IMPORTANCE Preeclampsia is a hypertensive disorder of pregnancy that poses serious maternal and infant health risks. Previous systematic reviews have established benefits of low-dose aspirin taken during pregnancy to prevent preeclampsia and its sequelae.

OBJECTIVE To update evidence for the US Preventive Services Task Force (USPSTF) on effectiveness of aspirin use in preventing preeclampsia in individuals at increased risk based on clinical risk factors or measurements associated with higher disease incidence than in the general population.


STUDY SELECTION Good- and fair-quality randomized clinical trials (RCTs) of low-dose aspirin use during pregnancy to prevent preeclampsia among individuals at increased risk; studies conducted in general populations to evaluate potential harms.

DATA EXTRACTION AND SYNTHESIS Dual article screening and risk-of-bias assessment. Study data abstracted into prespecified forms, checked for accuracy. Random-effects meta-analysis.

MAIN OUTCOMES AND MEASURES Diagnosis of preeclampsia; adverse pregnancy health outcomes and complications including eclampsia, perinatal mortality, preterm birth, small for gestational age, and potential bleeding harms or infant/child harms from aspirin exposure.

RESULTS A total of 23 randomized clinical trials (RCTs) (N = 26,952) were included; 18 were conducted among participants at increased preeclampsia risk. Aspirin dosages ranged from 50 mg/d to 150 mg/d. Most trials enrolled majority White populations selected based on a range of risk factors. The incidence of preeclampsia among the trials of participants at increased risk ranged from 4% to 30%. Aspirin use was significantly associated with lower risk of preeclampsia (pooled relative risk [RR], 0.85 [95% CI, 0.75-0.95]; 16 RCTs [n = 14,093]; I² = 0%), perinatal mortality (pooled RR, 0.79 [95% CI, 0.66-0.96]; 11 RCTs [n = 13,860]; I² = 0%), preterm birth (pooled RR, 0.80 [95% CI, 0.67-0.95]; 13 RCTs [n = 13,619]; I² = 49%), and intrauterine growth restriction (pooled RR, 0.82 [95% CI, 0.68-0.99]; 16 RCTs [n = 14,385]; I² = 41%). There were no significant associations of aspirin use with risk of postpartum hemorrhage (pooled RR, 1.03 [95% CI, 0.94-1.12]; 9 RCTs [n = 23,133]; I² = 0%) and other bleeding-related harms, or with rare perinatal or longer-term harms. Absolute risk reductions for preeclampsia associated with aspirin use ranged from −1% to −6% across larger trials (n >300) and were greater in smaller trials. For perinatal mortality, absolute risk reductions ranged from 0.5% to 1.1% in the 3 largest trials.

CONCLUSIONS AND RELEVANCE Daily low-dose aspirin during pregnancy was associated with lower risks of serious perinatal outcomes for individuals at increased risk for preeclampsia, without evident harms.
Preeclampsia is a systemic hypertensive disorder of pregnancy thought to arise from abnormal placentation and systemic inflammatory processes and characterized by increased blood pressure, accompanied by proteinuria or other signs. The condition can vary in severity, have an unpredictable course, and increases risks for serious maternal health complications such as eclamptic seizures, stroke, organ damage, and death. It also poses serious neonatal and infant risks, including intrauterine growth restriction, low birth weight, preterm birth, placental abruption, stillbirth, and neonatal death.

The estimated incidence of preeclampsia in the US increased from 38.4 per 1000 deliveries in 2005 to 46.6 per 1000 deliveries in 2014, and the majority of this increase has been cases of preeclampsia with severe features (11.6 to 17.4 cases per 1000 deliveries) and preeclampsia occurring in the presence of chronic hypertension (3.7 to 6.7 per 1000 deliveries). Inequities in health are observed, especially for Black women giving birth in the US; preeclampsia was estimated to occur in 69.8 per 1000 deliveries among Black women compared with 43.4 per 1000 deliveries among White women, contributing to higher overall maternal morality for Black women.

In 2014 the US Preventive Services Task Force (USPSTF) recommended the prescription of low-dose (81 mg/d) aspirin after 12 weeks of gestation to asymptomatic pregnant women who are at high risk for preeclampsia (B recommendation). The current review of the evidence regarding the effectiveness of aspirin in reducing the risk for preeclampsia and adverse maternal, perinatal, and child outcomes, along with potential harms of aspirin use, was conducted to inform a USPSTF update to its current recommendation.

Methods

Scope of Review
An analytic framework was developed with 3 key questions (KQs) (Figure 1) that examined the effectiveness of aspirin in reducing adverse maternal, perinatal, child, or combined health outcomes in studies conducted among pregnant persons selected based on the presence of clinical risk factors or physical measures known to be associated with an increased risk of preeclampsia (KQ1); in preventing preeclampsia (KQ2); and the potential harms of aspirin use to prevent preeclampsia during pregnancy (KQ3). Additional methodological details are publicly available in the full evidence report.

Data Sources and Searches
To identify studies published since the previous review, literature searches were conducted from January 2013 through May 15, 2020, in MEDLINE, PubMed (for publisher-supplied records only), EMBASE, and the Cochrane Central Register of Controlled Trials (eMethods in the Supplement). Additional studies were sought by reviewing reference lists of other systematic reviews. Ongoing surveillance was conducted after May 2020 through January 22, 2021, to identify newly published studies that might affect the findings of the review. This was accomplished through article alerts and targeted searches of journals with a high impact factor and journals relevant to the topic. The last surveillance on January 22, 2021, identified no new studies.

Data Extraction and Quality Assessment
Two reviewers independently evaluated articles from the previous review in addition to citations and full-text articles from the literature searches against prespecified inclusion criteria (Figure 2; eTable 1 in the Supplement). For the KQ1 and KQ2 questions of effectiveness, randomized clinical trials (RCTs) and individual participant data meta-analyses of pregnant persons at increased risk for preeclampsia were considered for inclusion. Risk of preeclampsia was determined based on personal sociodemographic characteristics, medical history, diagnostic measurements or assays, or risk prediction models. For KQ3 evaluating harms, these criteria were expanded to include RCTs conducted in lower-risk or average-risk populations and comparative observational studies of pregnant persons exposed to aspirin for preeclampsia prevention over the course of pregnancy, as well as their similarly exposed fetuses, infants, and children. Studies limited to persons seeking fertility treatments were not included. Only studies of daily aspirin (≥50 mg/d) for the primary prevention of preeclampsia were considered for inclusion; studies evaluating nonaspirin antiplatelet medications or aspirin combined with other potentially active interventions (eg, dietary supplements, weight loss), or studies of aspirin aimed at preventing other complications of pregnancy such as miscarriage, were excluded. The review was limited to studies conducted in countries with “very high” Human Development Index (2016) scores, as published by the United Nations Development Programme. Studies were also limited to those published in English and deemed good or fair quality based on USPSTF quality rating standards.

Data Synthesis and Analysis
Data were synthesized separately for each KQ, and tables were created to describe study results for all included outcomes, with stratification by intervention and study population characteristics. Summary tables were used to describe important features of the evidence, including study design and setting, internal validity, and important characteristics about patients and interventions. Pooled estimates of the relative risks of health outcomes associated with aspirin use were generated using random-effects
restricted maximum likelihood models (REMLs) with Knapp-Hartung correction. This analytic approach overcomes limitations of other random-effects models that have been found to generate overly precise confidence limits, especially when pooling fewer than 20 studies. For results approaching the margins of statistical significance and for analyses with low t values, sensitivity analyses with the Knapp-Hartung correction were used to adjust the standard errors, and the more conservative results were reported. For rare outcomes (ie, perinatal mortality), sensitivity analyses were conducted using the Peto odds ratio method, as well as pooled analyses including and excluding studies that had no events in either study group, to assess the robustness of the final REML risk ratio pooled estimates.

To examine subgroup differences, stratified forest plots were generated using the Cochran Q statistical test of group differences and REML meta-regression analyses using the Knapp-Hartung correction; the more conservative result was reported. Variables anticipated a priori to be potential sources of heterogeneity included aspirin dosage, timing, and duration; population risk characteristics (eg, incidence of preeclampsia in the control condition, strategy for selecting participants); study size; and control condition (ie, placebo vs no treatment). For comparisons of effects by population risk of preeclampsia, studies in which more than 12% of participants developed preeclampsia in the control group were compared with studies having lower incidence rates. This threshold was selected to distinguish studies conducted in the highest-risk populations (~3× general population risk). Studies that used laboratory or imaging tests were compared with those relying only on clinical history and examinations. Sensitivity analyses were conducted to estimate pooled effects under more and less conservative statistical approaches. For each KQ, the statistical heterogeneity of included studies was estimated with I² statistics and τ. The distribution of trial results was examined with funnel plots and Peters tests to assess whether there was evidence of small-study effects.

Stata version 16.1 (StataCorp) was used for all analyses. All significance testing was 2-sided, and results were considered statistically significant if P < .05.

The strength of evidence was rated for each KQ based on consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective analysis reporting), and study quality (ie, study limitations).

Results
Two reviewers evaluated 3749 citations and 183 full-text articles against inclusion criteria, and 23 studies (33 articles) met inclusion criteria for this systematic review (Figure 2). Nineteen RCTs were carried forward from the previous USPSTF report, and 4 new RCTs were identified for inclusion (Table 1). For KQ1 and KQ2, 18 trials were included that enrolled pregnant individuals at increased risk of preeclampsia. For KQ3, 5 additional trials enrolling pregnant individuals at average risk of preeclampsia were included. Six large, multisite trials were included in the review (for KQ1 and KQ2: the US-based Maternal Fetal Medicine Unit Network Trial in High Risk Women [MFMU-HR] [n = 2539], the Collaborative Low-dose Aspirin Study in Pregnancy [CLASP] trial [n = 9364], and the Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention [ASPRE] trial...
Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality

US Preventive Services Task Force
Clinical Review & Education

The use of aspirin to prevent preeclampsia and related morbidities and mortality has been extensively studied. Key risk factors used included metabolic disease, diabetes (prepregnancy or gestational), history of small-for-gestational-age, maternal age, and intrauterine growth restriction (IUGR). Risk assessment frequently involved age/medical history and personal characteristics. Abnormal Doppler readings were used in 6 studies. Other methods included angiotensin II sensitivity, second trimester hemoglobin concentration, and use of a prediction model that combined maternal demographic factors and clinical measurements.

Key Question 1. Does aspirin reduce adverse maternal, perinatal, and child, or combined health outcomes in pregnant persons at increased risk of preeclampsia?

Key Question 1a. Does the effectiveness of aspirin for reducing adverse health outcomes vary by subpopulations defined by personal characteristics or preeclampsia risk factors?
<table>
<thead>
<tr>
<th>Source, country/countries</th>
<th>Study quality</th>
<th>No. randomized</th>
<th>Increased risk criteria</th>
<th>Aspirin dosage, mg</th>
<th>Timing of aspirin initiation; discontinuation</th>
<th>Age, mean (range), y</th>
<th>White, %</th>
<th>Nulliparous, %</th>
<th>Previous preeclampsia, %</th>
<th>Chronic hypertension, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPRE Rolnik et al, 2017</td>
<td>Good</td>
<td>1776</td>
<td>Risk prediction model findings at 11-13 wk gestation</td>
<td>150</td>
<td>11-14 wk; 36 wk</td>
<td>31.5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>67.1</td>
<td>67.3</td>
<td>10.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Ayala et al, 2013</td>
<td>Good</td>
<td>350</td>
<td>Receiving pregnancy care at high-risk obstetric unit owing to range of factors</td>
<td>100</td>
<td>12-16 wk; delivery&lt;sup&gt;c&lt;/sup&gt;</td>
<td>30.7</td>
<td>NR</td>
<td>52.2</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Benigni et al, 1989</td>
<td>Fair</td>
<td>33</td>
<td>Presence of hypertension or previous history of fetal death due to placental insufficiency, severe IUGR, early-onset preeclampsia (&lt;32 wk)</td>
<td>60</td>
<td>12 wk; delivery</td>
<td>31.5</td>
<td>NR</td>
<td>NR</td>
<td>42.7</td>
<td>33.3</td>
</tr>
<tr>
<td>Caspi et al, 1994</td>
<td>Good</td>
<td>48</td>
<td>Uncomplicated twin pregnancies</td>
<td>100</td>
<td>Start of the second trimester; delivery&lt;sup&gt;d&lt;/sup&gt;</td>
<td>28.3</td>
<td>NR</td>
<td>36</td>
<td>NR</td>
<td>2</td>
</tr>
<tr>
<td>CLASP, 1994</td>
<td>Good</td>
<td>9364</td>
<td>Increased risk determined by clinician based on range of factors including obstetric history, family history, patient and pregnancy characteristics</td>
<td>60</td>
<td>12 to 32 wk; delivery</td>
<td>28.5</td>
<td>NR</td>
<td>27.9</td>
<td>NR</td>
<td>20</td>
</tr>
<tr>
<td>Davies et al, 1995</td>
<td>Fair</td>
<td>122</td>
<td>Hemoglobin concentration greater than 13.2 g/dL</td>
<td>75</td>
<td>18 wk; delivery</td>
<td>25.0</td>
<td>95.8</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gallery et al, 1997</td>
<td>Fair</td>
<td>108</td>
<td>Chronic hypertension or previous early, severe preeclampsia</td>
<td>100</td>
<td>17 to 19 wk; 2 wk before planned delivery</td>
<td>28.5 (22-38)</td>
<td>95.5</td>
<td>42.5</td>
<td>19.3</td>
<td>54.7</td>
</tr>
<tr>
<td>Grab et al, 2000</td>
<td>Fair</td>
<td>43</td>
<td>Early IUGR, impaired uteroplacental blood, chronic hypertension or previous stillbirth, growth restriction, or preeclampsia</td>
<td>100</td>
<td>18 wk; 38 wk</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>41.9</td>
<td>44.2</td>
</tr>
<tr>
<td>Hermida et al, 1997</td>
<td>Good</td>
<td>100</td>
<td>Receiving pregnancy care at high-risk hospital unit owing to broad range of preeclampsia factors</td>
<td>100</td>
<td>12 to 16 wk; delivery&lt;sup&gt;e&lt;/sup&gt;</td>
<td>30.2</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>McParland et al, 1990</td>
<td>Fair</td>
<td>106</td>
<td>Nulliparous with persistent abnormal Doppler flow-velocity waveforms at 24 wk gestation</td>
<td>75</td>
<td>24 wk; delivery</td>
<td>26.1</td>
<td>69.0</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>MFMU-HR Caritis et al, 1998</td>
<td>Good</td>
<td>2539</td>
<td>Presence of diabetes, chronic hypertension, multifetal gestation, previous preeclampsia</td>
<td>60</td>
<td>13 to 26 wk; delivery or if preeclampsia developed</td>
<td>26.5</td>
<td>32.7</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

(continued)
<table>
<thead>
<tr>
<th>Source, country/countries</th>
<th>Study quality</th>
<th>No. randomized</th>
<th>Increased risk criteria</th>
<th>Aspirin dosage, mg</th>
<th>Timing of aspirin initiation; discontinuation</th>
<th>Age, mean (range), y</th>
<th>White, %</th>
<th>Nulliparous, %</th>
<th>Previous preeclampsia, %</th>
<th>Chronic hypertension, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morris et al, 1996</td>
<td>Fair</td>
<td>102</td>
<td>Nulliparous with abnormal Doppler ultrasound findings at 17-19 wk gestation</td>
<td>100</td>
<td>18 wk; NR</td>
<td>23.8</td>
<td>NR</td>
<td>100</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Sciacchitino et al, 2017</td>
<td>Good</td>
<td>186</td>
<td>Abnormal Doppler ultrasound findings at 11-14 wk gestation</td>
<td>150</td>
<td>11 to 14 wk; delivery</td>
<td>32.9</td>
<td>NR</td>
<td>63.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Schiff et al, 1989</td>
<td>Good</td>
<td>65</td>
<td>Nulliparity, twin gestation, history of preeclampsia, or positive rollover test</td>
<td>100</td>
<td>28 or 29 wk to 38 wk</td>
<td>27.4</td>
<td>100</td>
<td>NR</td>
<td>16.9</td>
<td>0</td>
</tr>
<tr>
<td>Viinikka et al, 1993</td>
<td>Fair</td>
<td>208</td>
<td>Presence of hypertension or previous severe preeclampsia</td>
<td>50</td>
<td>16 wk; delivery</td>
<td>33.0</td>
<td>NR</td>
<td>24.5</td>
<td>11.1</td>
<td>88.9</td>
</tr>
<tr>
<td>Villa et al, 2013</td>
<td>Fair</td>
<td>152</td>
<td>Range of preeclampsia risk factors accompanied by abnormal Doppler ultrasound findings at 12-14 wk gestation</td>
<td>100</td>
<td>12 to 14 wk; 35 wk or delivery (whichever came first)</td>
<td>30.9 (20-40)</td>
<td>NR</td>
<td>20.7</td>
<td>30.6</td>
<td>16.5</td>
</tr>
<tr>
<td>Wallenburg et al, 1986</td>
<td>Good</td>
<td>46</td>
<td>Angiotensin-II sensitivity infusion and blood pressure test</td>
<td>60</td>
<td>28 wk; delivery</td>
<td>24 (17-38)</td>
<td>NR</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Yu et al, 2003</td>
<td>Good</td>
<td>560</td>
<td>Abnormal Doppler ultrasound findings at 22-24 wk gestation</td>
<td>150</td>
<td>22 to 24 wk; 36 wk</td>
<td>29 (23-33)</td>
<td>62.3</td>
<td>25.1</td>
<td>9.9</td>
<td>0</td>
</tr>
<tr>
<td>General population (included for harms only)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hauth et al, 1993</td>
<td>Good</td>
<td>606</td>
<td>NA</td>
<td>60</td>
<td>No later than 22 wk; delivery</td>
<td>20.4</td>
<td>28.5</td>
<td>100</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>MFMU-LR</td>
<td>Good</td>
<td>3135</td>
<td>NA</td>
<td>60</td>
<td>13 to 25 wk; delivery</td>
<td>20.5</td>
<td>17.9</td>
<td>100</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Mone et al, 2018</td>
<td>Fair</td>
<td>362</td>
<td>NA</td>
<td>75</td>
<td>11 to 13 wk; 36 wk</td>
<td>33.5 (19-44)</td>
<td>96.8</td>
<td>100</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Rotchell et al, 1998</td>
<td>Good</td>
<td>3647</td>
<td>NA</td>
<td>75</td>
<td>12 to 32 wk; delivery</td>
<td>NR</td>
<td>NR</td>
<td>44</td>
<td>NR</td>
<td>0.4</td>
</tr>
<tr>
<td>Subtil et al, 2003</td>
<td>Good</td>
<td>3294</td>
<td>NA</td>
<td>100</td>
<td>14 to 20 wk; 34 wk</td>
<td>24.7</td>
<td>NR</td>
<td>100</td>
<td>NR</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: ASPRE, Combined Multimarker Screening and Randomized Treatment With Aspirin for Evidence-based Preeclampsia Prevention; CLASP, Collaborative Low-dose Aspirin Study in Pregnancy; IUGR, intrauterine growth restriction; MFMU-LR, Maternal Fetal Medicine Unit Network Trial enrolling low- and average-risk participants; NA, not applicable; NR, not reported.

* All studies placebo-controlled except for Mone et al, which had a usual-care control.

b Median (range).

c Treatment time of day randomly assigned (morning, afternoon, or evening).

d Treatment time of day, morning. *Treatment time of day, evening.
Eighteen trials (n = 15,908) reported maternal, perinatal, or child health outcomes for daily aspirin use (50 mg/d to 150 mg/d) compared with a matching placebo starting as early as 11 weeks or as late as 32 weeks of gestation and continuing until late pregnancy or delivery. In pooled analyses, aspirin was consistently associated with a reduced risk of perinatal mortality, preterm birth, and SGA/IUGR (Table 2). Fifteen trials reported perinatal mortality (n = 15,527). No individual study reported a statistically significant difference in perinatal mortality, but all were underpowered for the outcome; however, the pooled estimate showed a statistically significant 21% reduction in the risk of perinatal mortality associated with aspirin use (pooled risk ratio [RR], 0.79 [95% CI, 0.66-0.96]; 11 RCTs [n = 13,860]; I² = 0%). (Figure 3). Thirteen trials reported on preterm birth (<37 weeks of gestation) (n = 15,213). Results across these trials were consistently in the direction of a preventive benefit of daily aspirin use, with no trial finding more cases of preterm birth in the aspirin group than in the placebo group. The pooled result showed an estimated 20% reduced risk of preterm birth associated with intervention (pooled RR, 0.80 [95% CI, 0.67-0.95]; 13 RCTs [n = 13,619]; I² = 49%) (Figure 4). Trials rarely reported cases of spontaneous preterm birth separately from induced preterm birth, and few studies reported the number of cases of early preterm (<34 weeks of gestation) and extremely preterm (<28 weeks of gestation) birth. Sixteen trials reported on

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**Table 2. Summary of Meta-analysis Results**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies reporting outcome (No. of observations randomized)</th>
<th>Pooled analysis, No. of studies (No. analyzed)¹</th>
<th>Pooled RR, random-effects model (95% CI)ᵇ</th>
<th>I², %</th>
<th>τ²</th>
<th>ARD</th>
<th>Relative risk, median (IQR)</th>
<th>ARD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal mortality</td>
<td>15 (15,527)</td>
<td>11 (13,860)</td>
<td>0.79 (0.66-0.96)</td>
<td>0.0</td>
<td>0</td>
<td>31.5</td>
<td>-6.3 to 2.9</td>
<td>0.96 (0.59-1.10)</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>13 (15,213)</td>
<td>13 (13,619)</td>
<td>0.80 (0.67-0.95)</td>
<td>48.7</td>
<td>0.02</td>
<td>12.1</td>
<td>-19.5 to 0</td>
<td>0.65 (0.35-0.90)</td>
</tr>
<tr>
<td>SGA/IUGR</td>
<td>16 (15,767)</td>
<td>16 (14,385)</td>
<td>0.82 (0.68-0.99)</td>
<td>41.2</td>
<td>0.04</td>
<td>3.0-2.2</td>
<td>-25.7 to 4.9</td>
<td>0.63 (0.48-0.97)</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>16 (15,767)</td>
<td>16 (14,093)</td>
<td>0.85 (0.75-0.95)</td>
<td>0.0</td>
<td>0.07</td>
<td>1.43</td>
<td>-30.4 to 4.1</td>
<td>0.72 (0.31-0.89)</td>
</tr>
<tr>
<td>Postpartum hemorrhage</td>
<td>11 (23,583)</td>
<td>9 (23,133)</td>
<td>1.03 (0.94-1.12)</td>
<td>0.0</td>
<td>0.38</td>
<td>2.84</td>
<td>-4.2 to 9.1</td>
<td>1.02 (0.94-1.23)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>13 (25,761)</td>
<td>10 (24,970)</td>
<td>1.15 (0.76-1.72)</td>
<td>25.3</td>
<td>0.07</td>
<td>6.56</td>
<td>-0.6 to 1.8</td>
<td>1.21 (0.96-2.07)</td>
</tr>
<tr>
<td>Fetal intracranial bleeding</td>
<td>9 (23,959)</td>
<td>6 (23,719)</td>
<td>0.90 (0.51-1.57)</td>
<td>19.2</td>
<td>0.06</td>
<td>2.06</td>
<td>-0.3 to 0.6</td>
<td>0.94 (0.74-1.08)</td>
</tr>
</tbody>
</table>

Abbreviations: ARD, absolute risk difference; RR, risk ratio; SGA/IUGR, small for gestational age/intrauterine growth restriction. ¹ Studies that reported no events in both study groups were excluded from the pooled analysis. ² Restricted maximum likelihood model with Knapp-Hartung confidence intervals.
SGA/IUGR (n = 15,757), and all but 231,40 reported fewer cases in the aspirin group than in the placebo group. The pooled result indicated an estimated 18% reduced risk of having an infant that was SGA/IUGR for women who took aspirin (pooled RR, 0.82 [95% CI, 0.68-0.99]; 16 RCTs [n = 14,385]; $I^2 = 41\%$) (Figure 5). Direct maternal health consequences of preeclampsia were extremely rare and include eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, stroke, organ failure, and

### Table 1: Preterm Birth Before 37 Weeks’ Gestation, Sorted by Study Size

<table>
<thead>
<tr>
<th>Source</th>
<th>Preeclampsia incidence with placebo, %</th>
<th>Aspirin dose, mg</th>
<th>Events, No./total</th>
<th>Risk ratio (95% CI)</th>
<th>Favors aspirin</th>
<th>Favors placebo</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benigni et al., 1989</td>
<td>30</td>
<td>60</td>
<td>2/17</td>
<td>5/16</td>
<td>0.38 (0.08-1.67)</td>
<td>0.82</td>
<td>1.00</td>
</tr>
<tr>
<td>Wallenburg et al., 1986</td>
<td>9</td>
<td>100</td>
<td>11/24</td>
<td>14/23</td>
<td>0.75 (0.44-1.30)</td>
<td>0.68</td>
<td>0.28</td>
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<tr>
<td>Schiff et al., 1989</td>
<td>14</td>
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<td>1/50</td>
<td>5/50</td>
<td>0.20 (0.02-1.65)</td>
<td>0.51</td>
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</tr>
<tr>
<td>Hermida et al., 1997</td>
<td>14</td>
<td>100</td>
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<td>5/50</td>
<td>0.58 (0.15-2.29)</td>
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<td>75</td>
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<td>1/60</td>
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<td>0.35 (0.15-0.80)</td>
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<tr>
<td>Ayala et al., 2013</td>
<td>19</td>
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<td>67/276</td>
<td>75/278</td>
<td>0.90 (0.68-1.20)</td>
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<tr>
<td>Muñoz et al., 1997</td>
<td>8</td>
<td>60</td>
<td>686/3992</td>
<td>761/3982</td>
<td>0.90 (0.82-0.99)</td>
<td>28.30</td>
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</tr>
</tbody>
</table>

### Table 2: Small for Gestational Age or Intrauterine Growth Restriction, Sorted by Study Size

<table>
<thead>
<tr>
<th>Source</th>
<th>Preeclampsia incidence with placebo, %</th>
<th>Aspirin dose, mg</th>
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<td>1.00</td>
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</tr>
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</table>
### Benefits on Preeclampsia Prevention

**Key Question 2.** Does aspirin prevent preeclampsia in pregnant persons at increased risk for preeclampsia?

**Key Question 2a.** Does the effectiveness of aspirin for reducing preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia risk factors?

Sixteen included RCTs (n = 15 767) reported on the effectiveness of aspirin to prevent preeclampsia (Table 2). Aspirin was associated with statistically significant reduction in the risk of preeclampsia compared with placebo (pooled RR, 0.85 [95% CI, 0.75-0.95]; 16 RCTs [n = 14 093]; $I^2 = 0%$) (Figure 6). Across these studies, the incidence of preeclampsia in the placebo condition ranged from 4% to 30%, reflecting the broad range of criteria used for identifying increased-risk populations. Effects were consistent across the included studies; all but 2 small studies reported effects in the direction of a treatment benefit.42,49 Of the 3 largest trials, 2 using 60-mg/d aspirin dosages reported approximately 10% risk reductions with confidence intervals that crossed null,36,42 and the recent ASPRE trial using a 150-mg/d aspirin dosage reported data indicating a 28% reduced risk of preeclampsia compared with placebo (pooled RR, 0.72 [95% CI, 0.54-0.98]). ASPRE subgroup comparisons did not indicate significant differences in effects by the timing of aspirin initiation or dosage (eFigure 7 in the Supplement), and there was evidence of small-study effects for studies reporting preeclampsia incidence (Peters $P = .04$).

Nine RCTs (n = 2789) reported the effectiveness of aspirin for prevention of gestational hypertension. Meta-analysis of this outcome showed inconsistency of effects, imprecision, and higher statistical heterogeneity than for more commonly reported outcomes and did not include the 2 largest trials (pooled RR, 0.74 [95% CI, 0.46-1.18]; 9 RCTs [n = 2591]; $I^2 = 51%$); however, the direction of association was similar to the results for preeclampsia (eFigure 1 in the Supplement).

### Harms

**Key Question 3.** What are the harms of aspirin use to prevent preeclampsia during pregnancy?
Key Question 3a. Do the harms of aspirin use to prevent preeclampsia vary by subpopulations defined by personal characteristics or preeclampsia risk factors?

Data from 21 trials provided evidence on potential harms of daily low dosages of aspirin. Sixteen of the included trials reporting harms outcomes were conducted among pregnant individuals at increased preeclampsia risk and 5 trials among average-risk populations. The most consistently reported harms outcomes were placental abruption, postpartum hemorrhage, and fetal intracranial bleeding. Other reported perinatal outcomes included cephalohematoma, congenital malformations and anomalies, and respiratory distress syndrome. No greater risk of placental abruption, postpartum hemorrhage, or fetal intracranial bleeding was identified among participants treated with aspirin compared with those who were not (Table 2), nor were there differences within studies for less commonly reported and more rare perinatal harms. There were no significant differences in these risks by aspirin dosage or gestational age at initiation. Longer-term follow-up from 1 large multicenter trial was also reassuring, finding no difference in child developmental harms with aspirin use.

When comparing the trials conducted among average-risk vs increased-risk populations, there were no statistically significant differences in the risk of placental abruption ($P = .49$), postpartum hemorrhage ($P = .12$), or fetal intracranial bleeding ($P = .34$), and the relative risks in the increased-risk population studies were closer to 1 (Table 2; eFigures 2-4 in the Supplement). There were no statistically significant differences in the risk of abortion or postpartum hemorrhage by aspirin dosage or timing (eFigures 8 and 9 in Supplement).

Participants withdrew from treatment for a variety of reasons. It was common for participants to withdraw due to nonmedical reasons, including relocating, changing their minds about trial participation, or nonadherence with treatment. Adherence, when reported, was generally high, although reported in a variety of ways. A common reporting measure of adherence in the trials was the number of women who were found to be taking at least 80% of their treatment medication; this number ranged from 72% to 88%. Adherence based on the proportion of pills taken was selectively reported and ranged from 94% to 97%. Medical reasons for withdrawal included concerns regarding asthma attacks, increased bleeding time, increased activity of aspartate amino transferase in serum, urticaria, and epigastric pain. Women also withdrew from trials after miscarriage or the termination of pregnancy.

Discussion

Overall, the low to moderate statistical heterogeneity and consistency of effects across a range of outcomes supports the conclusion that low-dose aspirin is effective for preventing preeclampsia and related perinatal morbidity and mortality for individuals at increased risk for preeclampsia. The evidence is summarized by KQ in Table 3. This synthesis reported on 3 new studies not included in the previous USPSTF review, contributing to a more precise estimate of the association between aspirin and the prevention of perinatal mortality, indicating a range of effects spanning a 4% to 44% reduction in fetal and neonatal deaths. Otherwise, the new studies did not alter the previous findings of reduced risks of preeclampsia, preterm birth, and SGA/IUGR, or the previous null findings for reported bleeding harms. For individuals at increased risk of preeclampsia, daily low-dose aspirin therapy was associated with a lower risk of preeclampsia, preterm birth, SGA/IUGR, and perinatal mortality. Trial data derived from more than 25 000 pregnant individuals randomized to daily aspirin use did not reveal any serious harms. While very rare harms cannot be ruled out, large registry and cohort studies of potential harms not included in this review because aspirin exposure was for any indication, gestation, or dosage have not found clear evidence of teratogenic or other serious health effects.

The results of this review are consistent with findings from other systematic reviews, including a recent Cochrane Collaboration review and an older individual participant meta-analysis conducted by the Paris Collaborative Group (Paris IPD-MA) using data from trials published before 2006. The Cochrane review included 77 trials conducted with 40 249 participants and their infants and incorporated available Paris IPD-MA data. The Cochrane review results were mostly consistent with the findings of this review despite differences in terms of included study design characteristics, preeclampsia risk levels, risk-of-bias exclusions, and statistical methods.

Subgroup comparisons using data included in this review did not identify consistent differences across outcomes in the magnitude of effects related to the timing of treatment initiation, the dosage of aspirin used, or personal characteristics such as smoking history, parity, and body mass index (BMI), nor were the approaches to assessing preeclampsia risk or the incidence of preeclampsia observed in the study population related to differences in effectiveness. Timing of aspirin initiation across the trials was broad, ranging from initiation in the first (11-12 weeks) to third (36-38 weeks) trimester, and there was not clear evidence that aspirin effectiveness for preeclampsia prevention varied based on timing of initiation, consistent with the Cochrane and Paris IPD-MA reviews. Trials also varied broadly in the dosage of aspirin used (50 mg/d to 150 mg/d), but dosage was not significantly associated with effectiveness in aggregate comparisons, also consistent with findings of other reviews. At 2 important questions related to aspirin dosage could not be addressed based on the available evidence included in this review. First, it is not clear whether women with a higher BMI require a higher dose of aspirin based on the trial evidence. Second, only 2 of the included studies implemented dosages of 150 mg/d, and one of them (ASPRE, a new large trial) did not report postpartum hemorrhage outcomes, which limits the information available for assessing potential bleeding harms with a higher dosage.

The generalizability of the evidence across specific racial and ethnic populations is limited, given that a majority of participants in the included trials were White. This is troubling in light of the greater morbidity from preeclampsia experienced by Black women in the US and well-documented disparities in maternal health and birth outcomes arising from racism and systemic racial inequities. These inequities also contribute to underrepresentation in research. Only 1 US trial of women at increased risk for developing preeclampsia (MFMU) enrolled substantial numbers of Black and Hispanic study participants, and none of the included...
### Table 3. Summary of Evidence

<table>
<thead>
<tr>
<th>KQ1: Benefits of aspirin use on health outcomes</th>
<th>No. of studies (study designs [No. of observations])</th>
<th>Summary of findings</th>
<th>Consistency and precision</th>
<th>Other limitations</th>
<th>Strength of evidence</th>
<th>Applicability</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 RCTs (10 good quality, 8 fair quality [n = 15 908])</td>
<td>Aspirin was associated with a reduced risk of perinatal mortality (pooled RR, 0.79 [95% CI, 0.66-0.96]; I² = 0%), preterm birth (pooled RR, 0.80 [95% CI, 0.67-0.95]; I² = 49%), and SGA/IUGR (pooled RR, 0.82 [95% CI, 0.68-0.99]; I² = 41%) Limited subpopulation data, but within-trial comparison suggested greater effectiveness in nonsmokers</td>
<td>Reasonably consistent; reasonably precise</td>
<td>Small-study effects could not be ruled out for SGA/IUGR and preterm delivery Rare maternal health outcomes, such as eclampsia and maternal mortality, occurred too infrequently to estimate preventive effectiveness Subgroup effects limited by modest number of included studies and few within-trial subgroup analyses reported</td>
<td>Moderate for perinatal health benefits Studies in prenatal care settings in US or comparable settings; however, mostly White participants Different criteria for identifying at-risk populations Aspirin dose, 50-150 mg/d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| KQ2: Benefits of aspirin use on preeclampsia prevention | 16 RCTs (10 good quality, 6 fair quality [n = 15 767]) | Aspirin was associated with a statistically significant reduction in the risk of preeclampsia compared with placebo (pooled RR, 0.85 [95% CI, 0.75-0.95]; I² = 0%) No evidence of statistical difference in the magnitude of preeclampsia risk reduction related to the timing of treatment initiation, the dosage of aspirin used, or personal characteristics such as smoking history, parity, and BMI | Reasonably consistent evidence for aspirin benefit Reasonably precise 15% reduced risk of preeclampsia associated with daily aspirin use | Small-study effects could not be ruled out and might lead to some overestimation of pooled risk estimate Confounding of study size with other study and participant characteristics could influence subgroup comparisons Subgroup effects limited by modest number of included studies and few within-trial subgroup analyses reported | Moderate Studies in prenatal care settings in US or comparable settings; however, mostly White participants Different criteria for identifying at-risk populations Aspirin dose, 50-150 mg/d |

| KQ3: Harms of aspirin use | 21 RCTs (16 increased-risk and 5 average-risk populations; 14 good quality, 7 fair quality [n = 26 757]) | Studies conducted among average-risk and increased-risk populations did not find any clear evidence of harms associated with daily aspirin use (<150 mg) taken during the second or third trimester of pregnancy Studies conducted among average-risk and increased-risk populations did not find any clear evidence of harms associated with daily aspirin use (<150 mg) taken during the second or third trimester of pregnancy Studies conducted among average-risk and increased-risk populations did not find any clear evidence of harms associated with daily aspirin use (<150 mg) taken during the second or third trimester of pregnancy | Reasonably consistent evidence of null effects for bleeding harms of daily aspirin, especially among pregnant individuals at increased preeclampsia risk Reasonably precise evidence for null effects, but less precise for especially rare harms | No differences were found within a limited set of studies reporting other rare perinatal harms | Moderate for no difference in bleeding harms between groups, low for very rare or inconsistently reported harms Studies in prenatal care settings in US or comparable settings; however, mostly White participants Different criteria for identifying at-risk populations Aspirin dose, 50-150 mg/d Harms from trials in average-risk and increased-risk populations |

Abbreviations: BMI, body mass index; KQ, key question; RCT, randomized clinical trials; RR, risk ratio; SGA/IUGR, small-for-gestational age/intrauterine growth restriction.

* Direction and magnitude of effects within and across important perinatal health outcomes, with low to moderate statistical heterogeneity.

b Confidence intervals did not cross null, including for rare outcomes such as perinatal mortality, for which even small effects are clinically important.

c Postpartum hemorrhage greater than 1000 mL, longer-term developmental harms, congenital malformations.
A common set of risk factors were cited in the previous USPSTF recommendation for aspirin prophylaxis. The risk factors known to be independently associated with the highest likelihoods of developing preeclampsia include history of preeclampsia, multifetal gestation, chronic hypertension, type 1 or type 2 diabetes, renal disease, and autoimmune diseases (eg, systemic lupus erythematosus, antiphospholipid antibody syndrome). Risk factors more modestly associated with increased preeclampsia risk include maternal age older than 35 years, obesity (BMI >30), and nulliparity and the presence of multiple risk factors heightens risk. While these risk factors and others have been identified, evidence is limited with respect to best practices for identifying women at risk of preeclampsia that would benefit from aspirin prophylaxis.

Of the 18 included trials among increased risk populations, 14 used multiple risk factors to identify study participants at risk for preeclampsia and the baseline characteristics of the study populations varied significantly, resulting in a broad range of preeclampsia incidence in the control groups (4%-30%). Studies that used clinical history risk factors in conjunction with clinical tests or imaging consistently recruited populations with high incidence of preeclampsia (18% and 23%), but several studies using clinical risk factors alone achieved similarly high levels of preeclampsia incidence ranging from 8% to 20%. Subgroup analyses did not show any differences in aspirin effectiveness when comparing studies that used clinical history risk factors alone vs those that incorporated clinical tests or imaging. Only 1 trial used a previously developed risk prediction model. Reviews comparing the test performance attributes of available risk assessment models have found limitations in their readiness for clinical application, including significant differences in accuracy depending on the validation cohort used. Further data would be needed to determine whether the use of a risk prediction model that requires multiple historical and physical measures to generate a risk estimate is superior to other clinical risk assessment approaches and whether widespread implementation into routine practice is feasible.

Implementation trials comparing different approaches to risk assessment and aspirin allocation in clinical settings would be particularly valuable.

Limitations
The evidence review has several limitations. First, the search was limited to English-language literature, and only trials conducted in settings with very high Human Development Index scores were included. Studies rated as poor quality were also excluded from analysis. However, other reviews without these exclusions have not found substantively different results.

Second, there was evidence of small-study effects for some outcomes. Such effects can be observed when smaller studies with null or negative findings are absent from the literature (ie, publication bias) or due to reported and unreported differences between smaller and larger trials. Given the presence of small-study effects, it is possible that pooled effect sizes were overestimated for preeclampsia and preterm birth prevention; alternatively, the smaller effect sizes observed in the largest trials could be attributed to their common design features (eg, the 2 largest trials used 60-mg/d aspirin dosages). Third, confounding of study size and study design characteristics, as well as the number of studies available for analysis, limited the interpretation of aggregate subgroup comparisons since it was not possible to conduct multivariable meta-regression.

Fourth, across the trials, approaches to identify individuals at increased preeclampsia risk varied, as did inclusion and exclusion criteria, generating a broad range of absolute risks for the study outcomes. No studies reported head-to-head comparisons of different protocols or risk assessment strategies, and only 1 trial, which was underpowered for drawing conclusions, was designed to compare the effectiveness for different risk populations. Interaction tests for subgroup differences within trials were uncommon and, when available, did not generally identify differences in effectiveness by the factors examined. More research will be needed to determine the optimal aspirin protocol and identify key populations most likely to obtain preventive benefits.

Conclusions
Daily low-dose aspirin during pregnancy was associated with lower risks of serious perinatal outcomes for individuals at increased risk for preeclampsia, without evident harms.
ARTICLE INFORMATION

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Author Contributions: Dr Henderson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Henderson, Vesco, Senger. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Henderson, Vesco, Senger. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Redmond. Administrative, technical, or material support: Senger, Thomas, Redmond. Supervision: Henderson.

Conflict of Interest Disclosures: Dr Vesco reported receiving grants from Pfizer to develop and test a novel menopause curriculum for medical residents. No other disclosures were reported.

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Role of the Funder/Sponsor: USPSTF investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure that the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not reflect the official position of AHRQ or the US Department of Health and Human Services.

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Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF recommendation statement. It did not undergo additional peer review after submission to JAMA.

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USPSTF Report: Aspirin Use to Prevent Preeclampsia and Related Morbidity and Mortality


91. Al-Rubaij Z, Askie LM, Ray JG, Hudson HM, Lord SJ. The performance of risk prediction models for pre-eclampsia using routinely collected maternal characteristics and comparison with models that include specialised tests and with clinical guideline decision rules: a systematic review. BMJ. 2016;352:i1441-i1452. doi:10.1136/bmj.i1471-0528.14029


