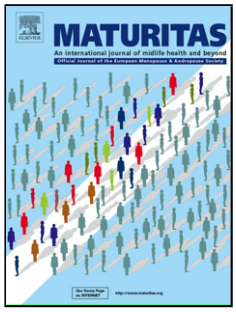

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Determinants of future cardiovascular health in women with a history of preeclampsia

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Preeclampsia, cardiovascular disease, risk assessment, screening, prevention

Highlights

- Female-specific risk factors, among which preeclampsia, may have additional value in cardiovascular screening.
- Non-invasive imaging techniques can be helpful to detect early-stage cardiovascular lesions as a sign of subclinical atherosclerotic disease.
- Preliminary studies show positive effects of short-term lifestyle interventions following preeclampsia.
- There is a need for clinical practice guidelines that provide long-term strategies in women after preeclampsia in pregnancy to improve cardiovascular health.

Abstract

Women who develop preeclampsia have an increased risk of cardiovascular disease (CVD) later in life. However, current guidelines on cardiovascular risk assessment and prevention are unclear on how and when to screen these women postpartum, and about the role of a positive history of preeclampsia in later-life CVD risk management. The aim of this review is to discuss the present knowledge on commonly used cardiovascular screening modalities available to women with a history of preeclampsia, and to discuss recent developments in early detection of CVD using cardiovascular imaging.

Furthermore, we explore how female-specific risk factors may have additional value in cardiovascular screening, in particular in relatively young women, although their implementation in clinical practice is challenged by inconsistent results and lack of long-term outcome data. Non-invasive imaging techniques, e.g. coronary artery intima-media thickness (CIMT), can be helpful to detect subclinical atherosclerotic disease, and coronary artery calcium scoring (CACS) has shown to be effective in early detection of cardiovascular damage. However, whilst more short-term and long-term follow-up studies are becoming available, few studies have investigated women with a history of preeclampsia in the fourth and fifth decade of life, when early signs of premature CVD are most likely to become apparent. Further studies are needed to inform new and improved clinical practice guidelines, and provide long-term strategies to effectively prevent CVD, specifically targeted at women with a history of preeclampsia. Additionally, evaluation of feasibility, cost-effectiveness and implementation of CVD screening and prevention initiatives targeted at former preeclampsia patients are needed.

1 Introduction

Preeclampsia is a leading cause of maternal and neonatal morbidity and mortality that affects up to 2-5% of all pregnancies. After delivery, preeclampsia usually resolves within a few days. However, the focus of research on preeclampsia is slowly shifting towards its long-term complications. In particular, a well-established association exists between preeclampsia and an increased risk of CVD later in life.[1-7] However, routine cardiovascular screening in women who have had preeclampsia is hindered by conflicting results on the prevalence of CVD risk factors postpartum and uncertainty about optimal timing, and the relatively unexplored role of female-specific risk factors. The aim of this review is to discuss the present knowledge, opportunities for and concerns of cardiovascular screening in women with a history of preeclampsia, in particular in view of new developments in risk factor assessment and cardiovascular imaging.

1.2 Preeclampsia: prevalence and definitions

Preeclampsia is defined as a syndrome consisting of gestational hypertension (systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation) coinciding with one or more of the following new-onset conditions: de novo proteinuria, maternal organ dysfunction or placental dysfunction.[8] About 3-5% of pregnancies are affected, and besides peripartum hemorrhage, preeclampsia is the second most important direct cause of maternal mortality worldwide.[9, 10]

1.3 Preeclampsia as an early indicator of cardiovascular risk

For most women affected by preeclampsia, including those cases with severe early-onset disease, clinical features resolve within days after delivery of the baby and placenta. In spite of the short-term clinical recovery, recent evidence consistently shows that long-term cardiovascular health in former preeclamptic patients is compromised. [1-7] Original cohort studies that have investigated the incidence of CVD events after preeclampsia are listed in Table 1. Outcomes of these studies have now been the subject of a number of excellent systematic reviews and meta-analyses. In summary, women who have been diagnosed with preeclampsia in any of their pregnancies have an approximated twofold risk of developing major CVD events (i.e. myocardial infarction and stroke) and an almost fourfold increased risk of developing hypertension compared with women who do not develop preeclampsia. It appears that CVD events following preeclampsia generally occur at a much younger age than in other women within the same population.[1, 4, 5, 11] In a recent study by our group, we estimated the onset of

hypertension, type 2 diabetes mellitus, myocardial infarction and stroke after preeclampsia to be on average 8-10 years earlier than in women with normal pregnancy outcomes.[12] The risk of CVD events is more pronounced in the subgroup of women with so-called *early-onset* preeclampsia (generally defined as preeclampsia occurring before 34 weeks of gestation).[4, 13] In these women, there is a 7- to 8-fold increased incidence of ischemic heart disease, cerebrovascular disease, and peripheral arterial disease later in life.[1, 6] The mechanisms underlying this increase in life-time cardiovascular risk are complex and much debated. Preeclampsia and atherosclerosis are likely to share common pathological features, including similar contributing risk factors (e.g. hypertension, obesity, inflammation), characteristic alterations of the vessel wall (intimal thickening, fat accumulation in middle to large arteries) and endothelial cell dysfunction.[14] One could argue that pregnancy serves as a "stress test" for cardiovascular health, and that preeclampsia is associated with temporary vascular compromise, which subsides after pregnancy but reappears with ageing as CVD later in life (see Figure 1). Following this hypothesis, preeclampsia may therefore be considered as a "red flag" and offer opportunities for early-life identification of high risk individuals, susceptible to premature atherosclerosis and CVD events, and serve as a potent risk marker to select a target population eligible for intervention trials at a young age to prevent further development of CVD. However, given the complexity and interaction of risk factors leading up to long-term increased CVD risk, as well as limited data on development of CVD risk over time (in particular in the fourth and fifth decade of life), the question arises how this information can best be used to design cardiovascular risk screening and prevention programs.

2 Screening for subclinical cardiovascular disease after preeclampsia

2.1 Estimation of global cardiovascular risk

Both the American Heart Association (AHA) and the European Society of Cardiology (ESC) recommend cardiovascular risk assessment in men and women from the age of 40 years onwards. Although the two guidelines agree on this recommendation, their proposed risk estimation algorithms differ: AHA promotes the use of the race- and sex-specific Pooled Cohort Equations, whereas ESC recommends the use of the Systematic Coronary Risk Evaluation Project (SCORE).[15, 16] These risk assessment tools overlap, apart from the parameters: race, high-density lipoprotein (HDL) cholesterol, stratification for the use of blood pressure lowering medication, which are only used in the Pooled Cohort Equations. Most CVD risk factor screening programs are based on these well-established algorithms, although there is growing evidence for sex-specific differences in risk factor prevalence and in their contribution to

development of CVD.[17, 18] In their latest recommendations, both U.S. and European guidelines now do include statements on cardiovascular risk assessment in women with a history of preeclampsia. The 2011 AHA guideline on prevention of CVD in women recommends to obtain a detailed obstetric history when a woman presents for the first time, and recommends to monitor and control CVD risk factors in women after a pregnancy complicated by preeclampsia.[19] However, no recommendations are made with respect to the questions of when to start screening, what targets to use, and what potential value a positive history of preeclampsia may have in improving risk classification.[15, 15, 16, 19] Similar, the 2014 AHA guideline on stroke also points towards the role of preeclampsia as a potential identifier of stroke risk. However, the practical recommendations are no different from the AHA guideline for CVD prevention in women.[20] More recently, in a multidisciplinary guideline from the Netherlands focused on cardiovascular risk management after reproductive disorders current evidence for the association between reproductive disorders – amongst which PE – and the development of CVD has been updated and evaluated.[21] The authors advise on specific screening after preeclampsia based on current global CVD risk assessment protocols and blood pressure measurement at regular intervals postpartum, but note a lack of strong evidence and absence of longitudinal studies addressing the development of cardiovascular risk over time.

2.2 Major and contributing CVD risk factors

Current evidence suggests that women with a history of preeclampsia show a high prevalence of major traditional CVD risk factors, as well as other contributing factors and non-traditional risk factors.[22-27] An overview of studies on established and novel CVD risk factors in women with a history of preeclampsia, including anthropometric measures, circulating markers and imaging modalities, is presented in Table 2. In a recent meta-analysis by Hermes et al. several traditional risk factors for CVD (glucose, insulin, triglycerides, total cholesterol, HDL-cholesterol, low-density lipoprotein (LDL) cholesterol and homocysteine levels) were confirmed to be associated with previous preeclampsia in comparison to same-age women with a history of an uncomplicated pregnancy.[28] Moreover, in a recent study, we found that it is not uncommon to find the presence of a combination of multiple independent major CVD risk among women with a history of early-onset preeclampsia within the first few years postpartum, with over half of women exhibiting 2 or more major risk factors and up to 20% of women with 3 or more major risk factors.[22] Despite these high prevalences, however, the estimated 10-year absolute risk of a cardiovascular event calculated by the Framingham Risk Score (FRS) was low for virtually all women.[22] This is explained by their relative young age, as these women are still

premenopausal and CVD event rates are low. It can be speculated that assessment of CVD risk based on FRS 10-year predictions is likely to substantially underestimate the actual risk and estimations of life-time risk may be more appropriate for these women.[29-32] In general, there is increasing support for the concept of using lifetime risk rather than the 10-year CVD risk, or the relative risk scores, in CVD screening programs, comparing individual CVD risk with the "ideal risk" of age-matched controls, to facilitate early identification of women at an increased risk of premature CVD. In addition, studies using surrogate endpoints of CVD, e.g. elevated carotid intima-media thickness (cIMT) and coronary artery calcium scoring (CACS), show more progression of subclinical atherosclerosis in women with a high lifetime cardiovascular disease risk compared with women with a low lifetime cardiovascular disease risk.[33, 34] Indeed, the recent update of the SCORE algorithm includes a specific relative risk chart for women to estimate lifetime risk, which can be helpful for clinicians.[30] In summary, in spite of increased attention for long-term follow-up after preeclampsia, effective and timely identification of women at risk of CVD remains a challenge. Tracking of CVD risk factor profiles after preeclampsia from the initial screening in the first years postpartum into the later stages of life is needed, and novel risk models that incorporate preeclampsia as a risk factor for CVD need to be developed.

2.3 Non-traditional markers of CVD risk

Because preeclampsia and CVD share common pathophysiological pathways, biomarkers used in prediction of preeclampsia might be useful in predicting CVD later in life. Novel cardiovascular biomarkers include markers associated with endothelial dysfunction and inflammation (intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-10 (IL-10), E-selectin), thrombosis (homocysteine, von Willibrand factor (VWF), fibrinogen, fibronectin, D-dimer, plasminogen activator inhibitor-1 (PAI-1), tissue plasminogen activator (tPA)), vasoconstriction (endothelin) and angiogenesis (vascular endothelial growth factor (VEGF), soluble Fms-like tyrosine kinase-1 (sFLT-1) and tumor necrosis factor alpha (TNF-a)).[35] Several of these markers have been shown to be elevated up to 20 years after pregnancy and may be involved in the pathogenesis of both preeclampsia and atherosclerosis, although the data are somewhat conflicting and heterogeneous.[24, 36] In a recent meta-analysis on biomarker levels in women with a history of preeclampsia, for most of these novel biomarkers a trend towards higher levels was found in women with a history of a hypertensive pregnancy compared with controls with normotensive pregnancies, although only homocysteine levels were shown to be significantly higher.[35] Despite initial promising observations in prospective cohort studies, the implementation of novel biological markers in

addition to the repertoire of traditional cardiovascular risk factors is still much debated and is not routinely recommended in clinical practice.[34, 37] It appears that for women, the contribution of novel markers to CVD risk stratification may be more promising than for men, as demonstrated by e.g. the recently developed Reynolds Risk Score for women that incorporates baseline CRP levels into the estimated CVD risk algorithm.[38] In a short-term follow-up study that included mostly term and mild cases of hypertensive disease in pregnancy tested 2.5 years postpartum, the Reynolds Risk Score and the more traditional risk algorithms (SCORE and Framingham Risk Scores), we more or less equivalent in estimating predicted 10-year CVD risk.[39] It will be interesting the see whether or not these risk algorithms perform differently in cohorts with longer-term (>10 years) postpartum follow-up, and whether or not novel risk markers (in particular inflammatory markers) may prove to be beneficial in improving CVD risk prediction in models specifically designed to predict CVD in women with previous preeclampsia.

2.4 Cardiovascular imaging

Recent advances in noninvasive cardiovascular imaging have enabled early detection of signs of subclinical atherosclerosis and indirect measures of arterial compliance.[40-42] This may be helpful as surrogate endpoints for intervention studies, as well as potentially add to global CVD risk assessment and guide treatment decisions.[43-47] Subclinical atherosclerosis is commonly assessed by carotid intima-media thickness (cIMT), coronary artery calcium score (CACS), coronary computed tomography angiography (CCTA) and cardiac magnetic resonance imaging (CMR).[5, 46-58] In recent years, some groups have started to evaluate these imaging techniques in former preeclampsia patients, as discussed below.

2.4.1 Carotid intima-media thickness

CIMT is associated with the development of atherosclerosis and serves as an early indicator of CVD risk.[59-63] In a recent study in adults aged under the age of 45 years variation in cIMT was shown to be an early independent marker of later-life first-time myocardial infarction or stroke, although with modest discriminative power (hazard ratio (HR) 1.40 per standard deviation (SD) increase in cIMT, 95% confidence interval (CI) 1.11 – 1.76).[64] Since preeclampsia appears to be associated with premature atherosclerosis, cIMT may be of particular interest for early detection of vascular abnormalities in these women. Current studies exploring cIMT in women with previous preeclampsia have shown mixed results. In most studies, cIMT is increased in women after an episode of a hypertensive pregnancy [5, 49-

51, 53, 55], although numbers are small and one study could not confirm these findings.[54] Furthermore, the added value of including cIMT in the current risk profiles in the general population is uncertain and it is not likely to improve risk classification.[15, 65] Given the limited data available, it is unknown to what extend cIMT contributes to risk classification in formerly preeclamptic women.

2.4.2 Coronary artery calcium score

Coronary artery calcium score (CACS) is a non-invasive measurement of subclinical coronary atherosclerosis using low-dose (1 milliSievert) computed tomography (CT) scanning of the coronary arteries without administration of an intravenous contrast medium. CACS is a strong and independent predictor of cardiovascular events.[66, 67] The additional value of CACS for CVD risk classification has mostly been demonstrated in asymptomatic persons with an intermediate risk of CVD, i.e. an estimated 10-year event risk of 5%-20% based on traditional cardiovascular screening.[46, 48, 68-73] Two retrospective cohort studies have evaluated CACS in women with a history of hypertensive pregnancy disorders, and both found a positive association between CACS and self-reported hypertension in pregnancy.[74, 75] There are no published prospective studies yet to evaluate CACS in previous preeclamptic patients. Although CACS is a non-invasive measurement, holds great promise as a CVD risk marker, and provides the most direct evidence for cardiovascular damage, radiation dose and costs should be taken into account when considering CACS for risk assessment. The value of CACS will probably only be evident in individuals above the age of 45 years, as calcification of atheromatous plaques occurs relatively late in the development of atherosclerosis. More recently, evaluation of early-stage coronary artery atherosclerotic lesions by coronary computed tomography angiography (CCTA) has been suggested. This technique may have the advantage over CACS of being able to identify non-calcified plaques, and estimate the total atherosclerotic burden of the coronary artery tree.[76-78] In a number of retrospective cohort studies, it was shown that with CCTA, even in persons with very low CACS, a substantial presence of non-calcified plaques (or “plaque burden”) can be found.[76, 79, 80] However, CCTA requires a higher radiation dose (3-4 milliSievert) and the use of intravenous contrast. To our knowledge, studies evaluating CCTA in women with a history of PE have not been conducted so far. Radiation dose, use of intravenous contrast material, and extra costs may limit the use of CCTA in younger age groups. In summary, there is growing interest in CACS and possibly low dose CCTA for CVD risk assessment in the general population.[44] CACS seems to be the most promising imaging marker and the AHA guideline now recommends considering CACS if the treatment decision is inconclusive based on global CVD risk assessment.[15]

2.4.3 Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) is a non-invasive imaging technique that enables detailed soft tissue characterization and can assess different parameters of cardiovascular function, as well as macrovascular and microvascular features of CVD without using ionizing radiation.[45, 81] In addition, enhancement of CMR with adenosine perfusion MRI (also called 'adenosine stress MRI') can be used to identify both ischemic coronary artery disease as well as non-obstructive coronary disease in symptomatic women without major plaques.[82] It is unclear whether or not there is a role for adenosine stress MRI in the detection of cardiac dysfunction in asymptomatic women. However, CMR can be used to identify macroscopic fibrosis with late gadolinium enhancement, and evaluate early (preclinical) myocardial fibrosis with so-called T1 mapping.[83, 84] In addition, CMR may be used as an alternative technique to evaluate aortic stiffness, which is strongly related to systolic hypertension and is associated with future cardiovascular events.[85, 86] Although sensitivity of CMR is high, the specificity is moderate for detecting major coronary artery lesions, and the availability and costs of CMR equipment currently limit large-scale use.[45] Another problem is the uncertainty of translating abnormal CMR findings observed at a young age to actual later-life CVD event risks, as longitudinal studies with sufficient follow-up time are not available. The use of CMR for screening purposes in asymptomatic, high-risk populations, such as women with a history of preeclampsia, needs to be further explored to establish a more conclusive role for CMR in the screening of CVD risk after preeclampsia.

3 Opportunities for prevention

Guidelines for CVD risk management increasingly include recommendations for cardiovascular prevention in women with a history of preeclampsia. However, and as demonstrated in this review, optimal screening and prevention in this high-risk group of young – apparently healthy – women still needs to be evaluated further.[16, 19, 21] In current practice, women who experienced preeclampsia are considered as "cured" after delivery and referred back to primary care without a plan for cardiovascular follow-up or prevention.[87] Question arises as to whether these women should be offered specific prevention strategies. Important to the debate on screening in this population is the observation that estimated 10-year CVD risks is low in this young age group despite multiple modifiable risk factors being present shortly postpartum. It seems rational to implement CVD screening and prevention on the basis of the expected high 'lifetime' risk of CVD in these women. However, uncertainties exist about the development and contribution of risk factors over time, and further efforts

are needed to evaluate progression of early-life risk exposures with ageing, in particular *after* the first 10 years postpartum (or roughly from the age of 40 years onwards), when actual signs of CVD are expected to occur. Another question arises as how to organize effective screening and intervention programs in these women. Currently, a few clinics have initiated postpartum CVD risk assessment and counseling for women with who experience (mostly severe) preeclampsia at six to twelve months postpartum, offering global CVD risk assessment and an advice on lifestyle modifications.[88] A recent report from Cusimano et al. (2014) describing the experiences of a recently set-up maternal health clinic for CVD risk assessment after pregnancy complications (including gestational hypertension and preeclampsia), suggests that women are highly motivated to optimize lifestyle in the postpartum period, although only 40% of the booked patients showed up at the initial appointment.[89-91] It may be useful to consider targeted clinics that incorporate self-management (and eHealth) applications to improve adherence to postpartum prevention programs in women with reproductive disorders. A multidisciplinary approach, frequent interactions, and a more integrated women's health approach to simultaneously target young women with reproductive disorders associated with increased CVD risk, e.g. women with polycystic ovary syndrome (PCOS), preeclampsia and premature ovarian failure, can be considered.[92][93]

4 Summary and conclusions

In spite of a call for increased attention for long-term CVD risks after preeclampsia, translating this knowledge to clinical practice and population health initiatives remains a challenge. In this review, we set out to provide an overview of current data on CVD risk screening after preeclampsia and have aimed to discuss new and promising screening modalities and important caveats in CVD risk stratification and implementation. Importantly, in our view, identification of women with high risk, i.e. those women who will benefit most from early screening and prevention measures, remains the key to successful postpartum intervention studies. Routine use of biomarkers and modern CVD imaging techniques holds promise in research settings, but needs to be further evaluated before being implemented in clinical practice. Improved lifestyle interventions programs, developed for the general population, in particular those making use of smart technologies, merit further investigation. Continuing awareness of the high risk of premature CVD after preeclampsia should be raised among patients, specialists, and general practitioners to promote healthy cardiovascular lifestyles and ensure timely detection of CVD.

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Table 1: overview of original cohort studies assessing CVD after preeclampsia

First author, year	Total study-population	Cases	Controls	Primary outcome	Follow up
Bhattacharya, 2011	34854	PE (n=2026), PIH (n=8891)	Normal blood pressure (n=23937)	CV event, IHD, stroke, hypertension (all fatal/non-fatal)	26 – 48 years
Callaway, 2011	2112	Hypertensive disorder of pregnancy (HDP, n=191)	No HDP (n=1921)	Hypertension	21 years (age at FU 46.41 years, SD 4.97 years)
Callaway, 2007	3639	HDP (n=333)	No HDP (n=3306)	DM, self-reported anthropometrics	21 years
Carr, 2009	31463	PE (n=2032)	No PE (n=29431)	DM	Median 8.2 years (IQ-range 4.8; 13.2 years)
Cassidy, 2009	498	HDP (n=52)	No HDP (n=446)	CAC score, CVD risk factors (hypertension, dyslipidemia), self-reported DM2, CHD, stroke	Mean 27 years
Engeland, 2011	226832	PE (n=8832)	No PE (n=215988)	Diabetes Mellitus	Mean 3.7 years (0-6 years)
Freibert 2011	3909	HDP (n=222) Preterm birth (n=324)	Pregnancy without complications (2558)	Self-reported non-fatal MI, AP, heart failure, arrhythmia	Unknown (age ≥ 50 years)
Funai, 2005	37061	PE (n=1070)	No PE (n=35991)	Fatal CV event	Median 30 years (24.5 – 36.5 years)
Garovic, 2010	4782	HDP (n=643)	Normotensive pregnancy (n=3421)	Fatal/non-fatal IHD, Non-fatal stroke, DM (all self-reported); hypertension, dyslipidemia	Unknown (median age ≥ 38 years)
Hannaford, 1997	214356	Toxemia (n=3000)	No toxemia (n=18451)	IHD & stroke (fatal/ non-fatal), hypertension	Unknown
Haukkamaa, 2009	767	PE (n=35), PIH (n=61)	Healthy parous (n=489) and nulliparous (n=182) controls	Non-fatal IHD, hypertension IMT, lipids, DM2	Unknown (≥ 30 years, mean age 55-57 years))
Henriques, 2014	60	PIH (n=30)	Uncomplicated pregnancy (n=30)	FMD anthropometric variables, metabolic	Mean 15.2 years (10 – 20 years, SD 3.5 years)

				variables	
Irgens, 2001	626272	PE term (21506), PE preterm (2649)	No PE, term (n=576099)	IHD & stroke (fatal)	0 – 25 years
Jonsdottir, 1995	7543	HDP (n=374)	General population (n=7169)	Fatal IHD	0 – 59 years
Kaaja, 2005	3559	PE (n=397)	No PE (n=3162)	DM2, dyslipidemia, hypertension, heart failure, AP	28 years
Kestenbaum, 2003	124141	PIH (n=10687), mild PE (n=15508), severe PE (n=5044)	Normotensive pregnancy (n=92902)	Fatal/non-fatal CV event	Mean 7.8 years (IQ-range 4.8; 7.6; 10.6 years)
Libby, 2006	7178	PE (n=810)	No PE (n=6377)	DM2	Unknown (median age 71 years, IQ-range 67; 75/76 years)
Lin, 2011	1132064	PE/eclampsia	No PE/eclampsia	Fatal/non-fatal CV event & MI, IHD	1 – 6 years
Lykke, 2010	782287	PIH (n=7449), Mild PE (26810), Severe PE (n=7016)	No hypertensive disorder (n=741012)	CV event (fatal), IHD & stroke (fatal/ non-fatal) hypertension, DM	Median 14.8 years (0.25 – 30.2 years)
Magnussen, 2009	15065	HDP (n=1433)	No HDP (n=13632)	Hypertension, DM2, dyslipidemia	Mean 16.3 – 16.6 years (SD 8.2 years)
Mongraw, 2010	14403	PE (n=481)	No PE (n=13922)	Fatal CV event	Median 37 years
Ray, 2005	1026265	PE (n=36982), PIH (n=20942)	No maternal placental syndrome (n=950885)	Fatal/non-fatal CV event	Median 8.7 years
Shalom, 2013	22814	HDP (n=2072)	No HDP (n=20742)	Hypertension Any relevant hospitalization	10-12 years
Skjaerven, 2012	836147	All PE (n=34824) - Term PE (n=26708) - Preterm PE (n=5886)	All no PE (n=801323) Term no PE (n=712181)	Fatal CV event	7 – 42 years
Smith, 2001	129920	PE (n=22781)	No PE (n=107139)	Fatal/non-fatal IHD	15 – 19 years
Wang, 2011	5807	HDP (n=1092)	No HDP (4715)	Fatal/non-fatal stroke	Mean 6.64-6.4 (SD 1.57

					years)
Wikstrom, 2005	403550	Hypertensive disease (n=20469) - PIH (n=9718) - mild PE (n=9718) - severe PE (n=2815)	Uncomplicated pregnancy (n=347870)	Fatal/non-fatal IHD	14 years (?)
Wilson, 2003	2790	PIH (n=951) PE (n=1043)	No HDP (n=796)	Fatal/non-fatal IHD, stroke, hypertension, VTE and kidney disease	10 – 48 years
Wu, 2014	944474	HDP (n=13633) - PIH (n=2361) - chron hypertension (n=731) - PE (n=8609) - superimposed PE (n=594)	No HDP (n=13633)	ESRD, DM2	Median 9 years (IQ-range 7.09-10.02 years)

LPE = preeclampsia, PIH = pregnancy induced hypertension, HDP = hypertensive disorders of pregnancy, PCOS = polycystic ovary syndrome, POI = primary ovarian insufficiency, CV = cardiovascular, CVD = cardiovascular disease, IHD = ischemic heart disease, CHD = coronary heart disease, MI = myocardial infarction, AP = angina pectoris, IMT = intima media thickness, FMD = flow-mediated dilatation, ESRD = end-stage renal disease, CAC score = coronary artery calcium score, VTE = venous thromboembolism, IQ = inter quartile, SD = standard deviation

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Table 2: items used in cardiovascular screening

Level or occurrence of items compared to healthy women

Screening method	Short term (< 5 years)	Long term (> 5 years)
Items commonly used in CVD risk assessment		
Gender	n.a.	n.a.
Age	n.a.	n.a.
Race	Unchanged[1]	Unknown[2]
Total cholesterol	Increased in most studies[1, 3-5]	Unchanged or marginally increased in most studies[3, 6-13]
HDL cholesterol	Decreased in most studies[1, 3-5]	Unchanged or marginally decreased in most studies[3, 6-14]
Systolic BP	Increased in most studies[1, 3-5][15-17]	Increased in most studies[2, 3, 6-13, 18]
BP medication	Increased[15]	Increased[3, 6-13]
Diabetes	Unchanged[1]	Unchanged[2]
Smoking	Unchanged[6][15]	Inconclusive (unchanged or decreased)[4, 17]
Metabolic syndrome	Increased[2, 3, 6-13]	Increased[1]
Family history of CVD	Unchanged[6]	Increased in most studies[4, 15]
BMI	Increased in most studies[3, 6-13]	Inconclusive (unchanged or increased)[1, 4, 5, 15, 17]
Triglycerides	Unchanged in most studies[2, 3, 6-13]	Unchanged or marginally increased[1, 4, 5]
Glucose	Increased in most studies[2, 3, 6-14]	Inconclusive (unchanged or increased)[1, 3-5]
HbA1c	Unknown	Inconclusive (unchanged or increased)[2, 3, 6-13]
Non-classic biomarkers		

CRP	Inconclusive (unchanged or increased)[3, 6, 12]	Inconclusive (unchanged or increased)[3, 5]
Fibrinogen		Unchanged[2, 3, 6-11, 11-14]
ICAM **	Unchanged[6]	Unchanged[19]
VCAM **	Unchanged[19]	Inconclusive (unchanged or increased)[19]
Homocysteine **	Increased[12, 19]	Increased[4, 19]
VWF **	Inconclusive (unchanged or increased)[19]	Inconclusive (unchanged or increased)[19]
Fibrinogen **	Inconclusive (unchanged or increased)[19]	Inconclusive (unchanged or increased)[19]
Imaging modalities		
IMT	Increased[12, 19]	Inconclusive (unchanged or increased)[4, 5]
FMD	Decreased[8-10, 12, 20, 21]	Unchanged[5]
CACS	Not performed	Increased[12]
cCTA	Not performed	Not performed
CMR	Not performed	Not performed
Other modalities		
ECG		Inconclusive (unchanged or increased)[13, 22]

** controls nulliparous healthy controls; ** used in meta-analysis*

LHDL-cholesterol = high-density lipoprotein cholesterol, BP = blood pressure, CVD = cardiovascular disease, BMI = body-mass index, HbA1c = hemoglobin A1c, CRP = c-reactive protein, ICAM = intercellular adhesion molecule, VCAM = vascular cell adhesion molecule, VWF = von Willibrand

factor, IMT = intima-media thickness, FMD = flow-mediated dilatation, CACS = coronary artery calcium score, CCTA = coronary computed tomography angiography, CMR = cardiac resonance imaging, ECG = electrocardiography

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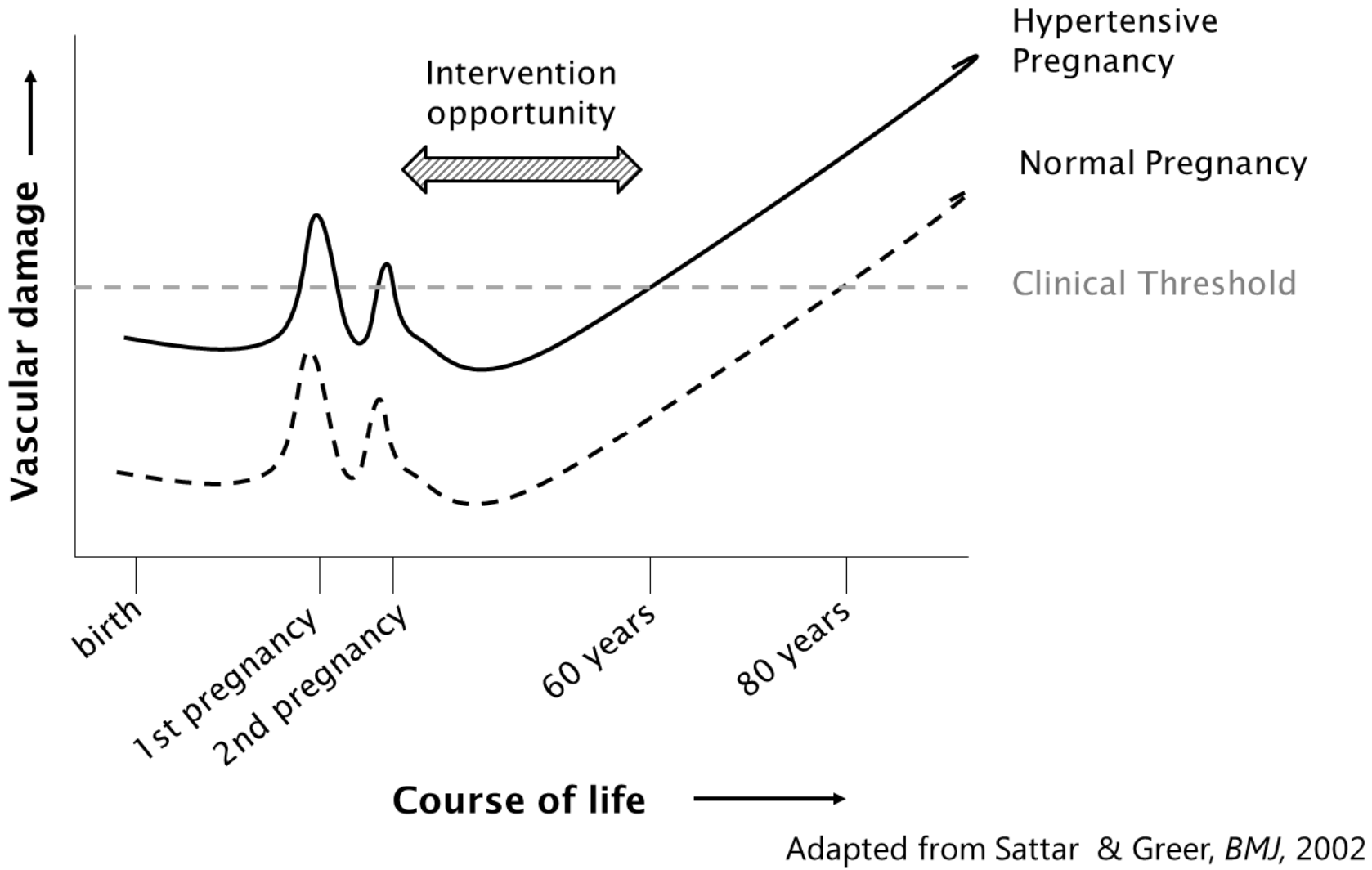
1 **Figure 1: preeclampsia and CVD**



Adapted from Sattar & Greer, *BMJ*, 2002

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