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Research Article

Moderation of Breastfeeding Effects on Adult Depression by Estrogen Receptor Gene Polymorphism

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Breastfeeding is known to benefit both the mother's and the child's health. Our aim was to test the interactive effects between estrogen receptor 1 (ESR1) rs2234693 and breastfeeding when predicting the child's later depression in adulthood. A sample of 1209 boys and girls from the Young Finns Study were followed from childhood over 27 years up to age 30–45 years. Adulthood depressive symptoms were self-reported by the participants using the Beck Depression Inventory. Breastfeeding as well as several possibly confounding factors was reported by the parents in childhood or adolescence. Breastfeeding tended to predict lower adult depression, while ESR1 rs2234693 was not associated with depression. A significant interaction between breastfeeding and ESR1 was found to predict participants' depression ($P = .004$) so that C/C genotype carriers who had not been breastfed had higher risk of depression than T-allele carriers (40.5% versus 13.0%) while there were no genotypic differences among those who had been breastfed. In sex-specific analysis, this interaction was evident only among women. We conclude that child's genes and maternal behavior may interact in the development of child's adult depression so that breastfeeding may buffer the inherited depression risk possibly associated with the C/C genotype of the ESR1 gene.

1. Introduction

Depression is a major mental health problem in western countries, affecting working-age young adults in particular [1]. The etiology of depression is complex and involves genetic, neurobiological, psychological, and social factors. Furthermore, recent research has demonstrated that adult vulnerability to depression may have its origins already in early childhood [2], which emphasizes the value of life-course studies of depression.

A large research literature has investigated the potential role of maternal behavior in the development of children's mental and behavioral problems. In particular, breastfeeding

has been shown to have beneficial effects for children's physical health and cognitive development [3–5]. Emerging evidence suggests that breastfeeding might also have favorable effects on children's mental health. In a study on 5-year-olds, breastfeeding duration was associated with lower prevalence of children's mental health problems [6]. Other studies demonstrated that children who had not been breastfed in infancy had a higher risk for clinical depression in early adulthood [7] and hostility in adulthood [8].

However, genetic background may determine, in part, the sensitivity and responsiveness of individuals to environmental influences. For instance, in a study of breastfeeding

and children's cognitive development, a polymorphism of the FADS2 gene (rs174575) was observed to moderate the beneficial effect of breastfeeding so that only individuals carrying the C allele of the FADS2 benefitted from breastfeeding and had higher IQ than those who had not been breastfed [9]. Genetic effects such as this may help to explain inconsistencies between different studies that have not taken genetic background into account.

In the present study, we hypothesized that a similar moderating genetic effect by estrogen-related gene might be observed in the association between breastfeeding and adult depression of offspring. We concentrated on a gene affecting estrogen functioning, estrogen receptor 1 (ESR1). Estrogen, and especially estrogen receptor functioning, has been linked to major mental health problems, for example, schizophrenia [10, 11] and depression [11, 12], and estrogen is related to breastfeeding and might therefore influence the maternal effect of breastfeeding. Estrogen receptor 1 (ESR1) gene codes for estrogen receptor α , and the ESR1 PvuII is a functional polymorphism suggestively associated with severe mental health problems [13], for example, psychosis [10] and depression [14, 15]. In a sample of individuals diagnosed with schizophrenia, the CC genotype of the ESR1 PvuII polymorphism was associated with lower expression of ESR1 mRNA in the prefrontal cortex [16], which may lead to an inability to respond normally to brain estrogen. However, breastfeeding and maternal care associated with it might buffer against this risk. High maternal care has been shown to increase levels of estrogen receptor α mRNA in female rat offspring [17, 18]. In addition, breastfeeding might increase levels of oxytocin which has been shown to increase the expression of estrogen receptor α in prairie voles [19]. Thus, it is plausible that breastfeeding increases the expression of ESR1 mRNA directly or indirectly (via oxytocin) also in human brain.

The aim of this longitudinal, prospective cohort study is to test whether there is an association between breastfeeding and adult depression of offspring and whether this association is moderated by the ESR1 genotype. We hypothesized that the coincidence of environmental and genetic risk factors is most detrimental to the child's mental health, that is, that individuals who carry the possibly vulnerable CC genotype and who lack the buffering maternal effect (i.e., breastfeeding) against it, are in especially high risk to developing depression.

2. Methods

2.1. Participants. The present study is part of a prospective longitudinal study known as the Cardiovascular Risk in Young Finns Study, which started in 1980 with 3596 participants: boys and girls from age groups of 3, 6, 9, 12, 15, and 18 years. Participants were derived from rural and urban surroundings in different parts of Finland to ensure geographical representativeness of the Finnish population. Complete details of the cohort have been published elsewhere [20, 21]. There have been seven followups of the same participants, and the present study utilizes the baseline and

first (in year 1983), fourth (in year 1992), fifth (in year 1997), sixth (in year 2001), and seventh (in year 2007) followups. The study was approved by local ethics committees, and all participants gave their written informed consent.

The present sample consisted of 725 women and 484 men (1209 total participants) for whom data on the ESR1 genotype, breastfeeding in childhood, and adult depression at age 30–45 were available. Those selected for the final sample were younger (37.2 versus 37.56 years, $P = .05$), more often women (60.0% versus 46.4% $P < .001$), had higher educated mother (10.2 versus 9.9 years, $P = .001$), had more often nuclear family background (89.9% versus 83.1% $P < .001$), earlier birth order (2.0 versus 2.2 $P = .003$) and fewer siblings (2.7 versus 2.8 $P = .016$) than those who due to missing data were left out from the analyses.

2.2. Measures

2.2.1. Depressive Symptoms. Depressive symptoms were self-reported by the participants in 2007 when they were 30–45 years old using two different versions of the Beck Depression Inventory (BDI): (1) in the original 21-item BDI-II, for each item the participants choose from 4 alternative response statements the most suitable one (scored from 0 to 3), and the sum of these responses is calculated. Here, the BDI-II was scored both as a continuous and a dichotomous variable. The categorization of the latter was based on the previously established cut-off point for clinical depression ($0 = 0–13$, $1 = 14–63$) [22]. (2) In a modified version of the BDI, which has been used in several previous studies of the present cohort [23–26], participants rated 21 items of the second mildest statements of the original BDI instrument using a 5-point Likert-type scale and the mean of these responses was calculated. The modified BDI scale was also measured in 1992, 1997, and 2001, when participants were 15–30, 20–35, and 24–39 years old. Thus, the depression outcomes included (1) continuously coded BDI-II score, (2) dichotomously coded BDI-II clinical depression, and (3) continuously coded depressive symptoms of the modified BDI instrument.

2.2.2. Breastfeeding. In 1983 parents of the participants reported (1) whether the participants had been breastfed as infants ($0 = \text{no}$, $1 = \text{yes}$) and (2) the duration of breastfeeding in months. The questions of breastfeeding did not differentiate between partial and exclusive breastfeeding. Although the assessment of breastfeeding was retrospective, it has been shown that mothers' reports of breastfeeding history after 20 years are highly reliable and valid [27]. In Finland, practically all mothers and infants are regularly checked in antenatal clinics during pregnancy and in child health centers after birth from where parents get the child's personal record card with them. Thus, parents can check the information regarding breastfeeding from the participant's personal record cards obtained from child health centers. In a previous study with the present cohort, breastfed men were shown to have better brachial endothelial function than formula fed-men [28], supporting the validity of the breastfeeding measure.

2.2.3. ESR1 rs2234693 Genotyping. Genomic DNA was extracted from peripheral blood leukocytes using a commercially available kit and Qiagen BioRobot M48 Workstation according to the manufacturer's instructions (Qiagen Inc., Hilden, Germany). Estrogen receptor 1 (ESR1, rs2234693) polymorphism was genotyped by employing the 5' nuclease assay and fluorogenic allele-specific TaqMan MGB probes [29], using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA, USA) and commercially available TaqMan assay (assay ID C_3163590_10). The samples were pipetted using an automated TECAN Freedom EVO-100 instrument (Tecan Group Ltd., Männedorf, Switzerland). The PCR reactions containing genomic DNA, $1 \times$ Universal PCR Master Mix, 900 nM of each primer, and 200 nM of each probe are performed in 384-well plates using the standard protocol in a total volume of 5 μ L. End-point fluorescence is measured after PCR and genotype calling carried out by the allelic discrimination analysis module (ABI Prism SDS software, ABI, Foster City, CA, USA). Random duplicates were used as quality control.

2.2.4. Covariates. Mother's age at childbirth, her educational years, the family structure (1 = nuclear family versus 0 = single-parent household or child of only one of the parents), number of children in family, and birth order of the child (all assessed in 1980) were included as covariates because they may have affected the mother's decision to breastfeed and indicate wider family atmosphere. Child's birth weight and whether the child was born full term (1 = full term 0 = preterm) were also taken into account.

2.3. Statistical Analyses. When predicting continuously coded depression scores, the main effects of breastfeeding and ESR1, and the interaction effect between the two, were assessed with analysis of covariance, adjusted for participants' age and sex. For the dichotomous BDI-II, the corresponding analysis was carried out using logistic regression analysis. The models were then further adjusted for maternal age at childbirth, maternal educational years, family structure, number of children in family, participant's birth order, birth weight, and whether the participant was born full term. Sex differences in the ESR1-breastfeeding interaction effect were tested with three-way interactions between sex, breastfeeding, and ESR1 genotype. Given that the repeated measurements of the modified BDI were available for 4 measurement times, we also fitted a multilevel regression model in which all the measurement times were pooled together and each participant could contribute 1 to 4 person-observations to the dataset. Multilevel regression modeling takes into account the nonindependence of the observations in calculating standard errors of the estimates. All the analyses were conducted using PASW 18.0 software.

3. Results

Descriptive statistics for the sample are shown in Table 1. Age- and sex-adjusted partial correlations between the study variables are shown in Table 2. Having been breastfed at

infancy was related to younger age of mother, being born full term, and having higher birth weight. Longer duration of breastfeeding was related to older mothers, later birth order, and higher number of children in the family.

Table 3 shows mean levels of depression by breastfeeding status and ESR1 genotype, which suggest no consistent main effects for these variables. There was a tendency for breastfeeding to be associated with a lower depression risk, particularly with depression assessed with the continuously coded BDI-II scores, but this association was not observed with other measures of depression.

Next we examined the interaction effects between ESR1 and breastfeeding in predicting depression. There was a significant interaction effect when predicting continuous BDI-II score ($F(2, 1201) = 5.47, P = .004$) and a marginally significant interaction effect in the same direction when predicting dichotomous BDI-II $P = .071$ (TC:OR (95% CI) = 0.74 (0.18–3.01) $P = .67$; CC:OR (95% CI) = 5.18 (0.92–29.14) $P = .06$; breastfed TT carriers as the reference category) and the modified BDI score ($F(2, 1201) = 2.28, P = .102$). The age- and sex-adjusted interaction effects are illustrated in Figure 1. Among participants who had not been breastfed, individuals carrying the C/C genotype had higher risk of BDI-II depression (40.5% versus 13.0%), higher BDI-II mean scores (12.80 versus 5.74), and higher modified-BDI mean scores (2.55 versus 2.11) when compared to combined group of carriers of T/T and T/C genotypes. The C/C genotype was not associated with increased depression risk in participants who had been breastfed. Stated the other way around, the interaction effect indicated that breastfeeding was associated with lower risk of depression in those carrying the C/C genotype but not associated with depression in carriers of T/T or T/C genotypes. These interaction effects were little affected when the models were further adjusted for childhood covariates (continuous BDI-II score ($F(2, 1194) = 5.50, P = .004$), BDI-II $P = .074$ (TC:OR (95%) = 0.75 (0.18–3.09) $P = .70$; CC:OR (95%) = 5.35 (0.93–30.82) $P = .06$; breastfed TT carriers as the reference category), and modified BDI score ($F(2, 1194) = 2.37, P = 0.094$).

Statistically significant three-way interaction effects between sex, breastfeeding status, and ESR1 were observed when predicting continuous BDI-II ($F(2, 1196) = 4.93, P = .007$), and modified BDI ($F(2, 1196) = 4.58, P = .010$). However, when predicting dichotomous BDI-II the three-way interaction was not observed ($P = 0.47$). When the above analyses were fitted separately in men and women, the interaction effect was observed only in women (Figure 2). In women who had not been breastfed in infancy, carriers of the C/C genotype had higher risk of BDI-II depression (59.8% versus 13.9%), higher BDI-II mean scores (19.46 versus 6.37), and higher modified-BDI mean scores (3.20 versus 2.12) than those carrying the T/T or T/C genotype.

In addition, when testing whether the interaction between ESR1 genotype and breastfeeding would replicate when predicting modified BDI in different years, replication was found when predicting BDI in 1992 ($F(2, 1300) = 4.86, P = .008$) and 2001 ($F(2, 1294) = 3.28, P = .038$). Although the interaction was not statistically significant when predicting modified BDI in 1997 ($F(2, 1151) = 1.322$,

TABLE 1: Characteristics of the study group ($N = 1209$).

Variable	Total sample $N = 1209$		Women $N = 725$		Men $N = 484$		P value [‡]
	Value ^{†a}	Range	Value [†]	Range	Value [†]	Range	
Family and childhood variables							
Maternal age at childbirth	27.30 (5.57)	16–48	27.15 (5.67)	16–48	27.52 (5.41)	18–46	.254
Maternal educational years	10.23 (3.16)	2–22	10.10 (3.05)	2–22	10.43 (3.31)	4–22	.079
Family structure [§]							.315
Nuclear family	1087 (89.9)		657 (90.6)		430 (88.8)		
Other	122 (10.1)		68 (9.4)		54 (11.2)		
Birth order	2.00 (1.40)	1–14	2.01 (1.42)	1–11	1.98 (1.37)	1–14	.663
Number of children in family	2.65 (1.60)	1–15	2.70 (1.68)	1–14	2.59 (1.47)	1–15	.238
Birth status [§]							.599
Full term	1059 (87.6)		638 (88.0)		421 (87.0)		
Premature	150 (12.4)		87 (12.0)		63 (13.0)		
Birth weight	3501 (527)	1040–5750	3463 (518)	1300–5250	3558 (535)	1040–5750	.002
Breastfeeding status [§]							.063
Breastfed	1122 (92.8)		681 (93.9)		441 (91.1)		
Not breastfed	87 (7.2)		44 (6.1)		43 (8.9)		
Duration of breastfeeding	3.82 (3.67)	0–36	3.99 (3.87)	0–36	3.57 (3.33)	0–36	.048
Participant's adulthood variables							
Sex [§]							
Male	484 (40.0)						
Female	725 (60.0)						
Age in 2007	37.21 (4.91)	30–45	37.18 (4.91)	30–45	37.26 (4.91)	30–45	.768
ESR1 PvuII [§]							.052
T/T	420 (34.7)		246 (33.9)		174 (36.0)		
T/C	595 (49.2)		375 (51.7)		220 (45.5)		
C/C	194 (16.0)		104 (14.3)		90 (18.6)		
Depressive symptoms in 2007	2.06 (0.66)	1.00–4.67	2.12 (0.67)	1.00–4.67	1.97 (0.64)	1.00–4.63	<0.001
BDI in 2007 (continuous)	5.24 (6.41)	0–46	6.13 (6.79)	0–46	3.92 (5.58)	0–40	<0.001
BDI in 2007 (dichotomous) [§]							.001
Depression	127 (10.5)		93 (12.8)		34 (7.0)		
No depression	1082 (89.5)		632 (87.2)		450 (93.0)		

[†] Values are means (and standard deviations) unless otherwise indicated.

[‡] Gender differences, Pearson's chi-square for categorical variables, t -ratio for continuous variables.

[§] Values are numbers (and percentages) of participants.

$P = .267$), the association was in same direction. Pooling the 4 measurement times into a single multilevel model resulted in a dataset with 5017 person-observations from 1603 unique participants. In a multilevel regression, the interaction between ESR1 genotype with breastfeeding predicted modified BDI in both only age- and sex-adjusted ($F(2, 1613) = 3.59, P = 0.028$) and fully adjusted ($F(2, 1612) = 3.69, P = 0.025$) models. The three-way interaction effect between sex, breastfeeding status, and ESR1 was statistically significant ($F(2, 1621) = 4.721, P = 0.009$), implying that those women who had CC genotype and who had not been breastfed had higher modified-BDI mean score (2.93 versus 2.19) than T-allele carriers who had been breastfed, as suggested by the regression models for depressive symptoms in 2007 (Figure 2).

4. Discussion

The present study appears to be the first to show that an interaction between breastfeeding status and gene polymorphism may predict the development of child's depression later in life. The results suggest that whether or not the child is breastfed may modify the effect of estrogen receptor 1 (ESR1) rs2234693 on depression 30 to 45 years later in life. Those who were not breastfed and had the C/C genotype had especially high risk of developing depression compared to other groups. Gender differences were also observed, the effect being evident only among women. The interaction effect was independent of a number of childhood covariates reflecting early developmental environment.

TABLE 2: Age- and sex-adjusted correlations between variables.

	1	2	3	4	5	6	7	8	9	10	11	12
(1) Maternal age at childbirth												
(2) Maternal educational years	-.06*											
(3) Nuclear family	.07*	-.02										
(4) Birth order	.57***	-.21***	.04									
(5) Number of children in family	.36***	-.15***	.10**	.80***								
(6) Full term	.04	-.04	.08**	.09**	.05							
(7) Birth weight	.08**	-.01	.07*	.11***	.06*	.43***						
(8) Breastfed	-.10***	.03	.03	.01	.03	.19***	.18***					
(9) Duration of breastfeeding	.15***	-.04	-.00	.18***	.13***	.08**	.08**	.29***				
(10) ESR1 PvuII	.03	.02	-.01	.02	-.02	.00	.07*	.03	-.01			
(11) Depressive symptoms in 2007	-.02	-.02	-.03	-.00	.01	.00	-.02	-.04	.04	-.03		
(12) BDI in 2007 (continuous)	-.02	.01	-.04	-.02	-.03	-.00	-.03	-.06*	.04	.00	.75***	
(13) Clinical depression (BDI)	-.03	.02	-.03	-.02	-.03	-.02	-.03	-.05	.01	-.01	.58***	.78***

*** $P < 0.001$, ** $P < 0.01$, and * $P < 0.05$.

TABLE 3: Age- and sex-adjusted main effects of breastfeeding and ESR1 predicting depression.

	BDI-II dichotomous depression		BDI-II continuous depression		BDI modified depression	
	OR (95% CI)	<i>P</i>	Mean (std. error)	<i>P</i>	Mean (std. error)	<i>P</i>
Breastfeeding		.054		.047		.151
Yes	1.00		5.14 (0.19)		2.05 (0.02)	
No	1.82 (0.99–3.36)		6.55 (0.68)		2.16 (0.07)	
ESR1 genotype		.872		.766		.486
T/T	1.00		5.33 (0.31)		2.09 (0.03)	
T/C	0.93 (0.62–1.40)		5.11 (0.26)		2.04 (0.03)	
C/C	0.86 (0.48–1.54)		5.45 (0.46)		2.04 (0.05)	

Breastfeeding may affect child’s depression through at least two different mechanisms. There may be a direct nutritional link from breast milk to child’s hormone and neurotransmitter functioning. Breastfeeding is known to affect child’s brain development through nutritional processes involving fatty acids [30], and this effect might be mediated via hormonal processes. On the other hand, breastfeeding may be a proxy measure of maternal behavior toward the child or of a wider family atmosphere [31]. Breastfeeding mothers may be more child-oriented, have more contact with the child, and be more sensitive and less hostile toward the child. It has been suggested that mothers have higher oxytocin release after breastfeeding, and this may intensify mother’s bonding to the infant [32]. Other suggestions assume that some mothers are bonded to the infant before birth, but not all [33]. A study reported that first reaction towards their newborns among about 40 percent of first time mothers was indifference, but this was changed to affection in a week among most of the mothers [34]. Thus breastfeeding may be especially important to the maternal bonding among those whose bonding did not develop during pregnancy. Early suckling and skin-to-skin contact have been shown to predict better mother-infant interaction in one year of age as well as more self-regulated and less irritable children [35]. Thus, the idea of sensitive period shown in many other species may also be

relevant in humans. Oxytocin is hypothesized to increase in both the mother’s and the infant’s brain when the infant starts to suckle the mother’s nipple in skin-to-skin contact after birth [36, 37]. At least among rats, suckling alters brain functioning similarly as oxytocin administration as was observed in a study utilizing functional magnetic resonance imaging [38]. Skin-to-skin contact in form of massage has also shown to decrease aggression among preschool children [39], which might be related to oxytocin effects.

Oxytocin, on the other hand, alters estrogen expression, at least among prairie voles [19]. Lower expression of ESR1 mRNA may be related to many major mental health problems. C/C genotype of ESR1 rs2234693 is suggested to be “a risk genotype” related to schizophrenia and other psychoses [10, 16] and might relate to other mental health problems, like depression [14], as well. It is possible that C/C genotype carriers have inherited a vulnerability to mental health problems, which however might be neutralized by breastfeeding. Breastfeeding may increase the expression of ESR1 mRNA among C/C genotype carriers, who initially seem to have a low expression of ESR1 mRNA, and thus buffer the risk related to mental health problems among C/C genotype carriers. Finally, as estrogen is a known female sex-hormone, the observed sex difference could be expected because estrogen might be suggested to be a more important

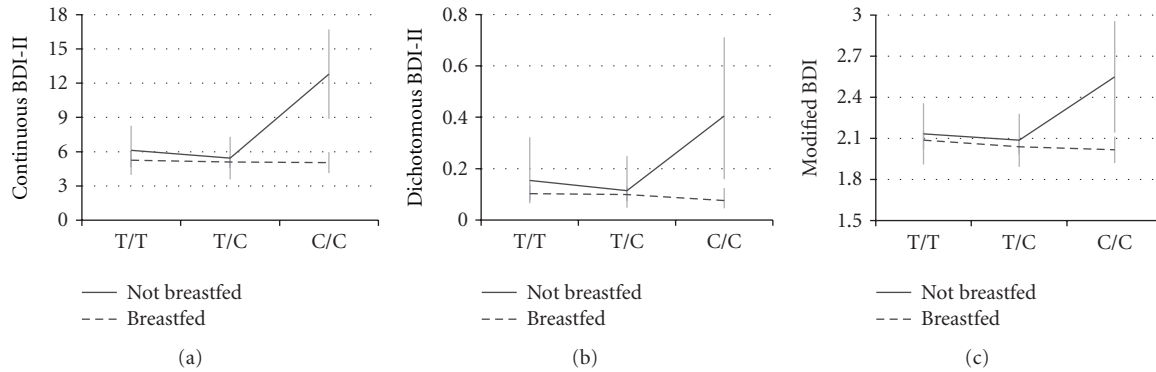


FIGURE 1: Adult depression by estrogen receptor 1 genotype (ESR1) and being breastfed at infancy. The vertical lines are 95% confidence intervals.

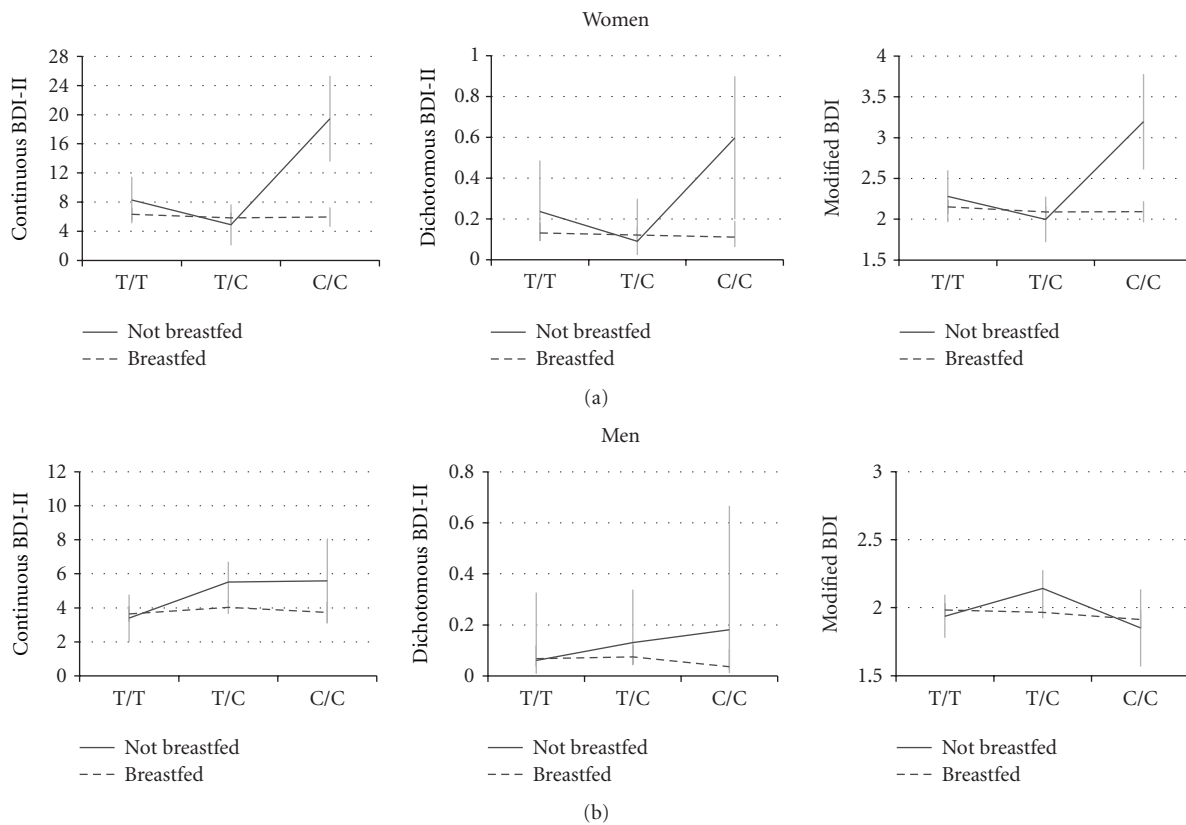


FIGURE 2: Adult depression by estrogen receptor 1 genotype (ESR1) and being breastfed at infancy separately in women and men. The vertical lines are 95% confidence intervals.

determinant of depression vulnerability in women than in men [40].

There are study limitations that need to be taken into account when interpreting the results. First, we could not control mothers' depression or their genetic background, which might introduce confounding into the results. Depressed mothers may be more reluctant to breastfeed [41, 42] and depression may pass from the mother to her child either via environmental factors or due to shared genetic background. Second, breastfeeding was assessed retrospectively when participants were 6–21 years old. However,

maternal reports of duration of breastfeeding 20 years later have been shown to have high validity [27]. Third, due to selective dropout, those included in the final sample had a more advantageous family background, which may limit the generalizability of the results. In addition, the number of participants carrying the C/C genotype and who were not breastfed was relatively small ($n = 10$) which increases the risk that the present results might be due to chance. Replication of these findings is therefore essential.

Our study benefits from a large population-based sample followed over a long period of time and from the use of

two different measures of depressive symptoms. Depressive symptoms were self-reported by the participants in adulthood in 30–45 years of age while breastfeeding was reported by the participants' mothers over two decades before when participants were 6–21 years old, which reduces the influence of common informant bias to the results.

In conclusion, the present study suggests that child's genes and maternal behavior interact in the development of child's adult depression. Breastfeeding—and possibly the maternal care associated with it—may confer a protective effect especially to individuals who may have inherited a possible susceptibility to mental health problems in the form of specific estrogen receptor genotype.

Abbreviations

ESR1 gene:	Estrogen receptor 1 gene
FADS2 gene:	Fatty acid desaturase 2 gene
IQ:	Intelligence quotient
mRNA:	Messenger ribonucleic acid
BDI:	Beck's Depression Inventory.

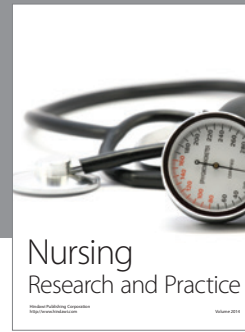
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