# Psychological Distress During Pregnancy and the Development of Pregnancy-Induced Hypertension: A Prospective Study

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## ABSTRACT

**Objective:** Pregnancy-induced hypertension (PIH) is associated with serious complications in both the mother and the unborn child. We examined the possible association between trajectories of maternal psychological distress symptoms and PIH separately in primiparous and multiparous women.

**Methods:** Pregnancy-specific negative affect (P-NA) and depressive symptoms were assessed prospectively at each trimester using the Tilburg Pregnancy Distress Scale pregnancy negative affect subscale (P-NA) and the Edinburgh Depression Scale (EDS). Data on PIH were collected from medical records. Growth mixture modeling analysis was used to identify trajectories of P-NA and EDS. The independent role of P-NA and EDS symptom trajectories on developing PIH was examined using multivariate logistic regression models.

**Results:** One hundred (7.6%) women developed PIH and were compared with 1219 women without hypertension or other complications during pregnancy. Three P-NA trajectories were identified: low stable (reference group; 90%), decreasing (5.2%), and increasing (4.8%). The latter two classes showed persistently and significantly higher P-NA symptoms during pregnancy compared with the reference group. In multiparous women, high P-NA scores (belonging to classes 2 and 3) were related to PIH (odds ratio [OR] = 6.91, 95% confidence interval [CI] = 2.26–21.2), independent of body mass index (OR = 1.17, 95% CI = 1.06–1.27) and previous PIH (OR = 14.82, 95% CI = 6.01–32.7). No associations between P-NA and PIH were found in primiparous women. EDS trajectories were not related to PIH in both primiparous and multiparous women.

**Conclusions:** In multiparous women, persistently high levels of P-NA symptoms but not depressive symptoms were independently associated with development of PIH.

**Key words:** pregnancy-induced hypertension, pregnancy distress, depression, negative affect, growth mixture modeling, trajectories.

## INTRODUCTION

Pregnancy-induced hypertensive disorders (PIH), affecting 1 of 10 women, are one of the most common medical complications during pregnancy and among the main causes of maternal, fetal, and neonatal mortality and morbidity (1,2). In Europe, it is even the most prevalent cause of perinatal maternal death (3). Therefore, increasing our understanding of its etiology and potential risk factors is an important public health objective.

Hypertensive disorders during pregnancy include a spectrum of four clinical entities with increasing severity (1,4). PIH refers to a systolic blood pressure greater than 140 mm Hg and a diastolic blood pressure less than 90 mm Hg, which develops after 20 weeks of pregnancy. When PIH co-occurs with superimposed proteinuria (reflecting organ damage) and symptoms such as headache or severe fluid retention with edema, it is called preeclampsia (4). The next step in the spectrum is preeclampsia with convulsions: eclampsia. The most extended and life-threatening stage is the HELLP syndrome (hemolysis elevated liver enzymes and low platelets). These conditions might be associated with various complications in the mother during pregnancy such as placental abruption, cerebrovascular events, pulmonary edema, dysfunction of the central nervous system, and oliguria (1). Furthermore, numerous studies linked PIH and preeclampsia to adverse birth outcomes, such as small for gestational age, low birth weight, and intrauterine growth retardation, preterm birth, and cesarean delivery (1,5). Also, women with PIH are at an increased risk for developing hypertension, cardiovascular disease, diabetes mellitus, and kidney disease later in life (6,7), as well as for decreased cognitive abilities and mental disorders (8,9).

The etiology and pathophysiology of PIH are largely unknown, but disturbed placentation, induced by maternal immunologic, as well as genetic and environmental factors are plausible contributing factors (4,10,11). Maternal risk factors related to PIH include primiparity, first child born at older age, chronic hypertension, obesity, diabetes mellitus, renal diseases, and thyroid dysfunction (4,12,13). For the preeclampsia syndrome, there is growing evidence that it is part of a spectrum of "disorders of placentation" including

**ANOVA** = analysis of variance, **BMI** = body mass index, **EDS** = Edinburgh Depression Scale, **PIH** = pregnancy-induced hypertension, **P-NA** = pregnancy-related negative affect, **SD** = standard deviation, **TPDS** = Tilburg Pregnancy Distress Scale

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fetal growth restriction, preterm rupture of membrane, and premature delivery (13). Moreover, there is evidence that there are at least two subtypes: early and late-onset preeclampsia. Early preeclampsia seems to have primarily a placental cause, whereas late-onset preeclampsia seems to be an interplay between placenta involution and a maternal genetic predisposition to cardiovascular and metabolic disorders (13). Late-onset preeclampsia accounts for 80% to 95% of all eclampsia cases worldwide (14).

Another possible determinant of PIH that has received only little attention is psychological distress. Psychological distress can be defined as "a state of emotional suffering characterized by symptoms of depression and anxiety sometimes accompanied by somatic symptoms" (15). This lack of attention is surprising because in the general population, research repeatedly showed that acute and sustained stress is associated with elevated blood pressure, a major risk factor for developing cardiovascular disease (16–18).

In a meta-analysis of 13 studies, psychological distress in pregnant women was found to be a *possible* risk factor for PIH and preeclampsia (19). Methodological limitations included the reliance on retrospective self-report measures and the use of different types of assessment tools. In addition, the definition of the control group (without PIH) was often unclear, whereas it is well known that up to 30% of pregnant women in "control" groups develop serious other complications throughout gestation, such as gestational diabetes and inappropriate weight gain, which are also linked to poor obstetric outcomes (1). Therefore, the possible role of distress in women who develop PIH should preferably be compared with that of a healthy control group with a physiological pregnancy without other complications. A recent systematic review that focused specifically on the association of depression with hypertension during pregnancy proposed a possible association between hypertension in pregnancy and depression and antidepressant medication, but the authors concluded that more research is needed (20). Furthermore, negative affect (NA), that is, the experience of negative emotions and poor self-concept (21), is a marker of psychological distress that has been relatively neglected in the literature on hypertensive disorders in pregnancy. This is more surprising given the fact that meta-analyses showed that women who develop preeclampsia—which is commonly restricted to the perinatal period—are at 2-fold increased risk for cardiovascular risk and death (3.7-fold increased risk for hypertension and 1.8-fold for stroke) (22). Nonetheless, various studies propose that NA is a possible risk factor for the development of cardiovascular disease in the general population (23,24). Although there are many birth cohorts in the world looking at biological determinants of pregnancy complications, there are very few cohorts that have included measures of psychological risk factors for these complications, possibly explained by insufficient epidemiological power including stratification for parity.

No previous studies have measured distress at various time points during pregnancy and linked this to the development of PIH (which develops after 20 weeks of gestation). More knowledge about these time trajectories is important for the following reasons. First, during early gestation, pregnancy distress may predominantly be related to concerns about fetal health that in general decrease after a standardized ultrasound at 20 weeks confirming normal fetal development (25). Furthermore, psychological distress is multifactorial in terms of etiology and heterogeneous with regard to its behavioral and biological correlates, with a large variability in symptom profiles both between and within individuals over time (26). A statistical approach that can consider these individual differences in distress symptoms over time is growth mixture modeling. This approach can be used to classify women according to latent classes into groups, based on similarities in the course of symptom profiles rather than differences (27,28). It is also well known that, in the case of preeclampsia, primiparity is an important risk factor (4,12,13). Immune maladaptation with defective spiral artery remodeling of the placenta is the prevailing interpretation for this increased risk of nulliparous women (13,29). Moreover, in multiparous women, an important risk factor for PIH is an episode of previous PIH. Because biological and immunological risk factors differ according to parity, this suggests that looking at the possible associations between pregnancy distress and PIH should preferentially be studied in primiparous and multiparous women separately. The possible explanation is the altered immune response due to T-memory cells that differentiate after a first conception (30). This in turn requires cohorts with a large sample size for appropriate epidemiological power.

The aim of the current study was to examine the association between trajectories of pregnancy-specific distress and development of PIH, using growth mixture modeling. The main outcome was PIH in primiparous and multiparous women separately, and the predictors were the psychological distress trajectories (pregnancy-specific NA [P-NA] and symptoms of depression), adjusted for confounders of PIH.

## METHODS

### Participants

The current study sample was a subsample of women participating in the Holistic Approach to Pregnancy and the first Postpartum Year (HAPPY) study, a longitudinal cohort study of which the details have been described previously (31). The following exclusion criteria were used: a multiple pregnancy, taking antidepressant medication before week 20 of pregnancy, severe psychiatric disorder (e.g., schizophrenia, borderline personality disorder, or bipolar disorder), and a documented history of chronic disease (e.g., diabetes I, thyroid dysfunction). Eligibility criteria included enrollment during the first 14 weeks of pregnancy and sufficient understanding of the Dutch language to complete the questionnaires. Of the 3160 eligible women who were approached, 2219 (74%) participated and provided written informed consent. One hundred eleven of these women did not complete the assessments of P-NA and depressive symptoms during pregnancy. The time window to assess pregnancy distress symptoms of the remaining 2108 women was set at approximately 2 weeks of 12, 22, and 32 weeks of gestation (i.e., 10–14, 20–24, and 30–34 weeks). Of these women, 278 did not complete questionnaires within this time frame, which resulted in a sample of 1831 women. Because this study aimed to compare women who developed PIH with a control group consisting of healthy pregnant women with an uncomplicated pregnancy, women with other gestational complications were excluded from further analysis, including other "disorders of placentation": fetal growth restriction, preterm rupture of membrane, and premature birth. However, women who developed PIH plus another obstetric complication were included. We also excluded—for both PIH and control groups—women with other obstetric complications such as gestational diabetes and inappropriate weight gain. This resulted in a total of 512 exclusions. This resulted in a final sample of 1319 women to be included in the data-analyses: healthy controls with uncomplicated pregnancy and women who developed PIH. There were six women with essential hypertension, and because this is not an obstetric complication, they were kept in the study but not defined as PIH.

### Procedures

Participants were recruited by 17 community midwife practices and the obstetric departments of 2 large hospitals in Southeast Brabant, the Netherlands, from January 2013 to September 2014. In each trimester of pregnancy (12, 22, and 32 weeks), participants received written or online questionnaires to assess demographic features and levels of pregnancy distress. Data on pregnancy

complications and PIH were collected from obstetrical records after childbirth by a research midwife. Women who were diagnosed with high blood pressure before 20 weeks of gestation were considered as having "unknown essential hypertension," and their medical treatment was according to standard clinical guidelines (e.g., with methyldopa, β-adrenergic blocking agents); these women were therefore not considered to have PIH and not included in the control group. The Ethical Board of Tilburg University (protocol number EC-2012.25) and the Medical Ethical Committee of the Máxima Medical Centre in Veldhoven approved the study.

## Measures

### Pregnancy-Induced Hypertension

PIH was defined as the development of a systolic blood pressure ≥140 mm Hg and a diastolic blood pressure ≥90 mm Hg (at least two blood pressure readings) after 20 weeks of pregnancy in previously normotensive women. After birth, participants' obstetric records were examined regarding the diagnosis of PIH. In the current study, PIH was categorized as either "no hypertension developed after 20 weeks of pregnancy" or "hypertension developed after 20 weeks of pregnancy with or without organ damage," including women with (pre)eclampsia and HELPP syndrome. As healthy controls, we included only women without PIH but also without other obstetric complications (such as gestational diabetes) in the analyses.

### Pregnancy Distress

Psychological distress during pregnancy was operationalized as symptoms of pregnancy-related NA and depression during pregnancy at 12, 22, and 32 weeks of gestation, and assessed with the Tilburg Pregnancy Distress Scale (TPDS) (32) and the Dutch version of the Edinburgh (postnatal) Depression Scale (E(P)DS) (33), respectively.

The TPDS is a 16-item self-rating scale used to measure pregnancy-related emotional distress over the past 7 days. The TPDS was developed to measure pregnancy-specific psychological functioning and consists of two subscales: NA (11 items) and "partner involvement" (5 items). The TPDS was developed from in-depth interviews with primiparous and multiparous women, women who recently gave birth to a child (<4 weeks), and midwives and maternity nurses who take care of mother and baby at home during the first postpartum week (32). During these interviews, several themes emerged, from which the items for a questionnaire were derived. The TPDS-NA includes items referring to worries about fetal health and delivery. As such, we believe that these symptoms are part of general anxiety symptoms reflecting women's worries for specific conditions in the perinatal period: fetal health and delivery. Only the NA subscale was used in the current study. Items were rated on a 4-point Likert-type scale resulting in total scores ranging from 0 to 33, with higher scores indicating more NA. Among Dutch pregnant women, the TPDS has a good internal consistency overall (Cronbach $\alpha = .78$) as well as for the NA subscale (Cronbach $\alpha = .80$) (32). The NA subscale was evaluated as excellent in terms of its internal consistency (34). The reliability and validity of this scale have been further documented in a study of pregnant women (35). Because it consists of pregnancy-specific items, it is defined as P-NA throughout this article.

Depressive symptoms during pregnancy were measured using the 10-item EDS. This scale measures depressive symptoms over the past 7 days on a 4-point scale, with total scores ranging from 0 to 30. Higher scores indicate more depressive symptoms. It was originally developed for postpartum women (36), but it has also been validated in pregnant women (37,38). In the current study, the Cronbach α values of the EDS at 12, 22, and 32 weeks of pregnancy were .82, .84, and .83, respectively. The correlations between the EDS and the TPDS-NA at different trimesters varied between 0.43 and 0.47. ($p < .001$).

### Covariates

#### *Demographic Variables*

At 12 weeks of gestation, the demographic characteristics of participating women were collected. These demographics included age (in years), educational level, ethnicity, and employment (yes or no).

#### *Obstetric Information*

Information on parity (primiparous or multiparous), previous miscarriage or abortion, (un)planned pregnancy, weeks of gestation at birth, and prematurity (<37 weeks of pregnancy) were obtained from obstetric records. Multiparous women were asked whether they had been diagnosed with PIH during their previous pregnancy (yes or no).

#### *Life-style Habits*

Intake of alcohol during pregnancy and smoking habits were assessed at 12, 22, and 32 weeks of gestation (yes or no). Furthermore, body mass index (BMI) before pregnancy was calculated.

#### *Psychiatric History*

A previous diagnosis of depression was assessed at 12 weeks of gestation.

## Statistical Analyses

Descriptive statistics (frequencies, means, standard deviations [SD]) were used to outline the baseline characteristics of the study sample as well as mean and SD scores for the EDS and the P-NA at different trimesters.

Growth mixture modeling with longitudinal latent class analysis was conducted to identify trajectories of women's P-NA symptoms and depressive symptoms separately across three time points (12, 22, and 32 weeks of gestation) using Mplus version 8.1 (39). The scores on the P-NA and EDS at 12, 22, and 32 weeks of gestation were used. Only linear growth factors could be estimated, because three time points were included. We started with a one-class model. Next, we fitted models with increasing numbers of classes. In the current study, each class represented a trajectory of P-NA or EDS symptoms during pregnancy. To identify the optimal number of classes, Bayesian information criterion values (40) and significant Lo-Mendell-Rubin likelihood ratio test (27,41) were considered as fit indices. The class membership of all participants in the study sample according to P-NA and depressive symptoms throughout pregnancy that showed the best model fit were exported to SPSS for subsequent analyses.

Moreover, we used Hayes' SPSS PROCESS macro 3.5 to examine the potential moderating effect of parity and trajectories of EDS and P-NA in the relationship between the trajectories and PIH. Differences in demographics, life-style habits, psychiatric history, obstetrics, and PIH were compared between each trajectory of P-NA and EDS symptoms using $\chi^2$ tests for categorical variables and *t* tests and analysis of variance (ANOVA) for continuous variables, for primiparous and multiparous women separately.

Multiple logistic regression analyses were performed with PIH as the dependent variable. The independent variables were the trajectories of pregnancy distress (P-NA and EDS symptoms). Data are presented as odds ratios (ORs) with 95% confidence intervals (CIs). We examined the interaction between P-NA and primiparous/multiparous pregnancy and subsequently performed the logistic regression analyses in primiparous and multiparous women separately as described previously. We adjusted for possible covariates based on previous literature, such as BMI and previous pregnancy hypertension (13), and performed the analyses in primiparous and multiparous women separately (IBM Statistics, Statistical Package for the Social Sciences; SPSS; version 25).

# RESULTS

## Participant Characteristics

In total, 100 of 1319 women (7.6%) developed PIH after 20 weeks of gestation. Table 1 presents the characteristics of these 100 women and 1219 healthy controls according to parity. Primiparous (women, $n = 677$) developed PIH twice as often in comparison to multiparous women ($n = 642$; 70 versus 30, $\chi^2(1) = 15.1$, $p < .001$). Compared with healthy primiparous women ($n = 607$), primiparous women who developed PIH ($n = 70$) had a significant higher BMI ($t(675) = 4.2$, $p < .001$), had a lower gestational age at birth ($t(675) = 3.3$, $p = .001$), and more often had a preterm birth ($\chi^2(1) = 10.9$, $p = .001$; Table 1). Multiparous

**TABLE 1.** Characteristics of Women Who Developed PIH in Current Pregnancy and Healthy Controls, Sorted by Parity

| | Primiparous Women ($n$ = 677) | | | | Multiparous Women ($n$ = 642) | | | |
|---|---|---|---|---|---|---|---|---|
| | Women With PIH ($n$ = 70) | | Women Without PIH ($n$ = 607) | | Women With PIH ($n$ = 30) | | Women Without PIH ($n$ = 612) | |
| | $n$ (%) | Mean (SD) | $n$ (%) | Mean (SD) | $n$ (%) | Mean (SD) | $n$ (%) | Mean (SD) |
| Demographics | | | | | | | | |
| Age, y | | 29.51 (3.83) | | 29.26 (3.43) | | 30.51 (3.63) | | 31.48 (3.28) |
| High educational level[a] | 39 (56.2) | | 388 (63.9) | | 16 (53.8) | | 425 (69.6) | |
| Paid job | 66 (93.8) | | 577 (95.0) | | 28 (92.3) | | 555 (90.7) | |
| White women | 67 (96.3) | | 599 (98.8) | | 30 (100.0) | | 603 (98.5) | |
| Life-style habits | | | | | | | | |
| BMI prepregnancy, kg/m$^2$ | | 25.68 (4.58)* | | 23.41 (3.66)* | | 26.24 (5.25)* | | 23.42 (3.71)* |
| Alcohol use during pregnancy | 2 (2.5) | | 23 (3.8) | | 0 (0.0) | | 21 (3.4) | |
| Smoking during pregnancy | 4 (6.3) | | 37 (6.2) | | 2 (6.7) | | 32 (5.3) | |
| Obstetrics | | | | | | | | |
| Pregnancy | | | | | | | | |
| Previous miscarriage/abortion | 15 (21.3) | | 112 (18.7) | | 13 (43.3) | | 203 (33.2) | |
| Unplanned pregnancy | 4 (5.0) | | 42 (7.0) | | 2 (5.2) | | 31 (5.0) | |
| Previous PIH | — | | — | | 13 (33)* | | 20 (3.3) | |
| Delivery | | | | | | | | |
| Weeks of gestation at birth | | 38.5 (2.24)* | | 39.5 (2.11)* | | 38.9 (1.11)* | | 39.88 (1.27)* |
| Preterm birth (<37 wk) | 12 (17.1)* | | 38 (6.3)* | | 0 (0.0) | | 11 (1.8) | |
| Psychiatric history | | | | | | | | |
| Previous episode of depression | 9 (12.9) | | 97 (16) | | 4 (13.3) | | 98 (16) | |

PIH = pregnancy-induced hypertension; SD = standard deviation; BMI = body mass index.

* Significant at .05 using $\chi^2$ tests for categorical variables and $t$ tests for continuous variables.

[a] High = bachelor's degree or higher.

**TABLE 2.** Model Fit Indices for Deciding the Number of Classes of Negative Affect: Growth Mixture Models

| | 1 | 2 | 3[a] | 4 | 5 |
|---|---|---|---|---|---|
| BIC | 32,889.688 | 32,516.83 | 32,282.14 | 32,194.83 | 32,144.31 |
| Entropy | — | 0.87 | 0.89 | 0.84 | 0.83 |
| BLRT | — | <0.001 | <0.001 | <0.001 | <0.001 |
| LMR-LRT | — | <0.01 | <0.01 | 0.17 | 0.07 |

BIC = Bayesian information criterion; BLRT Bootstrapped likelihood ratio test; LMR-LRT = Lo-Mendell-Rubin likelihood ratio test.

For each model, all classes had free (equal) intercept growth factor variances and the slope growth factor variances fixed to zero.

[a] Indicates the final model.

women who developed PIH ($n$ = 30) had a significantly higher BMI ($t(640) = 3.50$, $p = .002$), delivered at a lower gestational age ($t(640) = 3.80$, $p < .001$), and had a history of PIH more often ($\chi^2(1) = 52.2$, $p < .001$), compared with healthy multiparous controls ($n$ = 612).

## Trajectories of P-NA Symptoms

Based on the fit index statistics (Bayesian information criterion, Lo-Mendell-Rubin likelihood ratio test, and bootstrapped likelihood ratio test), the two-class growth mixture model of P-NA fitted the data significantly better than the one-class model (Table 2). The three-class model surpassed the two-class model and was chosen to best represent the trajectories of P-NA in our sample.

The trajectories in this three-class model were readily interpretable, were clinically relevant, and had adequate entropy. Although some classes were rather small, they all met the criteria of containing at least 1% of the participants of the total sample. Figure 1 illustrates these three trajectories of P-NA during pregnancy. The first class (trajectory) was labeled as the low stable group and represents the reference group consisting of 1191 women (90%; class 1). Women in this class showed a stable and low-intensity pattern of P-NA symptoms during gestation. The second class consisted of 69 women (5%) who showed a pattern reflecting a high level of P-NA early in pregnancy, which decreased over time (decreasing pattern). In the third class, 64 women (5%) had a moderately high mean P-NA score at the first trimester that increased significantly toward the end of gestation (increasing pattern). In both class 2 and class 3, the mean P-NA scores were persistently and significantly higher throughout pregnancy compared with the reference group: the lowest mean (SD) score in the increasing group was 10.25 (4.40) at 12 weeks, whereas the lowest mean (SD) P-NA symptom scores in the decreasing group was 13.03 (4.68) at 32 weeks. In the low stable group, the mean (SD) P-NA scores varied between 5.65 (3.17) at 12 weeks and 5.11 (3.16) at 22 weeks.

## Sample Characteristics in Relation to Trajectories of P-NA Scores

For the entire group, there was a significant difference between primiparous and multiparous women regarding the P-NA-trajectories, where multiparous women belonged to the low stable trajectory (94%) significantly more often than primiparous women (84%): $\chi^2(1) = 31$, $p < .001$. The characteristics of the women in each trajectory of P-NA are presented for primiparous (Table 3) and multiparous (Table 4) women separately. When we compared primiparous women with increasing P-NA scores (class 3) to primiparous women with low stable scores (class 1, reference group; Table 3), they were significantly younger, smoked more often, and had an unplanned pregnancy more often.

Compared with the reference group with low stable P-NA scores (class 1), women with decreasing P-NA scores (class 2) were less educated ($\chi^2(1) = 4.08$, $p = .043$), had lower employment rates ($\chi^2(1) = 3.99$, $p = .045$), and more often reported a previous episode of depression ($\chi^2(1) = 41.4$, $p < .001$). Compared with the reference group with low stable P-NA scores (class 1), primiparous women with increasing P-NA scores (class 3) were younger ($t(618)$, 2.48, $p = .014$), smoked more often ($\chi^2(1) = 6.57$, $p = .010$), and more often reported an unplanned pregnancy ($\chi^2(1) = 5.18$, $p = .023$) and a previous episode of depression

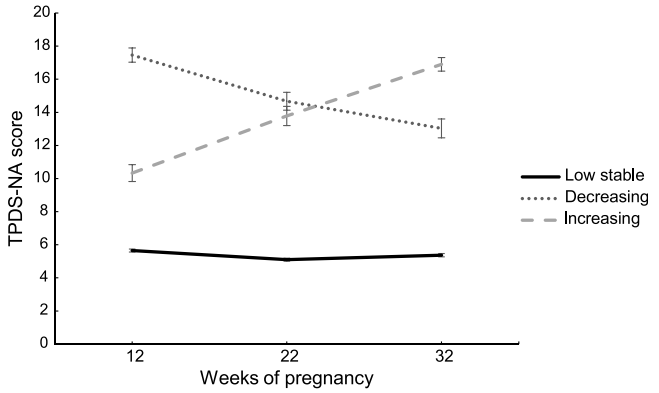


**FIGURE 1.** Trajectories for pregnancy negative affect in a sample of 1324 women. TPDS-NA = Tilburg Pregnancy Distress Scale–Negative Affect subscale.

**TABLE 3.** Characteristics of 677 Primiparous Women According to Different Trajectories of Negative Affect Symptom Scores (P-NA)

| | Class 1: Low Stable, Reference Group ($n$ = 581; 85.8%) | | Class 2: Decreasing ($n$ = 57; 8.4%) | | Class 3: Increasing ($n$ = 39; 5.8%) | |
|---|---|---|---|---|---|---|
| | $n$ (%) | Mean (SD) | $n$ (%) | Mean (SD) | $n$ (%) | Mean (SD) |
| Demographics | | | | | | |
| Age, y | | 29.38 (3.41) | | 29.23 (3.90) | | 27.97 (3.69) |
| High educational level[a] | 373 (64.2)* | | 34 (59.6)* | | 22 (56.4) | |
| Paid job | 555 (95.5)* | | 51 (89.5)* | | 36 (92.3) | |
| White women | 574 (98.8) | | 57 (100.0) | | 39 (100.0) | |
| Life-style habits | | | | | | |
| BMI prepregnancy, kg/m$^2$ | | 23.56 (3.70) | | 24.56 (4.78) | | 24.17 (4.29) |
| Alcohol during pregnancy | 21 (3.6) | | 2 (3.5) | | 2 (5.1) | |
| Smoking during pregnancy | 31 (5.3)* | | 3 (5.3) | | 6 (15.4)* | |
| Obstetrics | | | | | | |
| Previous miscarriage/abortion | 114 (19.6) | | 8 (14.0) | | 6 (15.4) | |
| Unplanned pregnancy | 35 (6.0)* | | 4 (7.0) | | 6 (15.4)* | |
| Weeks of gestation at birth | | 39.39 (2.05) | | 39.64 (1.32) | | 38.49 (3.78) |
| Preterm birth (<37 wk) | 41 (7.1) | | 3 (5.3) | | 6 (15.4) | |
| Pregnancy-induced hypertension | 60 (10.3) | | 6 (10.5) | | 4 (10.3) | |
| Psychiatric history | | | | | | |
| Previous episode of depression | 70 (12.0)* | | 25 (43.9)* | | 9 (23.1)* | |
| P-NA scores | | | | | | |
| 12 wk | | 6.34 (3.15)* | | 17.47 (3.68)* | | 11.18 (4.19)* |
| 22 wk | | 5.63 (3.27)* | | 14.91 (4.54)* | | 14.85 (4.90)* |
| 32 wk | | 5.78 (3.34)* | | 13.11 (4.67)* | | 17.63 (3.33)* |

P-NA = pregnancy-specific NA; SD = standard deviation; BMI = body mass index.

* Significant at .05 using $\chi^2$ tests for categorical variables and $t$ tests/analysis of variance for continuous variables.

[a] High = bachelor's degree or higher.

**TABLE 4.** Characteristics of 642 Multiparous Women According to Different Trajectories of Negative Affect Symptom Scores (P-NA)

| | Class 1: Low Stable, Reference Group ($n$ = 605; 94.3%) | | Class 2: Decreasing ($n$ = 12; 1.9%) | | Class 3: Increasing ($n$ = 25; 3.9%) | |
|---|---|---|---|---|---|---|
| | $n$ (%) | Mean (SD) | $n$ (%) | Mean (SD) | $n$ (%) | Mean (SD) |
| Demographics | | | | | | |
| Age, y | | 31.42 (3.26) | | 31.42 (2.94) | | 31.36 (4.53) |
| High educational level[a] | 420 (69.4) | | 7 (58.3) | | 15 (60.0) | |
| Paid job | 554 (91.6)* | | 12 (100.0) | | 17 (68.0)* | |
| White | 598 (98.8) | | 12 (100.0) | | 25 (100.0) | |
| Life-style habits | | | | | | |
| BMI prepregnancy, kg/$^{m2}$ | | 23.60 (3.91) | | 24.52 (3.40) | | 22.83 (3.26) |
| Alcohol during pregnancy | 19 (3.1) | | 1 (8.3) | | 1 (4.0) | |
| Smoking during pregnancy | 33 (5.5) | | 1 (8.3) | | 0 (0.0) | |
| Obstetrics | | | | | | |
| Previous miscarriage/abortion | 198 (32.6)* | | 8 (66.7)* | | 10 (40.0) | |
| Unplanned pregnancy | 28 (4.6) | | 1 (8.3) | | 3 (12.0) | |
| Weeks of gestation at birth | | 39.84 (1.29) | | 39.89 (1.02) | | 39.85 (1.01) |
| Preterm birth (<37 wk) | 11 (1.8) | | 0 (0.0) | | 0 (0.0) | |
| Pregnancy-induced hypertension | 24 (4.0)* | | 2 (16.7)* | | 4 (16.0)* | |
| Pregnancy-induced hypertension during previous pregnancy | 30 (5.0) | | 1 (8.3) | | 2 (8.0) | |
| Psychiatric history | | | | | | |
| Previous episode of depression | 90 (14.9) | | 4 (33.3) | | 7 (28.0) | |
| P-NA scores | | | | | | |
| 12 wk | | 5.00 (2.96)* | | 17.42 (3.09)* | | 9.00 (3.65)* |
| 22 wk | | 4.62 (2.90)* | | 13.45 (3.50)* | | 12.12 (3.80)* |
| 32 wk | | 4.98 (3.11)* | | 12.64 (4.50)* | | 15.88 (2.74)* |

P-NA = pregnancy-specific NA; SD = standard deviation; BMI = body mass index.

* Significant at .05 using independent-sample $t$ test for continuous variables and $\chi^2$ tests for categorical variables.

[a] High = bachelor's degree or higher.

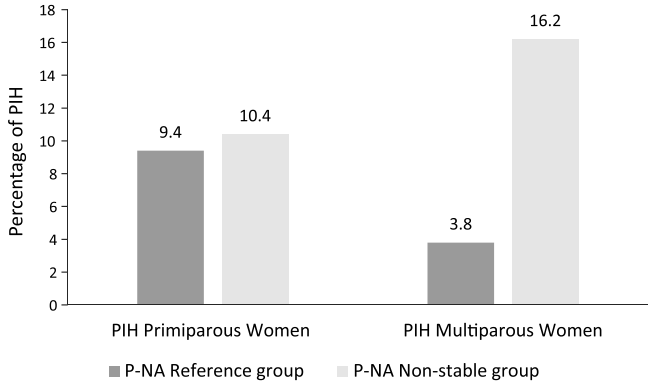


**FIGURE 2.** Development of PIH in primiparous ($n$ = 677) and multiparous ($n$ = 642) women, for the P-NA reference and P-NA nonstable group. PIH = pregnancy-induced hypertension; P-NA, pregnancy-related negative affect.

($\chi^2(1) = 3.99$, $p = .045$). Both class 2 and class 3 primiparous women had significant higher P-NA scores at all trimesters compared with the reference group (ANOVA, $p < .001$, large effect sizes), which reflects the way groups were calculated. Regarding other characteristics, no significant differences were found between the three classes.

Table 4 shows similar characteristics according to P-NA classes in multiparous women. Compared with the reference group (class 1), multiparous women with decreasing P-NA (class 2) scores more often reported a previous miscarriage or abortion ($\chi^2(1) = 6.09$, $p = .014$). Compared with the reference group, class 3 multiparous women (with increasing P-NA scores) had significant lower employment rates ($\chi^2(1) = 15.71$, $p < .001$) and more often developed PIH during their current pregnancy ($\chi^2(1) = 8.18$, $p = .004$; Table 4). Like primiparous women, and reflecting the classification procedure, women of both class 2 and class 3 had significantly higher mean P-NA scores at all trimesters (ANOVA, $p < .001$, large effect size).

## Association Between Trajectories of P-NA With the Development of PIH

Because overall P-NA levels were high in both classes 2 and 3 and to increase statistical power, we merged these classes together for multivariate logistic regression analysis. This resulted in 605 multiparous women in the reference group (class 1) and 37 women in classes 2 and 3 combined. The prevalence of history of PIH in these two groups was 30 of 605 (4.9%) and 3 of 37 (8.1%), respectively. There was a significant interaction between the P-NA trajectory classes (nonstable: classes 2 and 3 versus reference group: class 1) and parity (multiparous versus primiparous) as related to the development of PIH ($B = 1.47$, SE = 0.61, $p = .016$). The association between the P-NA trajectory class and PIH was significant for multiparous women only ($B = 1.59$, SE = 0.49, $p = .001$), but not for primiparous women ($B = 0.12$, SE = 0.32, $p = .75$). Because of theoretical reasons (see Introduction) and the statistically significant interaction between P-NA class with parity, subsequent analyses were conducted for multiparous and primiparous women separately. For multiparous women, the incidence of PIH (dependent variable) was compared between the merged nonstable P-NA group ($n$ = 37) and the reference group ($n$ = 605). As shown in Figure 2, the incidence of PIH in multiparous women was higher in women with nonstable P-NA (16.2%) compared with the reference group (3.8%; OR = 4.89, 95% CI = 1.86–12.88, $p = .001$). Next, we adjusted for the a priori identified variables that also differed at a univariate level (Table 4): unemployment, BMI, and previous PIH. There was no violation of assumptions (multicollinearity and outliers) for the logistic regression analysis. The multivariable model was significant ($\chi^2((4), n = 642) = 56.085$, $p < .001$), and women with persistently high P-NA scores (class 2 and class 3) were almost seven times more likely to develop PIH compared with those with persistently low P-NA scores (Table 5).

A similar analysis was performed for primiparous women. In primiparous women, the incidence of PIH was 10.4% in those with nonstable P-NA, whereas this was 9.4% for the reference group (OR = 1.12, 95% CI = 0.55–2.29, $p = .752$; Figure 2). We also adjusted for age, education, BMI, previous episode of depression, smoking, and unplanned pregnancy. No violation of assumptions (multicollinearity and outliers) was found for the logistic regression analysis. The multivariable model was significant ($\chi^2((6), n = 642)) = 20.29$, $p = .002$), but like the unadjusted model, no significant association between primiparous women with nonstable P-NA versus the reference group was found (OR = 0.91, 95% CI = 0.43–1.93). Only BMI was significantly and independently related to PIH in primiparous women (OR = 1.13, 95% CI = 1.07–1.20).

We also examined a "basic predictive model" examining the predictive value of P-NA scores at 12 weeks, without examining

**TABLE 5.** Adjusted ORs for the Association of Negative Affect (Independent Variable) and PIH (Dependent Variable) in Multiparous Women Comparing Women With Persistently High Levels of P-NA Scores (Increasing/Decreasing Pattern, $n$ = 35) With the Reference Group (Low Stable P-NA Scores, $n$ = 607)

| Predictor | OR (95% CI)[a] | $p$ |
|---|---|---|
| High P-NA scores throughout pregnancy | 6.91 (2.26–21.2) | .001 |
| BMI | 1.17 (1.06–1.27) | <.001 |
| Previous PIH | 14.82 (6.01–32.7) | <.001 |
| Unemployment | 0.40 (0.67–2.42) | .32 |

OR = adjusted odds ratio; P-NA = pregnancy-specific negative affect; CI = Confidence interval; BMI = body mass index; PIH = pregnancy-induced hypertension.

ORs are based on the multivariable model in which PIH is the dependent variable and all other variables are the mutually adjusted independent variables.

trajectories, and found that this variable did not predict PIH in primiparous women, at a univariate level (OR = 0.87, 95% CI = 0.45–1.88) and after adjustment (OR = 0.98, 95% CI = 0.93–1.05). In multiparous women, P-NA scores at 12 weeks did predict PIH at a univariate level (OR = 1.11, 95% CI = 1.02–1.21), and the association was attenuated after adjustment for covariates (OR = 1.08, 95% CI = 0.99–1.20, $p$ = .08).

### Trajectories of Depressive Symptoms

Growth mixture modeling of EDS scores during pregnancy also showed a three-class solution: a low stable, an increasing, and a decreasing trajectory, which have been described in detail elsewhere (42). In primiparous and multiparous women, the incidences of PIH in all three EDS classes were similar: between 9% and 13% in primiparous and between 4% and 7% in multiparous women. Similar multiple logistic regression analyses were performed for primiparous and multiparous women separately with PIH as the dependent variable and comparing the (merged) increasing and decreasing EDS trajectories to the reference group, adjusting for important confounders. No significant associations were found between the EDS trajectories and PIH in primiparous or in multiparous women (OR = 1.07 [95% CI = 0.54–2.13] and OR = 1.45 [95% CI = 0.55–3.88], respectively). In addition, depression at 12 weeks, without examining trajectories, was also not predictive of PIH: adjusted OR = 0.97 (95% CI = 0.91 = 1.04) for primiparous women and adjusted OR = 1.10 (95% CI = 0.94–1.21) for multiparous women.

## DISCUSSION

We identified three different trajectories of P-NA during gestation: low stable (class 1, reference group, 90% of the total sample), decreasing (class 2, 5.2% of the sample), and increasing (class 3, 4.8% of the sample). The mean P-NA symptom scores in classes 2 and 3 were significantly and substantially higher throughout pregnancy compared with the reference low stable class. Furthermore, important determinants of distress during pregnancy (43) were associated with belonging to the class of women with increasing (class 2) and decreasing (class 3) P-NA scores, compared with the reference group, both for multiparous and primiparous women. Multiparous women of classes 2 and 3 were at increased risk for developing PIH compared with the reference group with low stable P-NA scores throughout pregnancy. In primiparous women, no association was found between trajectories of P-NA scores and PIH. Finally, depressive symptoms trajectories were not related to the incidence of PIH in both primiparous and multiparous women.

The significant association between P-NA symptoms and PIH found in the present study is consistent with the literature reporting associations between psychological distress and gestational hypertensive disorders (19,44,45). The current article is among the first to measure distress at various time points during pregnancy while considering the individual differences in symptom profiles over time. PIH develops after 20 weeks of gestation. In the present study, P-NA symptoms were already measured at 12 weeks of gestation, and those multiparous women with persistently high scores during pregnancy were at risk for developing PIH. Several previous studies did not find a relationship between psychological distress and PIH (11,46,47). Methodological limitations of those studies included a case-cohort and cross-sectional design, only one assessment of distress, small sample size, and no differentiation in parity. These limitations are addressed, at least in part, in the present study.

In the current study, the association between P-NA and PIH was only observed in multiparous women and not in primiparous women (Figure 2). Although we showed that there was no significant difference in the prevalence of a history of PIH between the reference group and P-NA group, we believe that the power was not sufficient to reject the hypothesis that a history of PIH mediates the relationship between P-NA and PIH in multiparous women. This could also explain the lack of association between P-NA and PIH in primiparous women, as they have no history of PIH to ruminate on. It is possible that immune maladaptation plays a major role in the development of PIH in primiparous women, whereas stress might have a greater influence in multiparous women. Although the exact etiology of preeclampsia is still to be determined, there is evidence that preeclampsia is related to a maternal immune reaction in the placenta in response to paternal antigens (48). In normal pregnancy, there is a skew toward type 2 immunity (30,49). This type of immune stimulation also activates a subset of memory T cells that has the potential for long-term survival. In the case of re-exposure to antigens in a second pregnancy (from the same father), memory T cells undergo rapid expansion and mediate more robust T-effector functions (30,49). Thus, the skewed type 2 immune response is less pronounced in multiparous women in response to paternal antigens, resulting in less defective trophoblast invasion with poor spiral arterial development eventually leading to placental dysfunction (48). Placental dysfunction is thought to be one of the main causes of PIH (13). This explains why, in general, PIH is much less common in multiparous women. The fact that, in multiparous women, high levels of NA were associated with the development of PIH (adjusted for a history of PIH) is consistent with the findings in the general population showing that acute and sustained stress is associated with elevated blood pressure (16–18). It is interesting to note that multiparous women with high P-NA levels at early gestation had a miscarriage twice more often compared with the reference group (Table 4). With increasing (successful) gestation, the P-NA levels decreased but remained significantly higher than the levels of the reference group.

Psychological distress and emotions are known to affect immunoregulatory mechanisms (50,51). In the case of stress, the hypothalamic-pituitary-adrenal axis is activated signaling to the adrenal cortex to produce glucocorticoids. These glucocorticoids in turn affect various cellular functions during gestation (52). In general, individuals with chronic psychological distress are at risk for increased morbidity and mortality, because of blunted components of cellular immunity (53). Increased levels of stress during pregnancy may result in high levels of glucocorticoids, which might in turn result in blunted memory T-cell activity and consequently less pronounced immune stimulation in multiparous women. These processes could contribute to an increased risk of subsequent PIH in multiparous women. In contrast, it has also been reported that primiparous women show higher levels of cortisol during pregnancy compared with multiparous women, partially explained by distress (54).

The fact that P-NA at 12 weeks of gestation, before PIH onset, predicted later development of PIH in multiparous women implicates the possible clinical relevance of the current study. Future research should focus on possible intervention strategies, set up during the first trimester of gestation with a screening of multiparous women. It could be interesting to evaluate a psychological intervention to those with high P-NA scores, which is aimed at the reduction of distress symptoms and possibly resulting in lower PIH incidence.

In the current study, depressive symptoms were not related to development of PIH in primiparous nor multiparous women. Some previous studies also found an increased risk of preeclampsia in moderate to severe depressed women (55,56), whereas others failed to detect such associations (11,46,47). A recent study found that the risk for pregnancy hypertension was only observed in depression and anxiety with related use of antidepressants and anxiolytics (57). In the current study, the use of these psychotropic drugs was an exclusion criterion to participate. Furthermore, the correlations between EDS scores and P-NA scores in the current study were between 0.43 and 0.47 at different trimesters, showing that despite of a certain overlap between these two constructs (18%–22% explained variance), depression and NA are two distinct entities. Previous research on type D personality, a construct reflecting the simultaneous presence of NA and social inhibition, also showed only marginal overlap with depression (58). Also, it has been shown that anxiety, another component of negative affectivity, has a more pronounced effect on the hypothalamic-pituitary-adrenal axis compared with depression (59,60). The focus of the current study is pregnancy-related NA. Anxiety is part of this construct, but the P-NA construct also includes other components of NA. In addition to NA symptoms, prepregnancy BMI and history of PIH were also significantly and independently related to PIH in the present study. These determinants have been consistently reported before in the literature (1).

The generalizability of the study results might be reduced by the fact that women participating in this study were more often highly educated and more often had a paid job compared with the general population in the Netherlands (61). In addition, there was minimal variability of ethnic composition in the present sample, which is not representative of the general Dutch population. However, comparing obstetrical data from the current study with data from the general pregnant population in the Netherlands, the current sample was representative regarding features such as parity, reported rates of previous abortion, unplanned pregnancy, and term of gestation at birth (62,63).

This study has several strengths but also limitations that need to be considered. A unique strength of this study is the application of growth mixture modeling analyses to symptoms of distress, which were assessed in each trimester of pregnancy. This allowed for identification of individual trajectories of changes in distress during pregnancy. Other strengths are the relatively large sample size ($n$ = 1324) and the prospective design of the study. An important limitation of the study is the fact that we did not discriminate between preeclampsia and pregnancy hypertension and within the preeclampsia group between early and late onset. Moreover, data on (preventive) treatment of PIH were not available (aspirin or antihypertensive medication). Second, despite the relatively large sample size, the class sizes (increasing and decreasing trajectories) were rather small in different subgroups according to parity, although the criteria of sufficient sample size of latent class analysis were met (>1% of the total sample). This underlines the need for even larger future studies to conduct analyses in subgroups with sufficient statistical power, especially discriminating between early- and late-onset preeclampsia. Because "other" pregnancy complications were excluded from the control group but not the PIH group, it is possible that these other complications might have confounded the observed association between P-NA and PIH. A fourth limitation is that more than three consecutive assessments could have increased the power of the trajectory model and could have allowed us to assess quadratic growth modeling. Another limitation is the prior mentioned generalizability of the study outcomes. The high rate of highly educated women was not related to selection bias because the area where the HAPPY study was carried out was nominated by the international think-tank Intelligent Community Forum as the "smartest area of the world" in 2011. Furthermore, another limitation of the study is that only 30 multiparous women developed PIH, which may limit the power of the study despite the overall large sample size.

In conclusion, this study indicates that three distinct trajectories of P-NA symptoms occur during gestation: increasing P-NA scores, decreasing P-NA scores, and low stable P-NA scores (used as reference). In addition, women with high P-NA scores were at risk for developing PIH compared with the reference group, but this was only found for multiparous and not in primiparous women. No associations were found between depressive symptom trajectories and PIH. This study highlights the need for additional research into the relationship between P-NA and PIH in large samples for replication and further distinction between primiparous and multiparous women and differentiation between early- and late-onset preeclampsia.

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