OBJECTIVE: The objective of the study was to evaluate the effects of maternal exposure to severe life events during different stage of gestation on preterm birth and infant birthweight.

STUDY DESIGN: A sample of 1800 women who delivered after 32 weeks’ gestation were assessed with questionnaires that measured stressful life events during different stages of pregnancy. Demographic characteristics and birth outcomes were collected through the interviews and medical charts.

RESULTS: There was an increased risk of preterm birth among women with higher levels of life events stress during the first trimester (adjusted risk ratio, 2.40; 95% confidence interval, 1.13–5.09) and second trimester (adjusted risk ratio, 2.86; 95% confidence interval, 1.26–6.47). Each unit increase of perceived life events stress during first trimester was associated with a 99.09 g decrease in infant birthweight.

CONCLUSION: Prenatal severe life events, especially in the first trimester, may play an important role in increasing the risk of preterm birth and low birthweight.

Key words: birthweight, life events, pregnancy, preterm birth, stress

uate the unique contribution of maternal life events stress to preterm birth and birthweight, it is important to exclude other potential factors. Therefore, the individual-level factors known to be associated with maternal stress and birth outcome including income, education, age, complication with pregnancy, history of the pregnancy outcome, infant sex, and psychosocial factors were controlled in this study.

**MATERIALS AND METHODS**

**Study subjects**

This study is part of a prospective longitudinal project, which investigates the influence of prenatal psychosocial stress on the pregnancy outcome and postnatal development of infants.

Subjects were recruited from 3316 married pregnant women who received the third-trimester prenatal visit in the Department of Gynecology and Obstetrics of Hefei Maternal and Child Health Hospital from March to November 2008. A total of 2552 pregnant women participated in the project willingly.

In this study, women with age greater than 35 years (n = 147), delivery before 32 weeks of gestation (n = 14), or medically indicated preterm birth (n = 22), stillbirth (n = 11), birth defect (n = 12), pregnancy with assisted reproductive technology (n = 6), mental disorder (n = 2), complications with pregnancy including diabetes mellitus, hypertension, abnormal heart function, glandula thyreoida disease, intrahepatic cholestasis of pregnancy, moderate and severe anemia (n = 429), or a history of abnormal pregnancy outcome (including premature birth, spontaneous abortion, fetal death, stillbirth, birth defect, neonatal death) (n = 240), or superfetation (n = 48) were excluded from the study.

Samples of 1800 pregnant women were admitted. The study was approved by the ethical committee of the Anhui Medical University, and informed consent was obtained from the participants.

**Investigational methods**

All the participants were recruited from obstetric clinics who received prenatal check-ups after 32 completed weeks. With informed consent, they were required to complete a questionnaire including Life Events Checklist, Social Support Scale, and Coping Style Questionnaire. Demographic characteristics and pregnancy history were assessed through the interview, and delivery outcomes including gestational age at birth and birthweight were obtained from medical charts after delivery.

**Dependent variables**

The main birth outcomes for the study were gestational age at birth and birthweight. Preterm births (births with gestational age <37 completed weeks) were calculated from the gestational age (in completed weeks) based on the difference between the date of the last menstrual period and the date of delivery which were obtained from hospital records. Low birthweight was defined as an infant with weight less than 2500 g.

**Independent variables**

Participants were invited to answer a 19-item inventory of stressful life events to assess the occurrence of specific events during the first trimester (0-12 weeks), second trimester (13-24 weeks), and third trimester (25-36 weeks), respectively. According to the 19-item checklist of life events, which was designed on the basis of previous investigations, participants were asked to indicate whether the event had occurred during pregnancy, using a dichotomous (yes-no) response scale. If the event occurred, they were asked to weight their perception of its impact on their lives, from no impact (0) to extreme impact (4). The sum of the value of each event ratings were used to assess perception of stress.

This assumes that the effects of the stressful life events are cumulative and additive across the various events. Total value of self-perceived impact rating of 0, 1, and 2 or greater is defined as no stress, modest stress, and severe stress, respectively.

The checklist was adapted from the Life Event Scale with a little modification, which included merging some items that usually occur during pregnancy and deleting some unsuitable items. All the 19 items could be classified into 4 domains as financial (4 items including, husband lost job, subject herself lost job, fortune loss, and stolen from or cheated), emotion (6 items including, moved to new address, live apart, housing stress, fright, family member gambling, and spouse went to jail), traumatic events (5 items including, husband ill, husband died, subject herself ill, family member ill, and family member died), and spousal related (4 items including, divorce, argument with partner, in-fight, and poor marital relation). Two blank items were added into the checklist in case of any missing life events that might be excluded from the 19 items mentioned above.

**Covariates**

Covariates were considered on findings in other studies of risks for preterm birth. The individual-level variables reported are maternal age (20-24, 25-29, 30-34 years), measures of maternal socioeconomic characteristics (income, education), and psychosocial factor (social support and coping style). Income level was categorized as perceived status (lower, medium, or higher). Educational attainment was similarly categorized as middle school and less (≥9 years), or high school and beyond (>9 years of completed schooling).

The Chinese Revised Edition of the Social Support Scale including 10 items with the total score range from 12 to 64 was used to assess social support as a buffer of stress and categorized as lower support, medium-low support, medium-high support, and high support by using quartiles. The more scores, the more psychological resources.

In addition, the Chinese Revised Edition of the Coping Style Questionnaire including 10 items with the total score range from 10 to 50 assessed negative coping style to stress and was categorized as lower negative coping (NC), medium-low NC, medium-high NC, and high NC by using quartiles. The more scores, the more tendency to using negative coping style to stress.

**Statistical analysis**

Interquartile ranges of coping style and social support subscale were used in statistical analyses. Crude risk ratios (RRs)
and 95 percent confidence intervals (CIs) were generated for associations of maternal socioeconomic characteristics and psychosocial factors with preterm birth and low birthweight using the \( \chi^2 \) test. Confounding by covariates for association between life events stress and preterm was assessed by univariate analysis.

Adjusted risk ratios were generated with regression modeling using the SPSS binary logistic regression (SPSS Inc, Chicago, IL). The unadjusted regression coefficients of linear regression model were generated for the association between prenatal life events stress and birthweight, and adjusted regression coefficients were given after controlling for gestation age at birth and other maternal-level covariates. SPSS software (Statistical Package for the Social Sciences, version 10.0) was used for all statistical analyses.

### RESULTS

As shown in Table 1, the majority of respondents had completed high school and beyond (82.8%). Maternal income levels of the respondents showed considerable variations. More than three-quarters of the respondents reported a medium income (73.6%), and the lower income category had 14.4%.

In this study, the mean gestational age at delivery was \( 38.96 \pm 1.53 \) weeks, ranging from 32 to 42 weeks, with 96 preterm births (5.3%). The mean birthweight was 3363.61 ± 458.45 g, ranging from 1500 to 5500 g, with 55 low birthweight infants (3.1%). In all infants, there were 957 boy infants (53.2%) and 843 girl infants (46.8%).

Additionally, Table 1 shows the different birth outcomes of the newborns according to the demographic and psychosocial characteristics of those pregnant women. An increased risk for preterm birth occurred among women who were at a lower age at delivery (RR, 2.46; 95% CI, 1.63–3.73), had a lower education level (RR, 2.76; 95% CI, 1.85–4.10), and lower income level (RR, 2.01; 95% CI, 1.28–3.16). Women with lower age at delivery (RR, 2.74; 95% CI, 1.57–4.78), lower educational level (RR, 3.61; 95% CI, 2.15–6.06), and lower income level (RR, 1.90; 95% CI, 1.02–3.54) had a higher risk of low birthweight. Lower social support and higher negative coping did
not increase the risk of preterm birth and low birthweight.

Table 2 presents different levels of perceived life events stress during the first, second, and third trimesters according to the demographic and psychosocial characteristics of those pregnant women. There were significant differences of prenatal life events stress during the third trimester according to age and educational level but not the first and second trimester.

Mothers with different incomes had no significant differences in life events stress exposure during the first, second, and third trimesters. There were significant differences in prenatal life events stress during the first trimester according to social support but not the second and third trimesters. Women who had high NC scores were more likely to be exposed in severe life events stress during pregnancy.

Table 3 presents crude and adjusted risk ratios with 95 percent confidence intervals for associations between life events stress during different stage of pregnancy and preterm birth. The risks of preterm birth in relation to maternal exposure to severe life events during the first (RR, 2.60; 95% CI, 1.29–5.22) or second trimesters (RR, 2.86; 95% CI, 1.32–6.22) were significantly increased. There was more than 2-fold increase in risk of preterm birth in mothers who were exposed to severe life events stress in the first and second trimesters.

The RR of preterm birth in relation to life events stress in the first trimester is 2.60 (95% CI, 1.29–5.22) without adjustment and 2.40 (95% CI, 1.13–5.09) after adjustment, which was affected by adjustment for age at birth, education, income, social support, negative coping style, and infant sex. But the RR of preterm birth in relation to severe life events stress in the second trimester was not affected by adjustment. Life events exposure during the third trimester did not increase the risk of preterm birth.

The association between maternal exposure to severe life events stress during different stages of pregnancy and birthweight is shown in Table 4. Mother exposure to stressful life events stress during the first trimester but not the second and third trimesters was inversely and significantly associated with birthweight, and each unit increase of life events stress during the first trimester was associated with a 122.97 g decrease in infant birthweight (model 1).
Analyses were performed to determine the mediating effect of all stiffness estimates used in this study on the relation between maternal exposure to severe life events stress during different stages of pregnancy and birthweight. When gestational age at birth was accounted into the model, regression coefficient of mother exposure to stressful life events in the first trimester changed from −122.97 g/unit to −100.18 g/unit (model 2). The association of maternal exposure to stressful life events in the second and third trimesters with birthweight was not significant in model 2. When adding maternal-level covariates (maternal age at delivery, educational level, income, social support, negative coping, infant sex) into the model, changes in the regression coefficient from −100.18 g/unit to −99.09 g/unit were observed (model 3). The association of maternal exposure to stressful life events in the second and third trimesters with birthweight was also not significant in model 3.

In the aforementioned linear regressions linking life events and birthweight, life events in each trimester were modeled simultaneously. Additionally, we analyzed it separately and found life event stress in the second or third trimester still have no predictive significance in models if entered alone. Additionally, we have also analyzed the interaction by entering the interaction between stress exposure and coping and social support into regression models, but we found no interactive effect on birthweight.

### TABLE 3
Risk ratios for life events stress during pregnancy on preterm birth

<table>
<thead>
<tr>
<th>Perceived impact rating of life events stress</th>
<th>n (n = 1800)</th>
<th>Preterm birth</th>
<th>Crude</th>
<th>Confounder adjustmenta</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (n = 96)</td>
<td>%</td>
<td>RR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Exposure in the first trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1576</td>
<td>76</td>
<td>4.8</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>138</td>
<td>10</td>
<td>7.2</td>
<td>1.54</td>
</tr>
<tr>
<td>≥2</td>
<td>86</td>
<td>10</td>
<td>11.6</td>
<td>2.60</td>
</tr>
<tr>
<td>Exposure in the second trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1647</td>
<td>84</td>
<td>5.1</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>93</td>
<td>4</td>
<td>4.3</td>
<td>0.84</td>
</tr>
<tr>
<td>≥2</td>
<td>60</td>
<td>8</td>
<td>13.3</td>
<td>2.86</td>
</tr>
<tr>
<td>Exposure in the third trimester</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1694</td>
<td>90</td>
<td>5.3</td>
<td>1.00</td>
</tr>
<tr>
<td>1</td>
<td>64</td>
<td>3</td>
<td>4.7</td>
<td>0.88</td>
</tr>
<tr>
<td>≥2</td>
<td>32</td>
<td>3</td>
<td>7.1</td>
<td>1.37</td>
</tr>
</tbody>
</table>

CI, confidence interval; RR, relative risk.

a Adjustment for maternal age at birth (20–24, 25–29, 30–34 years), education (≤9, >10 years), income (lower, medium, higher), social support (low support, medium-low support, medium-high support, high support), negative coping (low support, medium-low support, medium-high support, high support), infant sex, and interaction of life events stress among first, second, and third trimesters.


### TABLE 4
Association between life events stress during pregnancy and birthweight

<table>
<thead>
<tr>
<th>Score of perceived life events stress</th>
<th>MODEL 1a</th>
<th>MODEL 2b</th>
<th>MODEL 3c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>SE</td>
<td>B, 95% CI</td>
</tr>
<tr>
<td>Exposure in first trimester</td>
<td>−122.97</td>
<td>22.27</td>
<td>−166.64, −79.29</td>
</tr>
<tr>
<td>Exposure in second trimester</td>
<td>−19.93</td>
<td>26.17</td>
<td>−71.27, 31.40</td>
</tr>
<tr>
<td>Exposure in third trimester</td>
<td>−1.11</td>
<td>30.97</td>
<td>−61.85, 59.63</td>
</tr>
</tbody>
</table>

CI, confidence interval.

a Model 1 is a crude estimate of life events stress during different gestational ages on birthweight, F = 11.01, P < .01; b Model 2 is adjusted for gestational age at birth, F = 117.81, P < .01; c Model 3 includes maternal age at birth, years mother received education, income level (1, 2, 3 was defined as lower, medium, and higher, respectively); score of social support; score of negative coping style; and infant sex, F = 60.86, P < .01.

COMMENT
Previous psychosocial-birth outcome studies had some limitations in lack of confounding or effect adjustment. In this study, participants being from the same region and having similar cultural backgrounds, confounding effects resulted from biomedical factors on psychosocial-preterm association were controlled through strict selection criterion for subjects, and women who delivered prior to 32 weeks were excluded because we can not exactly evaluate the life events for the whole third trimester if the pregnant woman gave birth before 32 weeks, which could result in undervaluing the effect of life events in the whole third trimester on birth outcomes. Potential confounding effects would be minimized as much as possible.

In the present study, we found the increased risk of preterm birth or low birthweight among women with more life events stress during pregnancy; this result was consistent with previous studies. Other studies reported that exposure to severe life events may evoke the risk ratio of other severe abnormal delivery outcomes such as congenital malformations and SGA in very preterm babies. Although there was a somewhat modest association between stressful life events and abnormal delivery outcomes, but biomechanisms through which stress may contribute to preterm birth are not well understood, these findings neither clearly support nor contradict the existence of distinct pathways that explain the stress-preterm birth association.

In this study, we were interested in investigating the time-specific effects of prenatal life events stress on birth outcomes. We found that maternal exposure to severely stressful life events during the first and second trimesters, but not the third trimester, increased the risk of preterm birth and that exposure in the first trimester, but not in the second and third trimesters, had greater effect on the birthweight of neonate.

The significance of the timing of exposure observed in this study was partially consistent with results from recent studies. Khashan et al reported that mothers exposed to severe life events stress before conception or during pregnancy may have babies with significantly lower birthweight.

Lederman et al declared that women in the first trimester of pregnancy at the time of the World Trade Center event delivered infants with significantly shorter gestation and a smaller head circumference compared with women at later stages of pregnancy, and the finding supported the idea that the early trimester of pregnancy might be the crucial time of life events stress having an impact on fetal growth and birth outcome. However, our findings were inconsistent with the reports from Khashan et al and Precht et al, among which Khashan et al reported severe life events, particularly in the 6 months before pregnancy, may increase the risk of preterm and very preterm birth, whereas Precht et al reported infants whose mother had been exposed to severe life events during the year before pregnancy but not during the pregnancy had increased risks of being born as small for gestational age in preterms.

One reason for the inconsistency may be the different definition of exposure. In their studies, the investigators defined only the death or serious illness of close relatives as severe life events; the other reason may be the different control: in their studies the control was the pregnant women without death or serious illness of close relatives, but there may be other life events such as financial events and emotional events occurring to these controls.

The mechanisms underlying which timing of prenatal stress exposure played a crucial role in its effect on birth outcomes were not clear. We hypothesized that changes in fetal development and onset of labor may occur through actions on the placenta because it is derived from the developing blastocyst and undergoes critical development during this period of early prenatal stress.

Psychosocial stress has been shown to be associated with elevated maternal cortisol levels during pregnancy. Increased cortisol levels resulting from prenatal stress during the early period in pregnancy could be harmful, but high levels of the placental enzyme, 11-beta-hydroxysteroid-dehydrogenasetype 2 (11B-HSD2), protect the developing fetus by converting cortisol to the inactive form, cortisone. Animal studies indicate that inhibition of this enzyme in pregnant rats results in offspring with lower birthweight.

Correspondingly, the placentas of women who demonstrated intrauterine growth restriction have shown decreased 11B-HSD2 gene expression. The activity of 11B-HSD2 is influenced by several factors. For example, rats exposed to acute stress showed an immediate increase in activity of 11B-HSD2 by 160%, whereas there was no change following 6 days of chronic stress exposure. However, when the women were exposed to chronic stress, they failed to show an up-regulation of enzyme activity, indicating that chronic stress may be detrimental for healthy pregnancy.

Also, increased levels of catecholamines including norepinephrine and epinephrine, which are secreted during stress, can down-regulate 11B-HSD2 gene expression in human placental cells. Therefore, future research should be focused on whether the imbalanced maternal hormonal milieu influenced by perturbations occurring in the early period of pregnancy could result in fetal original impairments such as functional alteration in insulin-like growth factor system and hypothalamic-pituitary-adrenocortical axis responsiveness.

There were different findings with regard to relations among maternal psychological stress, coping style, and birth outcome in previous research. In this study, social support and coping style were analyzed as covariates, but we found lower levels of social support and higher negative coping scores did not increase the risk of preterm birth and low birthweight. Moreover, social support and coping style did not modify the associations between prenatal stress, preterm, and birthweight.

Our findings were consistent with results from other studies. The potential reason could be that social support and coping style could influence pregnancy outcome through a buffering impact of general psychological stress, but its buffering effect is, at most, small.
among women with high levels of stress, such as severe life events, in this study. Additionally, the impact of the interactive effect between social support and coping and psychosocial stress on birth outcome might be associated with the cultural backgrounds of different countries.

In spite of the revealing findings, the study has some limitations that should be noted. First, for the stratification by occurred period of maternal life events and the perceived impact rating of stress, the number of women in some categories was small, resulting in limited power.

Second, the survey collected data only from women with live births, so the findings can only be generalized to mothers with live births. Women with severe life events stress resulting in spontaneous abortions or stillbirths are likely to be missed in estimating the magnitude of psychosocial stress effects in pregnancy on birth outcomes.

Third, a major limitation of life events inventories as a measure of maternal stress is the difficulty in determining whether the items used were properly selected from the universe of all events most likely to be encountered by mothers in their gestational period.

Fourth, recall bias in our study was inevitable, even though it was reduced to a great extent. Additionally, our design which excluded subjects with delivery before 32 gestational weeks might result in underevaluating the effect of life event stress in the first and second trimesters on birth outcomes, although we found that the early pregnancy was the crucial time of life events stress having an impact on fetal growth and birth outcome.

An advantage of this study was the evaluation methodology for life events stress. Different from other studies, perceived stimulus intensity instead of counts of life events was used as analysis indicators, which could better estimate the quantity of stimulus of life events stress. Additionally, perceived data collection before delivery could eliminate the problem of reporting being influenced by outcome.

Whereas the effect of severe life events stress on the risk of preterm birth and low birthweight was modest, the findings remain significant. First, the etiology of preterm birth and low birthweight remains poorly understood, and these findings suggest the possibility of several causative mechanisms worthy of further investigation. Moreover, although the effect is relatively modest, preterm birth remains the single largest contributor to perinatal mortality in the developed world. Consequently, even a moderate effect at a population level can contribute significantly to morbidity and mortality.

The present study suggested that severe life events stress may play an important role in increasing the risk of preterm birth and low birthweight. More importantly, our study showed the timing of prenatal stress exposure was a key factor in these relations. Health planners seeking to reduce the incidence of preterm birth and low birthweight need to consider the role of maternal psychological stresses when designing intervention programs.

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