.86
UGT1A Block 4						
A						
0	1			1		
1	0.52 (0.17-1.55)			0.73 (0.39-1.34)		
2	0.23 (0.03-1.99)			0.32 (0.07-1.38)		
Additive	0.50 (0.22-1.13)	0.10	0.98	0.65 (0.40-1.04)	0.07	0.86
B						
0	1			1		
1	1.71 (0.59-4.91)			2.65 (1.39-5.04)		
2	1.96 (0.18-21.48)			1.25 (0.35-4.53)		
Additive	1.57 (0.67-3.64)	0.30	0.98	1.55 (1.06-2.27)	0.02	0.86

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Supplementary table 4.9 – continued from previous page

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513)) OR (95%CI)	p	FDR q
C						
0	1			1		
1	1.32 (0.25-7.02)			0.69 (0.16-3.02)		
2	-			-		
Additive	1.32 (0.25-7.02)	0.74	0.98	0.69 (0.16-3.02)	0.63	0.94
D						
0	1			1		
1	2.01 (0.55-7.36)			1.16 (0.39-3.43)		
2	-			-		
Additive	2.01 (0.55-7.36)	0.29	0.98	1.16 (0.39-3.43)	0.79	0.94
E						
0	1			1		
1	1.88 (0.33-10.63)			0.19 (0.03-1.40)		
2	-			-		
Additive	1.25 (0.31-5.00)	0.75	0.98	0.19 (0.03-1.36)	0.10	0.86
F						
0	1			1		
1	1.25 (0.44-3.54)			1.83 (0.99-3.39)		
2	-			0.92 (0.26-3.26)		
Additive	0.93 (0.41-2.09)	0.85	0.98	1.26 (0.85-1.87)	0.26	0.91
UGT1A Block 5						
A						
0	1			1		
1	0.41 (0.11-1.58)			0.93 (0.50-1.75)		
2	0.89 (0.09-8.74)			-		
Additive	0.62 (0.20-1.87)	0.39	0.98	0.74 (0.45-1.23)	0.25	0.91
B						
0	1			1		
1	0.89 (0.31-2.57)			1.67 (0.89-3.14)		
2	0.69 (0.07-6.50)			0.99 (0.32-3.08)		
Additive	0.86 (0.37-1.99)	0.72	0.98	1.20 (0.80-1.79)	0.38	0.91
C						
0	1			1		
1	1.15 (0.36-3.68)			1.01 (0.49-2.12)		
2	4.83 (0.28-84.00)			1.76 (0.20-15.53)		
Additive	1.45 (0.54-3.92)	0.46	0.98	1.09 (0.56-2.10)	0.80	0.94
D						
0	1			1		
1	2.71 (0.94-7.79)			1.11 (0.59-2.11)		
2	-			1.06 (0.23-4.82)		
Additive	1.68 (0.73-3.86)	0.22	0.98	1.08 (0.65-1.80)	0.78	0.94

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Supplementary table 4.9 – continued from previous page

Haplotype	LETS (N=104) OR (95%CI)	p	FDR q	MEGA (N=513)) OR (95%CI)	p	FDR q
E						
0	1			1		
1	0.74 (0.19-2.90)			0.98 (0.49-1.96)		
2	1.42 (0.14-14.90)			0.66 (0.08-5.21)		
Additive	0.96 (0.34-2.65)	0.93	0.98	0.92 (0.52-1.64)	0.79	0.94