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Title: Routine first trimester combined screening for preterm preeclampsia in Australia: a multicenter clinical implementation cohort study

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Synopsis

First trimester screening for preterm preeclampsia accurately identifies women at high risk of complications and low-risk women suitable for less intensive antenatal care.

Keywords: Preeclampsia, Prediction, First trimester combined screening, Biomarkers, Stillbirth, Aspirin, Pregnancy outcomes

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Abstract

Objective: To assess pregnancy outcomes following first trimester combined screening for preterm preeclampsia in Australia.

Methods: We compared pregnancy outcomes of women with singleton pregnancies who underwent first trimester combined preeclampsia screening with the Fetal Medicine Foundation algorithm between 2014 and 2017 in Melbourne and Sydney, Australia, with those from women who received standard care. The primary outcomes were preterm preeclampsia and screening performance. Effect estimates were presented as risk ratios with 95% confidence intervals.

Results: A total of 29,618 women underwent combined screening and 301,566 women received standard care. Women who had combined screening were less likely to have preeclampsia, preterm birth, small neonates, and low Apgar scores than the general population. Women with high-risk results (≥ 1 in 100) were more likely to develop preterm preeclampsia (2.1% *versus* 0.7%, risk ratio [RR] 3.04, 95% CI 2.46–3.77), while low-risk women (risk < 1 in 100) had lower rates of preterm preeclampsia (0.2% *versus* 0.7%, RR 0.26, 95% CI 0.19–0.35) and other pregnancy complications.

Conclusions: First trimester screening for preeclampsia in clinical practice identified a population at high risk of adverse pregnancy outcomes and low-risk women who may be suitable for less intensive antenatal care.

Introduction

Preeclampsia is a major cause of maternal and perinatal morbidity and mortality, and constitutes one of the main reasons for medically indicated preterm birth.[1] The identification of high-risk women according to maternal risk factors alone is suboptimal, failing to identify more than half of those who will later develop the disease and deliver at preterm gestations.[2] This includes risk scoring methods, such as those recommended by the American College of Obstetrics and Gynecology (ACOG) and the National Institute for Health and Care Excellence (NICE), which identify only 40% of women who will later develop preterm preeclampsia.[3] In contrast, preterm preeclampsia prediction at 11–14 weeks could be doubled with the use of algorithms that combine maternal characteristics, medical history, and biomarkers (mean arterial pressure [MAP], mean uterine artery pulsatility index [UtPI] on Doppler ultrasound, and

serum pregnancy-associated plasma protein A [PAPP-A] and placental growth factor [PLGF]), detecting approximately 80% of preterm preeclampsia.[2]

In high-risk women, aspirin prophylaxis at a daily dose of 150 mg from the first trimester reduces the rate of preterm preeclampsia by 62% (95% CI 26 – 80%).[4] In the Aspirin for Evidence-Based Preeclampsia Prevention (ASPRE) trial, combined screening had a similar performance in a larger European obstetric population to that of previous model development.[5] However, despite the effectiveness of contingent aspirin based on the Fetal Medicine Foundation (FMF) competing risks algorithm, large-scale studies evaluating the outcomes and performance of screening in clinical practice are lacking. Wider implementation has been hindered by concerns regarding external validity and cost.

This multicenter study aims to assess pregnancy outcomes and performance of first trimester combined screening for preeclampsia using the FMF algorithm in clinical practice in Australia.

Materials and Methods

Data source and study population

This was a retrospective cohort study of prospectively collected screening data and pregnancy outcomes obtained through data linkage. We studied all consecutive women with singleton pregnancies who underwent combined screening for preeclampsia at 11–14 weeks' gestation between 2014 and 2017 in two large private Fetal Medicine practices in metropolitan Melbourne (six sites) and Sydney (ten sites), Australia, plus one public hospital Maternal-Fetal Medicine Unit in Sydney. In Australia, first trimester ultrasound is not routinely offered in the public system but has high uptake in the private sector with out-of-pocket costs. To our knowledge, these were the only practices providing first trimester combined preeclampsia screening in the two states during the study period.

Combined screening data from Melbourne sites were linked to pregnancy outcomes available in the Victorian Perinatal Data Collection (VPDC), while those from Sydney sites were linked to pregnancy outcomes available in the New South Wales (NSW) Perinatal Data Collection (PDC). Probabilistic linkage was performed by the Centre of

Victorian Data Linkage and the NSW Centre for Health Record Linkage, respectively, based on concordance with predetermined identifiers (e.g., mother and neonate birth date, first name and last name, sex of neonate, address). In addition, pregnancy outcomes of all other women with consecutive singleton pregnancies who did not undergo combined screening in Victoria between 2014 and 2017 were collected. During the study period, standard care in the state of Victoria included identification of risk factors from maternal history according to local guidelines.[6]

The Victorian and NSW PDC are population surveillance systems that capture over 100 items regarding maternal characteristics, obstetric conditions, procedures, pregnancy, and birth outcomes of all pregnancies after 20 weeks' gestation or fetal weight greater than 400 grams if gestational age is unknown, using the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM). Previous validation studies suggest that these data are accurate and reliable and can be used with high confidence for population health reporting and research.[7]

Ethics approval was obtained from the Monash University Human Research Ethics Committee (approval number #14414) and the NSW Population and Health Services Research Ethics Committee (approval number #2017/HRE1003). All women gave verbal consent for screening, and written informed consent was not necessary as preeclampsia risk calculation was offered as part of routine care in the participating centers.

Combined screening procedure

All women with viable singleton pregnancies presenting to one of the participating centers for an ultrasound at 11–14 weeks were offered combined screening for preterm preeclampsia. Gestational age at the time of ultrasound was determined by measuring fetal crown-rump length.[8] Calculation of individual risks for preeclampsia with delivery before 37 weeks' gestation was performed using the FMF competing risks algorithm.[9] Variables utilized in the risk calculation were maternal factors (such as maternal age, weight, height, smoking status, history of chronic hypertension, pre-existing diabetes mellitus, systemic lupus erythematosus, anti-phospholipid syndrome,

and previous pregnancy with preeclampsia), MAP, UtPI, PAPP-A and PLGF. MAP was measured with validated automated devices following a standardized protocol.[10] Color Doppler ultrasound was used to measure the left and right UtPI, and the mean value was recorded. Sonographers, who rotate between sites in each practice, were trained prior to commencement of the study on how to measure the UtPI using a standardized technique and were certified by the FMF.[11] Quality assessment demonstrated measurement of UtPI consistently within the expected range.[12] Serum PAPP-A and PLGF concentrations were measured by automated devices (PAPP-A and PLGF 1-2-3™ kits, DELFIA® Xpress random-access platform; PerkinElmer Inc. Wallac Oy, 20101 Turku, Finland, or B.R.A.H.M.S Kryptor: Thermo-Fisher Scientific Inc. North Ryde, NSW, Australia).

Measured values of MAP, UtPI, PAPP-A and PLGF were expressed as multiples of the median (MoM), using previously published equations.[13-16] Median biomarker MoM values were monitored at three-monthly intervals for quality assurance and to allow feedback, retraining or implementation of correction factors when necessary.[12] Women with estimated risks of preterm preeclampsia of 1 in 100 or higher were deemed high risk, while those with risks below 1 in 100 were considered low risk. Risks were disclosed in ultrasound reports, with a recommendation to consider aspirin prophylaxis in high-risk women.

Outcome measures

The primary outcomes of the study were delivery with preeclampsia before 37 weeks' gestation and the performance of screening. Other reported outcomes include preeclampsia at any gestational age, gestational hypertension, preterm birth, delivery of a low birthweight (<2,500 grams) or small-for-gestational-age neonate (birthweight <10^{th} and <3^{rd} percentiles according to local charts),[17] Apgar score <4 at five minutes, and stillbirth or neonatal death at or after 24 weeks' gestation. The relevant ICD-10-AM codes were used to identify maternal medical and obstetric conditions. Information on aspirin use was not available.

Statistical analyses

Categorical variables were reported as absolute numbers and percentages and compared between groups using the Chi-squared test. Continuous variables were reported as the mean and standard deviation or median and interquartile range, depending on the distribution, and compared between the groups using independent-samples t-tests. As a measure of socio-economic status, we used the Index of Relative Socioeconomic Disadvantage (IRSD), which summarizes information about the economic and social resources of people and households within an area. The Index has a base of 1,000 for Australia, with scores below 1,000 indicating disadvantage. Pregnancy outcomes of women in the screened population were compared to those of the general obstetric population. Effect estimates were reported as risk ratios (RR) with 95% confidence intervals (CI). When comparing the overall screened population with the general population, we calculated adjusted risk ratios using modified Poisson regression models with robust variance estimation to account for differences in baseline characteristics. Adjustments were not made when comparing high- and low-risk groups because maternal characteristics are already considered in the risk calculation.

To assess screening performance, detection rate and false-positive rate were calculated. Model calibration was investigated by inspecting calibration plots of observed rates of preterm PE in relation to predicted probabilities by risk decile, separately in the low- and high-risk groups to investigate a possible effect of aspirin prophylaxis. Since data on aspirin treatment were not available, we estimated the treatment-adjusted screening performance by calculating the number of cases that would have been avoided by treatment in the high-risk group based on different hypothetical proportions of high-risk women treated with aspirin. The estimated reduction in preterm preeclampsia was calculated assuming an expected reduction based on the adjusted odds ratio (0.38, 95% CI 0.20 – 0.74) from the ASPRE trial following treatment with aspirin 150 mg daily from 11–14 to 36 weeks' gestation or birth,[4] which is consistent with the risk reduction observed in the latest meta-analysis in women treated with aspirin at a daily dose ≥100 mg from before 16 weeks' gestation.[18]

Statistical analyses were conducted in the statistical package Stata (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC), and two-sided p-values below 0.05 were considered statistically significant. Reporting of the results followed the STROBE guidelines.

Results

Overall, 29,618 women underwent first trimester combined preeclampsia screening (7,718 in Melbourne and 21,900 in Sydney), and 301,566 women received standard care with no combined screening in Victoria. Table 1 summarizes the baseline characteristics of the study population. Screened women had significantly higher age (mean 33.3 [4.3] *versus* 30.9 [5.2] years, p <0.001), lower BMI (median 23.3 [21.1–26.3] *versus* 24.5 [21.8–28.6] kg/m^2, p <0.001) and higher socioeconomic status (median IRSD 1,063 [1019–1095] *versus* 1,023 [957–1067], p <0.001). Screened women were more commonly nulliparous, less likely to smoke during pregnancy and to have chronic hypertension or pre-existing diabetes, and more likely to have systemic lupus erythematosus or antiphospholipid syndrome than women who received standard care (all p <0.001).

Biomarker distribution and pregnancy outcomes

Of the 29,618 screened women, 4,068 (13.7%) were deemed high-risk for preterm preeclampsia and 25,550 (86.3%) were low risk. Compared to low-risk women, high-risk women had significantly higher MAP (median 1.06 [1.00–1.13] *versus* 0.95 [0.89–1.01] MoM, p <0.001) and UtPI (median 1.27 [1.04–1.51] *versus* 1.01 [0.84–1.22] MoM, p <0.001), and significantly lower PAPP-A (median 0.85 [0.56–1.26] *versus* 1.17 [0.82–1.66] MoM, p <0.001) and PLGF (median 0.69 [0.49–0.95] *versus* 1.05 [0.83–1.32] MoM, p <0.001).

Table 2 displays the rates of adverse pregnancy outcomes of women who had and who did not have combined screening. After adjustment for potential confounders, screened women were less likely to have preeclampsia (adjusted risk ratio [aRR] 0.70, 95% CI 0.58–0.84, p <0.001), preterm birth (aRR 0.92, 95% CI 0.88–0.97, p = 0.001), neonates with low birthweight (aRR 0.89, 95% CI 0.85–0.94, p < 0.001) or <3rd percentile (aRR 0.91, 95% CI 0.83–0.99, p = 0.03), and low Apgar scores at five minutes (aRR 0.73, 95% CI 0.63–0.85, p < 0.001), and were more likely to have gestational hypertension (aRR 1.08, 95% CI 1.00–1.17, p = 0.04), compared to the general population.

High-risk women were more likely to develop preterm preeclampsia (2.1% *versus* 0.7%, RR 3.04, 95% CI 2.46–3.77, p <0.001) and other adverse pregnancy outcomes such as preterm delivery (11.5% *versus* 7.1%, RR 1.62, 95% CI 1.49–1.77, p <0.001) and birthweight <3rd percentile (4.5% *versus* 2.1%, RR 2.10, 95% CI 1.82–2.42, p <0.001) than the general population (Table 3).

Conversely, low-risk women had significantly lower rates of all measured outcomes, including preterm preeclampsia (0.2% *versus* 0.7%, RR 0.26, 95% CI 0.19–0.35, p <0.001), preterm birth (5.0% *versus* 7.1%, RR 0.70, 95% CI 0.67–0.74, p <0.001), birthweight <3rd percentile (1.5% *versus* 2.1%, RR 0.70, 95% CI 0.62–0.77, p <0.001), low Apgar scores at five minutes (0.5% *versus* 1.1%, RR 0.47, 95% CI 0.40–0.56, p <0.001), stillbirth (2.3 per 1,000 *versus* 3.5 per 1,000, RR 0.65, 95% CI 0.50–0.85, p = 0.001) and neonatal death (0.6 per 1,000 *versus* 1.1 per 1,000, RR 0.56, 95% CI 0.34–0.92, p = 0.02).

Predictive performance

Combined screening detected 65.2% (95% CI 56.4–73.2%) of the preterm preeclampsia cases, at a false-positive rate of 13.4% (95% CI 13.1–13.8%). Good calibration was observed in the low-risk group (slope 0.93, Figure 1A), whilst there was overestimation of risks suggesting treatment effect in the high-risk group (slope 0.63, Figure 1B).

The treatment-adjusted detection rate would be 66.7% (95% CI 58.1–74.5%) if 10% of the high-risk group received treatment, 73.1% (95% CI 65.8–79.6%) if 50% of the high-risk group received treatment, and 80.9% (95% CI 75.4–85.7%) if 90% of the high-risk group received treatment with aspirin, with a progressive decrease in false-positive rate from 13.4% (95% CI 13.0–13.8) to 13.1% (95% CI 12.7–13.5). Treatment-adjusted measures of disease frequency and screening performance are shown in Table 4.

Discussion

Main findings

In this multicenter implementation study in Australia, women who had combined screening had significantly lower rates of preeclampsia and other pregnancy complications than the general population. These differences remained after adjustments

for possible confounders. High-risk women had higher rates of preterm preeclampsia and other adverse pregnancy outcomes compared to the general obstetric population. Conversely, low-risk women had lower rates of all adverse pregnancy outcomes studied.

Strengths and limitations

To our knowledge, this was the largest study conducted to date on the clinical implementation of first trimester preeclampsia screening. The use of population-wide data allowed for comparison of outcomes between the groups with a high precision of the estimates.

The main limitation of the study is that pregnancy outcomes obtained through data linkage may be subject to some degree of misclassification. However, this methodology has previously demonstrated reliable results and correctly identified about 95% of the preeclampsia cases.[7, 19] Data on ethnicity and mode of conception, though used in the algorithm, were not available for analysis and could not be adjusted for. Adjusting for surrogates such as age and socioeconomic status may have, at least partly, accounted for confounding by these variables. Previous studies have highlighted that screening performance can be largely underestimated if prediction is followed by effective treatment.[2, 20] By preventing many cases of preterm preeclampsia,[4, 18] aspirin effectively converts true-positive into false-positive results of screening.[20] As data on aspirin intake were unavailable, we adjusted the performance estimates for the treatment effect adopting varying hypothetical proportions of high-risk women treated with aspirin.

Clinical implications

Risk scoring according to maternal characteristics and medical history alone has been the primary screening approach for preeclampsia and is recommended by leading institutions. However, previous studies demonstrated that such method detects only 40% of preterm preeclampsia cases,[2, 3] and that low physician compliance leads to aspirin treatment of less than 30% of high-risk women.[2, 21] In contrast, combined screening has been externally validated[22, 23] and is superior to risk factor-based

screening, increasing the detection of preterm preeclampsia cases to about 80%.[2, 24] When followed by treatment of high-risk women with 150 mg of aspirin daily initiated before 16 weeks, the combined approach is associated with higher physician compliance,[21] reduces the incidence of preterm preeclampsia by 62%,[4] and is highly cost-effective.[25] These benefits of combined screening over routine care were demonstrated in our study.

The observed detection of preterm preeclampsia was 65.2%, but this increased significantly when the effect of aspirin was accounted for. Our findings highlight the importance of future studies evaluating the accuracy of models to adjust for treatment effects. Despite a slightly higher screen-positive rate than previously reported,[24] the screening performance was comparable to other non-intervention studies.[2, 24]

Our data is in keeping with a similar implementation study in the United Kingdom, where the transition from screening based on the NICE guidelines to first trimester combined screening demonstrated a decrease in the rates of preterm preeclampsia and higher rates of compliance with aspirin prophylaxis by health professionals.[21] Our data suggests that combined screening can effectively identify high-risk women at increased risk of adverse pregnancy outcomes who benefit from aspirin prophylaxis and close surveillance, and low-risk group with very low rates of obstetric complications that may be suitable for less intensive monitoring of maternal blood pressure and fetal growth. Therefore, combined screening allows individualized antenatal care and offers valuable information to mothers and their treating clinicians.

In conclusion, implementation of first trimester combined preeclampsia screening with individualized risk assessment is feasible in clinical practice. This approach identifies both a population at high risk of adverse outcomes and a low-risk population that may be suitable for less intensive antenatal care.

Author contributions

DLR, RJS, JH, FSC and AM conceptualised the study. DLR, RJS, DW, FSC and AM were responsible for the data collection, and the study. DLR and RJS analysed the data and drafted the manuscript. All authors approved the final of manuscript.

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Conflicts of interests

SM, FSC and AM were employees of the Monash IVF group during the study period. EW is an employee of Victoria's Department of Health and Human Services. The other authors report no conflicts of interest.

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Figure Legend

Figure 1. Calibration plots comparing observed and predicted risks of preterm preeclampsia in the low-risk (A) and high-risk (B) groups with superimposed Lowess curves.

Table 1. Baseline characteristics of the study population.

	Screened (n=29,618)	**Standard care (n=301,566)**	**p-value**
Maternal age, in years, mean (SD)	33.3 (4.3)	30.9 (5.2)	<0.001
Maternal BMI, in kg/m^2, median (IQR)	23.3 (21.1–26.3)	24.5 (21.8–28.6)	<0.001
Parity			
Nulliparous	14,610 (49.4)	132,761 (44.0)	<0.001
Parous	14,978 (50.6)	168,800 (56.0)	
IRSD score, median (IQR)	1,063 (1019–1095)	1,023 (957–1067)	<0.001
Chronic hypertension	290 (1.0)	3,697 (1.2)	<0.001
Systemic lupus erythematosus	73 (0.2)	297 (0.1)	<0.001
Antiphospholipid syndrome	34 (0.11)	143 (0.05)	<0.001
Pre-existing diabetes	238 (0.8)	3,094 (1.0)	<0.001
Smoking during pregnancy	550 (1.9)	28,478 (9.9)	<0.001
Previous preeclampsia	587 (2.0)	N/A	-
Family history of preeclampsia (mother)	824 (2.8)	N/A	-
Previous fetal growth restriction	235 (0.8)	N/A	-

Data are given as absolute numbers and percentages unless otherwise stated.

Percentages may not add to 100% due to rounding to one decimal place.

BMI: Body mass index; SD: Standard deviation; IQR: Interquartile range; IRSD: Index of Relative Socioeconomic Disadvantage; N/A: Not available.

Table 2. Maternal and neonatal outcomes in screened population and in general (standard care) population.

Outcome	Screened (n=29,618)	Standard care (n=301,566)	Crude risk ratio (95% CI)	Adjusted risk ratio (95% CI)
Preterm preeclampsia	132 (0.4)	2,096 (0.7)	0.64 (0.54–0.76) p < 0.001	0.70 (0.58–0.84) p < 0.001
All preeclampsia	455 (1.5)	7,340 (2.4)	0.63 (0.57–0.89) p < 0.001	0.69 (0.63–0.76) p < 0.001
Gestational hypertension	753 (2.5)	7,066 (2.3)	1.09 (1.01–1.17) p = 0.03	1.08 (1.00–1.17) p = 0.04
Birth <32 weeks	278 (0.9)	4,435 (1.5)	0.64 (0.57–0.72) p < 0.001	0.83 (0.74–0.95) p = 0.004
Spontaneous preterm birth <32 weeks	127 (0.4)	1,445 (0.5)	0.89 (0.75–1.07) p = 0.23	1.10 (0.91–1.33) p = 0.30
Birth <37 weeks	1,736 (5.9)	21,283 (7.1)	0.83 (0.79–0.87) p < 0.001	0.92 (0.88–0.97) p = 0.001
Spontaneous preterm birth <37 weeks	777 (2.6)	8,855 (2.9)	0.89 (0.83–0.96) p = 0.002	1.00 (0.93–1.08) p = 0.93
Birthweight <2,500 grams	1,354 (4.6)	17,295 (5.7)	0.80 (0.76–0.84) p < 0.001	0.89 (0.85–0.94) p < 0.001
Birthweight <3rd percentile	562 (1.9)	6,466 (2.1)	0.89 (0.81–0.96) p = 0.005	0.91 (0.83–0.99) p = 0.03
Birthweight <10th percentile	2,572 (8.7)	26,137 (8.7)	1.00 (0.96–1.04)	1.00 (0.96–1.04)

			p = 0.91	p = 0.90
Apgar <4 at five minutes	190 (0.6)	3,424 (1.1)	0.56 (0.49–0.65)	0.73 (0.63–0.85)
			p < 0.001	p < 0.001
			0.74 (0.58–0.93)	0.90 (0.71–1.14)
Stillbirth	76 (2.6 per 1,000)	1,049 (3.5 per 1,000)	p = 0.01	p = 0.38
			0.72 (0.48–1.10)	0.94 (0.61–1.45)
Neonatal death	24 (0.8 per 1,000)	336 (1.1 per 1,000)	p = 0.001	p = 0.78

Data are given as absolute numbers and percentages.

CI: Confidence interval.

Risk ratios adjusted with a modified Poisson models for age, body mass index, parity, socioeconomic status as given by IRSD (Index of Relative Socioeconomic Disadvantage), smoking, chronic hypertension, systemic lupus erythematosus, antiphospholipid syndrome, and pre-existing diabetes.

Table 3. Maternal and neonatal outcomes in screened population by risk groups and in general (standard care) population.

Outcome	High risk ≥ 1 in 100 (n=4,068)	Risk ratio (95% CI)	Low risk < 1 in 100 (n=25,550)	Risk ratio (95% CI)	Standard care (n=301,566)
Preterm preeclampsia	86 (2.1)	3.04 (2.46–3.77) p < 0.001	46 (0.2)	0.26 (0.19–0.35) p < 0.001	2,096 (0.7)
All preeclampsia	231 (5.7)	2.33 (2.05–2.65) p < 0.001	224 (0.9)	0.36 (0.32–0.41) p < 0.001	7,340 (2.4)
Gestational hypertension	307 (7.5)	3.22 (2.89–3.60) p < 0.001	446 (1.7)	0.74 (0.68–0.82) p < 0.001	7,066 (2.3)
Birth <32 weeks	89 (2.2)	1.49 (1.21–1.83) p < 0.001	189 (0.7)	0.50 (0.44–0.58) p < 0.001	4,435 (1.5)

Spontaneous preterm birth <32 weeks	31 (0.8)	1.59 (1.12-2.27) p = 0.01	96 (0.4)	0.78 (0.64-0.96) p = 0.02	1,445 (0.5)
Birth <37 weeks	466 (11.5)	1.62 (1.49–1.77) p < 0.001	1,270 (5.0)	0.70 (0.67–0.74) p < 0.001	21,283 (7.1)
Spontaneous preterm birth <37 weeks	142 (3.5)	1.19 (1.01-1.40) p = 0.04	635 (2.5)	0.85 (0.78-0.92) p < 0.001	8,855 (2.9)
Birthweight <2,500 grams	445 (10.9)	1.91 (1.75–2.08) p < 0.001	909 (3.6)	0.62 (0.58–0.66) p < 0.001	17,295 (5.7)
Birthweight <3rd percentile	183 (4.5)	2.10 (1.82–2.42) p < 0.001	379 (1.5)	0.70 (0.62–0.77) p < 0.001	6,466 (2.1)
Birthweight <10th percentile	633 (15.6)	1.80 (1.67–1.93) p < 0.001	1,939 (7.6)	0.88 (0.84–0.92) p < 0.001	26,137 (8.7)
Apgar <4 at five minutes	53 (1.3)	1.15 (0.88–1.50) p = 0.32	137 (0.5)	0.47 (0.40–0.56) p < 0.001	3,424 (1.1)
Stillbirth	18 (4.4 per 1,000)	1.27 (0.80–2.02) p = 0.31	58 (2.3 per 1,000)	0.65 (0.50–0.85) p = 0.001	1,049 (3.5 per 1,000)
Neonatal death	8 (2.0 per 1,000)	1.76 (0.88–3.55) p = 0.11	16 (0.6 per 1,000)	0.56 (0.34–0.92) p = 0.02	336 (1.1 per 1,000)

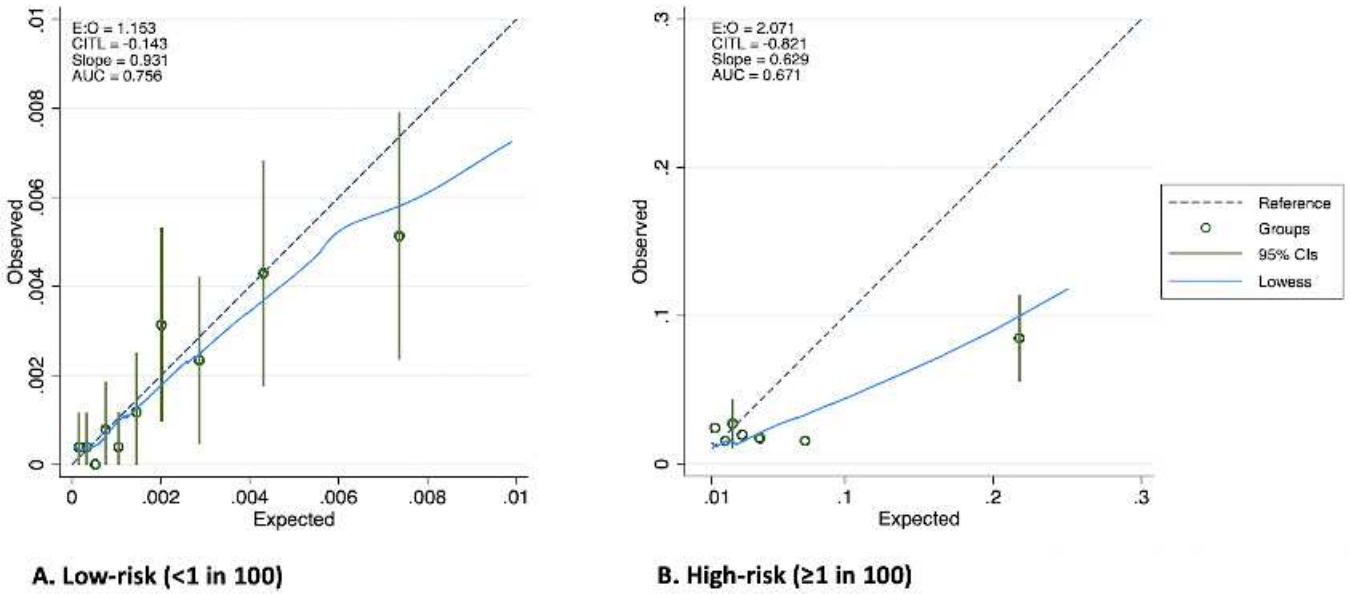
	Proportion of high-risk treated with aspirin								
	10%	**20%**	**30%**	**40%**	**50%**	**60%**	**70%**	**80%**	**90%**
Disease Frequency									
Expected reduction in PE, %	6.2%	12.4%	18.6%	24.8%	31.0%	37.2%	43.4%	49.6%	55.8%
Odds ratio	0.94	0.88	0.81	0.75	0.69	0.63	0.57	0.50	0.44
Expected detected cases*, n	92	98	106	114	125	137	152	171	195
Cumulative incidence, %	0.5	0.5	0.5	0.5	0.6	0.6	0.7	0.7	0.8
(95% CI)	(0.4–0.6)	(0.4–0.6)	(0.4–0.6)	(0.5–0.6)	(0.5–0.7)	(0.5–0.7)	(0.6–0.8)	(0.6–0.8)	(0.7–0.9)
Screening performance									
Sensitivity / Detection rate, %	**66.7**	**68.1**	**69.7**	**71.2**	**73.1**	**74.9**	**76.8**	**78.8**	**80.9**
(95% CI)	**(58.1–74.5)**	**(59.8–75.6)**	**(61.8–76.9)**	**(63.6–78.1)**	**(65.8–79.6)**	**(67.9–81.0)**	**(70.3–82.5)**	**(72.8–84.0)**	**(75.4–85.7)**
Specificity, %	86.5	86.5	86.6	86.6	86.6	86.6	86.7	86.7	86.8
(95% CI)	(86.1–86.9)	(86.1–86.9)	(86.2–86.9)	(86.2–87.0)	(86.2–86.9)	(86.3–87.0)	(86.3–87.1)	(86.4–87.1)	(86.4–87.2)
False-positive rate, %	13.4	13.4	13.4	13.3	13.3	13.3	13.2	13.2	13.1
(95% CI)	(13.0–13.8)	(13.0–13.8)	(13.0–13.8)	(13.0–13.7)	(12.9–13.7)	(12.9–13.7)	(12.8–13.6)	(12.8–13.5)	(12.7–13.5)
Positive predictive value, %	2.3	2.4	2.6	2.8	3.1	3.4	3.7	4.2	4.8
(95% CI)	(1.8–2.8)	(2.0–2.9)	(2.1–3.1)	(2.3–3.4)	(2.6–3.7)	(2.8–4.0)	(3.2–4.4)	(3.6–4.9)	(4.2–5.5)
Negative predictive value, %	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8	99.8
(95% CI)	(99.8–99.9)	(99.8–99.9)	(99.8–99.9)	(99.8–99.9)	(99.8–99.9)	(99.8–99.9)	(99.8–99.9)	(99.8–99.9)	(99.8–99.9)
Area under the ROC curve	0.77	0.77	0.78	0.79	0.80	0.81	0.82	0.83	0.84

(95% CI)	(0.73–0.81)	(0.73–0.81)	(0.74–0.82)	(0.75–0.82)	(0.77–0.83)	(0.78–0.84)	(0.79–0.85)	(0.80–0.86)	(0.81–0.86)

Table 4.

Observed number of cases, cumulative incidence of preterm preeclampsia, and measures of screening accuracy in the screened population with adjustment for varying assumed proportions of the high-risk population treated with aspirin.

PE: Preeclampsia; CI: Confidence interval; ROC: Receiver-operating characteristics. *Including those prevented by aspirin in the high-risk group.



A. Low-risk (<1 in 100)

B. High-risk (≥1 in 100)

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