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Impact of USPSTF Recommendations for Aspirin for Prevention of Recurrent Preeclampsia

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Abstract

BACKGROUND—The U.S. Preventive Services Task Force (USPSTF) recommends low-dose aspirin for the prevention of preeclampsia among women at high risk for primary occurrence or recurrence of disease. Recommendations for the use of aspirin for preeclampsia prevention were issued by the USPSTF in September 2014.

OBJECTIVES—To evaluate the incidence of recurrent preeclampsia in our cohort before and after the USPSTF recommendation for aspirin for preeclampsia prevention.

STUDY DESIGN—This is a retrospective cohort study designed to evaluate rates of recurrent preeclampsia among women with a history of preeclampsia. We utilized a two hospital, single academic institution database from August 2011 through June 2016. We excluded multiple gestations and included only the first delivery for women with multiple deliveries during the study period. The cohort of women with a history of preeclampsia were divided into two groups, “before” and “after” the release of the USPSTF 2014 recommendations. Potential confounders were accounted for in multivariate analyses, and relative risk and adjusted relative risk were calculated.

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RESULTS—17,256 deliveries occurred during the study period. A total of 417 women had a documented history of prior preeclampsia; 284 women “before” and 133 women “after” the USPSTF recommendation. Comparing the before and after groups, the proportion of Hispanic women in the after group was lower and the method of payment differed between the groups ($P < .0001$). The prevalence of type 1 diabetes was increased in the after period, but overall rates of pregestational diabetes were similar (6.3% before versus 5.3% after; $P > .05$). Risk factors for recurrent preeclampsia included maternal age >35 years (RR, 1.83; 95% CI, 1.34–2.48), Medicaid insurance (RR, 2.08; 95% CI, 1.15–3.78), type 1 diabetes (RR, 2.13; 95% CI, 1.37–3.33), and chronic hypertension (RR, 1.96; 95% CI, 1.44–2.66). The risk of recurrent preeclampsia was decreased by 30% in the after group (adjusted relative risk (aRR), 0.70; 95% CI, 0.52–0.95).

CONCLUSION—Rates of recurrent preeclampsia among women with a history of preeclampsia decreased by 30% after release of the USPSTF recommendation for aspirin for preeclampsia prevention. Future prospective studies should include direct measures of aspirin compliance, gestational age at initiation, and explore the influence of race and ethnicity on the efficacy of this primary prevention.

Keywords

aspirin; preeclampsia; prevention

INTRODUCTION

Preeclampsia is a common obstetrical complication that affects 5 to 10% of pregnancies and is a major cause of multi-organ dysfunction and maternal morbidity resulting from generalized endothelial dysfunction.¹ Preeclampsia often results in fetal growth restriction and medically-indicated preterm delivery with associated neonatal morbidity of prematurity (e.g. respiratory issues, neonatal intensive care unit admission).

Estimates of recurrent preeclampsia risk vary with most reports citing a risk of 15–25%,^{2–4} although 65% of women with preeclampsia onset in the second trimester experienced recurrent preeclampsia in one study.⁵ The variation in reported recurrence risk is likely explained by differences in patient populations including differences in known risk factors for recurrent preeclampsia (severity of preeclampsia, gestational age at onset).⁶ In one prospective study from Sweden in 2009, among gravidae affected by preeclampsia in their first pregnancy, the risk of recurrent preeclampsia was 14.7% in the second pregnancy and 31.9% in the third pregnancy.² In this study, the authors advocated for two distinct preeclamptic cohorts, one of which experience severe, recurrent, and generally earlier onset and are affected by chronic maternal, genetic, and environmental factors.

The underlying etiology and pathophysiology of both primary and recurrent preeclampsia is incompletely understood but is thought to involve dysfunctional cytotrophoblastic invasion, placental ischemia, and release of inflammatory and endothelial mediators.^{7, 8} At a mechanistic level, via inhibition of the cyclooxygenase (COX) enzymes, aspirin decreases the ratio of thromboxane to prostacyclins resulting in net increased uteroplacental blood flow.^{9, 10} Thus, aspirin retains the biological plausibility to reduce the occurrence of preeclampsia by relatively well-defined pharmacologic mechanisms.

In September 2014, the U.S. Preventive Services Task Force (USPSTF) published their recommendations regarding the use of low-dose aspirin for preeclampsia prevention for pregnant women at increased risk for preeclampsia, including women with a prior history of both early and late gestation preeclampsia.¹¹ Their recommendations were based on a systematic review and meta-analysis suggesting that aspirin was associated with absolute risk reductions of 2% to 5% for preeclampsia (relative risk (RR), 0.76, 95% CI; 0.62–0.95), 1% to 5% for intrauterine growth restriction (RR, 0.80; 95% CI, 0.65–0.99), and 2% to 4% for preterm birth (RR, 0.86; 95% CI, 0.76–0.98).¹² Since publication of these recommendations, multiple meta-analyses have suggested an observable and significant impact of initiation of first or early mid-trimester initiation of low-dose aspirin therapy for the prevention of both primary and recurrent preeclampsia among at-risk gravidae.^{13, 14} However, evidence of a population-based impact of the USPSTF recommendation has not yet been undertaken. The objective of this study was to evaluate the clinical impact of the USPSTF recommendation for low- dose aspirin for preeclampsia prevention on rates of recurrent preeclampsia.

METHODS

Study design, subjects, and database characteristics

This research study was approved by the Baylor College of Medicine Institutional Review Board (H-26364; H-33382; most recent approval May 16, 2016). This is a retrospective nested cohort study designed to evaluate rates of preeclampsia among women with a history of preeclampsia before and after the late 2014 USPSTF recommendation aspirin for preeclampsia prevention recommendations. Women with a history of preeclampsia were the cohort of interest due to the highest risk for recurrence and ability to standardize over time. In addition, it is possible that baseline co-morbid occurrences rendering risk for primary preeclampsia (*i.e.*, chronic hypertension, type 1 and type 2 diabetes, morbid obesity) increased in the reference population. For these reasons, we chose to specifically examine the occurrence of recurrent preeclampsia rather than the occurrence of the disease overall.

We utilized a two hospital, single academic institution database of deliveries from August 2011 through June 2016. Based in Houston, Texas, PeriBank is a comprehensive, institutional database and biobank focusing on detailed clinical data and accompanying specimens collected at delivery and curated at Baylor College of Medicine. A detailed description of PeriBank has been published previously.¹⁵ At the time of admission, gravidae were enrolled by trained PeriBank research personnel after written informed consent was obtained. Up to 4,900 variables of clinical data were sought from the electronic medical record, prenatal records, and by in-person interview. The quality of the data was ascertained by regular verification of a subset of the inserted clinical data and by at least one board-certified maternal-fetal medicine physician scientist (K.M.A.) as previously published.¹⁵ Clinical data that were extracted for this study comprise the patient history (including prior and familial occurrence of preeclampsia, smoking status, nicotine and substance use, familial obstetrical history, and prenatal care clinics and providers), socioeconomic status (education, income, immigration status) and residential and workplace data (each trimester

of pregnancy residence and work place five-digit zip code). Not all 4,900 potential PeriBank variables were employed in this analysis.

Inclusion criteria—Subjects included in the current study were enrolled in our PeriBank database between August 2011 and June 2016 (N=17,256 deliveries). The index pregnancy is the most recent pregnancy in the database for each subject. All women with a history of preeclampsia in a prior pregnancy were identified. Women with multiple gestations were excluded, and only the first pregnancy during the time period for each woman was included. Women were assigned to the before and after groups based on the date of delivery for the index (most recent) pregnancy.

Outcome measures and data analysis

The primary outcome in this analysis was the incidence of recurrent preeclampsia in the index pregnancy. All clinical and demographic data for pregnancies enrolled into our study were obtained from PeriBank. Preeclampsia was defined by American College of Obstetrics and Gynecology (ACOG) diagnostic criteria. Of note, the diagnostic criteria for preeclampsia changed in 2013 before the guideline was implemented.^{16, 17} A history of preeclampsia is documented in our database as is the gestational age at prior delivery; however, the severity of preeclampsia is not specified. The use of magnesium sulfate and preterm delivery were utilized as surrogates for preeclampsia with severe features. Preterm delivery was defined as delivery prior to 37 weeks of gestation. Groups of interest were compared by chi-square or Fisher's exact test for categorical variables, t-test for normally distributed continuous variables, and Wilcoxon rank sum test for non-normal continuous variables. Linear regression was performed for the trend in recurrent preeclampsia in the before and after groups.

In an effort to control for potential confounders, multivariate modeling was undertaken. Generalized linear models (GLMM, Proc GENMOD in SAS version 9.4) were used for estimation of Relative Risk (RR), adjusted RR and corresponding 95% confidence intervals for binomial outcome variables (preeclampsia in this pregnancy [primary outcome], preterm birth, and magnesium sulfate for use in labor [secondary outcomes]). Generalized linear mixed models (Proc GLIMMIX in SAS version 9.4) was used for estimation of least square means (LSM) for non-normally distributed continuous outcome variables and comparison between study groups. Possible confounders were assessed initially and controlled for by including them in the regression models. Adjustments were made for maternal age, Hispanic ethnicity, method of payment, gestational age at first visit, type 2 diabetes, chronic hypertension, and gestational age at diagnosis of preeclampsia in last pregnancy. $P < .05$ was considered statistically significant. The number needed to treat (NNT) was calculated as the inverse of absolute risk reduction (absolute risk reduction = control event rate (before) less the experimental event rate (after)).

RESULTS

During the study period, 17,256 deliveries were captured in our PeriBank database. A total of 417 pregnancies were identified as high risk for preeclampsia based on a history of preeclampsia; 284 pregnancies “before” and 133 pregnancies “after” the USPSTF

recommendation for low-dose aspirin for preeclampsia prevention (Table 1). Comparing before and after groups, the proportion of Hispanic gravidae in the after group was lower and the method of payment differed between the groups ($p < .0001$). The prevalence of type 1 diabetes was increased in the after period, but overall rates of pregestational diabetes were similar (6.3% before versus 5.3% after, $p > .05$). There were no significant differences in maternal age ($p = .585$), African American race ($p = .252$), gestational age at first visit ($p = .055$), BMI ($p = .969$), smoking status ($p = .445$), chronic hypertension ($p = .178$), gestational age of diagnosis for prior preeclampsia ($p = .209$), gestational age at delivery this pregnancy ($p = .917$), or preterm delivery this pregnancy ($p = .826$).

Maternal age >35 years (RR, 1.83; 95% CI 1.34–2.48), Medicaid payment (RR, 2.08; 95% CI 1.15–3.78), type 2 diabetes (RR, 2.13; 95% CI 1.37–3.33), and chronic hypertension (RR, 1.96; 95% CI 1.44–2.66) were risk factors for recurrent preeclampsia (Table 2; Figure 1). Hispanic ethnicity (RR, 1.07; 95% CI, 0.76–1.50), African American race (RR, 1.42; 95% CI, 0.98–2.06), BMI >30 (RR, 1.34; 95% CI, 0.88–2.03), smoking (RR, 0.91; 95% CI, 0.27–3.06), and prior preterm preeclampsia (RR, 1.38; 95% CI, 0.99–1.92) were not significantly associated with recurrent preeclampsia. As expected, gravidae who experience recurrent preeclampsia were more likely to be delivered preterm (RR, 3.28; 95% CI, 2.46–4.39).

Recurrent preeclampsia occurred in fewer women after the USPSTF recommendation based on adjusted analyses (32.4% before versus 16.5% after; aRR, 0.70; 95% CI, 0.52–0.95) (Table 3, Figure 2A and 2B). There was a downward trend in the incidence of recurrent preeclampsia prior to the intervention, but the slope was not significant in the before or after period ($P = 0.086$ and $P = 0.965$, respectively). When the data was limited to two years before and two years after the recommendation, there was not a decreasing trend in preeclampsia rates, and the difference between before and after groups remained significant ($P = 0.02$, Figure 2C and 2D). There was no significant difference in the use of magnesium sulfate for seizure prophylaxis during labor (25.0% before versus 18.3% after; aRR, 0.71; 95% CI, 0.46–1.10) or preterm delivery (24.3% before versus 23.3% after; aRR, 0.99; 95% CI, 0.68–1.43). The NNT to prevent one case of preeclampsia for all women with a history of preeclampsia in our cohort was 6.

COMMENT

Rates of recurrent preeclampsia among women with a history of preeclampsia decreased by 30% after the USPSTF recommendation for low-dose aspirin for preeclampsia prevention. The decreased incidence of recurrent preeclampsia was not accounted for by differences in known accompanying risk factors for preeclampsia in our multivariable analysis. The quarterly representation of data in Figure 2B similarly shows no evidence of seasonal variation in the incidence of recurrent preeclampsia, suggesting that temporal seasonal variation alone could not account for our findings.^{18, 19} Paradoxically, we did observe a higher proportion of at-risk women who did not experience recurrent preeclampsia which argues against change in regional referral patterns or birthrates affecting our results.

Several randomized controlled trials (RCTs) and meta-analyses have been conducted to test the hypothesis that aspirin can reduce the incidence of preeclampsia.^{20–23} Two large trials from the Maternal-Fetal Medicine Unit (MFMU) Network and the Collaborative Low-Dose Aspirin Study in Pregnancy (CLASP) provided most of the data for subsequent meta-analyses.^{24, 25} The MFMU conducted a multicenter, randomized placebo controlled trial of low-dose aspirin for the prevention of preeclampsia in 2,503 women.²⁴ The study population was women deemed to be at high risk of preeclampsia based on pregestational diabetes requiring insulin, chronic hypertension, multifetal gestations, or a history of preeclampsia in prior pregnancies. They found that aspirin did not lower the incidence of preeclampsia in any of these groups (RR, 0.90; 95% CI, 0.77–1.06). CLASP was a multinational trial including 9,364 women who were enrolled to prevent or treat preeclampsia and fetal growth restriction.²⁵ They found a 12% nonsignificant decrease in proteinuric preeclampsia in the aspirin group (RR, 0.88; 95% CI, 0.75–1.03).

A subsequent meta-analysis published in 2003 that included 14 trials of over 12,000 women showed that aspirin reduced the incidence of preeclampsia and perinatal death (OR, 0.86; 95% CI, 0.76–0.96 and OR, 0.79; 95% CI, 0.64–0.96, respectively).²⁶ In 2007, the PARIS Collaborative Group published a meta-analysis with individual patient level data from 31 trials including 32,217 women. Women who received aspirin had 10% reduction in the relative risk of preeclampsia (RR, 0.90; 95% CI, 0.84–0.97), delivery before 34 weeks (RR, 0.90; 95% CI, 0.83–0.98), and pregnancy with a serious adverse outcome (RR, 0.90; 95% CI, 0.85–0.96).²⁷ More recent studies have examined the effect of prophylactic anticoagulation in addition to aspirin on placenta-mediated complications with conflicting results.^{28–30} The evidence regarding the dose-dependent efficacy and impact of gestational age at initiation are similarly poorly defined.^{31, 32}

One novel finding of our study was related to estimates of at-risk recurrence when our cohort was stratified by its inherent racial and ethnic variation. Interestingly, the relative proportion of Hispanic women experiencing recurrent preeclampsia in the post-USPSTF recommendation strata was lower, while the proportion of African American gravidae and those with chronic hypertension was higher. Since our cohort is largely Hispanic, we cannot distinguish whether these observations are due to relative over or underpowering. However, the data trend is of potential interest and, although difficult to ascertain from this study alone, these findings potentially suggest that there may be racial and ethnic variation in responsiveness to low-dose aspirin prophylaxis for recurrence of preeclampsia. The results of our study differ substantially from previous trials in that our effect size was much larger (overall effect sizes from larger trials were small with an approximately 10% reduction).^{24, 25} However, our results are in agreement with the meta-analysis that prompted the USPSTF recommendation (RR, 0.76; 95% CI, 0.62–0.95).¹² We speculate that in our patient population, which is largely Hispanic, aspirin may be particularly effective. Future pharmacogenomics studies and analyses may benefit from study design aimed to directly assess whether aspirin has varying degrees of effectiveness for preventing preeclampsia among different races and ethnicities; this would be in alliance with current precision medicine initiatives.

Our study has both limitations and strengths. Limitations of our study include the retrospective nature and inability to control for all potential confounders. Another limitation includes the lack of data on which women received aspirin, individual subject compliance with aspirin, and gestational age at initiation of therapy. As an observational study, we are unable to assert a causal association; our findings suggest a temporal association with the USPSTF aspirin guideline for prevention of preeclampsia with robust adjustments for potential confounders which did not explain our findings. Additionally, by design, our cohort included only women with a history of preeclampsia and did not include women without a history of preeclampsia with other risk factors for preeclampsia including those for whom aspirin is recommended (e.g., multifetal gestation, chronic hypertension, pregestational diabetes, renal disease, and autoimmune disease).¹¹ However, a history of preeclampsia is the predictor for preeclampsia with reported 7-fold relative risk³³, and the overall primary rate of preeclampsia is virtually unchanged across populations and over generations. Thus, the strata within which we chose to examine recurrence is a strength of our approach and limits ascertainment bias inherent to large population-based studies. Similarly, the large number of deliveries and manually abstracted data, rather than utilization of diagnosis codes, strengthen the validity of our results over other population-based analyses.

Finally, the greatest strength of our study was its ability to estimate the effect of release of a USPSTF recommendation for the use of low-dose aspirin at a population-wide level, inclusive of inherent imperfect use and application. We observed a 30% risk reduction across the population which could not be explained by any factor other than the temporal introduction of such guidelines. The clinical use of aspirin for the prevention of preeclampsia is estimated to decrease the rate of recurrent preeclampsia in women at the highest risk of recurrence in our practice, and our NNT estimate across the entirety of the population over time was 6. Aspirin is a low cost intervention with widespread availability and proven ability to reduce morbidity and healthcare costs.^{34, 35} The future for the study of aspirin for preeclampsia prediction is bright including planned studies to incorporate early screening tests for preeclampsia to determine eligibility for aspirin use.^{36, 37} Future studies should include women with indications for aspirin other than a history of preeclampsia and further explore the influence of race and ethnicity on the preventive efficacy of low-dose aspirin.

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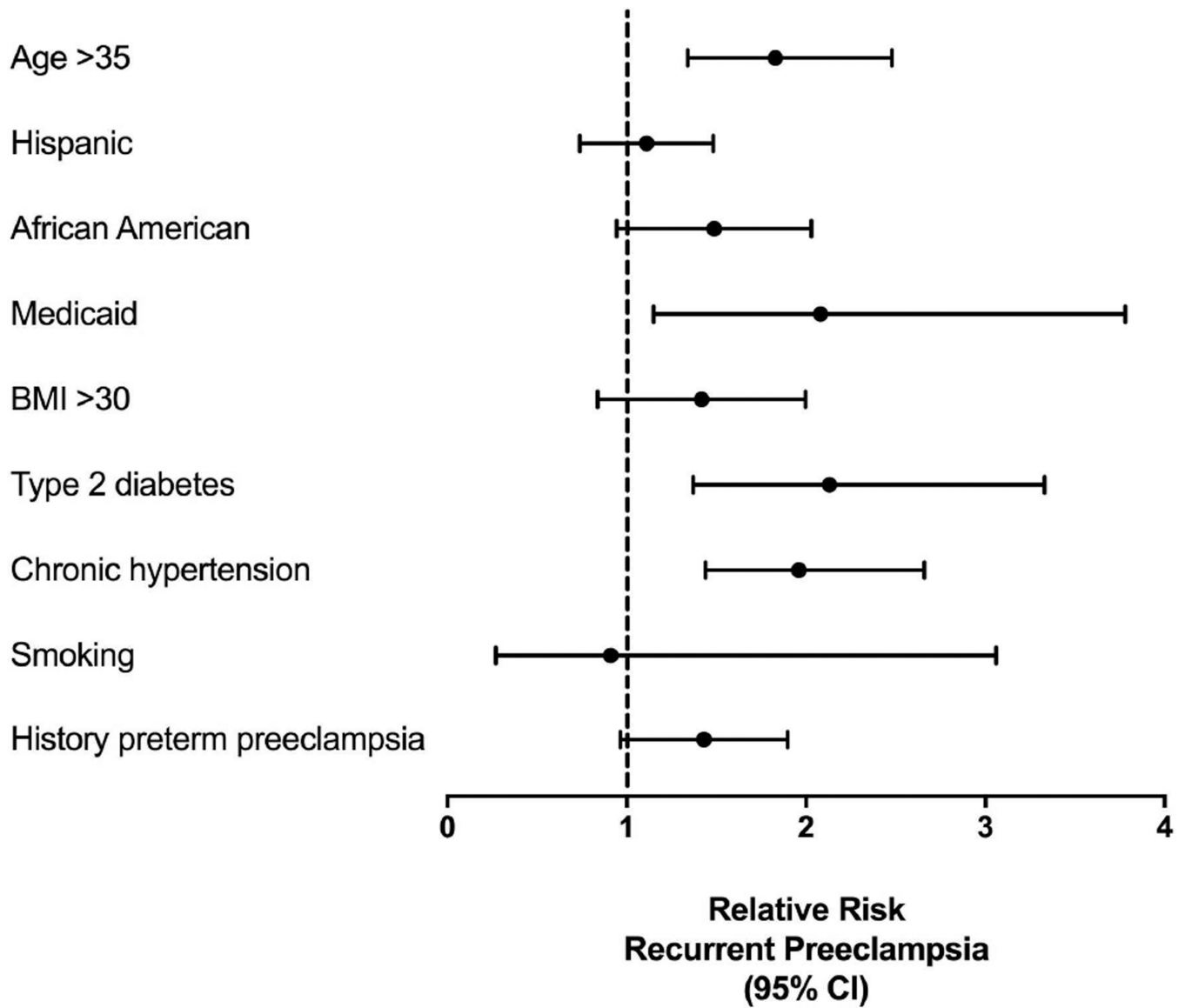


Figure 1. Forest plot of risk factors for recurrent preeclampsia among the cohort overall, with relative risk and 95% confidence intervals. BMI=body mass index

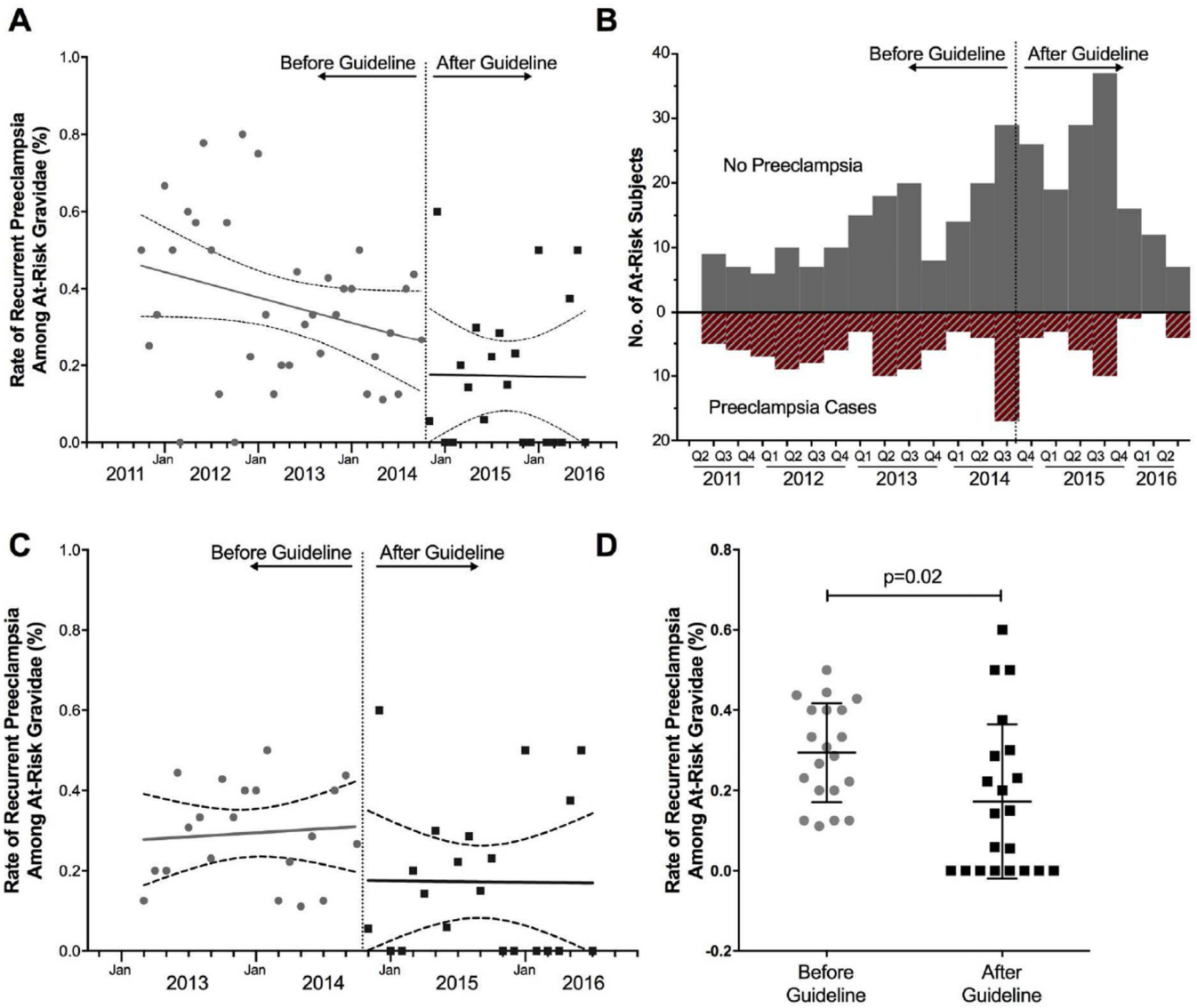


Figure 2. Pregnancies affected by recurrent preeclampsia (and those not affected) over time, before and after the USPSTF recommendation for aspirin for preeclampsia prevention. “At-risk” was defined by gravidae documented as having had preeclampsia in a prior pregnancy. A. Trends in rates of recurrent preeclampsia 2011–2016. B. Bar graph of recurrent preeclampsia by quarter 2011–2016. C. Trend in rates of recurrent preeclampsia 2013–2016 (2 years before and after the USPSTF recommendation). D. Scatter plot of rate of recurrent preeclampsia 2013–2016 (2 years before and after the USPSTF recommendation).

Table 1

Baseline characteristics comparing pregnancies complicated by previous preeclampsia before and after the USPSTF recommendation for low-dose aspirin.

Characteristic	BEFORE USPSTF guideline for aspirin N=284	AFTER USPSTF guideline for aspirin N=133	P-value
Maternal age, mean (SD)	30.04 (6.05)	30.40 (6.44)	0.585
Race and ethnicity			
Hispanic, N (%)	217 (76.4%)	66 (49.6%)	<0.0001 *
African American, N (%)	39 (13.7%)	24 (18.1%)	0.252
Method of payment, N (%)			<0.0001 *
Medicaid	104 (36.6%)	52 (39.1%)	0.626
Chip	116 (40.9%)	27 (20.3%)	<0.0001 *
Private	26 (9.2%)	50 (37.6%)	<0.0001 *
Other	38 (13.4%)	4 (3.0%)	0.007 *
Gestational age at first visit, median (IQR)	13 (9–19)	11.5 (9–15)	0.055
BMI, median (IQR)	33.6 (30.0–37.9)	33.70 (29.4–39.1)	0.969
Smokers, N (%)			0.445
Current	7 (2.5%)	1 (0.8%)	
Never/Ever	277 (97.5%)	132 (99.3%)	
Pregestational diabetes, N (%)			
Type 1	2 (0.7%)	5 (3.8%)	0.036 *
Type 2	16 (5.6%)	2 (1.5%)	0.064
Chronic hypertension, N (%)	58 (20.4%)	35 (26.3%)	0.178
Gestational age prior preeclampsia, median (IQR)	37 (34–40)	36 (35–38)	0.209
Gestational age at delivery this pregnancy, median (IQR)	38 (37–39)	38 (37–39)	0.917
Preterm delivery this pregnancy, N (%)	69 (24.3%)	31 (23.3%)	0.826

* significant based on $p < 0.05$

Table 2

Comparison of pregnancies complicated by recurrent preeclampsia versus no recurrent preeclampsia.

Characteristic	Recurrent preeclampsia N=114	No recurrent preeclampsia N=303	Relative Risk (95% CI)
Maternal age >35 years, N (%)	42 (36.8%)	59 (19.5%)	1.83 (1.34–2.48)*
Race and ethnicity			
Hispanic, N (%)	79 (69.3%)	204 (67.3%)	1.07 (0.76–1.50)
African American, N (%)	23 (20.2%)	40 (13.2%)	1.42 (0.98–2.06)
Method of payment, N (%)			
Medicaid	47 (41.2%)	109 (36.0%)	2.08 (1.15–3.78)*
CHIP	39 (34.2%)	104 (34.3%)	1.88 (1.03–3.46)*
Private	11 (9.7%)	65 (21.5%)	1.0
Other	17 (14.9%)	25 (8.3%)	2.80 (1.45–5.40)*
BMI >30, N (%)	85/106 (80.2%)	209/285 (73.3%)	1.34 (0.88–2.03)
Pregestational diabetes, N (%)			
Type 1	0	7 (2.3%)	--
Type 2	10 (8.8%)	8 (2.6%)	2.13 (1.37–3.33)*
Chronic hypertension, N (%)	41 (36.0%)	52 (17.2%)	1.96 (1.44–2.66)*
Smokers, N (%)			0.91 (0.27–3.06)
Current	2 (1.8%)	6 (2.0%)	
Ever/Never	112 (98.3%)	297 (98.0%)	
Preterm (<37 weeks) prior preeclampsia, N (%)	57/106 (53.8%)	122/286 (42.7%)	1.38 (0.99–1.92)
Preterm delivery (<37 weeks) this pregnancy, N (%)	58 (50.9%)	42 (13.9%)	3.28 (2.46–4.39)*

* significant based on relative risk 95% confidence interval that does not contain 1.

Table 3

Outcomes among women with a history of preeclampsia before and after the USPSTF recommendation for low-dose aspirin.

Outcome	BEFORE USPSTF guideline for aspirin N=284	AFTER USPSTF guideline for aspirin N=133	Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)
Preeclampsia this pregnancy, N (%)	92 (32.4%)	22 (16.5%)	0.51 (0.34–0.77)*	0.70 (0.52–0.95)*
Magnesium sulfate during labor, N (%)	69 (25.0%)	24 (18.3%)	0.73 (0.48–1.11)	0.71 (0.46–1.10)
Preterm delivery, N (%)	69 (24.3%)	31 (23.3%)	0.96 (0.66–1.39)	0.99 (0.68–1.43)

* significant based on relative risk 95% confidence interval that does not contain 1.

Adjusted for maternal age, Hispanic ethnicity, method of payment, gestational age at first visit, type 2 diabetes, chronic hypertension, and gestational age previous preeclampsia