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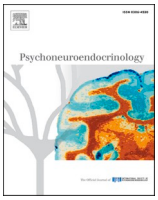

Predictors of irritability symptoms in mildly depressed perimenopausal women

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ABSTRACT

Objective: Irritability is a highly burdensome complaint, commonly, but not universally, linked with depressive symptoms. While increased variability in estradiol has been associated with depressive symptoms during perimenopause, more insight is needed into reproductive hormone dynamics and other factors that predispose perimenopausal women to irritable mood.

Methods: Among 50 mildly depressed perimenopausal women (mean (SD) age 48.4 (3.9) years), severity of irritability symptoms (on Symptom Questionnaire Hostility subscale, range 0–23) was assessed weekly for eight weeks, concurrent with potential predictors. Associations between these were examined using generalized estimating equating models.

Results: Most women (82.0%) reported having moderate to severe irritability at least once. However, the severity of irritability was highly variable from week-to-week (between-subject mean coefficient of variation [CV] 72.9% and within-subject mean CV 63.7%). In multivariate analyses, less variable serum estradiol levels (standardized β within-person CV −0.23 95%CI [−0.32, −0.14], $p < 0.001$), greater depression severity (0.45 [0.35, 0.56], $p < 0.001$), younger age (−0.23, [−0.28, −0.09], $p < 0.001$), and more frequent vasomotor symptoms (0.14 [0.05, 0.23], $p = 0.002$) were associated with more irritability. Depression severity explained the largest portion of the variance in irritability, but still not more than 20.3%. Neither crude values, weekly change in, or variability of progesterone or FSH levels were associated with irritability.

Conclusions: Irritability was highly prevalent among mildly depressed perimenopausal women. In contrast to depressive symptoms, decreased rather than increased variability in estradiol levels was associated with more irritability. This highlights that irritable mood can be disentangled from depressive symptoms in perimenopausal women and might be linked with different estradiol dynamics.

1. Introduction

Irritability, defined as a low threshold for experiencing frustration or anger, is prevalent during the perimenopause (Freeman et al., 2008; Bromberger et al., 2003; Mauas et al., 2014). Perimenopausal women complain 41.2% more often about irritability compared to premenopausal women (Bromberger et al., 2003). Though often coincidental with depression (Fava et al., 2010), irritability is a distinct dysphoric mood state (Toohey and DiGiuseppe, 2017). Its presence decreases quality of life, (Berk et al., 2017) and is associated with greater severity

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of depressive symptoms (Perlis et al., 2009). In addition to this personal burden, irritability, more than depressive symptomatology, may provoke excessive frustration among others (Reinares et al., 2006). Unfortunately, identification of underlying processes that predispose perimenopausal women to irritability, has garnered little attention. Patterns of reproductive hormones are of particular interest as the perimenopause is characterized by more marked fluctuations of serum estradiol, alternating with periods of sustained lower and unchanging levels of estradiol, resulting in less predictable ovulation (Hale et al., 2014; Butler and Santoro, 2011). Moreover, previous research has shown that greater variability in estradiol levels (Freeman et al., 2006; Gordon et al., 2016a, 2016b; Joffe et al., 2020), and absence of ovulation as measured with progesterone (Joffe et al., 2020), is associated with more depressive symptomatology during the perimenopause.

Three large studies have examined risk factors for irritability, defined using a single question, in midlife women transitioning from pre- to post-menopause (Freeman et al., 2008; Bromberger et al., 2003, 2001). Only one of these, the Penn Ovarian Aging Study, investigated reproductive hormone patterns (Freeman et al., 2008). This study showed that mean levels of estradiol or follicle stimulation hormone (FSH) obtained every nine to twelve months over nine years were not associated with concurrent moderate to severe irritability (Freeman et al., 2008). However, measuring hormone levels approximately annually does not capture the dynamics of the perimenopause, and other hormones of interest, such as progesterone, were not examined. The two other studies that investigated menopause-related risk factors for irritability in women across the menopausal transition originated from the Study of Women's Health Across the Nation (SWAN) cohort. Here it was shown that more frequent vasomotor symptoms (VMS) and difficulty sleeping were associated with higher odds of severe irritability (Bromberger et al., 2003, 2001).

Together, insight in menopause-related factors and specific hormone dynamics that predispose perimenopausal women to irritability is limited, but much needed. In the current study, we sought to determine which characteristics influence vulnerability to irritability as part of a dysphoric mood presentation during the perimenopause. To accomplish this, we conducted an eight-week observational study in perimenopausal women with untreated depressive symptoms, whereby weekly assessments of reproductive hormones and other predictors were obtained concurrent with assessment of irritability and depressive symptoms using well validated questionnaires.

2. Methods

2.1. Participants

Data were derived from 50 perimenopausal women who were enrolled in an eight-week observational study. Perimenopausal status was defined using the Stages of Reproductive Aging Workshop (STRAW) criteria (Harlow et al., 2012). Subjects were included based on mild-to-moderate depressive symptoms defined as a score 10–25 on the Montgomery-Åsberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), and/or moderate irritability, defined as a score > 7.7 on the Hostility scale of the Symptom Questionnaire (SQ) (Kellner, 1987) to ensure that the sample represented the rich variety of mood symptoms that manifest during the perimenopause. Details of exclusion criteria are described in our previous work reporting the association of estradiol and progesterone variability with depressive symptoms severity (Joffe et al., 2020). All participants provided written informed consent for study procedures, which were approved by the Partners HealthCare Institutional Review Board and conducted at Massachusetts General Hospital and Brigham and Women's Hospital. The dataset is comprised of 420 visits collected in 50 women in whom information on irritability occurring during the past week was available.

Every week, women rated their level of irritability for the preceding seven days. Irritability was measured using the 23-item Hostility scale of the SQ (Kellner, 1987). Items were rated as yes or no, and a total score was calculated by summing up the individual item scores (range 0–23). A higher score indicates more irritability, and a score > 7.7 is indicative of at least moderate irritability (Kellner, 1987). The SQ has been validated and found to be highly sensitive in detecting irritability in populations characterized by subclinical affective symptoms (Kellner, 1987; Benasi et al., 2020). Internal consistency was good in previous studies (Kellner, 1987; Grussu and Quatraro, 2013) and at our baseline assessment (Cronbach's alpha $= 0.87$). To provide insight into the variability of irritability within and between women, both within-person coefficient of variation (CV) ([personal SD irritability $\text{scores}_{\text{visit 1–9}}$ / personal mean irritability $\text{scores}_{\text{visit 1–9}}$]*100%) and between-person CV ([population SD irritability $\text{scores}_{\text{visit 1–9}}$ / population mean irritability $\text{scores}_{\text{visit 1–9}}$]*100%) were calculated. However, absolute irritability scores were used for the prediction model as the dependent variable, as described below.

2.2. Hormonal predictors

Serum levels of estradiol were measured weekly by liquid chromatography-mass spectrometry (LC-MS) (Mayo Clinic, Rochester, NY), with 10 pg/ml as the lower limit of detection and an inter-assay coefficient of variation of 8.6%. Participants with values below the detection limit (14 participants with 83 datapoints [19.7% of all data points]) were imputed with the value of 9 pg/ml. As a sensitivity analyses, measures were imputed with a different method. To this, we replaced the left-censored data (observations that are not quantified, but are known to be less than the detection limit) by a random draw from a distribution computed between zero and the lower limit of detection, imputing it using a log-transformation of the distribution (range of imputation from minus infinity to log10 pg/ml) (Helsel, 2011). Serum progesterone was measured by chemiluminescence immunoassays (Abbott Architect ci8200 and Beckman Coulter, Fullerton, CA). The lower level of detection of the assays was 0.10 ng/ml and 0.08 ng/ml, respectively. Serum follicle stimulation hormone (FSH) was measured by a chemiluminescence immunoassay (Ab bott Architect ci8200) that had a lower level of detection of 0.05 IU/l. The inter-assay CVs of the progesterone and FSH assays were $\leq 10\%$. From these values, we investigated three different hormonal predictors. The first contained the crude hormone levels. The second comprised a measure of variability of estradiol, progesterone and FSH within an individual woman. This within-person CV was calculated by dividing the within-subject standard deviation [SD] of hormone $\text{level}_{\text{visit 1–9}}$ by the within-subject mean hormone $\text{level}_{\text{visit 1–9}}$ multiplied by 100%. The third comprised a value of weekly changes in hormone levels which was calculated by subtracting the value of hormone $\text{level}_{\text{visit x-1}}$ from the value of hormone $\text{level}_{\text{visit x}}$. This way, we tested whether the magnitude of change in hormone levels over the preceding week was associated with irritability levels during that same week.

2.3. Other predictors

At baseline, age, race, education, measured body mass index (BMI), recent stressful events, and lifetime history of Major Depressive Disorder (MDD) were collected. Race was collected as "Caucasian" ($n = 30$, 60.0%), "Black" ($n = 18$, 36.0%), "Native American" ($n = 1$, 2.0%), and "Asian" ($n = 1$, 2.0%). For model simplicity however, race was dichotomized into Caucasian versus non-Caucasian. Whether participants obtained a college degree was used to define education level. Lifetime MDD history was assessed by psychiatrists using an unstructured clinical interview. Number of recent stressful life events were self-reported using Life Experience Survey (LES) (Sarason et al., 1978). Severity of depressive symptoms was assessed weekly using the 10-item clinician-rated MADRS (ranges from 0 to 60, higher scores indicating higher severity). A score of 7–19 and 20–34 is commonly used to indicate mild and moderate depression, respectively (McDowell, 2006).

Subjective daily VMS were assessed consistent with our previous approach, averaging number of VMS for the preceding week based on daily diary reporting (Joffe et al., 2020). Bi-weekly, participants completed the 7-item self-rated Insomnia Severity Index (ISI) questionnaire to measure the severity of insomnia over the last two weeks (Bastien et al., 2001). As scores reflected the severity of insomnia of the past two weeks, scores were used during two adjacent assessments to match the frequency of the weekly assessed predictors and outcome.

2.4. Statistical analyses

Sample characteristics were presented with means ± standard deviation (SD), median with Interquartile Range (IQR), or by frequencies with percentages, dependent on the type and distribution of the variable. As the data involved multiple within-person observations, we used generalized estimating equation (GEE) models with robust standard errors to determine the association of potential predictors with irritability, accounting for within-woman correlation (Herring, 2013). GEE models with different covariance structures were fitted using restricted maximum likelihood estimation, with "unstructured" chosen based on the Quasi-Akaiki Information Criterion. All GEE models were adjusted for the time between visits, and both independent (if not dichotomous) and dependent variables were standardized by subtracting the sample mean of the variable and dividing the result by the variable's sample SD (z-scoring) to ease comparability of the strengths of the associations.

First, we examined which variables predicted irritability. After univariate models were determined, multivariate models were examined by adjusting for predictors that achieved statistical significance in univariate analyses. For all these analyses, missing datapoints on estradiol (n = 2, 0.5%), FSH (n = 1, 0.2%), progesterone (n = 5, 1.2%), severity of depressive symptoms (n = 1, 0.2%), VMS (n = 61, 14.5%), or severity of insomnia (n = 56, 13.3%) were not imputed. Hence, these missings reduced the amount of available datapoints for some of the univariate models, and the multivariate model. Finally, the explained variance of irritability by variables that were significant in the multivariate analyses was determined by calculating the R2 of each of the variables (standardized β variable^2*100%).

Two post-hoc analyses were conducted. We first explored whether within-person mean estradiol might confound the association between variability of estradiol and irritability because the within-person CV is affected substantially by the mean value for each participant. To account for this possibility, we added within personal-mean estradiol to the multivariate model. In a separate analysis, we explored to what extent the direction of the association between the weekly changes in estradiol and irritability varied between women, consistent with a recent study (Gordon et al., 2020). We calculated for each woman the association of both crude and absolute values of weekly changes in estradiol with irritability and examined whether the association for each women was best described by absolute changes (increase and decrease in estradiol) or crude changes (increase or decrease, depending on the direction of the β) based on which β was largest in magnitude for a given woman.

Statistics were conducted using RStudio (R version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria, 2016. URL: https://www.R-project.org/), with main packages '*gee*' (version 4.13–19), '*gmodels*' (version 2.18.1), and '*ggplot2*' (version 3.2.1) packages. As multiple tests were performed, we calculated an adjusted False Discovery Rate [FDR] P cut-off value to avoid the inflation of false-positive findings. A P-value of < 0.017 was considered statistically significant.

3. Results

3.1. Sample characteristics

The characteristics of 50 perimenopausal women in the study are shown in Table 1. Subjects had a mean (SD) age of 48.4 (3.9) years and were on average slightly overweight (mean BMI [SD], 27.6 [6.6]). Most women (82.0%) reported having moderate to severe irritability at least once during follow-up. On average, irritability severity was within the subclinical range (median irritability score 5.5, IQR 3–9), but it differed substantially week-to-week, both between and within individual women. On average, the values of between-person variability over the eight-week study period (mean CV 72.9%) were greater than the within-person variability over the same timespan (mean CV 63.7%). Although one quarter (28.0%) of women had a history of MDD, the entire sample was only mildly depressed during the 8-week study (mean MADRS score 10.8 [6.5]).

3.2. Univariate analyses

Results of univariate and multivariate analyses are shown in Table 2 and Fig. 1. In univariate analyses, less variability in estradiol and higher depression severity were each associated with more irritability (standardized β for within-person CV estradiol −0.12 with 95% Confidence Interval [CI] [−0.20, −0.03], p < 0.007, and for depression severity 0.40 [0.311, 0.49], p < 0.001). More frequent VMS, younger age, and higher BMI each significantly predicted more irritability (standardized β [95%CI] 0.12 [0.02, 0.21], p = 0.015, −0.12 [−0.21, −0.04], p = 0.005, and 0.24 [0.15, 0.34], p < 0.001, respectively). Neither absolute values, nor weekly changes in levels of estradiol, progesterone and FSH were predictive of irritability. Variability in progesterone and FSH were also not associated with irritability.

Table 1
Characteristics of 50 perimenopausal women.

	Perimenopausal women (n = 50)	
	Mean / No.	SD / %
Age, mean (SD), y	48.4	3.9
Race, no. Caucasian (%)	27	54.0
Education, no. college degree (%)	22	44.0
BMI (kg/m^2), mean (SD)	27.2	6.6
Lifetime history of MDD, no. (%)	14	28.0
Depression severity (MADRS), mean (SD)	10.8	6.5
VMS frequency, mean (SD)	2.6	3.1
Insomnia severity (ISI), mean (SD)	10.6	5.1
Serum reproductive hormone levels		
Estradiol, mean (SD), pg/ml	86.6	101.0
Progesterone, mean (SD), ng/ml	2.0	4.2
FSH, mean (SD), IU/L	34.5	36.6
One-week change estradiol, mean (SD), pg/ml[a]	0.1	103
One-week change progesterone, mean (SD), ng/ml[a]	0.1	5.5
One-week change FSH, mean (SD), IU/L[a]	-0.2	12.2
Variability estradiol, mean (SD)[b]	76.6	41.4
Variability progesterone, mean (SD)[b]	107.0	69.9
Variability FSH, mean (SD)[b]	49.1	25.0
Irritability severity (Hostility scale SQ), mean (SD)	6.4	4.8
Visits with at least moderate irritability (Hostility scale SQ >7.7), no (%)	143	44.6

Abbreviations: BMI, body mass index (calculated as weight in kilograms / by height in meters squared); FSH, follicle stimulating hormone; ISI, Insomnia Severity Index; MADRS, Montgomery-Åsberg Depression Rating Scale; SQ, Symptom Questionnaire; VMS, Vasomotor symptoms

To convert estradiol pg/ml to pmol/l multiply by 3.67. To convert progesterone ng/ml to nmol/l multiply by 3.18.

Age, Caucasian race, college graduate, BMI, history of MDD were determined at study entry. All other variables were assessed at every visit.

[a] Differences in hormone levels between two successive visits (hormone level$_{visit\ x}$ – hormone level$_{visit\ x\text{-}1}$).

[b] Within-person coefficient of variation ([within-subject standard deviation [SD] of hormone level$_{visit\ 1–9}$ / within-subject mean hormone level$_{visit\ 1–9}$]* 100%).

Table 2
Associations of potential predictors with severity of irritability symptoms in 50 perimenopausal women with mild-to-moderate depressive symptoms.

	Irritability (Hostility scale SQ)					
	Univariate[a]			Multivariate[b]		
	β	95% CI	p	β	95% CI	p
Sex hormones						
Estradiol	-0.03	-0.11, 0.06	.58			
Progesterone	-0.04	-0.14, 0.05	.37			
FSH	0.02	-0.14, 0.09	.69			
Variability estradiol[d]	-0.12	-0.20, -0.03	.007	-0.23	-0.32, -0.14	< .001
Variability progesterone[d]	-0.003	-0.10, 0.09	.94			
Variability FSH[d]	-0.07	-0.16, 0.02	.13			
One-week change estradiol[c]	0.08	-0.01, 0.18	.09			
One-week change progesterone[c]	-0.01	-0.10, 0.08	.78			
One-week change FSH[c]	0.05	-0.07, 0.17	.42			
Age	-0.12	-0.21, -0.04	.005	-0.23	-0.32, -0.14	< .001
Caucasian race	-0.04	-0.24, 0.15	.64			
Education	-0.13	-0.32, 0.07	.20			
Stressful life events	0.06	-0.16, 0,03	.19			
BMI	0.24	0.15, 0.34	< .001	0.12	0.02, 0.21	.017
VMS frequency	0.12	0.02, 0.21	.015	0.14	0.05, 0.23	.002
Insomnia severity	0.12	0.02, 0.22	.02			
Depression severity	0.40	0.31, 0.49	< .001	0.45	0.35, 0.56	< .001
Lifetime history of MDD	0.04	-0.18, 0.27	0.70			

Abbreviations: BMI, body mass index (calculated as weight in kilograms / by height in meters squared); FSH, follicle stimulating hormone; SQ, Symptom Questionnaire; VMS, Vasomotor symptoms
Estimates are standardized B-coefficients determined by generalized estimating equation analyses.
[a] Adjusted for days between visits.
[b] Adjusted for [a] and for predictors that achieved statistical significance in univariate analyses
[c] Crude differences in hormone levels between two successive visits (hormone $level_{visit\ x}$ – hormone $level_{visit\ x\text{-}1}$)
[d] Within-person coefficient of variation ([within-subject standard deviation [SD] of hormone $level_{visit\ 1–9}$ / within-subject mean hormone $level_{visit\ 1–9}$]* 100%)

3.3. Multivariate analyses

In multivariate analyses, lower estradiol variability, worse depression severity, younger age, and more frequent VMS remained independently associated with more irritability (standardized β [95%CI] −0.23 [−0.32, −0.14], $p < 0.001$, 0.45 [0.35, 0.56], $p < 0.001$, −0.23 [−0.32, −0.14], $p < 0.001$, 0.14 [0.05, 0.23], $p = 0.002$, respectively). See also Table 2 and Fig. 1. Depression severity explained the largest proportion of the variance in irritability (20.3%), followed by age and estradiol variability (both 5.3%), and VMS frequency (2.0%).

3.4. Sensitivity analyses

A different imputation approach for estradiol levels below the detection limit did not change the findings meaningfully (data not shown).

3.5. Post hoc analyses

We explored whether the within-person mean estradiol might confound the association between variability of estradiol and irritability. As shown in Fig. 2, there was a positive association between the mean and SD in estradiol levels for each participant. However, addition of mean estradiol to the multivariate model did not change the effect size of estradiol variability on irritability symptoms (change in β within-person CV estradiol = 0.0%). Variability in estradiol still significantly predicted irritability (standardized β [95%CI] −0.23 [−0.31, −0.14], $p < 0.001$), but mean estradiol levels did not (−0.08 [−0.15, −0.001], $p = 0.05$).

As a second post-hoc analysis, we explored whether inter-individual differences in the direction of the associations between the weekly changes in estradiol and irritability might explain why the overall variability variable of estradiol was a predictor of irritability, but the weekly change variable was not (Gordon et al., 2020). The within-woman association of both crude and absolute values of weekly changes in estradiol with irritability varied greatly between women in strength and direction (range β for crude values of weekly changes: −26.50 to 5.09; for absolute values of weekly changes: −3.10 to 4.00). Analysis of the largest association in magnitude for each woman showed that some were sensitive to increases of estradiol (8.5%), some to decreases of estradiol (8.5%), and some to either increases or decreases (6.4%). However, for the majority (76.6%) of women, these associations were not significant.

4. Discussion

Irritability was highly prevalent in this cohort of mildly depressed perimenopausal women with weekly assessments over eight weeks. Women who had less variable serum estradiol levels, more frequent VMS, or who were younger, reported more irritability, associations that were independent of depression severity. Our results emphasize that irritability is an important symptom domain in mild depression during the perimenopause which can be disentangled from depressive symptoms and have hormonal risk factors that do not match those of depressive symptoms.

The finding that less variable estradiol levels, in contrast to crude levels, were predictive of more irritability, underlines the importance of measuring hormone serially in order to capture their dynamics, rather than obtain a single hormone level value. Importantly, the association was not driven by the propensity of low variability of estradiol to be accompanied by low mean levels of estradiol. Previous studies in perimenopausal women examining variability in estradiol in relation to the specific mood symptoms of irritability are lacking. We and others have shown that greater weekly estradiol variability is associated with more depressive symptoms (Gordon et al., 2016a, 2016b; Joffe et al., 2020). Hence, our findings might be extrapolated to suggest that, while suppression of estradiol variability might improve depressed mood, but not ameliorate irritability. This interpretation is supported by findings from two randomized controlled trials in 178 premenopausal and 725 early postmenopausal women, showing that estrogen supplementation improves depressive symptoms but worsens or does not have change irritability symptoms (Lundin et al. 2017; Gleason et al., 2015; Santoro et al., 2017). However, our findings are not consistent with those of a smaller trial (n = 16 for intervention and n = 18 for placebo) of perimenopausal depressed women showing that estradiol treatment improves both irritability and depressive symptoms more than placebo (Schmidt et al., 2000). Taken together, these findings suggest that

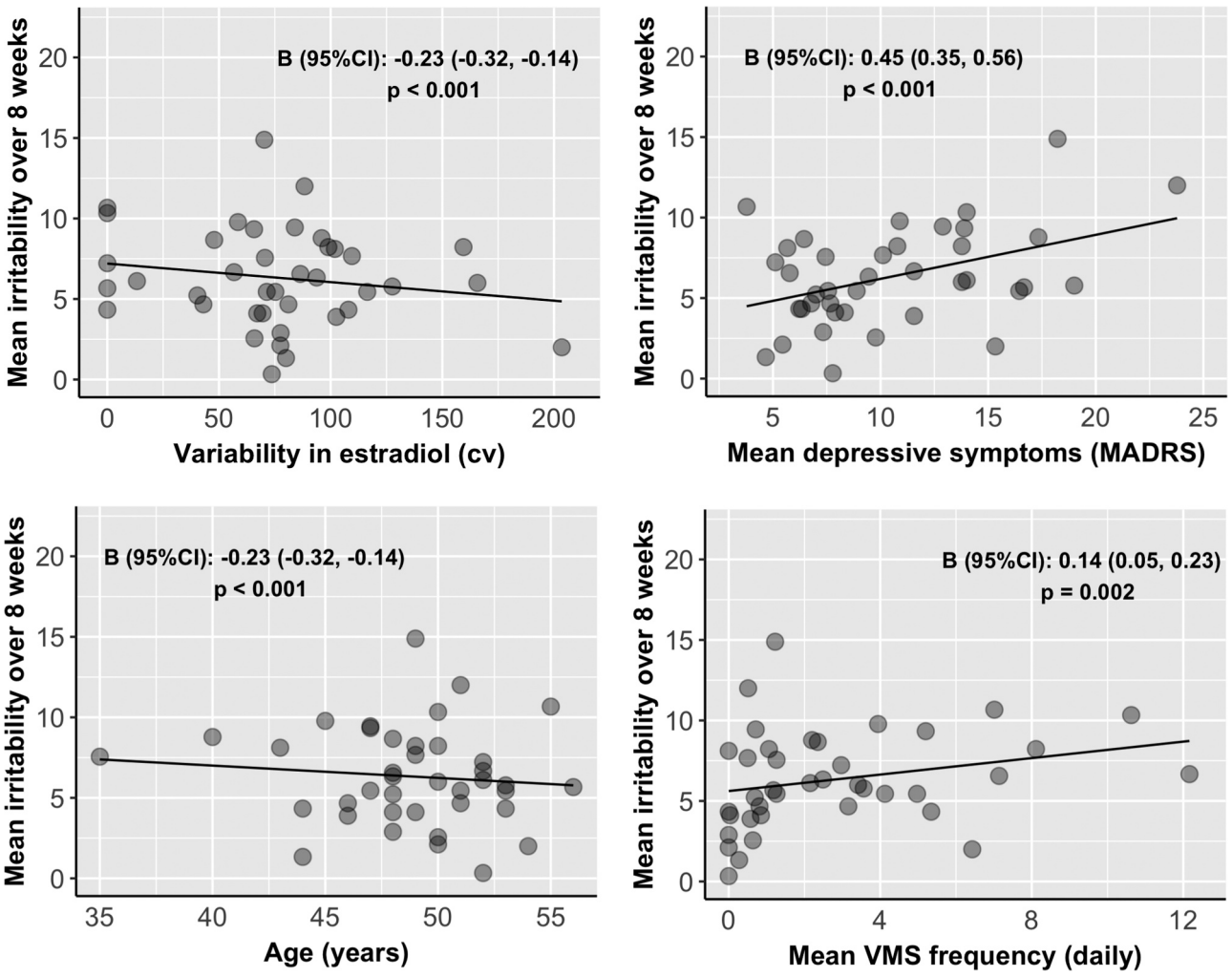

Fig. 1. Predictors of irritability that achieved the significance threshold in the multivariate analyses in 50 perimenopausal women with mild-to-moderate depressive symptoms. Abbreviations: cv, coefficient of variation; MADRS, Montgomery Åsberg Depression Rating Scale; VMS, vasomotor symptoms. Significant predictors of irritability in perimenopausal women in multivariate analysis. Regression lines were fitted. Note that this is a presentation of the mean raw data per participant and that this does not fully correspond with the way the data was analyzed (multilevel).

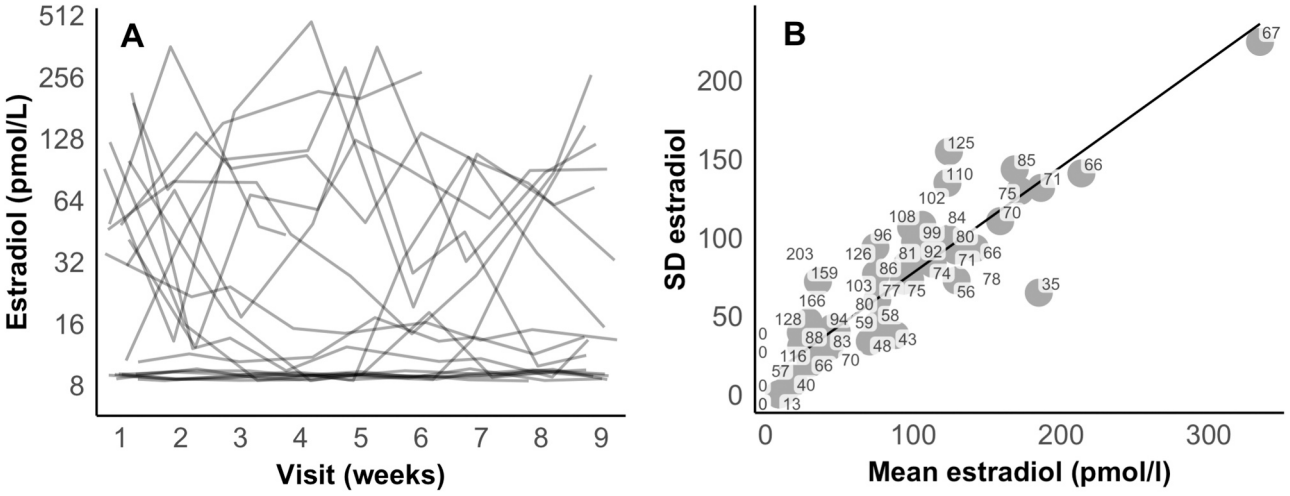

Fig. 2. Variability of serum estradiol levels over 8 weeks (a) and the association of mean serum estradiol levels with SD estradiol (b), showing that women with more variability in estradiol also have on average higher mean estradiol levels over the visits compared to women with less estradiol variability. Fig. A shows lines that represent serum estradiol levels within individual women selected from the upper and lower quintiles of the within-person coefficient of variation of estradiol (n = 20). Fig. B shows dots for the intersection of mean estradiol and the SD of estradiol for each of the participants (n = 50). The dots are labeled with the corresponding within-person coefficient of variation (in %) for estradiol.

different hormonal mechanisms may underlie irritability and depressive symptoms as mood symptoms that can be disentangled during the perimenopause, although further studies are needed to examine the specific mechanisms involved.

There are many potential ways through which estradiol may be involved in affect regulation and dysregulation. Evidence supporting this statement is reviewed in detail elsewhere (Rubinow and Girdler, 2011), but include the following: (a) Estradiol can regulate gene transcription by intracytoplasmic receptor binding. These estrogen receptors are predominantly located in regions of the limbic system, such as the amygdala (Barth et al., 2015). This system is important for emotion regulation and implicated in affective disorders such as depression, but also premenstrual dysphoric disorder (PMDD) in which irritability is a cardinal symptom (Wharton et al., 2012) (b). Estradiol can alter release of all classical neurotransmitters, such as serotonin (Barth et al., 2015). The role of serotonin in the pathophysiology of affective disorders is supported by numerous findings using indirect measures of central serotonin and its transmission (Wharton et al., 2012) (c). E2 modulates systems implicated in the pathophysiology of affective disorders such as the hypothalamic-pituitary-adrenal (HPA) axis and the immune system (Pitsillou et al., 2019). However, the exact mechanism underlying the results of the present study remain to be elucidated, and further speculation is beyond the scope of this publication.

The time span during which one might expect changes in estradiol to relate to irritability, is unknown. We observed that, in contrast with overall variability, week-to-week changes in estradiol were not associated with concurrent irritability levels. These findings suggest that weekly changes in estradiol do not explain changes in irritability during that same week. In studies of hormonal links with perimenopausal depressive symptoms, others (Gordon et al., 2020) have highlighted the importance of accounting for the between-women variability in the direction of the association between estradiol levels and mood, indicating that mood in some women may relate to changing levels regardless of the direction of the change while the direction of the change (increase versus decrease) might have a more important effect on mood for others. Hence, analyzing all women together, might "cancel out" a significant finding. We observed that a quarter of the women were sensitive to estradiol changes, but that the direction of the association between weekly estradiol change and irritability varied in direction and strength. While this variation in directions of the associations may have "cancelled out" an effect, the vast majority of women did not have any association of weekly change in estradiol level with irritability, which likely explains why we did not observe that irritability levels were associated with weekly estradiol changes.

In contrast to estradiol, progesterone levels were not associated with irritability. As the perimenopause is characterized by a reduction in progesterone peaks due to a reduction in the number of ovulatory cycles (O'Connor et al., 2009), our results suggest that sensitivity to variability in progesterone is not a risk factor for irritability during the perimenopause. Alternatively, we might not have been able to detect variability progesterone as levels were collected weekly, which may have missed an ovulatory peak in progesterone during the intervening days.

Our observation that during the study women reported irritability of at least moderate severity at almost half of the visits highlights how prevalent irritability is among perimenopausal women who are mildly depressed. Though depression severity was the strongest predictor of irritability, it explained less than a quarter of the variance of irritability, indicating that irritability and depressive symptoms, when measured with validated questionnaires, are correlated but commonly represent distinct mood states. Irritability is a unique mood symptom in that it is not considered a core diagnostic symptom of MDD among adults (AP Association, 2013). Moreover, MDD is typically characterized by apathy and flattened affect, the reverse of irritability. When women with MDD manifest irritability as one of the symptoms of a current depressive episode, they have more severe depressive and anxiety symptoms (Perlis et al., 2009), and are more likely to have a chronic course (Fava et al., 2010), and a lower quality of life (Perlis et al., 2005) than those with MDD but no irritability. In addition, early reductions in irritability predict favorable antidepressant treatment outcomes independently of depressive symptom severity (Jha et al., 2019). These observations suggest that depressive and irritability symptoms are often comorbid and each warrant therapeutic attention to optimize well-being in perimenopausal women with affective illness.

Non-hormonal risk factors for perimenopausal irritability, such as VMS and younger age, are consistent with those observed for depression severity during the perimenopause (Gordon et al., 2016a, 2016b; Bromberger et al., 2001, 2003, 2007, 2010; Avis et al., 1994). However, some predictors of depressive symptomatology, such as higher BMI, more stressful life events, and a history of MDD (Joffe et al., 2020; Bromberger et al., 2007; Gordon et al., 2016a, 2016b), were not predictive of irritability in our sample. Previous research showed that a history of premenstrual syndrome (PMS), rather than of MDD, is associated with irritability in women transitioning from pre- to postmenopause (Freeman et al., 2008), Unfortunately, we were unable to examine the association with PMS as retrospective reports about PMS were missing in half of our study population. However, it is possible that perimenopausal irritability may have more in common with a history of PMS, which uniquely has irritability as a cardinal symptom, than with previous MDD. This supports our observation that perimenopausal irritability and depression are overlapping dysphoric mood states which can be disentangled in both their psychiatric history associations and in their concurrent reproductive hormone dynamics.

Strengths of this study include the weekly, concurrent assessment of irritability and depressive symptoms, reproductive hormones, and other potential predictors of irritability in a well-characterized cohort of perimenopausal women. This is important because concurrent examination of predictors with the outcome provides more robust insight into the real-time risk factors for irritability symptom during this dynamic phase of a woman's life. To the best of our knowledge, this is the first study to investigate hormone dynamics rather than absolute levels in relation to irritability, a critical advance in our understanding given the nature of hormonal fluctuations in the perimenopause. In addition, estradiol was assayed using the gold-standard LC/MS, which has improved reliability over immunoassays in the low estradiol range (Demers, 2008). This study also has some limitations. First, use of observational data precludes any causal inference. Second, the weekly assessments of predictors and irritability didn't capture day-to-day variability. This may have limited the statistical power to measure within-person variability. Future studies should elucidate whether this difference in time-span is relevant. Finally, generalizability of results to pre- or postmenopausal women without mild-to-moderate depressive symptomatology might be limited owing to women's susceptibility for depressive symptomatology during the perimenopause and to the unique patterns of variability seen in reproductive hormones during this reproductive transition.

Findings from this study reveal the high prevalence of irritability in mildly depressed perimenopausal women. These women were more likely to report worse severity of irritability when they had less variable estradiol levels, were younger, and had more frequent VMS. Though some predictors overlap with those for depression severity, the decreased rather than increased variability in estradiol appears to be an irritability-specific risk factor. Although our findings need to be replicated, our results indicate that an irritable mood among depressed perimenopausal women may be related to neural processes responding to a differential estradiol profile.

Declaration of competing interest

A.E. de Wit, Dr. Giltay, Dr. de Boer, M. Nathan, A. Wiley, and Dr. Crawford, report no financial relationships with commercials interests. H Joffe's research program is supported by grants from NIH, V Foundation, Merck, Pfizer, Que-Oncology, and NeRRe/KaNDy. H Joffe is also

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CRediT authorship contribution statement

Anouk E. de Wit: Writing - original draft; Formal analysis; Methodology; Conceptualization; Visualization; Validation; Investigation; Data curation. **Erik J. Giltay**: Writing - original draft; Formal analysis; Methodology; Supervision; Conceptualization; Visualization; Validation; Investigation. **Marrit K. de Boer**: Writing - review & editing; Conceptualization. **Margo Nathan**: Writing - review & editing; Conceptualization. **Aleta Wiley**: Project administration; Resources; Software; Data curation. **Sybil Crawford**: Writing - review & editing; Formal analysis; Methodology; Conceptualization. **Hadine Joffe**: Funding acquisition; Writing - review & editing; Methodology; Supervision; Conceptualization; Investigation.

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