Cardiovascular mortality in women in their forties after hypertensive disorders of pregnancy in the Netherlands: a national cohort study

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Summary

Background Hypertensive disorders of pregnancy are associated with cardiovascular disease later in life. Given that hypertensive disorders of pregnancy often occur at a relatively young age, there might be an opportunity to use preventive measures to reduce the risk of early cardiovascular disease and mortality. The aim of this study was to assess the risk of cardiovascular mortality in women after a hypertensive disorder of pregnancy.

Methods In this population-based cohort study, the Netherlands Perinatal Registry (PRN) and the national death registry at the Dutch Central Bureau for Statistics were linked. We analysed women in the Netherlands with a first birth during 1995–2015 to determine the association between cardiovascular mortality and hypertensive disorders of pregnancy (based on recorded diastolic blood pressure or proteinuria, or both). We analysed the association between the highest diastolic blood pressure measured in pregnancy and cardiovascular mortality and constructed survival curves to assess cardiovascular mortality after hypertensive disorders of pregnancy, specifically pre-eclampsia and gestational hypertension. To differentiate between the severity of hypertensive disorders of pregnancy, cardiovascular mortality was assessed in women with a combination of hypertensive disorders of pregnancy with preterm birth (gestational age <37 weeks) and growth restriction (birthweight in the 10th percentile or less). All hazard ratios (HRs) were adjusted for maternal age.

Findings Between Jan 1, 1995, and Dec 31, 2015, the PRN contained 2 462 931 deliveries and 1 625 246 women. In 1 243 890 women data on their first pregnancy were available and were included in this analysis after linkage, with a median follow-up time of 11·2 years (IQR 6·1–16·3). 259 177 (20·8%) women had hypertensive disorders of pregnancy, and of these 45 482 (3·7%) women had pre-eclampsia and 213 695 (17·2%) women had gestational hypertension; 984 713 (79·2%) women did not develop hypertension in their first pregnancy. Compared with women without hypertensive disorders of pregnancy, the risk of death from any cause was higher in women who had hypertensive disorders (HR 1·30 [95% CI 1·23–1·37], $p<0·001$), pre-eclampsia (1·65 [1·48–1·83]; $p<0·0001$), and gestational hypertension (1·23 [1·16–1·30]; $p<0·0001$). Those women with pre-eclampsia had a higher risk of cardiovascular mortality compared with those without any hypertensive disorders of pregnancy (adjusted HR 3·39 [95% CI 2·67–4·29]), as did those with gestational hypertension (2·22 [1·91–2·57]). For women with a history of hypertensive disorders of pregnancy combined with preterm birth (gestational age <37 weeks) and birthweight in the 10th percentile or less, the adjusted HR for cardiovascular mortality was 6·43 (95% CI 4·36–9·47), compared with women without a hypertensive disorder of pregnancy. The highest diastolic blood pressure measured during pregnancy was the strongest risk factor for cardiovascular mortality (for 80–89 mm Hg: adjusted HR 1·47 [95% CI 1·00–2·17]; for 130 mm Hg and higher: 14·70 [7·31–29·52]).

Interpretation Women with a history of hypertensive disorders of pregnancy have a risk of cardiovascular mortality that is 2–3 times higher than that of women with normal blood pressure during pregnancy. The highest measured diastolic blood pressure during pregnancy is an important predictor for cardiovascular mortality later in life; therefore, women who have hypertensive disorders of pregnancy should be given personalised cardiovascular follow-up plans to reduce their risk of cardiovascular mortality.

Funding None.

Introduction

Hypertension in pregnancy includes pre-eclampsia and gestational hypertension, which complicates 6–10% of pregnancies, and is a leading cause of maternal and neonatal morbidity and mortality.[1–5] Pre-eclampsia is defined as the onset of hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) in combination with any organ failure.[6]

Research in context

Evidence before this study
Cardiovascular disease is a leading cause of morbidity and mortality in women. Hence, there is an urgent need for more knowledge on antecedents to cardiovascular disease in women. Hypertensive disorders of pregnancy are related to cardiovascular disease later in life, possibly leading to cardiovascular mortality. We searched PubMed for papers published between September, 2018, and Jan 30, 2022, to identify all relevant English articles on cardiovascular mortality after a hypertensive disorder of pregnancy. The search strategy included the following terms: "hypertensive disorder(s) of pregnancy", "hypertensive pregnancy disorder(s)", "preeclampsia", "blood pressure", "cardiovascular disease", "cardiovascular mortality", "long term", and "follow-up".

Added value of this study
To our knowledge, no large nationwide studies exist on the cardiovascular mortality risk after a hypertensive pregnancy

disorder in the first decade after birth. Additional risk factors for cardiovascular mortality, such as gestational age of less than 37 weeks, neonatal birthweight in the 10th percentile or less, and the highest diastolic blood pressure during pregnancy were identified. The higher cardiovascular mortality in these relatively young women (<50 years) with a history of hypertensive disorder of pregnancy underscores the need for targeted preventive measures soon after a pregnancy complicated by any hypertensive disorder.

Implications of all the available evidence
In light of our findings, since serious cardiovascular events might already have occurred at a young age, a bespoke cardiovascular follow-up should be designed for women with a history of hypertensive disorders of pregnancy.

Gestational hypertension is defined as the onset of hypertension during pregnancy without organ involvement.

Cardiovascular disease is a leading cause of morbidity and mortality in women.[5,7] Therefore, there is an urgent need for more knowledge on antecedents to cardiovascular disease in women.[7] Hypertensive disorders of pregnancy are related to cardiovascular disease later in life.[8] Given that hypertension in pregnancy occurs at a relatively young age, pregnancies complicated by hypertensive disorders could offer an opportunity for preventive strategies.[9]

Higher cardiovascular mortality rates in women with a history of hypertensive disorders of pregnancy have been described in several cohort studies.[10–17] However, these studies only included women with a long-term follow-up after giving birth of 15–50 years or women aged 56–66 years in their analysis. Few data are available concerning cardiovascular mortality in the first 20 years after giving birth, in women in their forties. Studies suggest that the severity of the hypertensive disorder of pregnancy is correlated with the onset of cardiovascular disease. For example, pre-eclampsia has been correlated with a higher cardiovascular risk compared with gestational hypertension.[8] If hypertensive disorders of pregnancy are associated with higher cardiovascular mortality within the first 20 years after delivery, this finding would emphasise the need for targeted preventive measures soon after a pregnancy complicated by any hypertensive disorder.

To address this issue, we designed a national linkage study between the Netherlands Perinatal Registry (PRN), with deliveries between Jan 1, 1995, and Dec 31, 2015, and the national death registry at the Dutch Central Bureau for Statistics (CBS) to assess the association between blood pressure in nulliparous women to determine their risk of cardiovascular mortality. Further, we analysed the risk of cardiovascular mortality for different hypertensive

disorders of pregnancy and the effect of the severity of the hypertensive disorder on cardiovascular mortality.

Methods
Study design and data sources
In this population-based cohort study, we linked PRN with CBS. PRN is a nationwide database covering deliveries from 22 weeks of gestation onwards. The database contains information on 96–98% of all deliveries and newborn admissions and readmissions until 28 days after delivery in the Netherlands. Data are obtained by a validated linkage from four different registries: the LVR1 registry (midwives), the LVRh registry (general practitioners), the LVR2 registry (obstetricians), and the LNR registry (paediatricians or neonatologists).[18] For this study, we only used the data from obstetricians—the LVR2 registry, in which there are around 120 000 deliveries recorded each year—because pregnancies with complications, including hypertensive disorders of pregnancy, are managed by obstetricians and are therefore registered in the LVR2 registry. LVR2 data were available from Jan 1, 1985, to Dec 31, 2015.

LVR2 data on outcome of the pregnancy and delivery were linked with the national death registry on the basis of the date of birth of the mother and the four-digit zipcode of the mother. Because causes of death were available from Jan 1, 1995, to Jan 1, 2017, we used data from women in this register whose first delivery was represented in the LVR2 registry from Jan 1, 1995, to Dec 31, 2015. If the linkage of the mother to the CBS mortality database was unsuccessful (eg, because of loss to follow-up in the CBS database), women were excluded from analysis. After linkage, a unique maternal code was generated on the basis of the date of birth of the woman and the date of birth of their child or children, to obtain information on all deliveries per woman. For any woman

who had died, these women were registered by the cause of death, as defined by CBS.

The Medical Research Involving Human Subjects Act (WMO) does not apply to this study. Official ethics approval of this study by the Medical Ethics Review Committee of VU University Medical Center (Amsterdam, Netherlands) was not required. The Dutch Perinatal Registry board approved the use of their database for the purpose of this study (approval number 16.41).

Definitions and variables

CBS coded the cause of death with the 10th International Statistical Classification of Diseases and Related Health Problems (ICD-10). We subdivided the cause of death of women into four groups: cardiovascular mortality (ICD-10 code I00-I99), death due to cancer (ICD-10 code C00-D48), other causes of death (remaining ICD codes), and unknown causes of death.

In PRN, hypertension was defined as a blood pressure of 90 mm Hg or higher (reported as highest measured diastolic blood pressure during gestation). In the LVR2 database, information on systolic blood pressure is unavailable. Hypertensive disorders of pregnancy were pre-eclampsia and gestational hypertension. Pre-eclampsia was defined as the combination of a diastolic blood pressure of 90 mm Hg or higher (reported as highest measured diastolic blood pressure during gestation) and the presence of 300 mg or higher proteinuria in 24 h, because this was the definition of pre-eclampsia at the time of the reported pregnancies according to the International Society for the Study of Hypertension in Pregnancy guidelines. Gestational hypertension was defined as a diastolic pressure of 90 mm Hg or higher without proteinuria. To differentiate between severity of hypertensive disorder of pregnancy, cardiovascular mortality was assessed in women with a combination of hypertensive disorders of pregnancy with preterm birth (gestational age <37 weeks) and growth restriction (neonatal birthweight in the 10th percentile or less).[19] Highest diastolic blood pressure, proteinuria, and birthweight are accurately coded in the LVR2 registry and were therefore analysed in detail in this study.

All pregnancies were analysed and coded for the presence of hypertensive disorder of pregnancy and subcoded into pre-eclampsia or gestational hypertension and no hypertensive disorders of pregnancy. In the case of unknown proteinuria and reported diastolic blood pressure of 90 mm Hg or higher, the pregnancy was coded as gestational hypertension. In the case of unknown diastolic blood pressure, women were coded as having no hypertensive disorders of pregnancy.

Pregnancies were also coded for maternal age at delivery and presence of a multiple-birth pregnancy. Details on how the coding of the main pregnancy characteristics is displayed in the LVR2 are available in the appendix (p 1).

In the LVR2 registry, predisposing risk factors, such as chronic hypertension, heart or kidney disease, diabetes, and ethnicity were not accurately coded, therefore, we have not included these factors in our analyses. A post-hoc sensitivity analysis for cardiovascular mortality in women with hypertensive disorders of pregnancy, pre-eclampsia, or gestational hypertension, and those with no hypertensive disorders of pregnancy was performed, excluding the women with missing data on proteinuria, blood pressure, or gestational age.

Outcomes

We analysed cardiovascular mortality with all first pregnancies of women in the database. We compared cardiovascular mortality rates in women with hypertensive disorders of pregnancy with those without hypertensive disorders of pregnancy. The highest diastolic blood pressure measured in pregnancy was subcategorised to evaluate the effect of the severity of hypertension on cardiovascular mortality.

Cohort

Using the unique maternal personal code from the CBS, women in the linked cohort were analysed as either having a history of hypertensive disorders of pregnancy or no history of hypertensive disorders of pregnancy. Overall mortality risk in women with hypertensive disorders of pregnancy was analysed.

We analysed the cardiovascular mortality in women and divided them into eight groups on the basis of an increasing highest measured diastolic blood pressure during their first pregnancy (diastolic blood pressure of <70 mm Hg, 70–79 mm Hg, 80–89 mm Hg, 90–99 mm Hg, 100–109 mm Hg, 110–119 mm Hg, 120–129 mm Hg, and 130 mm Hg and higher). Women whose blood pressure was unknown were not included in the analysis. Women with recorded hypertensive disorders of pregnancy were classified as having had either pre-eclampsia or gestational hypertension. We analysed cardiovascular mortality in women according to whether they had pre-eclampsia, gestational hypertension, or no hypertensive disorders of pregnancy. Additionally, we analysed cardiovascular mortality in women with a combination of hypertensive disorders of pregnancy with preterm birth (gestational age <37 weeks) and growth restriction (birthweight in the 10th percentile or lower),[19] to differentiate between the severity of hypertensive disorders of pregnancy. Age of death and subcauses of cardiovascular mortality were analysed using the ICD-10 codes between women with or without pre-eclampsia and gestational hypertension.

Statistical analysis

Baseline characteristics between women with pre-eclampsia, women with gestational hypertension, and women without hypertensive disorders of pregnancy were compared using the one-way ANOVA for continuous values and χ^2 tests for categorical factors. Cox regression models were used to calculate mortality risks in women with a history of hypertensive disorders of

Figure 1: **Study profile**
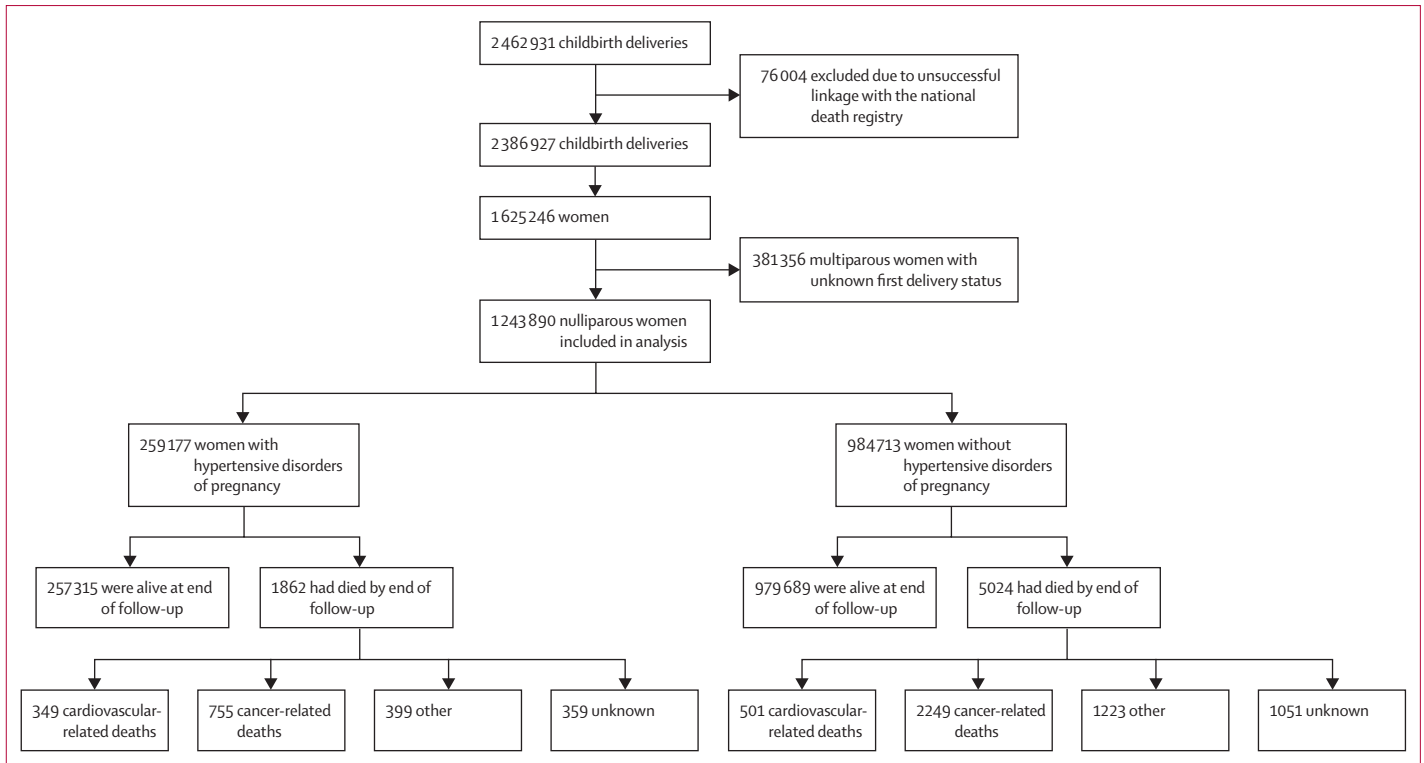
	Pre-eclampsia (n=45 482)	Gestational hypertension (n=213 695)	No hypertensive disorders of pregnancy (n=984 713)
Maternal age at first birth, years (SD)	29·2 (4·86)	29·5 (4·53)	28·9 (4·85)
Highest diastolic blood pressure measured, mm Hg (SD)	104·0 (9·47)	96·8 (7·43)	76·3 (6·60)
Mean gestational age, days/weeks+days (SD)	261/ 37+2; (SD 21·7)	275/ 39+2; (SD 15·8)	277/ 39+4; (SD 16·4)
Birthweight, g (SD)	2740 (843)	3258 (672)	3328 (620)
Multiple births, n (%)	2853 (6·3%)	7121 (3·3%)	21113 (2·1%)

Data are mean (SD) or median (IQR).

Table 1: **Baseline demographic and clinical characteristics for nulliparous women with pre-eclampsia, gestational hypertension, and no hypertensive disorders of pregnancy**

pregnancy at different follow-up times. The first delivery date was used as start of follow-up time. Women were followed up (ie, death status was obtained [cause of death or alive]) until death or end of follow-up (Jan 1, 2017). Hazard ratios (HRs) were used to measure the effect of hypertensive disorders of pregnancy on cardiovascular mortality over time.

We created survival curves for cardiovascular mortality for the different blood pressure groups as well as for women with pre-eclampsia, women with gestational hypertension, and women without hypertensive disorders

of pregnancy. All HRs were adjusted for maternal age given that age is associated with both hypertensive disorders of pregnancy and (cardiovascular) mortality and, thus, a possible confounder. The level of significance was defined as less than 0·05 and HRs were expressed with a 95% CI.

All analyses were conducted in the CBS microdata environment, using SPSS (version 22.0).[20]

Role of the funding source

There was no funding source for this study.

Results

Between Jan 1, 1995, and Dec 31, 2015, PRN contained 2 462 931 deliveries from nulliparous and multiparous women. 76 004 (3·1%) deliveries could not be linked with the national death registry. After linkage, 1 243 890 women whose first pregnancy was known remained for analysis (figure 1). The median follow-up time from the first pregnancy to cardiovascular mortality in all nulliparous women was 11·2 years (IQR 6·1–16·3; for median follow-up times for all groups see appendix p 1). Of 1 243 890 nulliparous women included in the analysis, 259 177 (20·8%) women had hypertensive disorders of pregnancy (45 482 [3·7%] women had pre-eclampsia and 213 695 [17·2%] women had gestational hypertension), and 984 713 (79·2%) women did not develop hypertension in their first

	Number of cardiovascular mortalities	Number of women alive	p value	HR (95% CI) for cardiovascular mortality	Adjusted HR (95% CI) for cardiovascular mortality*
Hypertensive disorders of pregnancy	349	257 315	<0·0001	2·47 (2·16–2·83)	2·40 (2·10–2·76)
Hypertensive disorder of pregnancy in the form of pre-eclampsia	79	45 102	<0·0001	3·43 (2·70–4·34)	3·39 (2·67–4·29)
Hypertensive disorder of pregnancy in the form of gestational hypertension	270	212 213	<0·0001	2·28 (1·97–2·65)	2·22 (1·91–2·57)
Hypertensive disorder of pregnancy and preterm birth (<37 weeks of gestation)	87	37 600	<0·0001	4·21 (3·35–5·28)	4·08 (3·25–5·12)
Hypertensive disorder of pregnancy combined with preterm birth (<37 weeks of gestation) and fetal growth restriction (birthweight in the 10th percentile or less)	27	6635	<0·0001	6·62 (4·49–9·75)	6·43 (4·36–9·47)

Data are n or HR (95% CI) unless otherwise stated. HR=hazard ratio. *Adjusted for maternal age at birth.
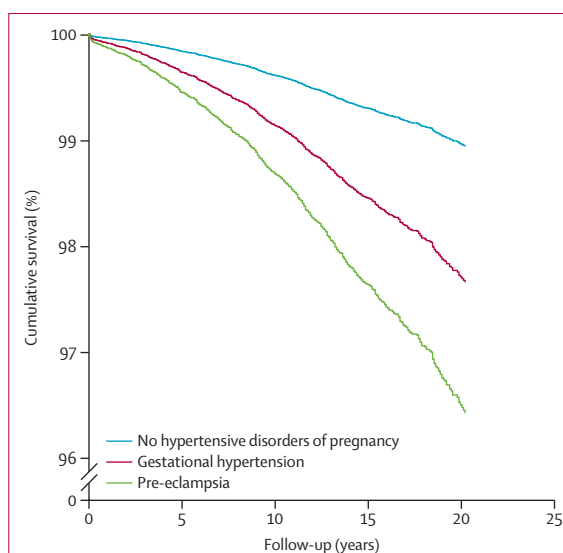
Table 2: Results for cardiovascular mortality risk in women with hypertensive disorders of pregnancy (pre-eclampsia or gestational hypertension) in their first pregnancy compared with those with no hypertensive disorder of pregnancy

pregnancy. Demographic characteristics at the start of follow-up are shown in table 1.

At the end of follow-up, 1 237 004 (99·4%) women were still alive. Of the 6886 women who died, 850 (12·3%) died due to cardiovascular causes, 3004 (43·6%) due to cancer, 1622 (23·6%) due to other causes, and in 1410 (20·5%) of the women the cause of death remained unknown (figure 1). Compared with women without hypertensive disorders of pregnancy, the HR of dying (regardless of the cause) was 1·65 (95% CI 1·48–1·83; p<0·0001) in women who had pre-eclampsia and 1·23 (1·16–1·30; p<0·0001) for women with gestational hypertension.

The adjusted HR for risk of cardiovascular mortality in women with hypertensive disorders of pregnancy compared with women without hypertensive disorders of pregnancy was 2·40 (95% CI 2·10–2·76). In women with gestational hypertension, the adjusted HR for cardiovascular mortality was 2·22 (95% CI 1·91–2·57) compared with women without hypertensive disorders of pregnancy, and in those with pre-eclampsia the adjusted HR was 3·39 (95% CI 2·67–4·29) compared with women without hypertensive disorders of pregnancy. Risk of cardiovascular mortality was higher in women when hypertensive disorders of pregnancy led to an iatrogenic preterm delivery before 37 weeks of gestation (early onset). The highest risk of cardiovascular mortality was shown in women with early-onset hypertension (gestational age <37 weeks) combined with a fetal growth restriction (table 2, figure 2). In 72 (0·006%) women the gestational age data were missing, in 24 839 (2·0%) of the women proteinuria data were missing, and in 51 384 (4·1%) of the women diastolic blood pressure data were missing.

We did a sensitivity analysis that excluded women missing diastolic blood pressure, proteinuria, or gestational age information. In the sensitivity analysis, women with hypertensive disorders of pregnancy, pre-eclampsia, or gestational hypertension, adjusted for maternal age, all had higher risks of cardiovascular mortality compared with those women with no hypertensive disorders of pregnancy (appendix p 1).

Figure 2: Survival of women after pre-eclampsia, gestational hypertension, and no hypertensive disorders of pregnancy

When analysing cardiovascular mortality in the eight diastolic blood pressure groups, the cardiovascular mortality risk increased in proportion to the highest diastolic blood pressure measured during pregnancy, compared with women with a diastolic blood pressure of less than 70 mm Hg. Cardiovascular mortality was significantly higher in women with a blood pressure of 90–99 mm Hg compared with women with a diastolic blood pressure of less than 70 mm Hg (adjusted HR 2·31 [95% CI 1·54–3·47]) and gradually increased in all higher blood pressure groups, where women in the highest blood pressure group (130 mm Hg and higher) had the highest cardiovascular mortality risk (14·7 [7·31–29·52]; table 3, figure 3).

Mean age of cardiovascular death was 41·0 years (SD 7·2) in women with hypertensive disorders of pregnancy and 40·6 years (SD 7·5) in women without this condition.

	Number of cardiovascular mortalities	Number of women alive	p value; adjusted p value	HR (95% CI) for cardiovascular mortality	Adjusted HR (95% CI) for cardiovascular mortality*
Diastolic blood pressure <70 mm Hg (reference)	28	84 847	..	1·0 (ref)	1·0 (ref)
Diastolic blood pressure 70–79 mm Hg	152	391 680	p=0·86; p=0·94	1·04 (0·69–1·55)	0·99 (0·66–1·48)
Diastolic blood pressure 80–89 mm Hg	290	451 809	p=0·02; p=0·05	1·59 (1·08–2·35)	1·47 (1·00–2·17)
Diastolic blood pressure 90–99 mm Hg	148	144 544	p<0·0001; p<0·0001	2·54 (1·69–3·80)	2·31 (1·54–3·47)
Diastolic blood pressure 100–109 mm Hg	108	78 207	p<0·0001; p<0·0001	3·33 (2·20–5·05)	3·07 (2·02–4·65)
Diastolic blood pressure 110–119 mm Hg	60	26 553	p<0·0001; p<0·0001	5·01 (3·20–7·85)	4·62 (2·95–7·24)
Diastolic blood pressure 120–129 mm Hg	22	6574	p<0·0001; p<0·0001	7·08 (4·05–12·37)	6·54 (3·74–11·43)
Diastolic blood pressure 130 mm Hg	11	1437	p<0·0001; p<0·0001	15·83 (7·88–31·81)	14·70 (7·31–29·52)

Data are n or HR (95% CI) unless otherwise stated. HR=hazard ratio. *Adjusted for maternal age at birth.

Table 3: Results for cardiovascular mortality risk in women according to highest diastolic blood pressure in pregnancy
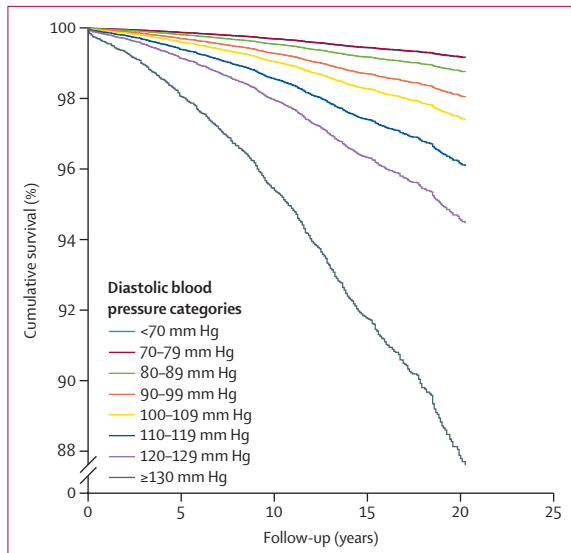
Figure 3: Survival of nulliparous women with different highest diastolic blood pressures compared with women with a diastolic blood pressure of less than 70 mm Hg during pregnancy

17 (4·8%) of 349 women with hypertensive disorders of pregnancy who had a cardiovascular death died within a year after birth due to cardiovascular disease. Most common causes of cardiovascular mortality in women with hypertensive disorders of pregnancy were cerebrovascular diseases (n=116 [33·2%]; specifically subarachnoid haemorrhage), other forms of heart disease (n=83 [23·8%]); specifically cardiac arrest, and ischaemic heart disease (n=73 [21·0%]); specifically acute myocardial infarction.

Discussion

In this large nationwide study, we focused on cardiovascular mortality in women younger than 50 years after a hypertensive disorder of pregnancy in the first pregnancy. We found a marked increase in risk of cardiovascular mortality in proportion to an increase in highest diastolic blood pressure. Our results indicate that women with a history of hypertensive disorders of pregnancy had an increased risk for cardiovascular mortality. The median follow-up time was 11·2 years (IQR 6·1–16·3) after first pregnancy at a mean maternal age of 29 years, indicating that for some women their cardiovascular (mortality) risk is already present at a relatively young age. Cardiovascular mortality risk was highest among women with a severe hypertensive disorder of pregnancy, defined as hypertensive disorders of pregnancy resulting in a delivery less than 37 weeks of gestational age and the presence of growth restriction at birth.

After subdividing the hypertensive disorders of pregnancy in women with pre-eclampsia and women with gestational hypertension, women with pre-eclampsia had a higher risk of cardiovascular mortality compared with women with gestational hypertension. This outcome can be explained by pre-eclampsia being a disorder complicated by multiorgan failure, including cerebrovascular, cardiac, and coagulation disorders.[21] Nonetheless, women with a history of gestational hypertension—an under-represented group in studies of cardiovascular risk—still maintained a significantly higher risk for cardiovascular mortality than those without a hypertensive disorder of pregnancy, suggesting that hypertension is a major risk factor. However, the exact mechanism of the shared link between hypertensive disorders of pregnancy and cardiovascular disease later in life remains unclear. Possible pathogenetic mechanisms described in hypertensive disorders of pregnancy are dysfunctional placentation leading to impaired angiogenesis.[21] An elevated release of antiangiogenic peptide results in endothelial damage, which manifests in placental ischaemia, hypertension, and multiorgan damage. A potential role for angiogenic peptides in atherosclerosis in cardiovascular disease could be a shared pathway.[21,22] The shared risk factors, such as hypertension, obesity, insulin resistance, and hyperlipidaemia, support the common link. Women

developing hypertensive disorders of pregnancy could have either a latent unfavourable cardiovascular profile which might be present before pregnancy and be revealed during pregnancy. Another plausible hypothesis is that endothelial dysfunction and vascular damage, caused or worsened by hypertensive disorders of pregnancy, potentiates a cascade of events resulting in cardiovascular disease later in life.[8]

If pregnancy acts as a stress test, this profile, disguised as a hypertensive disorder of pregnancy, is revealed during pregnancy. Our findings of a higher overall mortality risk and cardiovascular mortality risk are aligned with previous studies that have linked hypertensive disorders of pregnancy with cardiovascular mortality.[8,11,12,23,24] Although the finding of higher cardiovascular mortality in women with hypertensive disorders of pregnancy matches with previous studies, these studies had a relatively long follow-up time, resulting in older women at the end of follow-up. This finding could underestimate an early effect of hypertensive disorders of pregnancy on cardiovascular mortality, excluding the young women affected by hypertensive disorders of pregnancy from cardiovascular risk management. The death rate at the age of approximately 40 years can only be partly attributed (less than 5%) to maternal death due to pregnancy per se. This finding suggests an increased risk in cardiovascular mortality unmasking itself as soon as the first 10 years post partum, which is in line with the latest research on cardiovascular disease.[10,25] It also implies that once a pregnancy is complicated by hypertensive disorders of pregnancy, awareness for cardiovascular mortality should not be postponed. Furthermore, in our study, cardiovascular mortality risk was highest in women with hypertensive disorders of pregnancy who delivered preterm (<37 weeks) and who gave birth to a child with low birthweight. Women with an extremely high diastolic blood pressure had the highest cardiovascular mortality risk, 14 times higher than women with a diastolic blood pressure less than 70 mm Hg. This finding highlights the importance of hypertension alone being a major risk factor. Additional awareness post partum should be created for women with a severe form of hypertensive disorder of pregnancy.

Despite extensive research that supports the notion that hypertensive disorders of pregnancy are an independent risk factor for the development of cardiovascular disease later in life, follow-up programmes that include specific diagnostic and treatment strategies remain unavailable. Most cardiovascular guidelines acknowledge hypertensive disorders of pregnancy as a risk factor. However, the recommendations in the existing guidelines are inconsistent. Some guidelines state insufficient evidence exists to inform on any recommendation, whereas other guidelines advise cardiovascular risk assessment at 1 year post partum or advise only when the individual is aged 50 years.[26–30] Lifestyle changes (smoking cessation, BMI regulation), blood pressure measurements, and basic cardiovascular screening are pragmatically recommended, even though the clinical outcomes have not been well studied. In light of our findings, because serious cardiovascular events might already have occurred at a young age, a bespoke cardiovascular follow-up should be designed. We recommend doing a randomised controlled trial that compares the current follow-up in women at risk of cardiovascular mortality versus a tailor-made follow-up, including lifestyle changes, regular blood pressure measurements, and a simple cardiovascular screening. This research could be of great potential to improve understanding on clinical outcome and cost-effectiveness of the current recommendations.

The most important strength of the study is the prospective follow-up of a large 21-year nationwide cohort of women after pregnancy being linked to the national death registry of the Netherlands. The availability of the highest measured diastolic blood pressure has given us the opportunity to consider blood pressure as a continuous variable instead of the hard cutoff of 90 mm Hg.

Several limitations apply when interpreting our results. The change to a more aggressive management in hypertensive disorders of pregnancy over time might have resulted in a better cardiovascular outcome for women who delivered later in the cohort. After publication of the HYPITAT 1[31] and HYPITAT 2[32] studies in 2009 and 2015, management of hypertensive disorders of pregnancy during pregnancy became more aggressive, leading to earlier delivery of babies in women with hypertensive disorders of pregnancy. This finding implies that women in this cohort with deliveries in the 1980s and 1990s had a longer exposure to hypertensive disorders of pregnancy, which could have resulted in worse cardiovascular outcomes for these women. However, in the study by Hermes and colleagues,[33] no notable difference was reported in cardiovascular profile 2·5 years post partum in women with hypertensive disorders of pregnancy who were induced compared with those who were monitored expectantly. Also, due to missing data necessary for linkage between the LVR2 registry and the national mortality database, linkage was unsuccessful in 3% of deliveries and, therefore, these women were excluded. This might have resulted in a selection bias. Because of the low number of mortality cases, we could not adjust for many possible confounders. It was also not possible to correct for confounders such as pre-existing cardiovascular morbidity, BMI, gestational diabetes, and smoking and clinical symptoms, because this information is not accurately registered or not complete in the PRN or LVR2 registry. It is possible that the cardiovascular mortality risk found in these women could partly be explained by these underlying cardiovascular morbidities. Also, because the birth registry was linked to the death registry, only cardiovascular mortality was analysed. We can only make assumptions on the development of chronic hypertension in the time between the hypertensive disorders of pregnancy and cardiovascular mortality. Data on onset of chronic hypertension would be very valuable as it is thought that

progression to chronic hypertension is the main driver of cardiovascular events in women with a history of hypertensive disorders of pregnancy.

Because systolic blood pressure and other indices of pre-eclampsia-related end-organ damage (including clinal symptoms and laboratory results) were not available, the definition of hypertensive disorders of pregnancy was inevitably based on diastolic blood pressure and presence of proteinuria. We cannot rule out potential misclassification of hypertensive pregnancy because in 2·0% of all women the presence of proteinuria was missing and in 4·1% of all women the blood pressure information was missing. These missing data might have resulted in women with pre-eclampsia being misclassified as those with gestational hypertension but also women with a history of hypertensive disorder of pregnancy being misclassified as those without a hypertensive disorder of pregnancy. We tried to overcome this misclassification by performing a sensitivity analysis, in which the HRs for cardiovascular mortality did not differ. In this study, only the registry information of the obstetricians was used because women with hypertensive disorders of pregnancy would probably have had their deliveries in a hospital. When the applied definitions in this study were used in a random year (2010) in the LVR2 records from the PRN registry, the prevalence rates of hypertensive disorders of pregnancy, pre-eclampsia, and gestational hypertension in this study were similar to the prevalence of pre-eclampsia, gestational hypertension, and hypertensive disorders of pregnancy in PRN.

In conclusion, our study reported a risk of cardiovascular mortality for women with a history of hypertensive disorders of pregnancy that was 2–3 times higher than that for women without hypertensive disorders of pregnancy. The highest measured diastolic blood pressure is an important predictor for death due to cardiovascular mortality later in life. Our results highlight the need for the development of a cardiovascular management programme that is designed to follow up women directly after hypertensive pregnancy.

Contributors

SMW had access to the data and was responsible for the conception and design of the work, data collection, analysis and interpretation, the writing of the article, and final approval of the version before publication. MdB was responsible for data interpretation, critical revision of the article, and final approval before publication. PWT was responsible for the conception and design of the work, data interpretation, critical revision of the article, and final approval of the version before publication. WH was responsible for critical revision of the article and final approval of the version before publication. ACJR had access to the data and was responsible for the data statistics, analyses, and interpretation, critical revision of the article, and final approval of the version before publication. BWM was responsible for design of the work, data interpretation, critical revision of the article, and final approval of the version before publication. CJMdG was responsible for the conception and design of the work, data interpretation, critical revision of the article, and final approval of the version before publication.

Declaration of interests

BWM declares consulting fees at an hourly rate from ObsEva, Merck KGaA, and Guerbet. BWM also declares having received an investigator

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