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Aromatase (CYP19A1) gene variants, sex steroid levels, and late-life depression

Running title: Aromatase and late-life depression

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DATA AVAILABLE STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abstract

Background: Sex differences in psychiatric disorders are common and could involve sex steroids. Aromatase, the product of the *CYP19A1* gene, is the key enzyme in the conversion of androgen to estrogen. Whether *CYP19A1* variants could be associated with depression differently in men and women has not been examined.

Methods: This population-based study included 405 men and 602 women aged ≥65 years. A clinical level of depression (DEP) was defined as having a score >16 on the Centre for Epidemiology Studies Depression scale or a diagnosis of current major depression based on the Mini-International Neuropsychiatric Interview and according to DSM-IV criteria. Seven single-nucleotide polymorphisms (SNPs) spanning the *CYP19A1* gene were genotyped and circulating levels of estradiol and testosterone were determined. Multivariable analyses were adjusted for age, body mass index, ischemic pathologies, cognitive impairment, and anxiety.

Results: Five SNPs were associated with DEP in women specifically and this varied according to a history of major depression (p-values 0.01 to 0.0005). Three SNPs were associated with an increased risk of late life DEP in women without a history of major depression, while two SNPs were associated with a decreased DEP risk in women with a history of major depression and were also associated with higher estradiol levels.

Conclusions: Variants of the *CYP19A1* gene appear to be susceptibility factors for late-life depression in a sex-specific manner. The

polymorphisms decreasing the risk of recurrent depression in postmenopausal women also influence estradiol levels.

KEYWORDS: Aromatase; elderly; estradiol; late-life depression; population-based study; sex difference.

1 INTRODUCTION

Estrogens are formed from the conversion of androgens by CYP19A1 (cytochrome P450 family 19 subfamily a member 1), also known as aromatase. This enzyme is required for estrogen synthesis in males and females in steroidogenic gonadal and extra-gonadal tissues such as adipose tissue, bone, and brain (Shay et al., 2018) and is abundantly expressed in several brain areas (Azcoitia et al., 2011). Aromatase is essential throughout the lifespan in males and females, and peripheral aromatization of androgens in adipose tissue is the primary source of endogenous estrogen for postmenopausal women.

Aromatase has been associated with hormone levels, endometriosis, prostate cancer, bone metabolism, and obesity (Westberg & Eriksson, 2008). Several studies have also reported associations between genetic variants of *CYP19A1* and neuropsychiatric disorders (Janicki et al., 2013, Kravitz et al., 2006a, Kravitz et al., 2006b, Rosenfeld et al., 2018, Shay et al., 2018, Song et al., 2019). However, despite the clear role played by steroids in several psychiatric disorders, especially depression throughout the reproductive life including the postmenopausal period (Ancelin et al., 2007), the possible influence of polymorphisms in sex steroid-related genes has not been adequately examined.

Few studies have considered how variants in sex steroid genes may be differentially associated with depression in males and females. This is despite evidence for sexually dimorphic structural and functional brain differences across the lifespan, and the recognized sex differences which characterize several neuropsychiatric disorders (Ruigrok et al., 2014). This may be especially important for depression, because prevalence, age of onset, symptomatology and etiology differ between the sexes, and steroid hormones could influence brain development and onset of depression throughout life (Ancelin et al., 2007, Kockler & Heun, 2002). Age may be another determining factor, given reported symptomatology and etiologic differences in early and late-onset depression (Blazer, 2003, Kendler et al., 2009, Taylor et al., 2013) as well as age-associated neurobiological changes (Fiske et al., 2009).

Thus, while there is some evidence that the *CYP19A1* gene may constitute a susceptibility factor for late-life depression, this hypothesis has yet to be tested within a prospective study in the elderly general population. In this study, we were able to take into account sex differences, and multiple causes of depression, including vascular factors and a history of affective disorder. In conjunction with steroid level estimations, the present study could clarify the role of the *CYP19A1* gene in late-life depression.

The aims of this study were to determine: (i) the potential sex-specific associations between *CYP19A1* variants and depression in an older population; (ii) whether past depression was an effect modifier of this association, and thus whether the associations were specific for late-life depression; (iii) whether these same genetic variants were associated with estradiol and testosterone levels.

2 METHODS

2.1 Participants

The data were derived from the longitudinal ESPRIT study of neuropsychiatric disorders in elderly (Ritchie et al., 2004). Eligible participants, aged 65+ and non-institutionalized, were recruited by random selection from the electoral rolls between 1999 and 2001. Ethics approval was given by the national ethics committee (Sud Méditerranée III and University Hospital of Kremlin-Bicêtre, France) and all participants provided informed consent. Of the 2190 non-demented elderly recruited, participants not assessed for current psychiatric symptomatology (n=29) and having missing covariate data (n=252) were excluded from this analysis and 1007 provided buccal samples for genotyping. Compared to the participants included in the analysis, those excluded had a lower educational level, were older, and more likely to have cognitive impairment, cardiovascular ischemic pathologies, hypertension, current depressive symptomatology, and to use antidepressants ($p \leq 0.0002$).

2.2 Outcome

Lifetime depression and anxiety disorders were diagnosed using the Mini-International Neuropsychiatry Interview (MINI), a standardized psychiatric examination validated in the general population (Sheehan et al., 1998) according to the DSM-IV criteria (Ritchie et al., 2004). Positive cases were reviewed by a panel of psychiatrists. The Center for Epidemiologic Studies-Depression Scale (CES-D), validated in the elderly, was used to evaluate current depressive symptomatology (Radloff, 1977). Participants with at least a MINI diagnosis of

current major depression or high levels of depressive symptomatology (CES-D>16) at baseline, were defined as having a clinical level of depression (DEP) (Ancelin et al., 2010).

2.3 *CYP19A1* genotyping

The *CYP19A1* gene is localized on 15q21.2 and spans 130,554 bases (51,208,057-51,338,610 GRCh38/hg38). *CYP19A1* polymorphisms were chosen based on common (MAF≥0.05) tag SNPs identified using the Haploview program (Barrett et al., 2005), and Caucasian genotype data from the International HapMap Project (www.hapmap.org; version3_releaseR2, ethnicity:CEU+TSI). The most commonly studied SNPs previously associated with depression (Kravitz et al., 2006a) or other neuropsychiatric disorder (Butler et al., 2010, Corbo et al., 2009, Iivonen et al., 2004, Janicki et al., 2013, Kravitz et al., 2006b, Medway et al., 2014, Rosenfeld et al., 2018, Shay et al., 2018, Song et al., 2019) were selected, while ensuring adequate coverage across the gene. These included *rs936306, rs1902586,* and *rs749292* within exon 1, *rs1062033* and *rs767199* within intron 1, *rs1065778* within intron 3, and *rs10046* (3'UTR exon 10). Linkage disequilibrium was moderately high to low across the region (**Figure S1)**. *CYP19A1* genotyping was performed by LGC Genomics (Hoddesdon,UK) using the KASP SNP genotyping system with a very low error rate (Ancelin et al., 2013a, Freeman et al., 2003).

2.4 Socio-demographic and clinical variables

The standardized interview recorded socio-demographic characteristics, lifestyle, and physical health, including history of cardiovascular ischemic pathologies (angina pectoris, myocardial infarction, stroke, cardiovascular surgery, arteritis). All drugs used in the preceding month were recorded from medical prescriptions or drug packages. Blood pressure, weight, and height were measured. Plasma total-

estradiol and total-testosterone were measured by a sensitive direct radioimmunoassay with 2pg/mL (7.3pmol/L) and 0.02ng/mL (0.06nmol/L) respectively, as limit of quantification as described (Carcaillon et al., 2014, Scarabin-Carre et al., 2014). Cognitive impairment was defined as having a score<26 at the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Dementia was diagnosed by a neurologist as part of a standardized examination and validated by independent neurologists (Ancelin et al., 2013b).

2.5 Statistical Analysis

Chi-squared tests were used to compare the distribution of *CYP19A1* genotypes with those predicted under the Hardy-Weinberg equilibrium (HWE). Linkage disequilibrium between the SNPs was calculated using Haploview version4.2 (Barrett et al., 2005). Associations between *CYP19A1* polymorphisms and DEP were assessed using logistic regression adjusted for age. Multivariate models further adjusted for health-related variables, namely cognitive impairment, body mass index, and cardiovascular pathologies, as well as history of major depression and anxiety disorder, due to their association with prevalent DEP ($p<0.15$) and/or the potential association with *CYP19A1* polymorphisms (Baghaei et al., 2003, Kravitz et al., 2006b, Rosenfeld et al., 2018, Shay et al., 2018, Wang et al., 2016). Given the potentially unique etiology of late-life depression, including influence of sex-steroids, stratified analysis was undertaken to determine whether history of depression influenced the associations.

The association between *CYP19A1* SNPs and levels of estradiol and testosterone was investigated in 15% of the participants. Since the distribution of raw estradiol is typically skewed, values were log-transformed. The associations between *CYP19A1* SNPs and steroid levels were evaluated using ANCOVA and adjusting for age. SAS (v9.4, SAS Institute, NC) was used for the statistical analyses with a

significance level of p<0.05. Given that seven SNPs were investigated, the Bonferroni corrected p-value was 0.0071.

3 RESULTS

3.1 Population characteristics

At baseline of the 1007 participants, 25.4% were identified as having DEP, 4.3% used antidepressant, and 25% had a history of major depression. Currently depressed participants were more frequently women (p<0.0001) and depressed women and men were more likely to have a history of major depression, as well as current anxiety disorder and to use antidepressants, compared to non-depressed participants (p<0.01) (**Table 1**). The *CYP19A1* genotype frequencies were not significantly different from those predicted by HWE (p>0.10 for all SNPs). Owing to the very small number of homozygotes for the minor allele of both *rs1902586* and *rs936306* (<4%), these homozygotes were combined with the heterozygotes for analysis.

3.2 *CYP19A1* polymorphisms and prevalent DEP

Among men, in the age-adjusted logistic regression model, none of the seven SNPs were significantly associated with DEP (**Table 2**). In women, significant associations were observed between DEP and four SNPs, in age-adjusted (Table 2) and multivariate-adjusted logistic regression models (**Table S1**). There was some evidence that past major depression modified these associations in women, and stratified analysis was then undertaken. Strong significant associations were found between three SNPs, *rs10046*, *rs1065778,* and *rs767199*, and increased risk of DEP for women without past major depression (**Table 3**). The heterozygotes had more than double the risk of DEP

compared to homozygotes for the major alleles. Conversely, in women with a history of major depression the minor alleles of *rs1902586* and *rs936306* were associated with a 90% and 73% respectively, decreased risk of DEP. In the multivariate model, findings remained unchanged or strengthened especially for *rs1902586* (Table S1). Three of the associations remained significant at the Bonferroni-corrected significance level.

Since antidepressant treatment could have an effect on the level of DEP, we also performed a sensitivity analysis by including current antidepressant users in our definition of DEP. Very similar associations were observed (**Table S2).**

3.3 *CYP19A1* polymorphisms and steroid levels

In men, no significant associations were found between *CYP19A1* polymorphisms and either estradiol or testosterone levels (**Table S3).** In women, the minor allele of *rs1902586* was associated with >2-fold higher total estradiol (non-log transformed scale) compared to the major homozygote, with a similar trend for the minor allele of *rs936306* (**Table 4**). The same data were found with the estradiol/testosterone ratio, whereas no significant associations were found with testosterone. The same pattern was observed for *rs1902586* when considering the women without a history of major depression (n=56); the level of estradiol was 2.1-fold higher (p=0.061) and the ratio of estradiol/testosterone was 2.9-fold higher (p=0.036) in the carriers of the minor allele compared to the major homozygotes (data not shown). No significant associations where found in those with past major depression but the small numbers (n=25) preclude drawing definite results.

4 DISCUSSION

As the first study to examine the association between variants in the aromatase gene and clinical levels of depression in the elderly, we report that variation in the *CYP19A1* gene was strongly associated with late-life depression in women specifically. Our findings were independent of potential confounders, especially physical and mental health, but varied according to the history of major depression. The minor alleles of *rs1902586* and *rs936306* were associated with a decreased risk of DEP of 73% and 90%, respectively in the women who also had a history of major depression. These variants were also associated with higher estradiol levels. These findings are consistent with the neuroprotective effects of estradiol on depression in women (Ancelin et al., 2007), as the *CYP19A1* variants associated with higher estradiol levels, were also associated with a reduced risk of depression. A different pattern was seen for *rs10046, rs1065778,* and *rs767199*, which, in women, were significantly associated with a more than 2-fold increased risk of late-life onset of depression specifically (*i.e.* current DEP in the absence of past major depressive episodes).

Only one multiethnic study examined *CYP19A1* as a risk factor for depression in pre- and peri- menopausal women at midlife (Kravitz et al., 2006a). A significant association was found between *rs936306* and depressive symptoms in 162 Japanese women but not in the other racial/ethnic groups including U.S. Caucasian. The TT minor homozygote was associated with an increased risk compared to CC or TC but the confidence intervals were large due to the small numbers. Further, they did not correct for multiple comparisons and did not control for somatic or neuropsychiatric comorbidity. No significant associations were found with the three other SNPs they investigated, including *rs749292*. The reasons for these inconsistencies may result from differences in population characteristics

including age (42 to 52 years) and/or menopausal status, as well as allele frequency differences between ethnic groups. Depression is also known to be a heterogeneous and multi-factorial disease likely to be caused by a number of environmental, biological, and genetic factors with varying interactions across the lifespan (Levinson, 2006, Taylor et al., 2013). Different etiologies have been reported for initial and recurrent depression (Burcusa & Iacono, 2007, Lewinsohn et al., 1999) as well as for early and late-onset depression (Blazer, 2003, Kendler et al., 2009) including vascular depression (Taylor et al., 2013). For women, hormonal fluctuations throughout the reproductive life, especially at menopause, can also result in mood disorder (Ancelin et al., 2007). Given the potential genetic associations between *CYP19A1* and age-related pathologies (Rosenfeld et al., 2018, Shay et al., 2018, Song et al., 2019, Wang et al., 2016, Westberg & Eriksson, 2008), it seems conceivable that certain genes may be specifically associated with late-life depression.

Sexually dimorphic effects of aromatase on brain function and various neurobehavioral responses have been reported in animal models, as well as in humans with mutations in the gene encoding aromatase (Shay et al., 2018). Aromatase expression and activity is necessary for proper neurobehavioral development in males and females. Later in life, sex differences in aromatase may affect neurological diseases such as depression and Alzheimer's disease, which tend to be more frequent in females than males (Shay et al., 2018). In contrast with depression, a number of studies have examined the associations between several *CYP19A1* variants and cognitive impairment or Alzheimer's disease (Shay et al., 2018, Song et al., 2019). A recent meta-analysis examined eight polymorphisms in *CYP19A1* gene, of which *rs10046* and *rs767199* but not *rs1065778* and *rs1062033,* weakly increased Alzheimer's disease susceptibility. All studies included predominantly women, and sex differences were not examined (Song et al., 2019). Only a few studies have examined men and women separately and they reported an association exclusively in women (Butler et al., 2010, Corbo et al., 2009,

Medway et al., 2014). Surprisingly, no study has controlled for psychiatric comorbidity despite potential bidirectional association between depression and dementia (Geda et al., 2013). In our study, demented participants were excluded and the associations were robust and independent of cognitive impairment and vascular risk factors.

Genomic organization of the *CYP19A1* gene is complex with, in humans, a regulatory and 5′ UTR region of 93 kb, and a coding region (exons 2–10) of ~30 kb. Its expression is regulated in a tissue- or signaling pathway-specific manner by means of at least ten different exon 1/promoters. Genetic polymorphisms of *CYP19* may be involved in mechanisms such as mRNA stabilization, enhancing of transcription or posttranslational regulation of expression.

In our study, SNPs displaying significant positive associations with late-onset DEP were located in intron 1 (*rs767199*), intron 3 (*rs1065778)*, and the 3'UTR exon 10 (*rs10046*) parts of the gene. *Rs10046* appears to have a functional role and has been linked to aromatase deficiency. The C/T transition is in the 3'UTR of the mRNA, with putative impact on the mRNA stability or regulation of termination of translation (Kristensen et al., 2000). The T allele is associated with higher levels of mRNA expression of CYP19 in breast cancer (Kristensen et al., 2000), and may contribute to regulation independently of the promoter, by resulting in different stable transcripts of the alleles (Kristensen & Borresen-Dale, 2000). The other SNPs located nearby, could also be functionally important as they have been associated with other health-related outcomes (Butler et al., 2010, Iivonen et al., 2004, Janicki et al., 2013, Kravitz et al., 2006b, Medway et al., 2014, Song et al., 2019). Conversely, *rs1902586* and *rs936306* were associated with current DEP only in the women with a lifetime history of major depression but not in those with new onset episodes in later life. They also were negatively

associated with estradiol levels. These two SNPs are in close proximity and are located in the 5'UTR region. The *rs1902586* is positioned within the brain-specific promoter/first untranslated exon "I.f" region, upstream of exon 2 (Anthoni et al., 2012, Sebastian & Bulun, 2001) and *rs936306* flanks this region. This suggests that this very specific exon/promoter I.f might have a role in the steroid-related vulnerability to recurrent depression in older women. This region regulates expression of the aromatase gene in distinct neurons of the hypothalamus (Yilmaz et al., 2009).

Some studies have also examined the association between *CYP19A1* polymorphisms and sex hormone levels, although findings have not been consistent, and this may differ in pre- and post-menopausal women and according to ethnicity (De Castro et al., 2005, Dunning et al., 2004, Sowers et al., 2011, Sowers et al., 2006). The minor homozygotes of *rs936306* and *rs749292* have been associated with lower testosterone-to-estradiol ratio and higher rates of estradiol decline during the menopause transition, but this was not found in Caucasian women (Sowers et al., 2011, Sowers et al., 2006). Among postmenopausal women, the T allele of *rs10046* was significantly associated with higher estradiol levels and higher estradiol to testosterone ratio in only one (Dunning et al., 2004) of four studies (see for review (Olson et al., 2007)).

In our sample of Caucasian women, we also failed to find significant associations with steroid levels for *rs749292* and *rs10046* and a trend was observed for the minor allele of *rs936306* with higher estradiol level and lower estradiol-to-testosterone ratio. In addition, we found a significantly higher estradiol level and estradiol-to-testosterone ratio with *rs1902586* which has not been examined previously in relation to hormone levels. There could be several reasons for the lack of association with steroid levels despite highly significant

associations with DEP (Ancelin et al., 2007). In animals, ovarian steroids have higher concentrations in brain than plasma, and the turnover rate of brain sequestration of blood-borne sex steroids is also high (Pardridge et al., 1980). Circulating levels may therefore not adequately reflect etiology in relation to disorders associated with decline in estrogen levels. This may be attributed to differences in estrogen, progesterone, and testosterone kinetic diffusion rates across the blood–brain barrier; the possibility of distinct affinity binding and steroid receptor content in the brain; and the presence of localized brain neurosteroids and localized metabolism via aromatase (Ancelin et al., 2007). The rate of change of hormonal levels rather than the absolute value might thus be more relevant to psychiatric outcomes as suggested by the prevalence of depression during pregnancy, postpartum, and following surgical menopause. Lastly, serum levels of sex steroids may also be influenced by genes other than those coding for enzymes, for example, genes coding for sex steroid receptors (Ryan & Ancelin, 2012, Westberg & Eriksson, 2008).

Interestingly we observed evidence of a heterosis effect, whereby the heterozygotes of *rs10046*, *rs1065778,* and *rs767199* were associated with increased risk of late-life DEP in women. Such effect may actually occur in up to 50% of all gene association studies, particularly in Europeans (Comings & MacMurray, 2000). Heterosis has been reported with certain *CYP19A1* polymorphisms for testosterone level (Sowers et al., 2006), estradiol decline (Sowers et al., 2011), Alzheimer's disease (Song et al., 2019), coronary heart disease (Wang et al., 2016), as well as endometriosis in Caucasian but not Asian women (Yi et al., 2016). Several explanations have been proposed (Comings & MacMurray, 2000), including a hypothetical independent third factor causing a hidden stratification of the sample such that the depressive phenotype would be associated with either one set of homozygote subjects or the alternate homozygosity set. This may also include interactions with other genes (epistasis interaction has been reported between *CYP19* and estrogen receptor (De

Castro et al., 2005, Kim et al., 2011) or *IL10* (Medway et al., 2014)), environmental factors, or age-related incident factors such as vascular changes (Comings & MacMurray, 2000). Another explanation is based on an inverted U-shaped response curve in which either too little or too much gene expression is deleterious, with optimal gene expression occurring in heterozygotes.

Study limitations include bias from excluding participants with missing data, who were in poorer health and more likely to be depressed thus reducing the overall study power. Although the size of our study was relatively large for a study of this kind (with data both on steroid levels and *CYP19A1* genotyping), the analysis included 256 depressed participants, thus potentially limiting the overall power of the study. Further studies are needed to replicate our data in large population samples, especially in men, in order to validate our findings. French law prohibits questioning participants about ethnicity, however prior genotyping data of these participants indicated that >99% were white Europeans (Ancelin et al., 2013a). This is supported by the similarity of the *CYP19A1* genotype frequencies with those published in white Europeans (Butler et al., 2010, Iivonen et al., 2004, Janicki et al., 2013, Medway et al., 2014) (and http://www.ncbi.nlm.nih.gov/projects/SNP/). The steroid analyses were performed on 15% of the participants. They were based on one measurement using direct radioimmunoassay rather than the more sensitive gas chromatography mass spectrometry method, which would have allowed detection of very low levels of estradiol (Stanczyk & Clarke, 2010). This may have led to attenuation of the associations but was less likely to detect false associations. However, validation studies showed excellent correlations between both methods (Carcaillon et al., 2014, Scarabin-Carre et al., 2014). Besides, both estradiol and testosterone are neurosteroids subject to endogenous synthesis within the brain from cholesterol precursors and the blood concentration does not necessarily reflect the biologically active forms at the tissue level.

Our study has several strengths. This is the first study of late-life depression to investigate associations with several *CYP19A1* polymorphisms in community-dwelling elderly men and women separately, with a strong *a priori* biological rationale while also examining the impact on circulating steroid levels. The use of a community-dwelling rather than clinical population has ensured the inclusion of a more representative sample of DEP participants. DEP was assessed by trained staff using two distinct measures validated in the general population, including a structured DSM-IV based diagnostic interview (Radloff, 1977, Sheehan et al., 1998). We controlled for a large number of covariates thus minimizing any confounding. Associations remained notably significant after controlling for vascular factors and cognitive impairment and after excluding demented cases.

Our findings provide strong epidemiological support for *CYP19A1* polymorphisms as independent susceptibility factors for late-life depression in a sex-specific manner. Some variants increase the risk of late-onset depression in women, whereas others influence estradiol levels and appear protective for late-life depression in the high-risk group of women with past major depression. We cannot exclude that in addition, other hormones not examined in this study (*e.g.* androstenedione which can also be converted to estrone by aromatase) and other related genetic factors (e.g. type 1 17β-hydroxysteroid dehydrogenase, the bidirectional enzyme converting estrone to estradiol) could also be associated with depression. In addition to the effects of single genetic variants, complex traits may also be influenced by gene-environment and gene-gene interactions. Large longitudinal studies are needed to replicate our original findings combining genetic and hormonal level data in diverse populations taking into account additional factors such as ethnicity, age, and phase of female reproductive life. Comprehensive functional genomic studies will also be needed before drawing definite conclusions concerning the role of aromatase in depression.

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TABLE 1 Baseline characteristics of participants in relation to prevalent DEP† (N=1007)

	MEN (N=405)				WOMEN (N=602)			
Characteristics	NON-DEP	DEP	DEP vs non-	Wald	NON-DEP	DEP	DEP vs non-	Wald

	(n=337, 83.21%)	(n=68, 16.79%)	DEP (OR [95% CI]‡)	test p-value	(n=414, 68.77%)	(n=188, 31.23%)	DEP (OR [95% CI]‡)	test p-value
Age (years) mean (SD)	71.25 (4.23)	72.35 (4.56)	1.06 [1.00;1.12]	0.06	71.54 (4.52)	71.83 (4.44)	1.01 [0.98;1.05]	0.47
Education (≥12 years schooling)	132 (39.17)	23 (33.82)	0.79 [0.46;1.38]	0.41	99 (23.91)	21 (11.17)	0.40 [0.24;0.67]	0.0004
Body mass index (kg/m^2):								
Normal (<25)	157 (46.59)	21 (30.88)	1	0.034	270 (65.22)	121 (64.36)	1	0.82
Overweight (25-29)	160 (47.48)	40 (58.82)	1.86 [1.05;3.30]	0.045	115 (27.78)	49 (26.06)	0.95 [0.64;1.42]	0.32
Obese (≥30)	20 (5.93)	7 (10.30)	2.72 [1.02;7.25]		29 (7.00)	18 (9.58)	1.37 [0.73;2.57]	
Cardiovascular ischemic pathologies§	47 (13.95)	15 (22.06)	1.65 [0.86;3.18]	0.14	31 (7.49)	12 (6.38)	0.83 [0.41;1.65]	0.59
Hypertension (>160/95 mm Hg or	132 (39.17)	34 (50.00)	1.45 [0.85;2.47]	0.17	178 (43.00)	75 (39.89)	0.85 [0.60;1.22]	0.39

treated)								
Cognitive impairment (MMSE score<26)	22 (6.53)	6 (8.82)	1.33 [0.52;3.43]	0.55	40 (9.66)	34 (18.09)	2.06 [1.26;3.38]	0.004
History of major depression	38 (11.28)	19 (27.94)	3.17 [1.68;5.98]	0.0004	115 (27.78)	76 (40.43)	1.78 [1.24;2.56]	0.002
Antidepressant use	2 (0.59)	4 (5.88)	11.40 [2.03;64.1]	0.006	13 (3.14)	24 (12.77)	4.48 [2.22;9.01]	<0.0001
Current anxiety disorder	19 (5.64)	11 (16.18)	3.41 [1.53;7.60]	0.003	51 (12.32)	52 (27.66)	2.73 [1.77;4.22]	<0.0001

MMSE: Mini-Mental State Examination.

†Corresponds to current major depression (DSM-IV) or a CES-D score ≥16.

‡All logistic models adjusted for age except for age (unadjusted).

§A history of angina pectoris, myocardial infarction, stroke, cardiovascular surgery and arteritis.

TABLE 2 Logistic regression analysis for the association between *CYP19A1* polymorphisms and prevalent DEP† in men and women

	MEN (N=405)				WOMEN (N=602)				
SNP and genotype	Non-DEP %	DEP %	OR [95% CI]‡	p	Non-DEP %	DEP %	OR [95% CI]‡	p	p-interaction (x past major depression)
rs10046, n	*326*	*66*			*398*	*182*			
CC	27.91	25.76	-	-	27.64	23.63	-	-	0.04
TC	48.47	51.51	1.19 [0.63;2.25]	0.60	48.99	55.49	1.32 [0.86;2.03]	0.20	
TT	23.62	22.73	1.10 [0.51;2.36]	0.81	23.37	20.88	1.04 [0.62;1.75]	0.88	
rs1065778, n	*334*	*65*			*409*	*183*			
AA	32.04	26.15	-	-	31.54	23.50	-	-	0.16
AG	45.81	55.39	1.52 [0.81;2.85]	0.20	48.17	56.83	1.58 [1.04;2.41]	0.03	
GG	22.15	18.46	1.09 [0.49;2.43]	0.83	20.29	19.67	1.30 [0.77;2.19]	0.32	
rs767199, n	*332*	*67*			*407*	*181*			
GG	34.34	32.84	-	-	33.66	24.86	-	-	0.15
AG	43.67	47.76	1.17 [0.64;2.13]	0.60	47.67	58.01	1.65 [1.09;2.50]	0.017	
AA	21.99	19.40	0.99 [0.47;2.10]	0.98	18.67	17.13	1.24 [0.73;2.13]	0.43	
rs1062033, n	*332*	*67*			*407*	*184*			
GG	39.46	38.81	-	-	38.57	33.15	-	-	0.37
CG	42.47	46.27	1.13 [0.63;2.00]	0.68	45.95	50.54	1.29 [0.88;1.90]	0.20	
CC	18.07	14.92	0.90 [0.40;1.99]	0.79	15.48	16.31	1.23 [0.72;2.07]	0.45	
rs749292, n	*332*	*64*			*407*	*184*			
GG	37.65	34.37	-	-	37.59	36.41	-	-	0.42
AG	45.18	48.44	1.21 [0.66;2.19]	0.54	45.70	46.20	1.05 [0.71;1.55]	0.80	
AA	17.17	17.19	1.16 [0.53;2.58]	0.71	16.71	17.39	1.08 [0.65;1.80]	0.76	
rs1902586, n	*336*	*68*			*413*	*185*			
GG	91.07	91.18	-	-	88.86	94.59	-	-	0.059

	MEN (N=405)				WOMEN (N=602)				
SNP and genotype	Non-DEP %	DEP %	OR [95% CI]‡	p	Non-DEP %	DEP %	OR [95% CI]‡	p	p-interaction (x past major depression)
AG+AA	8.93	8.82	1.04 [0.41;2.63]	0.93	11.14	5.41	0.46 [0.23;0.93]	0.03	
rs936306, n	*333*	*66*			*406*	*185*			
CC	72.97	72.73	-	-	68.23	80.00	-	-	0.035
TC+TT	27.03	27.27	1.01 [0.56;1.83]	0.98	31.77	20.00	0.54 [0.36;0.82]	0.004	

†Corresponds to current major depression (DSM-IV) or a CES-D score ≥16.

‡Adjusted for age (continuous).

TABLE 3 Logistic regression analysis for the association between *CYP19A1* polymorphisms and DEP† in women according to history of major depression

	Without history of major depression (N=411)				With history of major depression (N=191)			
SNP and genotype	Non-DEP %	DEP %	OR [95% CI]‡	p	Non-DEP %	DEP %	OR [95% CI]‡	p
rs10046, n	*288*	*109*			*110*	*73*		
CC	29.86	19.27	-	-	21.82	30.14	-	-
TC	46.53	60.55	2.02 [1.15;3.54]	0.014	55.45	47.94	0.61 [0.30;1.26]	0.18
TT	23.61	20.18	1.32 [0.67;2.60]	0.42	22.73	21.92	0.62 [0.26;1.49]	0.28
rs1065778, n	*294*	*110*			*115*	*73*		
AA	33.33	21.82	-	-	26.96	26.03	-	-
AG	45.92	60.91	2.02 [1.19;3.45]	0.0096	53.91	50.68	0.95 [0.47;1.92]	0.88
GG	20.75	17.27	1.26 [0.64;2.50]	0.50	19.13	23.29	1.16 [0.49;2.76]	0.73
rs767199, n	*296*	*110*			*111*	*71*		
GG	35.13	22.73	-	-	29.73	28.17	-	-
AG	45.95	62.73	2.10 [1.24;3.55]	0.0055	52.25	50.70	0.99 [0.49;2.00]	0.98
AA	18.92	14.54	1.18 [0.58;2.40]	0.64	18.02	21.13	1.12 [0.46;2.71]	0.81

	Without history of major depression (N=411)				With history of major depression (N=191)			
SNP and genotype	Non-DEP %	DEP %	OR [95% CI]‡	p	Non-DEP %	DEP %	OR [95% CI]‡	p
rs1062033, n	*292*	*110*			*115*	*74*		
GG	40.41	31.82	-	-	33.91	35.13	-	-
CG	44.52	53.64	1.52 [0.93;2.48]	0.09	49.57	45.95	0.86 [0.44;1.66]	0.64
CC	15.07	14.54	1.22 [0.62;2.43]	0.57	16.52	18.92	1.02 [0.43;2.43]	0.96
rs749292, n	*295*	*110*			*112*	*74*		
GG	38.98	34.55	-	-	33.93	39.19	-	-
AG	44.41	49.09	1.24 [0.77;2.02]	0.38	49.11	41.89	0.74 [0.38;1.43]	0.37
AA	16.61	16.36	1.11 [0.58;2.13]	0.76	16.96	18.92	0.94 [0.40;2.21]	0.89
rs1902586, n	*298*	*111*			*115*	*74*		
GG	89.60	91.89	-	-	86.96	98.65	-	-
AG+AA	10.40	8.11	0.76 [0.35;1.65]	0.48	13.04	1.35	0.10 [0.01;0.76]	0.026
rs936306, n	*292*	*111*			*114*	*74*		
CC	69.18	74.77	-	-	65.79	87.84	-	-
TC+TT	30.82	25.23	0.75 [0.46;1.24]	0.27	34.21	12.16	0.27 [0.12;0.60]	0.001

†Corresponds to current major depression or a CES-D score ≥16.

‡Adjusted for age (continuous).

TABLE 4 Association between *CYP19A1* polymorphism and the level of estradiol or testosterone in women (n=87)

		log [Estradiol (pg/ml)]			Testosterone (ng/ml)			log [Estradiol/Testosterone]		
SNP and genotype	N	Mean†	SD†	p	Mean†	SD†	p	Mean†	SD†	p
rs10046										
CC	24	0.84	0.08	0.89	0.33	0.03	0.93	1.38	0.10	0.91
TC	48	0.83	0.06		0.32	0.02		1.36	0.07	
TT	14	0.78	0.11		0.34	0.04		1.31	0.12	
rs1065778										
AA	25	0.82	0.08	0.87	0.32	0.03	0.91	1.37	0.09	0.91
AG	48	0.84	0.06		0.33	0.02		1.37	0.07	
GG	13	0.77	0.11		0.35	0.04		1.31	0.13	
rs767199										
GG	25	0.83	0.08	0.94	0.32	0.03	0.87	1.39	0.09	0.81
AG	48	0.81	0.06		0.34	0.02		1.32	0.07	
AA	12	0.79	0.11		0.33	0.04		1.34	0.13	
rs1062033										
GG	31	0.83	0.07	0.99	0.33	0.03	1.00	1.37	0.08	0.94
CG	44	0.82	0.06		0.33	0.02		1.34	0.07	

SNP and genotype	N	log [Estradiol (pg/ml)]			Testosterone (ng/ml)			log [Estradiol/Testosterone]		
		Mean†	SD†	p	Mean†	SD†	p	Mean†	SD†	p
CC	11	0.82	0.12		0.33	0.05		1.38	0.14	
rs749292										
GG	30	0.86	0.07	0.45	0.34	0.03	0.91	1.39	0.08	0.48
AG	48	0.78	0.06		0.32	0.02		1.32	0.07	
AA	9	0.94	0.13		0.32	0.05		1.51	0.15	
rs1902586										
GG	78	0.79	0.04	0.017	0.33	0.02	0.13	1.32	0.05	0.011
AG+AA	8	1.14	0.14		0.25	0.05		1.75	0.16	
rs936306										
CC	59	0.78	0.05	0.13	0.33	0.02	0.96	1.32	0.06	0.20
TC+TT	27	0.92	0.08		0.33	0.03		1.46	0.09	

†Adjusted for age.

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