ORIGINAL RESEARCH

Early Pregnancy Cardiovascular Health and Subclinical Atherosclerosis

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Background—Assessing and optimizing cardiovascular health (CVH) early in life, such as in pregnancy, could lead to a longer lifetime spent in better CVH and reduce the risk of cardiovascular disease. This might especially benefit women with a hypertensive disorder of pregnancy (HDP) who are more likely to develop atherosclerosis and cardiovascular disease. We hypothesized that CVH in pregnancy is related to later life CVH and carotid intima-media thickness (CIMT), and that these associations differ between women with a normotensive pregnancy and women with an HDP.

Methods and Results—This study was conducted within the prospective population-based Generation R Study. CVH in pregnancy was based on 5 metrics (blood pressure, total-cholesterol, glucose, smoking, and body mass index). Postpartum CVH additionally included physical activity and diet scores, according to the American Heart Association classification. Postpartum CVH and CIMT were measured 10 years after pregnancy. Results were analyzed for women with a normotensive pregnancy and those with an HDP. Women with a normotensive pregnancy (n=1786) and women with an HDP (n=138) were evaluated from early pregnancy until 10 years postpartum. Better CVH in early pregnancy was associated with a smaller CIMT and better postpartum CVH in all women, especially in those with an HDP (CIMT: −9.82 μm [95% CI: −17.98, −1.67]).

Conclusions—Already in pregnancy, better CVH is associated with a smaller CIMT and better CVH 10 years postpartum, especially in women with an HDP. As pregnancy is an incentive for women to improve lifestyle, assessing CVH in pregnancy might help improve postpartum CVH and reduce cardiovascular disease risk. **(*J Am Heart Assoc*. 2019;8:e011394. DOI: 10.1161/JAHA.118.011394.)**

Key Words: American Heart Association • cardiovascular research • carotid intima-media thickness • health outcomes • preeclampsia/pregnancy

Women with a hypertensive disorder of pregnancy, such as gestational hypertension and preeclampsia, have a 2- to 9-fold increased risk of developing cardiovascular disease (CVD) later in life.[1] This most likely results from the abundance of cardiovascular risk factors, such as hypertension and obesity, in these women.[2–5] The conventional approach to CVD prevention is to optimize classical risk factors such as hypertension and diabetes mellitus. However, communication of CVD risk to young individuals with a low absolute 10-year CVD risk is challenging. An alternative manner for CVD risk communication is to focus on cardiovascular health (CVH) as is advocated by the American Heart Association which developed the CVH score.[6] The score includes 3 health factors (blood pressure, total-cholesterol, and glucose concentration) and 4 health behaviors (body mass index [BMI], smoking habit, diet, and physical activity) each categorized as "poor", "intermediate" or "ideal" and weighted accordingly (0, 1, or 2 points, respectively). In the general population, better CVH is associated with lower CVD morbidity and mortality and with a smaller carotid intima-media thickness (CIMT).[6] CIMT is a marker of subclinical atherosclerosis and therefore insightful in women around reproductive age who are mostly still too young for having any hard CVD outcomes, such as a myocardial infarction or stroke.[7]

For most women, pregnancy is a natural moment to voluntarily seek medical care and improve physical health, which makes it a potentially interesting moment to assess

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Accompanying Data S1 and Tables S1 through S6 are available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.011394

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Received November 2, 2018; accepted May 22, 2019.

Clinical Perspective

What Is New?

- Women with a hypertensive disorder of pregnancy have an increased risk of cardiovascular disease later in life.
- Assessing and optimizing their cardiovascular health early in life, such as in pregnancy, could lead to a longer lifetime spent in better health and reduce the risk of cardiovascular disease.
- To our knowledge, this study is the first to show that better cardiovascular health in early pregnancy is already associated with better cardiovascular health 10 years after pregnancy and with a smaller carotid intima-media thickness, especially in women with a hypertensive disorder of pregnancy.

What Are the Clinical Implications?

- Assessing and optimizing cardiovascular health in early pregnancy could lead to a better cardiovascular health and carotid intima-media thickness in the long-term.
- This is a relatively easy procedure that might help to reduce the risk of future cardiovascular disease, especially in women with a hypertensive pregnancy disorder.

CVH.[8,9] Currently it is not known whether CVH in pregnancy is related to postpartum subclinical atherosclerosis and CVH later in life. Assessing and improving CVH in women with a hypertensive disorder of pregnancy might be even more beneficial than in women with a normotensive pregnancy as they are more likely to develop atherosclerosis and CVD later in life.

The objective of this study was to determine the association between early pregnancy CVH and postpartum CIMT and CVH, in women with a normotensive pregnancy and women with a hypertensive disorder of pregnancy.

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.

Design and Study Population

This study was embedded in the Generation R Study, a population-based prospective cohort from early pregnancy onwards.[10,11] Approval was obtained from the Medical Ethics Committee of Erasmus Medical Center, Rotterdam, the Netherlands (MEC 198.782/2001/31) and the procedures followed were in accordance with institutional guidelines.[12] All women included in this study provided written informed consent to use and publish their data. We included women with a live born singleton, available data on CVH in early pregnancy and information on at least 1 of our 2 primary outcomes 10 years after pregnancy (CIMT or CVH). Women were excluded when they participated with >1 child (visits with the second and/or third child were excluded; only including visits with the first child) or when they were pregnant 10 years after pregnancy. The final population for analysis comprised 1924 women (Figure).

Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy were defined as having gestational hypertension or preeclampsia in the index pregnancy. These outcomes were validated and indexed according to the 2011 criteria of the International Society for the Study of Hypertension in Pregnancy. A systolic blood pressure

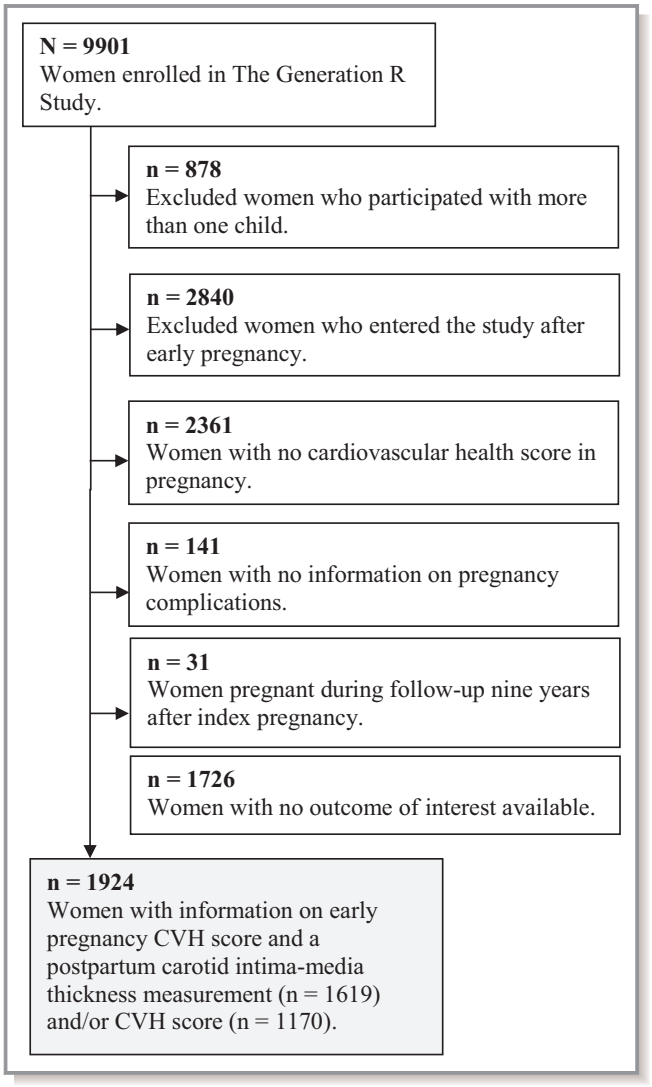

Figure. Flowchart. CVH indicates cardiovascular health.

≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg after 20 weeks of gestation was classified as gestational hypertension or as preeclampsia in case of proteinuria with no evidence of a urinary tract infection in a random urine sample.[13,14]

CVH Metrics and CIMT

The CVH score in early pregnancy (gestational age 13.2 weeks [90% range 10.6, 17.1]) included information on blood pressure, BMI, smoking-habit, and non-fasting total-cholesterol, and glucose concentrations. Information on physical activity and dietary intake was not available in such matter as required for constructing the CVH score. Blood pressure was measured in sitting position in the right upper arm with the validated Omron 907® automated digital oscillometric sphygmomanometer (OMRON Healthcare Europe B.V., Hoofddorp, the Netherlands) by trained assistants wearing normal clothing (no white coats). The mean value of 2 blood pressure readings over a 60-second interval was documented.[15] BMI (kg/m^2) was calculated after measuring maternal height (cm) and weight (kg) without shoes. Information on smoking was obtained from a questionnaire. Total-cholesterol (mmol/L) and glucose (mmol/L) concentrations were measured from non-fasting EDTA blood samples. Sample processing and storage procedures have been described previously.[11]

We assessed postpartum CVH 10 years after pregnancy (90% range 10.0, 10.8 years). Blood pressure was measured in supine position in the right upper arm with the validated automatic sphygmomanometer Datascope Accutorr Plus (Paramus, NJ).[16] The average of the last 3 out of 4 blood pressure measurements was used for further analyses. BMI (kg/m^2) was derived from maternal height (cm) and weight (kg) without shoes. Information on smoking, diet, and physical activity was obtained from questionnaires. Non-fasting total-cholesterol (mmol/L) concentration measured from plasma samples 6 years after pregnancy was used as a proxy for total-cholesterol concentration 10 years after pregnancy. Detailed information on storage and processing has been described previously.[17] Non-fasting glucose concentration (mmol/L) was measured 10 years after pregnancy through a finger-prick test with the HemoCue Glucose 201 DM System (HemoCue, Angelholm, Sweden).[18]

CIMT was measured 3 times at both common carotid arteries with the Logix E9 ultrasound device (General Electric Healthcare, Wauwatosa, WI), 10 years after pregnancy. CIMT readers were masked to CVH status and information about the index pregnancy. The average of all measurements was standardized for age and blood pressure by 2 graders and used for further analyses. There was good agreement between both graders with an intraclass correlation coefficient of 0.91.

Both in pregnancy and 10 years after, each CVH metric was categorized as poor, intermediate, or ideal and weighted accordingly (0, 1, and 2 points, respectively). The CVH score in early pregnancy included 5 metrics and ranged from 0 to 10 points. The postpartum CVH score included 7 metrics and ranged from 0 to 14 points, in accordance with the CVH score created by the American Heart Association.[6] Having <5 ideal CVH metrics was defined as low CVH. Details on the computation of the CVH score are provided in Table 1 and Data S1.

Covariates

Information on maternal age and gestational age was obtained during the measurements of the early pregnancy CVH metrics.[13] Information on pre-pregnancy BMI, smoking, education level, ethnicity, pre-pregnancy hypertension, diabetes mellitus, and hypercholesterolemia, gestational diabetes mellitus, medication intake (antihypertensive medication, glucose, and cholesterol regulation medication), CVD, and menopause was obtained through questionnaires in pregnancy and during follow-up. Information on pregnancies before and after the index pregnancy was obtained through an interview 10 years after pregnancy.

Statistical Analyses

We examined the distribution of pregnancy and follow-up characteristics for all women with a normotensive pregnancy and those with a hypertensive disorder of pregnancy, and with one of our 2 outcomes of interest (Tables 2 and 3). The presented *P* values are the result of Student *t* test for variables with a normal distribution, the Kruskal–Wallis test for variables with a skewed distribution and Chi square test and Fisher exact test for categorical variables. We imputed missing values in confounders that were used for linear and logistic regression analyses. To identify whether the data were missing at random we conducted a Little's Missing Completely At Random test, which was not significant (*P* value: 0.783), indicating data were missing completely at random. We used the Markov Chain Monte Carlo multiple imputation procedures to reduce potential bias attributable to missing data.[19] This method assumes no monotone missing pattern. Data were analyzed in each set separately, and pooled estimates from the 5 imputed data sets were used to report the effect estimates and their 95% CI. For the multiple imputation procedure we performed 10 iterations.[20] In this study 1.4% of women had missing information on education level, 0.21% on ethnicity, and 10.1% on gravidity during follow-up. We tested the robustness of the imputation procedure by comparing our results based on analyses with imputed confounders to our results

Table 1. Cardiovascular Health Score Classifications

	Poor (0)	Intermediate (1)	Ideal (2)
Blood pressure, mm Hg	SBP ≥140 and/or DBP ≥90 mm Hg	SBP 120 to 139 and/or DBP 80 to 89 mm Hg, or treated to goal	SBP/DBP <120/80 mm Hg
Body mass index, kg/m^2	≥30 kg/m^2	25 to 29.99 kg/m^2	<25 kg/m^2
Smoking	Current	Former, quit ≤12 months	Never/quit >12 months
Diet* (number of ideal food groups)	0 to 1	2 to 3	4 to 5
Physical activity*	Inactive	Moderately active	Active
Total cholesterol, mmol/L	≥6.2 mmol/L	5.2 to 6.2 mmol/L, or treated to goal	<5.2 mmol/L
Glucose, mmol/L	≥7.0 mmol/L	5.55 to 7.0 mmol/L, or treated to goal	<5.55 mmol/L

DBP indicates diastolic blood pressure; SBP, systolic blood pressure.
*Not included in the cardiovascular health score in early pregnancy.

based on analyses with non-imputed confounders. No differences were observed.

Because of the skewed distribution of the postpartum CVH score, we applied a quadratic transformation to this outcome. To facilitate the interpretation of our findings we used z-scores for the quadratic postpartum CVH score. To relate early pregnancy CVH to postpartum CIMT and CVH we performed linear and logistic regression analyses (Table 4). Results are presented for women with a normotensive pregnancy and those with a hypertensive pregnancy disorder to highlight potential differences between both groups. Confounders that were included in the regression models were selected based on their associations with the exposure and outcomes of interest and based on previous studies. The confounders selected included: age and gestational age at early pregnancy CVH determination, education level, ethnicity, gravidity during follow-up and time interval between pregnancy and follow-up.

A non-response analysis was performed to test for potential differences in baseline characteristics between women with an early pregnancy CVH score available and those who did not (Table S1).

Glucose concentration was obtained non-fasting, whereas the CVH score requires the inclusion of fasting glucose. To determine to which extent the inclusion of non-fasting glucose in and after pregnancy influenced our results, we performed sensitivity analyses. Firstly, we reclassified early pregnancy (Table S2) and postpartum (Table S3) glucose categories by using the cutoffs of the International Diabetes Federation for "ideal" (<7.8 mmol/L), "intermediate" (7.8–11.0 mmol/L) and "poor" (≥11.1 mmol/L) non-fasting glucose concentrations.[21,22] Secondly, we excluded the glucose metric from the early pregnancy CVH score (Table S2) and postpartum CVH score (Table S3).

BMI cut-offs for non-pregnant adults were used to construct the early pregnancy CVH score. This might have resulted in a misclassification of BMI as some women might have had substantial gestational weight gain by this time. We attempt to eliminate the influence of gestational weight gain and to determine the degree of misclassification by replacing early pregnancy BMI with pre-pregnancy BMI, which was obtained through a questionnaire (Table S4).

We examined the association between each individual CVH score metric and the outcomes in women with a previous normotensive pregnancy and those with a previous hypertensive disorder of pregnancy (Table S5).

To determine the influence of pregnancy on cardiovascular outcomes we examined the association between a pre-pregnancy measurement (BMI) and the CVH score and CIMT after pregnancy over the course of a normotensive pregnancy and an hypertensive disorder of pregnancy (Table S6).

Information on diet and physical activity were not available in pregnancy, but were included in the CVH score after pregnancy. We tested whether excluding these metrics from the postpartum CVH score changed our results (data not shown). We also tested whether having had a hypertensive disorder of pregnancy before or after the index pregnancy affected our results by excluding these women from the analyses (data not shown).

For the statistical analyses we used Statistical Package of Social Sciences version 24.0 for Windows (SPSS Inc Chicago, IL).

Results

Table 2 shows the baseline and follow-up characteristics for women with a normotensive pregnancy and those with a hypertensive disorder of pregnancy. Women were on average 30.8 years old and 13.2 weeks pregnant when they entered

Table 2. Maternal Characteristics

Outcomes	Normotensive Pregnancy n=1786	Hypertensive Disorder of Pregnancy n=138	*P* Value*
During index pregnancy			
Maternal age, y	30.8 (4.6)	30.8 (4.3)	0.88
Gestational age, wks	13.2 (10.6, 17.1)	12.9 (10.8, 17.4)	0.18
Ethnicity, n (%)			0.48
White	1448 (81.3)	116 (84.1)	
African descent	146 (8.2)	9 (6.5)	
Asian/South Asian	142 (8.0)	12 (8.7)	
Other	46 (2.6)	1 (0.7)	
Education, n (%)			0.08
None/primary	107 (5.8)	8 (5.8)	
Secondary	717 (40.7)	69 (50.4)	
Higher	937 (53.2)	60 (43.8)	
First pregnancy, n (%)	883 (49.5)	95 (68.8)	<0.001
CVH score, median (90% range)	8.0 (5.0, 10.0)	8.0 (4.0, 10.0)	<0.001
Pre-existing hypertension, n (%)	17 (1.0)	0	0.25
Blood pressure, n (%)			<0.001
Poor	72 (4.0)	21 (15.2)	
Intermediate	596 (33.4)	61 (44.2)	
Ideal	1118 (62.6)	56 (40.6)	
BMI, n (%)			<0.001
Poor	147 (8.2)	24 (17.4)	
Intermediate	420 (23.5)	49 (35.5)	
Ideal	1219 (68.3)	65 (47.1)	
Smoking, n (%)			0.84
Poor	275 (15.4)	20 (14.5)	
Intermediate	181 (10.1)	16 (11.6)	
Ideal	1330 (74.5)	102 (73.9)	
Cholesterol, n (%)			0.61
Poor	145 (8.1)	11 (8.0)	
Intermediate	499 (27.9)	44 (31.9)	
Ideal	1142 (63.9)	83 (60.1)	
Glucose, n (%)			0.02
Poor	14 (0.8)	4 (2.9)	
Intermediate	154 (8.6)	16 (11.6)	
Ideal	1618 (90.6)	118 (85.5)	
During follow-up			
Age, y	41.2 (4.6)	41.1 (4.3)	0.88
More than once pregnant, n (%)	1482 (92.4)	104 (83.2)	<0.001
Hypertensive disorder of pregnancy†	67 (3.8)	28 (20.3)	<0.001
Menopause, n (%)	38 (2.4)	4 (3.1)	0.58‡

Continued

Table 2. Continued

Outcomes	Normotensive Pregnancy n=1786	Hypertensive Disorder of Pregnancy n=138	*P* Value*
Medication, n (%)			
Antihypertensive	19 (1.1)	11 (8.0)	0.11
Cholesterol regulating	11 (0.6)	1 (0.7)	1.0‡
Glucose regulating	7 (0.4)	2 (1.4)	1.0‡
Diabetes mellitus, n (%)	12 (0.7)	2 (1.4)	0.29‡

Values are numbers with valid percentages, means (SD) for variables with a normal distribution and medians (90% range) for values with a skewed distribution. Confounders were imputed. BMI indicates body mass index; CVH, cardiovascular health; n, number.

*The *P* value is the result of Student *t* test for variables with a normal distribution, the Kruskal–Wallis test for variables with a skewed distribution and Chi square test for categorical variables.

†In any other pregnancy than the index pregnancy.

‡Fisher exact test.

the study. The majority of women were white and higher educated. Women with a hypertensive disorder of pregnancy were more often primiparous and had a worse blood pressure, BMI, and glucose level in early pregnancy compared with women with a normotensive pregnancy. Nine years after pregnancy they had a larger CIMT (588.5 μm [±71.7] versus 572.6 μm [±70.0]), lower CVH (9.0, 90% range; 5.0, 12.0 versus 10.0, 90% range; 6.0, 13.0), more often <5 ideal CVH metrics (81.2% versus 62.3%) and a worse blood pressure and BMI compared with women with a normotensive pregnancy (Table 3).

In Table 4 we examined the association between the CVH score in early pregnancy and the CIMT and CVH score 10-year postpartum, in women with a normotensive pregnancy and those with a hypertensive disorder of pregnancy. A higher CVH score in early pregnancy was associated with a smaller CIMT 10 years after pregnancy in both groups (−5.21 μm [−7.40, −3.01], *P*<0.001 and −9.82 μm [−17.98, −1.67], *P* 0.02, respectively). Table 3 also shows that a higher CVH score in early pregnancy was associated with a higher postpartum CVH score in both groups (z-score 0.26 [95% CI: 0.23, 0.30], *P*<0.001 and z-score 0.25 [95% CI: 0.13, 0.37], *P*<0.001, respectively) and a lower risk for having <5 ideal postpartum CVH metrics (RR 0.75 [0.70, 0.80], *P*<0.001 and 0.70 [0.46, 0.91], *P* 0.002).

Compared with women with a CVH score in early pregnancy those without were on average slightly younger (0.3 years) and they enrolled earlier in pregnancy (0.2 weeks) (Table S1).

Table S2 shows that the association between early pregnancy CVH, CIMT, and postpartum CVH remains unchanged after reclassifying the glucose metric of the CVH score in early pregnancy according to the International Diabetes Federation criteria or by excluding the glucose metric from the early pregnancy CVH score. Also, applying identical adjustments to the postpartum glucose metric and thus the postpartum CVH score did not change our main results (Table S3). Table S4 shows that replacing the BMI metric of the early pregnancy CVH score by pre-pregnancy BMI did not change the association between early pregnancy CVH and postpartum CVH.

We show in Table S5 that smoking and cholesterol level were the CVH factors strongest associated with CIMT in women with a previous hypertensive disorder of pregnancy, whereas in previous normotensive women those were BMI and blood pressure. The CVH score after pregnancy was mainly driven by BMI and cholesterol level in women with a previous hypertensive disorder of pregnancy, whereas in women without a previous hypertensive disorder of pregnancy all 5 metrics in pregnancy were associated with the CVH score after pregnancy.

Table S6 shows that pre-pregnancy BMI is associated with the CVH score after pregnancy in all women in this study. Pre-pregnancy BMI is not associated with CIMT after pregnancy in women with a previous hypertensive disorder of pregnancy, whereas it is positively associated with CIMT in women with a previous normotensive pregnancy.

Lastly, excluding the diet and physical activity metrics from the postpartum CVH score did not change the association between early pregnancy CVH and postpartum CVH (data not shown). Also, excluding women who had had a hypertensive disorder of pregnancy before or after the index pregnancy did not change the results (data not shown).

Discussion

This large prospective cohort study shows that better CVH in early pregnancy is associated with a smaller CIMT, especially in women with a hypertensive disorder of pregnancy later in life. Also, better CVH in early pregnancy is associated with

Table 3. CIMT and CVH 10 Years After Pregnancy

Outcomes	Normotensive Pregnancy n=1786	Hypertensive Disorder of Pregnancy n=138	*P* Value*
CIMT, μm (mean, SD)	572.6 (70.0)	588.5 (71.7)	0.02
CVH score, median (90% range)	10.0 (6.0, 13.0)	9.0 (5.0, 12.0)	<0.001
Blood pressure, n (%)			<0.001
Poor	67 (3.8)	24 (17.8)	
Intermediate	361 (20.7)	47 (34.8)	
Ideal	1313 (75.4)	64 (47.4)	
BMI			<0.001
Poor	278 (15.6)	40 (29.0)	
Intermediate	507 (28.4)	44 (31.9)	
Ideal	999 (56.0)	54 (39.1)	
Smoking, n (%)			0.41
Poor	248 (15.8)	24 (18.5)	
Intermediate	47 (3.0)	6 (4.6)	
Ideal	1271 (81.2)	100 (76.9)	
Diet, n (%)			0.07
Poor	415 (28.3)	46 (37.7)	
Intermediate	965 (65.9)	68 (55.7)	
Ideal	85 (5.8)	8 (6.6)	
Physical activity, n (%)			0.82
Poor	52 (3.3)	4 (3.1)	
Intermediate	289 (18.4)	21 (16.3)	
Ideal	1226 (78.2)	104 (80.6)	
Cholesterol, n (%)†			0.35
Poor	133 (8.7)	13 (10.9)	
Intermediate	363 (23.6)	33 (27.7)	
Ideal	1040 (67.7)	73 (61.3)	
Glucose, n (%)			0.42
Poor	397 (26.8)	33 (29.2)	
Intermediate	674 (45.4)	55 (48.7)	
Ideal	413 (27.8)	25 (22.1)	
Ideal CVH metrics, n (%)			<0.001
0	23 (2.1)	1 (1.2)	
1	27 (2.5)	8 (9.4)	
2	92 (8.5)	14 (16.5)	
3	207 (19.1)	25 (29.4)	
4	327 (30.1)	21 (24.7)	
5	306 (28.2)	13 (15.3)	
6	100 (9.2)	3 (3.5)	
7	3 (0.3)	0	

Values are numbers with valid percentages, means (SD) for variables with a normal distribution and medians (90% range) for values with a skewed distribution. BMI indicates body mass index; CIMT, carotid intima-media thickness; CVH, cardiovascular health.
*The *P* value is the result of Student *t* test for variables with a normal distribution, the Kruskal–Wallis test for variables with a skewed distribution and Chi square test for categorical variables.
†Measured 6 years after pregnancy.

better CVH and a lower risk of having <5 ideal CVH metrics 10 years after pregnancy.

Interpretation of Main Findings

Our findings on the negative association between CVH in pregnancy and CIMT are in line with those of a previous study conducted in 490 American male twins (mean age 55.4 [±3.1 years]).[23] The study showed that better CVH was independently associated with a smaller CIMT. Another American study of 1933 participants with mean age of 59±7.5 years demonstrated that having ≥3 ideal CVH metrics was associated with a smaller CIMT.[24] Several studies have compared the CIMT of women with a hypertensive disorder of pregnancy to that of women with a normotensive pregnancy.[25–28] During pregnancy, but also 5 and 25 years after, CIMT was consistently larger in women with a hypertensive disorder of pregnancy compared with women with a normotensive pregnancy. Though the underlying pathophysiology of carotid intima-media thickening is most likely multifactorial, cardiovascular risk factors (or adverse CVH metrics), such as hypertension, obesity, smoking, a high cholesterol, and diabetes mellitus, have been identified as key elements in this process.[29,30] The prevalence of these cardiovascular risk factors is higher amongst women with a hypertensive disorder of pregnancy compared with women with a normotensive pregnancy, which might explain their tendency to a larger CIMT.[5,31,32] It seems plausible that improving adverse CVH metrics early in life will slow down carotid intima-media thickening and possibly reduce long-term atherosclerotic risk and CVD risk. Increasing 5 units in the total CVH score (ranging from 0 to 14) has previously been associated with a 0.05 mm smaller CIMT.[23] We realize that these and our effect estimates on the association between early pregnancy CVH and CIMT seem small. Nevertheless, we consider them substantial as even a small increase in CIMT of 0.1 mm has previously been associated with a 15% higher risk of developing CVD.[33]

Table 4. The Association Between CVH in Early Pregnancy and CIMT and CVH 10 Years After Pregnancy

	Normotensive Pregnancy		Hypertensive Disorder of Pregnancy	
Outcomes 10 Years After Pregnancy	CVH in Early Pregnancy	*P* Value	CVH in Early Pregnancy	*P* Value
CIMT, μm (Beta, 95% CI)	−5.21 (−7.40, −3.01)	<0.001	−9.82 (−17.98, −1.67)	0.02
CVH score (Z-score)	0.26 (0.23, 0.30)	<0.001	0.25 (0.13, 0.37)	<0.001
<5 ideal CVH metrics, RR (95% CI)	0.75 (0.70, 0.80)	<0.001	0.70 (0.46, 0.91)	0.002

Values are regression coefficients and are based on linear and logistic regression analysis. Beta coefficients and relative risks represent the change in outcome per one point increase in the early pregnancy CVH score. Values were adjusted for: age and gestational age at early pregnancy CVH determination, education level, ethnicity, and gravidity during index pregnancy. CIMT indicates carotid intima-media thickness; CVH, cardiovascular health; RR, relative risk.

CVH Later in Life

Population studies showed that only a minority of individuals have 7 ideal CVH metrics (0.1%–2.3%), indicating the rarity of optimal CVH in the general population.[6,34,35] Individuals with fewer ideal CVH metrics are more at risk of developing CVD.[34,35] In our study, the percentage of women with a hypertensive disorder of pregnancy having <5 ideal CVH factors after pregnancy was 81.2%. This was substantially higher compared with that of women aged 20 to 39 years from the National Health and Nutrition Examination Survey study, a large population-based study, where ±64% of women had <5 ideal CVH metrics.[36] Compared with women participating in the National Health and Nutrition Examination Survey study, those with a hypertensive disorder of pregnancy more often had a poor blood pressure and glucose level during and after pregnancy, whereas they were less often smokers. Total cholesterol was similar between both studies, with the majority of women having ideal total-cholesterol concentrations at both time points. Other studies also showed that women with a hypertensive disorder of pregnancy have on average a higher blood pressure in early pregnancy and thereafter.[4] Improving blood pressure as early in pregnancy might help reduce their risk of future hypertension. As blood pressure is closely related to other metrics of the CVH score, such as BMI and physical activity, improving the whole CVH score in early pregnancy might yield a faster reduction in blood pressure than treating blood pressure alone.[37] Our results show that early pregnancy CVH is closely associated with CVH later in life. This suggests that women with good CVH in early pregnancy are likely to have similar CVH after pregnancy. Improving CVH in early pregnancy will likely result in a longer lifetime spent in better health, thereby reducing the risk of CVD.[38–40] Most likely, it is even better and more cost effective to improve CVH before pregnancy, as was demonstrated in previous studies.[41,42] We demonstrate that pre-pregnancy BMI is associated with CVH and CIMT after pregnancy. Though the association with CIMT was not significant in women with a previous hypertensive disorder of pregnancy. A possible explanation for this finding might be that other factors than BMI, eg, the hypertensive disorder of pregnancy itself or a genetic predisposition, are stronger associated with CIMT in women with a previous HDP. Additionally, we showed that in women with a previous HDP, cholesterol and smoking were associated with CIMT and not BMI. Previous studies demonstrated that smoking and cholesterol are risk factors of carotid intima-media thickening through an upregulation of local inflammation.[43,44] Though optimizing pre-pregnancy CVH seems useful, the majority of women do not seek medical help until they are pregnant, which complicates optimization of preconception health by healthcare providers. Raising awareness for healthy lifestyle changes, eg, through government healthcare campaigns and education from a young age onwards, might improve preconception CVH.[45] Improvement of maternal CVH in early pregnancy might also benefit the offspring by reducing the risk of suboptimal developmental programming and consequently reducing predisposition to CVD.[46] For most women, pregnancy is a natural moment to seek medical care. Women are also more motivated to adapt healthful behavior, with the health of the offspring being the most important motivator.[8,9] Projecting on the health of the offspring could be an effective method to frame healthful changes during pregnancy. Healthcare providers (eg, obstetrician, midwife, or general practitioner) could assess the CVH score in early pregnancy and motivate women to adapt healthier lifestyle behaviors, while treating CVH factors if necessary.

Strengths and Limitations

Results of our study should be interpreted within the context of some limitations. First, we used total-cholesterol concentration 6 years after pregnancy as a proxy for the cholesterol metric 10 years after pregnancy because of unavailability of the latter. A recent study showed that total-cholesterol concentration remains fairly stable over a 4-year interval for stable weight individuals.[47] Total-cholesterol concentration slightly decreased in individuals with progressive weight loss (estimated 0.16 mmol/L per 4 years) and progressive weight gain (estimated 0.21 mmol/L per 4 years). As we used a

3 years interval between measuring total-cholesterol concentration and the other CVH metrics and only 6.6% of the total population showed progressive weight gain/loss (data not shown), we feel confident that using this proxy will not have influenced our results substantially. Second, we used non-fasting glucose concentrations to calculate the CVH scores whereas the AHA designed the score with fasting glucose concentrations. As a result, more women were grouped in the "poor" category for this CVH metric both in and after pregnancy. To determine the effect of using non-fasting glucose concentrations, we performed 2 sensitivity analyses (1) after reclassifying the glucose metric according to the International Diabetes Federation criteria for "ideal", "intermediate" and "poor" non-fasting glucose concentrations and (2) after excluding the glucose metric from our CVH score. The absolute CVH scores changed in both analyses. However, the strength and direction of all associations remained the same. Third, we applied BMI cut-offs for non-pregnant adults to construct the early pregnancy CVH score. As the mean gestational age of the early pregnancy CVH score was 13.2 weeks (90% range 10.6, 17.1), some women might have had substantial gestational weight gain by this time. This might have resulted in a misclassification of BMI. However, replacing early pregnancy BMI by pre-pregnancy BMI (obtained through a questionnaire) did not change our main results (Table S4). Fourth, we observed some differences between women with and without a CVH score in pregnancy. Some cardiovascular risk factors were more favorable in women without a CVH score available in pregnancy (blood pressure and smoking status), whereas others (BMI and education level) were more disadvantageous in these women. Including women with a poorer blood pressure and smoking status in our study might have positively influenced the strength of our results, but not the differences of the observed associations between women with a previous normotensive pregnancy and those with a previous hypertensive disorder of pregnancy. Fifth, similar to most population studies, we did not perform preconceptional measurements. Therefore, we cannot exclude the possibility that CIMT was already larger before pregnancy in women with a hypertensive disorder of pregnancy. Nevertheless, the CVH score in early pregnancy was associated with postpartum CIMT and will in practice be relatively easy and cheap to calculate, as opposed to CIMT for which an ultrasound device is required, during a point in life at which women naturally seek health care. Sixth, the CVH score was designed for the general population. This is the first study to examine the CVH score in pregnant women. Results should therefore be interpreted with caution until future studies have replicated similar results. Lastly, results might not be generalizable to all ethnicities as the majority of women in our study were white (81.4%).

Conclusions

Better CVH in pregnancy is associated with less subclinical atherosclerosis after pregnancy and better CVH 10 years after pregnancy. This is relevant for all women, but especially in those with a hypertensive disorder of pregnancy. Improving CVH in early pregnancy will likely result in a longer lifetime spent in better health, thereby reducing the risk of CVD. As pregnancy is an incentive for women to improve lifestyle, future studies should evaluate whether the CVH score in pregnancy is useful for early cardiovascular counseling to optimize CVH.

Acknowledgments

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and the Faculty of Social Sciences of the Erasmus University, Rotterdam; the Municipal Health Service, Rotterdam area; the Rotterdam Homecare Foundation; and the Stichting Trombosedienst and Artsenlaboratorium Rijnmond, Rotterdam, the Netherlands. We gratefully acknowledge the contributions of the general practitioners, hospitals, midwives, and the pharmacies in Rotterdam.

Author Contributions

Dr. Benschop analyzed the data and wrote the article. Dr. Schalekamp-Timmermans, Drs. Schelling, Professor Steegers, and Dr. Roeters van Lennep 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.

Sources of Funding

The Generation R Study was made possible by financial support from the Erasmus Medical Center, Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development, the Netherlands Organization for Scientific Research, the Ministry of Health, Welfare and Sport, and the Ministry of Youth and Families. Professor Vincent Jaddoe received additional grants from the Netherlands Organization for Health Research and Development (grant nos. 90700303, 916.10159 and VIDI 016.136.361) and a Consolidator Grant from the European Research Council (ERC-2014-CoG-64916). This study was made possible by additional funding of the Dutch Heart Foundation (grant number 2013T083).

Disclosures

None.

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Supplemental Material

Data S1.

The CVH score in pregnancy included five metrics (blood pressure, BMI, smoking, total-cholesterol concentration and glucose concentration). The postpartum CVH score was defined according to the classification of the American Heart Association by combining seven health metrics (blood pressure, BMI, smoking, diet, physical activity, total-cholesterol concentration and glucose concentration). For each metric, women were grouped into the poor (0 points), intermediate (1 point) or ideal (2 points) category. The corresponding points of all seven metrics created the CVH score in early pregnancy (ranging from 0 to 10) and postpartum (ranging from 0 to 14). Each metric had the same weight. Women were categorized one group lower for the metrics blood pressure, total-cholesterol and glucose when they received treatment for hypertension, hypercholesterolemia or diabetes (e.g. from ideal to intermediate group for blood pressure). Consequently, these women could not obtain an ideal score for these metrics. The diet metric included five food groups. Women could obtain 1 point for each ideal food group, with a total of five points for an ideal diet. Ideal food groups included: ≥4.5 cups of fruit and vegetables per day, < 1500mg sodium per day, ≥3 servings of 1 ounce fiber-rich whole grains per day, ≤450 kcal of sugar-sweetened beverages per week and ≥2 servings of fish per week. Physical activity was classified as inactive, moderately active (1-149 minutes per week moderately active or 1-74 minutes per week vigorously active) and active (≥150 minutes per week moderately active or ≥75 minutes per week vigorously active).

The total number of postpartum CVH metrics categorized as ideal created a separate score, ranging from 0 to 7. Less than five ideal postpartum CVH metrics was defined as low CVH.

Table S1. Comparison of women with and without a CVH score in early pregnancy.

Characteristics during index pregnancy	Women with CVH score (n=5199)	Women without CVH score (n=3822)	*P*-value
Maternal age, years	29.7 (5.1)	29.8 (5.6)	0.13
Gestational age, weeks	13.4 (10.6, 17.2)	15.8 (11.1, 24.8)	<0.001
Ethnicity, n (%)			<0.001
Caucasian	2868 (75.6)	3278 (71.7)	
African descent	430 (11.3)	682 (14.9)	
Asian/South Asian	367 (9.7)	438 (9.6)	
Other	127 (3.3)	173 (3.8)	
Education, n (%)			<0.001
None/primary	357 (9.6)	548 (13.3)	
Secondary	1753 (47.1)	1950 (47.2)	
Higher	1612 (43.3)	1629 (39.5)	
First pregnancy, n (%)	1833 (48.1)	2185 (44.3)	<0.001
Blood pressure, n (%)			0.004
Poor	227 (5.9)	193 (4.5)	
Intermediate	1273 (33.3)	1367 (31.9)	
Ideal	2322 (60.8)	2726 (63.6)	
BMI, n (%)			<0.001
Poor	429 (11.2)	651 (15.1)	
Intermediate	941 (24.6)	1266 (29.4)	
Ideal	2452 (64.2)	2390 (55.5)	
Smoking, n (%)			0.02
Poor	739 (19.3)	670 (17.6)	
Intermediate	385 (10.1)	342 (9.0)	
Ideal	2698 (70.6)	2800 (73.5)	
Cholesterol, n (%)			0.06
Poor	291 (7.6)	35 (6.5)	
Intermediate	1052 (27.5)	124 (22.9)	
Ideal	2479 (64.9)	383 (70.7)	
Glucose, n (%)			0.12

Poor	40 (1.0)	31 (1.6)
Intermediate	344 (9.0)	186 (9.6)
Ideal	3438 (90.0)	1720 (88.8)

BMI, body mass index; EP-CVH, early pregnancy cardiovascular health; PP-CVH, postpartum cardiovascular health. Values are numbers with valid percentages, means (SD) for variables with a normal distribution and median (90% range) for values with a skewed distribution.

Table S2. The association between the CVH score in early pregnancy, CIMT and the postpartum CVH score when glucose in pregnancy is classified according to the IDF criteria or excluded from the early pregnancy CVH score.

Outcome	**CVH score in early pregnancy according to the IDF criteria**	***P*-value**	**CVH score in early Pregnancy excluding glucose**	***P*-value**
CIMT, μm (Beta, 95% CI)	-5.52 (-7.67, -3.37)	<0.001	-5.78 (-7.98, -3.58)	<0.001
Postpartum CVH score (Beta, 95% CI)	0.26 (0.23, 0.30)	<0.001	0.26 (0.23, 0.30)	<0.001

CIMT, carotid intima-media thickness; CVH, cardiovascular health; IDF, International Diabetes Federation. Values are regression coefficients (beta) with corresponding 95% CI and are based on linear regression analysis. Beta coefficients represent the change in outcome per one point increase in the early pregnancy CVH score. Values were adjusted for: age and gestational age at early pregnancy CVH determination, educational level, ethnicity, years after pregnancy and gravidity after pregnancy.

Table S3. The association between the CVH score in early pregnancy and the postpartum CVH score when postpartum glucose is classified according to the IDF criteria or excluded from the postpartum CVH score.

Outcomes	CVH score in early pregnancy	*P*-value
Postpartum CVH according to the IDF criteria (Beta, 95% CI)	0.27 (0.23, 0.30)	<0.001
Postpartum CVH excluding glucose (Beta, 95% CI)	0.28 (0.25, 0.31)	<0.001

CVH, cardiovascular health; IDF, International Diabetes Federation.
Values are regression coefficients (beta) with corresponding 95% CI and are based on linear regression analysis. Beta coefficients represent the change in outcome per one point increase in the early pregnancy CVH score. Values were adjusted for: age and gestational age at early pregnancy CVH determination, educational level, ethnicity, years after pregnancy and gravidity after pregnancy.

Table S4. The association between the CVH score in early pregnancy and the postpartum CVH score when pre-pregnancy BMI is used to categorize the early pregnancy CVH score.

Outcomes ten years after pregnancy	**CVH score in early pregnancy**	***P*-value**
CVH score (Beta, 95% CI)	0.26 (0.22, 0.30)	<0.001

CVH, cardiovascular health.
Values are regression coefficients (beta) with corresponding 95% CI and are based on linear regression analysis. Beta coefficients represent the change in outcome per one point increase in the early pregnancy CVH score. Values were adjusted for: age and gestational age at early pregnancy CVH determination, educational level, ethnicity, years after pregnancy and gravidity after pregnancy.

Table S5. The association between the individual metrics of the CVH score in early pregnancy and CIMT and CVH ten years after pregnancy.

Outcomes ten years after pregnancy	**Normotensive pregnancy**		**Hypertensive disorder of pregnancy**	
	Exposure in pregnancy	***P*-value**	**Exposure in pregnancy**	***P*-value**
	Smoking		**Smoking**	
CIMT, μm (Beta, 95% CI)	-2.84 (-7.38, 1.69)	0.22	-19.76 (-36.10, -3.42)	0.02
CVH score, (Z-score)	0.33 (0.25, 0.41)	<0.001	0.04 (-0.27, 0.34)	0.82
< 5 ideal CVH metrics, RR (95% CI)	0.73 (0.64, 0.82)	<0.001	0.80 (0.42, 1.08)	0.43
	BMI		**BMI**	
CIMT, μm (Beta, 95% CI)	-12.07 (-17.28, -6.85)	<0.001	-0.03 (-17.01, 16.95)	0.98
CVH score, (Z-score)	0.46 (0.37, 0.56)	<0.001	0.46 (0.19, 0.72)	0.001
< 5 ideal CVH metrics, RR (95% CI)	0.46 (0.37, 0.58)	<0.001	0.42 (0.10, 0.91)	0.01
	Blood pressure		**Blood pressure**	
CIMT, μm (Beta, 95% CI)	-12.77 (-18.26, -7.28)	<0.001	3.67 (-15.18, 22.52)	0.70
CVH score, (Z-score)	0.12 (0.03, 0.22)	0.01	0.29 (-0.03, 0.60)	0.08
< 5 ideal CVH metrics, RR (95% CI)	0.82 (0.72, 0.91)	<0.001	0.79 (0.46, 1.03)	0.11
	Cholesterol		**Cholesterol**	
CIMT, μm (Beta, 95% CI)	-0.67 (-3.27, 1.93)	0.80	-22.32 (-41.05, -3.59)	0.03
CVH score, (Z-score)	0.38 (0.29, 0.48)	<0.001	0.45 (0.14, 0.75)	0.004
< 5 ideal CVH metrics, RR (95% CI)	0.78 (0.68, 0.87)	<0.001	0.76 (0.44, 1.02)	0.09
	Glucose		**Glucose**	

CIMT, μm (Beta, 95% CI)	-8.05 (-17.88, 1.78)	0.11	-19.61 (-47.25, 8.03)	0.17
CVH score, (Z-score)	0.34 (0.13, 0.54)	0.001	0.29 (-0.27, 0.84)	0.31
< 5 ideal CVH metrics, RR (95% CI)	0.76 (0.58, 0.97)	0.02	0.72 (0.18, 1.14)	0.32

CIMT, carotid intima-media thickness; CVH, cardiovascular health; RR, relative risk. Values are regression coefficients and are based on linear and logistic regression analysis. Beta coefficients and odds ratios represent the change in outcome per one point increase in the early pregnancy CVH score. Values were adjusted for: age and gestational age at early pregnancy CVH determination, educational level, ethnicity and gravidity during index pregnancy.

Table S6. The association between pre-pregnancy BMI and CIMT and CVH ten years after pregnancy.

Outcomes ten years after pregnancy	**Normotensive pregnancy**		**Hypertensive disorder of pregnancy**	
	Pre-pregnancy BMI	***P*-value**	**Pre-pregnancy BMI**	***P*-value**
CIMT, μm (Beta, 95% CI)	1.88 (0.96, 2.81)	<0.001	0.14 (-2.67, 2.96)	0.92
CVH score, (Z-score)	-0.08 (-0.09, -0.06)	<0.001	-0.07 (-0.11, -0.03)	0.002
< 5 ideal CVH metrics, RR (95% CI)	1.1 (1.08, 1.12)	<0.001	1.05 (1.0, 1.08)	0.05

CIMT, carotid intima-media thickness; CVH, cardiovascular health; RR, relative risk. Values are regression coefficients and are based on linear and logistic regression analysis. Beta coefficients and odds ratios represent the change in outcome per one point increase in the early pregnancy CVH score. Values were adjusted for: age and gestational age at early pregnancy CVH determination, educational level, ethnicity and gravidity during index pregnancy.