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Cardiovascular health and vascular age after severe preeclampsia: A cohort study

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HIGHLIGHTS

- One year after preeclampsia, the most common adverse cardiovascular health factor is blood pressure.
- Lower cardiovascular health is associated with more subclinical atherosclerosis.
- Lower cardiovascular health relates to a larger gap between chronological and vascular age.

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ABSTRACT

Background and aims: Severe preeclampsia increases lifetime-risk for cardiovascular disease (CVD). It remains unclear when this risk translates to subclinical atherosclerosis and whether this is related to cardiovascular health (CVH) after pregnancy. Our aims were (1) to determine CVH after severe preeclampsia, (2) to relate CVH to carotid intima-media thickness (CIMT), as a marker of subclinical atherosclerosis and (3) to relate CVH to chronological and vascular age.

Methods: A prospective cohort study was performed in women with previous severe pre-eclampsia. CVH, proposed by the American Heart Association, was assessed one year after pregnancy. The CVH score (range 0–14) includes seven metrics (blood pressure, total-cholesterol, glucose, smoking, physical activity, diet and body mass index [BMI]), each weighted as poor (0), intermediate (1) or ideal (2). Vascular age was determined by CIMT. We related CVH to delta age (chronological age - vascular age).

Results: In 244 women, the median CVH score was 10 (90% range 7.0, 13.0). Low CVH (< 10) was associated with a larger CIMT than high CVH (≥12) (median 626.3 μm *vs.* 567.0 μm, respectively). Higher CVH was also associated with a lower vascular age (−2.0 years, 95%CI −3.3, −0.60). Women with low CVH had a larger delta age (22.5 years [90% range −3.9, 49.6) than women with high CVH (16.5 years [90% range −11.9, 43.3).

Conclusions: CVH is inversely related to subclinical atherosclerosis and to vascular age one year after severe preeclampsia. Especially low CVH is associated with a large difference between chronological age and vascular age. CVH counseling might provide the opportunity for timely cardiovascular prevention.

1. Introduction

Preeclampsia is a hypertensive disorder of pregnancy, characterized by hypertension and proteinuria [1,2]. Severe preeclampsia, affecting 1.4% of pregnancies in the western world, is characterized by maternal organ damage and/or fetal growth restriction and is a leading cause of both maternal and infant morbidity and mortality [1,3,4]. One year after pregnancy these women have an increased risk of cardiovascular risk factors, such as hypertension, obesity and dyslipidemia, making them two to seven times more susceptible to develop cardiovascular disease (CVD) in later life compared to women with a normotensive pregnancy [5–7]. In young individuals, such as women who recently experienced preeclampsia, CVD end-points are rare. Therefore, in young populations the carotid intima-media thickness (CIMT) is often

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used as a marker of subclinical atherosclerosis and advanced vascular ageing [8]. Additional to these markers we were interested in cardiovascular health (CVH) as better CVH is associated with a lower risk of CVD and all-cause mortality [9,10]. In 2010, the American Heart Association (AHA) created the CVH score in order to reduce the risk of death from stroke and CVD by improving CVH [11,12]. The AHA CVH score is based on the combination of four health behaviors (body mass index [BMI], smoking habit, diet and physical activity) and three health factors (blood pressure, total-cholesterol and glucose concentration) [8]. We hypothesized that a lower CVH score one year after pregnancy is associated with a larger CIMT and higher vascular age. The aims of this study were threefold: (1) to determine CVH in women who experienced severe preeclampsia, (2) to relate CVH to CIMT, as a marker of subclinical atherosclerosis and (3) to relate CVH to chronological and vascular age.

2. Materials and methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

2.1. Design and study population

The present study has a descriptive design and complies with the Declaration of Helsinki. The Medical Ethics Committee of Erasmus Medical Center approved the research protocol and informed consent has been obtained from all participants. This study did not receive funding. We included women who were referred to the Follow-Up Pre-EClampsia (FUPEC) outpatient clinic in Erasmus Medical Center, the Netherlands within nine months to three years after delivery, between April 2011 and January 2017. FUPEC provides long-term multidisciplinary cardiovascular follow-up after severe preeclampsia for all women throughout the Netherlands. Details have previously been described [6]. Women were excluded when they were diagnosed with acute fatty liver disease or mild preeclampsia during the index pregnancy, when they were pregnant during follow-up or within 9 months previous to follow-up and when they had no information or no complete information available on postpartum CVH. The final population for analysis comprised 244 women (Fig. 1).

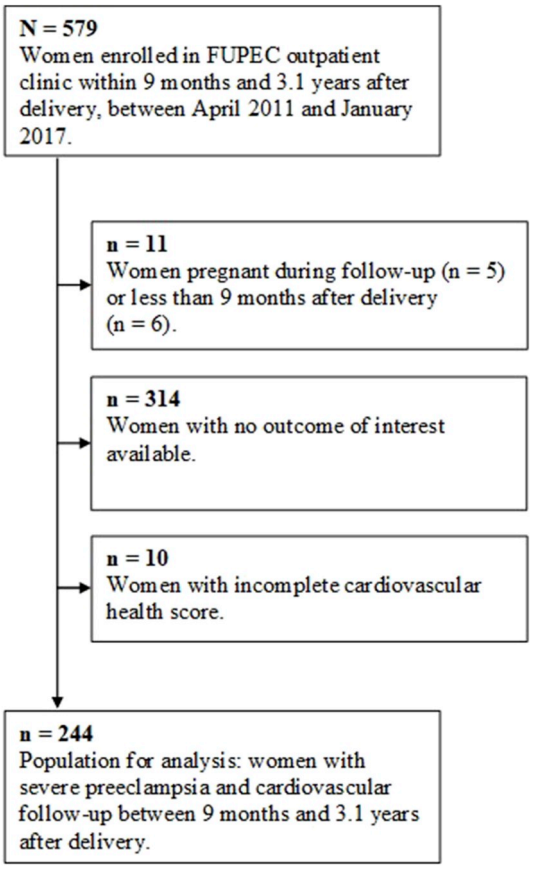

Fig. 1. Flowchart.
FUPEC, follow-up pre-eclampsia.

2.2. Severe preeclampsia

We previously reported the criteria for severe preeclampsia [1,6]. In brief, the diagnosis was based on the American College of Obstetricians and Gynecologists (ACOG) 2002 criteria as new onset hypertension (systolic blood pressure [SBP] ≥ 140 mmHg and/or diastolic blood pressure [DBP] ≥ 90 mmHg) after 20 weeks of gestation, the presence of proteinuria with no evidence of urinary tract infection in a random urine sample and ≥1 of the following criteria: SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg, thrombocytopenia, impaired liver function, severe proteinuria (≥5 g/24-h), cerebral or visual disturbances, pulmonary edema, epigastric or right upper-quadrant pain, or fetal growth restriction [1]. Superimposed severe preeclampsia was diagnosed as a hypertension exacerbation after 20 weeks of gestation in combination with new-onset proteinuria or an exacerbation of prior proteinuria or maternal multiorgan and/or fetal involvement [13]. Early-onset preeclampsia were defined as a delivery before 34 weeks of gestation.

2.3. Pregnancy and postpartum information

Pregnancy characteristics were obtained from medical files and midwifery charts. Questionnaires (3 months and one year postpartum) provided information on ethnicity, education, medical history, medication prescription, smoking, breastfeeding and pregnancies after the index pregnancy [14,15]. We cross-checked information from the questionnaires with the information from medical files and midwifery charts.

2.4. Cardiovascular health score

The CVH score is composed of seven metrics (blood pressure, total-cholesterol, glucose, smoking, physical activity, diet and BMI) according to the AHA classification [11]. The CVH metrics were obtained one year postpartum (90% range 0.95–3.0 years). Information on blood pressure, smoking, physical activity, diet and BMI were acquired by a trained research assistant. Blood pressure was measured in sitting position after a minimum rest of 5 min. A validated oscillometric device was used to measure blood pressure in the right upper arm. Weight and height were measured without wearing shoes or heavy clothing. BMI was calculated as weight divided by height squared (kg/m^2). Information on smoking, physical activity and diet was obtained from a questionnaire one year postpartum which was cross-checked by the research assistant during the follow-up visit. Non-fasting blood samples were collected to measure total-cholesterol and glucose concentrations (mmol/L). Samples were directly analyzed in the Vascular Medicine laboratory of Erasmus Medical Center, Rotterdam with the Vital Scientific (Merck) Selectra E Chemistry Analyzer (Vital Scientific N.V., Dieren, the Netherlands).

The diet metric included a combination of five food groups including fruit, vegetables, fish, fiber-rich whole grains, sodium and sugar-sweetened beverages. Each ideal food group could receive one point. Ideal food groups included: ≥4.5 cups of fruit and vegetables per day, < 1500 mg sodium per day, ≥3 servings of 1 ounce of fiber-rich whole grains per day, ≤450 kcal of sugar-sweetened beverages per day and ≥2 servings of fish per week. Physical activity was categorized as inactive, moderately active (1–149 min per week moderately active or

1–74 min per week vigorously active) and active (≥150 min per week moderately active or ≥75 min per week vigorously active) [11].

Each CVH metric was categorized as poor, intermediate or ideal and weighted accordingly with zero, one or two points (S1) [11]. The sum of all metrics created the CVH score, ranging from zero to 14 points. The total number of ideal CVH metrics ranged from zero to seven where having less than five ideal CVH metrics was defined as low CVH. Women treated for hypertension, hypercholesterolemia or diabetes and who were treated to goal (ideal category) were assigned to the intermediate category of the metric they were treated for.

2.5. Carotid intima-media thickness

CIMT was measured after pregnancy (median 3.3 years, 90% range 0.35, 7.2). Two ultrasonic devices were used with a validated automated CIMT capturing method (Panasonic CardioHealthStation, Yokohama, Japan and Esaote MyLab^{TM}One, Maastricht, the Netherlands) [16]. Both devices measure in B-mode but the Esaote device combines B-mode imaging with integrated radio frequency-data (RF-data) technology [17,18]. The latter provides direct measurement quality feedback. CIMT was measured three times at both sides over 1 cm length and at least 0.5 cm proximal of the bifurcation of the common carotid artery [19]. The presence of plaque was determined by visualizing both common carotid arteries and the bifurcations. The average of the CIMT on both sides was used for further analyses. Vascular age (years) was calculated with the sex specific formula: (CIMT - 321.7)/4.971 and compared to the 50th CIMT percentile across age in a large review including 24871 individuals worldwide [8].

2.6. Statistical analyses

We examined the missing data pattern and the percentage of missing values in the confounders that were used for linear and logistic regression analysis: ethnicity (0.4%) and pre-pregnancy BMI (20.8%). Values were missing at random. To deal with bias due to missing values we imputed confounders with the Markov Chain Monte Carlo multiple imputation method, which assumed no monotone missing data pattern. We performed ten iterations and created five separate datasets [20]. The pooled estimates and corresponding 95% confidence intervals (95% CI) are presented in this manuscript. Tables 1 and 2 present pregnancy and follow-up characteristics of the total population. Values are numbers with valid percentages, means (SD) for variables with a normal distribution and medians (90% range) for values with a skewed distribution. Normality was tested through the Shapiro-Wilk test. The outcomes CIMT, chronological age, vascular age and delta age (chronological age – vascular age) were normally distributed. However, we decided to present medians with 90% range as these were more insightful. We performed linear and logistic regression analyses to relate CVH to vascular age for women with a CIMT measurement (Table 3). We examined CIMT, chronological age, vascular age and delta age in women with low CVH (< 10), medium CVH (10 and 11) and high CVH (≥12) (Table 4 and Fig. 2). Confounders (pre-pregnancy BMI, age at study entry, ethnicity, gravidity during follow-up and time interval between pregnancy and follow-up) were selected based on previous studies and their association with the exposure and outcome of interest. Students *t*-test and Chi-square test were used to examine differences between women with early and late-onset preeclampsia. We tested whether CIMT differed between women measured with the CardioHealthStation or Esaote ultrasound device through interaction analysis (data not shown). Stratification of our analyses was not necessary as the *P*-value for interaction was > 0.10. The computation of the CVH score requires the inclusion of fasting glucose concentration. Therefore, we performed a sensitivity analysis to determine to which extent the usage of non-fasting glucose influenced our results. Criteria of the International Diabetes Federation (IDF) were used to reclassify non-fasting glucose into 'ideal' (< 7.8 mmol/L), 'intermediate' (7.8–11.0 mmol/L) and 'poor' (≥11.1 mmol/L) (S2). Thereafter, we determined whether the ranking of our results changed after exclusion of the glucose metric from the CVH score (S2). Lastly, we compared baseline characteristics between women included and not included in this study (data not shown). Statistical analyses were performed with Statistical Package of Social Sciences version 24.0 for Windows (IBM Corp., Armonk, NY, USA).

Table 1
Baseline characteristics.

Outcomes	Total (n = 244)
Characteristics during index pregnancy	
Maternal age, years	31.2 (5.1)
Ethnicity, n (%)	
Caucasian	191 (78.6)
African descent	37 (15.2)
Asian/South-Asian	15 (6.1)
Pre-existing hypertension, n (%)	38 (15.6)
Nulliparity, n (%)	176 (70.4)
Pre-pregnancy BMI (kg/m^2)	24.4 (19.1, 35.6)
First trimester SBP	120.3 (15.0)
First trimester DBP	74.2 (11.6)
Smoking, n (%)	23 (9.5)
Gestational age at delivery, weeks	31.3 (25.6, 39.1)
Maternal characteristics during follow-up	
Time postpartum CVH assessment, years	1.0 (0.95, 3.0)
Time postpartum CIMT assessment, years	3.3 (0.35, 7.2)
Education, n (%)	
None/primary	8 (4.7)
Lower secondary	80 (46.8)
Upper secondary	10 (5.8)
Academic	73 (42.7)
Medication, n (%)	
Antihypertensive	55 (22.6)
Cholesterol regulating	6 (2.5)
Glucose regulating	1 (0.4)
Breastfeeding, n (%)	13 (5.3)

BMI, body mass index; CIMT, carotid intima-media thickness; CVH, cardiovascular health; DBP, diastolic blood pressure; SBP, systolic blood pressure.
Values are numbers with valid percentages, means (SD) for variables with a normal distribution and median (90% range) for values with a skewed distribution.

3. Results

Baseline and follow-up characteristics are presented in Table 1. Women were on average 31 years old at the beginning of pregnancy, mostly Caucasian (78.6%) and 15.6% had pre-existing hypertension. One year postpartum, 22.6% of women used antihypertensive medication and 5.3% were breastfeeding.

3.1. Cardiovascular health

Table 2 shows that the median CVH score was 10.0 (7.0, 13.0) and ideal CVH was rare (2.9%). The individual CVH health metrics blood pressure, BMI and diet were mostly categorized as poor or intermediate.

3.2. CIMT and vascular age

Carotid imaging showed a median CIMT of 588.5 (90% range 469.1, 721.9) and 14.9% plaque formation (Table 2). Vascular age, derived from CIMT, was on average 17.5 years older than chronological age (53.8 years [90% range 30.0, 80.4] *vs.* 36.3 years [90% range 26.0, 45.7], respectively).

Table 2
Cardiovascular risk, cardiovascular health, vascular age and CIMT.

Outcomes	Total (n = 244)
Cardiovascular health	
CVH score, median (90% range)	10.0 (7.0, 13.0)
CVH score metrics	
Blood pressure, n (%)	
Poor	83 (34.0)
Intermediate	76 (31.1)
Ideal	85 (34.8)
BMI	
Poor	58 (23.8)
Intermediate	75 (30.7)
Ideal	111 (45.5)
Smoking, n (%)	
Poor	33 (13.5)
Intermediate	8 (3.3)
Ideal	203 (83.2)
Diet, n (%)	
Poor	59 (24.2)
Intermediate	140 (57.4)
Ideal	45 (18.4)
Physical activity, n (%)	
Poor	2 (0.8)
Intermediate	25 (10.2)
Ideal	217 (88.9)
Cholesterol, n (%)	
Poor	14 (5.7)
Intermediate	70 (28.7)
Ideal	160 (65.6)
Glucose, n (%)	
Poor	5 (2.0)
Intermediate	28 (11.5)
Ideal	211 (86.5)
Ideal CVH metrics, n (%)	
0	0
1	2 (0.8)
2	14 (5.7)
3	49 (20.1)
4	77 (31.6)
5	72 (29.5)
6	23 (9.4)
7	7 (2.9)
Vascular age, years (90% range)	53.8 (30.0, 80.4)
Chronological age at the time of CIMT measurement, years (90% range)	36.3 (26.0, 45.7)
*CIMT, μm (mean, SD)	588.5 (469.1, 721.9)
*Plaque, n (%)	18 (14.9)

BMI, body mass index; CIMT, carotid intima-media thickness; CVH, cardiovascular health.
Values are numbers with valid percentages and medians (90% range). Available in a subsample of women (n = 123).

Table 3
Cardiovascular health and vascular age after pregnancy.

Exposure	Vascular age, years (Beta, 95% CI)	p-value	Vascular age ≥ p75 (OR, 95% CI)	*p*-value
CVH score	−2.0 (−3.3, −0.60)	0.005	0.68 (0.52, 0.88)	0.003

CVH, cardiovascular health.
Values are regression coefficients (beta and OR) with corresponding 95% CI and are based on linear and logistic regression analysis. Values were adjusted for age at study entry, ethnicity, gravidity during follow-up and time interval between pregnancy and follow-up.

3.3. Cardiovascular health, CIMT and vascular age

We examined the association between CVH, CIMT and vascular age (Tables 3 and 4 and Fig. 1). A higher CVH score was associated with a lower vascular age and a lower risk of having a vascular age above the 75th percentile (Table 3). Women with a CVH score < 10.0 had a larger CIMT (Table 4) and delta age (22.5 years [90% range −3.9, 49.6) than women with a CVH ≥12.0 (16.5 years [90% range −11.9, 43.3) (Fig. 2).

Table 4
Carotid intima-media thickness per cardiovascular health category.

Exposure	Carotid intima-media thickness (μm)
Cardiovascular health score	
< 10.0 (n = 43)	626.3 (464.1, 752.4)
10.0–12.0 (n = 49)	579.8 (482.8, 705.0)
≥12.0 (n = 31)	567.0 (450.6, 764.3)

Values are medians with corresponding 90% range and are not imputed.

3.4. Reclassification of glucose and non-response analyses

S2 shows the association between the CVH score and vascular age after reclassifying glucose categories according to the IDF criteria and after excluding glucose from the CVH score. Results remained similar to those presented in Table 3.

We compared women included and excluded from this study (data not shown). Women who were not included were on average slightly older during follow-up (33.8 [SD 6.7] years *vs.* 32.3 [SD 5.4] years). We observed no differences between both groups in ethnicity and education.

4. Discussion

4.1. Main findings

This study shows that the CVH score is inversely associated with subclinical atherosclerosis and vascular age one year after pregnancy. Low CVH (< 10.0) was associated with a larger difference between chronological age and vascular age than high CVH (≥12.0).

4.2. Interpretation

4.2.1. Cardiovascular health after severe preeclampsia

Severe preeclampsia is associated with an increased lifetime-risk of CVD. It remains unclear when this risk translates to subclinical vascular disease, such as subclinical atherosclerosis. Subclinical vascular disease can often be treated and even reversed, thereby reducing CVD risk. Detecting subclinical vascular disease shortly after pregnancy could allow for early identification and treatment of specific risk factors, such as hypertension, obesity and diabetes, which are all combined in the CVH score [5,21]. Population studies have shown a linear association between the exposure time to classical cardiovascular risk factors, a low CVH score and the risk of future CVD [22–24]. So far, the CVH score had not yet been determined in women with a history of preeclampsia. Nor had it been related to subclinical vascular disease in these women. We can therefore not compare our results to a similar population. Though several studies have examined CVH, only the NHANES study examined women who were of similar age to those included in our analyses [25]. Women in the NHANES study are derived from the general US population and had more often lower CVH (less than five ideal CVH metrics) than women in our study: 64.5% *vs.* 58.2% [25]. Individual CVH metrics were mostly similar between both study populations except for blood pressure, which was more often categorized as poor in women with previous severe preeclampsia. This is in line with other studies which showed that a substantial number of women have hypertension after severe preeclampsia [6,21]. While we did not observe differences in BMI and diet between our study and the NHANES, we would expect to observe these differences when our results could have been compared to Dutch women of similar age. BMI and dietary intake are on average unhealthier in Americans than in individuals from the Netherlands as has previously been demonstrated

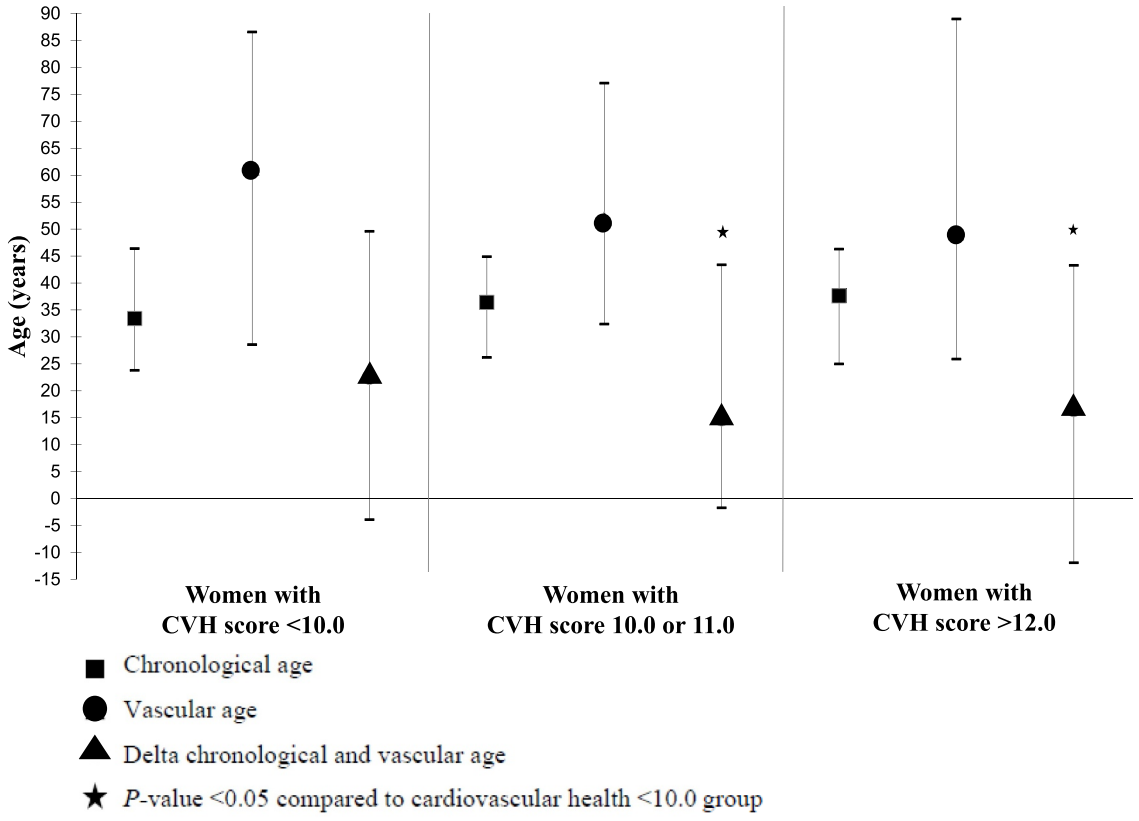

Fig. 2. Chronological age, vascular age and delta age per cardiovascular health category.

by the World Health Organization; the percentage of women with obesity was in 2016 nearly twice as high in the US compared to the Netherlands (34.7% *vs.* 18.3%) [26,27]. The severity of preeclampsia is associated with the risk of CVD [21]. Whether CVH is associated with preeclampsia or the severity of preeclampsia is thus far unknown. As our cohort consists exclusively of women with severe preeclampsia we cannot address this issue. However, we expect that women with severe preeclampsia will have worse CVH than those with mild preeclampsia as the former is associated with a higher rate of hypertension, and higher cholesterol and glucose levels, which all contribute to worse CVH [6,28].

4.2.2. CIMT and vascular age

CIMT has been demonstrated to be useful in calculating vascular age amongst women from 14 countries worldwide [8,29]. A larger CIMT was associated with a higher vascular age. Previous studies also showed that women with a history of preeclampsia have on average a larger CIMT than women who had a normotensive pregnancy [30,31]. Thus far, vascular age, based on CIMT, had not been studied in these women. Our study is the first to show that vascular age in women with a history of severe preeclampsia was on average 17.5 years older than their chronological age. When women had a higher CVH score they were more likely to have a lower vascular age and smaller delta age, taken into account confounding factors, such as age and ethnicity [19,32]. A previous study amongst mono- and dizygotic twins without clinical CVD also showed that higher CVH was associated with a smaller CIMT [33]. The observation was largely determined by health factors (blood pressure, total-cholesterol and glucose concentration) and not by health behaviors. Of all CVH metrics, blood pressure had the strongest association with CIMT and vascular age in our study (data not shown).

The association between preeclampsia and vascular age might at least partly be explained through endothelial dysfunction, which is characterized by impaired vasodilatation, and a prothrombotic and proinflammatory status [34]. Endothelial dysfunction has previously been associated with vascular ageing, characterized by CIMT thickening [35]. Alongside traditional cardiovascular risk factors for endothelial dysfunction, e.g. diabetes, hypertension, smoking and age, preeclampsia has also been associated with endothelial and vascular dysfunction both before pregnancy and years after [34,36].

CIMT is not only a marker of subclinical atherosclerosis but also a predictor of CVD [37]. An increase of 100 μm has previously been associated with a ten to 18% increased risk of CVD [37]. Our study shows that one point increase in the CVH score corresponds to a two year decrease in vascular age, which corresponds with a 10 μm decrease in CIMT. Additionally, previous studies demonstrated that carotid intima-media thickening can be slowed down or even reversed through blood pressure control, exercise, a healthy diet and cholesterol lowering therapy [38–42]. Improving CVH, especially in women with a CVH score < 10.0, might therefore be very beneficial in reducing the risk of subclinical atherosclerosis.

4.2.3. Future implications

Future studies should examine the CVH score and CIMT at different time points after a severe preeclampsia and compare results with those of women with a normotensive pregnancy. Moreover, the association between CVH improvement and CIMT reduction should be examined. Finally, the implementation of the CVH score and vascular age in cardiovascular guidelines for the follow-up of women with severe preeclampsia should be evaluated.

4.2.4. Strengths and limitations

The strength of this study is that it is the first study that determines the association between CVH and subclinical atherosclerosis in women with previous severe preeclampsia. Additionally, these women were diagnosed according to uniform criteria and underwent standardized cardiovascular follow-up. This study has some limitations. The majority

of women in this study were Caucasian (78%). Therefore, results might not be generalizable to other ethnicities. In 50.4% of women, CIMT was not available due to later implementation of this measurement in the FUPEC outpatient clinic. In addition, CIMT was not standardized for device type. The Esaote ultrasound device used RF-data technology, which provides direct feedback on the quality of the CIMT measurement. This technology is believed to be superior to other CIMT technologies [18]. Consequently, CIMT measured with the Panasonic ultrasound might be underestimated. Though CIMT is considered a good representative of subclinical coronary atherosclerosis, it has some limitations. CIMT is slightly less accurate than corotid plaque measurement in 10-year CVD prediction (area under the curve 0.61 *vs.* 0.64) [43]. Also, the false negative predictive value of carotid plaque measurement for 10-year CVD risk is slightly lower than that of CIMT (4.0%; 95% CI 3.6–4.7% *vs.* 4.7%; 95% CI 4.2–5.5%) [43]. Lastly, a recent small study showed that CIMT is less accurate in predicting vascular risk after preeclampsia compared to intima thickness or the ratio between intima and media thickness [31]. Total-cholesterol and glucose were retrieved non-fasting. The original CVH score was designed to include fasting total-cholesterol and glucose concentrations. Total-cholesterol concentrations remain fairly stable between pre-prandial and postprandial state, but for glucose we might have overestimated the percentage of women in the poor category. To determine the effect of including non-fasting glucose concentrations, we performed sensitivity analyses (1) after excluding the glucose metric from our CVH score and (2) after reclassifying the glucose metric according to the IDF criteria for 'ideal', 'intermediate' and 'poor' non-fasting glucose concentrations. Results remained similar. Due to the descriptive design of this study, differences in the observed associations between women with previous severe preeclampsia and women with a previous normotensive pregnancy cannot be examined. Lastly, we cannot exclude the possibility of residual confounding, e.g. household income and air pollution [44].

4.3. Conclusion

The CVH score is inversely associated with subclinical atherosclerosis and vascular age one year after severe preeclampsia. Especially low CVH is associated with a large difference between chronological age and vascular age. CVH counseling might provide the opportunity for timely cardiovascular prevention and ultimately a reduction in CVD.

Author contributions

LB analyzed the data and wrote the article. SJCS, JJD and JRL contributed to the design of the study, analyses, writing the article, interpretation of the data, revisions and gave input at all stages of the study. All authors have approved the final version of the manuscript. This study was made possible by funding of the Dutch Heart Foundation, The Netherlands (grant number 2013T083).

Ethics approval

The Medical Ethics Committee of Erasmus Medical Center has approved the research protocol on April 11, 2016 (MEC-2016-200) and informed consent has been obtained from all participants.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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