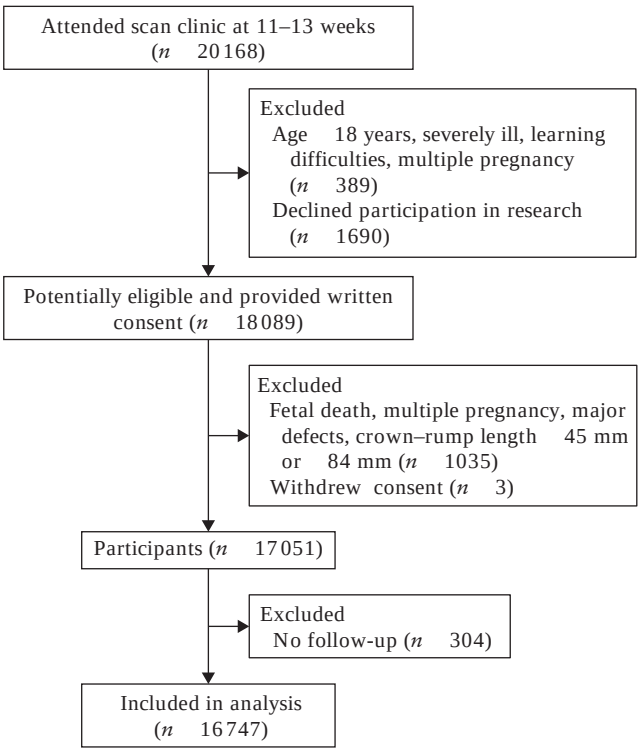
trial (ASPRE) reported that, in women with singleton pregnancy and at high-risk for PE, aspirin (150 mg/day) *vs* placebo from 11 to 14 until 36 weeks' gestation was associated with a 62% (95% CI, 26–80%) reduction in the incidence of preterm PE, but had no significant effect on the incidence of term PE[6]. A systematic review and meta-analysis of 16 trials involving a combined total of 18 907 participants, including the ASPRE trial, reported that aspirin reduces the risk of preterm PE by 67% (95% CI, 43–81%), provided that the daily dose was ≥ 100 mg and onset of therapy was < 16 weeks; aspirin had no significant effect on incidence of term PE[7].

In the UK, identification of the high-risk group that could benefit from aspirin is based on maternal characteristics and medical history as defined by the National Institute for Health and Care Excellence (NICE) guideline[8]. According to the guideline, women should be considered to be at high risk of developing PE if they have any one major factor (history of hypertensive disease in previous pregnancy, chronic kidney disease, autoimmune disease, diabetes mellitus or chronic hypertension) or any two moderate factors (first pregnancy at age ≥ 40 years, interpregnancy interval > 10 years, body mass index at first visit ≥ 35 kg/m^2 or family history of PE)[8]. The performance of such an approach, which essentially treats each risk factor as a separate screening test with



1 Flowchart summarizing screening and follow-up of study participants.

Aspirin from <14 weeks to delivery or 36 weeks' gestation was taken by 749 (4.5%) of 16 747 in the study population. The daily dose was 75 mg in 730 (97.5%) and 150 mg in 19 (2.5%). Aspirin was taken by 400 (23.2%) women in the NICE screened-positive group and 349 (2.3%) in the NICE screened-negative group. The reported reasons for treatment in the latter group were previous history of miscarriage (= 153), stillbirth (= 26), fetal growth restriction (= 25), placental abruption (= 8), thrombophilia (= 18), cardiovascular surgery (= 3), family history of PE (= 6), current pregnancy conceived by fertilization (= 34), high body mass index (= 21), low serum PAPP-A found at screening for fetal trisomies (= 47), one episode of high blood pressure in the first trimester of pregnancy (= 6), medical history of LYNCH syndrome (= 1) and Raynaud's disease (= 1).

The screen-positive rate by the NICE method was 10.3% (1727 of 16 747) and the DR for all-PE was 30.4% (95% CI, 26.3–34.6%). In screening by the Bayes' theorem-based method using a combination of maternal factors, MAP and PAPP-A, the DR of all-PE was 42.5% (95% CI, 38.0–46.9%) and the difference in DR between the two methods was 12.1% (95% CI, 7.9–16.2%) (Table 2).

Aspirin was taken by 256 patients who were screen positive by both the NICE method and the mini-combined test, by 144 patients who were screen positive by the NICE method and screen negative by the mini-combined test, and by 48 patients who were screen negative by the NICE method and screen positive by the mini-combined test.

After adjustment for the effect of aspirin (30% reduction in rate of all-PE) in those receiving this drug, the DR of the NICE method was 31.5% (95% CI, 27.3–35.7%), that of the Bayes' theorem-based method was 42.8% (95% CI 38.3–47.2%) and the difference between the two methods was 11.3% (95% CI, 7.1–15.5%) (Table 2).

1 Baseline characteristics of study participants (= 16 747)

Gestational age at screening (weeks)	12.8 (12.4–13.2)
Maternal age (years)	31.5 (27.4–35.1)
Maternal body mass index (kg/m^2)	24.7 (22.0–28.7)
Racial origin	
White	12 112 (72.3)
Black	2404 (14.4)
South Asian	1384 (8.3)
East Asian	414 (2.5)
Mixed	433 (2.6)
Conception	
Natural	16 046 (95.8)
Assisted by use of ovulation drugs	126 (0.8)
Assisted by use of fertilization	575 (3.4)
Cigarette smoker	1132 (6.8)
Mother had pre-eclampsia	543 (3.2)
Medical history	
Chronic hypertension	143 (0.85)
SLE/APS	40 (0.24)
Diabetes mellitus	119 (0.71)
Renal disease	29 (0.17)
Obstetric history	
Nulliparous	7714 (46.1)
Parous without pre-eclampsia	8641 (51.6)
Parous with pre-eclampsia	392 (2.3)
Interval from last pregnancy (years)	2.7 (1.5–4.7)
Screen-positive by NICE guidelines[8]	1727 (10.3)
Aspirin intake during pregnancy	749 (4.5)
NICE screen-positive group	400 (23.2)
NICE screen-negative group	349 (2.3)

Data are given as median (interquartile range) or (%). NICE, National Institute for Health and Care Excellence; APS, antiphospholipid syndrome; SLE, systemic lupus erythematosus.

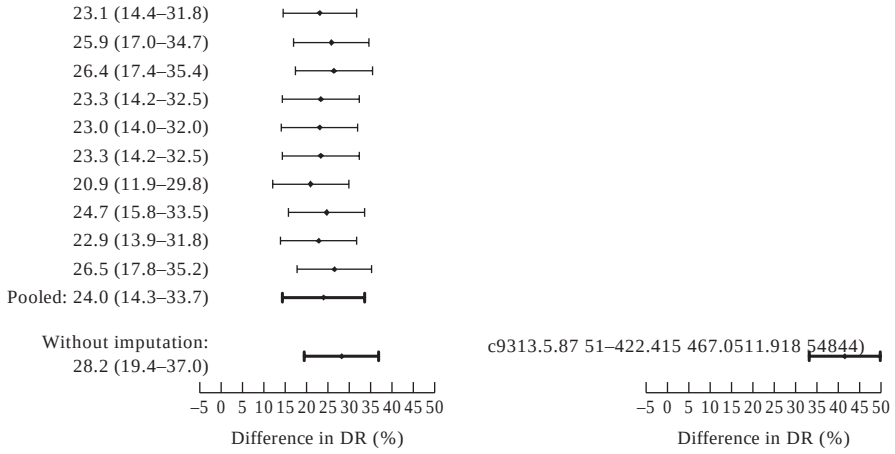
The performance of screening for preterm PE by the Bayes' theorem-based methods and the method advocated by NICE are summarized in Table 2 and shown in Figure 3. The DR of the NICE method for preterm PE was 40.8% (95% CI, 32.8–48.9%), which was lower than that of the Bayes' theorem-based method using maternal factors, MAP and PAPP-A (53.5%; 95% CI, 45.3–61.7%), maternal factors, MAP and PlGF (69.0%; 95% CI, 61.4–76.6%) and maternal factors, MAP, PlGF and UtA-PI (82.4%; 95% CI, 76.1–88.7%).

The results of multiple imputation to data on the incidence of preterm PE that would have occurred had

Table 2 Performance of screening for pre-eclampsia according to National Institute for Health and Care Excellence (NICE) guidelines[8] and method combining maternal factors and biomarkers

		Detection rate (% (95% CI))	
Screening method	Screen positive (n (%, 95% CI))	Fixed false positive rate	Fixed false positive rate*
All-pre-eclampsia (*n* = 473)			
NICE guidelines	144 (30.4, 26.3–34.6)	—	—
Maternal factors + MAP + PAPP-A	201 (42.5, 38.0–46.9)	12.1 (7.9–16.2)	11.3 (7.1–15.5)
Preterm pre-eclampsia (*n* = 142)			
NICE guidelines	58 (40.8, 32.8–48.9)	—	—
Maternal factors + MAP + PAPP-A	76 (53.5, 45.3–61.7)	12.7 (4.7–20.7)	10.5 (2.3–18.8)
Maternal factors + MAP + PlGF	98 (69.0, 61.4–76.6)	28.2 (19.4–37.0)	24.0 (14.3–33.7)
Maternal factors + MAP + PlGF + UtA-PI	117 (82.4, 76.1–88.7)	41.6 (33.2–49.9)	35.1 (25.1–45.0)

*Assumes that aspirin reduces risk of all pre-eclampsia by 30% and risk of preterm pre-eclampsia by 60%. MAP, mean arterial pressure; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.



serum PAPP-A was 42.5% and the DR for preterm PE by a combination of maternal factors, MAP, UtA-PI and PlGF was 82.4%.

Table 4 Incremental benefit in detection rate of preterm pre-eclampsia, at screen-positive rate of 10%, when a single biomarker is added to a specific combination of one or more biomarkers

	Detection rate (%)			
				P
MF vs MF + MAP	41.55	49.30	7.75 (1.6 to 14.6)	0.0291
MF vs MF + UtA-PI	41.55	61.97	20.42 (12.9 to 28.5)	< 0.0001
MF vs MF + PlGF	41.55	59.15	17.61 (10.1 to 25.7)	< 0.0001
MF vs MF + PAPP-A	41.55	45.07	3.52 (−1.7 to 9.2)	0.2673
MF + MAP vs MF+ MAP + PlGF	49.30	68.31	19.01 (11.7 to 27.0)	< 0.0001
MF + MAP vs MF+ MAP + UtA-PI	49.30	73.94	24.65 (16.7 to 33.0)	< 0.0001
MF + MAP + UtA-PI vs MF + MAP + UtA-PI + PlGF	73.94	81.69	7.75 (2.3 to 14.1)	0.0153
MF + MAP + PlGF vs MF + MAP + PlGF + UtA-PI	68.31	81.69	13.38 (8.0 to 20.2)	< 0.0001
MF + UtA-PI + PlGF vs MF+ UtA-PI + PlGF + MAP	70.42	81.69	11.27 (5.3 to 18.2)	0.0014

Values in parentheses are 95% CI. MAP, mean arterial pressure; MF, maternal factors; PAPP-A, pregnancy-associated plasma protein-A; PlGF, placental growth factor; UtA-PI, uterine artery pulsatility index.

Discussion

Recent evidence suggests that the target for first-trimester screening should be severe PE leading to preterm birth, rather than all-PE. There are two reasons for this suggested change in clinical practice. First, aspirin is considerably more effective than previously thought in reducing the risk of preterm PE[6,7]. A recent meta-analysis reported that aspirin reduces the risk of preterm PE by 67%, provided that the daily dose of the drug is ≥ 100 mg and the gestational age at onset of therapy is < 16 weeks[7]

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