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The role of allelic variation in estrogen receptor genes and major depression in the Nurses Health Study

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Abstract

Purpose—The role of exogenous and endogenous sex hormones in the etiology of depression remains elusive, in part because sex hormone variation is often correlated with behaviors, life stage changes, and other factors that may influence depression. Estrogen receptor alpha (ESR1) and beta (ESR2) are known to regulate gene expression and estrogen response in areas of the brain associated with major depression and are unlikely to be correlated with exogenous factors that may influence depression.

Methods—We examined whether functional polymorphisms in these genes are associated with lifetime major depression and chronic major depression among a sample of women from the Nurses' Health Study II (N=2,576). DSM-IV depressive disorder symptoms were assessed by structured interview in 2007. Genotyping was performed on DNA extracted from blood using Taq-man.

Results—Women with the AA alleles of ESR2 RS4986938 had the higher prevalence of lifetime major depression than women with other allele frequencies (36.7% for those with AA versus 28.5% with GA and 29.1% with GG, $p=0.02$) and chronic major depression (14.7% for those with AA versus 9.3% with GA and 9.1% with GG, $p=0.01$). History of post-menopausal hormone (PMH) use modified the association of ESR1 polymorphism RS2234693 with any lifetime depression; specifically, those with the TT allele had the highest risk of lifetime depression among PMH users, and the lowest risk of depression among non-PMH users (p -value for interaction=0.02). Further, carriers of the AA alleles in ESR1 polymorphism RS9340799 had increased prevalence of lifetime major depression only among lifetime PMH-users ($p=0.007$).

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Conclusions—Our findings support the hypothesis that estrogen receptor polymorphisms influence risk for major depression; the role of estrogen receptors and other sex steroid-related genetic factors may provide unique insights into etiology.

Keywords

estrogen; depression; nurses; estrogen receptor alpha; estrogen receptor beta; hormones; post-menopausal hormone use

Introduction

Approximately one in five women in the US will experience an episode of major depression in their lifetime [1], and approximately 4% of women will suffer from chronic major depression. Major depression is associated with significant functional disability [2] and is estimated to be among the top causes of disability-adjusted life years lost worldwide [3]. Women are approximately twice as likely to experience depression compared with men, and underlying causes of these sex differences remain inadequately understood.

Given the substantial sex difference in depression, a potential role for gonadal hormones, especially estrogen, in the incidence and persistence of depression has generated substantial interest [4]. Epidemiologically, changes in mood often co-occur with changes in estrogen levels among women. Depression incidence and recurrence is increased during developmental phases such as puberty [5] and menopause [6,7] during which estrogen levels are rapidly changing [8], as well as during the luteal phase of the menstrual cycle [9,10] and postpartum [11]. Substantial evidence supports a role for exogenous regulation of estrogen in reducing depression and depressive symptoms, including hormone replacement therapy [12,4] and hormonal contraceptives [13,14]. Yet important questions about the role of estrogen in major depression remain unanswered; developmental stages in which hormone levels are fluctuating, such as puberty and menopause, coincide with other life events and potentially stressful experiences. Several studies have demonstrated that the relation between puberty and depression, for example, is inconsistent and better explained by psychosocial than biological factors [15,16].

Genes involved in the production and regulation of estrogen may provide a source of variation with which to examine the impact of estrogen on depression. The genetic sequence that is inherited from parents precedes any life events and developmental changes that may also influence the development of depression, thus examination of such genetic associations can prove a rigorous method to understand depression etiology [17,18]. Estrogen exerts an influence on many biological systems through the activation of two receptors, ER- α and ER- β [19]. These receptors are transcribed from two genes, ESR1 and ESR2, respectively, and allelic variation in these two receptors, especially ESR1, is associated with health outcomes such as breast cancer [20,21], high density lipoprotein cholesterol [22], and all-cause mortality [23], and there has been growing interest in the way in which allelic variation in these genes may influence depression. To date, population-based studies that have evaluated the role of allelic variation in estrogen receptors and depression have been mixed (evidence reviewed in [24]); most [25–29] but not all [30–32] studies have found a null or weak

association with ESR1 allelic variation. Those studies that have documented an association have generally found that carriers of the TT alleles in RS2234693 on ESR1 are at higher risk compared with CC alleles [31], though studies differ in whether the relation is observed only among males [33], only among females [31], or both [34]. Fewer studies have examined ESR2 variation [31,32], also with mixed findings. Variation in outcome measurement may contribute to this inconsistency. Most studies have used non-diagnostic measures of depression and have not captured potential differences in intermittent versus chronic major depression.

Further, postmenopausal hormone (PMH) use has proven beneficial for alleviation of depressive symptoms during the menopausal transition [35,36]. Emerging evidence indicates that variation in ESR polymorphisms interacts with PMH [31,37], such that women with particular allelic structures experience a greater protective effect of PMH on depression than other women. If this finding can be replicated, it may suggest avenues for pharmacogenetic treatment interventions for depression among post-menopausal women. However, existing evidence for the role of PMH use in the relation between estrogen receptor polymorphisms and depression is limited.

The present study examines the association between allelic variation in ESR1 and ESR2 with lifetime major depressive episodes and chronic major depression in the Nurses' Health Study II, a longitudinal study of women followed biennially since 1989. First, we examine whether allelic variation in ESR1 and ESR2 is associated with lifetime occurrence of major depression or chronic depression. Second, we examine whether use of PMH modifies the effect of estrogen receptor allelic variation on lifetime occurrence of major depression or chronic depression.

Methods

Sample

The Nurses' Health Study II includes 116,678 female nurses who have received biennial questionnaires since 1989. In 2008, 60,894 women were mailed a supplementary questionnaire that assessed trauma exposure and PTSD symptoms; 54,282 participants returned the questionnaire (response rate=89%); 80% reported at least one lifetime traumatic event and 53% of those women agreed to be interviewed. From these women, 2,112 probable cases of PTSD and 2,001 matched controls were identified through a brief PTSD questionnaire. Seventy-three percent of these women (N=3,013) completed more in-depth interviews, and 2,612 subjects provided blood samples. Preliminary analyses indicated that ESR2 allelic variation differed among those self-identifying as White versus non-White (RS125604, $\chi^2=13.4$, $df=1$, $p=0.0002$; RS4986938, $\chi^2=8.9$, $d.f.=2$, $p=0.01$). Because less than 5% of the sample identified as non-White, all analyses were conducted among those women self-identifying as non-Hispanic White. In summary, the present study analyzes data from the 2,576 women with valid DNA samples.

Demographics of the sample are provided in Online Table 1. Approximately 73% of the sample was between 50–60 years of age at the 2007 interview, and an additional 6% were over the age of 60; the remainder of the sample was between 40–49. By highest parental

education in childhood, in 25.4% of the sample, at least one parent was college educated or higher, 26.4% had a parent with some college, and the remainder had parents with high school education or less. We note that because the sample is comprised of nurses, there is little variation in respondent education. By US Census tract median income, the distribution was as follows: <\$40,000 (9.4%); \$40–49,999 (19.9%); \$50–59,999 (31.0%); \$60–79,999 (18.1%); \$80,000+ (21.7%). Approximately two-thirds of the woman had used PMH, with an even distribution between <2 years (33.1%), 2–8 years (35.9%), and 8+ years (31.0%).

Measures

DNA Extraction and Genotyping Methods—Whole blood derived genomic DNA was isolated from 400µl of whole blood using the DNA Mini kit (Qiagen, Valencia, CA).

All samples were genotyped using the ABI PRISM 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA), in 384-well format. The 5' nuclease assay (TaqMan®) was used to distinguish the 2 alleles of a gene. PCR amplification was carried out on 5–20ng DNA using 1 × TaqMan® universal PCR master mix (No Amp-erase UNG) in a 5µl reaction volume. Amplification conditions on an AB 9700 dual plate thermal cycler (Applied Biosystems, Foster City, CA) were as follows: 1 cycle of 95°C for 10min, followed by 50 cycles of 92°C for 15s and 60°C for 1 min. TaqMan® assays were ordered using the ABI Assays-on-Demand service. We analyzed four alleles in ESR1 and ESR2. In ESR1, we examined rs2234693 and rs9340799. In ESR2, we examined rs1256049 and rs4986938. In ESR2 polymorphism rs1256049, we combined individuals with the GA and AA allelic structure given the low sample size with AA structure (0.08% of the sample). There were no associations between any ESR1 polymorphisms with any ESR2 polymorphisms. In Table 1 we provide information on the distribution of specific alleles within these four polymorphisms within the sample and by demographic subgroup.

Depression—Major depression was assessed in a 2007 phone interview with the Patient Health Questionnaire (PHQ-9), an extensively used depression scale with good reliability and validity [38]. Additional questions regarding symptom clustering (“Did these experiences or feelings you’ve had ever seem to go together or happen at the same time?”) and duration (“What was the longest period of time during which you were having these problems?”) were administered to assess DSM-IV criteria for major depression. Respondents were asked about the occurrence of symptoms in their lifetime and in the past month; they were also asked how many separate times symptoms occurred together (a measure of the number of depression episodes experienced during the respondent’s lifetime) and how long symptoms lasted. Respondents meeting criteria for DSM-IV depression in at least one time point in their lifetime were considered cases; remaining women were considered non-cases.

We considered women to have chronic depression if they met DSM-IV criteria for a major depressive episode and they reported two or more episodes or an episode that lasted at least one year; all other women were considered non-cases for chronic depression.

Postmenopausal hormone use (PMH)—We included two measures of PMH use: whether or not the woman ever used PMH (62.0%), and among users, the number of years

of use. Years of use were categorized as less than 2 (33.1%), 2–8 (35.9%), and 8+ based on the distribution of years of use in the data. In Table 1 we include descriptive statistics on years of use by estrogen receptor variation as well as demographic subgroups.

Covariates—Because depression is differentially distributed across demographic groups, we explored associations between estrogen receptor polymorphisms and respondent's reported highest parental education in childhood and age based on the 2007 questionnaire data. We also examined US Census tract household median income based on home address in 2007.

Statistical analysis—Analysis proceeded in three steps. First, we examined the distribution of estrogen receptor polymorphisms across demographic subgroups and by history of PMH use, using chi-square tests to assess significant differences at $\alpha < 0.05$. Second, we examined the prevalence of lifetime major depression as well as chronic major depression across estrogen receptor polymorphisms. Differences across groups were tested with chi-square tests. Third, we examined the interaction between estrogen receptor polymorphisms, PMH, and any depression as well as chronic depression. We tested for interaction on a multiplicative scale using F-tests and additionally examined the association between estrogen receptor polymorphisms and any depression as well as chronic depression in analyses subset by years of PMH use. All analyses were conducted using SAS Version 9.0.

All analyses were conducted both unadjusted and adjusted for median household income, using logistic regression and extracting risk ratios from marginal distributions due to high prevalence of outcome in some subgroups. In the sample prior to weighting, PTSD was associated with a 5.18 (95% CI 4.07, 6.58) increased risk of chronic major depression and a 4.46 (95% CI 3.67, 5.43) increased risk of major depression. Because women were selected for the sub-study based on whether or not they had probable PTSD, we estimated an inverse probability weight for selection into the sub-study. The sample was weighted to represent the distribution of PTSD cases and non-cases in the overall Nurses Health Study, which reflected each woman's probability of being selected into the subsample, with a separate weight for cases and controls. Weighting based on selection factors in nested case control studies where the data are being reused for a different outcome is suggested in the biostatistical literature, and similar weighting procedures have been implemented in other analyses of Nurses Health study subsamples where case control data are reused for other outcomes [39]. Prevalence estimates and risk ratios are based on the weighted sample. Interaction analyses were conducted by unadjusted and adjusted for adjusted for median household income given the significant differences observed in allele frequencies.

Results

Covariate distributions of ESR1 and ESR2 genotypes

Table 1 provides distributions of estrogen receptor polymorphisms by demographic subgroups and PMH use. By demographics, there were no associations, save that the AA carriers of ESR2 allele RS4986938 were overrepresented among those in the highest Census

tract household median income ($\chi^2=16.7$, $df=8$, $p=0.03$). Because of this significant association, we adjusted for Census tract household median income in subsequent analyses.

Those with the GG genotype of ESR2 allele RS1256049 were less likely to be lifetime PMH users (61.5%) compared with GA/AA genotype carriers (72.7%) ($\chi^2=7.2$, $df=1$, $p=0.01$). Among users, those with the TT genotype of RS2234693 were more likely to be long-term users (8+ years, 34.6%) compared with those with the CC (27.8%) or CT genotype (30.2%), $\chi^2=12.2$, $df=4$, $p=0.02$.

Association between estrogen receptor polymorphism and depressive episodes

Table 2 shows the association between estrogen receptor polymorphisms and any major depressive episode and chronic depression ($N=2,576$). Those with the highest lifetime prevalence of major depression were carriers of the AA alleles in ESR2 polymorphism RS4986938, at 36.7%. AA carriers had significantly higher risk of major depression compared with GG (29.1%) and GA carriers (28.5%), $\chi^2=7.2$, $df=1$, $p=0.02$. This finding also held when considering chronic major depression as an outcome. AA carriers had a significantly higher prevalence (14.7%) compared with GA (9.3%) and GG (9.1%) carriers, $\chi^2=9.2$, $df=2$, $p=0.01$.

These associations were confirmed in unadjusted and adjusted regression analyses (Table 3). Those with the AA allele of RS4986938 had 1.71 times the risk of chronic major depression (95% C.I. 1.18–2.48) compared with GA carriers, and 1.47 times the risk (95% C.I. 1.12–1.94) of any major depressive episode, adjusted for median household income.

Further, those with the TT allele of RS2234693 had 1.37 times the risk (95% C.I. 1.02–1.84) of chronic major depression compared with CT carriers, adjusted for median household income.

Interaction between post-menopausal hormone use and estrogen receptor genotype

Table 4 shows the lifetime prevalence of depressive episodes and chronic depression by post-menopausal hormone use as well as ESR1 and ESR2 polymorphisms. Overall, women with any use of PMH had higher prevalence of lifetime major depression (32.4%) compared with women who never used (26.3%), and lifetime risk of depressive episodes and chronic depression increased as length of time using PMH increased.

There was evidence of an interaction between lifetime of PMH use and allele variation in ESR-1 polymorphisms RS2234693 (unadjusted, $p=0.01$; adjusted, $p=0.02$) and RS9340799 (unadjusted, $p=0.007$; adjusted, $p=0.007$) in lifetime major depression. TT carriers of RS2234693 had the highest risk of lifetime major depression among PMH users (36.9%) and the lowest risk of lifetime major depression among non-PMH users (21.1%). When examining RS9340799, GA and GG carriers had a similar prevalence of lifetime major depression whether they were PMH users or not; AA carriers with a history of PMH use, however, had a higher prevalence of lifetime major depression (35.7%) compared with AA carriers who did not have a history of PMH use (22.5%). Results for chronic major depression were similar, although interactions did not reach statistical significance.

There were no interactions between polymorphisms and PMH use for chronic depression or for any ESR2 genes (RS1256049: lifetime major depression, $p=0.12$, chronic major depression, $p=0.24$; RS4986938, lifetime major depression, $p=0.69$, chronic major depression, $p=0.61$), and no interactions between length of PMH use with either ESR1 (RS2234693: lifetime major depression, $p=0.19$, chronic major depression, $p=0.38$; RS9340799, lifetime major depression, $p=0.12$, chronic major depression, $p=0.69$) or ESR2 polymorphisms (RS1256049: lifetime major depression, $p=0.94$, chronic major depression, $p=0.81$; RS4986938, lifetime major depression, $p=0.30$, chronic major depression, $p=0.41$).

In online Table 1, we also provide risk ratios for the association between each polymorphism and chronic as well as lifetime major depression, stratified by PMH use, and additionally controlled for PTSD and medical household income. Results support those in Table 3 in direction and magnitude; the interaction of PMH use and allele frequency in RS2234693 remained statistically significant ($\chi^2=4.39$, $p=0.01$).

Discussion

The present study uses a large, population-based sample of US women to examine associations between allelic variation in estrogen receptor genes and major depression. We document three central findings. First, we document associations between polymorphisms in the ESR2 gene and lifetime major depression. Specifically, those at highest risk for lifetime and chronic major depression are those homozygous for the A allele of ESR2 gene RS4986938. This association persisted after controlling for covariates. For ESR1 polymorphisms, main effect associations were observed with increased risk for chronic major depression among those with the TT allele of RS2234693. Stratification by PMH use showed evidence of interaction; those with the TT allele of RS2234693 had the highest prevalence of lifetime depression among PMH users and the lowest prevalence of lifetime depression among non-PMH users. Finally, AA carriers of RS9340799 who were PMH users had a higher prevalence of lifetime major depression than PMH non-users. There was no evidence of an interaction between ESR2 genes and PMH use in association with lifetime or chronic depression, and no interaction between length of PMH use and either ESR1 or ESR2 polymorphisms.

Numerous studies have examined the role of ESR1 genetic variation in major depression (recently reviewed in [24]) and other psychiatric disorders [40]. While there is little evidence of an association between genetic variation in ESR1 genes and mild or moderate depression, a growing number of studies have documented an association with the TT allele of ESR1 gene RS2234693 with chronic or severe depression [31,41]. Our results are consistent with this body of literature, though we extend the literature by showing that women with the TT allele have a heightened prevalence of major depression, only if they were PMH users. Given the that the Nurses Health Study II is a population-based sample with diagnostic measures of major depression, the present study adds rigor to this literature. However, the literature is not entirely consistent; a recent study of almost 4,000 dementia-free older women found that those with the TT allele were less likely to have depression compared CC/CT carriers, and GA carriers of RS9340799 were at increased risk compared

with AA carriers [31]. We suggest that inconsistency in the results may stem from the interaction of this polymorphism with PMH use.

We found evidence for an association between RS9340799 and lifetime major depression among PMH users; one other study has documented that the AA allele of this polymorphism is associated with lifetime depression [41] and several other studies have shown an association with depression at the time of the interview [32,42,31]. Those with the AA allele in our data did have the highest prevalence of chronic major depression (10.8% versus 9.7% and 9.5% for those with GA and GG, respectively), however the association was not robust. Thus, our results for RS9340799 are in line with previous literature though not confirmatory.

To date, this is the first study to our knowledge that has documented an association between RS4986938 and lifetime as well as chronic major depression. Two previous studies have published null results for this allele [32,31]; further study and replication in other samples is necessary before firm conclusions can be drawn. Regarding RS1256049, few previous studies have examined it in relation to depression risk, and results have been inconsistent. Ryan et al. [31] documented an increased risk of depression among carriers of the A allele of RS1256049, but only those who were lifetime non-users of PMH. We did not document robust modification in RS1256049 allele risk by PMH use, and the direction of the association was that A allele carriers had higher risk of depression among lifetime PMH users rather than among non-users.

This study has several implications for our understanding of the role of hormones in depression as well as the potential for pharmacogenetic treatment for depression using PMH, though substantially more data is needed before firm conclusions can be made. Substantial epidemiological and clinical evidence indicates that PMH therapy may be an effective treatment for depression symptoms among peri- and post-menopausal women [35,43]. Our data indicate further research should explore the possibility that carriers of the TT allele of ESR1 RS2234693 and carriers of the AA allele of ESR1 RS9340799 may respond differently to hormone therapy during menopause with respect to mood, though inconsistency in these results with other studies caution against firm conclusions [31]. Several issues compromise robust conclusions from this body of research more generally. First, lifetime users of PMH were, overall, at higher risk for lifetime depression and chronic depression compared with non-users in our data. There is a risk of confounding by indication in interpretation of these observational data, as women with a history of depression may be more likely to use PMH to treat depressive symptoms during the menopausal transition, though to our knowledge there is no empirical evidence for such an effect. In fact, given the data from the Women's Health Initiative and other trials indicating a potentially increased risk of dementia among those using conjugated equine estrogen plus medroxyprogesterone acetate [4,44–46], previous research has suggested that women with depression histories are more likely to be prescribed antidepressants than PMH for depressive symptoms in the menopausal transition [4,47,48]. We did not have sufficient information on the timing of onset of depressive symptoms to fully establish temporality of PMH use and onset or recurrence of depression, thus the use of PMH for treatment of depression symptoms remains a potential alternative explanation of our findings. Ryan et al. 2011a, did not report the lifetime risk of depression among PMH users compared with non-

users, thus comparison across study was not possible. Nevertheless, even if some women with depressive symptoms were treated with PMH, our data indicate that women with the TT allele of ESR1 receptor RS2234693 and the AA allele of ESR1 receptor RS9340799 were at highest risk for lifetime and chronic depression among PMH users, suggesting that examination of estrogen receptor variation may be an important adjunct to PMH therapy in the future. Finally, emerging evidence also indicates that certain alleles in ESR1 receptors may influence anxiety disorders such as phobia among PMH users [37], thus further investigation of the role of estrogen receptors in other psychiatric disorders in the context of PMH use are an important future direction of this research.

Allelic variation in estrogen receptor genes may act on depressive symptoms through several mechanisms, including through transcription, metabolism, and genetic expression of neurotransmitter systems. Estrogen receptors are expressed in numerous biological systems, including several brain regions. ESR2 in particular is found in high concentration in the hippocampus, entorhinal cortex and thalamus, regions that are involved in mood regulation [49,4]. Animal models have documented that the effects of estradiol on depressive symptoms are mediated by ESR2 activation [50,51]. Allelic variations in these genes are functional and found to influence gene expression as well as transcription factor binding [52,40]. As such, variation in ESR genes that regulate cellular concentration of estrogen and estrogen response may underlie the association between polymorphism variation and major depression observed in the present study and other studies. The specific role of these alleles in the regulation and metabolization of estrogen remains inadequately understood. For example, some but not all [26,53–55] preliminary evidence indicates increased serum estradiol levels for those with the C allele of rs2234693; we found that C carriers in our adjusted regression analysis had decreased risk of chronic depression compared with homozygous T carriers.

Several limitations of the present study are noted. First, we are not examining onset of depression after PMH use; in fact most women will have had depression onset of depression prior to first use of PMH. As noted above, women with a history of depression may be more likely to be prescribed PMH during the transition through menopause. Thus, these analyses should be followed by analyses with more granular longitudinal depression information. Second, lifetime history of DSM-IV major depression was assessed retrospectively in 2007. Thus, there may be error in the reporting. However, this sample is well known for the accuracy of reporting of current health status [56,57]. While this does not preclude the potential for misclassification due to recall error, we note that women in the present sample are likely to be health conscious and thus the validity of prior health status information may be better than samples of non-health professionals. On that note, we acknowledge that the present sample is comprised of nurses, and may not be representative of the general population of women with respect to depressive symptoms. Further, we conducted analyses among non-Hispanic White women who comprised the majority of the sample, as variation in ESR2 genes differed by race; thus, results may also not be generalizable to women with other ethnic and racial backgrounds. Finally, we note that we found a significant association between allele frequency and median household income of the census tract. While there is no plausible explanation for a causal effect of allele frequency on household income, we note that such an association limits our ability to conclude that the genetic allele frequency

distributions are relatively random in the population. However, we controlled for median household income in all analyses due to the observed association.

In summary, the present study supports the hypothesis that estrogen receptor polymorphisms influence risk for major depression, including novel data on the role of ESR2 polymorphisms, which are understudied. Both the genetic architecture and the hormonal underpinnings of major depression and other common psychiatric disorders remain inadequately understood; the role of estrogen receptors and other sex steroid-related genetic factors may provide unique insights into etiology. Examination of exogenous sources of moderation of the effects of such genes, such as PMH use, is increasingly recognized as important not only for etiological understanding of the actions of genes but also for pharmacogenetic specificity for the treatment of major depression.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Declaration of Interest:

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Table 1

Demographic and covariate distribution of ESR1 and ESR2 polymorphisms in the analytic sample, N=2,527

		ESR-alpha						ESR-beta					
		RS2234693			RS9340799			RS1256049			RS4986938		
		CC	CT	TT	AA	GA	GG	GG	GA/AA	GG	GA	AA	
	Total sample	N=511	N=1254	N=682	N=1046	N=1128	N=280	N=2361	N=148	N=990	N=1168	N=300	
	%	%	%	%	%	%	%	%	%	%	%	%	
US Census Tract Median Household Income	<\$40,000	9.4	10.1	8.5	10.4	9.8	9.3	9.9	9.4	9.6	10.3	7.0	
	\$40-49,999	19.9	20.0	19.5	20.4	21.0	19.2	17.5	19.8	21.2	17.6	18.1	
	\$50-64,999	31.0	31.5	30.9	31.4	30.9	30.7	31.0	30.6	38.4	31.8	30.4	
	\$65-79,999	18.1	19.4	18.6	16.3	17.1	18.1	19.7	18.2	14.4	18.2	18.1	
	\$80,000+	21.7	19.1	22.7	21.6	21.2	22.7	21.9	22.1	16.4	22.1	26.4	
		$\chi^2=6.3$, df=8, p=0.62						$\chi^2=3.3$, df=8, p=0.91					
Highest parental education in childhood	High school or less	48.2	48.1	48.8	47.7	49.8	47.1	44.9	43.8	48.6	47.8	49.6	45.8
	Some college	26.4	24.7	27.3	25.0	24.8	28.5	25.2	32.2	26.0	25.5	26.2	28.1
	College or more	25.4	27.2	23.9	26.7	25.2	24.5	29.9	24.0	25.5	26.7	24.2	26.1
		$\chi^2=3.4$, df=4, p=0.50						$\chi^2=6.8$, df=4, p=0.14					
Age (in 2007)	40-44	3.4	4.3	3.0	3.2	3.3	3.0	5.5	3.4	3.4	3.4	3.3	
	45-49	17.5	15.1	18.8	17.0	18.0	18.0	16.1	17.6	15.8	18.8	17.6	14.7
	50-54	36.6	37.4	34.6	38.3	37.6	36.0	34.7	36.1	40.4	37.1	36.2	35.8
	55-59	36.5	35.8	38.0	35.6	35.2	37.1	36.9	36.8	35.6	34.8	36.7	41.1
	60+	6.0	7.4	5.6	5.9	5.9	6.0	6.9	6.1	4.8	6.0	6.1	5.0
		$\chi^2=10.0$, d.f.=8, p=0.27						$\chi^2=6.4$, d.f.=8, p=0.60					
Post menopausal hormone (PMH) use	Any	62.0	60.3	63.4	62.5	62.3	61.9	60.8	61.5	72.7	60.9	62.4	63.7
	None	38.0	39.7	36.6	37.5	37.7	38.1	39.3	38.5	27.3	39.1	37.6	36.3
	<2 years	33.1	28.8	33.8	34.4	36.0	31.4	31.0	33.3	30.4	33.5	33.0	31.0

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		ESR-alpha						ESR-beta					
		RS2234693			RS9340799			RS1256049			RS4986938		
		CC	CT	TT	AA	GA	GG	GG	GA/AA	GG	GA	AA	
	Total sample	N=511	N=1254	N=682	N=1046	N=1128	N=280	N=2361	N=148	N=990	N=1168	N=300	
		%	%	%	%	%	%	%	%	%	%	%	
		43.4	36.0	31.0	32.6	36.4	43.0	35.8	37.3	38.2	34.7	35.9	
	2-8 years	27.8	30.2	34.6	31.4	32.3	26.0	30.9	32.4	28.3	32.3	33.2	
		31.0											
		$\chi^2=12.2, d.f.=4, p=0.02$			$\chi^2=8.1, d.f.=4, p=0.09$			$\chi^2=0.4, df=2, p=0.84$					
								$\chi^2=3.2, d.f.=4, p=0.52$					

Table 2

Prevalence of lifetime major depression as well as chronic major depression by ESR1 and ESR2 polymorphisms, among non-Hispanic Whites in a subsample of the Nurses Health Study (N=2,527)

		N	% with lifetime major depression		% with lifetime chronic major depression	
			% = 30.2		% = 10.3	
			%	Chi-square, df, p-value	%	Chi-square, df, p-value
ESR1	RS2234693	CC	31.7	$\chi^2=1.8$, df=2, p=0.40	10.0	$\chi^2=4.6$, df=2, p=0.10
		CT	28.7		9.0	
		TT	30.7		12.0	
	RS9340799	AA	30.5	$\chi^2=2.6$, df=2, p=0.28	10.8	$\chi^2=1.2$, df=2, p=0.55
		GA	29.0		9.7	
		GG	34.0		9.5	
ESR2	RS1256049	GG	29.7	$\chi^2=1.7$, df=1, p=0.19	10.1	$\chi^2=0.3$, df=1, p=0.57
		GA/AA	34.9		11.5	
		GG	29.1		9.1	
	RS4986938	GA	28.5	$\chi^2=7.2$, df=1, p=0.02	9.3	$\chi^2=9.2$, df=2, p=0.01
		AA	36.7		14.7	

Association between ESR1 and ESR2 polymorphisms and lifetime major depression as well as chronic major depression, among non-Hispanic Whites in a subsample of the Nurses Health Study (N=2,527)

Table 3

		Chronic major depression		Major depression	
		Unadjusted	Adjusted for household income	Unadjusted	Adjusted for household income
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
ESR1	RS2234693	CC	1.12 (0.79, 1.58)	1.11 (0.79, 1.57)	1.16 (0.92, 1.45)
		CT	Ref	Ref	Ref
		TT	1.38 (1.03, 1.85)*	1.37 (1.02, 1.84)*	1.10 (0.89, 1.35)
	RS9340799	AA	1.12 (0.85, 1.47)	1.12 (0.85, 1.47)	1.07 (0.88, 1.30)
		GA	Ref	Ref	Ref
		GG	0.98 (0.63, 1.51)	0.97 (0.63, 1.51)	1.26 (0.95, 1.68)
	RS1256049	GG	Ref	Ref	Ref
		GA/AA	1.15 (0.71, 1.88)	1.13 (0.70, 1.85)	1.25 (0.87, 1.80)
ESR2	RS4986938	GG	0.98 (0.74, 1.31)	0.98 (0.73, 1.30)	1.03 (0.85, 1.24)
		GA	Ref	Ref	Ref
		AA	1.68 (1.16, 2.45)**	1.71 (1.18, 2.48)**	1.46 (1.11, 1.92)**

* p<0.05;

** p<0.01

Table 4

Prevalence of lifetime major depression as well as chronic major depression by ESR1 and ESR2 polymorphisms among non-Hispanic Whites in the Nurses Health Study subsample stratified by lifetime post-menopausal hormone use (N=2,435)

		ESR1 genes															
		% lifetime major depression				% lifetime chronic major depression				% lifetime major depression							
		RS2234693								RS9340799							
		CC	CT	TT	CC	CT	TT	AA	GA	GG	AA	GA	GG				
PMH Use	N	%	%	%	%	%	%	%	%	%	% (N)	%	%				
	Ever	1510	32.6	29.7	36.9	11.3	8.7	15.0	35.7	28.8	34.7	12.7	9.5				
	Never	925	31.0	25.8	21.1	8.5	8.5	7.3	22.5	27.7	34.6	7.8	9.4				
P-value for interaction		unadj p=0.01, adj p=0.02				unadj p=0.08, adj p=0.08				unadj p=0.007, adj p=0.007				unadj p=0.11, adj p=0.10			
Length of PMH use among users	< 2 years	493	25.6	29.7	32.9	8.6	9.3	14.7	31.1	28.5	30.6	12.4	8.8	11.8			
	2-8 years	535	31.4	28.1	41.0	10.0	7.5	16.8	39.8	25.6	30.6	13.3	8.3	11.4			
	8+ years	462	41.8	31.5	37.0	15.8	9.5	13.5	36.8	32.7	44.9	12.2	11.5	14.1			
P-value for interaction		unadj p=0.29, adj p=0.19				unadj p=0.51, adj p=0.38				unadj p=0.26, adj p=0.12				unadj p=0.88, adj p=0.69			

		ESR2 genes															
		% with lifetime major depression				% with lifetime chronic major depression				% with lifetime major depression							
		RS1256049								RS4986938							
		GG	GA/AA	GG	GA/AA	GG	GA/AA	GG	GA	AA	GG	GA	AA				
PMH Use	N	%	%	%	%	%	%	%	%	%	%	%	%				
	Ever	1510	31.5	41.2	10.8	14.8	31.0	31.2	38.1	9.8	10.5	14.7	14.7				
	Never	925	26.5	20.6	8.7	4.8	25.6	23.9	34.9	7.8	7.2	14.7	14.7				
P-value for interaction		unadj p=0.09, adj p=0.12				unadj p=0.20, p=0.24				unadj p=0.70, adj p=0.69				unadj p=0.59, adj p=0.61			
Length of PMH use among users	< 2 years	493	29.2	42.1	10.7	18.0	30.0	28.1	39.4	1.0	9.8	20.2	20.2				
	2-8 years	535	31.2	41.3	10.2	12.5	29.9	30.8	41.9	8.6	9.9	13.5	13.5				
	8+ years	462	34.0	41.1	11.5	14.5	33.5	35.0	30.2	10.9	12.0	9.6	9.6				

		ESR2 genes								
		% with lifetime major depression		% with lifetime chronic major depression		% with lifetime major depression		% with lifetime chronic major depression		
		RS1256049				RS4986938				
		GG	GA/AA	GG	GA/AA	GG	GA	AA	GA	AA
	years									
P-value for interaction		unadj p=0.89, adj p=0.94		unadj p=0.85, adj p=0.81		unadj p=0.42, adj p=0.30		unadj p=0.52, adj p=0.41		

Unadj=unadjusted; Adj=adjusted for age, parental education, and median income of participant's census tract