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Risk factors for pre-eclampsia in clinical practice guidelines: comparison with the evidence

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The project was conceived by LAM, PvD, VF, TE and GS. All authors contributed to the writing, critical review, and approved the final version of the manuscript. The PRECISE Network contributed to study design, and provided constructive challenge as part of developmental of a suite of conceptual frameworks for placental disease.

ABSTRACT

OBJECTIVE: To compare pre-eclampsia risk factors identified by clinical practice guidelines (CPGs) with risk factors from hierarchical evidence review, to guide pre-eclampsia prevention.

DESIGN: Our search strategy provided hierarchical evidence of relationships between risk factors and pre-eclampsia, using Medline (Ovid), January 2010-January 2021.

SETTING: Published studies and CPGs.

POPULATION: Pregnant women.

METHODS: We evaluated strength of association and quality of evidence (GRADE). CPGs (N=15) were from previous systematic review.

MAIN OUTCOME MEASURE: Pre-eclampsia.

RESULTS: Of 78 pre-eclampsia risk factors, 13 (16.5%) arise only during pregnancy. Strength of association was usually 'probable' (n=40, 51.3%), and quality of evidence low (n=35, 44.9%). The 'major' and 'moderate' risk factors proposed by 8/15 CPGs were not well-aligned with evidence; of 10 'major' risk factors (alone warranting aspirin prophylaxis), associations with pre-eclampsia were definite (n=4), probable (n=5), or possible (n=1), based on moderate (n=4), low (n=5), or very-low (n=1) quality evidence. Obesity ('moderate' risk factor), was definitely associated with pre-eclampsia (high-quality evidence). The other ten 'moderate' risk factors had probable (n=8), possible (n=1), or no (n=1) association with pre-eclampsia, based on moderate (n=1), low (n=5), or very-low (n=4) quality evidence. Three risk factors not identified by CPGs had probable associations (high-quality): overweight, booking 'prehypertension', and early pregnancy BP 130-139/80-89mmHg.

CONCLUSIONS: Pre-eclampsia risk factors in CPGs are poorly aligned with evidence, particularly for the strongest risk factor, obesity. There is a lack of distinction between risk factors identifiable in early pregnancy and those arising later. A refresh of strategies advocated by CPGs is needed.

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KEY WORDS: pre-eclampsia, risk factors, determinants, prevention, outcomes

TWEETABLE ABSTRACT

Pre-eclampsia risk factors in practice guidelines are poorly aligned with evidence, especially for obesity.

INTRODUCTION

Pre-eclampsia complicates 2-4% of pregnancies worldwide, and its incidence is rising given trends in advanced maternal age of pregnancies and rising body mass.(1) Pre-eclampsia is the hypertensive disorder of pregnancy (HDP) associated with the greatest risk of maternal and fetal morbidity and mortality. As such, a large part of prenatal care is devoted to the detection of pre-eclampsia, through blood pressure (BP) and proteinuria screening.(2) However, as there is currently no approved disease-modifying treatment for pre-eclampsia, current best practice remains the identification of at-risk women, use of preventative therapy(3), management of hypertension and other organ manifestations should pre-eclampsia develop, and ultimately, timed birth as the only intervention that initiates resolution of this syndrome.

There is international consensus that screening for pre-eclampsia risk should occur in early pregnancy, to evaluate whether there is an indication for evidence-based preventative measures (e.g., aspirin).(4) Whilst adding biochemical markers and ultrasonographic factors to clinical risk factors can double identification of women who will develop pre-eclampsia before 37 weeks' gestational age (i.e., preterm pre-eclampsia),(5) clinical risk factors remain important for pre-eclampsia prediction, including those risk factors that develop *later* in pregnancy and mandate enhanced surveillance and timed birth.

Clinical practice guidelines (CPGs) are intended to advise clinicians on high-quality, evidence-based practice. We previously conducted a systematic review of international CPGs for the HDPs, assessing and comparing the quality of CPGs and their recommendations.(6) While almost all current CPGs for pregnancy hypertension list risk factors for pre-eclampsia, the quality of the documents vary, as do

the screening recommendations.(6) This variability can be difficult to understand, given the limited referencing permissible when guidelines are published in peer-reviewed journals.

As part of the development of a framework of pre-eclampsia risk factors,(7) we undertook an evidence review of the determinants of pre-eclampsia (Elawad T. A conceptual framework for the determinants of pre-eclampsia. A dissertation submitted in partial fulfilment of the requirements for the degree at the University of London, Department of Women and Children's Health, Faculty of Life Sciences and Medicine). In this analysis, we sought to compare the risk factors for pre-eclampsia identified in CPGs, and the underlying evidence base.

METHODS

Systematic review of CPGs

In a previous systematic review, 17 CPGs were identified for guidance on the diagnosis, evaluation, and management of HDPs.(6) Full details of our methodology have been published.(6)

In brief, we searched online databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Health Technology Assessments, the Database of Abstracts of Reviews of Effects, and grey literature), using appropriate key words and MeSH subject headings, from Jan 2009-Oct 2019, to identify CPGs meeting our eligibility criteria.(6) A CPG was defined as an evidence-based document that offered structured advice for healthcare professionals, referenced primary literature, and was issued by a professional medical society, government body, or similar organization. Included were CPGs in English, French, Dutch or German that covered diagnosis, assessment and management of at least one HDP, or were explicit updates to the CPGs in Gillon *et al.*(8). Excluded were publications that were adapted only from existing CPGs or were local or regional in scope when there was a relevant national document.

CPG quality was assessed by two independent reviewers (of GS, LAM, and PvD) using the Appraisal of Guidelines for Research & Evaluation Instrument II (AGREE-II) tool,(9) and disagreements resolved through consensus. AGREE II has six domains, including rigor of development, the domain that best represents the standard of literature search and overall quality of evidence used in guideline development. For the 15 CPGs deemed to be clinically useful after AGREE-II assessment, structured tables were used to abstract pre-eclampsia risk factors from recommendations, tables, bullet points, or text.(8) Previously reported was summary information about risk factors designated by CPGs as 'major' or 'moderate'; here, this information is presented by risk factor and CPG, along with details of other risk factors listed and types of sources cited, according to in-text citation.

Evidence review for pre-eclampsia risk factors

We used the methods of Hiatt et al(10) to develop a comprehensive model for the determinants of

pre-eclampsia. A broad group of experts in pre-eclampsia was assembled from the Epidemiology Working Group of the PREgnancy Care Integrating translational Science, Everywhere (PRECISE) Network.(7) A working model of determinants of pre-eclampsia was expanded from variables found to have significant associations with pre-eclampsia by pooled results in umbrella reviews (i.e., systematic reviews of systematic reviews).(11,12)

Literature search

The search strategy was developed in consultation with a clinical librarian (HE) at the British Medical Association. In brief, Medline (Ovid) was searched from January 2010-January 2021, using key words covering all potential determinants of pre-eclampsia. The highest level of evidence supporting a relationship between a risk factor and pre-eclampsia was identified in a hierarchical fashion. Umbrella reviews were sought that focussed on pre-eclampsia, and only if none were identified, were key words broadened to identify any studies in pregnancy. If no relevant umbrella reviews were identified, then the process was repeated to identify relevant systematic reviews. If no systematic reviews were identified or identified for all risk factors of interest, then large observational studies (including secondary analyses of trials) were sought, searching individually for relevant risk factors. Observational studies with at least 1000 participants were targeted as in Bartsch *et al.*,(13) to be more representative of the general population and to have sufficient statistical power to assess less prevalent, but potentially important, risk factors.(14) Smaller observational studies, case reports or series, qualitative reviews, and editorials were excluded. (For details, including key words, see **Table S3**.)

Data extraction

Titles and abstracts of articles were screened to assess eligibility. Potentially-eligible studies underwent full-text review. Data abstracted were general study characteristics, strength of association between each risk factor and pre-eclampsia (as relative risk [RR], odds ratios [OR], or diagnostic OR [DOR] reported, adjusted where possible, or calculated from the prevalence of pre-

eclampsia among women with and without the risk factor), and characteristics necessary to assess study quality. Subcategories of a potential risk factor were also considered, such as body mass index (BMI) categorisation as overweight or obese.

As in Hiatt et al,(10) strength of association between risk factors and the outcome of interest (pre-eclampsia) was evaluated as definite, probable, possible, and not significant(15). The evaluation was based on point estimates, extracted as reported or calculated from primary data using previously published cut-offs(10),(16) (**Table 1**). If a study reported outcomes as proportions, a RR was calculated as a simple ratio between those with the risk factor of interest and those without. Results of I^2 statistic were also extracted (or calculated from the Q statistic) to reflect heterogeneity. RR and OR were used interchangeably for the model, as pre-eclampsia occurs in <10% of the unexposed population, making the OR a reasonable approximation of the RR.(17)

Recommendations prepared by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) were used to assess the quality of the evidence, as high, moderate, low, or very low. A cross-disciplinary team (M-LV, KP, TE, CEL, MW-K, MV, JF, RS, HDM) adapted GRADE criteria through consensus into a standardised process for this pregnancy project, to minimize discrepancies between reviewers. (18,19) **Table 1** shows that as a starting point, umbrella or systematic reviews were considered to be of high-quality and observational studies of low quality;(20) however, the final quality rating for each methodology could be modified based on additional characteristics - decreased based on study limitations (risk of bias), important inconsistency, indirectness, imprecise data, or publication bias, and increased based on large effect size or dose-response gradient. One reviewer (TE) assessed the quality of the evidence using these GRADE criteria, and any uncertainty was resolved by discussion and consensus reached with a second and third reviewer (CEL, RS).

Comparison of CPG risk factors with the literature

A descriptive comparison of pre-eclampsia risk factors was made between those identified in CPGs and those identified from the literature search. Strength of association with pre-eclampsia and quality of underlying evidence were assigned and compared with the CPG overall designation of risk factors as 'major' or 'moderate'. Risk factors are presented according to traditional history-taking, as demographics and social determinants of health, past history, family history, and current pregnancy.

RESULTS

CPGs

The 15 CPGs (21–44) previously identified by AGREE-II as 'clinically useful' were included in this analysis, as in the prior systematic review (**Table S2**).(6) In brief, most CPGs (n=13) were national in scope and produced by professional societies. On the AGREE-II 'rigor of development' domain, few CPGs scored ≥ 80% (21–24)(43)(41) and some scored <40%(35,36)(33)(44)(37–39)(42).

All but the Brasilian guideline (i.e., 14/15 CPGs), listed risk factors for pre-eclampsia.(6) Just over half of CPGs (8/14), stratified risk factors into levels of importance. When listed as 'major'/'high' and 'moderate' risk factors (n=6; NED, IRL, European Society of Cardiology [ESC](26), American College of Obstetricians and Gynecologists [USA] (30–32), National Institute for Health and Care Excellence, United Kingdom [UK], Polish Society of Hypertension [POL]), aspirin was recommended for one 'major' risk factor or at least two 'moderate' factors. Other CPGs presented lists of risk factors to identify "increased risk"; sometimes highlighting among factors those associated with a particularly high risk, designated here as 'major' (n=2; Society of Obstetricians and Gynaecologists of Canada [CAN](28,29), Ministry of Health, New Zealand [NZL]), or otherwise presenting a list with no associated strength of association (n=6; World Health Organization [WHO], Society of Obstetric Medicine of Australia and New Zealand [SOMANZ] (43), French Society of Hypertension [FRA] (34), La Société Tunisienne de Gynécologie Obstétrique, Tunisia [TUN], International Society for the Study of Hypertension in Pregnancy [ISSHP](27), and German Society of Gynecology and Obstetrics [DEU](40)).

CPGs varied with regards to provision of in-text citations for risk factors. Three CPGs cited no such supporting literature (WHO, IRL, ESC), which when provided, was not necessarily linked with risk factors cited. Supporting publications were guidelines (CAN, SOMANZ, NZL, DEU, POL, NED, UK), systematic reviews (CAN, SOMANZ, NZL, DEU, ISSHP, NED, USA), observational studies (CAN, SOMANZ, NZL, DEU, USA, FRA, TUN, UK), narrative reviews (CAN, SOMANZ, NZL, DEU, FRA, UK),

commentaries (CAN, SOMANZ, NZL, DEU, FRA), books (CAN, SOMANZ, NZL, DEU), and a health technology assessment report (UK). Some guidelines quoted systematic reviews published more than 10 years prior (e.g., Duckitt *et al.* 2005(45), cited by CAN, SOMANZ, NZL, DEU; and Conde-Agudelo *et al.* 2000(46), cited by USA) rather than more recent ones (e.g., Bartsch *et al.* 2016(13), cited by NED, ISSHP, USA).

Evidence

Eighty pre-eclampsia risk factors were identified. Two, proposed by one CPG each, were not considered further because they were considered both vague and covered by individual conditions already included as risk factors: any 'prior adverse pregnancy outcome', and any 'placental insufficiency in obstetric history'.

Table 2 presents the 78 risk factors for pre-eclampsia, according to their strength of association and quality of evidence, and whether they are generally evident in early pregnancy (n=60, white table cells, and n=4 footnoted due to lack of evidence), or become evident only as pregnancy progresses (n=8, blue table cells, and n=6 footnoted due to lack of evidence), recognizing that there are some additional factors that could be both, such as anxiety or anemia. First, there were ten 'major' and 11 'moderate' risk factors as designated by CPGs, two of which were both (i.e., multiple pregnancy and ART) and all of which can be identified in early pregnancy. Second, the strength of association and quality of evidence for risk factors were not closely aligned. For risk factors designated as 'major' by CPGs (in bold), associations ranged from definite to possible and quality of evidence from moderate to very low. For risk factors designated as 'moderate' by CPGs, (in italics), associations ranged from definite to none, and quality of evidence from high to very low.

Our hierarchical search strategy identified 41 studies to support or refute determinants of pre-eclampsia: two umbrella reviews(11,12) that supported 25 risk factors, 14 systematic reviews or meta-analyses covering an additional 15 risk factors(48–61), and 25 large observational studies supporting 28 additional risk factors(62–86). Our strategy identified no evidence meeting our criteria for 10 risk factors.

Table 3 shows the 78 risk factors evaluated were from demographics and social determinants of health (n=8); past medical (n=27), obstetric (n=10) and family (n=5) histories, and conditions arising early or later during the current pregnancy (n=28). Strength of association and quality of evidence are presented along with the CPGs which endorsed them.

Definite associations

There were eight risk factors with definite associations with pre-eclampsia (shown in dark green, **Table 3**), in demographics (adolescence), past medical history (obesity, chronic hypertension, pre-gestational diabetes mellitus [DM] considered as type 1 and 2 DM separately, severe anemia), past obstetric history (prior pre-eclampsia), and current pregnancy (fetal trisomy 13).

Obesity (i.e., BMI ≥30 kg/m^2) was the only risk factor with a 'definite' association with pre-eclampsia based on high-quality evidence (n=14 CPGs). No CPG, even those that highlighted only a subgroup with BMI ≥35 mg/kg^2 (NED, IRL, TUN, NZL, ESC, UK, POL), endorsed obesity as 'major', whereas 6/14 regarded it as 'moderate'.

Moderate-quality evidence supported four risk factors that were generally highly-endorsed by CPGs: prior pre-eclampsia (n=10 CPGs, 4/10 as 'major'), chronic hypertension (n=13, 8/13 'major'), and type 2 DM (n=14 as 'pre-gestational DM', 8/14 'major'), and trisomy 13 (n=1).

Low-quality evidence supported three risk factors: adolescence (endorsed only by WHO), type 1 DM (n=14 as 'pre-gestational DM', 8/14 'major'), and severe anaemia (not endorsed).

Probable associations

The majority of associations (n=39) with pre-eclampsia were probable (shown in medium green, **Table 3**).

High-quality evidence supported three risk factors. Overweight (i.e., BMI 25.0-29.9 kg/m^2) and Stage 1 hypertension (defined as systolic BP 130-139mmHg and/or diastolic BP 80-89mmHg at booking or <20 weeks')(47) were endorsed by few CPGs (i.e., n=2 and 3, respectively), and none as 'major' or 'moderate'. No CPGs endorsed prehypertension at booking as a risk factor.

Moderate-quality evidence supported six risk factors: the highly-endorsed antiphospholipid antibody syndrome (APAS, n=12 CPGs, 8/12 'major') and family history of pre-eclampsia in the mother or sister (n=5, 1/5 'major' and 3/5 'moderate'). Other risk factors were endorsed by one CPG each (i.e.,

obstructive sleep apnea, smoking, and any infection in the index pregnancy). No CPG endorsed prior stillbirth.

Low-quality evidence supported 25 risk factors, including five that were highly-endorsed by CPGs: maternal age >40 years (n=10 CPGs, 5/10 as 'moderate' with an 11th CPG identifying maternal age >35 years as 'moderate'), systemic lupus erythematosus (SLE, n=8, 7/8 'major'), chronic kidney disease (CKD, n=14, 8/14 'major'), multiple pregnancy (n=14, 2/14 'major' and 5/14 'moderate'), and nulliparity (n=12, 6/12 as 'moderate').

Very low-quality evidence supported five risk factors, including the well-endorsed ART (n=7 CPGs, 1/7 'major' and 1/7 'moderate'); oocyte donation, specified in 3/7 of the CPGs that specified ART, was listed as both a 'major' and 'moderate' risk factor in different guidelines.

Possible associations

There were 13 possible associations with pre-eclampsia (shown in very light green, **Table 3**). Moderate quality evidence supported only urinary tract infection in the index pregnancy (n=1 CPG). Low-quality evidence supported six risk factors, including 'prior HDP' endorsed by n=4 CPGs, all as a 'major' risk factor. Very low-quality evidence supported six risk factors, including interpregnancy interval ≥10 years that was endorsed by many CPGs (n=9) and frequently as a 'moderate' risk factor (in 6/9).

Not significant

According to our methodology, no association could be demonstrated for eight risk factors, all based on very low-quality evidence (**Table 3**). Three were endorsed by a single CPG: prior small-for-gestational-age (SGA) infant (as 'moderate'), fetal trisomy 18, and vaginal bleeding in early pregnancy.

According to our methodology, no rigorous evidence was found to evaluate ten risk factors. With the exception of 'autoimmune disease' (as a group), endorsed by many CPGs (n=9, 5/9 as 'major', these

risk factors were endorsed by one or two CPGs: increased pre-pregnancy triglycerides (n=1), family history of early-onset CVD (n=1), gestational hypertension (n=2), FGR (n=1), hyperplacentation unspecified, fetal hydrops [n=2] and gestational trophoblastic disease [n=2]), fetoplacental triploidy (n=1), and cocaine use (n=1).

A summary of risk factors with a demonstrated association with pre-eclampsia are presented in Table 4.

DISCUSSION

Summary of findings

CPG-recommended pre-eclampsia risk factors are not well-aligned with published evidence. 'Major' risk factors usually have definite to probable associations with pre-eclampsia, based on moderate-to very low-quality evidence, with two exceptions. 'Prior HDP' has a possible association, based on low-quality evidence. 'Autoimmune disease' has no supporting evidence, but includes conditions for which there is low-quality evidence (e.g., RA). 'Moderate' risk factors in general have weaker relationships with pre-eclampsia, based on lower-quality evidence, but maternal obesity is a notable exception.

Indeed, obesity is the strongest evidence-informed pre-eclampsia risk factor, having a definite association with pre-eclampsia, based on high-quality evidence. Also, there are other evidence-informed risk factors that are neither 'major' nor 'moderate' in guidelines, particularly maternal overweight and stage 1 hypertension or prehypertension at booking, based on high-quality evidence.

A number of pre-eclampsia risk factors are of particular relevance to low- and middle-income countries (LMICs). Some factors have associations with pre-eclampsia that are definite (i.e., adolescence, severe anemia) or probable (i.e., sickle cell disease, anemia); yet, only adolescence is listed and then only by the WHO. While no association with preeclamspia is demonstrable for other risk factors (i.e., HIV, tuberculosis, and malaria), the quality of evidence is very low.

CPGs focus on pre-eclampsia risk factors identified in early pregnancy to guide low-dose aspirin therapy. However, there are additional, well-supported risk factors that become evident as pregnancy progresses and influence investigations, maternal-fetal surveillance, and/or timed birth. Examples include common conditions in pregnancy, like anemia (particularly severe), infections, gestational weight gain, and GDM.

Comparison with current literature

To our knowledge, this is the first evidence-informed comparison of pre-eclampsia risk factors with those endorsed by CPGs. Deserving of specific mention is the only 'possible' association between pre-eclampsia and 'prior HDP'; this risk factor was cited as 'major' by four CPGs, whereas the others cited 'prior pre-eclampsia' as the major risk factor, and for that, there is a definite relationship.

While we demonstrated a lack of close alignment between guideline risk factors and evidence, it was not usually possible to understand why. Guidelines usually cite one reference in support of all risk factors listed, with relative importance recognised by 'major' or 'moderate' designations without further citations. Very few CPGs included a broad array of higher-order evidence, such as systematic reviews and large observational studies, as in our analysis; the most highly-cited systematic review was over 15 years old(45). No CPG cited umbrella reviews that could have been incorporated into 2019 guidelines(11),(12). It is common for CPGs to cite other guidelines, often with little or no citation of primary evidence for risk factors, even when CPGs had high scores on rigor of development. All of this contributes to the sense that while there has been much focus on quality rating scales for guidelines, further improvement is necessary before CPGs will effectively translate evidence into practice in the field of pregnancy hypertension.

Pre-eclampsia risk assessment, by a count of 'major' or 'moderate' risk factors, detects fewer cases of preterm pre-eclampsia than a multivariable approach(5),(88). Also, the most important risk factors identified by CPGs are not aligned with published prediction models(89) that most commonly identify as important: BMI (19/40 models), uterine artery pulsatility index (17/40), angiogenic markers (16/40 for each of PlGF or PAPP-A), ethnicity (14/40), and BP (12/40); the absence of angiogenic imbalance as a risk factor for pre-eclampsia in CPGs is notable. Also, 'major' CPG risk factors were not as well-supported in these models: prior pre-eclampsia (9/40 models), chronic hypertension (2/40), pre-gestational diabetes (0 but 2/40 included fasting blood glucose), CKD (0 although 1/40 included serum creatinine), SLE (0), APAS (0), ART (6/40), multiple pregnancy (0), and prior HDP (0).(89)

While some may regard universal aspirin administration as preferable to reconsideration of pre-eclampsia risk screening, this is debated. Aspirin compliance is suboptimal among even women identified as high-risk (90) and pregnant women are averse to taking medication in pregnancy, particularly when small risks have been identified. (91) Also, universal administration of aspirin would not address prevention of term pre-eclampsia or risk factors that require alternative approaches (e.g., exercise for sedentary lifestyle).

Given that screening for pre-eclampsia risk should be implemented for all pregnant women, a recent systematic review emphasised the importance of the 'population attributable risk', related not only to strength of association and quality of evidence for the risk factor and pre-eclampsia, but also to how commonly the risk factor occurs, and whether its relationship with pre-eclampsia is modifiable.(13) For example, addressing a risk factor with a strong association with pre-eclampsia but low population prevalence (e.g., APAS), will have little impact on pre-eclampsia incidence at the population level; this is more likely to be affected by addressing a more common risk factor (e.g., overweight), even if the association with pre-eclampsia is not as strong.

Strengths and limitations

Strengths of this paper include the comprehensive search strategies to identify CPGs(6) and evidence for individual risk factors, and use of published methodology to evaluate strength of association and quality of evidence.(10) We offer a unique perspective on gaps between practice recommendations and evidence-informed risk factors, even within guidelines rated as high-quality. We have distinguished between risk factors evident in early pregnancy and those that emerge as pregnancy progresses; this pragmatic and comprehensive approach acknowledges that pre-eclampsia risk may evolve and the risk of adverse outcomes can be mitigated by close surveillance and timed birth, either to minimise the risk of complications once pre-eclampsia develops, or to prevent pre-eclampsia from developing at term gestational age.

Limitations of our analysis include that international CPGs are almost exclusively from high-income

countries, so it is unsurprising that they may not address risk factors of unique or particular importance to LMICs (e.g., malaria or seasonality). Despite following published methodology,(10) we restricted our search to Medline, to focus on a peer-reviewed, curated collection of citations of articles in journals approved and indexed to have MeSH terms. We excluded as evidence small observational studies (<1000 participants) on which some risk factors have been identified; quality of evidence may be improved by future systematic reviews or large studies. Finally, while we used strength of association criteria for RR and OR interchangeably, the low incidence of pre-eclampsia (2-4% of pregnancies) makes use of OR unlikely to have exaggerated the association.

Conclusions

Pre-eclampsia risk factors advocated by CPGs were poorly-aligned with evidence, consisting primarily of umbrella and other high-quality systematic reviews(13),(11),(12). With the availability of multivariable prediction models in early and later pregnancy, digital health technologies for data processing, and an awareness that pre-eclampsia risk may evolve as pregnancy progresses, we are well-placed to refresh our strategy to identify throughout pregnancy, the women at increased risk of pre-eclampsia, and modify their likelihood of pre-eclampsia and/or pre-eclampsia adverse outcomes, accordingly.

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This article has a Video Abstract presented by Laura A. Magee.

Table 1: Strength of association between risk factors and pre-eclampsia based on point estimates of various summary measures*

	Quality of evidence						
	High		Moderate		Low		Very low
Initially	Umbrella review or systematic review		-		Observational study (N> 1000)		-
Evaluation/scoring	Risk of bias	Inconsistency¶	Indirectness¶	Imprecision¶	Publication bias¶	Magnitude of effect¶	Dose-gradient response
	1↓ Lack of inclusion or discussion of sensitivity analysis AND/OR 1↓ Study limitations	1↓ I^2 > 50%	Excludes women from population 1↓ serious: 2↓ Very serious	1↓ Sample size <1000 or not reported AND/OR 1↓ CI crosses 1.0	1↓ Asymmetrical funnel plots or no men-tion of public-cation bias AND 1↓ evidence of very strong publication bias	1↑ Large: RR >2-5 or 0.5-0.2 OR 2↑ Very large: RR> 5 or < 0.2	1↑ if existent
Final	High		Moderate		Low		Very low

Strength of association	RR or Or† (↑risk)	RR or Or† (↓ risk)	DOR‡	LR+	LR-	High	Moderate	Low	Very low
Definite	≥3.00	<0.33	≥100	>10	<0.1				
Probable	1.50-2.99	0.33-0.67	>25 to <100	5.01-10.0	0.10-0.19				
Possible	1.10-1.49	>0.67-<0.9	>4 to ≤25	2.01-5.0	0.20-0.50				
Not significant	0.90 to 1.09		1-4	1.0-2.0	0.51-0.99				

DOR (diagnostic odds ratio), LR (likelihood ratio), LR+ (positive LR), LR- (negative LR), NS (not significant), OR (odds ratio), RR (relative risk)

** The initial grade category was altered, by one or two categories (up to the left, or down to the right), depending on characteristics other than the study design, according to GRADE.*
Ł Based on Hiatt et al.(10).
‡ Based on LR+ and LR- criteria and definition of DOR as LR+/LR-.
¶ Inconsistency was defined as variation between studies (heterogeneity), indirectness whether the paper answered the question we aimed to answer; imprecision defined according to the confidence interval of the summary estimates, publication bias as a tendency towards publication of studies that showed positive results, and magnitude of effect as determined by the RR.

Table 2: Matrix of risk factors for pre-eclampsia, according to strength of association and quality of evidence

			Quality of evidence			
			HIGH (N=4)	**MODERATE** (N=11)	**LOW** (N=35)	**VERY LOW** (N=18)
Strength of association	**DEFINITE** (N=8)	CPGs	*Obesity (BMI ≥30kg/m²)*	**Prior pre-eclampsia** **Chronic hypertension** **Type 2 DM**	Adolescence **Type 1 DM**	-
				Fetal trisomy 13		
		New	-	**-**	Severe anemia	-
	PROBABLE (N=39)	CPGs	Overweight Early pregnancy Stage 1 hypertension†	**Antiphospholipid antibody syndrome** Smoking (↓risk) Obstructive sleep apnea *Family history in mother or sister*	*Maternal age >40 yrs* **Systemic lupus erythematosus‡** **Chronic kidney disease** Thrombophilia *Nulliparity* ***Multiple pregnancy*** New or change in partner *Family history (relation unspecified)* Prior miscarriage at ≤10 weeks with same partner (↓risk) Methamphetmine use Sub-Saharan African South Asian *Maori*	***Artificial reproductive technology*** *African-American ethnicity*
				Any infection in current pregnancy	Excessive weight gain GDM	Fetal trisomy 21

		New	Booking pre-hypertension ł	Prior stillbirth	Sickle cell disease Rheumatoid arthritis ǂ Polycystic ovarian syndrome Periodontal disease Helicobacter pylori Depression Placental abruption prior pregnancy Prior preterm birth Anaemia Family history of CVD	Recurrent miscarriage Barrier contraception
	POSSIBLE (N=13)	CPGs	-	-	**Prior HDP** Prior lower maternal birthweight or preterm birth Abnormal uterine artery Doppler in current pregnancy Pacific Islander	*Interpregnancy interval ≥10 yr* Duration of sexual relationship <12 months Family history in the father *Low socioeconomic status*
		New	-	Urinary tract infection (current pregnancy)	Hepatitis B infection Previous miscarriage (timing and number unspecified)	Stress Endometriosis
	NOT SIGNIFICANT (N=8)	CPGs	-	-	-	*Prior SGA infant* Vaginal bleeding in early (current) pregnancy
						Fetal trisomy 18
		New	-	-	-	Thalassemia HIV Tuberculosis Anxiety
						Malaria (current pregnancy)

BMI (body mass index), CVD (cardiovascular disease), DM (diabetes mellitus), HDP (hypertensive disorder of pregnancy, HIV (human immunodeficiency virus), SGA (small-for-gestational age)

** Those factors listed in **bold** type are those listed by one or more CPG as a 'major' risk factor, those in italics are listed as a 'moderate' risk factor. Factors in white cells are known in early pregnancy, whereas those in blue cells are risks that become evident as pregnancy progresses. For definitions, see **Table 2**. The following factors endorsed by CPGs are excluded, as there was no rigorous evidence identified to evaluate their association with pre-eclampsia: 'autoimmune disease' as a group, elevated prepregnancy triglycerides, family history of early-onset CVD, gestational hypertension, FGR, fetal triploidy, hyperplacentation (not otherwise specified), fetal hydrops, gestational trophoblastic disease, and cocaine use.*

Ł According to American College of Cardiology/American Heart Association criteria, prehypertension is systolic BP <120-129mmHg with diastolic BP <80mmHg, and Stage 1 hypertension is systolic BP 130-139mmHg and/or diastolic BP 80-89mmHg(47).

ǂ Abnormal uterine artery Doppler included bilateral notching, or an increased pulsatility or resistance index persisting beyond 24 weeks gestational age.

Table 3: Risk factors for pre-eclampsia*

RISK FACTOR (and Conceptual Framework reference(s) when uavailable)	**CONCEPTUAL FRAMEWORK**		**CLINICAL PRACTICE GUIDELINES** (6)		
	Strength of association†	**Quality of evidence‡**	**N endorsing risk factor**	**'High, major or strong'**	**'Moderate'**
DEMOGRAPHICS					
Maternal age					
Adolescence(54)	Definite	Low	N=1 (WHO)	None	None
Advanced maternal age (>40 yr in CPGs)(11)	Probable	Low	N=10 (NLD, CAN, SOMANZ, IRL, TUN, NZL, ESC, DEU, UK, POL)	None	N= 5 [NLD, IRL, ESC, UK, POL]
Ethnicity					
African-American(66)	Probable	Very low	N=2 (USA, DEU)	None	N=1 (USA)
(sub-Saharan) African(78)	Probable	Low	N=1 (NZL)	None	None
South Asian(72)	Probable	Low	N=1 (NZL)	None	None
Pacific Islander(73)	Possible	Low	N=1 (NZL)	None	None
Maori(75)	Probable	Low	N=1 (NZL)	None	None
Low socioeconomic status(67)	Possible	Very low	N=1 (USA)	None	N=1 (USA)
PAST MEDICAL HISTORY					
BMI (kg/m²)					
Obesity (BMI ≥30) (11,12)	Definite	High	N=7 (WHO, CAN, SOMANZ, FRA, ISSHP, USA, DEU)	None	N=1 (USA)
BMI ≥35 (11,12)			N=7 (NLD, IRL, TUN, NZL, ESC, UK, POL)	None	N=5 (NLD, IRL, ESC, UK, POL)
Overweight (BMI 25.0-29.9)(11)	Probable	High	N=2 (CAN, SOMANZ)	None	None
Chronic hypertension(11)	Definite	Moderate	N=13 (WHO, NLD, CAN, IRL, FRA, TUN, ISSHP, NZL, ESC, USA, DEU, UK, POL)	N= 8 (NLD, CAN, IRL, NZL, ESC, USA, UK, POL)	None
Pregestational DM					
Type 2(11)	Definite	Moderate	N=14 (WHO, NLD, CAN, SOMANZ, IRL, FRA, TUN, ISSHP, NZL, ESC, USA, DEU, UK, POL)	N= 8 (NLD, CAN, IRL, NZL, ESC, USA, UK, POL)	None
Type 1(58)	Definite	Low			
Anemia					

RISK FACTOR (and Conceptual Framework reference(s) when uavailable)	**CONCEPTUAL FRAMEWORK**		**CLINICAL PRACTICE GUIDELINES** (6)		
	Strength of association†	**Quality of evidence‡**	**N endorsing risk factor**	**'High, major or strong'**	**'Moderate'**
Severe anemia(74)	Definite	Low	None	-	-
Anemia(61)	Probable	Low	None	-	-
Sickle cell disease(48)	Probable	Low	None	-	-
Thalassemia(74)	NS	Very low	None	-	-
Obstructive sleep apnea(11)	Probable	Moderate	N=1 (USA)	None	None
Autoimmune/rheumatic disease					
Antiphospholipid syndrome(11)	Probable	Moderate	N=12 (NLD, CAN, SOMANZ, IRL, TUN, ISSHP, NZL, ESC, USA, DEU, UK, POL)	N= 8 (NLD, CAN, IRL, NZL, ESC, USA, UK, POL)	None
Systemic lupus erythematosus(11)	Probable	Low	N=8 (NLD, IRL, TUN, ESC, NZL, USA, UK, POL)	N=7 (NLD, IRL, ESC, NZL, USA, UK, POL)	None
Rheumatoid arthritis(64)	Probable	Low	None	-	-
Unspecified	-	-	N=9 (WHO, NLD, IRL, SOMANZ, TUN, ESC, USA, DEU, UK)	N= 5 (NLD, IRL, ESC, USA, UK)	None
Chronic kidney disease(11,12)	Probable	Low	N=14 (NLD, IRL, FRA, ESC, UK, POL, TUN, WHO, CAN, SOMANZ, ISSHP, NZL, USA, DEU)	N=8 (NLD, IRL, ESC, UK, POL, CAN, NZL, USA)	None
Polycystic ovarian syndrome(11,12)	Probable	Low	None	-	-
Thrombophilia(60)	Probable	Low	N=2 (CAN, USA)	None	None
Infection					
Periodontal disease(11,12)	Probable	Low	None	-	-
Helicobacter pylori infection(51)	Probable	Low	None	-	-
Hepatitis B infection(11,12)	Possible	Low	None	-	-
HIV(57)	NS	Very low	None	-	-
Tuberculosis(71)	NS	Very low	None	-	-
Mental health					
Depression(12)	Probable	Low	None	-	-
Stress(11,12)	Possible	Very low	None	-	-
Anxiety(49)	NS	Very low	None	-	-

RISK FACTOR (and Conceptual Framework reference(s) when uavailable)	**CONCEPTUAL FRAMEWORK**		**CLINICAL PRACTICE GUIDELINES** (6)		
	Strength of association†	**Quality of evidence‡**	**N endorsing risk factor**	**'High, major or strong'**	**'Moderate'**
Lower maternal birthweight or preterm delivery(62)	Possible	Low	N=1 (CAN)	None	None
Increased prepregnancy triglycerides	-	-	N=1(CAN)	None	None
PAST OBSTETRIC HISTORY					
Prior pre-eclampsia(11)	Definite	Moderate	N=10 (WHO, NLD, CAN, SOMANZ, FRA, TUN, ISSHP, NZL, USA, DEU)	N=4 (NLD, CAN, NZL, USA)	None
Prior stillbirth(11)	Probable	Moderate	None	-	-
Prior abruption(11)	Probable	Low	None	-	-
Prior pre-term birth(84)	Probable	Low	None	-	-
Prior HDP(53)	Possible	Low	N=4 (IRL, ESC, UK, POL)	N=4 (IRL, ESC, UK, POL)	None
Endometriosis(55)	Possible	Very low	None	-	-
Prior SGA (or low birthweight) (11)	NS	Very low	N=1 (USA)	None	N=1 (USA)
Prior miscarriage					
At ≤10 weeks with same partner(68)	Probable (↓risk)	Low	N=1 (CAN)	None	None
Recurrent (77)	Probable	Very low	None	-	-
Timing and number unspecified (76)	Possible	Low	None	-	-
FAMILY HISTORY					
Pre-eclampsia					
Relation unspecified(52)	Probable	Low	N=5 (SOMANZ, IRL, ESC, DEU, UK)	None	N=3 (IRL, ESC, UK)
In mother or sister (69)	Probable	Moderate	N=5 (NLD, CAN, NZL, USA, POL)	N=1 (NZL)	N= 3 (NLD,USA, POL)
In father of baby (70)	Possible	Very low	N=1 (NZL)	None	None
Cardiovascular disease (any) (69)	Probable	Low	None	-	-
Early onset	-	-	N=1 (CAN)	None	None
CURRENT PREGNANCY					
Trisomies					
Trisomy 13(81)	Definite	Moderate	N=1 (DEU)	None	None
Trisomy 21(80)	Probable	Very low			

RISK FACTOR (and Conceptual Framework reference(s) when uavailable)	**CONCEPTUAL FRAMEWORK**		**CLINICAL PRACTICE GUIDELINES** (6)		
	Strength of association†	**Quality of evidence‡**	**N endorsing risk factor**	**'High, major or strong'**	**'Moderate'**
	(↓ risk)				
Trisomy 18(82)	NS	Very low			
Fetoplacental triploidy	-	-	N=1 (SOMANZ)	None	None
Smoking(11)	Probable (↓ risk)	Moderate	N=1 (CAN)	None	None
Nulliparity(11,12)	Probable	Low	N=12 (WHO, NLD, CAN, SOMANZ, IRL, TUN, NZL, ESC, USA, DEU, UK, POL)	None	N=6 (NLD, IRL, ESC, USA, UK, POL)
Early pregnancy BP					
Booking sBP120-129 (with dBP <80mmHg)(85)	Probable	High	None	-	-
Early pregnancy sBP≥130 or dBP ≥ 80 mmHg(85)	Probable	High	N=3 (CAN, NZL, SOMANZ)	None	None
Gestational hypertension	-	-	N=2 (CAN, FRA)	None	None
FGR	-	-	N=1 (CAN)	None	None
Abnormal uterine artery Doppler¶(11)	Possible	Low	N=3 (CAN, FRA, DEU)	None	None
Infection (any) (11,12)	Probable	Moderate	N=1 (CAN)	None	None
Urinary tract infection(50)	Possible	Moderate	None	-	-
Malaria(11)	NS	Very low	None	-	-
Multiple pregnancy(11)	Probable	Low	N=14 (WHO, NLD, CAN, SOMANZ, IRL, FRA, TUN, ISSHP, NZL, ESC, USA, DEU, UK, POL)	N=2 (CAN, USA)	N= 5 (NLD, IRL,ESC, UK, POL)
Excessive weight gain in pregnancy(59)	Probable	Low	N=1 (CAN)	None	None
GDM(63)	Probable	Low	N=2 (USA, DEU)	None	None
Barrier contraception(56)	Probable‖	Very low	None	-	-
New or change in partner(65)	Probable	Low	N=2 (CAN, NZL)	None	None
Duration sexual relationship <12 months with current partner(56)	Possible	Very low	N=1 (CAN)	None	None

RISK FACTOR (and Conceptual Framework reference(s) when uavailable)	**CONCEPTUAL FRAMEWORK**		**CLINICAL PRACTICE GUIDELINES** (6)		
	Strength of association†	**Quality of evidence‡**	**N endorsing risk factor**	**'High, major or strong'**	**'Moderate'**
ART (includes IVF, sperm donation, oocyte donation)(11)	Probable	Very low	N=7 (NLD, NZL, DEU, CAN, FRA, ISSHP, USA)	N=1 (NZL)	N=1 (NLD)
Interpregnancy interval ≥ 10 yrs(83)	Possible	Very low	N= 9 (NLD, CAN, SOMANZ, IRL, NZL, ESC, USA , UK, POL)	None	N= 6 (NLD, IRL, ESC, USA, UK, POL)
Vaginal bleeding in early pregnancy(86)	NS	Very low	N=1 (CAN)	None	None
Other hyperplacentation					
Unspecified	-	-	N=1 (WHO)	None	None
Fetal hydrops	-	-	N=2 (SOMANZ, DEU)	None	None
Gestational trophoblastic disease	-	-	N=2 (CAN, SOMANZ)	None	None
Illicit drug use					
Cocaine	-	-	N=1 (CAN)	None	None
Methamphetamine use (79)	Probable**	Low**	N=1 (CAN)	None	None

ART (assisted reproductive technologies), BMI (body mass index), BP (blood pressure), dBP (diastolic blood pressure), DM (diabetes mellitus), FGR (fetal growth restriction), GDM (gestational diabetes mellitus), HDP (hypertensive disorder of pregnancy), HIV (human immunodeficiency virus), IVF (in vitro fertilisation), NS (not significant), sBP (systolic blood pressure), SGA (small for gestational age)

** All factors increase the risk of pre-eclampsia unless otherwise indicated (by a ↓ arrow).*
*† Strength of association was assessed according to relative risk and odds ratio criteria in **Table 1**.*
*‡ Quality of evidence was assessed according to GRADE criteria, detailed in **Table S4**.*
§ Socioeconomic status was based on income.
¶ Abnormal uterine artery Doppler included bilateral notching, or an increased pulsatility or resistance index persisting beyond 24 weeks gestational age.
‖ The association between barrier contraception and pre-eclampsia was observed among nulliparous women.
*** This assessment was based on a large observational (retrospective cohort study) excluded from a systematic review which was restricted to case-control studies and had a far smaller number of women (≈500) with methamphetamine exposure.* (87)

Table 4: Risk factors for pre-eclampsia

Strength of association with pre-eclampsia	Risk factors for pre-eclampsia	
	Present at antenatal care booking	**Emerge as pregnancy progresses**
DEFINITE ASSOCIATION	Obesity	
	Prior pre-eclampsia	Fetal trisomy 13
	Chronic hypertension	
	Type 2 DM	
	Adolescence	Severe anaemia
	Type 1 DM	
PROBABLE ASSOCIATION	Overweight	
	Early pregnancy Stage 1 hypertension	
	Booking pre-hypertension ŧ	
	Antiphospholipid antibody syndrome	Any infection in current pregnancy
	Smoking (↓risk)	
	Obstructive sleep apnea	
	Family history in mother or sister	
	Maternal age >40 yrs	Excessive weight gain
	Race/ethnicity: Sub-Saharan African, South Asian, Maori	GDM
	Past medical history:	Anaemia
	Systemic lupus erythematosus‡	
	Chronic kidney disease	
	Anaemia	
	Thrombophilia	
	Sickle cell disease	
	Rheumatoid arthritis‡	
	Polycystic ovarian syndrome	
	Helicobacter pylori	
	Periodontal disease	
	Depression	
	Past obstetric history:	
	Prior miscarriage at ≤10 weeks with same partner (↓risk)	

	Prior stillbirth	
	Placental abruption prior pregnancy	
	Prior preterm birth	
	Family history (relation unspecified)	
	Family history of CVD	
	This pregnancy:	
	New or change in partner	
	Nulliparity	
	Multiple pregnancy	
	Methamphetmine use	
	Artificial reproductive technology	Fetal trisomy 21
	African-American ethnicity	
	Recurrent miscarriage	
	Barrier contraception	
POSSIBLE ASSOCIATION		Urinary tract infection (current pregnancy)
	Prior HDP	
	Prior lower maternal birthweight or preterm birth	
	Abnormal uterine artery Doppler in current pregnancy	
	Pacific Islander	
	Hepatitis B infection	
	Previous miscarriage (timing and number unspecified)	
	Interpregnancy interval ≥10 yr	
	Duration of sexual relationship <12 months	
	Family history in the father	
	Low socioeconomic status	
	Stress	
	Endometriosis	

BMI (body mass index), CVD (cardiovascular disease), DM (diabetes mellitus), HDP (hypertensive disorder of pregnancy, HIV (human immunodeficiency virus), SGA (small-for-gestational age)

** Factors in the darkest shading were based on high quality evidence. Factors in moderate shading were based on moderate quality evidence. Factors in*

light shading were based on low quality evidence. Factors that are not shaded were based on very low quality evidence. The following factors endorsed by CPGs are excluded, as there was no rigorous evidence identified to evaluate their association with pre-eclampsia: 'autoimmune disease' as a group, elevated prepregnancy triglycerides, family history of early-onset CVD, gestational hypertension, FGR, fetal triploidy, hyperplacentation (not otherwise specified), fetal hydrops, gestational trophoblastic disease, and cocaine use. Based on very low quality evidence, the following factors were not supported as being associated with pre-eclampsia: prior SGA infant, vaginal bleeding in early (current) pregnancy, fetal trisomy 18, thalassemia, HIV, tuberculosis, anxiety, malaria (current pregnancy).

Ł According to American College of Cardiology/American Heart Association criteria, prehypertension is systolic BP <120-129mmHg with diastolic BP <80mmHg, and Stage 1 hypertension is systolic BP 130-139mmHg and/or diastolic BP 80-89mmHg(47).

ǂ Abnormal uterine artery Doppler included bilateral notching, or an increased pulsatility or resistance index persisting beyond 24 weeks gestational age.

References

Please see manuscript bibliography for references corresponding to citations in tables.