

## Worrying yourself sick? Association between pre-eclampsia onset and health-related worry in pregnancy



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### ABSTRACT

Psychosocial stress may influence pregnancy health. We examined the relationship between worry about pregnancy health and pre-eclampsia. General stress, mental health, and self-reported pregnancy health worry were measured in a study of 10,037 U.S. nulliparous women. Logistic regression found a dose-response relationship between first trimester pregnancy-health worry and subsequent pre-eclampsia onset, controlling for health history ( $Beta = 0.40$ ,  $SE = 0.09$ ,  $P < 1 \times 10^{-6}$ ). A machine learning regularized regression found a significant relationship between worry and pre-eclampsia onset, controlling for all other potential predictors of pre-eclampsia measured at baseline, suggesting that worry plays a unique role in pre-eclampsia risk.

### 1. Introduction

Psychosocial stress during pregnancy has been identified as a potential contributor to adverse pregnancy events, including pre-eclampsia [1,2]. Here, we conducted both a logistic and a machine learning regression analysis to examine the relationship between a pregnant woman's feelings of worry in the first trimester of pregnancy with her subsequent risk of pre-eclampsia onset in a large observational cohort of nulliparous women.

Pre-eclampsia is a widely-recognized leading risk factor for maternal mortality [3]. It is also a significant contributor to premature delivery, which is the leading cause of neonatal morbidity and mortality in the United States [4]. Certain factors, such as racial discrimination or poverty, may contribute to both psychosocial stress and adverse pregnancy events [5], suggesting a more indirect effect of stress on adverse outcomes. The stress associated with those factors may also directly influence disease susceptibility. In this study, we examined the association of the feelings of worry about health that occur during early pregnancy (first trimester) with the subsequent onset of pre-eclampsia.

### 2. Methods

Using data from the Nulliparous Pregnancy Outcomes Study: Monitoring Mothers-to-Be (nuMoM2b), we examined the relationship between patient self-reported worry about pregnancy onset conditions and confirmed pre-eclampsia onset. The NuMoM2b study was a prospective cohort study of 10,037 nulliparous women with singleton gestations conducted across 8 U.S. sites [6]. Worry about the effect of ongoing health problems on a woman's pregnancy was measured during the first trimester (visit 1 between 6+0 and 13+6 weeks' gestation) with the following question, "Are you feeling bothered, upset or worried at this point in your pregnancy – about the effect of ongoing health problems such as high blood pressure or diabetes on your pregnancy?" Participants responded on a 3-point Likert scale. Stress and mental health were also measured at Visit 1 by the State-Trait Anxiety Inventory-Trait Subscale [7], Perceived Stress Scale [8], and Edinburgh Postnatal Depression Scale [9], respectively. Participants also reported

any family history of pre-eclampsia at a second trimester visit (visit 2 between 16+0 and 21+6 weeks' gestation and at least 4 weeks after visit 1).

Pre-eclampsia onset was extracted from the medical record post-delivery. Pre-eclampsia included mild and severe pre-eclampsia, and eclampsia. Pre-eclampsia was defined as new-onset hypertension ( $\geq 140$  mm Hg systolic or  $\geq 90$  mm Hg diastolic) occurring on 2 or more occasions, at least 4 h apart, and at gestational weeks' greater than 20 weeks 0 days, with proteinuria of  $\geq 300$  mg in a 24 h urine collection, or protein/creatinine ratio of 0.3 mg/dL or more. In the absence of proteinuria, it was defined as new-onset hypertension with the new onset of at least one of the following: severe hypertension ( $\geq 160$  mm Hg systolic or  $\geq 110$  mm Hg diastolic), thrombocytopenia (platelet count less than  $100,000 \times 10^9/L$ ), renal insufficiency (serum creatinine concentrations greater than 1.1 mg/dL or doubling of serum creatinine concentration), impaired liver function (elevated blood concentrations of liver transaminases to twice normal concentration), pulmonary edema, or new-onset headache unresponsive to medication. Severe pre-eclampsia was defined as either new-onset severe hypertension or new-onset hypertension with evidence of end-organ dysfunction as outlined above or eclampsia. More detailed definitions for these outcomes in the nuMom2b data can be found in previous publications [10,11].

### 3. Results

Overall, approximately 6% of participants ( $n = 611$ ) had a pre-eclampsia diagnosis ( $n = 263$  with mild pre-eclampsia,  $n = 343$  with severe pre-eclampsia, and  $n = 5$  with eclampsia). There were 8838 participants who filled out the pregnancy-health worry questionnaire, reducing the number of pre-eclampsia cases available for analysis to 525. Using simple logistic regression, we found a dose-response relationship between worry about pregnancy-onset health conditions at the pregnant woman's first visit and subsequent pre-eclampsia onset (Fig. 1),  $Beta = 0.58$ ,  $SE = 0.08$ ,  $P < 1 \times 10^{-13}$ ,  $N = 8838$ ). This relationship held after controlling for pre-existing clinical conditions (specifically, diabetes and hypertension documented prior to pre-

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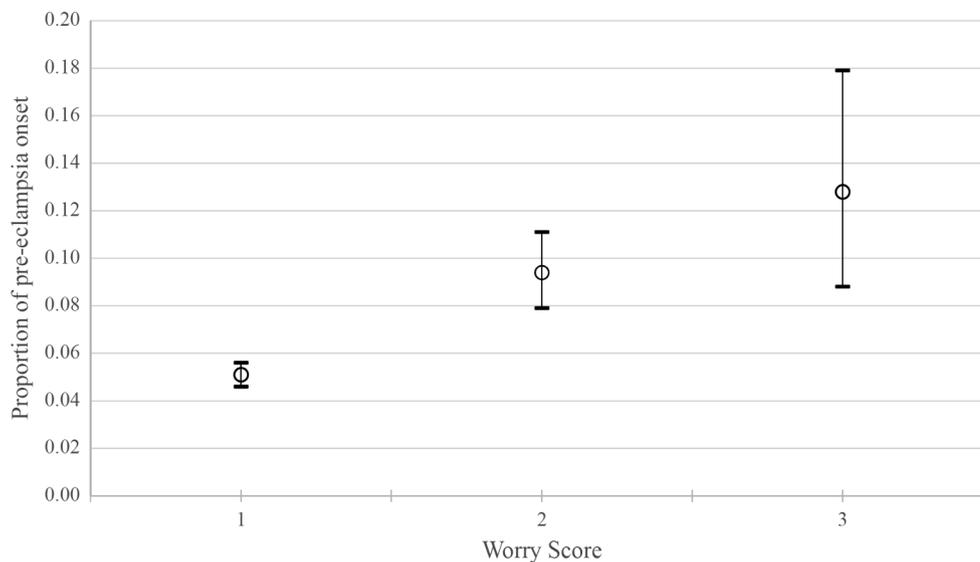


Fig. 1. Proportion, with 95% confidence intervals, of women developing pre-eclampsia at each level of baseline worry about pregnancy-related health among 8838 nulliparous women across 8 U.S. sites.

eclampsia onset), both of which could explain worry about the effect of ongoing pregnancy-related health problems, ( $Beta = 0.40$ ,  $SE = 0.09$ ,  $P < 1 \times 10^{-6}$ ,  $N = 8450$ ).

Using machine learning regularized regression (LASSO), we modeled the onset of pre-eclampsia from baseline pregnancy-related health worry and other measured potential direct influences (e.g. diabetes status, hypertension status) and indirect influences (e.g., demographics, stress and mental health, experienced discrimination, and family history) on pre-eclampsia onset.

LASSO selected worry about pregnancy-onset health conditions as an important predictor of pre-eclampsia using cross-validation, even after including every other variable available (over 200 measures) in the nuMom2b dataset available measured simultaneously at the first visit. After controlling for all variables selected by the LASSO at visit 1, the relationship between pregnancy-related health worry and pre-eclampsia onset remained statistically significant, ( $Beta = 0.02$ ,  $SE = 0.006$ ,  $P = .01$ ,  $N = 7972$ ). Similarly, after controlling for all variables selected by the LASSO at visit 2 or before (including the presence of diabetes and hypertension, as well as family risk factors), the relationship remained statistically significant ( $Beta = 0.01$ ,  $SE = 0.007$ ,  $P = .04$ ,  $N = 6720$ ).

#### 4. Discussion

From a large observational cohort study, we found that women who worried about the onset of poor health during early pregnancy, controlling for other relevant health indicators, were 2–3 times more likely to develop pre-eclampsia. Although further research is required to determine if this worry is reflective of a patient's ability to manage potential new health conditions or of underlying physiological stress tendencies not captured by the administered study measures, these results are supportive of psychosocial stress having a direct impact on the subsequent onset of adverse pregnancy events. Including a brief assessment of worry in early prenatal care could help providers better identify those patients at greater risk for future pre-eclampsia onset. Additionally, interventions to manage patient concerns about pregnancy-related health conditions could have important positive health effects for the maternal-infant duo.

#### Declaration of Competing Interest

The authors are co-founders of NAIMA Health LLC.

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