ORIGINAL ARTICLE

Maternal stress during pregnancy and gestational duration: A cohort study from the Danish National Birth Cohort

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Abstract

Background: Preterm birth is one of the most important contributors to neonatal mortality and morbidity. Experiencing stress during pregnancy may increase the risk of adverse birth outcomes, including preterm birth. This association has been observed in previous studies, but differences in measures used limit comparability.

Objective: The objective of the study was to investigate the association between two measures of maternal stress during pregnancy, life stress and emotional distress, and gestation duration.

Methods: Women recruited in the Danish National Birth Cohort from 1996 to 2002, who provided information on their stress level during pregnancy and expecting a singleton baby, were included in the study. We assessed the associations between the level of life stress and emotional distress in quartiles, both collected at 31 weeks of pregnancy on average, and the rate of giving birth using Cox regression within intervals of the gestational period.

Results: A total of 80,991 pregnancies were included. Women reporting moderate or high levels of life stress vs no stress had a higher rate of giving birth earlier within all intervals of gestational age (e.g. high level: 27–33 weeks: hazard ratio (HR) 1.38, 95% confidence interval (CI) 1.04, 1.84; 34–36 weeks: 1.10, 95% CI 0.97, 1.25; 37–38 weeks: 1.21, 95% CI 1.15, 1.28). These associations between life stress and preterm birth were mainly driven by pregnancy worries. For emotional distress, a high level of distress was associated with shorter length of gestation in the preterm (27–33 weeks: 1.38, 95% CI 1.02, 1.86; 34–36 weeks: 1.05, 95% CI 0.91, 1.19) and early term (1.11, 95% CI 1.04, 1.17) intervals.

Conclusions: Emotional distress and life stress were shown to be associated with gestational age at birth, with pregnancy-related stress being the single stressor driving the association. This suggests that reverse causality may, at least in parts, explain the earlier findings of stress as a risk factor for preterm birth.

1 | BACKGROUND

Preterm delivery constitutes a major public health concern since preterm birth and its complications are the leading causes of neonatal and childhood mortality.[1-3] Preterm born children are also at greater risk of various health and developmental problems such as respiratory conditions, cerebral palsy, cognitive impairment and vision and hearing loss.[4-8] It has recently been shown that long-term outcomes such as education, neurodevelopmental disabilities and emotional and behavioural problems vary across the full spectrum of gestational ages at birth.[9-11] The risk factors contributing to different degrees of preterm birth also vary.[11,12]

Maternal stress and distress are frequent conditions in pregnancy[13,14] and some authors have found sub-optimal birth outcomes, including mortality, intra-uterine growth retardation and shorter gestation, to be associated with prenatal stress.[15] However, studies have reported conflicting evidence of the impact of maternal stress on preterm birth. Many studies[16-19] have been conducted on small samples, which may limit their credibility. Moreover, there is a great variability in the measurements used to assess stress during pregnancy, which could explain some of the heterogeneity in results between studies. Stress assessments during pregnancy encompass stressful life events, disasters, chronic stressors, daily hassles or emotional symptoms such as anxiety or depression.[18-20] The impact of an acute major life event may differ from the more common stressors,[21] with the appraisal of the stressfulness of these situations by the women being an important contributing factor.[22,23]

The aim of this study is to assess the association between emotional distress and life stress during pregnancy, respectively, and gestational age at birth, using data from a large cohort study of pregnant women.

2 | METHODS

2.1 | Cohort selection

The data for this study were from the Danish National Birth Cohort (DNBC). Between 1996 and 2002, over 100,000 pregnant women from Denmark were recruited into the DNBC through participating general practitioners during their first pregnancy visit around 6–12 weeks of gestation. Information was prospectively collected on early life exposures and the development of different health issues. A detailed description of the cohort has already been published elsewhere.[24] Two computer-assisted telephone interviews during pregnancy, the first one at 16.9 weeks on average (SD = 4.3) and the second one at 31.5 weeks (SD = 3.0), were used to obtain information on the mother's lifestyle, sociodemographic characteristics, health and reproductive history.

Synopsis

Study question

Does gestational age at birth differ according to level of experienced stress during pregnancy?

What's already known

Stress is a condition often experienced during pregnancy. Some past studies have found an association between perinatal stress and birth outcomes, but others showed conflicting evidence.

What this study adds

Using Cox regression analyses in intervals of gestational age at birth, we found that life stress was associated with the rate of birth at any given gestational age, but these associations were solely driven by pregnancy-related stress. These findings suggest reverse causality, with women having higher stress due to already present signs of a possible preterm birth.

In this study, the pregnancies were eligible for inclusion if they did not end in either miscarriage or abortion and if the gestational age at birth was known (n = 95,034). Pregnancies were excluded if women were expecting twins or triplets (n = 2079) or if they did not complete both pregnancy interviews (n = 11,964). All pregnancies from the same mother within the study period were considered for inclusion. The final analysis population consisted of 80,991 pregnancies in 75,842 women as some women had more than one pregnancy during the recruitment period (Figure S1).

2.2 | Exposures

Stress was measured as self-reported life stress and emotional distress of the mother during pregnancy. The data used to create the scores were collected during the second pregnancy interview, at around 31 weeks of gestation. Both exposures were assessed by the questions listed in Table 1, all questions covering the full pregnancy period up to the time of interview. The life stress items all pertain to different types of burdens or worries during pregnancy, covering the most common areas of daily living. The emotional distress items focus on the feelings of the mother during pregnancy. The available data for emotional distress in DNBC consisted of six items selected from the Symptom Checklist 90 (SCL-90),[25] three measuring depressive

TABLE 1 Items included in the life stress and emotional distress scores. Danish National Birth Cohort, 1996–2002

Life stress items Have you felt worried or burdened during pregnancy by any of the following things? You may answer: no, a little or a lot.	Emotional distress items How have you been feeling during pregnancy? You may answer: no, a little or a lot.
• Have you been burdened by financial troubles?	• Have you felt frightened and anxious without reason?
• Have you been burdened by your housing situation?	• Have you felt that the future looked hopeless?
• Have you been burdened by your work situation?	• Have you felt under a constant pressure?
• Have you been burdened by the relations to your partner?	• Have you felt nervous or at unease?
• Have you been burdened by relations to family and friends?	• Have you felt sad and blue?
• Have you been burdened by the pregnancy itself?	• Have you been more touchy and quick-tempered than usually?
• Have you been burdened by disease yourself?	• Have you felt that everything was a big effort?
• Have you been burdened by disease in family or close friends?	• Have you felt tense and exhausted?
• Have you been burdened by other things?	• Have you felt that the demands made on you were too big?

symptoms and three measuring anxiety. The last three items available were taken from the General Health Questionnaire (GHQ)[26] to measure general stress. Response options to all questions were "no", "a little" or "a lot", with a coding from 0 to 2. A score was generated for each measure, from their respective nine items, with a possible total ranging from 0 to 18. Mothers were then divided into four groups, for both life stress and emotional distress, according to cut-off values closest to the quartiles. Quartiles were chosen since the measures used in DNBC were not validated tools and thus had no standardised cut-offs. The first quartile was composed of mothers with a total score of 0, thus reporting no life stress or emotional distress. Mothers in the second quartile were considered to have a low level of life stress or emotional distress, a moderate level in the third quartile and a high level in the last quartile. Only women with complete answers to the respective 9 items were included, which excluded 274 pregnancies for the life stress measure and 320 pregnancies for the emotional distress measure.

2.3 | Outcome

Information on gestational age at birth was retrieved through linkage with the Medical Birth Registry, which covers all births in Denmark. The data on gestational age at birth in the register reflects the assisting midwife's best clinical judgement, based on maturity of the child combined with information on date of last menstrual period and ultrasound scanning from early second trimester. Gestational age at birth was recorded in days.

2.4 | Covariates

Confounders were selected a priori based on prior knowledge and the method of directed acyclic graph (Figure S2). They include maternal age,[3,8,11,12,27,28] education level,[3,8,27–31] having a spouse,[27,28,31] parity,[8,12,29] use of fertility treatment,[3,8,12,31,32] having diseases[3,8,27–29,31,33] or infections[3,27,31,34] during pregnancy

and the child's congenital anomalies.[3,11,12] Information on having a spouse, parity and fertility treatment was obtained from the first pregnancy interview (around 16 weeks). Parity was categorised as primiparous or multiparous. Having used fertility treatment to get pregnant and having a spouse were both dichotomized as yes/no variables. Information on non-communicable diseases and infections was self-reported during the second pregnancy interview (around 31 weeks). Non-communicable disease was defined as having any of the following self-reported conditions during pregnancy: hypertension, preeclampsia, diabetes, metabolic diseases, asthma, epilepsy or musculoskeletal diseases. Infection was defined as having any of the following self-reported infections during pregnancy: cystitis, inflammation of pelvis or kidney, vaginal infections or other infectious diseases. Age of the mother at delivery (in years) was obtained from the Central Person Register. The education information was obtained from the Danish Student Register and coded according to the International Standard Classification of Education (ISCED).[35] Highest level of education attained was categorised as low (ISCED levels 0–2), medium (ISCED levels 3–4) or high (ISCED levels 5–8). The child's congenital anomalies were obtained from the National Patient Register and categorised as a yes/no variable for having any congenital anomaly. Only major anomalies were included according to the EUROCAT classification.[36]

2.5 | Statistical analysis

Cox regression models were used to investigate the association between the level of life stress and emotional distress, respectively, and the rate of giving birth and, thereby, the length of gestation. Gestational age in days was used as the underlying time scale and the event was birth. Proportional hazard assumption on the full gestational age span was tested using the scaled Schoenfeld residuals. Since the proportional hazard assumption was not fulfilled, separate associations were studied within intervals of gestational age at birth to determine the hazard ratio of giving birth in each interval according to the level of life stress

or emotional distress. The intervals were as follows: very or moderate preterm (27–33 weeks), late preterm (34–36 weeks), early term (37–38 weeks), full term (39–41 weeks) and post-term (42–45 weeks). Delayed entry was considered in the models, with women entering the study on the day they completed the second pregnancy interview. Thus, for each interval, women were included either from the day they completed the questionnaire or from the first day of the considered period if they completed the interview in a previous interval. The follow-up ended at delivery, regardless of the outcome, with both livebirths and stillbirths included. Five sets of associations were thus estimated for both life stress and emotional distress, one per interval of gestational age at birth. The models were complete case analyses with the a priori selected covariates. The clustered nature of the data, that is that one woman could participate with more than one pregnancy, was taken into account in the analyses by using robust standard errors.

2.6 | Missing data

In the final analysis population, the missing data for exposures, outcome and covariates varied from 0 to 1.3%; therefore, multiple imputation was not undertaken. In the complete case analysis for both life stress and emotional distress, there was 3.3% missingness in total.

2.7 | Sensitivity analysis

In a sensitivity analysis, we assessed the impact of combining variables from 2 different standardised questionnaires to measure emotional distress. Alternative variables were created: general stress (3 questions from the GHQ), anxiety (3 questions from the SCL-90) and depression (3 questions also from the SCL-90). As with the 9-item scale, women were then divided in quartiles for each new variable. Cox regression models were conducted for each one, in the same manner as previously explained. A second sensitivity analysis was performed for the life stress exposure, excluding the question about being burdened by the pregnancy itself (Table 1, question 6, hereafter called pregnancy-related worries). Since it could be an indicator of a pregnancy-related problem possibly increasing the rate of preterm birth by itself, this was performed to address concerns about reverse causality. We categorised the new variable in quartiles and repeated the Cox regression analyses. Third, each item composing the life stress score was also investigated individually to determine whether the type of stressors could impact length of gestation differently. Finally, in addition to preeclampsia being a potential source of stress as any other pregnancy complications, stress could also be considered a risk factor of preeclampsia. Thus, we performed a sensitivity analysis excluding preeclampsia from the list of diseases.

2.8 | Ethics approval

The DNBC was approved by the Health Research Ethics Committee in Denmark (no. [KF] 01–471/94), and participants provided written informed consent.

3 | RESULTS

3.1 | Baseline characteristics

In the analysis population, 456 (0.6%) women gave birth very or moderately preterm, 2481 (3.1%) late preterm, 12,315 (15.2%) early term, 58,435 (72.1%) full term and finally 7304 (9.0%) children were born post-term. Across all intervals, 222 (0.3%) children were stillborn. The distribution of levels of life stress and emotional distress by each covariate is presented in Table 2. As expected, women with a lower educational level had a higher level of stress. The same was true for women not living with a partner or women suffering from a disease during pregnancy. The analysis sample with complete data on the outcome, exposure and covariates were 78,349 pregnancies for life stress and 78,313 pregnancies for emotional distress.

3.2 | Life stress, emotional distress and gestational age

Table 3 shows the unadjusted and adjusted hazard ratios of the association between levels of life stress or emotional distress during pregnancy and gestational age at birth in days, in each of the predefined intervals. After adjustment, moderate or high levels of life stress during pregnancy were associated with a higher rate of giving birth across the different gestational age periods compared with no life stress, with the highest relative rates in the earlier gestational ages. Indeed, the strongest association was observed in the very or moderate preterm interval, with women with a high level of life stress having an increased rate of giving birth of 38% when compared to women with no life stress. A high level of emotional distress was associated with the rate of giving birth in the preterm and early term intervals.

3.3 | Sensitivity analysis

When the analysis was repeated for life stress excluding the item concerning pregnancy-related worries, the association observed previously essentially disappeared in the two preterm intervals (Table 4). The association was attenuated but remained in the term periods. Moreover, when looking at each of the stressors individually, only pregnancy worries (both a little or a lot) and worries about the mother's own diseases (a lot) were associated with the increased rate (Table 5). All other assessed stressors had no clear association with gestational

TABLE 2 Participant characteristics by levels of life stress and emotional distress

Characteristics	All (n = 80,991)	Life stress levels				Emotional distress levels			
		None (n = 23,870)	Low (n = 17,622)	Moderate (n = 24,869)	High (n = 14,350)	None (n = 13,778)	Low (n = 30,410)	Moderate (n = 19,456)	High (n = 17,021)
Age (mean [SD])	30.4 (4.3)	30.4 (4.1)	30.5 (4.1)	30.5 (4.3)	30.3 (4.7)	30.9 (4.1)	30.4 (4.1)	30.3 (4.3)	30.1 (4.6)
Education levels									
Low (%)	23.6	21.3	21.6	23.6	29.2	19.2	21.7	24.0	30.1
Medium (%)	40.4	43.6	41.4	39.1	36.0	38.4	40.9	40.9	40.5
High (%)	35.7	34.8	36.7	36.9	34.3	42.2	37.2	34.7	28.9
Missing (%)	0.3	0.3	0.3	0.3	0.4	0.2	0.3	0.3	0.4
Living with a partner									
No (%)	1.9	0.6	0.9	1.7	4.8	1.0	1.3	2.1	3.5
Yes (%)	98.1	99.4	99.0	98.3	95.2	98.9	98.7	97.9	96.5
Missing (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Parity									
0 (%)	46.6	54.0	47.9	43.0	38.8	50.5	47.1	46.4	42.9
1+ (%)	53.3	45.9	52.1	56.9	61.2	49.4	52.8	53.6	57.1
Missing (%)	0.1	0.1	0.0	0.1	0.1	0.1	0.1	0.0	0.1
Fertility treatment									
No (%)	94.4	93.8	94.2	94.4	95.6	94.0	94.2	94.3	95.2
Yes (%)	5.6	6.1	5.8	5.6	4.4	6.0	5.8	5.6	4.7
Missing (%)	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.0
Non-communicable diseases									
No (%)	74.5	83.9	77.8	70.9	61.4	80.8	77.0	72.9	67.0
Yes (%)	24.2	15.3	21.0	27.6	36.8	18.3	22.0	25.7	31.3
Missing (%)	1.3	0.8	1.2	1.4	1.8	1.0	1.0	1.4	1.7
Infections									
No (%)	63.6	71.1	66.0	60.5	53.3	69.2	65.7	61.7	57.5
Yes (%)	35.2	28.0	32.8	38.1	44.8	29.9	33.2	36.9	40.8
Missing (%)	1.3	0.9	1.2	1.4	1.9	0.9	1.1	1.4	1.7
Congenital anomalies									
No (%)	95.6	95.8	95.5	95.6	95.3	95.8	95.6	95.6	95.4
Yes (%)	4.4	4.2	4.5	4.4	4.7	4.2	4.4	4.4	4.6
Missing (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

TABLE 3 Unadjusted and adjusted[a] hazard ratios (HRs) for the association between levels of life stress or emotional distress during pregnancy and the rate of giving birth, in sub-intervals of gestational age

	27–33 weeks		34–36 weeks		37–38 weeks		39–41 weeks		42–45 weeks	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Life stress										
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low	0.94 (0.71, 1.24)	0.92 (0.69, 1.23)	1.02 (0.91, 1.14)	1.04 (0.93, 1.17)	1.07 (1.02, 1.13)	1.07 (1.02, 1.13)	1.03 (1.00, 1.05)	1.02 (0.99, 1.04)	1.01 (0.95, 1.08)	1.01 (0.95, 1.08)
Moderate	1.29 (1.01, 1.62)	1.27 (0.99, 1.63)	1.08 (0.97, 1.19)	1.13 (1.02, 1.25)	1.09 (1.04, 1.15)	1.07 (1.02, 1.13)	1.05 (1.03, 1.07)	1.03 (1.01, 1.05)	1.09 (1.03, 1.16)	1.09 (1.03, 1.16)
High	1.37 (1.04, 1.79)	1.38 (1.04, 1.84)	1.06 (0.95, 1.20)	1.10 (0.97, 1.25)	1.26 (1.19, 1.32)	1.21 (1.15, 1.28)	1.08 (1.05, 1.10)	1.05 (1.02, 1.08)	1.01 (0.94, 1.08)	1.00 (0.93, 1.08)
Emotional distress										
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low	0.89 (0.67, 1.19)	0.89 (0.66, 1.19)	1.05 (0.94, 1.18)	1.03 (0.91, 1.16)	0.99 (0.93, 1.04)	0.98 (0.93, 1.03)	0.99 (0.97, 1.01)	0.98 (0.96, 1.00)	1.04 (0.97, 1.11)	1.03 (0.96, 1.10)
Moderate	1.13 (0.84, 1.52)	1.12 (0.83, 1.52)	1.09 (0.96, 1.24)	1.06 (0.93, 1.20)	1.03 (0.98, 1.09)	1.02 (0.96, 1.08)	1.00 (0.98, 1.03)	0.99 (0.97, 1.02)	1.02 (0.95, 1.10)	1.02 (0.94, 1.10)
High	1.41 (1.06, 1.89)	1.38 (1.02, 1.86)	1.09 (0.95, 1.24)	1.05 (0.91, 1.19)	1.14 (1.08, 1.21)	1.11 (1.04, 1.17)	1.03 (1.01, 1.06)	1.01 (0.99, 1.04)	1.08 (1.00, 1.17)	1.07 (0.99, 1.16)

[a] Adjusted for mother's age, education level, having a partner, parity, fertility treatment, non-communicable diseases, infections and the child's congenital anomalies.

age. When looking at the three underlying concepts for emotional distress separately, different results were observed (Table 4). The general stress measure from the GHQ showed no statistically significant association with the rate of giving birth. However, when taken separately, both high level of anxiety and depression from the SCL were associated with the rate of giving birth in all gestational age periods, but especially strong in the earliest interval. Lastly, the estimates obtained from the analysis excluding preeclampsia from the list of diseases were essentially the same as the ones including it (Table S1).

4 | COMMENT

4.1 | Principal findings

In this study, we found that moderate or high levels of life stress were associated with a higher rate of giving birth early in each of the predefined gestational age intervals when compared to women with no life stress. While this indicates that length of gestation is shorter across the full gestational age span for women experiencing stress, the intervals allowed the observation that the hazard ratios for that association decreased with increasing gestational age. However, these findings were solely driven by pregnancy-related worries and the mother's worries about her own health. When compared with women without emotional distress, we found that high level of emotional distress was associated with a shorter length of gestation in the preterm and early term intervals. From the emotional distress measure, only the anxiety and depression sub-measures were associated with the rate of giving birth.

4.2 | Strengths of the study

The DNBC's large size, prospective design and amount of data collected at each follow-up provide a unique opportunity to study the impact of prenatal stress on birth outcomes. A total of 80,991 pregnancies were included in the analyses which allowed to detect small associations. Another strength of the study is the linkage to a comprehensive medical birth registry for the measurement of gestational age at birth, which provides information on every birth in Denmark and secures full follow-up of the cohort. Also, the prenatal stress measures selected are of great relevance for the general population since they cover situations and feelings which can occur in everyday life, instead of rare and severe life events. The multiple stress measures analysed (i.e. life stress as a whole, chronic life stressors individually, emotional distress and its components of general stress, anxiety and depression) are strengths of the study as impact on length of gestation was found to differ between the different types of stress.

4.3 | Limitations of the data

The measures of life stress and emotional distress relied on self-report, covering 31.5 weeks of pregnancy on average, which could

have introduced some misclassification regarding their level of stress during this long period. Additionally, we do not have the timing of the prenatal stress experienced by the mothers, which has been suggested to have a role in the association between the stress exposure and birth outcomes.[37,38] Then again, the stress measures selected for this study mostly represent chronic stressors (e.g. financial troubles and partner relationship) that were probably experienced for the duration of the pregnancy. This does not apply to the pregnancy-related stress which could vary during the duration of the pregnancy. Also, even though the items for the emotional distress were taken from two standardised questionnaires, not all items from the original questionnaires were included in DNBC. This could impact the reliability of the measure of stress, anxiety and depression, leading to non-differential misclassification and underestimation of the association. The measures of stress used in this study are not standardised questionnaires and have not been used in previous research outside of DNBC publications. Their validity has thus not been tested. Moreover, some women gave birth preterm before they had the chance to provide information on their perceived stress during pregnancy. This explains the absence of extremely preterm births in the analyses and the relatively low prevalence of preterm births in general in this study. Additionally, even though the association of stress and length of gestation might not differ currently than from when the recruitment of DNBC took place, it is noteworthy that the data are 20 years old and that the specific sources of stress might have evolved. Lastly, only around 30% of eligible pregnancies in Denmark during the study period were recruited in the DNBC which can raise some concerns. Similar to what is observed in many cohort studies, the participants in DNBC were typically healthier and of higher socioeconomic status than the general population. However, the impact of non-participation in the DNBC on different exposure-outcome associations have been investigated several times and have shown that the selection bias was limited.[39,40]

4.4 | Interpretation

For emotional distress, when analysed in the different intervals, the finding that high level of emotional distress was associated with shorter length of gestation corroborates the work done by Tegethoff et al. in the same cohort.[41] Once divided into the three different sub-measures (i.e. general stress, anxiety and depression), the results remained aligned with previous literature. General stress having no impact on length of gestation is similar to some previous findings,[42,43] but not all.[23,37,44–46] Depression and anxiety have more consistently been associated with preterm birth[43,47,48] which is in line with our findings.

The observation that life stress was associated with giving birth preterm is in alignment with the literature on the impact of chronic life stressors on the length of gestation.[20,41,49] Interestingly, however, is that this association disappeared once the pregnancy worries were removed from the overall score. As expected, many studies looking at different measures of stress and anxiety during pregnancy

TABLE 4 Unadjusted and adjusted[a] hazard ratios (HRs) for the association between levels of life stress without pregnancy worries, and the three subscales of emotional distress (general stress, anxiety and depression pregnancy) and the rate of giving birth, in sub-intervals of gestational age

	27–33 weeks		34–36 weeks		37–38 weeks		39–41 weeks		42–45 weeks	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Life stress without pregnancy worries										
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low	1.05 (0.82, 1.35)	1.03 (0.80, 1.32)	1.02 (0.92, 1.13)	1.03 (0.92, 1.14)	0.99 (0.95, 1.04)	0.98 (0.94, 1.03)	1.01 (0.98, 1.03)	1.00 (0.98, 1.02)	1.03 (0.98, 1.10)	1.04 (0.98, 1.10)
Moderate	1.20 (0.95, 1.51)	1.21 (0.95, 1.53)	1.00 (0.90, 1.10)	1.02 (0.92, 1.13)	1.08 (1.04, 1.13)	1.06 (1.01, 1.11)	1.02 (1.00, 1.05)	1.01 (0.99, 1.03)	1.08 (1.02, 1.15)	1.09 (1.03, 1.16)
High	1.17 (0.85, 1.60)	1.11 (0.79, 1.55)	1.00 (0.87, 1.16)	1.01 (0.87, 1.18)	1.15 (1.08, 1.22)	1.11 (1.04, 1.18)	1.05 (1.02, 1.08)	1.03 (1.00, 1.07)	0.99 (0.91, 1.07)	0.98 (0.90, 1.07)
General stress										
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low	1.03 (0.83, 1.28)	1.09 (0.88, 1.36)	0.97 (0.88, 1.06)	1.01 (0.92, 1.11)	0.96 (0.92, 1.00)	0.95 (0.91, 0.99)	1.01 (0.99, 1.03)	0.99 (0.97, 1.01)	1.04 (0.99, 1.10)	1.03 (0.98, 1.09)
Moderate	1.30 (1.00, 1.70)	1.35 (1.03, 1.78)	0.92 (0.81, 1.04)	0.97 (0.86, 1.11)	1.02 (0.97, 1.08)	1.01 (0.95, 1.06)	1.04 (1.02, 1.07)	1.02 (0.99, 1.05)	0.99 (0.92, 1.06)	0.98 (0.91, 1.05)
High	1.03 (0.71, 1.48)	1.08 (0.73, 1.58)	0.95 (0.81, 1.11)	1.00 (0.85, 1.18)	1.07 (1.00, 1.15)	1.04 (0.97, 1.12)	1.04 (1.00, 1.07)	1.00 (0.97, 1.04)	1.10 (1.00, 1.21)	1.10 (1.00, 1.21)
Anxiety										
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low	1.13 (0.89, 1.43)	1.12 (0.88, 1.42)	1.00 (0.90, 1.10)	0.98 (0.89, 1.09)	1.02 (0.97, 1.06)	1.00 (0.96, 1.05)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.03 (0.97, 1.09)	1.03 (0.97, 1.09)
Moderate	1.28 (0.99, 1.66)	1.22 (0.94, 1.59)	1.08 (0.97, 1.21)	1.02 (0.91, 1.14)	1.08 (1.02, 1.13)	1.06 (1.00, 1.11)	1.01 (0.99, 1.04)	1.02 (0.99, 1.04)	1.06 (1.00, 1.13)	1.06 (0.99, 1.13)
High	1.55 (1.18, 2.02)	1.44 (1.09, 1.89)	1.24 (1.10, 1.39)	1.13 (1.00, 1.28)	1.19 (1.12, 1.25)	1.14 (1.08, 1.21)	1.04 (1.01, 1.06)	1.04 (1.01, 1.06)	1.08 (1.01, 1.17)	1.08 (1.00, 1.17)
Depression										
None	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Low	1.24 (1.00, 1.53)	1.22 (0.98, 1.51)	1.05 (0.96, 1.15)	1.03 (0.94, 1.13)	1.05 (1.01, 1.09)	1.03 (0.99, 1.08)	1.01 (0.99, 1.02)	1.00 (0.98, 1.02)	1.01 (0.95, 1.06)	1.01 (0.96, 1.07)
Moderate	1.15 (0.86, 1.53)	1.17 (0.87, 1.58)	1.03 (0.91, 1.17)	1.03 (0.91, 1.17)	1.11 (1.05, 1.17)	1.08 (1.03, 1.15)	1.03 (1.01, 1.06)	1.02 (0.99, 1.05)	1.05 (0.97, 1.12)	1.03 (0.96, 1.11)
High	1.80 (1.33, 2.45)	1.76 (1.28, 2.41)	0.98 (0.83, 1.15)	0.91 (0.76, 1.08)	1.26 (1.18, 1.35)	1.21 (1.13, 1.30)	1.06 (1.02, 1.09)	1.04 (1.00, 1.07)	0.97 (0.88, 1.08)	0.97 (0.87, 1.07)

[a]Adjusted for mother's age, education level, having a partner, parity, fertility treatment, non-communicable diseases, infections and the child's congenital anomalies.

TABLE 5 Unadjusted and adjusted[a] hazard ratios (HRs) for the association between 9 stressors individually and the rate of giving birth, in sub-intervals of gestational age

	27–33 weeks		34–36 weeks		37–38 weeks		39–41 weeks		42–45 weeks	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Financial troubles										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	1.20 (0.92, 1.58)	1.17 (0.88, 1.57)	0.85 (0.74, 0.97)	0.85 (0.74, 0.98)	1.04 (0.98, 1.10)	1.04 (0.98, 1.10)	1.00 (0.98, 1.03)	0.99 (0.96, 1.02)	1.08 (1.00, 1.16)	1.06 (0.99, 1.15)
A lot	0.83 (0.41, 1.66)	0.72 (0.34, 1.54)	0.91 (0.68, 1.21)	0.89 (0.66, 1.21)	1.08 (0.95, 1.22)	1.05 (0.93, 1.19)	1.04 (0.98, 1.11)	1.05 (0.99, 1.12)	0.97 (0.82, 1.15)	0.97 (0.82, 1.14)
Housing situation										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	0.93 (0.65, 1.33)	0.86 (0.59, 1.25)	0.92 (0.79, 1.08)	0.90 (0.76, 1.05)	0.99 (0.93, 1.06)	1.00 (0.93, 1.07)	0.97 (0.94, 1.00)	0.98 (0.95, 1.01)	1.01 (0.93, 1.10)	1.01 (0.93, 1.10)
A lot	1.37 (0.87, 2.14)	1.26 (0.79, 2.00)	0.93 (0.74, 1.17)	0.89 (0.70, 1.14)	1.09 (0.99, 1.21)	1.08 (0.98, 1.19)	1.02 (0.97, 1.07)	1.03 (0.98, 1.08)	1.02 (0.90, 1.16)	1.01 (0.88, 1.14)
Work situation										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	0.90 (0.71, 1.14)	0.86 (0.68, 1.10)	0.97 (0.88, 1.07)	0.99 (0.90, 1.09)	0.98 (0.94, 1.03)	0.99 (0.94, 1.03)	1.00 (0.98, 1.02)	0.99 (0.97, 1.02)	1.03 (0.98, 1.09)	1.04 (0.98, 1.10)
A lot	0.98 (0.70, 1.36)	0.97 (0.69, 1.37)	1.02 (0.88, 1.18)	1.01 (0.87, 1.17)	1.03 (0.96, 1.10)	1.00 (0.94, 1.07)	1.03 (1.00, 1.06)	1.01 (0.98, 1.04)	1.00 (0.92, 1.10)	1.02 (0.93, 1.11)
Partner relationship										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	1.10 (0.77, 1.57)	1.13 (0.78, 1.63)	0.91 (0.77, 1.07)	0.97 (0.82, 1.15)	1.08 (1.01, 1.16)	1.07 (1.00, 1.15)	1.05 (1.01, 1.08)	1.04 (1.00, 1.07)	1.00 (0.90, 1.11)	1.01 (0.91, 1.12)
A lot	1.41 (0.76, 1.65)	1.49 (0.76, 2.92)	1.09 (0.81, 1.48)	1.05 (0.74, 1.48)	1.16 (1.01, 1.32)	1.10 (0.95, 1.28)	1.02 (0.95, 1.10)	1.02 (0.95, 1.10)	1.08 (0.92, 1.26)	1.03 (0.87, 1.21)
Family and friends relationships										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	0.68 (0.43, 1.06)	0.65 (0.41, 1.04)	0.97 (0.82, 1.14)	0.98 (0.83, 1.15)	1.09 (1.02, 1.17)	1.09 (1.01, 1.17)	1.03 (1.00, 1.07)	1.03 (0.99, 1.06)	0.95 (0.86, 1.06)	0.94 (0.85, 1.05)
A lot	1.35 (0.67, 2.71)	1.39 (0.69, 2.80)	0.88 (0.60, 1.28)	0.90 (0.61, 1.33)	1.14 (0.98, 1.32)	1.10 (0.94, 1.28)	1.01 (0.94, 1.09)	1.00 (0.93, 1.08)	0.90 (0.71, 1.15)	0.92 (0.71, 1.18)
Pregnancy worries										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	1.20 (0.98, 1.47)	1.23 (1.00, 1.52)	1.05 (0.97, 1.15)	1.10 (1.00, 1.20)	1.07 (1.03, 1.11)	1.06 (1.02, 1.10)	1.04 (1.02, 1.06)	1.02 (1.00, 1.04)	1.06 (1.01, 1.11)	1.05 (1.00, 1.11)
A lot	1.69 (1.30, 2.20)	1.77 (1.34, 2.36)	1.31 (1.16, 1.48)	1.39 (1.22, 1.58)	1.44 (1.37, 1.52)	1.39 (1.31, 1.47)	1.12 (1.09, 1.15)	1.08 (1.05, 1.11)	0.95 (0.87, 1.04)	0.94 (0.86, 1.04)
Diseases of the mother										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	1.03 (0.78, 1.36)	1.06 (0.80, 1.40)	1.00 (0.89, 1.13)	0.99 (0.88, 1.12)	1.07 (1.02, 1.13)	1.04 (0.98, 1.09)	1.03 (1.00, 1.05)	1.01 (0.99, 1.04)	0.98 (0.91, 1.05)	0.97 (0.90, 1.04)
A lot	1.40 (0.97, 2.01)	1.42 (0.98, 2.07)	1.40 (1.20, 1.64)	1.35 (1.14, 1.59)	1.39 (1.30, 1.50)	1.30 (1.21, 1.40)	1.10 (1.06, 1.14)	1.07 (1.03, 1.12)	0.86 (0.76, 0.97)	0.85 (0.75, 0.97)

(Continues)

TABLE 5 (Continued)

	27–33 weeks		34–36 weeks		37–38 weeks		39–41 weeks		42–45 weeks	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Diseases of family and friends										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	0.88 (0.61, 1.27)	0.93 (0.64, 1.35)	0.86 (0.73, 1.01)	0.93 (0.79, 1.09)	0.98 (0.92, 1.05)	0.97 (0.91, 1.04)	0.99 (0.96, 1.03)	0.98 (0.95, 1.01)	1.03 (0.94, 1.13)	1.03 (0.94, 1.13)
A lot	1.28 (0.83, 1.99)	1.31 (0.83, 2.05)	0.97 (0.78, 1.20)	1.06 (0.86, 1.32)	1.09 (0.99, 1.19)	1.06 (0.96, 1.16)	1.01 (0.97, 1.05)	0.99 (0.95, 1.04)	1.01 (0.89, 1.14)	1.00 (0.88, 1.13)
Other worries										
No	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
A little	0.72 (0.39, 1.35)	0.76 (0.41, 1.43)	0.88 (0.69, 1.12)	0.90 (0.70, 1.15)	1.05 (0.95, 1.16)	1.04 (0.94, 1.15)	1.00 (0.95, 1.05)	0.99 (0.95, 1.04)	1.06 (0.93, 1.20)	1.05 (0.92, 1.19)
A lot	1.67 (1.03, 2.71)	1.51 (0.91, 2.53)	1.03 (0.79, 1.34)	1.03 (0.79, 1.35)	1.14 (1.02, 1.28)	1.09 (0.97, 1.23)	1.12 (1.06, 1.18)	1.11 (1.05, 1.18)	0.98 (0.82, 1.15)	0.97 (0.82, 1.16)

[a]Adjusted for mother's age, education level, having a partner, parity, fertility treatment, non-communicable diseases, infections and the child's congenital anomalies.

have found that pregnancy-related anxiety has the highest correlation with gestational age at delivery.[23,43,50,51] The findings that the life stress association with gestational age at birth was mainly driven by pregnancy or health-related worries and that anxiety and not general stress had an impact on preterm birth are supportive of each other. Women suffering from anxiety are generally more susceptible to also experiencing stress through their appraisal of different situations and environments,[38,50,52] and they could therefore also be at higher risk of experiencing more fears about the health and well-being of their child and their own. Pregnancy-related stress could thus be greatly influenced by the women's baseline anxiety level, especially if other health issues or past problems in pregnancy were encountered.

On the other hand, pregnancy-related worries and the mother's worries about her own health being the only stressors associated with gestational age at birth suggests that these associations may be due to reverse causality, where the mother is already being concerned about early indicators of pregnancy complications. Specifically in this case, the information on stress was collected quite late in the pregnancy, and thus the pregnancy stress might have been caused by early signs of a pregnancy-related problem which may lead to preterm birth. This challenges the results of previous studies and the underlying hypothesis of stress during pregnancy being an important risk factor for preterm birth. While this study cannot confirm the reverse causation hypothesis, it is critical enough to warrant more attention from future studies. Multiple measures of stress during the length of gestation, some measured early enough in pregnancy to precede any signs of a possible preterm birth, are necessary to explore the possibility that the associations previously found between stress and preterm birth are a consequence of reverse causality.

5 | CONCLUSIONS

In conclusion, by analysing data from this large cohort, we found emotional stress and life stress to be associated with a shorter length of gestation. The latter association was mainly driven by pregnancy worries and the mother's worries about her own health, which suggests that reverse causality may play a role in the associations reported by us and others between stress and risk of preterm birth.

AUTHOR CONTRIBUTIONS
JB, A-MNA, NHR and IF contributed to the study concept and design. JB, A-MNA, PKA and LC developed the analysis plan and JB and LC performed the analyses. JB prepared the first draft of the manuscript which was revised by A-MNA, LC, PKA, NHR and IF. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

Authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Applications to access the DNBC data can be submitted to the DNBC management and steering committee. More information on DNBC data access procedures can be found on their website (https://www.dnbc.dk/access-to-dnbc-data).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.