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REVIEW

Shared biomarkers between female diastolic heart failure and pre-eclampsia: a systematic review and meta-analysis

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Abstract

Evidence accumulates for associations between hypertensive pregnancy disorders and increased cardiovascular risk later. The main goal of this study was to explore shared biomarkers representing common pathogenic pathways between heart failure with preserved ejection fraction (HFpEF) and pre-eclampsia where these biomarkers might be potentially eligible for cardiovascular risk stratification in women after hypertensive pregnancy disorders. We sought for blood markers in women with diastolic dysfunction in a first literature search, and through a second search, we investigated whether these same biochemical markers were present in pre-eclampsia.This systematic review and meta-analysis presents two subsequent systematic searches in PubMed and EMBASE. Search I yielded 3014 studies on biomarkers discriminating women with HFpEF from female controls, of which 13 studies on 11 biochemical markers were included. Cases had HFpEF, and controls had no heart failure. The second search was for studies discriminating women with pre-eclampsia from women with non-hypertensive pregnancies with at least one of the biomarkers found in Search I. Search II yielded 1869 studies, of which 51 studies on seven biomarkers were included in meta-analyses and 79 studies on 12 biomarkers in systematic review.Eleven biological markers differentiated women with diastolic dysfunction from controls, of which the following 10 markers differentiated women with pre-eclampsia from controls as well: C-reactive protein, HDL, insulin, fatty acid-binding protein 4, brain natriuretic peptide, N terminal pro brain natriuretic peptide, adrenomedullin, mid-region pro adrenomedullin, cardiac troponin I, and cancer antigen 125.Our study supports the hypothesis that HFpEF in women shares a common pathogenic background with pre-eclampsia. The biomarkers representing inflammatory state, disturbances in myocardial function/structure, and unfavourable lipid metabolism may possibly be eligible for future prognostic tools.

Keywords Cardiac risk factors and prevention; Heart failure with preserved ejection fraction; Pre-eclampsia; Pathogenic biomarkers; Meta-analysis; Systemic review

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All authors take the responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Introduction

Cardiovascular disease (CVD) is the main cause of mortality in the Western world, and its prevalence worldwide is growing. The diagnosis of CVD is often delayed in women due to differences in clinical presentation and underlying pathophysiology compared to the male standard.[1–4] From post-menopausal age on, more women than men suffer from CVD.[4,5] Heart failure with preserved ejection fraction (HFpEF) is a common female manifestation of CVD at advanced age and forms a significant and growing public health burden. Diagnosis of HFpEF is challenging because of its long asymptomatic course.[6–8] Recent literature suggests biomarkers of inflammation, myocyte stress, and extracellular remodelling as

possible screening instruments specifically for HFpEF.[9,10] Early identification and treatment of women in high-risk groups could prevent this debilitating disease later in life.

Women with a history of a hypertensive pregnancy disorder, including pre-eclampsia, have an elevated cardiovascular risk.[11–13] In recent decades, pregnancy has been hypothesized as a cardiovascular stress test revealing elevated susceptibility for CVD at a relatively young age.[13] During pre-eclampsia, the clinical threshold for CVD is exceeded, and the biomarker profile in pre-eclamptic pregnancies may thus be an early reflection of the biochemical imbalance in CVD at advanced age. In consistency with this theory, recent literature has shown an increase of established CVD biomarkers in women during and after pre-eclampsia.[14–16] The incidence of HFpEF is higher in women than in men; therefore, we attend to the possibility of a shared pathogenic background with pre-eclampsia.

It has been hypothesized that women with hypertensive pregnancy disorders would be eligible for CVD preventive healthcare programmes. Currently, evidence is lacking on how to accurately map these women's cardiovascular status, and little is known about the common pathogenic mechanisms in pre-eclampsia and CVD.[12] Broader knowledge on the shared pathogenic pathways may provide biochemical markers with high sensitivity and specificity for the detection of (subclinical) CVD, and in particular HFpEF, in affected high-risk women.

The aim of this systematic literature review and meta-analysis was therefore to explore what is currently known in literature about shared biomarkers identifying both women with early signs of HFpEF and women with pre-eclampsia to unravel a shared pathogenic background and reveal biomarkers with possible future potential for HFpEF screening after pre-eclampsia.

Methods

So as to find corresponding biomarkers for diastolic heart failure (DHF) in women and pre-eclampsia, two subsequent, closely linked searches were performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Complete search queries are presented in the Supporting Information.

Search I: diastolic heart failure

Definitions

Definition of HFpEF was described in the guidelines of the European Society of Cardiology.[17] Briefly, two characteristics had to be apparent at echocardiography: firstly, evidence of left ventricular diastolic dysfunction; tissue Doppler E/E' >15 or 15> E/E' >8 and confirmation by blood flow Doppler or mitral valve/pulmonary veins, echo measures of left ventricular mass index/left atrial volume index, or electrocardiographically confirmed atrial fibrillation. Secondly, left ventricle systolic dysfunction had to be normal/mildly abnormal with left ventricular ejection fraction >50% and left ventricular end-diastolic volume index <97 mL/m^2.

Search strategy

A search in PubMed and EMBASE was performed from inception on 13 July 2015 that consisted of the following terms and a wide variety of their synonyms: DHF or preserved ejection fraction and biomarker.

Study selection

Eligible for inclusion in Search I were case-control and cohort studies comparing biomarker levels in women with DHF vs. women without heart failure or studies correlating biomarker levels with diastolic function through regression analysis. Studies were included if performed exclusively in women or if data were completely stratified by gender. Studies investigating patient groups with structural heart diseases or comorbidities unrelated to metabolic syndrome or heart failure were excluded.

Included studies were processed by a scoring form developed by three reviewers (L. A., A. B., and C. d. G.). Data extraction and scoring per article for disease definition, study design, patient and control group characteristics, biomarkers, blood sample collection and analysis was performed by L. A. and verified by A. B. The same reviewers independently scored bias risk and applicability concern for each included study according to the QUADAS-2 quality assessment tool for primary diagnostic accuracy studies.[18] Any fundamental inconsistencies were discussed with C. d. G.

Outcomes of interest

Primary outcomes were biomarkers in blood separating women with HFpEF from women without heart failure. The result of Search I, a list of biomarkers significantly different ($P < 0.05$) in HFpEF vs. controls, was taken along to Search II where primary outcomes were biomarkers in pre-eclampsia.

Search II: pre-eclampsia

Definitions

Pre-eclampsia was defined according to International Society for the Study of Hypertension in pregnancy criteria as de novo hypertension of ≥140/90 mm Hg in combination with proteinuria >0.3 g/24 h after 20 weeks gestational age.[19] To prevent unnecessary exclusion of older studies, pre-eclampsia could also be defined as a rise of systolic blood pressure >30 mm Hg or diastolic blood pressure >15 mm Hg with proteinuria in women with no history of chronic hypertension.[20] Early-onset, or severe, pre-eclampsia was defined as delivery before 34 weeks of gestation or blood pressure

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≥160/110 mm Hg or proteinuria >5 g/24 h. Late-onset, or mild, pre-eclampsia implied giving birth from 37th week of gestation.

Search strategy

We performed a search in PubMed and EMBASE from inception on 1 September 2015. The search strategy contained two components: (1) biomarkers for HFpEF in women from Searches I and II) pre-eclampsia. So as to fully explore the pathway of mid-region pro ADM (MRproADM), studies on its fully modulated version adrenomedullin (ADM) were also included in this review, leaving a total of 12 markers for Search II. Thus, the following terms with their synonyms and abbreviations were used: troponin I or brain natriuretic peptide (BNP) or N-terminal pro-BNP (NTproBNP) or high-density lipoprotein (HDL) or cancer antigen 125 (CA-125) or carcino-embryonic antigen (CEA) or C-reactive protein or ADM or MRproADM or fatty acid-binding protein 4 (FABP4) or insulin or glucose and pre-eclampsia.

Study selection

Case-control and cohort studies comparing pre-eclamptic with non-hypertensive pregnancies were eligible for inclusion in Search II. Biomarker levels had to be measured during pregnancy, and it had to be ≥1 of the biomarkers from Search I. To gain only data on pre-eclampsia, the studies that did not separate pregnancy-induced hypertension (without proteinuria) from pre-eclampsia and studies failing to exclude women with chronic hypertension were not incorporated in this review. Studies presenting their data in the right measurement unit and using mean with standard deviation/standard error to describe biomarker levels were eligible for meta-analysis.

Data extraction and determination of study characteristics, bias, and applicability was performed as in Search I.

Outcomes of interest

Primary outcomes were biomarkers differentiating pre-eclamptic from non-hypertensive pregnancies. Where possible, we performed subgroup analyses for biomarker levels in 'early-onset/severe', 'late-onset/mild' pre-eclampsia and in different pregnancy trimesters (most subgroup analyses are presented in the Supporting Information).

Data synthesis

Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) was used for meta-analyses. All data were continuous, and only raw numbers were used from the studies. Biomarkers' measurement units were converted according to the International System of Units (SI). A standardized mean difference was chosen for inconvertible measurement units. Weighting of studies was carried out by inverse variance so that larger studies would be given more weight than smaller ones and all analyses were performed with a randomized effect model because heterogeneity was to be expected. Heterogeneity was determined by I^2. GraphPad Prism 6 (GraphPad Software, San Diego California, USA) was used to visualize data and compare the group of means plus medians together through unpaired *t*-test or one-way ANOVA. Confidence intervals throughout this whole review were set at 95%, and for all effect estimates, statistical significance level was $P < 0.05$.

Results

Literature identification and study quality

The process of study inclusion and exclusion in systematic review and meta-analysis is depicted in *Figure 1*.

Search I Thirteen studies on biomarkers in HFpEF in women were included for systematic review, and we had insufficient results for meta-analysis. The included studies described 11 HFpEF markers in total: BNP NTproBNP, cardiac troponin I (c-Tn1), MRproADM, c-reactive protein, HDL, insulin, plasma glucose, FABP4, CA-125, and CEA. For reasons mentioned earlier, we added ADM, leaving 12 biomarkers for Search II.

Search II The search for biomarkers in HFpEF (Search I) and pre-eclampsia yielded 79 studies for systematic review of which 51 (on BNP, ADM, C-reactive protein, HDL, insulin, plasma glucose, and CA-125) were applicable for meta-analyses. We present most subgroup analyses on biomarkers in 'early onset/severe' or 'late onset/mild' in the Supporting Information.

Study characteristics

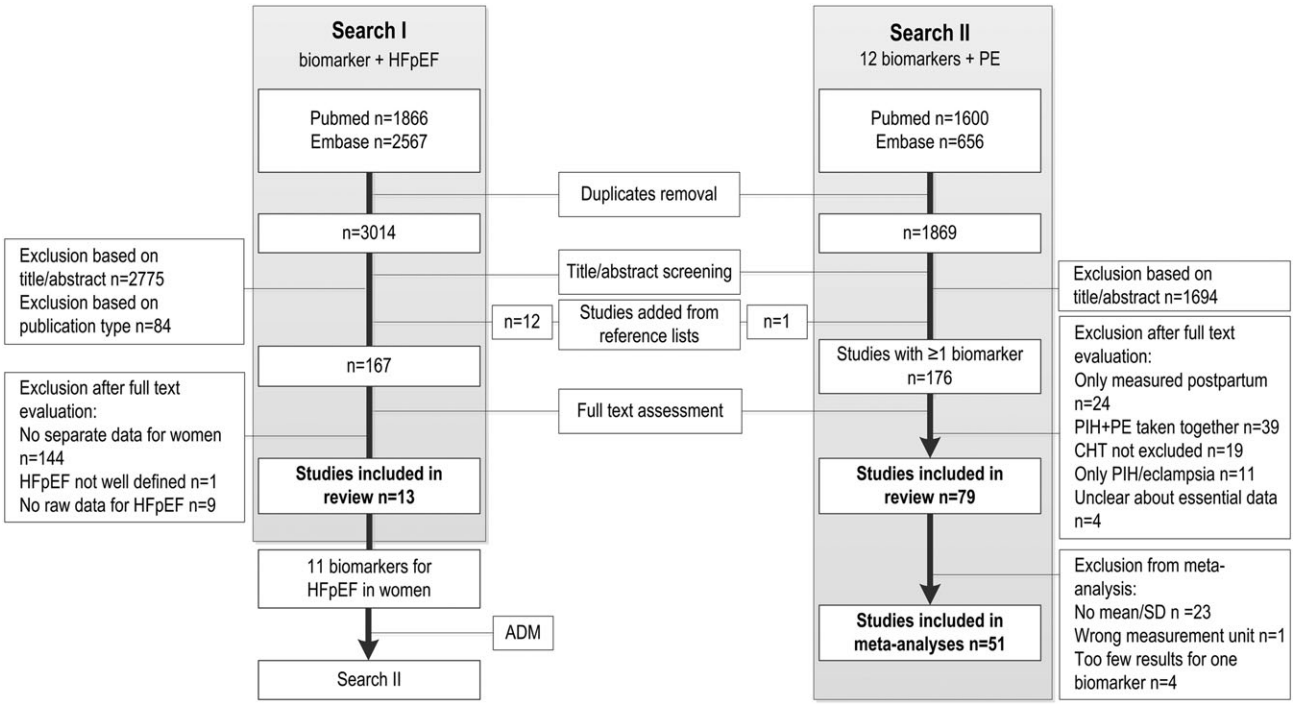
Characteristics of all included studies are presented in the Supporting Information, *Tables S1* (DHF) and *S2* (PE). Included studies were published between 1996 and 2015. With the QUADAS-2 score for study quality and applicability, 8.6% of all included studies got assigned a high and 28.6% an unclear bias risk. Furthermore, applicability concern was high in 28.5% and unclear in 33.5%. QUADAS-2 subsections are further visualized in the Supporting Information *Figure S2* in Data in Brief.

Cardiovascular risk markers in pre-eclampsia

C-reactive protein

Thirty-two studies in total reported on C-reactive protein levels,[21–52] of which 17 were applicable for meta-analysis.[21–23,29–34,37–39,41,42,47,49,50] A significantly higher C-reactive protein was found in women with pre-eclampsia than in non-hypertensive controls (*Figure 2*), and

Figure 1 Study selection process Searches I and II. CHT, chronic hypertension; HFpEF, heart failure with preserved ejection fraction; PE, pre-eclampsia; PIH, pregnancy-induced hypertension.



this correlation was stronger in severe than in mild pre-eclampsia (*Figure 3*).

High-density lipoprotein

Twenty-seven studies reported on HDL levels,[32,37,41,44,53–74] of which 24 studies could be included in a meta-analysis.[32,37,41,53–72] HDL level was lower in pre-eclampsia than in controls (mean difference −6.29 mmol/L; 95%CI −9.74−2.85; P = 0.0003) with the strongest effect in subgroup analysis for severe pre-eclampsia vs. controls (*Figure 4*).

Insulin, plasma glucose, and fatty acid-binding protein 4

Five studies reported on insulin levels.[37,45,55,62,75] Three met the requirements for a meta-analysis,[37,55,75] revealing higher insulin levels in pre-eclampsia than in controls with mean difference 1.31 μU/mL; 95%CI 0.93–1.70; $P < 0.00001$. Two studies reporting in median (IQR) revealed similar slightly elevated insulin levels in pre-eclampsia.[45,62]

Six studies reported on plasma glucose levels,[32,45,62,65,75,76] of which five were applicable for meta-analysis with 115 pre-eclampsia cases vs. 329 controls.[32,62,65,75,76] Overall, a non-significantly elevated glucose level was seen in pre-eclampsia vs. controls.

One study reported on FABP4 levels in pre-eclampsia compared with controls and found statistically higher FABP4 levels in pre-eclampsia vs. non-hypertensive pregnancy.[77]

Myocardial failure markers in pre-eclampsia

Brain natriuretic peptide and N-terminal pro-BNP

Seven studies reported on BNP levels,[78–84] of which three were applicable for a meta-analysis (*Figure 5*).[78–80]

In all seven studies and in meta-analysis, BNP levels were significantly higher in pre-eclampsia than in controls. Subgroup analyses revealed higher BNP levels for severe pre-eclampsia vs. control as well as severe vs. mild pre-eclampsia, P-values 0.0023 and 0.0391, respectively.

Three studies reporting on NTproBNP described elevated levels in pre-eclampsia vs. controls with P = 0.0103 (*Figure 6*),[85–87] with insufficient studies for meta-analyses.

Adrenomedullin, mid-region pro ADM, and cardiac troponin I

Seven studies reported on ADM levels,[88–94] of which five met the requirements for meta-analysis.[88–91,94] However, because these worked with inconvertible measurement units, two separate meta-analyses with inconsistent results were carried out. The first showed lower ADM in pre-eclampsia; mean difference −5.60 pmol/L; 95%CI −14.76–3.55; P = 0.23.[88,91,94] The second meta-analysis showed higher ADM in pre-eclampsia; mean difference 41.44 pg/mL; 95%CI 12.58–70.31; P = 0.005.[89,90] The two studies inapplicable for meta-analysis showed higher levels of ADM in pre-eclampsia vs. control.[92,93]

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Figure 2 C-reactive protein, pre-eclampsia vs. controls.

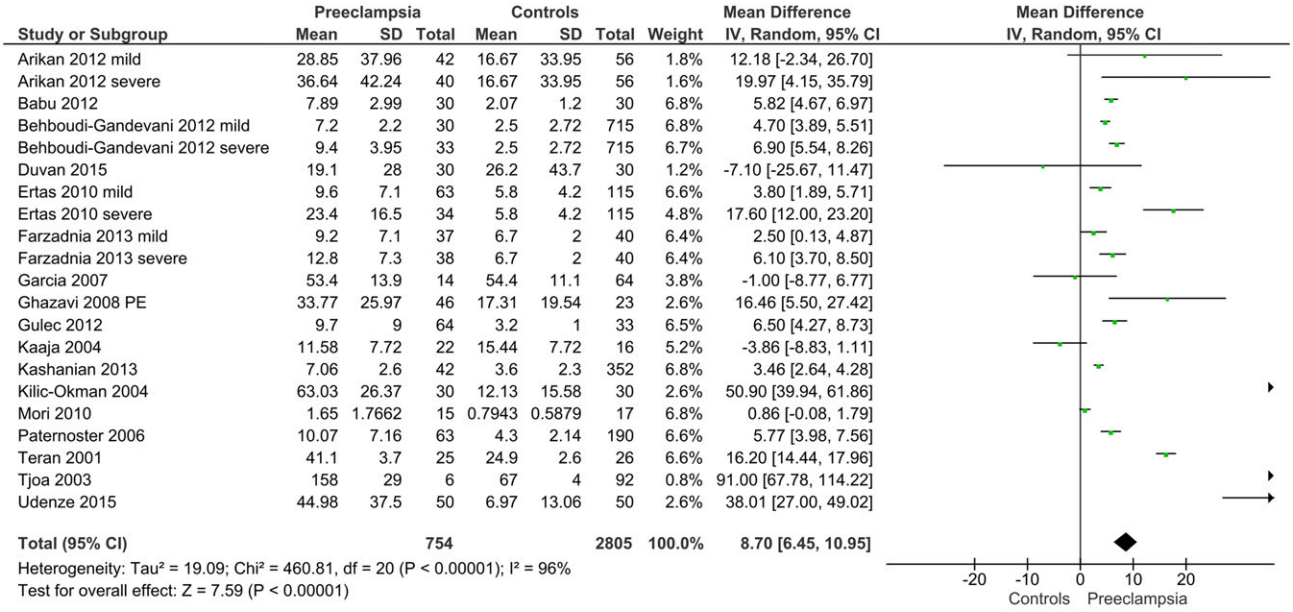


Figure 3 C-reactive protein, mild vs. severe pre-eclampsia.

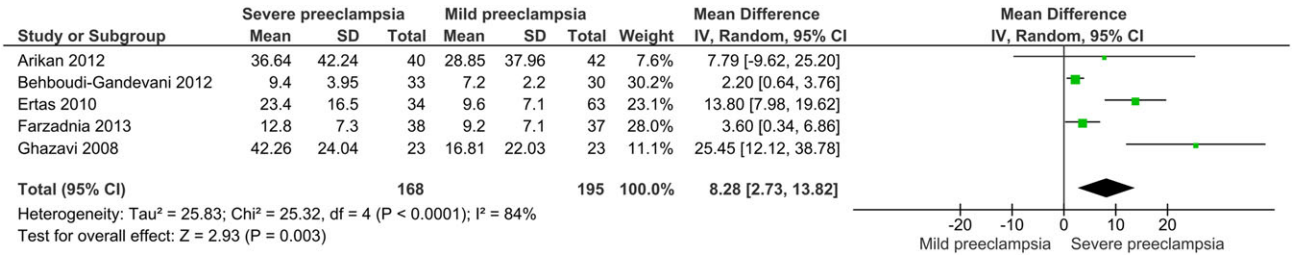
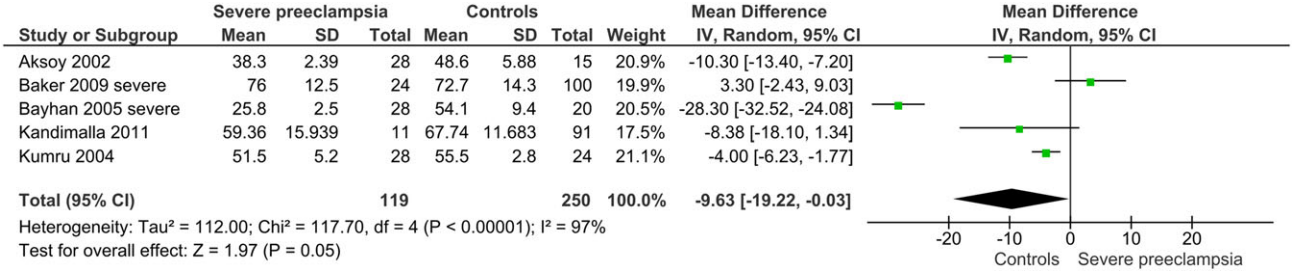


Figure 4 High-density lipoprotein, severe pre-eclampsia vs. controls.



Two studies on MRproADM described significantly higher levels in pre-eclampsia vs. controls.[95,96]

Two studies on c-Tn1 described elevated levels in pre-eclampsia compared with controls,[97,98] of which only one with statistically significant result.[97]

Tumour angiogenesis markers in pre-eclampsia

Cancer antigen 125 and carcino-embryonic antigen

Three studies reported on CA-125 levels in pre-eclampsia vs. controls,[26,99,100] of which two studies described significantly

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Figure 5 Brain-natriuretic peptide, pre-eclampsia vs. controls.

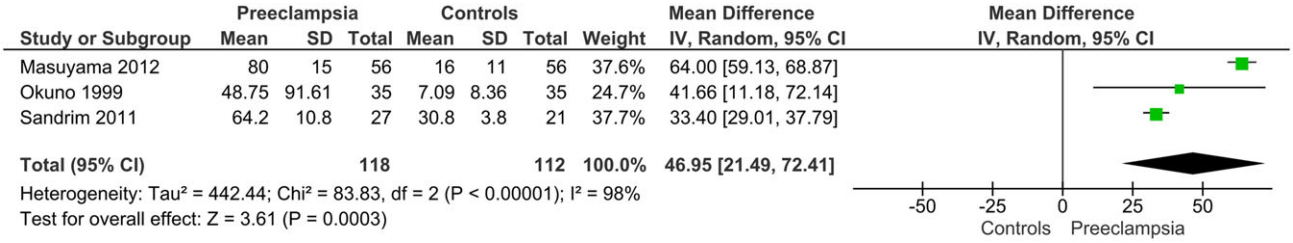
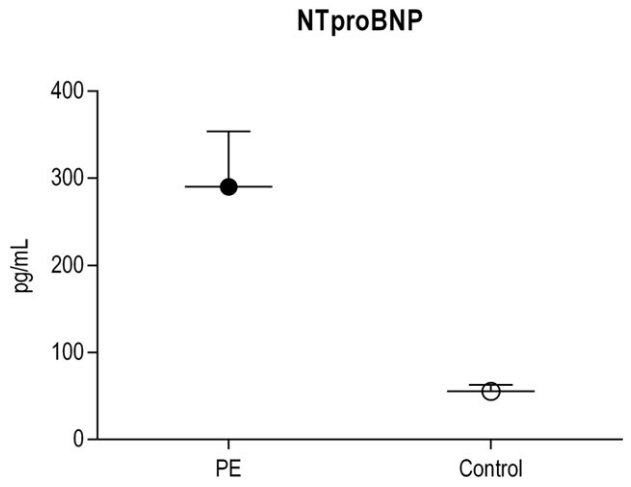


Figure 6 N-terminal pro-brain natriuretic peptide, pre-eclampsia vs. controls.



lower CA-125 levels in PE[99,26] and one did not show significantly different CA-125 levels between pre-eclampsia and controls.[100]

No studies exploring the CEA levels in pre-eclamptic vs. non-hypertensive pregnancies were found in our systematic literature search.

Discussion

Main findings

This systematic review and meta-analysis presents 10 biomarkers that both discriminate women with HFpEF from controls and discriminate women with pre-eclampsia from healthy pregnant women (C-reactive protein, HDL, insulin, FABP4, BNP, NTproBNP, ADM, MRproADM, c-Tn1, and CA-125) and thereby gives insight into a possibly common pathophysiology. We found a shared range of biomarkers which support the hypothesis that cardiovascular decompensation during a challenging phase such as pregnancy might be considered an early reflection of a metabolically and biochemically predisposed system for CVD. These markers may inspire future research on HFpEF screening programs after pre-eclampsia, and inflammatory markers may therein play a particularly important role.

Strengths and limitations

One of the strongest points of this review is that we analysed only the data on women. In recent decades has become clear how men and women differ in many manifestations of CVD including clinical picture, age of onset and diagnostic possibilities.[1,3,5] Because this is a relatively recent insight, we currently lack female-only data in for example cardiovascular risk management.

This broad literature search had a unique design transcending medical specialties: we composed a biomarker profile for women with HFpEF from all current literature and subsequently tested the existence of these same markers in women with pre-eclampsia; to our knowledge, this was the first systematic review in such direction. Furthermore, search and selection criteria, data extraction forms, and applicability scoring methods were developed by multiple investigators after careful consideration.

Selection bias was avoided as much as possible. Firstly, Search I had a wide design with no specific biomarkers in the search string. This allowed all possible biomarkers on HFpEF in literature to be selected for the review. Secondly, all studies from the DHF search that met the criteria 'DHF' and 'biomarker' were screened full text to see whether data for women were separately displayed. Thus, even if the authors' main focus was not on female biomarkers for DHF, as long as they displayed the data separately, the article could still be included in our review. Unfortunately, many HFpEF studies failed to present female data separately and had to be excluded after full text exploration. It is thus important for future studies on CVD to report by gender.

This review had some limitations regarding the characteristics of included studies. For instance, studies presenting data in median (IQR) were not compatible for meta-analysis. Moreover, not all studies could be taken into the same (meta-)analyses because of heterogeneity regarding measurement units, stratification methods, and ways of data presentation. Primary study outcomes especially varied greatly between DHF

studies, which stood in the way of performing a meta-analysis on the biomarker levels in DHF. If meta-analyses were applicable, they were often characterized by high heterogeneity. This might be partly explained by a methodological limitation because we included studies with older, and thus slightly different, definitions of pre-eclampsia. Another partial explanation for heterogeneity, which is hard to get a grip on, is the fact that most studies failed to report on pre-eclampsia disease status on moment of blood sampling. Lastly, some studies gave insufficient information on study design including inter-/intra assay variance, fasting state of the participants, maternal age, and gestational age at delivery.

There were also limitations regarding the design of current review. Firstly, this review only focused on biomarkers analysed during pregnancy to extrapolate markers that embody an evidently unbalanced cardiovascular system. Our study design was unable to determine whether (shortly) after hypertensive pregnancy the cardiovascular system returns to normal state or whether the biomarker levels remain elevated. Secondly, we focused on pre-eclampsia and not on pregnancy-induced hypertension without proteinuria, which is thought to be a different disease entity and might therefore yield a different view on cardiovascular risk prediction after hypertensive pregnancy. Thirdly, the markers we investigated are specific for HFpEF in women, which only partly cover one CVD. Despite the fact that HFpEF is one of the main CVD entities in women and it has a long subclinical course, it would be interesting to investigate whether other typical female CVDs, such as cerebrovascular accident, thrombo-embolism, and myocardial infarction at advanced age, are linked to pre-eclampsia through the same pathophysiological pathways as we found. Finally, this review does not cover women who have such serious cardiovascular malfunction that they fail to become pregnant in the first place and thus, by their nature, never develop pre-eclampsia.

Implications and future research

Current systematic review and meta-analysis presents representative biomarkers from several pathophysiological pathways in HFpEF as well as pre-eclampsia. This information might in future be implemented in prediction of cardiovascular risk in women with a history of pre-eclampsia through pathway activity screenings.

C-reactive protein appeared the biomarker best able to discriminate between all pre-eclampsia vs. controls, sampling trimesters, and pre-eclampsia severity subgroups. These findings accentuate the role inflammation plays in both female HFpEF and pre-eclampsia and suggest the possible use of C-reactive protein in cardiovascular risk screening in pregnancies complicated by hypertension. The inflammatory component of HFpEF has been mentioned previously,[10,101] with for example IL-6, TNF-α, interleukin receptors, and pentraxin 3 as potential HFpEF biomarkers.[10,102–105] To our knowledge, gender-specific data on this topic are currently lacking; thus with our women-only designed search, we probably overlooked a number of studies on inflammatory markers in HFpEF.

Brain natriuretic peptide and NTproBNP measurements have already been implemented in diagnostic criteria for HFpEF[17]. We found BNP and NTproBNP to be elevated in pre-eclampsia, which suggests a possible role for these biomarkers in screening for HFpEF specifically after PE. The absolute difference in BNP levels for pre-eclampsia vs. controls is smaller than for HFpEF vs. controls, suggesting a more subtle role for BNP in pre-eclampsia than in HFpEF. Nevertheless, elevated BNP and NTproBNP levels in pre-eclampsia indicate similar cardiac overstretching in pre-eclampsia as in DHF. In broader perspective, BNP levels in heart failure with reduced ejection fraction (HFrEF) usually exceed levels in HFpEF;[111,112] thus, BNP elevation in pre-eclampsia suggests that the disease gives higher risk to systolic heart failure or a mixed heart failure image. Elevated c-Tn1 levels in pre-eclampsia are directly suggestive of cardiomyocyte damage, whereas elevated ADM, MRproADM, BNP, and NTproBNP levels in pre-eclampsia suggest a compensatory mode in hypertensive pregnancy to protect the cardiovascular system from any further damage.

Despite the fact that only one study reported on higher FABP4 in pre-eclampsia, it might still be an interesting biomarker for HFpEF after PE, because recent literature describes this adipocyte fatty acid transporter as a key player between metabolic syndrome, inflammation, atherosclerosis, and CVD.[106]

Cancer antigen 125, a serosal glycoprotein antigen inter alia found on female reproductive tract epithelia, is a marker used for detection and clinical follow-up of several malignant and non-malignant serosal pathologies.[107,108] In two separate articles, it has been suggested that it may also function as a marker in both our entities of interest: pre-eclampsia[99] and heart failure,[109] our results support this view. The pathophysiology for CA-125 elevation in both pre-eclampsia and heart failure is difficult to address because a great variety of cell types produces CA-125.[110] The low specificity of CA-125 calls out for further research on the source of secretion in pre-eclampsia and heart failure before possible implementation in screening.

From this review, we can interpret that screening for HFpEF in women with a history of pre-eclampsia would have to include multiple biomarkers representing a variety of pathogenic pathways: firstly, because biomarker levels sometimes overlapped between cases and controls; and secondly, because numerous pathophysiological processes appeared to play part in both disease entities. So as to facilitate future screening within the shared pathogenic pathways between pre-eclampsia and HFpEF, longitudinal research is necessary to learn more about the course of representative biomarker levels over time and in relation to the developing clinical status before implementation into clinical practice would be possible.

Conclusions

Ten of the biomarkers differentiating women's HFpEF from controls, differentiated between pre-eclampsia and controls as well: C-reactive protein, HDL, insulin, FABP4, BNP, NTproBNP, ADM, MRproADM, c-Tn1, and CA-125. Our data suggest that there is a shared biomarker profile in HFpEF and pre-eclampsia and support the hypothesis that these disease entities share an intrinsic, vulnerable cardiovascular system with properties of metabolic syndrome and an elevated inflammatory state. Pre-eclampsia might be considered an early signal of underlying CVD. With this review and meta-analysis, we present biomarkers with potential for future implementation in cardiovascular risk screening in women at risk after pre-eclampsia.

Acknowledgement

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Conflict of interest

None declared.

Supporting information

Supporting information may be found in the online version of this article.

Figure S1. C-reactive protein levels for pre-eclampsia (PE) vs. non-hypertensive controls throughout pregnancy trimesters.
Figure S2. C-reactive protein for severe pre-eclampsia vs. controls.
Figure S3. High-density lipoprotein levels in 2nd and 3rd trimester for severe pre-eclampsia vs. controls.
Figure S4. QUADAS-2 bias risk and applicability concern scoring.
Table S1. Study characteristics of included studies from Search I, diastolic heart failure.
Table S2. Study characteristics of included studies from Search II, pre-eclampsia.

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