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Original Article

Hypertension during Pregnancy is Associated with Coronary Artery Calcium Independent of Renal Function

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Abstract

Background: Hypertension during pregnancy (HDP) increases the risk of future coronary heart disease (CHD), but it is unknown whether this association is mediated by renal injury. Reduced renal function is both a complication of HDP and a risk factor for CHD.
Methods: Logistic regression models were fit to examine the association between a history of HDP and the presence and extent of coronary artery calcification (CAC), a measure of subclinical coronary artery atherosclerosis, in 498 women from the Epidemiology of Coronary Artery Calcification Study (mean age 63.3 ± 9.3 years).
Results: Fifty-two (10.4%) women reported a history of HDP. After adjusting for age at time of study participation, HDP was associated with increased serum creatinine later in life ($p = 0.014$). HDP was positively associated with the presence of CAC after adjusting for age at time of study participation (OR = 2.7, 95% CI 1.4-5.4). This association was slightly attenuated with adjustment for body size and blood pressure (OR = 2.4, 95% CI 1.2-4.9) but was not further attenuated with adjustment for serum creatinine and urinary albumin/creatinine ratio (OR = 2.6, 95% CI 1.3-5.3). Results were similar for CAC extent.
Conclusions: HDP may increase a woman's risk of future CHD beyond traditional risk factors and renal function. Women with a history of HDP should be monitored for potential increased risk of CHD as they age.

Introduction

Hypertension during pregnancy (HDP), which includes gestational hypertension, transient hypertension of pregnancy, preeclampsia, and eclampsia, is the most common complication of pregnancy, affecting 5%–10% of all pregnancies in the United States.[1] Women with HDP (without preexisting hypertension) generally have resolution of their elevated blood pressure (BP) following delivery of the fetus.[2] There is increasing evidence, however, that a history of HDP may have long-term implications for a woman's health, including an increased risk of hypertension[3–5] and coronary heart disease (CHD).[6,7]

Women who have experienced HDP are also at increased risk for albuminuria,[3,8] a future kidney biopsy,[9] and development of end-stage renal disease (ESRD).[10] Preeclampsia and eclampsia, two of the most severe types of HDP, are often associated with a characteristic glomerular lesion, endotheliosis.[11,12] Although delivery of the fetus is thought to resolve endotheliosis, there is increasing evidence that although some cases completely resolve, other women who have experienced preeclampsia will go on to have evidence of longer-term renal damage.[13–15] Thus, we hypothesized that HDP causes both renal injury and subtle coronary artery injury that can eventually progress to detectable coronary artery disease (CAD) and cardiac events.[1,13,16,17] Even a subtle decrease in renal function in women with a history of HDP may also predict who is at risk of CHD.

Coronary artery calcification (CAC) is a marker of subclinical coronary artery atherosclerosis. The extent of CAC predicts the risk of CHD events.[18–20] Albuminuria among older (mean age 63 years)[21] but not younger adults (mean age 44 years)[22] and glomerular filtration rate (GFR)[23] are each associated with CAC presence and extent. Albuminuria is a

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potent predictor of future cardiovascular events, even among persons with a normal GFR.[24] Thus, it is of particular interest whether variation in renal function explains the increased risk of CHD in women with HDP.

We investigated whether a self-reported history of HDP, using a validated survey,[5] is associated with the presence and extent of CAC in 498 non-Hispanic white women participating in the Epidemiology of Coronary Artery Calcification (ECAC) Study, a community-based study in Rochester, Minnesota. We further evaluated whether measures of renal function, obtained at the same time as CAC measurement, explain the relationship between HDP and presence and extent of CAC.

Materials and Methods

Study participants

The Rochester Family Heart Study (RFHS), conducted between 1984 and 1991, identified households where ≥2 children were enrolled in Rochester, Minnesota, schools. Identified household members, as well as other relatives, were invited to participate in the RFHS; among the 3974 participants recruited into the RFHS, 2046 were females ranging in age from 5 to 92 years.[25,26] The ECAC Study, conducted between 1991 and 1998, examined 533 women ≥20 years of age from the RFHS and 334 women ≥20 years of age living in the vicinity of Rochester, who were not pregnant or lactating and never had coronary or noncoronary heart surgery.[27,28] Questions on reproductive history pertaining to HDP were asked of the 574 (316 RFHS and 258 non-RFHS) women participating in the follow-up ECAC examination conducted between December 2000 and February 2005. The present study is limited to this follow-up examination.

A total of 563 non-Hispanic white women with information on reproductive history had electron beam computed tomography (EBCT) examinations to measure the presence and extent of CAC. Twenty-nine women with prevalent CHD (defined as self-reported history of myocardial infarction [MI], stroke, or a positive angiogram), 10 missing risk factor information, 1 who had kidney transplantation, and 25 without a pregnancy lasting >6 months were excluded from analyses. The final study group consisted of 498 (289 RFHS and 209 non-RFHS) women. Study protocols were approved by the Mayo Clinic and University of Michigan Institutional Review Boards, and participants gave written informed consent.

Risk factor assessment

During follow-up examination interviews, women were asked about pregnancy history using a questionnaire[5] recently validated in a sample of women receiving care from the Mayo Clinic in Rochester who experienced a pregnancy between 1960 and 1979 (average time since pregnancy was ~27 years). This population is the same underlying population sampled by the ECAC Study. Self-reported history of preeclampsia, eclampsia, and toxemia was obtained from 103 women with a confirmed diagnosis of one of these conditions and 100 women who had confirmed normotensive pregnancies. Information gathered from the medical records was the standard used for the diagnosis of preeclampsia and was used to confirm the diagnosis based on current guidelines.[2] Of the 103 women with preeclampsia, eclampsia, or toxemia, 82 (79.6%) recalled the diagnosis; only 4 (4%) participants without a diagnosis of preeclampsia reported a history of these conditions. Thus, the questionnaire used in the ECAC Study has an estimated 80% sensitivity and 95% specificity.[5] Women in the ECAC Study with ≥1 pregnancy lasting >6 months who reported high BP or hypertension during a pregnancy (HDP) were considered to have HDP. Preeclampsia, eclampsia, and toxemia were defined either by self-report of these conditions or by self-report of protein in the urine during the pregnancy with hypertension.

Participants reported current medication use and history of smoking, physician-diagnosed hypertension, MI, angiographic evidence of a blocked coronary artery, stroke, or diabetes. Family history of premature CHD was defined as self-reported MI or coronary artery revascularization in a parent or sibling that occurred before age 60 years.[29,30] Height was measured by a wall stadiometer, weight was determined by electronic balance, and body mass index (BMI) was calculated. Waist circumference was measured at the umbilicus, hips were measured at the level of maximal circumference, and the waist/hip ratio was calculated.

Standard enzymatic methods were used to measure total cholesterol, high-density lipoprotein cholesterol (HDL-C), plasma glucose, triglycerides, and serum creatinine (SCr) after overnight fasting.[26] Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation in women with triglycerides <400 mg/dL.[31] Systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels were measured three times at least 2 minutes apart in the right arm with a random-zero sphygmomanometer (Hawksley and Sons, Lancing, Sussex, UK). The average of the second and third measurements was used. Pulse pressure (PP) was defined as SBP−DBP. Women were considered hypertensive if they reported a prior diagnosis of hypertension and use of prescription BP-lowering medication or if average SBP or DBP was ≥140 mm Hg or ≥90 mm Hg, respectively. Women were considered prehypertensive if their average SBP was between 120 and 139 mm Hg or DBP was between 80 and 89 mm Hg and if they did not report a prior diagnosis of hypertension or use of prescription BP-lowering medication.[32] Participants were considered diabetic if they reported using insulin or oral hypoglycemic agents or if they reported a physician diagnosis of diabetes.

The first voided urine was collected on the morning of the study visit and stored at −80°C until analyzed. Urine albumin and urine creatinine concentrations were measured by standard methods on a Hitachi 911 Clinical Chemistry Analyzer (Roche Diagnostics, Nutley, NJ). Urine albumin/urine creatinine ratio (UACR) was calculated and expressed as milligrams of albumin per gram of creatinine. Microalbuminuria was defined as a UACR >30 mg/g.[33] Estimated GFR (eGFR) was calculated using the Modification of Diet in Renal Disease equation that adjusts SCr for demographic variation (age, sex, and race).[34] Estimated GFR<60 mL/min per 1.73 m^2 body surface area was used to define women with GFR levels consistent with chronic kidney disease.[35]

Measurement of CAC

CAC was measured with an Imatron C-150 EBCT scanner (Imatron Inc., South San Francisco, CA).[36] A scan run con-

sisted of 40 contiguous 3-mm-thick tomographic slices from the root of the aorta to the apex of the heart. Scan time was 100 ms/tomogram. Electrocardiographic gating was used, and all images were triggered at end-diastole during 2–4 breath-holds. A radiological technologist scored the tomograms with an automated scoring system without knowledge of other EBCT examination results for the same participant.[37] CAC was defined as a hyperattenuating focus within 5 mm of the midline of a coronary artery, ≥4 contiguous pixels in size, and having CT numbers >130 Hounsfield units throughout. A score for each focus of CAC was calculated by multiplying the focus area (square millimeters) by a density measurement that was defined by the peak CT number in that focus.[38] Total CAC score was calculated as the sum of scores for all foci in the epicardial arteries.[38] Total CAC score was used to define categories of CAC extent based on cutoff points previously defined in women that are associated with increased risk of MI (0, 1–10, 11–100, and >100).[20] To reduce nonnormality, the total CAC score was natural log transformed after adding 1.

Statistical methods

A statistical significance level of 0.05 was used. All tests were two-sided. Our two selected measures of renal function, SCr and UACR, were both nonnormally distributed, so each measure was natural log-transformed (ln). Age-adjusted linear and logistic regression models (for continuous and discrete variables, respectively) were fit to examine differences in CHD risk factors and renal function measures between women with and without reported HDP.

Logistic regression models were fit to examine the association of HDP with CAC presence in the ECAC Study. We fit an unadjusted model; a model adjusted for age; a model adjusted for age, waist/hip ratio, DBP, and SBP; and finally, a model additionally adjusted for BMI, as done by others.[39] We then examined whether measures of renal function altered the association of HDP with CAC presence by fitting a logistic regression model additionally including ln(SCr) and ln(UACR). The final model considered also included diabetes status, menopause status, and BP-lowering medication use. Two-way interactions between renal function measures and all other model covariates were also considered.

Ordinal logistic regression models were fit to examine the relationship between HDP and CAC extent (CAC score categories of 0, 1–10, 11–100, and >100).[20] The models allowed estimation of the odds of being in a higher CAC score category compared with a lower CAC score category. Models were fit with the same risk factors and renal function measures as described. The proportional odds assumption was tested with the score test.

Results

Fifty-two women (10.4%) reported HDP. Of 50 women with complete pregnancy data, 24 (48.0%) reported the HDP was preeclampsia, eclampsia, or toxemia, and 21 (42.0%) reported the HDP occurred during the first pregnancy. The mean age of women with a history of HDP was significantly less than among those without a history of HDP ($p = 0.026$) (Table 1).

Age-adjusted differences in CHD risk factors between women with and without a history of HDP are presented in Table 1. Women who reported a history of HDP had significantly higher mean levels of SBP ($p = 0.006$) and PP ($p = 0.002$) and a significantly higher frequency of hypertension ($p = 0.014$), use of BP-lowering medications ($p = 0.020$), and diabetes ($p = 0.006$) compared with women without HDP.

Relationship of HDP and CAC with renal function

Women with HDP had a significantly higher mean ln(SCr) ($p = 0.014$) compared with women without HDP after adjusting for age; however, eGFR and ln(UACR) levels did not differ between women with and without HDP ($p = 0.081$ and $p = 0.974$, respectively) (Table 1).

UACR levels differed significantly between women with and without detectable CAC (mean ± standard deviation [SD] UACR 13.3 ± 52.7 vs. 4.6 ± 9.5 mg/g, respectively; $p = 0.004$ on ln scale after age-adjustment). SCr levels did not significantly differ between women with and without detectable CAC (mean SCr 68.6 ± 19.9 vs. 65.3 ± 12.0 μmol/L, respectively; $p = 0.694$ on ln scale after age-adjustment). eGFR levels did not significantly differ between women with and without detectable CAC (mean eGFR 86.2 ± 25.4 vs. 89.3 ± 19.2 mL/min per 1.73 m^2, respectively; $p = 0.348$ after age-adjustment).

Relationship of HDP with CAC presence in ECAC Study

Table 2 shows the association of HDP, unadjusted and adjusted for CHD risk factors, with CAC. HDP was significantly associated with the presence of CAC after adjusting for age and further adjustment for additional CHD risk factors. Women with HDP had a 2.4 (95% confidence interval [CI] 1.2-4.9) times greater odds of having detectable CAC ($p = 0.016$) than women without HDP after adjustment for selected CHD risk factors.

Next, we examined whether the association between HDP and CAC presence was explained by measures of renal function. After adjusting for ln(SCr) and ln(UACR), HDP remained statistically significantly associated with CAC presence ($p = 0.010$). In this model, a 1-unit increase in ln(UACR) was associated with a 1.3 (95% CI 1.1-1.7) times increased odds of having detectable CAC (data not shown). In this model, ln(SCr) was not significantly associated with CAC presence ($p = 0.372$) (data not shown). Finally, we further adjusted for menopausal and diabetes status and use of BP-lowering medication. In this model, HDP remained significantly associated with CAC presence (OR = 2.2, 95% CI 1.0-4.6, $p = 0.041$). There was no evidence of an interaction between HDP and either measure of renal function with CAC presence.

Of the women with HDP, 24 (48.0%) had preeclampsia. We compared CAC presence among three groups: those who had a history of normotensive pregnancy, those with a history of HDP (but not preeclampsia), and those with a history of preeclampsia. Inferences were similar to inferences obtained when women were dichotomized into those with and without HDP. We also examined whether timing of HDP (in first pregnancy or in a subsequent pregnancy) was associated with CAC presence. Inferences were again similar; regardless of when the HDP occurred, HDP was associated with CAC presence.

Relationship of HDP with CAC extent

The distribution of CAC extent (categories defined as CAC score of 0, 1–10, 11–100, and >100) is shown in Table 1, and

Table 1. Characteristics of 498 ECAC[a] Study Women at Time of EBCT Examination, by HDP Status[b]

Characteristic of women at time of examination	*Reported HDP*	*No reported HDP*	p[c]
Number in group	52 (10.4%)	446 (89.6%)	–
Age, years	60.6 ± 10.6	63.6 ± 9.1	0.026
Median age, years	61.0	63.2	–
(25th, 75th percentile)	(38.3, 80.6)	(33.8, 87.1)	–
BMI (kg/m^2)	30.1 ± 6.4	28.5 ± 5.9	0.135
Waist/hip ratio	0.87 ± 0.10	0.86 ± 0.10	0.335
SBP (mm Hg)	129.9 ± 23.2	125.4 ± 18.4	0.006
DBP (mm Hg)	69.8 ± 10.9	68.9 ± 9.1	0.623
PP (mm Hg)	60.1 ± 20.4	56.5 ± 15.6	0.002
Cholesterol (mmol/L)	5.3 ± 0.8	5.3 ± 0.9	0.698
HDL-C (mmol/L)	1.5 ± 0.4	1.6 ± 0.4	0.450
LDL-C (mmol/L)[d]	3.0 ± 0.7	3.0 ± 0.8	0.850
Triglycerides (mmol/L)	1.5 ± 0.8	1.6 ± 0.8	0.905
Fasting glucose (mmol/L)	5.6 ± 1.3	5.5 ± 1.1	0.185
Current smoker	6 (11.5%)	30 (6.7%)	0.409
Former smoker	22 (42.3%)	132 (29.6%)	0.073
Hypertension	29 (55.8%)	201 (45.1%)	0.014
Prehypertension	6 (11.5%)	82 (18.4%)	0.199
BP-lowering medications	28 (53.9%)	190 (42.6%)	0.020
Lipid-lowering medications	8 (15.4%)	116 (26.0%)	0.183
Diabetes	8 (15.4%)	27 (6.1%)	0.006
Family history of premature CHD	16 (30.8%)	141 (31.6%)	0.845
Number of pregnancies lasting >6 months	3.5 ± 1.8	3.6 ± 2.0	0.507
Postmenopausal[e]	46 (88.5%)	408 (92.1%)	0.111
Hormone replacement use[f]	15 (32.6%)	137 (33.6%)	0.866
SCr (μmol/L)	72.5 ± 24.5	66.5 ± 15.7	–
Median SCR (μmol/L)	66.3	61.9	–
(25th, 75th percentile)	(61.9, 81.8)	(57.5, 75.1)	
ln(SCr)	4.24 ± 0.29	4.17 ± 0.22	0.014
eGFR (mL/min per 1.73 m^2)	84.3 ± 27.8	87.9 ± 22.3	0.081
Median eGFR (mL/min per 1.73 m^2)	88.1	83.0	–
(25th, 75th percentile)	(30.7, 165.8)	(24.1, 175.8)	–
eGFR <60	41 (9.2%)	9 (17.3%)	0.014
UACR (mg/g)	18.8 ± 100.4	8.4 ± 25.0	–
Median UACR (mg/g)	3.1	3.1	–
(25th, 75th percentile)	(1.6, 5.4)	(1.8, 5.2)	
ln(UACR)	1.5 ± 1.2	1.5 ± 1.0	0.974
Microalbuminuria	22 (4.9%)	2 (3.9%)	0.817
CAC presence	35 (67.3%)	243 (54.5%)	0.004
Median CAC score	17.5	1.9	–
(25th, 75th percentile)	(0.0, 131.2)	(0.0, 81.4)	
ln(CAC score +1)	2.8 ± 2.4	2.2 ± 2.4	0.003
CAC score category			0.004
0	17 (32.7%)	203 (45.5%)	
1–10	7 (13.5%)	44 (9.9%)	
11–100	12 (23.1%)	106 (23.8%)	
>100	16 (30.8%)	93 (20.9%)	

[a]ECAC, Epidemiology of Coronary Artery Calcification; EBCT, electron-beam computed tomography; HDP, hypertension during pregnancy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; BP, blood pressure; CHD, coronary heart disease; SCr, serum creatinine; ln, natural log; eGFR, estimated glomerular filtration rate; UACR, urinary albumin creatinine ratio; CAC, coronary artery calcification; –, not tested.

[b]Data are *n* (%) or mean ± SD or median (25th, 75th percentile).

[c]*p* value is for the age-adjusted difference between women with HDP and those without HDP (except for age) and is from linear regression (continuous covariates) or logistic regression (discrete covariates).

[d]Five women (1 with HDP) missing LDL-C.

[e]Three women (all without reported HDP) missing menopause status information.

[f]Among postmenopausal women.

the association of HDP with CAC extent is shown in Table 3. After adjusting for age, HDP was significantly associated with CAC extent ($p = 0.002$). After adjusting for age, BMI, waist/hip ratio, DBP, and SBP, HDP continued to be significantly associated with CAC extent ($p = 0.007$). After further adjustment for renal function measures, HDP remained significantly associated with CAC extent ($p = 0.004$). Women with HDP had a 2.4 (95% CI 1.3-4.2) times greater odds of being in a higher CAC extent category compared with women without HDP. UACR was significantly associated with CAC extent

Table 2. Association of HDP with Presence of CAC in ECAC[a] Study

	OR (95% CI)	p
HDP unadjusted	1.72 (0.94-3.16)	0.081
HDP adjusted for age	2.72 (1.37-5.41)	0.004
HDP adjusted for age, waist/hip ratio, SBP, DBP	2.43 (1.20-4.91)	0.013
HDP adjusted for age, BMI, waist/hip ratio, SBP, DBP	2.41 (1.18-4.92)	0.016
HDP adjusted for age, BMI, waist/hip ratio, SBP, DBP, ln(SCr), ln(UACR)	2.58 (1.26-5.32)	0.010
HDP adjusted for age, BMI, waist/hip ratio, SBP, DBP, ln(SCr), ln(UACR), diabetes status, menopause status, and BP-lowering medication use	2.18 (1.03, 4.59)	0.041

[a]HDP, hypertension during pregnancy; CAC, coronary artery calcification; ECAC, Epidemiology of Coronary Artery Calcification; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ln, natural log; SCr, serum creatinine; UACR, urinary albumin creatinine ratio; BP, blood pressure.

($p = 0.009$); a 1-unit increase in ln(UACR) was associated with a 1.3 (95% CI 1.1-1.5) times greater odds of being in a higher rather than lower category of CAC extent after adjusting for age, HDP, BMI, waist/hip ratio, SBP, DBP, and ln(SCr). In the model, ln(SCr) was not significantly associated with CAC extent ($p = 0.640$). We further adjusted for menopausal and diabetes status and BP-lowering medication use. In this model, HDP remained significantly associated with CAC extent (OR = 1.9, 95% CI 1.1-3.5, $p = 0.032$).

Table 3. Association of HDP[a] with Extent of CAC, Defined Based on CAC Score Categories,[20] in ECAC Study

	OR (95% CI)	p
HDP unadjusted	1.62 (0.96-2.74)	0.069
HDP adjusted for age	2.50 (1.42-4.40)	0.002
HDP adjusted for age, waist/hip ratio, SBP, DBP	2.23 (1.26-3.98)	0.006
HDP adjusted for age, BMI, waist/hip ratio, SBP, DBP	2.22 (1.24-3.97)	0.007
HDP adjusted for age, BMI, waist/hip ratio, SBP, DBP, ln(SCr), ln(UACR)	2.36 (1.31-4.24)	0.004
HDP adjusted for age, BMI, waist/hip ratio, SBP, DBP, ln(SCr), ln(UACR), diabetes status, menopause status, and BP-lowering medication use	1.92 (1.06-3.48)	0.032

[a]HDP, hypertension during pregnancy; CAC, coronary artery calcification; ECAC, Epidemiology of Coronary Artery Calcification; OR, odds ratio; CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; ln, natural log; SCr, serum creatinine; UACR, urinary albumin creatinine ratio; BP, blood pressure.

The proportional odds assumption was not rejected in any model ($p > 0.1$ for all models). There was no evidence of an interaction between HDP and either measure of renal function with CAC extent.

Inferences regarding association with CAC extent were the same when we considered HDP as preeclampsia or no preeclampsia and when we considered the timing of HDP (in first pregnancy or in a subsequent pregnancy) (data not shown).

Discussion

In addition to providing evidence that HDP is a risk factor for subclinical coronary artery atherosclerosis, our study provides novel insight into understanding this risk factor association with subclinical disease. We hypothesized that diminished renal function could account for the increased presence and extent of subclinical coronary artery atherosclerosis associated with HDP. Instead, we found evidence that HDP was associated with the presence and extent of CAC, independent of renal function measures. Previously, a significant association between HDP and the presence of CAC was found in the Predictors of Response to Cardiac Resynchronization Therapy (PROSPECT) Study; however, PROSPECT did not investigate HDP's association with CAC extent nor were measures of renal function considered.[39] Here, we have extended the findings from the PROSPECT Study. In addition, the ECAC Study also had some information on preeclampsia.

Preeclampsia, which may be a multisystem disease with additional clinical presentations compared with the other HDP disorders, may differentially influence future CHD risk.[40] In the ECAC Study, inferences remained the same when we individually modeled preeclampsia or HDP without preeclampsia compared with normotensive pregnancy, suggesting that the spectrum of HDP, and not preeclampsia alone, was associated with future subclinical coronary artery atherosclerosis.

Neither our study nor the PROSPECT Study found an association between fasting glucose level and HDP. A small number of ECAC women ($n = 35$, 7%) had diabetes; after adjusting for age, women with HDP were 2.7 (95% CI 1.4-5.4) times more likely to have diabetes later in life than women without HDP. Diabetes is a strong independent predictor of CAC presence and extent[41] and is the most common cause of chronic kidney disease.[42] After including diabetes status in the final models in the present study, the association of HDP with CAC presence and extent provided similar inferences as before, although the odds ratio estimates were slightly attenuated. HDP is associated with gestational diabetes,[43] and gestational diabetes is a risk factor for future development of diabetes.[44] We have no information on history of gestational diabetes in the ECAC Study; thus, we cannot determine if this attenuation of effect is due to HDP additionally capturing some women with gestational diabetes. Future studies are needed to assess the individual and joint effects of HDP and gestational diabetes on future development of subclinical coronary artery atherosclerosis.

We used SCR instead of eGFR in our models because the study group was limited to white women, SCr measures were age-adjusted, and a validated equation for the general population does not exist.[45] However, inferences from models using eGFR rather than SCR were the same.

In this sample of relatively older women, some may not have accurately recalled history of HDP. Age was inversely associated with HDP in the ECAC Study; this could indicate a temporal trend in the diagnosis of HDP, a survival bias in that older women with HDP died before inclusion in the ECAC study, or a problem of recall bias. However, the questionnaire used to define HDP has been validated in an independent study.[5] Similarly, in a recent study comparing self-reported history of preeclampsia with diagnoses recorded in a hospital discharge database ($n = 2307$ women), positive and negative predictive values of self-reported preeclampsia were 59.2% and 99.2%, respectively.[46] It is more likely that women with HDP would incorrectly self-report as not having HDP rather than women without HDP self-reporting as having a positive history of HDP; thus, associations would be biased toward the null, and the strength of the relationship between HDP and CAC may be underestimated in the present study.

We did not have information on when HDP occurred during a pregnancy, whether or not the pregnancy was full-term, or the birth weight of the baby. Women with pre-existing, but undiagnosed, hypertension may have been incorrectly diagnosed with HDP during their prenatal care, as it may have been discovered for the first time during their pregnancy. Thus, our definition of HDP may include women who had chronic hypertension before their pregnancy. The prevalence of hypertension among young, white women of childbearing potential is rather low (6.2% among women 20–34 years of age and 16.5% among women 35–44 years of age)[47]; thus, it is unlikely that many women were misclassified in the current study. Additionally, only 2 women reported being diagnosed with hypertension prior to HDP. Excluding these 2 women from the analyses did not alter the inferences (data not shown).

The prevalence of detectable CAC was relatively high in the current study (55.8%). The estimated odds ratio may overestimate the true relative risk of having detectable CAC under the condition of high disease prevalence.[48] Inferences from the models (e.g., elevated risk of having detectable CAC presence among women with HDP compared with women without HDP), however remain the same whether using odds ratios or relative risks to quantify the association.

Our study group was restricted to white, non-Hispanic women, reflecting the population composition of the Rochester, Minnesota, area at the time of the study. Rates of HDP differ by race/ethnicity,[49,50] and there are racial differences in rates of hypertension,[47] renal disease,[42] and CAC burden.[51] Our results are most generalizable to populations of white, primarily postmenopausal, non-Hispanic women.

Although a direct relationship exists between CAC and both histological and *in vivo* measures of atherosclerotic plaque on a heart-by-heart, vessel-by-vessel, and segment-by-segment basis,[52–56] the absence of detectable CAC with EBCT does not necessarily mean an absence of coronary artery atherosclerosis. This measure likely underestimates total atherosclerosis in some individuals because CAC more closely represents calcified plaque burden than overall atherosclerosis.

Conclusions

Previous studies have shown an association between traditional CHD risk factors measured early in life and later subclinical coronary artery atherosclerosis and CHD events.[7,20,57–59] We have shown that HDP in early life predicts future reduced renal function and increased presence and extent of subclinical coronary artery atherosclerosis in older women. Importantly, a history of HDP in early life was an independent predictor of subclinical coronary artery atherosclerosis even after considering many traditional CHD risk factors measured in later life. While women may commonly delay focus on CHD health until midlife,[54] education and CHD risk factor monitoring may be especially important for women with HDP, starting at postpartum checkups and continuing across the life course, in order to reduce the CHD burden in women.

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Disclosure Statement

No competing financial interests exist.

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