Trajectory of Cardiovascular Risk Factors After Hypertensive Disorders of Pregnancy

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Trajectory of Cardiovascular Risk Factors After Hypertensive Disorders of Pregnancy

An Argument for Follow-Up

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See Editorial Commentary, pp 47–48

Abstract—Women with a history of a hypertensive disorder of pregnancy (HDP) are at increased risk of premature cardiovascular disease. Cardiovascular risk management guidelines emphasize the need for prevention of cardiovascular disease in these women but fail to provide uniform recommendations on when and how to start cardiovascular risk assessment. The aim of this study was to identify a window of opportunity in which to start cardiovascular risk factor assessment by investigating changes in blood pressure, lipids, and fasting glucose levels over time in women with a history of an HDP. We identified women with a history of a normotensive pregnancy (n=1811) or an HDP (n=1005) within a high-risk population-based cohort study. We assessed changes in blood pressure, lipids, glucose, 10-year cardiovascular risk and the occurrence of hypertension, dyslipidemia, and diabetes mellitus longitudinally using 5 measurements at 3-year intervals. Generalized estimating equations were used for statistical analysis, with age as the time variable, adjusting for multiple comparisons using the least significant differences method. In women with an HDP, the overall prevalence of hypertension (P<0.0001), dyslipidemia (P=0.003), and diabetes mellitus (P<0.0001) was significantly higher. They also developed hypertension and diabetes mellitus earlier. At age 35, few women with HDP need to be screened to detect clinically relevant hypertension: 9 need to be screened to detect 1 woman with a treatment indication as opposed to 38 women with history of a normotensive pregnancy. Our data supports cardiovascular follow-up of women with a history of an HDP starting within the fourth decade of life. **(*Hypertension*. 2019;73:171-178. DOI: 10.1161/HYPERTENSIONAHA.118.11726.)**

Key Words: cardiovascular disease ■ diabetes mellitus ■ dyslipidemia ■ hypertension ■ hypertension, pregnancy-induced ■ preeclampsia ■ risk factors

Pregnancy induces an extensive adaptation of the cardiovascular system, including a major increase in hemodynamic volume and cardiac output.[1–4] Pregnancy complications, such as hypertensive disorders of pregnancy (HDP), might be an indication of limited cardiovascular capacities. HDP occurrence thereby offers an opportunity to identify women at increased risk for cardiovascular diseases (CVD).[5–7] Accumulating evidence demonstrates an increased risk and accelerated development of CVD risk factors and CVD events later in life in women with a history of HDP compared with women with a history of a normotensive pregnancy (NP).[8–10]

In the international guidelines, such as the 2011 National Institute for Health and Care Excellence guideline, 2011 American College of Cardiology/American Heart Association's guideline, and the 2016 European Society of Cardiology guideline CVD prevention, preeclampsia is pointed out as a female-specific risk factor.[11–13] Although the guidelines acknowledge the strong rationale for cardiovascular screening and prevention, they fail to provide uniform recommendations in shaping this.[11,14–17] It remains to be determined how this risk should be weighed against the well-known lifestyle and traditional risk factors and at what moment in time which preventive measures should be taken.

Hypertension is the most common risk factor appearing in the first 2 decades after HDP, being present in 20% to 40% of women in their mid-40s.[18] Previous observational studies showed a common occurrence of hypertension after HDP.[19–22] In contrast to prevalent hypertension after HDP, dyslipidemia and diabetes mellitus after HDP are much less often reported.[23,24] Despite the common occurrence of hypertension after HDP, current practice does not include standardized cardiovascular assessment after HDP to identify women that may benefit from stringent follow-up or intervention strategies to prevent CVD onset. One of the factors that hampers

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implementation of such approach is insufficient insight into the changes in cardiovascular risk factors over time.[14,16,25] The aim of this study is to investigate development of elevated blood pressure (BP), elevated lipids and elevated fasting glucose levels, and CVD risk scores over time in women with and without previous HDP to generate evidence for the identification of a window of opportunity for screening and intervention in these HDP women.

Methods

Additional information on the data, materials, or analytic methods that support the findings of this study are available from the corresponding author on reasonable request.

PREVEND Study

The PREVEND study (Prevention of Renal and Vascular End-Stage Disease) is a prospective cohort study on the long-term natural course of renal, cardiac, and peripheral vascular events with a follow-up to 75 years of age.[26] In short, starting from 1997 to 1998, all inhabitants of the city of Groningen (the Netherlands), aged 28 to 75 years (85 421), were asked to participate in the study.

A total of 40 856 (47.8%) subjects responded to the call. Subjects with type 1 diabetes mellitus and women pregnant at the initiation of the study were excluded. The urinary albumin concentration was assessed in 40 856 responders. Subjects with a urinary albumin concentration ≥10 mg/L (n=7768) were invited to participate, of whom 6000 were enrolled. In addition, a randomly selected group with a urinary albumin concentration <10 mg/L (n=3394) was invited to participate in the cohort, of whom 2592 were enrolled. Five screenings took place between 1997 and 2012, consisting of a questionnaire, physical examination, and a blood and urine sample. The PREVEND study has been approved by the medical ethics committee of the University Medical Centre Groningen. Written informed consent was obtained from all participants.

Description of the Cohort

In total, 4301 women were included in the PREVEND study. For the current study, only women who reported any history of pregnancy and who answered the questions on hypertension during pregnancy at first or second visit were included. We excluded women who reported no previous pregnancy (n=1096) or an unknown outcome (n=389). If the answer to the question on hypertension during pregnancy was "no", we classified women as women with an NP (n=1008), and if this was "yes, allowed to do anything" or "yes, had to keep bed rest," we classified women as women with a patient-reported hypertensive pregnancy disorder (HDP; n=1005). No pregnancies were reported after the second visit.

Data were collected in 5 consecutive screening moments over a period of 15 years. BP, TC (total cholesterol), HDL-c (high-density lipoprotein cholesterol), and fasting glucose levels, were measured using routine clinical procedures and laboratory facilities. TC/HDL ratios were calculated dividing TC values by HDL-c values. Exact methods of clinical and laboratory measurements have previously been described elsewhere.[26] Prescription data from pharmacies were reviewed to assess the use of BP and lipid-lowering medication. We scored participants as hypertensive if they used BP-lowering medicine and diabetic if they reported this in the questionnaire or reported the use of glucose-lowering medication.

The 10-year cardiovascular risk scores were calculated according to the Pooled Cohort Equations.[27] Participants were considered to be at elevated risk if the predicted risk was ≥7.5%.[13] Microalbuminuria was defined as urine protein of 30 to 300 mg/24µ, macroalbuminuria as >300 mg/24µ.[28] The number needed to screen (NNS) to detect 1 participant with an indication for treatment of hypertension, dyslipidemia, or diabetes mellitus was calculated. Values above absolute treatment thresholds (BP >180/110 mm Hg, TC/HDL ratio >8, fasting glucose >11 mmol/L) or a Pooled Cohort Equations>7.5% or the use of BP, lipid, or glucose-lowering medication were defined as absolute treatment indications.

Statistical Analysis Strategy

Normally distributed data are presented as mean±SD, skewed data as median with 25th to 75th percentile. The data was collected and arranged per subject per visit. Age categories were used as a time-dependent predictor. Using generalized estimating equations with an independent correlation matrix, the time factor during follow up, the difference between HDP and NP women and the interaction between time and group was assessed. We chose to use generalized estimating equations over a linear mixed model because the aim is to uncover a population average rather than an individual effect.[29]

Some individuals would possibly remain in the same age category during 2 or even 3 consecutive visits, resulting in unequal weight of the measurements of certain participants. We used an identifying variable, defined as participant×visit to adjust for this in the analysis. In this way, the longitudinal data structure was not compromised. The effect of smoking, body mass index (BMI), and medication use (BP, blood glucose, and lipid-lowering) was assessed in generalized estimating equations analysis per outcome variable separately. Variables with a significant association with the outcome were added to the main analyses of that outcome to adjust for confounding.

The cohort was enriched with subjects with an elevated urinary albumin excretion. Albuminuria is associated with CVD, and thus a selection of women in worse cardiovascular condition might have taken place.[30] Because the distribution of micro and macroalbuminuria was similar in NP and HDPs, we did not expect this to affect the direction of our estimates and decided not stratify or adjust for this in our analysis. We did perform subanalyses in patients without albuminuria (NP, n=1590 and HDP, n=854) on mean BP, prevalence of BP-lowering medicine, and NNS for the indication for treatment of hypertension to support this hypothesis.

Statistical significance from generalized estimating equations analyses was described in differences between the 2 groups in 1 age category ($P_{category}$), between the groups overall (P_{group}), and between the slopes of the 2 groups ($P_{interaction}$). We adjusted for multiple comparisons using the least significant difference method. All statistical analyses were conducted using SPSS 22.0 (SPSS, Inc, Chicago, IL); a P value <0.05 was considered statistically significant. For visualizations, GraphPad Prism 5.01 (GraphPad Software, Inc, San Diego, CA) was used.

Results

Study Population

In total, 1005 women with HDP and 1811 women with NP were included in the analysis (Figure 1). The median age at the start of PREVEND was similar in both groups, as was the median follow up (Table). Most PREVEND participants were of European descent. Similar percentages of participants in both the NP and HDP group smoked or used alcohol. The prevalence of microalbuminuria was similar in both groups (9.9% versus 12%), as was macroalbuminuria (0.8% versus 1.1%).

Classical Risk Factors and Risk Score

The estimated mean systolic BP (SBP) and diastolic BP (DNP) per age category was adjusted for BMI, smoking, and BP-lowering medication (Figure 2A). Until the age of 55 years, SBP was ≈10 mm Hg higher in HDP women than in NP women (P_{group}<0.0001). Overall, SBP and DBP were at a significantly higher level in HDP women (P_{group}<0.0001). But the increase of SBP and BP over time was similar in HPD and NP women ($P_{interaction}$=0.15).

The use of BP-lowering medication per age category was adjusted for BMI and smoking (Figure 2B). After the age of 30 years, significantly HDP women used more BP-lowering medication than NP women. Overall, the use of BP-lowering medication was significantly higher in HDP women (P_{group}<0.0001) but showed no significant difference in

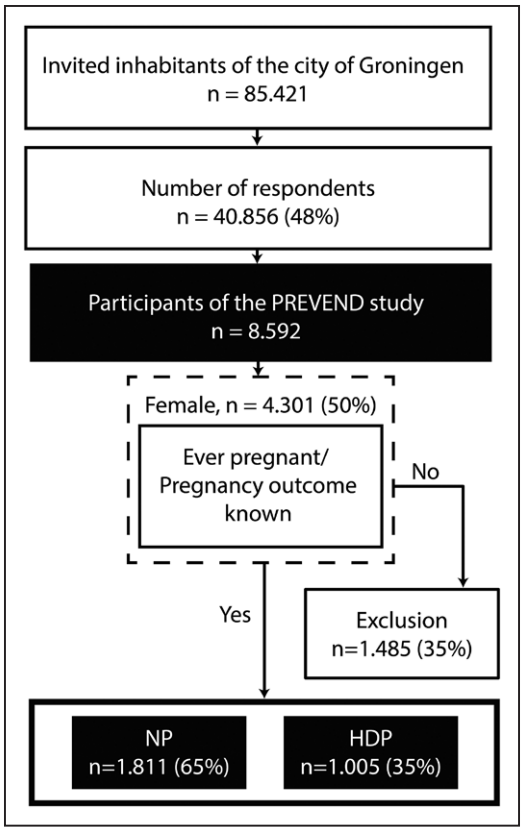

Figure 1. PREVEND study (Prevention of Renal and Vascular End-Stage Disease) and selection of patients for current analyses. HDP indicates history of hypertensive disorder of pregnancy; and NP, history of normotensive pregnancy.

increase over time ($P_{interaction}$=0.553). HDP women seemed to develop hypertension 10 to 15 years earlier than NP women, which was determined based on whether participants used BP-lowering medicine.

The estimated mean TC/HDL-c ratios per age category were adjusted for BMI, smoking, and use of lipid-lowering medication (Figure 2C). Before the age of 55 years, the TC/HDL ratio was significantly more unfavorable in HDP women than in NP women ($P_{category}$=0.01–0.03).

The use of lipid-lowering medication per age category was adjusted for BMI and smoking (Figure 2D). Until the age of 65 years, the use of lipid-lowering medication seemed higher in HDP women than NP women, but this difference did not hold over the entire follow up period. There is no overall group difference between HDP and NP women ($P_{group=}$0.86).

The estimated mean fasting glucose levels per age category was adjusted for BMI, smoking, and use of glucose-lowering medication (oral antidiabetics or insulin; Figure 2E). After the age of 45, fasting glucose levels were significantly higher in HDP women than in NP women ($P_{category=}$0.003). Overall, diabetes mellitus was more prevalent in HDP women ($P_{group=}$0.001; Figure 2F). The increase of diabetes mellitus prevalence over time was steeper in women after HDP than after NP ($P_{interaction}$=0.008).

The estimated 10-year CVD event risk according to the pooled cohort equations was calculated without adjustments

Table. Characteristics at Entry of the PREVEND Study

Characteristics	NP, n=1811 (65%)	HDP, n=1005 (35%)
General characteristics		
Age, y	49 (41, 58)	48 (39, 59)
White, n (%)	1706 (95)	968 (97)
Cardiovascular risk profile		
BMI, kg/m^2	26 (5)	27 (5)
SBP, mm Hg	122 (20)	130 (22)
DBP, mm Hg	70 (9)	74 (9)
Current smoker, n (%)	643 (36)	314 (31)
Ever smoked, n (%)	1557 (86)	860 (86)
Current alcohol use, n (%)	802 (45)	449 (46)
Ever alcohol use, n (%)	1058 (59)	573 (57)
Renal disease requiring dialysis, n (%)	7 (0.4)	1 (0.1)
Laboratory results		
Glucose, mmol/L	4.6 (4.2, 5.0)	4.7 (4.3, 5.1)
Total cholesterol, mmol/L	5.6 (4.8, 6.8)	5.7 (4.9, 6.5)
HDL cholesterol, mmol/L	1.4 (1.2, 1.7)	1.4 (1.2, 1.7)
eGFR, mL/min per 1.73 meter^2	100 (77.6, 122.5)	94.7 (72.0, 117.4)
Creatinine, mg/dL	64 (51, 77)	65 (51, 80)
Urine		
No microalbuminuria	1590 (87)	854 (85)
Microalbuminuria	179 (9.9)	119 (12)
Macroalbuminuria	15 (0.8)	11 (1.1)

Data are presented as mean±SD or median (25th, 75th percentile) unless otherwise stated. BMI indicates body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HDP, history of hypertensive disorder of pregnancy; PREVEND, Prevention of Renal and Vascular End-Stage Disease; NP, history of normotensive pregnancy; and SBP, systolic blood pressure.

(Figure 3A). From the age of 34 years onwards, more HDP women surpassed the clinically relevant threshold of 7.5% risk compared with NP women ($P_{group=}$0.006; Figure 3B). Overall, the estimated 10 years CVD event risk was significantly higher in HDP women than NP women (P_{group}<0.0001). The absolute CVD risk increase was also steeper in HDP women ($P_{interaction}$=0.002).

Number Needed to Screen

We calculated the estimated NNS as the number of participants that needed to be tested by a caregiver to detect one participant with an indication for treatment of hypertension, dyslipidemia, or diabetes mellitus.

At age 35 to 40, the NNS for hypertension was 1 in 9 for HDP women versus 38 in NP women (P_{group}<0.0001; Figure 4A). At age 40, the NNS to detect clinically relevant dyslipidemia was 18 in HDP women versus 56 in NP women (P_{group}=0.011; Figure 4B). After the age of 50, the NNS for diabetes mellitus was significantly lower in HDP women (NNS ≤22) versus NP women (NNS ≤45; Figure 4C).

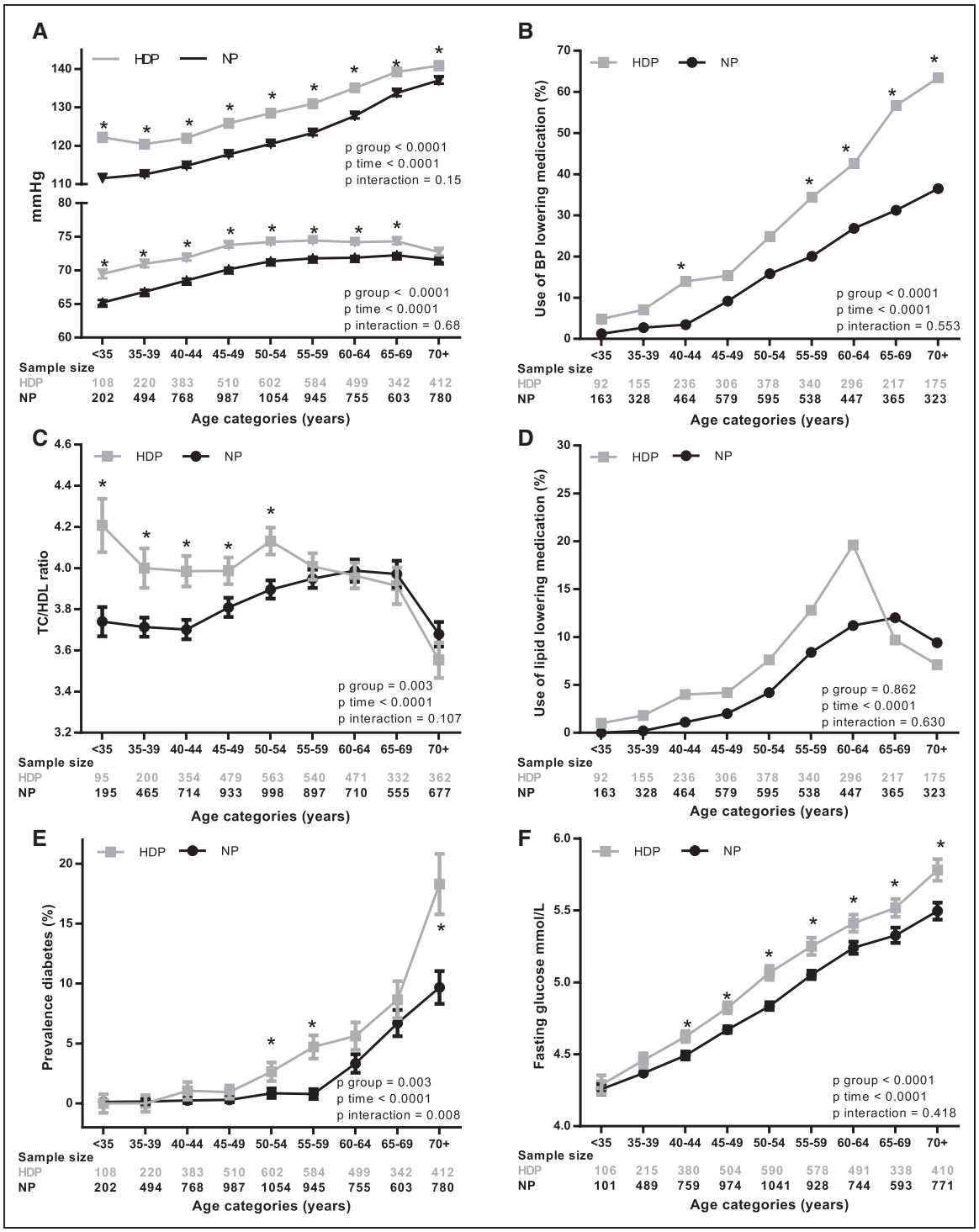

Figure 2. Metabolic profile per age category stratified for history of hypertensive disorder of pregnancy (HDP) versus history of normotensive pregnancy (NP). **A**, Mean systolic and diastolic blood pressure (BP; adjusted for the use of BP-lowering medication, body mass index [BMI], and smoking). **B**, Prevalence of the use of BP-lowering medication (adjusted for BMI). **C**, Mean total cholesterol (TC)/ HDL (high-density lipoprotein)-cholesterol ratio (adjusted for lipid-lowering medication, BMI, and smoking). **D**, Prevalence of the use of lipid-lowering medication (adjusted for BMI). **E**, Mean fasting glucose (adjusted for the use of antidiabetics, BMI, and smoking). **F**, Prevalence of diabetes mellitus (adjusted for BMI). *significant differences (P<0.05) within the age category.

Sub Analyses in Patients Without Albuminuria

In total, 854 women with HDP and 1590 women with NP were included in the subanalyses (figures not displayed in this article). The estimated mean SBP and diastolic BP per age category was adjusted for BMI, smoking, and BP-lowering medication. The estimated means showed similar patters as in the full cohort: in all age categories, SBP was ≈10 mm Hg higher in HDP women than in NP women (P_{group}<0.0001). Also, there was a significantly higher prevalence of use of BP-lowering medication in HDP women (P_{group}<0.0001). At age 35 to 40, the NNS for hypertension was 1 in 13 for HDP women versus 42 in NP women (P_{group}<0.0001).

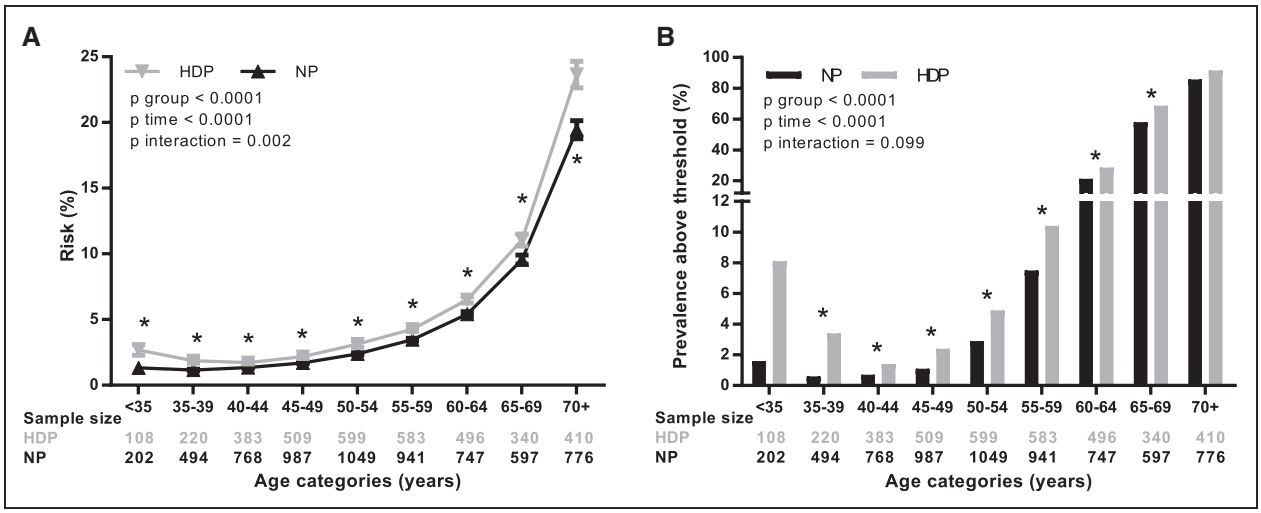

Figure 3. Cardiovascular risk score. **A**, Pooled cohort equations 10 years cardiovascular disease risk per age category stratified for NP (history of normotensive pregnancy) vs HDP (hypertensive disorder of pregnancy). **B**, The prevalence of women with CVD risk >7.5%. *significant differences (P<0.05) within the age category.

Discussion

In this study, we aimed to answer when and how cardiovascular prevention in HDP women should be commenced. We reported on longitudinal data illustrating how classical CVD risk factors develop in relation to hypertensive disorders during pregnancy in a population-based albuminuria enriched cohort (PREVEND study). We confirm that hypertension and diabetes mellitus develop earlier in HDP women. As early as age 35, the NNS to detect 1 woman with an indication for treatment of hypertension was 9 in HDP women versus 38 in NP women. These associations were similar in a subanalysis amongst women without albuminuria. This supports the argument that BP checkups should be started shortly postpartum.

In our data, BP was higher in HDP women than in NP women during the entire follow-up. In addition, the prevalence of hypertension increased faster in HDP women than in non-HDP women. This is in accordance with results from other large cohort studies.[19,31–33] However, BP did surprisingly not rise with increasing ages (natural course of BP).[34] This might be the result of survivor bias. Also, more women in both HDP and NP groups use more BP-lowering medicines when aging. Despite our efforts to adjust for this statistically, this medication use might have clouded the expected age-related increase of BP in the older ages. Nonetheless, the fast increase in the use of BP-lowering medication gives us other information: it indicates that even at young age, the severity of the hypertension was such that treatment was indicated.

But when do we need to follow up on our patients? A previous study associated the BP at 6 weeks postpartum to hypertension 2 years postpartum.[35] In our study, the NNS to detect hypertension is already significantly lower in HDP women at age 35 (9 in HDP versus 38 in NP women). We suggest combining this evidence into a follow-up program. The postpartum checkup is an opportunity to identify women at risk. Then, the BP in women with a slightly elevated pressure can be reevaluated after 2 years. Furthermore, these young women can monitor their own BP, which also increases patient involvement and patient empowerment.[18,36]

We showed an association between HDP and development of diabetes mellitus later in life, which is consistent with previous data.[37–39] The risk of diabetes mellitus was 2× higher in a large follow-up study 16.5 years after a pregnancy complicated by HDP, even in the absence of gestational diabetes mellitus.[37] The severity of disease and gestational age at delivery was associated with the risk for type 2 diabetes mellitus, with women with prior early-onset preeclampsia and preterm birth at highest risk.[38,39] Fasting glucose increased at age 40, but there was no increase in diabetes mellitus until age 50. However, also glucose levels that are below diagnostic thresholds, subclinical diabetes mellitus, are associated with endothelial damage and sequentially CVD.[40,41] Therefore, we might underestimate the actual contribution of glucose homeostasis disturbances to the cardiovascular risk.

Our data did not show a difference in lipid levels between HDP and NP women, which is consistent with previous data including our meta-regression analysis.[18,32] However, studies on lipid metabolism during pregnancy did show that higher LDL-c (low-density lipoprotein cholesterol) levels were associated with a higher incidence of preeclampsia.[30,42,43] Lipids might be involved in the endothelial inflammation present in HDP women during the index pregnancy, and abnormalities dissolve in the years after pregnancy. Furthermore, there might be a medication effect in our data, despite our efforts to adjust for this statistically.

The precise insight into how CVD risk factors develop over time in women with HDP from 30 to 75 years old has not yet been presented in the current literature. This longitudinal study comprised a large cohort where all measurements were uniformly assessed during a median follow-up of 12 years. But, for our analysis was conducted in a 95% white population, the result might not be generalizable to more mixed-race populations.

Unfortunately, we did not have information of the exact HDP phenotype or gestational age at delivery, which is considered a measure of the severity of HDP, nor was any information available on gestational age at delivery, birthweight, or

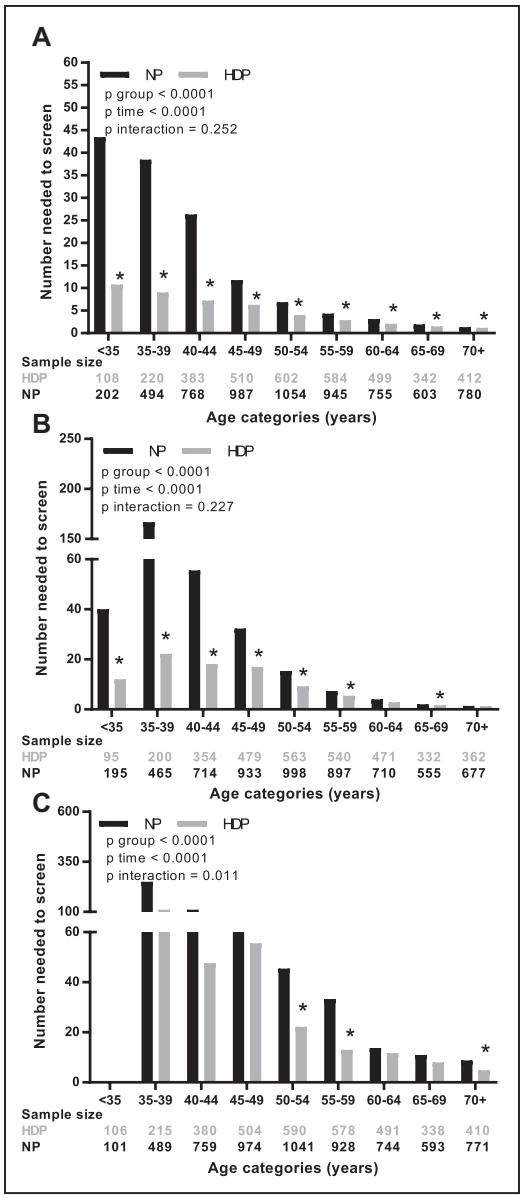

Figure 4. Numbers needed to screen to detect 1 patient with an indication for treatment for classical cardiovascular risk factors. **A**, Hypertension. **B**, Dyslipidemia. **C**, Diabetes mellitus. *significant differences (P<0.05) within the age category. HDP indicates history of hypertensive disorder of pregnancy; and NP, history of normotensive pregnancy.

recurrence of HDP.[44] Thus, we could not find the differences in severity of (recurrent) HDP among groups over time in our cohort. Future analysis stratified on HDP phenotype and gestational age at delivery could benefit from a more personalized approach in follow-up. We excluded women with unknown pregnancy outcome, which might have resulted in the overestimation of HDP prevalence because of recall bias. We do not expect this to affect the direction and strength of our associations measured. We did not have data on the date of birth from the index pregnancy, and, therefore, we were unable to calculate associations between follow up time postpartum and cardiovascular risk factors.

In our cohort, 35% of the women reported a history of HDP, which is considerably higher than the usual prevalence of 10%. Although this may suggest recall bias, previous validation analyses of self-reported history of HDP in this cohort showed a specificity of 94% and sensitivity of 84%.[45] Furthermore, in a different Dutch cohort of women as similar percentage was reported.[46] At the baseline examination of the PROSPECT study (Predictors of Response to Cardiac Resynchronization Therapy), women had been asked, "Did you suffer from high blood pressure during pregnancy?" If confirmative, women were regarded to have had a hypertensive disorder of pregnancy.[47] The prevalence of a history of high BP in pregnancy was 30.7%. The high prevalence is most likely a consequence of the fact that our measurement of hypertension in pregnancy includes women with not only brief and modest elevation of BP during pregnancy but also women with (pre)eclampsia.

This may have led to misclassification. The question was not directed toward the more severe hypertensive disorder of pregnancy, that is, preeclampsia. So, milder variants of hypertension in pregnancy have been included too. Therefore, one might question its effect on the validity and magnitude of our findings. If risk factors lead only to the development of severe elevated BP during pregnancy, then the magnitude of our finding is clearly an underestimation of the truth. The direction of the relations are, however, valid yet in truth may be actually stronger than the one that we observed.

Classical CVD scores are not considered well applicable to young women, which might have resulted in some overestimation of the cardiovascular risk[48]. However, compared with the Framingham risk score, pooled cohort equations calculations are more conservative.[48] Also, prediction models for disease risk are limited to 1 static measurement, whereas an actual patient's CVD is evolving and influenced by interventions.[49] Therefore, some prefer to assess the indication for treatment based on gain in healthy life expectancy.[49] Annual screening of BP of women with a history of preeclampsia proved to be cost-effective, with absolute costs, events, life years, and quality-adjusted life years taken into account.[50]

Perspectives

The next challenge is to find the appropriate intervention. The Dutch guideline on cardiovascular risk management after reproductive and pregnancy-related disorders focusses on lifestyle strategies (salt reduction, physical activity, smoking cessation), which have proved to be effective to reduce BP.[51]

Complicated pregnancy could well be used as a window of opportunity for screening and prevention of CVD. Our data supports cardiovascular follow-up of women with HDP starting within the fourth decade of life.

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Disclosures

None.

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Novelty and Significance

What Is New?

- We investigated the development of blood pressure, lipids and fasting glucose levels, and cardiovascular disease risk scores over time in women with and without previous history of hypertensive disorder of pregnancy to generate evidence for the identification of a window of opportunity for cardiovascular risk screening and intervention in these history of hypertensive disorder of pregnancy women.

What Is Relevant?

- Guidelines emphasize the need for prevention of cardiovascular disease in women with a history of hypertensive disorder of pregnancy, but fail to provide uniform recommendations on when and how to start cardiovascular risk assessment.

Summary

Complicated pregnancy could very well be used as a window of opportunity for screening and prevention of cardiovascular disease. Our data supports cardiovascular follow-up of women with history of hypertensive disorder of pregnancy starting within the fourth decade of life.