Influence of Childhood Maltreatment, Adulthood Stressful Life Events, and Affective Temperaments on Premenstrual Mental Symptoms of Nonclinical Adult Volunteers

Yumi Wakatsuki1
Takeshi Inoue2
Naoki Hashimoto1
Yota Fujimura2
Jiro Masuya2
Masahiko Ichiki2
Hajime Tanabe3
Ichiro Kusumi1

1Department of Psychiatry, Hokkaido University Graduate School of Medicine, Sapporo 060-8638, Japan; 2Department of Psychiatry, Tokyo Medical University, Tokyo 160-0023, Japan; 3Department of Clinical Human Sciences, Graduate School of Humanities and Social Sciences, Shizuoka University, Shizuoka 422-8529, Japan

Background: Previous studies have shown that childhood maltreatment is associated with premenstrual dysphoric disorder (PMDD). In this study we analyzed how multiple factors, such as childhood maltreatment, affective temperaments, and adult life events influence the severity of premenstrual mental (PMM) symptoms in nonclinical adult volunteers from the community.

Methods: A total of 204 participants were recruited and administered the following self-administered questionnaire surveys: PMDD scale, visual analogue scale, Patient Health Questionnaire-9, Life Experience Survey, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego autoquestionnaire version, and the Child Abuse and Trauma scale. In addition to single and multiple regression analyses, structural equation modeling was used for the statistical analyses.

Results: A history of neglect indirectly predicted PMM symptoms through affective temperaments in nonclinical adult volunteers. Three affective temperaments (irritable, cyclothymic, and anxious) directly predicted PMM symptoms.

Conclusion: This study is the first to report that childhood maltreatment, particularly neglect, indirectly predicted PMM symptoms through affective temperaments. The results of our study suggest that affective temperament is a mediator of the influence of childhood maltreatment on PMM symptoms.

Keywords: premenstrual mental symptoms, neglect, childhood maltreatment, affective temperament, TEMPS-A, structural equation modeling

Introduction
Premenstrual syndrome (PMS) is common in women during their reproductive years. Premenstrual dysphoric disorder (PMDD), which affects 2–9% of women, is considered to be the most severe form of PMS. Menstruation-associated symptoms can affect a woman’s life negatively and have a profound effect on productivity. PMDD increases work absenteeism, and reduces work productivity and quality of life. With the promotion of the social advancement of women, PMDD has drawn further attention. PMDD is characterized by affective and physical symptoms similar to major depressive disorder (MDD), which occur during the last week of the luteal phase of the menstrual cycle and resolve soon after the onset of menstruation. These symptoms include irritability/anger, depression, sadness,
mood swings, anxiety, tension, fatigue, difficulty concentrating, decreasing interest, overeating, hypersomnia/insomnia, and feeling “out of control.” Distress and/or impairment is present in the areas of work, school, social activities, or relationships with others. PMDD is considered to be a disease showing atypical depressive symptoms before menstruation. It is categorized as a separate diagnostic entity of “depressive disorders” in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).4

Two major types of environmental factors, i.e., early life stress and adult stressful life events, are risk factors for depressive symptoms or MDDs.5–9 In particular, childhood maltreatment worsens the course of MDD and treatment response during depressive episodes.10 Similarly, childhood maltreatment increases the risk of PMS and PMDD.11–14

In our previous study using structural equation modeling (SEM), we reported that affective temperaments evaluated by the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego auto-questionnaire version (TEMPS-A)15 are strong mediators for the effect of childhood maltreatment on depressive symptoms of nonclinical adult volunteers.16 Affective temperaments are also mediators between childhood maltreatment and well-being in nonclinical adult volunteers.17 Moreover, there are positive and negative interactions between childhood maltreatment, affective temperaments, and life events in adulthood on depressive symptoms of nonclinical adult volunteers.18 These results suggest that affective temperament is a mediator and moderator for childhood maltreatment and depressive symptoms in nonclinical adult volunteers.

PMDD is expected to share common pathologies with depression. To our knowledge, there are no studies that have analyzed the association between premenstrual mental (PMM) symptoms, affective temperaments, childhood maltreatment, and adult life events using SEM. Therefore, in this study we investigated how affective temperaments, childhood maltreatment, and adult stressful life events influence the severity of PMM symptoms in nonclinical adult volunteers from the community using SEM and multiple regression analysis.

Subjects and Methods

Subjects

This research was part of a larger study, part of which has been reported,17 which was conducted between January 2014 and January 2015 on 1020 Japanese adult volunteers from the community. A total of 204 subjects participated in the present study and provided responses to the questionnaires. The inclusion criteria were as follows: a) female, b) 20–45 years old, and c) menstruating (excluding pregnancy or menopause). Finally, 204 female subjects, who provided complete responses, were analyzed. Six questionnaires and a questionnaire on demographic data (age, years of education, employment status, marital status, presence of offspring, past history of psychiatric diseases, presence of physical and gynecological diseases, age of menarche, regularity of menstrual cycle) were distributed. The questionnaires were returned anonymously to researchers by mail. All of the subjects gave us written informed consent. This study was approved by the ethics committees of Hokkaido University Hospital (study approval no. 013–0184) and Tokyo Medical University (study approval no. T2018–0080), and was performed in accordance with the Declaration of Helsinki.

Questionnaires

Miyaoka et al19 developed the PMDD scale, which was based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) and was modified from the premenstrual symptoms screening tool developed by Steiner et al.20 Women check the severity of their symptoms during the past year retrospectively on a 4-point Likert scale from 1 to 4 (1 = none, 2 = mild, 3 = moderate, 4 = severe). The PMDD scale is divided into 2 parts, section A consists of 12 PMDD symptoms, which we refer to as “PMM symptoms” in this study. If the subject answers “yes”, i.e., 2–4 points, for at least 1 symptom, she is required to answer section B, which consists of 5 items regarding menstruation-associated disruption of activities or relationships. For statistical analyses, we used summary scores of sections A and B, which were sums of the scores of all items in each section. Following the method of the PMDD scale, the following other tests were performed regardless of the timing of testing in relation to menstruation, as the timing was confirmed to not affect the results (data not shown).

The Visual Analogue Scale (VAS) is a self-completed questionnaire that asks subjects to indicate the severity of 11 PMDD symptoms of DSM-5 criteria9 on a 100-mm line (depression/hopelessness, anxiety/tension, affective lability, irritability/anger, decreased interest, difficulty concentrating, fatigability/lack of energy, change in appetite/specific food cravings, hypersomnia/insomnia, feeling “out of control”,
and physical symptoms) of at 2 timepoints, in the presence of the most severe symptoms during the week before and after their menstrual period. For statistical analyses, percentage changes in the average VAS scores of 11 items from the week after to the week before the menstrual period were used.

The Japanese version of Patient Health Questionnaire-9 (PHQ-9) is a self-administered questionnaire to assess the severity of depressive symptoms. This study used a summary score of a total of 9 items, which evaluates the severity of depressive symptoms.

The Japanese version of the Life Experiences Survey (LES), a self-reported questionnaire, was used to evaluate the impact of life events during the past year. Subjects evaluate the positive or negative perceived impact of the events at the time of occurrence. Using a 7-point scale (extremely negative [-3] to extremely positive [+3]), a positive-change score and negative-change score are calculated by summing the impact ratings of positive and negative impacts, respectively.

The Japanese version of TEMPS-A is a self-administered questionnaire (true = 2, false = 1; 109 items for men and 110 for women), measuring the 5 temperament subscales, i.e., cyclothymic, depressive, irritable, anxious, and hyperthymic.

The Child Abuse and Trauma Scale (CATS), a 38-item self-rating questionnaire, asks participants to rate how frequently a particular abusive experience occurred to them during their childhood and adolescence, using a scale of 0–4 (0 = never; 4 = always). The CATS consists of 3 subscales—neglect/negative home atmosphere, punishment, and sexual abuse. The average score of each subscale was used for the statistical analysis. This study used the Japanese version of the CATS.

Data Analysis
A structural equation model (SEM) was designed based on the hypothesis shown in Figure 1. In this model, PMM symptoms are predicted by childhood maltreatment, affective temperaments, and adult stressful life events. The latent variable “TEMPS-A” was composed of 3 observed variables (cyclothymic, anxious, and irritable temperaments). We conducted SEM analysis with the maximum likelihood estimation by Mplus version 7.4 (Muthén & Muthén, Los Angeles, CA, USA). Direct and indirect effects among all of the variables and their statistical significance were obtained. The comparative fit index (CFI), the Tucker-Lewis Index (TLI), and root mean square error of approximation (RMSEA) were used for the evaluation of the model fit. A CFI > 0.95, a TLI > 0.95, and an RMSEA < 0.08 indicated an acceptable fit; and a CFI > 0.97, a TLI > 0.97, and an RMSEA < 0.05 indicated a good fit.

The Wilcoxon rank sum test was used for the comparison of the summary scores of PMDD scale section A between the 2 categories of demographic characteristics. Spearman rank correlation coefficients and multiple regression analysis were used to analyze the correlation between variables.

In this study, we aimed to analyze the effects of multiple variables on PMM symptoms of the PMDD scale by multivariate analysis. Because 20 factors were considered to be independent variables, 200 subjects were required for the analysis. A p-value of less than 0.05 was considered to indicate a statistically significant difference between 2 groups.

Results
Characteristics of the Subjects
Demographic characteristics, PMDD scale, PHQ-9, CATS, TEMPS, and LES scores of the 204 subjects are shown in Table 1. Age, summary scores of section B and section A+B on the PMDD scale, percentage change score of total...
Table 1 Characteristics of the Subjects in This Study

| Characteristics or Measures | Value (Number or Mean ± SD) | Correlation with PMDD Scale (Section A) (ρ) or Effect on PMDD Scale (Section A) (Mean ± SD, Wilcoxon Rank Sum Test) |
|-----------------------------|-----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Age (years)                 | 32.4 ± 6.8                  | ρ = –0.15*                                                                                                                                  |
| Years of education          | 14.9 ± 1.7                  | ρ = 0.021                                                                                                                                         |
| Employment status           | 174: 30                     | Employed (22.3 ± 7.7) vs Homemaker: (23.1 ± 7.3), n.s.                                                                                     |
| Marital status              | 91: 113                     | Married (21.2 ± 6.4) vs Unmarried (23.4 ± 8.4), n.s.                                                                                      |
| Presence of offspring       | 73: 131                     | Yes (21.0 ± 6.3) vs No (23.2 ± 8.2), n.s.                                                                                                    |
| Past history of psychiatric disease | 16: 188                  | Yes (23.2 ± 7.9) vs No (22.3 ± 7.6), n.s.                                                                                                      |
| Comorbidity of physical disease | 24: 180                   | Yes (23.6 ± 7.9) vs No (22.3 ± 7.5), n.s.                                                                                                      |
| Comorbidity of gynecological disease | 14: 190                  | Yes (24.9 ± 9.7) vs No (23.2 ± 8.2), n.s.                                                                                                      |
| Age of first menstruation   | 12.4 ± 5.5                  | ρ = 0.04, n.s.                                                                                                                                |
| Regular menstrual period    | 152: 52                     | Yes (21.9 ± 7.7) vs No (23.9 ± 6.3), n.s.                                                                                                      |
| PMDD scale                  |                             |                                                                                                                                                  |
| Section A+B                 | 29.2 ± 9.5                  | ρ = 0.98**                                                                                                                                     |
| Section A                   | 22.4 ± 7.7                  |                                                                                                                                                  |
| Section B                   | 6.8 ± 2.6                   | ρ = 0.63**                                                                                                                                     |
| Average percentage change scores of 11 items of VAS | 313 ± 445                  | ρ = 0.38**                                                                                                                                     |
| PHQ-9 score                 | 4.6 ± 5.0                   | ρ = 0.46**                                                                                                                                     |
| CATS (average score)        |                             |                                                                                                                                                  |
| Neglect                     | 0.72 ± 0.64                 | ρ = 0.39**                                                                                                                                     |
| Punishment                  | 1.48 ± 0.63                 | ρ = 0.10, n.s.                                                                                                                                   |
| Sexual abuse                | 0.06 ± 0.23                 | ρ = 0.14*                                                                                                                                       |
| TEMPS-A (average score)     |                             |                                                                                                                                                  |
| Depressive                  | 1.38 ± 0.16                 | ρ = 0.27**                                                                                                                                     |
| Cyclothymic                 | 1.24 ± 0.20                 | ρ = 0.39**                                                                                                                                     |
| Hyperthymic                 | 1.23 ± 0.17                 | ρ = –0.07, n.s.                                                                                                                                   |
| Anxious                     | 1.23 ± 0.20                 | ρ = 0.39**                                                                                                                                     |
| Irritable                   | 1.16 ± 0.16                 | ρ = 0.37**                                                                                                                                     |
| LES (change score)          |                             |                                                                                                                                                  |
| Negative                    | 1.05 ± 2.76                 | ρ = 0.17*                                                                                                                                       |
| Positive                    | 0.84 ± 2.02                 | ρ = 0.12, n.s.                                                                                                                                     |

Notes: Data are presented as means ± SD or numbers. ρ = Spearman rank correlation coefficient. *p < 0.05, **p < 0.001, n.s.: not significant.

VAS scores, neglect and sexual abuse scores on the CATS, depressive, cyclothymic, anxious, and irritable temperament scores on the TEMPS-A, and the negative change score of LES significantly correlated with the summary scores of PMDD scale section A. Raw data of the VAS scores of 11 items are shown in Supplementary Table 1. In this study, none of the participants were interviewed by psychiatrists. However, based on the diagnostic
algorithmic threshold of the “PMDD scale” for the screening of PMDD proposed by Miyaoka et al (2009),19 10 subjects (4.9%) were estimated to have PMDD. This value is similar to the 5.9% reported by Miyaoka et al (2009), who screened 327 women having menstruation aged between 20 and 45 years.

Stepwise Multiple Regression Analysis of Summary Scores of PMDD Scale Section A

Table 2 shows the results of stepwise multiple regression analysis, in which the summary score of PMDD scale section A was the dependent factor, and the following were 20 independent factors: age, years of education, employment status (employed = 1, homemaker = 0), marital status (married = 1, unmarried = 0), presence of offspring (yes = 1, no = 0), past history of psychiatric disease (yes = 1, no = 0), past history of physical disease (yes = 1, no = 0), comorbidity of gynecological disease (yes = 1, no = 0), age of first menstruation, regularity of menstrual period (regular = 1, irregular = 0), average scores of CATS (neglect, sexual abuse, and punishment), average scores of TEMPS-A subscales (depressive, cyclothymic, hypothyric, anxious, and irritable temperament), and positive and negative change scores of LES. PHQ-9 and VAS were not included in the stepwise multiple regression analysis because these measures of depressive symptoms are similar to the summary score of PMDD scale section A. In stepwise multiple regression analysis, age, cyclothymic and anxious scores on the TEMPS-A, and a negative change score on the LES were significant predictors of a summary score of PMDD scale section A (p < 0.001, adjusted R² = 0.27). Multicollinearity was denied in this multiple regression analysis.

Correlation Between CATS Subscale Scores and Temperament Scores on the TEMPS-A

Scores of 4 temperaments, excluding the hypothyric temperament score, had moderate positive correlations with neglect score, and weak positive correlations with punishment score (Table 3). The sexual abuse score was weakly positively correlated with scores of depressive, anxious, and irritable temperaments.

Analysis of SEM Data

To analyze the association between the scores of CATS, TEMPS-A, LES, and the summary scores of PMDD scale section A, a structural equation model was built from the results of single and multiple regression analyses (Figure 2). The standardized direct path coefficients are shown in Figure 2.

A good fit of the model was obtained as follows: RMSEA = 0.037, CFI = 0.993, and TLI = 0.982. The standardized path coefficients with solid lines in Figure 2 were significant (p < 0.001–0.05). Three temperament scores (cyclothymic, anxious, and irritable) on the TEMPS-A and the negative change score on the LES were significant predictors for the severity of PMM symptoms. The effect of the neglect subscale of CATS on summary score of PMDD scale section A was indirect and mediated by 3 temperament scores on the TEMPS-A (indirect standardized path coefficient = 0.337, p < 0.001). The effects of the sexual abuse subscale score of CATS on the negative change score on the LES and the effects of the negative change score on the LES on the summary score of PMDD scale section A were significant, but the indirect and direct effects of the sexual abuse subscale score of CATS on the summary score of PMDD scale section A were not significant (indirect standardized path coefficient = 0.026, p = 0.09).

Hyperthyric temperament was not included in the latent variable “TEMPS-A”, as it did not correlate with the summary score of PMDD scale section A (Table 1) or with any subscale of the CATS (Table 3). In another model that added depressive temperament to the latent variable “TEMPS-A”, the fit indices were not satisfactory.

Discussion

This is the first study to our knowledge showing that a history of neglect indirectly, but not directly, predicts the severity of
PMM symptoms of nonclinical adult volunteers. Furthermore, the effect was mediated by affective temperaments on TEMPS-A in a SEM. Cyclothymic, irritable, and anxious temperaments directly predicted the severity of PMM symptoms, and the negative change score of the LES mildly, but significantly, predicted the severity of PMM symptoms.

The first concern of these results is the impact of childhood maltreatment on PMM symptoms. In this study, neglect and sexual abuse on the CATS were

|          | Neg  | Pun  | Sex  | Dep  | Cyc  | Hyp  | Anx  | Irr  |
|----------|------|------|------|------|------|------|------|------|
| Neg      | 1.00 | 0.35** | 0.19** | 0.53** | 0.49** | 0.02 | 0.52** | 0.54** |
| Pun      | 1.00 | 0.09 | 0.26** | 0.23** | 0.10 | 0.24** | 0.22** |
| Sex      | 1.00 | 0.14* | 0.11 | 0.07 | 0.14* | 0.18* |
| Dep      | 1.00 | 0.47** | −0.09 | 0.56** | 0.42** |
| Cyc      | 1.00 | 0.22** | 0.56** | 0.69** |
| Hyp      | 1.00 | −0.00 | 0.13 |
| Anx      | 1.00 | 0.59** |
| Irr      | 1.00 | 0.00 |

Notes: $\rho =$ Spearman rank correlation coefficient, $^* p < 0.05$, $^{**} p < 0.01$.
Abbreviations: Neg, neglect subscale; Sex, sexual abuse subscale; Pun, punishment subscale; Dep, depressive temperament; Cyc, cyclothymic temperament; Hyp, hyperthymic temperament; Anx, anxious temperament; Irr, irritable temperament.

Figure 2 Results of covariance structure analysis of the SEM. Childhood maltreatment (CATS), affective temperament (TEMPS-A), adult stressful life events (LES), and severity of PMM symptoms (summary score of PMDD scale section A) of 204 nonclinical adult volunteers were analyzed. Rectangles indicate the observed variables and the latent variable is shown as an oval. The arrows with solid lines represent statistically significant paths (single solid lines: $p < 0.05$, double solid lines: $p < 0.001$), and the broken lines show nonsignificant paths. The numbers beside the arrows show the standardized coefficients (minimum: −1, maximum: 1).
significantly and positively correlated with the severity of PMM symptoms in nonclinical adult volunteers upon single regression analyses. However, in multiple regression analysis, none of the scores of the childhood abuse subscales predicted the severity of PMM symptoms. On the other hand, in the SEM of this study, a neglect score on the CATS indirectly predicted the severity of PMM symptoms, although a direct effect was not significant. This result is consistent with the hypothesis of previous studies that childhood maltreatment is associated with the etiology of PMDD.\textsuperscript{11,13} Soydas et al reported that patients with PMDD had higher total Childhood Trauma Questionnaire scores as well as higher scores of emotional abuse/emotional neglect, physical abuse, and sexual abuse than healthy controls.\textsuperscript{13} Bertone-Johnson et al suggested that childhood maltreatment, particularly emotional abuse and physical abuse, increases the risk of moderate-to-severe PMS.\textsuperscript{11} It is unclear why only neglect was associated with PMM symptoms in our present study, but these findings are consistent with our previous studies on nonclinical depressive symptoms and major depression. In our previous studies on the nonclinical general adult population\textsuperscript{16} and MDD patients,\textsuperscript{28} only a neglect score on the CATS significantly predicted the severity of depressive symptoms and MDD diagnosis on multiple regression analysis and multiple logistic regression analysis, respectively. The results of recent meta-analysis suggested that psychological abuse and neglect, as well as physical abuse, were strongly associated with the outcome of depression, and sexual abuse was less strongly associated.\textsuperscript{29} These findings highlight the potential impact of the more “silent” types of childhood maltreatment (other than physical and sexual abuse) on the development of depression.

The second concern is the association between childhood maltreatment and affective temperaments. In our previous studies of a nonclinical general adult population\textsuperscript{16} and MDD patients,\textsuperscript{28} neglect score, but not punishment or sexual abuse scores on the CATS was a significant predictor of depressive, cyclothymic, irritable, and anxious temperaments on multiple regression analyses. On the other hand, hyperthymic temperament was not significantly correlated with any subscale of childhood maltreatment in these studies.\textsuperscript{16,28} Pompili et al reported that psychiatric inpatients with a history of childhood maltreatment had a higher incidence of irritable temperament traits than nonabused patients.\textsuperscript{30} Consistent with previous studies, our present study showed an association between childhood maltreatment and depressive, cyclothymic, irritable, and anxious temperaments on univariate analyses.

Regarding the association between affective temperaments and PMM symptoms, to our knowledge, there has been only 1 study that noted an association between cyclothymic temperament, but not other affective temperaments, on the Affective and Emotional Composite Temperament Scale and PMDD screened by a questionnaire.\textsuperscript{31} Partly consistent with their study, in the multiple regression analysis of the present study, cyclothymic and anxious temperaments on the TEMPS-A were significant predictors for high scores of PMM symptoms. Depressive, cyclothymic, irritable, and anxious temperaments significantly and positively correlated with PMM symptoms in single regression analyses whereas hyperthymic temperament did not. Similar findings of depressive symptoms have been reported in nonclinical subjects and patients with MDD in earlier studies.\textsuperscript{16,28,32} Rovai et al noted that hyperthymic temperament, which is considered the most functional and desirable of the temperaments, is different from cyclothymic, depressive, irritable, and anxious temperaments, which are closer to mood, anxiety, and substance use disorders, and are associated with difficulty in emotional and behavioral adaptation to somatic diseases and life stressors.\textsuperscript{31} An epidemiological study in Lebanon reported that hyperthymic temperament has a uniquely protective effect on most mental disorders.\textsuperscript{34} Our previous study also suggested that hyperthymic temperament, in contrast to cyclothymic, irritable, and anxious temperaments, improves positive and negative affects and interpersonal sensitivity.\textsuperscript{17,35} Taken together, cyclothymic, irritable, and anxious temperaments may moderate PMM symptoms and the onset of PMDD.

In the SEM of this study, the effects of the sexual abuse subscale score of CATS on a negative change score on the LES and a negative change score on the LES on the severity of PMM symptoms were significant, but the sexual abuse subscale did not show a significant indirect effect on PMM symptoms. These results indicate the absence of positive mediation by a negative change score on the LES, but suggest a major role of increased appraisal of negative life events during the past year on current severity of PMM symptoms. Consistent with our results, a significant role of trauma history on the onset of PMDD has been reported.\textsuperscript{36,37} Interestingly, Gonda et al reported that women manifesting a more marked increase in symptoms from the late follicular through the late-luteal phase of the menstrual cycle are more likely to notice negative
subjective life events and are less likely to notice positive subjective life events. Hence, not only the objective severity of stress but also the subjective perception or severity of stress may contribute to PMM symptoms, as observed for depressive and anxiety symptoms.

Childhood maltreatment causes persistent hyperactivity of the hypothalamic-pituitary-adrenal axis, brain structural changes, and epigenetic changes in the amygdala and hippocampus. These biological effects may result in heightened stress responses. The biological reasons underlying the effects of childhood maltreatment can thus be explained.

The results of this study should be considered in light of the following limitations. Firstly, in our SEM model, the square sum of the multiple correlation coefficients was 0.29, suggesting that there might be other predictors (i.e., steroid hormones, other personality traits, etc.) associated with the severity of PMM symptoms. However, we did not perform hormonal tests to analyze the biological effects of menstruation on PMM symptoms. Secondly, there is the possibility of memory bias of childhood trauma, because childhood maltreatment was estimated retrospectively. Thirdly, although different effects have been reported between extrafamilial and intrafamilial abuse, we did not investigate these different effects. Finally, as this study only analyzed nonclinical adult volunteers from the community, the findings may not be generalizable to PMDD patients. In the future, the association between childhood maltreatment, affective temperaments, and adult life events should be prospectively studied using a large number of PMDD patients.

Conclusion
Analysis using the structural equation model showed that childhood maltreatment, particularly neglect, indirectly predicted PMM symptoms through affective temperaments. A major role of affective temperaments on the effect of childhood maltreatment on PMM symptoms was suggested.

Acknowledgements
This study was supported partly by a Grant-in-Aid for Scientific Research (no. 16K10194, T. Inoue) from the Japanese Ministry of Education, Culture, Sports, Science and Technology, Research and Development Grants for Comprehensive Research for Persons with Disabilities from the Japan Agency for Medical Research and Development, and SENSHIN Medical Research Foundation. We thank Dr. Yasuya Nakato and Ms. Yukiei Nakai for data collection.

Author Contributions
YW and TI designed the study and wrote the protocol. YW collected the data. All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure
TI has received personal fees from Mochida Pharmaceutical, Takeda Pharmaceutical, Eli Lilly, Janssen Pharmaceutical, MSD, Taisho Toyama Pharmaceutical, Yoshitomiakuhin, and Daiichi Sankyo; grants from Shionogi, Astellas, Tsumura, and Eisai; and grants and personal fees from Otsuka Pharmaceutical, Dainippon Sumitomo Pharma, Mitsubishi Tanabe Pharma, Kyowa Pharmaceutical Industry, Pfizer, Novartis Pharma, and Meiji Seika Pharma; and is a member of the advisory boards of Pfizer, Novartis Pharma, and Mitsubishi Tanabe Pharma. NH has received personal fees from Janssen Pharmaceutical, Yoshitomiakuhin, Otsuka Pharmaceutical, Dainippon Sumitomo Pharma, Novartis Pharma, and Meiji Seika Pharma. YF has received honoraria from Otsuka Pharmaceutical and grants from Otsuka Pharmaceutical, Novartis Pharma, and Shionogi. JM has received personal compensation from Otsuka Pharmaceutical, Eli Lilly, Astellas, and Meiji Yasuda Mental Health Foundation and grants from Pfizer. MI has received personal compensation from Otsuka Pharmaceutical, Pfizer, Eli Lilly, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Meiji Seika Pharma, Janssen Pharmaceutical, Takeda Pharmaceutical, MSD, Dainippon Sumitomo Pharma, and Eisai; grants from Otsuka Pharmaceutical, Eli Lilly, Eisai, Shionogi, Takeda Pharmaceutical, MSD, and Pfizer; and is a member of the advisory board of Meiji Seika Pharma. IK has received honoraria from Astellas, Daiichi Sankyo, Dainippon Sumitomo Pharma, Eisai, Eli Lilly, Janssen Pharmaceutical, Kyowa Hakko Kirin, Lundbeck, Meiji Seika Pharma, MSD, Mylan, Novartis Pharma, Ono Pharmaceutical, Otsuka Pharmaceutical, Pfizer, Shionogi, Shire, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical, Tanabe Mitsubishi Pharma, Tsumura, and Yoshitomiakuhin, and has received research/grant support from Astellas, Daiichi Sankyo, Dainippon Sumitomo Pharma, Eisai, Eli Lilly, Kyowa Hakko Kirin, Mochida Pharmaceutical, MSD, Novartis Pharma, Otsuka Pharmaceutical, Pfizer, Shionogi, and...
Takeda Pharmaceutical, and is a member of the advisory board of Dainippon Sumitomo Pharma. The authors report no other conflicts of interest associated with this work.

References
1. Clayton AH. Symptoms related to the menstrual cycle: diagnosis, prevalence, and treatment. J Psychiatr Pract. 2008;14:13–21. doi:10.1097/01.mpj.0000308491.54885.f8
2. Heinemann LA, Minh TD, Filonenko A, Uhl-Hochgraber K. Explorative evaluation of the impact of severe premenstrual disorders on work absenteeism and productivity. Womens Health Issues. 2010;20:58–65. doi:10.1016/j.whi.2009.09.005
3. Heinemann LA, Do Minh T, Filonenko A, Uhl-Hochgraber K. Explorative evaluation of the impact of premenstrual disorder on daily functioning and quality of life. Patient. 2010;3:125–132. doi:10.2165/1153750-000000000-00000
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Publication Inc.; 2013.
5. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry. 1999;156:837–841. doi:10.1176/ajp.156.6.837
6. Kendler KS, Kessler RC, Walters EE, et al. Stressful life events, genetic liability, and onset of an episode of major depression in women. Am J Psychiatry. 1995;152:833–842.
7. Kessler RC, Magee WJ. Childhood adversities and adult depression: basic patterns of association in a US national survey. Psychiatr. 1993;23:679–690. doi:10.1007/BF03329170052460
8. Wise LA, Zierler S, Krieger N, Harlow BL. Adult onset of major depressive disorder in relation to early life violent victimisation: a case-control study. Lancet. 2001;358:881–887. doi:10.1016/S0140-6736(01)06072-X
9. Ng QX, Yong BZJ, Ho CYX, Yeo WS. Early life sexual abuse is associated with increased suicide attempts: an update meta-analysis. J Psychiatr Res. 2018;99:129–141. doi:10.1016/j.jpsychires.2018.02.001
10. Nanni V, Uher R, Danese A. Childhood maltreatment predicts unfaorable course of illness and treatment outcome in depression: a meta-analysis. Am J Psychiatry. 2012;169:141–151. doi:10.1176/ajp.2011.11202335
11. Bertone-Johnson ER, Whitcomb BW, Missmer SA, Manson JE, Hankinson SE, Rich-Edwards JW. Early life emotional, physical, and sexual abuse and the development of premenstrual syndrome: a longitudinal study. J Womens Health (Larchmt). 2014;23:729–739. doi:10.1089/jwh.2013.4674
12. Girdler SS, Leserman J, Benevicius R, Klatzkin R, Pedersen CA, Light KC. Persistent alterations in biological profiles in women with abuse histories: influence of premenstrual dyshoric disorder. Health Psychol. 2007;26:201–213. doi:10.1037/0278-6133.26.2.201
13. Soydas EA, Albayrak Y, Sahin B. Increased childhood abuse in patients with premenstrual dyshoric disorder in a Turkish sample: a cross-sectional study. Prim Care Companion CNS Disord. 2014;16.
14. Girdler SS, Sherwood A, Hinderliter AL, et al. Biological correlates of abuse in women with premenstrual dyshoric disorder and healthy controls. Psychosom Med. 2003;65:849–856. doi:10.1097/01.PSY.0000085893.38201.CD
15. Aksikal HS, Aksikal KK, Haykal RF, Manning JS, Connor PD. TEMPS-A: progress towards validation of a self-rated clinical version of the temperament evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. J Affect Disord. 2005;85:3–16. doi:10.1016/j.jad.2004.12.001
16. Nakai Y, Inoue T, Toda H, et al. The influence of childhood abuse, adult stressful life events and temperaments on depressive symptoms in the nonclinical general adult population. J Affect Disord. 2014;158:101–107. doi:10.1016/j.jad.2014.02.004
17. Kanai Y, Takaesu Y, Nakai Y, et al. The influence of childhood abuse, adult life events, and affective temperaments on the well-being of the general, non-clinical adult population. Neuropsychiatr Dis Treat. 2016;12:823–832. doi:10.2147/NDDT.S100474
18. Nakai Y, Inoue T, Chen C, et al. The moderator effects of affective temperaments, childhood abuse and adult stressful life events on depressive symptoms in the nonclinical general adult population. J Affect Disord. 2015;187:203–210. doi:10.1016/j.jad.2015.08.011
19. Miyaoa Y, Akimoto Y, Ueda K, Kamo T. The reliability and validity of the newly developed PMDD scale. J Jpn Psychosom Obstet Gynecol. 2009;14:194–201.
20. Steiner M, Macdougall M, Brown E. The premenstrual symptoms screening tool (PSST) for clinicians. Arch Womens Menst Health. 2003;6:203–209. doi:10.1007/s00737-003-0018-4
21. Spitzer RL, Kroenke K, Williams JB, PHQ Primary Care Study Group. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. JAMA. 1999;282:1737–1744. doi:10.1001/jama.282.18.1737
22. Muramatsu K, Miyaoa H, Kamiyama K, et al. The patient health questionnaire, Japanese version: validity according to the mini-international neuropsychiatric interview-plus. Psychol Rep. 2007;101:952–960. doi:10.2466/pr0.101.3.952-960
23. Sarason IG, Johnson JH, Siegel JM. Assessing the impact of life changes: development of the life experiences survey. J Consult Clin Psychol. 1978;46:932–946. doi:10.1037/0022-006X.46.5.932
24. Matsumoto S, Akiyama T, Tsuda H, et al. Reliability and validity of TEMPS-A in a Japanese non-clinical population: application to unipolar and bipolar depressives. J Affect Disord. 2005;85:85–92. doi:10.1016/j.jad.2003.10.001
25. Sanders B, Beaver-Lausen E. The measurement of psychological maltreatment: early data on the child abuse and trauma scale. Child Abuse Negl. 1995;19:315–323. doi:10.1016/S0145-2134(94)00131-6
26. Tanabe H, Ozawa S, Goto K. Psychometric properties of the Japanese version of the Child Abuse and Trauma Scale (CATS). The 9th Annual Meeting of the Japanese Society for Traumatic Stress Studies; March 6, 2010; Kobe, Japan. (Japanese).
27. Schermelleh-Engel K, Moosbrugger H, Müller H. Evaluating the fit of structural equation models: tests of significance and descriptive goodness-of-fit measures. MPR Online. 2003;8:23–74.
28. Toda H, Inoue T, Tsunoda T, et al. The structural equation analysis of childhood abuse, adult stressful life events, and temperaments in major depressive disorders and their influence on refractoriness. Neuropsychiatr Dis Treat. 2015;11:2079–2090. doi:10.2147/NDDT.S82236
29. Infurna MR, Reichl C, Parzer P, Schimmenti A, Bifulco A, Kaess M. Associations between depression and specific childhood experiences of abuse and neglect: a meta-analysis. J Affect Disord. 2016;190:47–55. doi:10.1016/j.jad.2015.09.006
30. Popmili M, Innamorati M, Gonda X, et al. Affective temperaments and hopelessness as predictors of health and social functioning in mood disorder patients: a prospective follow-up study. J Affect Disord. 2013;150:216–222. doi:10.1016/j.jad.2013.03.026
31. Camara RA, Kohler CA, Maes M, et al. Affective temperaments and emotional traits are associated with a positive screening for premenstrual dyshoric disorder. Compr Psychiatry. 2016;71:33–38. doi:10.1016/j.comppsych.2016.08.008
32. Toda H, Inoue T, Tsunoda T, et al. Affective temperaments play an important role in the relationship between childhood abuse and depressive symptoms in major depressive disorder. Psychiatry Res. 2016;236:142–147. doi:10.1016/j.psychres.2015.12.016
33. Rozai L, Maremmani AG, Rugani F, et al. Do Akiskal & Mallya’s affective temperaments belong to the domain of pathology or to that of normality? Eur Rev Med Pharmacol Sci. 2013;17:2065–2079.
34. Karam EG, Salamoun MM, Yeretzian JS, et al. The role of anxious and hyperthymic temperaments in mental disorders: a national epidemiologic study. *World Psychiatry*. 2010;9:103–110. doi:10.1002/wps.2010.9.issue-2

35. Otsuka A, Takaesu Y, Sato M, et al. Interpersonal sensitivity mediates the effects of child abuse and affective temperaments on depressive symptoms in the general adult population. *Neuropsychiatr Dis Treat*. 2017;13:2559–2568. doi:10.2147/NDT.

36. Perkonigg A, Yonkers KA, Pfister H, Lieb R, Wittchen HU. Risk factors for premenstrual dysphoric disorder in a community sample of young women: the role of traumatic events and posttraumatic stress disorder. *J Clin Psychiatry*. 2004;65:1314–1322. doi:10.4088/JCP.v65n1004

37. Pilver CE, Levy BR, Libby DJ, Desai RA. Posttraumatic stress disorder and trauma characteristics are correlates of premenstrual dysphoric disorder. *Arch Womens Ment Health*. 2011;14:383–393. doi:10.1007/s00737-011-0232-4

38. Gonda X, Fountoulakis KN, Csukly G, et al. Association of a trait-like bias towards the perception of negative subjective life events with risk of developing premenstrual symptoms. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34:500–505. doi:10.1016/j.pnpbp.2010.02.004

39. McCrory E, De Brito SA, Viding E. The link between child abuse and psychopathology: a review of neurobiological and genetic research. *J R Soc Med*. 2012;105:151–156. doi:10.1258/jrsm.2011.110222

40. Boku S, Toda H, Nakagawa S, et al. Neonatal maternal separation alters the capacity of adult neural precursor cells to differentiate into neurons via methylation of retinoic acid receptor gene promoter. *Biol Psychiatry*. 2015;77:335–344. doi:10.1016/j.biopsych.2014.07.008

41. Toda H, Boku S, Nakagawa S, et al. Maternal separation enhances conditioned fear and decreases the mRNA levels of the neurotensin receptor 1 gene with hypermethylation of this gene in the rat amygdala. *PLoS One*. 2014;9:e97421. doi:10.1371/journal.pone.0097421

42. Fischer DG, McDonald WL. Characteristics of intrafamilial and extrafamilial child sexual abuse. *Child Abuse Negl*. 1998;22:915–929. doi:10.1016/S0145-2134(98)00063-5