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# Utility of the US Preventive Services Task Force for Preeclampsia Risk Assessment and Aspirin Prophylaxis

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## Abstract

**IMPORTANCE** The US Preventive Services Task Force (USPSTF) guidelines on preeclampsia risk assessment and aspirin prophylaxis (AP) have not been evaluated for clinical utility.

**OBJECTIVE** To evaluate which characteristics in the USPSTF guidelines identify risk status and the association of preeclampsia risk with AP recommendations.

**DESIGN, SETTING, AND PARTICIPANTS** This observational cohort study enrolled from July 2020 to March 2023 with data analysis performed from October to December 2024. Enrollment occurred at 11 centers throughout the US or via direct-to-participant recruitment. Pregnant participants aged 18 years or older with a singleton pregnancy less than 22 weeks' gestation were selected via convenience sampling.

**EXPOSURE** The exposures were clinical factors abstracted from medical records by research coordinators, which were stratified according to USPSTF definitions of low, moderate (parity, advanced maternal age [AMA], race, and body mass index), and high (chronic hypertension, prior preeclampsia, type 1 or 2 diabetes, kidney disease, and/or autoimmune conditions) risk.

**MAIN OUTCOMES AND MEASURES** Data collected included AP recommendation, presence of USPSTF-defined moderate risk factors or high risk factors, and any preeclampsia diagnosis. Effect sizes and relative risk (RR) were calculated within risk strata.

**RESULTS** Of 5684 participants (median [IQR] age, 30.9 [26.4-34.6] years; 267 [4.1%] Asian; 1191 [21.0%] Black; 990 Hispanic [17.4%]; 2764 [48.6%] White; and 472 [8.3%] with other race or ethnicity), 5046 (88.8%) were at increased risk of preeclampsia (3996 [70.3%] at moderate risk and 1050 [18.5%] at high risk). A total of 2438 participants (43.1%) received an AP recommendation. The overall preeclampsia rate was 12.1% (685 participants). The PE rates specific to USPSTF categories were 3.0% for those at low risk (19 of 638 participants), 10.5% for those at moderate risk (419 of 3996 patients), and 23.5% for those at high risk (247 of 1050 participants). Among individuals with 2 or more moderate risk factors but without any high risk factor, nulliparity was associated with significantly increased risk of preeclampsia (RR, 1.48; 95% CI, 1.35-1.62; $P < .001$), while AMA was associated with decreased risk (RR, 0.79; 95% CI, 0.65-0.96; $P = .02$); there was no association with obesity (RR, 1.11; 95% CI, 1.01-1.22; $P = .048$) or Black race (RR, 0.95; 95% CI, 0.80-1.14; $P = .63$). Of 1044 participants with any high risk factors, 856 (82.0%) were recommended AP and of 634 at low risk, 538 (85.9%) were not recommended AP. In contrast, of 1942 participants with 1 moderate risk

(continued)

## Key Points

**Question** What factors in the US Preventive Services Task Force (USPSTF) guidelines on preeclampsia risk assessment accurately estimate low, moderate, or high preeclampsia risk, and how is preeclampsia risk associated with aspirin prophylaxis (AP) recommendations?

**Findings** This cohort study of 5684 participants found that 88.8% were at increased risk (70.3% at moderate risk and 18.5% at high risk) of preeclampsia. Only 37% of those in the moderate risk category were recommended AP. High risk factors had sufficient value in estimating risk, but moderate risk factors had little value, leading to nonspecific AP recommendations.

**Meaning** These findings suggest that USPSTF guidelines provide little utility for estimating preeclampsia risk and subsequent AP recommendation among individuals at moderate risk for preeclampsia, which constitute the majority of the population.

+ Supplemental content

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*Abstract (continued)*

factor, 463 (23.8%) were recommended AP, and of 2032 with 2 or more moderate risk factors, 1024 (50.4%) were recommended AP.

**CONCLUSIONS AND RELEVANCE** In this prospective cohort study of 5684 singleton pregnancies, 89% of the population was assessed as having increased risk (moderate or high) of preeclampsia by USPSTF criteria. These findings suggest that moderate risk factors in the absence of high risk factors show no or low value for estimating the risk of developing preeclampsia, leading to nonspecific recommendations of AP in the moderate risk category.

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## Introduction

In recent decades, risk scoring algorithms have been successfully developed for a variety of adverse medical outcomes. These include cardiovascular events,[1] mortality in critical illness,[2] stroke occurrence, and thrombotic risk.[3] Similar attempts in reproductive medicine have been less successful, especially for preeclampsia.[4-6]

Preeclampsia is a leading cause of maternal and neonatal morbidity and mortality and affects an estimated 8% of pregnancies.[7,8] Hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia, have doubled between 2007 and 2019.[9] At the same time, the rate of maternal mortality has been rising in the US, which now has the worst maternal mortality rate among high-income countries.[10,11] These vital statistics highlight the need to develop risk stratification algorithms to assist in prevention and treatment strategies for preeclampsia.

The US Preventive Services Task Force (USPSTF) recommends risk assessment for preeclampsia based on clinical and demographic factors (**Box**).[12] Based on this rubric, a patient is considered at increased risk if they have 1 or more of high-risk conditions. The recommendation also states that anyone with 2 or more moderate risk factors should be considered at increased risk.[12] Initiation of low-dose aspirin prophylaxis (AP; 81 mg) between 12 to 28 weeks' gestation is recommended for

**Box. US Preventive Services Task Force Clinical Risk Assessment for Preeclampsia and Risk Category Delineation**

**High Risk Factors**

History of preeclampsia

Multifetal gestation[a]

Chronic hypertension

Pregestational type 1 or 2 diabetes

Kidney disease

Autoimmune disease (ie, systemic lupus erythematous or antiphospholipid syndrome)

**Moderate Risk Factors**

Nulliparity

Obesity (ie, body mass index >30 [calculated as weight in kilograms divided by height in meters squared])

Black race (due to social, rather than biological, factors)

Age 35 years or older

Family history of preeclampsia (ie, mother or sister)[a]

Lower income[a]

In vitro conception[a]

Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)[a]

**Risk Categories**

High risk category: 1 or more high risk factor with or without moderate risk factors

Moderate 1+ risk category: 1 or more moderate risk factors and no high risk factors

Moderate 1 risk category: 1 and only 1 moderate risk factor and no high risk factors

Moderate 2+ risk category: 2 or more moderate risk factors and no high risk factors

Low risk category: no moderate or high risk factors (restyle)[a]

[a]Not included in analysis and not present in the Miracle of Life study data collection.

individuals who have either at least 1 high risk factor or at least 2 moderate risk factors (Grade B recommendation) and should be considered for individuals with 1 moderate risk factor.[12] This recommendation is supported by both the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine.[13] The applicability of risk factors identified in individual and separate studies may not be generalizable to the risk assessment in broader clinical circumstances the further these circumstances deviate from the eligibility criteria of the original studies.[14] Furthermore, the ability for clinicians to adhere to this risk stratification system has been thought to be suboptimal, with prescribing rates of AP of less than 50% for those classified as being increased risk.[15]

Our objective was to evaluate the proportions of this racially and geographically diverse US population that fall into low, moderate and high risk categories for preeclampsia according to the risk stratification criteria of the USPSTF. A subsequent objective was to assess the rates of physician AP recommendations within these categories. We include racial designations in the present analysis because they are part of the USPSTF guidelines.

## Methods

This cohort study was approved by the Advarra institutional review board. As part of the Miracle of Life study, individuals with singleton pregnancies who met inclusion criteria were prospectively approached, written informed consent was sought, and, if consent was obtained, participants were enrolled before 22 weeks' gestation. For the analysis presented here, we included participants enrolled between July 2020 and March 2023 from all sites with a minimum enrollment of 200 participants. The study was conducted in accordance with the International Conference for Harmonisation of Technical Requirements Guideline for Good Clinical Practice (E6-R2, 2016), the US Figure of Health and Human Services guidelines on Protection of Human Subjects (45 CFR § 46), and the US Food and Drug Administration regulations on electronic records and signatures (21 CFR Part 11). This study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.[16]

### Enrollment

Pregnant patients aged 18 years or older were recruited either in person at 1 of 11 medical centers in the US or via direct-to-participant recruitment using social media. The clinical recruitment sites were Woman's Hospital in Baton Rouge, Louisiana; University of Pittsburgh Medical Center Magee-Womens Hospital in Pittsburgh, Pennsylvania; University of Texas Medical Branch in Galveston, Texas; Ochsner Health in New Orleans, Louisiana; Multicare Health System in Tacoma, Washington; Washington University Medical Center in St Louis, Missouri; University of California, San Diego in San Diego County, California; Beth Israel Medical Center in Boston, Massachusetts; Brigham and Women's Hospital in Boston, Massachusetts; The Ohio State University Wexler Medical Center in Columbus, Ohio; and Thomas Jefferson University Hospital in Philadelphia, Pennsylvania.

### Clinical Data Collection

Within 30 days after the end of pregnancy, clinical data (encompassing the prenatal record, laboratory results, imaging results, labor and delivery notes, and discharge summaries) were abstracted from the medical records by research coordinators. Maternal race and ethnicity was abstracted from the electronic medical record and categorized into the following categories: Asian, Black, Hispanic, White, and other race or ethnicity. The other race and ethnicity category included individuals whose medical record did not assign them to 1 of the 4 initial groups. These data included the presence or absence of USPSTF high risk factors and specific moderate risk factors for preeclampsia that were routinely available in the medical record (Box). Medical records did not routinely capture the following risk factors, preventing their assessment: in vitro conception, income status, and family history of preeclampsia. For the purposes of this study, we defined individuals as

being in the high risk category if they had at least 1 high risk factor. Individuals were defined as being in the moderate risk category (referred to as the moderate 1+ risk category) if they had at least 1 of the moderate risk factors but no high risk factors. Those in the moderate 1+ risk category were further subdivided into those with only 1 moderate risk factor (moderate 1 risk category) and those with 2 or more moderate risk factors (moderate 2+ risk category). Individuals were defined as being in the low risk category if they had no moderate or high risk factors. Whether or not AP was recommended (with or without a prescription) was also abstracted.

All information captured was deidentified and stored in a password-protected and secure web-based electronic data capture system (Medrio). The outcome of interest for this study was the diagnosis of preeclampsia.[7] Clinical monitoring was performed by trained monitors and any discrepant clinical diagnoses were resolved with site principal investigators (T.F.M., A.J., P.M.S., G.R.S., A.S., L.D.P., E.P.H., A.I.F., E.B.C., A.Y.C., D.G.K., V.B., R.C.B., C.G.B., J.R.B., K.R., and W.A.G.) and/or by an end point adjudication committee composed of 3 board-certified maternal-fetal medicine experts (M.A.E. and L.G) who were not members of any of the enrollment sites.

### Statistical Analysis

Several statistical tests were used to compare baseline characteristics between groups. A Pearson $\chi^2$ test was applied to assess associations between categorical variables. For categorical variables, contingency effect size (Cramér *V*) was also reported to quantify the magnitude of association between variables. Cramér *V* provides a measure of effect size ranging from 0 (no association) to 1 (perfect association), aiding in the interpretation of $\chi^2$ test results. For continuous variables, the Wilcoxon rank sum test (Mann-Whitney *U*) was used. Cohen *d* was calculated as a standardized measure of effect size to quantify the magnitude of differences between group means for continuous variables. This effect size is helpful in interpreting the practical significance of differences, with thresholds of 0.2, 0.5, and 0.8 representing small, medium, and large effect sizes, respectively. Relative risk (RR) was calculated with reference to individuals in the same USPSTF risk category (eg, high or moderate 1). RR is defined as the prevalence for the characteristic under consideration divided by the prevalence in the remaining group. The reference group should therefore be interpreted as the members of that risk category who do not share the characteristic under consideration. Because our sample may not perfectly capture the general risk of preeclampsia within the larger US population, examination within each risk category will provide a more balanced and generalizable estimate of risk while minimizing the possibility of introducing bias. This analysis was performed from October to December 2024 using R version 4.4.1 (R Project for Statistical Computing). Confidence intervals were estimated either analytically or by bootstrap analyses. Statistical significance was defined as a 2-sided $P < .05$.

## Results

A total of 6102 participants were enrolled. There were 418 individuals excluded (31 participants did not meet eligibility criteria, 322 were lost to follow-up or had incomplete data, 7 were removed per participant or sponsor request, and 58 were excluded per the adjudication committee), leaving a final sample size of 5684,[17] with an additional 32 participants removed when aspirin data were required. The study population had a median (IQR) age of 30.9 (26.4-34.6) years, and 267 (4.7%) were identified in the medical record as Asian, 1191 (21.0%) as Black, 990 (17.4%) as Hispanic, 2764 (48.6%) as White, and 472 (8.3%) as other race or ethnicity. The sensitivity, specificity, positive and negative predictive values with respect to the USPSTF guidelines are presented in **Table 1**. Overall the characteristics of our cohort were similar to those of the pregnant population in the US[18-26] Preeclampsia was diagnosed in 685 individuals (12.1%) (**Figure**, A) and gestational hypertension, exclusive of cases that later progressed to preeclampsia, occurred in 637 participants (11.2%). While the majority of preeclampsia was diagnosed at term, 276 participants (4.9%) received a diagnosis of preeclampsia prior to 37 weeks. AP was recommended for 2438 individuals (43.1%).

Of 5046 participants, 5046 (88.8%) were at increased (moderate or high risk) of preeclampsia. The majority of the population was in the moderate 1+ risk category (3996 participants [70.3%]), with substantially lower proportions in the low risk (638 participants [11.2%]) or high risk categories (1050 participants [18.5%] ) (Figure, B). There were 1953 participants (34.4%) with only 1 moderate risk factor (moderate risk 1 category), and a similar proportion (2043 participants [35.9%]) had 2 or more moderate risk factors (moderate risk 2+ category) (Table 1). See the eTable in Supplement 1 for all moderate or all low and moderate risk factors. A history of preeclampsia and chronic hypertension were associated with the highest incidence of developing preeclampsia (Table 1). Similarly, the

**Table 1. Summary Characteristics of Study Participants and Performance of Characteristics as a Preeclampsia Risk Factor**

| Characteristic | Participants, No. (%) (N = 5684) | Prevalence of preeclampsia, No. (%)a | Sensitivity, % (95% CI)[a] | Specificity, % (95% CI)[a] | PPV (95% CI)[a] | NPV (95% CI)[a] |
|---|---|---|---|---|---|---|
| Overall | 5684 (100) | 685 (12.1) | 0.74 (0.71-0.77) | 0.48 (0.47-0.50) | 0.16 (0.15-0.18) | 0.93 (0.92-0.94) |
| Aspirin recommended | 2438 (43.1) | 416 (17.1) | 0.88 (0.85-0.91) | 0.25 (0.23-0.27) | 0.19 (0.17-0.21) | 0.91 (0.88-0.93) |
| Preeclampsia | 685 (12.1) | 685 (100) | 0.74 (0.71-0.77) | NaN | 1.00 (1.00-1.00) | 0.00 (0.00-0.00) |
| Gestational hypertension | 637 (11.2) | 0 | NaN | 0.31 (0.28-0.35) | 0.00 (0.00-0.00) | 1.00 (1.00-1.00) |
| Maternal age, median (IQR), y | 30.9 (26.4-34.6) | NA | NA | NA | NA | NA |
| Advanced maternal age[b] | 1327 (23.3) | 178 (13.4) | 0.93 (0.89-0.96) | 0.21 (0.18-0.23) | 0.15 (0.13-0.18) | 0.95 (0.92-0.97) |
| Body mass index[c] | | | | | | |
| Median (IQR) | 27.6 (23.6-33.3) | NA | NA | NA | NA | NA |
| ≥30 | 2171 (38.3) | 353 (16.3) | 0.95 (0.93-0.97) | 0.15 (0.14-0.17) | 0.18 (0.16-0.19) | 0.94 (0.91-0.96) |
| Nulliparous | 2284 (40.2) | 351 (15.4) | 0.71 (0.66-0.75) | 0.44 (0.42-0.47) | 0.19 (0.17-0.21) | 0.89 (0.87-0.91) |
| Prior preeclampsia | 452 (8.0) | 138 (30.5) | 1.00 (1.00-1.00) | 0.00 (0.00-0.00) | 0.31 (0.27-0.35) | NaN |
| Chronic hypertension | 503 (8.8) | 141 (28.0) | 1.00 (1.00-1.00) | 0.00 (0.00-0.00) | 0.28 (0.24-0.32) | NaN |
| Type 1 or 2 diabetes | 174 (3.1) | 42 (24.1) | 1.00 (1.00-1.00) | 0.00 (0.00-0.00) | 0.24 (0.18-0.31) | NaN |
| Gestational diabetes | 573 (10.1) | 114 (19.9) | 0.80 (0.73-0.87) | 0.33 (0.29-0.39) | 0.23 (0.19-0.27) | 0.87 (0.83-0.92) |
| Smoker | 319 (5.6) | 43 (13.5) | 0.72 (0.59-0.85) | 0.41 (0.35-0.47) | 0.16 (0.11-0.21) | 0.90 (0.85-0.95) |
| Gestational age at delivery, median (IQR), w | 39.0 (37.9-39.7) | NA | NA | NA | NA | NA |
| Birth weight of baby, median (IQR), g | 3260.0 (2940.0-3590.0) | NA | NA | NA | NA | NA |
| Sex of baby | | | | | | |
| Male | 2924 (51.6) | 359 (12.3) | 0.73 (0.69-0.77) | 0.48 (0.47-0.50) | 0.16 (0.15-0.18) | 0.93 (0.91-0.94) |
| Female | 2746 (48.4) | 324 (11.8) | 0.75 (0.70-0.79) | 0.48 (0.46-0.50) | 0.16 (0.14-0.18) | 0.93 (0.92-0.95) |
| Maternal race and ethnicity | | | | | | |
| Asian | 267 (4.7) | 25 (9.4) | 0.52 (0.31-0.72) | 0.62 (0.56-0.68) | 0.12 (0.06-0.19) | 0.93 (0.89-0.96) |
| Black | 1191 (21.0) | 184 (15.4) | 0.93 (0.90-0.97) | 0.12 (0.10-0.14) | 0.16 (0.14-0.18) | 0.91 (0.86-0.96) |
| Hispanic | 990 (17.4) | 125 (12.6) | 0.63 (0.54-0.709) | 0.65 (0.61-0.68) | 0.20 (0.17-0.24) | 0.92 (0.90-0.94) |
| White | 2764 (48.6) | 308 (11.1) | 0.686 (0.633-0.74) | 0.55 (0.53-0.57) | 0.16 (0.14-0.18) | 0.93 (0.92-0.95) |
| Other[d] | 472 (8.3) | 43 (9.1) | 0.77 (0.64-0.89) | 0.53 (0.48-0.57) | 0.14 (0.10-0.19) | 0.96 (0.93-0.98) |
| USPSTF risk category[e] | | | | | | |
| Low | 638 (11.2) | 19 (3.0) | 0.00 (0.00-0.00) | 1.00 (1.00-1.00) | NaN | 0.97 (0.96-0.98) |
| Moderate 1 | 1953 (34.4) | 159 (8.1) | 0.00 (0.00-0.00) | 1.00 (1.00-1.00) | NaN | 0.92 (0.91-0.93) |
| Moderate 1+ | 3996 (70.3) | 419 (10.5) | 0.62 (0.57-0.66) | 0.50 (0.49-0.52) | 0.13 (0.11-0.14) | 0.92 (0.91-0.93) |
| Moderate 2+ | 2043 (35.9) | 260 (12.7) | 1.00 (1.00-1.00) | 0.00 (0.00-0.00) | 0.13 (0.11-0.14) | NaN |
| High | 1050 (18.5) | 247 (23.5) | 1.00 (1.00-1.00) | 0.00 (0.00-0.00) | 0.24 (0.21-0.26) | NaN |

Abbreviations: NA, not applicable; NaN, Not a Number; NPV, negative predictive value; PPV, positive predictive value; USPSTF, US Preventive Services Task Force.

[a] Confidence intervals were calculated from a nonparametric bootstrap (B = 1000).

[b] Aged 35 years or older at estimated due date.

[c] Body mass index was calculated as weight in kilograms divided by height in meters squared.

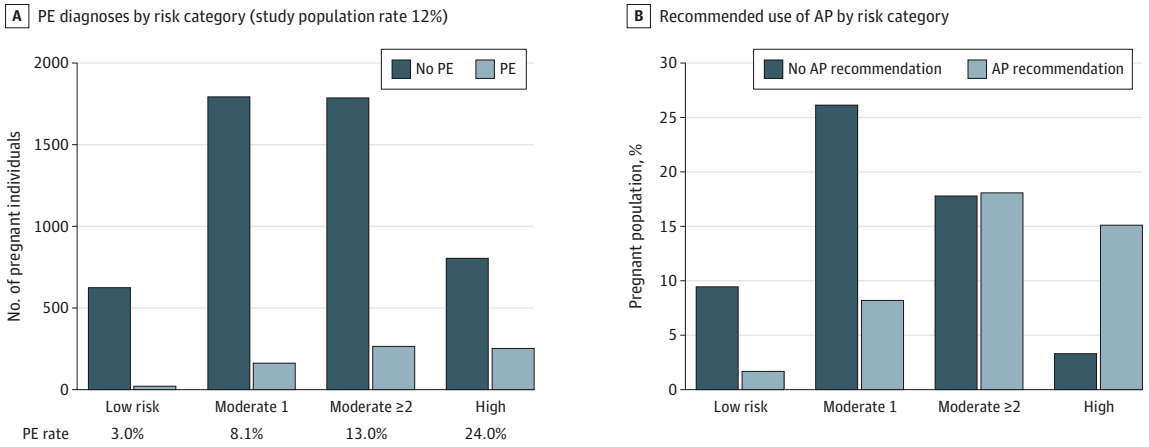
[d] Included individuals whose medical record did not assign them to 1 of the 4 initial groups.

[e] The high risk category includes those with at least 1 high risk factor (prior preeclampsia, chronic hypertension, type 1 or 2 diabetes, kidney disease, and/or autoimmune disease). The moderate risk category includes those with a BMI of 30 or greater, advanced maternal age, Black race, and/or nulliparity. The moderate 1 risk category includes those with 1 and only 1 of these moderate risk factors and the moderate 2+ risk category includes those with 2 or more moderate risk factors and no high risk factors. The low risk category includes those without any of the above moderate or high risk factors.

incidence of preeclampsia varied with maternal race, but maternal race conveyed limited information in the test performance characteristics (ie, sensitivity and specificity).

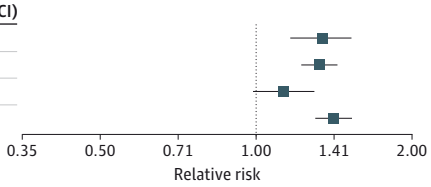
To avoid biasing results due to potential association with characteristics that are inclusive to the high risk category, we calculated RR within each remaining USPSTF risk category. The RR is calculated with reference to individuals sharing the same risk category (Table 1). Within the high risk category, the prevalence of preeclampsia was much higher than the population (247 individuals [23.5%])

**Figure. Preeclampsia (PE) Diagnoses, Aspirin Prophylaxis (AP) Recommendation, and Relative Risk for Preeclampsia Due to Moderate Risk Factors in Exclusive Risk Categories**



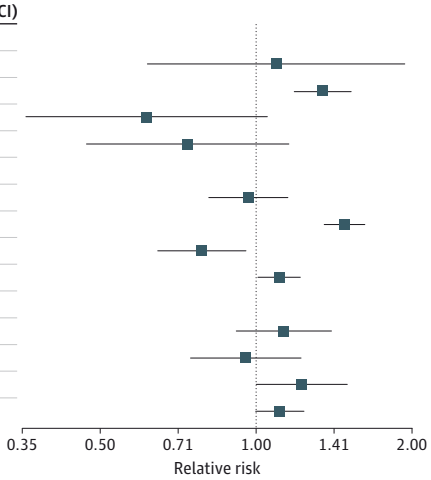

C Moderate risk factors in the entire study population

| All individuals | Relative risk (95%CI) |
|---|---|
| Black race[a] | 1.33 (1.17-1.53) |
| Nulliparous | 1.33 (1.22-1.44) |
| AMA | 1.13 (0.99-1.30) |
| BMI ≥30 | 1.41 (1.30-1.53) |




D Moderate risk factors in exclusive subsets by risk category

| Risk category | Relative risk (95%CI) |
|---|---|
| Moderate 1 | |
| Black race[a] | 1.09 (0.62-1.93) |
| Nulliparous | 1.34 (1.18-1.52) |
| AMA | 0.62 (0.36-1.05) |
| BMI ≥30 | 0.74 (0.47-1.16) |
| Moderate 2+ | |
| Black race[a] | 0.97 (0.81-1.15) |
| Nulliparous | 1.48 (1.36-1.62) |
| AMA | 0.79 (0.65-0.96) |
| BMI ≥30 | 1.11 (1.01-1.22) |
| High | |
| Black race[a] | 1.13 (0.92-1.40) |
| Nulliparous | 0.96 (0.75-1.22) |
| AMA | 1.22 (1.00-1.50) |
| BMI ≥30 | 1.11 (1.00-1.24) |




The high risk category includes those with at least 1 high risk factor: prior PE, chronic hypertension, type 1 or 2 diabetes, kidney disease, and/or autoimmune disease. The moderate risk category includes those with body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) of 30 or greater, advanced maternal age (AMA; 35 years or older at estimated due date), Black race, and/or nulliparity. The moderate 1 risk category includes those with 1 and only 1 of these moderate risk factors and the moderate 2+ risk category includes those with 2 or more moderate risk factors and no high risk factors.

[a] Black race, due to social, rather than biological factors

(Figure, A), and the presence of prior preeclampsia (RR, 1.44; 95% CI, 1.25-1.65; *P* < .001) or chronic hypertension (RR, 1.26; 95% CI, 1.10-1.44; *P* = .001) was associated with significantly increased risk of preeclampsia, while a history of diabetes (type 1 or 2) was not associated with risk above the prevalence in the high risk group (RR, 1.05; 95 CI, 0.76-1.44; *P* = .77).

When analyzing within the moderate risk category (ie, excluding those in the low and high risk categories), much of the statistical significance of moderate risk factors was lost. None of the racial categories, including Black, were associated with an increased risk when analyzed by risk category (1 moderate risk factor among Black participants: RR, 1.09; 95% CI, 0.62-1.93; *P* = .74; 2 or more moderate risk factors among Black participants: RR, 0.95; 95% CI, 0.80-1.14; *P* = .63) (**Table 2**). Patients for whom the only moderate risk factor was obesity or AMA did not have an increased risk of preeclampsia. Only nulliparity status was associated with a modestly increased risk (RR, 1.34; 95% CI, 1.19-1.52; P < .001) (Figure, D). If a moderate risk factor co-occurred with at least 1 other moderate risk factor, nulliparity remained significantly associated with a modestly increased risk for preeclampsia (RR, 1.48; 95% CI, 1.35-1.62; *P* < .001), and AMA was associated with reduced risk (RR, 0.79; 95% CI, 0.65-0.96; *P* = .02). Obesity was not associated with preeclampsia (RR, 1.11; 95% CI, 1.01-1.22]; *P* = .048). AMA, Black race, and obesity were each significantly associated with the high risk category (eFigure in Supplement 1) and there was a significant negative association between nulliparity and the high risk category (eFigure in Supplement 1). These association lead to population level increases in RR (Figure, C) but when analyzed in isolation from high risk factors, most moderate risk factors were not adding risk (Figure, D).

The recommendation of AP was not uniform across racial categories (**Table 3**). Despite Black maternal race being considered a USPSTF moderate risk factor (due to social, rather than biological, factors), two-thirds of Black patients (795 of 1190 patients [66.8%]) were recommended for AP. Among participants with obesity (BMI ≥30), a higher proportion were recommended AP (1222 of 2166 participants [56.4%]). A similar proportion of patients with AMA were recommended AP (716 of 1317 patients [54.4%]). Neither maternal smoking status nor status as a nullipara was associated with increased AP recommendation.

Overall, nearly one-half of participants with at least 1 USPSTF risk factor had AP recommended (2342 of 5018 participants [46.7.%]). While the majority of those in the high risk category received an AP recommendation (856 of 1044 participants [82.0%]), 188 (18.0%) did not. Patients with a history of preeclampsia, chronic hypertension, and/or diabetes prior to pregnancy were more likely to be recommended AP. Among the 634 patients in the low risk category, 96 (15.1%) received an AP recommendation, while 538 (85.9%) did not. Of the 3974 patients in the moderate risk category, 2488 (62.6%) did not receive an AP recommendation while 1486 (37.4%) did. However, as participants progressed from 1 to 2 or more moderate risk factors, the proportion recommended AP increased (1 moderate factor: 462 of 1942 patients [23.8%]; 2 moderate risk factors: 1024 of 2032 patients [50.4%]) (Figure, B).

## Discussion

This cohort study represents a large, contemporary, nationally representative observational sample in the US. Combining the USPSTF moderate and high risk categories, 89% of the study population had at least 1 risk factor for preeclampsia, and only a minority of the population were identified by USPSTF criteria as low risk. If the intended utility of the guidelines is to facilitate the focus of clinical attention and limited clinical resources on those at greatest risk of preeclampsia, identifying the majority of the population as at risk does not meet this end. While this analysis has specifically used the criteria of the USPSTF, examination of the American College of Obstetricians and Gynecologists and National Institute for Health and Care Excellence guidelines demonstrates only minimal differences in preeclampsia risk characterization.[27-29] It is, therefore, reasonable to expect that analytic consideration of these other guideline sets would yield similar results.

Table 2. Prevalence of Aspirin Prophylaxis and Preeclampsia and RR for High and Moderate Risk Factors Within Exclusive USPSTF Risk Categories

| Characteristic | Exclusive USPSTF risk category[a] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Low (n = 638) | | Moderate 1 (n = 1953 ) | | Moderate 2+ (n = 2043) | | High (n = 1050) | | | |
| | RR (95% CI) | *P* value[d] | RR (95% CI) | *P* value[d] | RR (95% CI) | *P* value[d] | RR (95% CI) | *P* value[d] | *P* value[b] | Effect size (95% CI)[c] |
| Aspirin prophylaxis recommended, No. (%) | 96 (15.0) | NA | 462 (23.6) | NA | 1024 (50.1) | | 856 (81.5) | NA | <.001 | 0.46 (0.44-0.48) |
| Developed preeclampsia, No. (%) | 19 (3.0) | NA | 159 (8.1) | NA | 260 (12.7) | NA | 247 (23.5) | NA | <.001 | 0.19 (0.16-0.21) |
| Age, median (IQR), y | 29.9 (26.9-32.3) | NA | 30.0 (26.1-33.1) | NA | 32.0 (26.0-36.3) | NA | 32.0 (27.9-35.9) | NA | <.001 | 0.03 (0.02-0.04) |
| BMI, median (IQR)[e] | 24.0 (22.0-27.0) | NA | 25.0 (22.0-28.0) | NA | 32.0 (26.0-36.0) | NA | 32.0 (27.0 -39.0 ) | NA | <.001 | 0.20 (0.18-0.22) |
| Prior preeclampsia | NaN | NA | NaN | NA | NaN | NA | 1.44 (1.25-1.65) | <.001 | NA | NA |
| Type 1 or 2 diabetes | NaN | NA | NaN | NA | NaN | NA | 1.05 (0.76-1.44) | .77 | NA | NA |
| Chronic hypertension | NaN | NA | NaN | NA | NaN | NA | 1.26 (1.10-1.44) | .001 | NA | NA |
| Nulliparous | NaN | NA | 1.34 (1.19-1.52) | <.001 | 1.48 (1.35-1.62) | <.001 | 0.96 (0.75-1.22) | .80 | NA | NA |
| Advanced maternal age[f] | NaN | NA | 0.62 (0.36-1.05) | .08 | 0.79 (0.65-0.96) | .02 | 1.21 (0.99-1.49) | .07 | NA | NA |
| BMI ≥30.0[e] | NaN | NA | 0.74 (0.47-1.16) | .20 | 1.11 (1.01-1.23) | .048 | 1.11 (0.99-1.23) | .09 | | NA |
| Maternal race and ethnicity | | | | | | | | | | |
| Asian | 4.07 (1.34-12.36) | .04 | 0.81 (0.42-1.55) | .63 | 0.84 (0.41-1.72) | .72 | 0.63 (0.24-1.62) | .40 | NA | NA |
| Black | NaN | NA | 1.09 (0.62-1.93) | .74 | 0.95 (0.80-1.14) | .63 | 1.12 (0.91-1.38) | .30 | NA | NA |
| Hispanic | 1.61 (0.99-2.63) | .12 | 1.14 (0.85-1.53) | .42 | 1.33 (0.97-1.82) | .10 | 1.22 (0.87-1.72) | .24 | NA | NA |
| White | 0.67 (0.37-1.20) | .16 | 1.00 (0.87-1.16) | >.99 | 0.98 (0.84-1.15) | .84 | 0.94 (0.80-1.10) | .47 | NA | NA |
| Other[g] | 0 (0-NaN) | .25 | 0.73 (0.39-1.36) | .37 | 0.91 (0.57-1.47) | .80 | 0.72 (0.42-1.24) | .28 | NA | NA |

Abbreviations: BMI, body mass index; NA, not applicable; NaN, not a number; RR, relative risk; USPTF, US Preventive Services Task Force.

[a] The high risk category includes those with at least 1 high risk factor (prior preeclampsia, chronic hypertension, type 1 or 2 diabetes, kidney disease, and/or autoimmune disease). The moderate risk category includes those with BMI of 30 or greater, advanced maternal age, Black race, and/or nulliparity. The moderate 1 risk category includes those with 1 and only 1 of these moderate risk factors, and the moderate 2+ risk category includes those with 2 or more moderate risk factors and no high risk factors. The low risk category includes those without any of the above moderate or high risk factors.

[b] Pearson $\chi^2$ test and Kruskal-Wallis rank sum test.

[c] Cramér *V* and $\eta^2$ along with bootstrap 95% CIs.

[d] $\chi^2$ or Fisher exact test.

[e] Calculated as weight in kilograms divided by height in meters squared.

[f] 35 years or older at estimated due date.

[g] Included individuals whose medical record did not assign them to 1 of the 4 initial groups.

Individual high risk factors were all associated with high rates of preeclampsia. However, the moderate risk characteristics were more difficult to interpret. The incidence of preeclampsia was intermediate between that of the low and high risk categories, but the RR associated with membership in the moderate risk category changed depending on whether other moderate risk characteristics were included. With the exception of nulliparity, which was consistent in its modest association with preeclampsia across the moderate 1 and moderate 2+ categories, the associations of the other moderate risk characteristics were not consistent. In this analysis, maternal race as an isolated factor was not associated with preeclampsia in any of the risk categories. Ultimately, this analysis suggests that risk stratification within the USPSTF guidelines mostly depends on high risk factors. As has been recently noted, the circumstances of enrollment in individual studies may lead to results being overgeneralized when risk factors identified in these studies are applied to broader clinical circumstances.[14] This is, in part, likely to be the explanation for the loss of association of some of the moderate risk factors with the risk of preeclampsia. The solution to this overgeneralization is to, as we have done, evaluate all risk factors within the same population. The high correlation of moderate risk factors with high risk category lends evidence to this hypothesis. Apart from a minor increased RR for nulliparous individuals without high risk factors, the interpretation and ultimate clinical utility of the moderate risk factors are likely limited.

Specific additional caution should be taken in using Black race as a risk factor. An ever-growing body of literature demonstrates that it is structural inequities rather than race that underlies health

**Table 3. Aspirin Recommendation Rates by USPSTF Risk Category and/or Risk Factors**

| Characteristic | No AP recommendation, No./total No. (%) | AP recommended, No./total No. (%) | *P* value[a] | Effect size (95% CI)[b] | Odds ratio (95% CI)[c] |
|---|---|---|---|---|---|
| Total | 3214/5652 (56.9) | 2438/5652 (43.1) | NA | NA | NA |
| Preeclampsia | 268/684 (39.2) | 416/684 (60.8) | <.001 | 0.44 (0.29-0.58) | 2.45 (1.78-3.22) |
| Risk category[d] | | | | | |
| Low risk | 538/634 (84.9) | 96/634 (15.1) | <.001 | 1.54 (1.39-1.69) | 0.03 (0.02-0.05) |
| Moderate 1 | 1480/1942 (76.2) | 462 /1942 (23.8) | <.001 | 1.10 (1.02-1.19) | 0.10 (0.08-0.12) |
| Moderate | 2488/3974 (62.6) | 1486/3974 (37.4) | <.001 | 0.51 (0.45-0.57) | 0.36 (0.31-0.41) |
| Moderate 2+ | 1008/2032 (49.6) | 1024/2032 (50.4) | .32 | 0.04 (0.00-0.10) | 1.04 (0.87-1.22) |
| High risk | 188/1044 (18.0) | 856/1044 (82.0) | <.001 | 1.39 (1.27-1.51) | 21.32 (15.46-28.76) |
| Maternal race | | | | | |
| Asian | 189/264 (71.6) | 75/264 (28.4) | <.001 | 0.90 (0.68-1.15) | 0.16 (0.09-0.25) |
| Black | 395/1190 (33.2) | 795/1190 (66.8) | <.001 | 0.69 (0.57-0.80) | 4.09 (3.19-5.21) |
| Hispanic | 713/985 (72.4) | 272/985 (27.6) | <.001 | 0.93 (0.81-1.05) | 0.15 (0.11-0.19) |
| White | 1614/2744 (58.8) | 1130/2744 (41.2) | <.001 | 0.35 (0.28-0.43) | 0.49 (0.42-0.57) |
| Other[e] | 303/469 (64.6) | 166/469 (35.4) | <.001 | 0.59 (0.41-0.75) | 0.31 (0.21-0.44) |
| Prior preeclampsia | 52/449 (11.6) | 397/449 (88.4) | <.001 | 1.75 (1.56-1.94) | 61.67 (33.06-109.18) |
| Chronic hypertension | 59/499 (11.8) | 440/499 (88.2) | <.001 | 1.74 (1.55-1.92) | 58.90 (32.36-100.96) |
| Type 1 or 2 diabetes | 17/173 (9.8) | 156/173 (90.2) | <.001 | 1.87 (1.56-2.17) | 106.16 (33.17-268.96) |
| Advanced maternal age[f] | 601/1317 (45.6) | 716/1317 (54.4) | <.001 | 0.18 (0.07-0.29) | 1.44 (1.16-1.79) |
| Body mass index ≥30[g] | 944/2166 (43.6) | 1222/2166 (56.4) | <.001 | 0.26 (0.18-0.35) | 1.69 (1.42-2.00) |
| Nulliparous | 1318/2272 (58.0) | 954/2272 (42.0) | <.001 | 0.32 (0.25-0.40) | 0.53 (0.44-0.61) |
| Gestational diabetes | 234/572 (41.0) | 338 (59.0) | <.001 | 0.37 (0.20-0.55) | 2.14 (1.498-3.02) |
| Smoker | 172/319 (53.9) | 147/319 (46.1) | .06 | 0.16 (0.01-0.38) | 0.76 (0.46-1.16) |

Abbreviations: AP, aspirin prophylaxis; USPSTF, US Preventive Services Task Force.

[a] Pearson $\chi^2$ test.

[b] Cohen *d* for difference between proportions with bootstrap 95% CI.

[c] Odds ratio of aspirin recommended to no aspirin recommendedwith corresponding bootstrap 95% CI.

[d] The high risk category includes those with at least 1 high risk factor (prior preeclampsia, chronic hypertension, type 1 or 2 diabetes, kidney disease, and/or autoimmune disease). The moderate risk category includes those with body mass index of 30 or greater, advanced maternal age, Black race, and/or nulliparity. The moderate 1 risk category includes those with 1 and only 1 of these moderate risk factors and the moderate 2+ risk category includes those with 2 or more moderate risk factors and no high risk factors. The low risk category includes those without any of the above moderate or high risk factors.

[e] Included individuals whose medical record did not assign them to 1 of the 4 initial groups.

[f] 35 years or older at estimated due date.

[g] Calculated as weight in kilograms divided by height in meters squared.

disparities.[30-35] Our prior work has demonstrated that the statistical significance of maternal race is lost with the introduction of appropriate pathophysiological biomarkers.[36] The individualization of risk based on maternal physiology represents a vital remedy to race-based disparity in preeclampsia risk assessment. It is consistent with other areas of medicine that have moved away from race-based clinical risk assessment.[37-39]

Clinician AP recommendation was not well aligned with USPSTF guidelines, especially in the moderate risk category. Overall, nearly one-half (46.7%) of those with at least 1 USPSTF risk factor had AP recommended, with 82% in the high risk category; 50% in moderate 2+ risk category; and 24% in the moderate 1 risk category. Given that fewer than 25% of patients comply with the clinician recommendation of AP,[40,41] the actual benefits may be even more limited.[42] These limitations are not specific to preeclampsia. The medical literature is replete with examples of general clinical characteristics that are used for risk stratification yielding only modest patient compliance with prophylaxis.[40] While physician endorsement of the utility of prophylaxis improves compliance,[40] the specification of an individual's level of risk, preferentially based on objective parameters based on maternal biology, represents a potential solution to this deficit.[43] An alternative approach would be to provide all pregnant patients with AP.[44-47] This strategy does not account for the potential trade-offs of risk involved in aspirin prophylaxis, given there is an evolving literature on the possible risks of aspirin administration.[48,49] This risk-benefit calculus might be acceptable only for those at high risk of preeclampsia, particularly when higher doses are considered (eg, 162 mg),[50] but may be excessive for those at lower risk levels. Additionally, while the USPSTF guidelines focus on AP, there are other known interventions that reduce the risk of preeclampsia in those at high risk, making it all the more important to effectively identify the right patients.[51] Finally, the potential for aspirin nonresponders has been demonstrated in other aspects of medical prophylaxis[52,53] but remains unexplored in obstetrics.

The incidence of preeclampsia in the US has proceeded with a continual increase over the past decades, with no evidence that this trend will abate.[8] The introduction of the USPSTF guidelines in 2021 did not alter the slope of this increase.[8] A portion of this increase has been associated with the decreasing baseline of cardiovascular health among reproductive-aged adults.[54-56] In that context, the utility of a screening protocol such as the USPSTF guidelines, which, at present, already identify the majority of the population as at some level of risk for preeclampsia, will become yet more limited. To compound the situation, up to 50% of these same individuals are not even aware of their preexisting hypertension.[57] With these alarming circumstances, risk stratification by maternal clinical or demographic characteristics will likely become more tenuous. Because fewer obstetrical clinicians are available to care for patients in the U.S,[58,59] and the health care system itself is under increasing strain,[60] the need to succinctly identify those at risk becomes more urgent. The obstetrical practice has excelled at developing then providing population-wide screening, with a simple blood test, for adverse outcomes such as aneuploidy and complications such as gestational diabetes.[61]

The success of these screening approaches suggests that a test to assess the risk of preeclampsia, based on its biological predictors,[17] would improve upon the present guidelines based on maternal clinical or demographic characteristics.[62-65] As shown in this analysis, guidelines are ineffective at estimating risk among those who are at moderate risk of preeclampsia. Future studies will need to assess such biomarkers and whether its use will produce population-level benefits.

## Limitations

The results of this study should be considered within the context of its design. The limitations are those inherent to large-scale observational research. AP recommendation was based on the medical record, precluding verification of aspirin use. We acknowledge that not all of the USPSTF moderate risk factors could be captured for analysis in this study. However, including fewer rather than more of these characteristics likely understates our findings by elevating the risk evaluation for some individuals while not altering the AP recommendation; our analysis is, if anything, conservative with regard to the true proportion of the population to be considered at moderate risk. As study

recruitment was partly through academic centers, it is oversampled for individuals with more complicated pregnancies and is, therefore, particularly informative in the setting of hypertensive diseases of pregnancy. Because these are the very centers and populations where the majority of perinatal morbidity and mortality reside, representation is fundamental to characterizing the burden of preeclampsia within the country as a whole.[66] The patients in the low risk category who were recommended AP (15%) may represent clinician misspecification, clinician concern over additional risk factors not typically captured in the medical record, or recommendations based on other concerns such as spontaneous preterm birth.[67-69] Additionally, American College of Obstetricians and Gynecologists recognizes that the universal provision of AP in populations where the majority of patients are at moderate or high risk is appropriate and as such, this would also contribute to the recommendation of AP among some low risk individuals.

## Conclusions

In this prospective cohort study of singleton pregnancies, we observed that 89% of the population was at increased risk of preeclampsia (either moderate or high) by USPSTF criteria. Except for nulliparity, moderate risk factors for preeclampsia had low or no value for preeclampsia risk assessment. AP recommendations were effectively implemented only for high and low risk categories. Here we show that moderate risk factors, in the absence of high risk factors, had no or low value for estimating the risk of developing preeclampsia, leading to nonspecific recommendation of AP in the moderate risk category.

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**Author Contributions:** Drs McElrath and Rasmussen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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## SUPPLEMENT 1.

**eTable.** Prevalence of Aspirin Prophylaxis and Preeclampsia and Relative Risk for Low and Moderate Risk Factors within Exclusive USPSTF Risk Categories**e**

**Figure.** Association Between Moderate Risk Factors for Preeclampsia and High Risk Factors

## SUPPLEMENT 2.

**Data Sharing Statement**