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Cardiovascular risk profile at the age of 40–45 in women with previous hyperemesis gravidarum or hypertensive disorders in pregnancy: A population-based study

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ABSTRACT

Objective: To assess midlife cardiovascular risk profiles in women with a history of hyperemesis or hypertensive disorders in pregnancy compared to women with none of the studied pregnancy complications.
Study design: Population-based study. Cardiovascular risk factors at the age of 40–45 among women with previous singleton births only were studied through linkage of the Norwegian Birth Registry and a Norwegian screening program (the Age 40 Program).
Main outcome measures: Family history of coronary heart disease, body mass index, smoking, physical activity, systolic and diastolic blood pressure, heart rate, cholesterol, triglycerides, antihypertensive treatment and diabetes.
Results: Among 178,231 women participating in the Age 40 Program with previous singleton births; 2140 (1.2%) had experienced hyperemesis and 13,348 (7.5%) hypertensive disorders in pregnancy. Women who had suffered from hyperemesis were less physically active. The differences in mean systolic blood pressure and body mass index were probably clinically irrelevant. In women with a history of hypertensive disorders in pregnancy, systolic and diastolic blood pressure and body mass index were higher, and they were more likely to report diabetes in midlife. Women who had suffered from hyperemesis or hypertensive disorders in pregnancy were less likely to be daily smokers.
Conclusion: Women with hypertensive disorders in pregnancy seemed to have an unfavorable cardiovascular risk profile in midlife compared to women with uncomplicated pregnancies. In contrast there was no consistent evidence of increased risk subsequent to hyperemesis gravidarum. The proportion of daily smokers was lower in women with either of the two pregnancy complications.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death in women [1,2], and factors related to their reproductive health is known to contribute to gender-specific risk for CVD [1,3]. Pregnancy complications, such as gestational diabetes, gestational hypertension, preeclampsia and placental abruption, are all associated with increased risk of developing CVD later in life [4–7]. Both the American and European guidelines now include pregnancy complications as a major risk factor for later CVD [1,8].

Hyperemesis gravidarum (hyperemesis), characterized by extreme nausea and vomiting in early pregnancy, is the most common cause of hospitalization in first trimester and affects 0.3–3.2% of all pregnant women [9,10]. The pathophysiology is not well understood, but different hypotheses have been suggested, involving placental dysfunction, gastrointestinal pathology, immunologic factors and endocrine and metabolic factors [11–14]. The literature is inconsistent when it comes to risk factors for hyperemesis, but cardiovascular (CV) risk

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factors like hypertension, overweight, diabetes mellitus, hypercholesterolemia and low socioeconomic status have all been reported to be associated with hyperemesis [15–17]. Previous studies have shown associations between hyperemesis and placental dysfunction disorders, such as preeclampsia and placental abruption [18–20]. In contrast to pregnancy-induced hypertension and preeclampsia, CV risk subsequent to hyperemesis have not yet been explored. These conditions may have some common features, and whether they share an increased long-term CV risk or not is important to study.

The aim of this study is to investigate CV risk factors at the age of 40–45 years among women with a history of hyperemesis or hypertensive disorders in pregnancy compared to women with neither hyperemesis nor hypertensive disorders in pregnancy, using large population-based data.

2. Materials and methods

2.1. Sources of data

From 1985 to 1999 the Norwegian health authorities conducted a screening program; the Age 40 Program [21]. Women and men aged 40–42 years in all Norwegian counties, except Oslo, were asked to participate. In addition, people aged 39–45 years were invited from a few counties. The participation rate among women varied between 57% and 91% during the entire period [22,23]. The main aim of the program was to investigate midlife CV risk factors.

All births in Norway are notified in the Medical Birth Registry of Norway (MBRN). This is mandatory, and is to be done within one week after discharge from the delivery unit. From 1967 all pregnancies ending after week 16 were notifiable in the MBRN [24].

2.2. Data linkage and study population

The personal identification number unique to every Norwegian resident was used to link data from the cohort of women who participated in the Age 40 Program to information from the MBRN. Our study sample comprised of women aged 40–45 participating in the Age 40 Program, with a history of singleton births only registered in the MBRN (Fig. 1). Ethical approval for the study was obtained from the Regional Committee for Medical and Health Research Ethics (2015/1347/REC South East). All participants in the Age 40 Program provided informed consent.

2.3. Pregnancy complications

In the MBRN maternal diseases before and during pregnancy are notified. From 1967 to 1998 pregnancy complications were reported in free text according to the International classification of Disease (ICD). Women with hyperemesis were registered with ICD-8 codes 638.0 (hyperemesis gravidarum with neuritis) and 638.9 (hyperemesis gravidarum without mention of neuritis) until 1998, and from 1999 and onwards hyperemesis was registered by the ICD-10 codes O21.0 (mild hyperemesis gravidarum), O21.1 (hyperemesis gravidarum with metabolic disturbances) and O21.9 (vomiting in pregnancy, unspecified) [25]. Gestational hypertension was defined as at least one measurement of systolic blood pressure ≥140 mmHg and/or 90 mmHg diastolic after 20th gestational week, without evidence of pre-existing hypertension. The MBRN defines pre-eclampsia as gestational hypertension combined with proteinuria. After 1998 the MBRN registration form was changed and check boxes for preeclampsia were introduced. In this study hypertensive disorders in pregnancy included gestational hypertension, preeclampsia and eclampsia.

2.4. Cardiovascular risk factors

The following outcomes were included from the Age 40 Program where each woman had one visit: Height and weight were measured to the nearest centimeter and half kilogram, respectively, and body mass index (BMI) was calculated. The average of the second and third measurements of systolic and diastolic blood pressure, in addition to heart rate, was registered (DINAMAP, Critikon, Tampa, USA). A non-fasting blood sample was analyzed for total cholesterol and

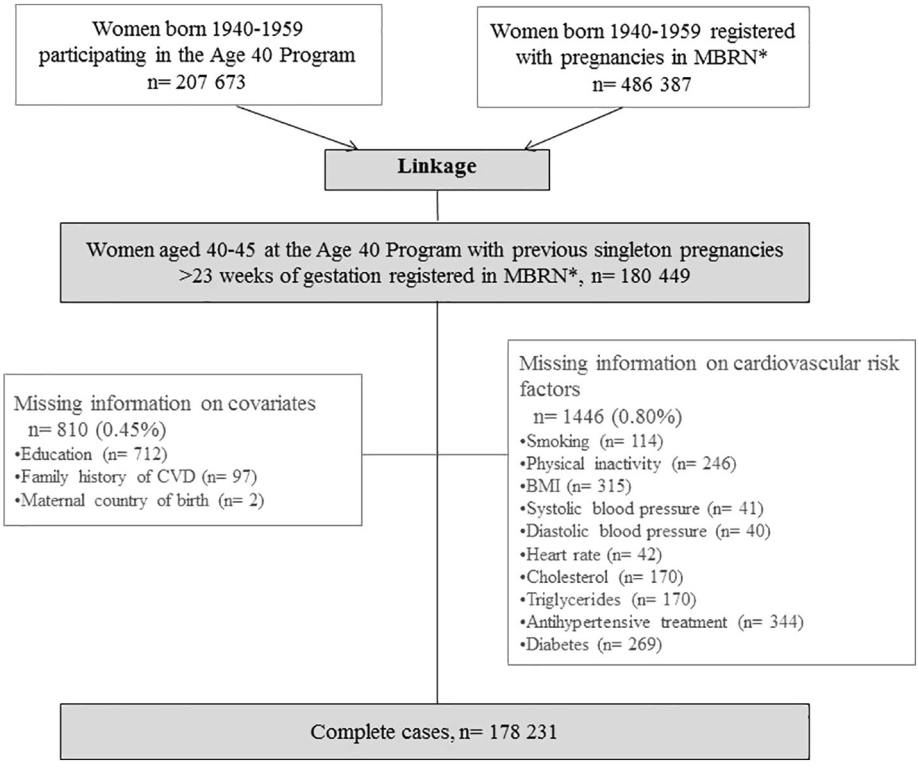

Fig. 1. Participant flow diagram. MBRN: Medical Birth Registry of Norway.

Table 1
Characteristics of the cohort (n = 178,231).

Maternal and pregnancy characteristics, mean (SD)	Women with hyperemesis gravidarum in pregnancy (n = 2140)	Women with hypertensive disorders in pregnancy[a] (n = 13,348)	Women with hyperemesis AND hypertensive disorders in pregnancy[a] (n = 189)	Women without hyperemesis or hypertensive disorders in pregnancy[a] (n = 162,554)
Age at first reg. pregnancy	23.4 (4.1)	23.8 (4.4)	23.4 (3.9)	23.5 (4.3)
Age at the Age 40 Program	41.3 (1.0)	41.3 (1.0)	41.4 (1.0)	41.4 (1.0)
Years from first pregnancy to health examination	17.9 (4.2)	17.6 (4.5)	17.9 (4.0)	17.9 (4.4)
Years from last pregnancy to health examination	11.7 (5.1)	11.4 (5.1)	11.4 (4.5)	12.7 (5.2)
Maternal and pregnancy characteristics, n (%)				
Maternal country of origin				
Norway	2019 (94.3)	12,781 (95.7)	182 (96.3)	154,376 (95.0)
Europe	67 (3.1)	395 (3.0)	4 (2.1)	5525 (3.4)
Africa	4 (0.2)	11 (0.1)	0	173 (0.1)
Asia	31 (1.5)	45 (0.3)	1 (0.5)	856 (0.5)
North-America	18 (0.8)	103 (0.8)	2 (1.1)	1401 (0.9)
South-America	1 (0.1)	10 (0.1)	0	166 (0.1)
Oceania	0	3 (0.02)	0	57 (0.04)
Highest level of education				
Basic	362 (16.9)	2273 (17.0)	24 (12.7)	28,742 (17.7)
Secondary	1195 (55.8)	8021 (60.1)	131 (69.3)	95,850 (59.0)
Tertiary	583 (27.2)	3054 (22.9)	34 (18.0)	37,962 (23.3)
Family history of CHD, yes	841 (39.3)	6050 (45.3)	103 (54.5)	66,713 (41.0)
Pre-gestational hypertension	5 (0.2)	283 (2.1)	6 (3.2)	278 (0.2)
Placental abruption in any pregnancy	31 (1.5)	325 (2.4)	3 (1.6)	1854 (1.1)
Parity				
Primipara	155 (7.2)	1430 (10.7)	11 (5.8)	20,430 (12.6)
Multipara	1985 (92.8)	11,918 (89.3)	178 (94.2)	142,124 (87.4)

Abbreviations: CHD coronary heart disease.
[a] Included gestational hypertension, preeclampsia and eclampsia.

triglycerides using an enzymatic method. Current use of antihypertensive medication was registered as yes/no. Smoking was classified into "never, former or daily smoking of cigarettes, cigars or pipes". "Reading, watching television or other sedentary activity in leisure time and less than 4 h of low-to-moderate intensive physical activity per week" or "0 h of hard physical activity (causing sweating or breathlessness) per week during leisure time" was defined as physical inactivity. Physical activity was also divided into a four graded scale: (1) inactive (defined as above), (2) moderate active: walking, cycling or other activity for at least 4 h a week or 3 or more hours a week of light physical activity or less than 1 h a week of hard physical activity, (3) intermediate active: light sports, heavy gardening or 1–2 h a week of hard physical activity, (4) intensive active: 3 or more hours a week of hard physical activity. Information on self-reported incidence of diabetes, stroke or myocardial infarction was asked by the following question: "Have you or have you had diabetes/stroke/myocardial infarction?"

2.5. Covariates

Information on the women's country of origin was obtained from Statistics Norway. Information on highest attained education registered in 1980–2001 was obtained from Statistics Norway and classified as basic (9 years (7 years in the 1960s)), secondary (10–12 years) or tertiary (≥13 years) [26]. Information on family history of coronary heart disease was obtained from the Age 40 Program, asked by the following question: "Have one or more of your siblings or parents had a myocardial infarction or angina pectoris?". Age at first birth was the women's age at first registered birth in the MBRN. Information on parity, hypertension before pregnancy and placental abruption in any pregnancy were obtained from the MBRN.

2.6. Statistical methods

Less than 1.5% of the women had missing values either in covariates or CV risk factors. Only complete cases on all variables were used for analyses in this population-based cross-sectional study (Fig. 1). Characteristics and CV risk factors among women with a history of either hyperemesis or hypertensive disorders in pregnancy or both were compared to women with neither hyperemesis nor hypertensive disorders complicating their pregnancies (hereafter referred to as reference group). Variables with a skewed distribution were logarithmically transformed to achieve normality. Medians (interquartile range) are presented for skewed distributed variables. Linear or logistic regression models were performed for multivariable analyses. Robust standard errors were used in all regression models to account for failure to meet the assumption of constant variance of the error term (homoscedasticity). Crude and adjusted β-coefficients or odds ratios (ORs) with 95% confidence interval (CI) were estimated. Based on prior knowledge [9,10,15,20,27] the following covariates were included in the adjusted analyses: the women's age at first pregnancy and year of birth, parity, education, ethnicity, hypertension before pregnancy and family-history of coronary heart disease. The analyses have been conducted in the statistical software STATA version 14.

2.6.1. Subgroup analyses

Women who experienced pregnancy complications in more than one pregnancy may have excessive risk of CVD [28]. Women with hyperemesis or hypertensive disorders in more than one pregnancy were identified in the population, and sub-analyses on repeated complicated pregnancies were conducted.

Smoking has been associated with a lower risk of hyperemesis [16] and preeclampsia [29], but a higher risk of CVD [30]. In order to investigate if there were any interactions between daily smoking and the associations between pregnancy complications and CV risk factors, an interaction term was added in the regression models.

3. Results

3.1. Cohort

Of the 180,449 women who attended the Age 40 Program at the age of 40–45 and with a previous singleton pregnancy > 23 weeks of gestation registered in the MBRN, 178,231 (98.8%) were complete cases and included in this study (Fig. 1). Among these, 2140 women (1.2%) had hyperemesis and 13,348 (7.5%) had hypertensive disorders during pregnancy. There were 189 women (0.1%) who had experienced both hyperemesis and hypertensive disorders in any pregnancy. The age at first registered pregnancy was similar across all groups, as were mean years from first pregnancy to participation in the Age 40 Program (Table 1). A larger proportion of women with hyperemesis had completed a higher degree of education at the time of the Age 40 Program compared to the reference group. For women not born in Norway, women with hyperemesis were more likely to be of Asian origin. Women with previous pregnancy complications were more often multipara at the time of the Age 40 Program. Women with a history of hypertensive disorders in pregnancy were more likely to have placental abruption in any pregnancy, pre-gestational hypertension and a positive family history of coronary heart disease (Table 1).

3.2. Cardiovascular risk factors

Women who suffered from hyperemesis had higher mean BMI and lower mean systolic blood pressure compared to women with none of the two pregnancy complications (Table 2). They were less likely to smoke on a daily basis and reported more physical inactivity. Other CV risk factors explored did not vary according to hyperemesis status in pregnancy (Table 2).

Compared to the reference group, women with a history of hypertensive disorders in pregnancy had higher BMI, higher mean systolic and diastolic blood pressure, heart rate, cholesterol and triglycerides at the age of 40–45 (Table 2). They were also more likely to be taking antihypertensive medication and reported more diabetes mellitus in midlife. Women with previous hypertensive disorders in pregnancy were less likely to smoke than the reference group. Physical inactivity did not vary accordingly (Table 2). Mean systolic and diastolic blood pressure were elevated at the age of 40–45 in women with previous hypertensive disorders in pregnancy independent from number of years since their last pregnancy (Fig. 2).

Few women had a history of both hyperemesis and hypertensive disorders in pregnancy (n = 189). These women had increased levels of most CV risk factors at the age of 40–45 (Table 2).

When dividing smoking-habits into daily, former and never smokers there was a higher proportion of never smokers among women with a history of hyperemesis (50.3%) or hypertensive disorders in pregnancy (45.5%) compared to the reference group (36.3%). Additionally, hyperemetic women were less likely to be former smokers at the age of 40 (20.1% vs 22.5%).

Women with hyperemesis were less likely to report both intermediate and intensive physical activity compared to the reference group. In contrast, women with hypertensive disorders in pregnancy reported the same amount of intensive physical activity as the reference group, but slightly less intermediate physical activity (results not shown).

3.3. Established cardiovascular disease

A total of 504 (0.3%) women reported to have had a CV event (in total 529 events, 416 S and 113 myocardial infarctions) before the Age 40 Program. The incidence of a myocardial infarction or stroke did not differ significantly between groups (results not shown).

Table 2
Cardiovascular risk factors at the age of 40 in women with previous hyperemesis gravidarum (n = 2140), hypertensive disorders in pregnancy (n = 13,348) or both (n = 189), compared to women with none of the pregnancy complications (n = 162,554).

Cardiovascular risk factors	Mean (SD)	Crude β-coefficient (95% CI)	Adjusted[a] β-coefficient (95% CI)
Body mass index (kg/m^2)			
No HG or HT	24.2 (3.7)	Reference	Reference
HG	24.4 (3.8)	0.28 (0.12, 0.44)	0.30 (0.14, 0.46)
HT	26.4 (4.9)	2.25 (2.16, 2.33)	2.18 (2.10, 2.27)
HG and HT	26.5 (5.1)	2.38 (1.65, 3.11)	2.23 (1.51, 2.96)
Systolic blood pressure (mmHg)			
No HG or HT	123.7 (13.6)	Reference	Reference
HG	122.7 (13.3)	−1.07 (−1.63, −0.50)	−0.84 (−1.40, −0.28)
HT	133.4 (16.5)	9.63 (9.34, 9.92)	9.47 (9.19, 9.76)
HG and HT	133.4 (17.6)	9.65 (7.14, 12.15)	9.34 (6.89, 11.79)
Diastolic blood pressure (mmHg)			
No HG or HT	74.9 (9.7)	Reference	Reference
HG	74.9 (9.7)	−0.07 (−0.48, 0.35)	0.14 (−0.27, 0.54)
HT	80.9 (11.0)	5.93 (5.74, 6.12)	5.92 (5.73, 6.11)
HG and HT	81.3 (12.2)	6.33 (4.59, 8.06)	6.30 (4.63, 7.98)
Heart rate (bpm)			
No HG or HT	76.9 (12.4)	Reference	Reference
HG	76.5 (11.4)	−0.44 (−0.92, 0.05)	−0.26 (−0.74, 0.23)
HT	79.1 (13.6)	2.18 (1.94, 2.41)	2.24 (2.00, 2.48)
HG and HT	78.1 (13.6)	1.22 (−0.72, 3.16)	1.35 (−0.60, 3.30)
Serum total cholesterol (mmol/L)			
No HG or HT	5.4 (1.0)	Reference	Reference
HG	5.4 (1.0)	−0.02 (−0.06, 0.02)	0.00 (−0.04, 0.04)
HT	5.5 (1.0)	0.12 (0.11, 0.14)	0.13 (0.11, 0.14)
HG and HT	5.5 (1.0)	0.08 (−0.06, 0.22)	0.07 (−0.06, 0.21)
Triglycerides (mmol/L), median (quartiles)			
No HG or HT	1.1 (0.8–1.6)	Reference	Reference
HG	1.1 (0.8–1.6)	0.01 (−0.02, 0.05)	0.02 (−0.02, 0.06)
HT	1.2 (0.9–1.8)	0.17 (0.15, 0.19)	0.17 (0.15, 0.18)
HG and HT	1.2 (0.9–1.9)	0.18 (0.05, 0.30)	0.16 (0.03, 0.28)
Cardiovascular risk factors	**n (%)**	**Crude OR (95% CI)**	**Adjusted[a] OR (95% CI)**
Antihypertensive treatment, n (%)			
No HG or HT	2128 (1.3)	Reference	Reference
HG	32 (1.5)	1.14 (0.81, 1.63)	1.17 (0.82, 1.68)
HT	1043 (7.8)	6.39 (5.92, 6.90)	5.71 (5.26, 6.20)
HG and HT	24 (12.7)	10.97 (7.13,16.86)	9.36 (5.79, 15.14)
Daily smokers, n (%)			
No HG or HT	67,022 (41.2)	Reference	Reference
HG	634 (29.6)	0.60 (0.55, 0.66)	0.62 (0.56, 0.68)
HT	4177 (31.3)	0.65 (0.63, 0.67)	0.65 (0.63, 0.68)
HG and HT	47 (24.9)	0.47 (0.34, 0.66)	0.46 (0.33, 0.65)
Physical inactivity, n (%)			
No HG or HT	33,695 (20.7)	Reference	Reference
HG	498 (23.3)	1.16 (1.05–1.28)	1.17 (1.05–1.29)
HT	2821 (21.1)	1.03 (0.98–1.07)	1.03 (0.98–1.07)
HG and HT	45 (23.8)	1.20 (0.86–1.67)	1.19 (0.85–1.66)
Diabetes mellitus, n (%)			
No HG or HT	870 (0.5)	Reference	Reference
HG	13 (0.6)	1.14 (0.66, 1.97)	1.12 (0.64, 1.95)
HT	182 (1.4)	2.57 (2.19, 3.02)	2.54 (2.16, 2.99)
HG and HT	4 (2.1)	4.02 (1.49, 10.84)	3.93 (1.46, 10.56)

Abbreviations: HG hyperemesis gravidarum, *HT* hypertensive disorders in pregnancy, *OR* odds ratio.

[a] Adjusted for women's age at first pregnancy and year of birth, parity, education, ethnicity, pre-gestational hypertension and family-history of coronary heart disease.

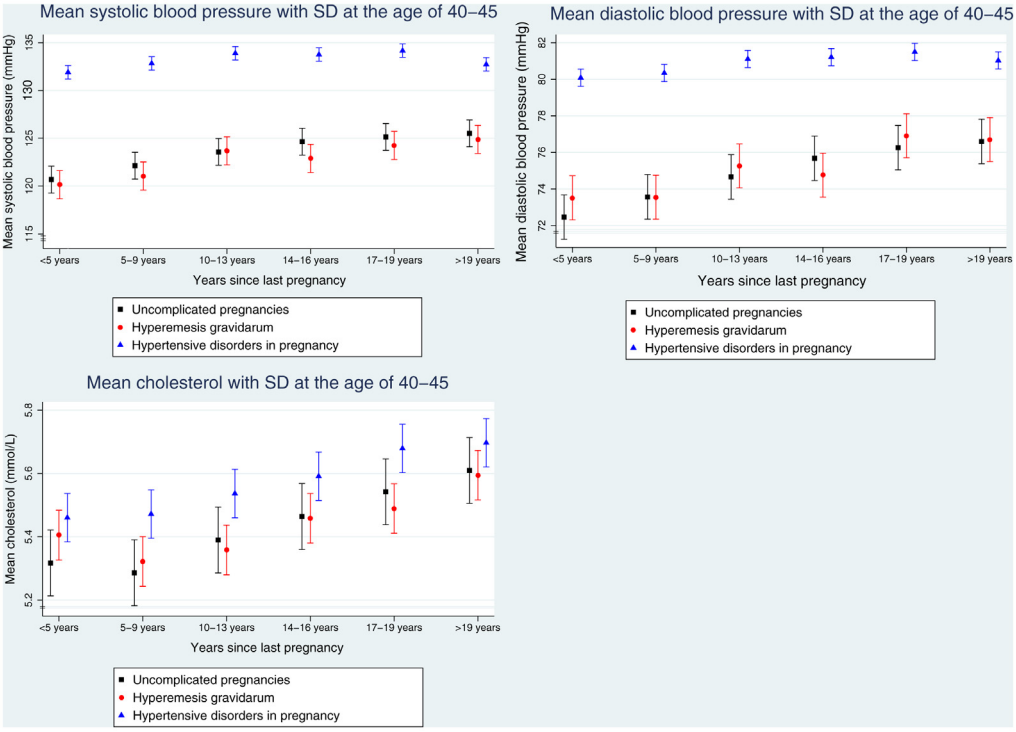

Fig. 2. Cardiovascular risk factors at the age of 40–45: Plot of mean systolic blood pressure, diastolic blood pressure and cholesterol with standard deviations at the age of 40–45 by groups reflecting years since last pregnancy.

3.4. Subgroup analyses

The proportion of daily smokers was significantly lower in women who suffered from hyperemesis in more than one pregnancy compared to the reference group. Other risk factors did not differ significantly between women who had experienced hyperemesis in several pregnancies and the reference group. Women with hypertensive disorders in more than one pregnancy had in general excessive CV risk compared to the reference group (Table 3). In addition, women with hypertensive disorders in more than one pregnancy had higher BMI ($p < 0.01$), systolic ($p < 0.01$) and diastolic ($p < 0.01$) blood pressure, heart rate ($p < 0.01$) and were more likely to report use of antihypertensive medication ($p < 0.01$) and diabetes mellitus ($p < 0.01$) in midlife compared to women with hypertensive disorders in only one pregnancy.

There was a significant interaction between hypertensive disorders in pregnancy and daily smoking for BMI (p-value < 0.01), heart rate (p-value < 0.01) and physical inactivity (p-value 0.03). There was no significant interaction between hyperemesis and smoking for any of the studied risk factors.

4. Discussion

4.1. Main findings

In this large population-based study women with hypertensive

Table 3
Analyses stratified on number of pregnancies with each pregnancy complication. Women without hyperemesis gravidarum or hypertensive disorders in pregnancy were used as reference group (n = 162,554).

Cardiovascular risk factors	Hyperemesis gravidarum *1 time* *(n = 1,935)*	Hyperemesis gravidarum *> = 2 times* *(n = 205)*	Hypertensive disorders in pregnancy[a] *1 time* *(n = 11,320)*	Hypertensive disorders in pregnancy[a] *> =2 times* *(n = 2,028)*
	β-coefficient		*β-coefficient*	
Body mass index (kg/m2)	0.32 (0.15, 0.49)	0.10 (−0.39, 0.58)	1.95 (1.87, 2.04)	3.48 (3.25, 3.72)
Systolic blood pressure (mmHg)	−0.76 (−1.36, −0.17)	−1.53 (−3.19, 0.14)	8.60 (8.29, 8.90)	14.45 (13.70, 15.19)
Diastolic blood pressure (mmHg)	0.22 (−0.21, 0.64)	−0.62 (−1.85, 0.61)	5.38 (5.18, 5.58)	8.98 (8.50, 9.47)
Heart rate (bpm)	−0.34 (−0.85, 0.17)	0.52 (−0.90, 1.94)	2.06 (1.81, 2.32)	3.25 (2.66, 3.84)
Serum total cholesterol (mmol/L)	0.00 (−0.04, 0.04)	−0.01 (−0.14, 0.12)	0.12 (0.10, 0.14)	0.18 (0.14, 0.23)
Triglycerides (mmol/L)	0.02 (−0.02, 0.06)	0.01 (−0.10, 0.11)	0.15 (0.13, 0.17)	0.26 (0.22, 0.31)
Self-reported incidence of:	*Odds ratio*		*Odds ratio*	
Daily smokers	0.65 (0.59, 0.72)	0.32 (0.22, 0.48)	0.69 (0.66, 0.72)	0.47 (0.42, 0.53)
Antihypertensive treatment	1.25 (0.87, 1.79)	0.44 (0.06, 3.17)	5.05 (4.62, 5.52)	9.92 (8.48, 11.60)
Physical inactivity	1.16 (1.04, 1.29)	1.20 (0.87, 1.67)	1.03 (0.98, 1.08)	1.02 (0.91, 1.13)
Diabetes mellitus	0.95 (0.51, 1.78)	2.84 (0.90, 8.92)	2.26 (1.88, 2.71)	4.28 (3.12, 5.85)

All analyses were adjusted for women's age at first pregnancy and year of birth, parity, education, ethnicity, hypertension before pregnancy and family-history of coronary heart disease.

[a] Included gestational hypertension, preeclampsia and eclampsia.

disorders in pregnancy had increased levels of most CV risk factors at the age of 40–45, but there was no consistent evidence of increased CV risk among women who had suffered from hyperemesis. Women who had experienced either hyperemesis or hypertension in pregnancy were less likely to be smokers compared to women without such history.

4.2. Strengths and weaknesses

One strength of this study is the population-based design which makes the results likely to be generalizable. The MBRN is a high quality register with mandatory reporting. The Age 40 Program was a nationwide screening program and the linkage to the MBRN for information on pregnancy complications makes the presence of recall bias unlikely. A possible limitation in register-based research is incorrect registrations. The registration of hyperemesis and hypertensive disorders in pregnancy in the MBRN has been validated [25,31,32]. There is no information on severity of hyperemesis and an assessment study found a relatively large proportion of false positive cases that might influence the associations in terms of reducing associations closer to null. Despite this, the study concluded that hyperemesis-registration in the MBRN is considered valid for use in large-scale epidemiological studies [25]. The positive predictive value of the gestational hypertension or preeclampsia diagnoses was high in previous validation studies, but the studies indicated that the MBRN may not be good for distinguishing between the different hypertensive disorders in pregnancy [31,32]. Based on this we have merged all hypertensive disorders in pregnancy into one category, and may therefore have lost the opportunity to differentiate between the different hypertensive disorders.

Given the fact that women included had to survive from their first pregnancy until the age of the health examination, there could be some bias present in the study (immortal person-time [33]). However, only a small proportion of women die at this age in Norway and it is unlikely that this had an impact on the studied associations. The Age 40 Program obtained only non-fasting blood samples, but fasting may not be necessarily required for determination of lipid profiles used in screening [34]. In line with other studies we found a larger proportion of women with Asian origin among women with hyperemesis [9], but as a reflection of the total population in Norway at that time [35] as many as 94–96% of the women in the present study had Norwegian origin. Hence, the results may not be generalizable to other more ethnically diverse populations. Other studies have found hyperemesis to be associated with both higher and lower socioeconomic status [15,20,36], but educational level is often measured at the time of delivery, and hyperemetic women tend to be of younger age at index pregnancy. In the present study, the highest obtained education was reported at a later time when most women have finished their studies and may be more representative. Both ethnicity and socioeconomic status are known to be associated with CV risk [37], and these factors' relations to hyperemesis are important to consider when potential consequences of hyperemesis are studied. In this study the analyses have been adjusted for these factors.

Even though pregnancy complications were reported several years before the health examination in the 40 s, we do not have information on CV risk factors at a prepregnancy state and should be careful to make inferences about causality. However, the present study showed that women with hypertensive disorders in pregnancy had increased blood pressure at the age of 40–45 regardless of time since last pregnancy, indicating a higher risk both short time and long time after their hypertensive pregnancy (Fig. 2).

There was no significant difference in incidence of self-reported myocardial infarction or stroke between the groups, which may be explained by the low number of events in a relatively young population.

4.3. Implications

American and European guidelines recommend CV screening of women with previous hypertensive disorders in pregnancy [1,8], but recommendations on when to start screening is lacking. The current study indicates that at the age of 40 (on average 17–18 years after index pregnancy) they were at increased risk. This is in line with previous studies investigating blood pressure approximately a decade after hypertensive pregnancies [38–43]. Despite not having longitudinal data, the present study indicates that blood pressure in affected women was increased already at 5 years postpartum (women aged 40–45). In the present study, women with previous hyperemesis did not share the same increased CV risk, indicating that they might not need the same CV follow-up. Although hypertensive disorders in pregnancy and hyperemesis in our study do not seem to belong to the same spectrum of diseases, we cannot rule out the possibility of placental involvement in the etiology of severe/late-onset hyperemesis as proposed in previous studies [20].

In this study we reported higher levels of most CV risk factors in midlife among women with hypertensive disorders in pregnancy, except physical inactivity and smoking. Smoking and physical inactivity are two important modifiable CV risk factors, and the fact that women with hypertensive disorders in pregnancy were less likely to smoke and reported the same amount of physical activity as the reference group reveals a more nuanced picture of their risk profile. High BMI and prepregnancy diabetes mellitus are known risk factors for preeclampsia [44] and we found these risk factors present also in midlife among women with a history of hypertensive disorders in pregnancy. These findings underscore the importance of follow-up in this group of women.

In contrast, women with a history of hyperemesis had a higher level of education, were less likely to smoke and had slightly lower systolic blood pressure. The lower proportion of smokers is likely to contribute to our previously published findings of lower long-term cancer mortality after hyperemesis [45]. Moreover, hyperemesis was associated with more inactivity and a slightly higher mean BMI, making the interpretation even more complex. The reported differences were small and probably of little clinical relevance. No significant interactions between hyperemesis and smoking for any of the studied risk factors were discovered. Residual confounding associated with lifestyle-factors in the studied associations should be considered.

4.4. Future research

In conclusion, we found that women with hypertensive disorders in pregnancy seemed to have an unfavorable CV risk profile in midlife, whereas this was not found subsequent to hyperemesis. The proportion of daily smokers was lower in women with previous hyperemesis as well as women with a history of hypertensive disorders in pregnancy. Future studies could explore if the severity of the studied pregnancy complications has an impact on subsequent CV risk. In addition, subsequent risk of CVD could be studied to investigate the impact of the different CV risk factors.

5. Conflicts of interest

S.F. and S.H. report grants from South-Eastern Norway Regional Health Authority. The remaining authors report no conflict of interest.

6. Contribution to authorship

S.F., S.H., Å.V.V. and Ø.N. designed the study. S.F. performed the statistical analyses. S.F. drafted the manuscript and all the other authors critically revised it. All authors have approved the final version of the article. S.F., S.H., Å.V.V. and Ø.N. are guarantors of the paper and affirm that the manuscript is an honest, accurate, and transparent account of the study being reported. All authors had access to the data (including statistical reports and tables) in the study and take responsibility of the integrity of the data and accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.preghy.2018.04.013.

References

[1] L. Mosca, E.J. Benjamin, K. Berra, J.L. Bezanson, R.J. Dolor, D.M. Lloyd-Jones, et al., Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: a guideline from the American Heart Association, Circulation 123 (2011) 1243–1262.
[2] N. Townsend, M. Nichols, P. Scarborough, M. Rayner, Cardiovascular disease in Europe – epidemiological update, Eur. Heart J. 36 (2015) (2015) 2696–2705.
[3] P.M. Cirillo, B.A. Cohn, Pregnancy complications and cardiovascular disease death: 50-year follow-up of the child health and development studies pregnancy cohort, Circulation 132 (2015) 1234–1242.
[4] R. Skjaerven, A.J. Wilcox, K. Klungsoyr, L.M. Irgens, B.E. Vikse, L.J. Vatten, R.T. Lie, Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study, BMJ 345 (2012) e7677.
[5] G. Lee, J. Tubby, Preeclampsia and the risk of cardiovascular disease later in life-A review of the evidence, Midwifery 31 (2015) 1127–1134.
[6] A.C. Staff, C.W.G. Redman, D. Williams, P. Leeson, K. Moe, B. Thilaganathan, et al., Pregnancy and long-term maternal cardiovascular health: progress through harmonization of research cohorts and biobanks, Hypertension 67 (2016) 251–260.
[7] L. DeRoo, R. Skjaerven, A. Wilcox, K. Klungsoyr, A.K. Wikstrom, N.H. Morken, et al., Placental abruption and long-term maternal cardiovascular disease mortality: a population-based registry study in Norway and Sweden, Eur. J. Epidemiol. 31 (2016) 501–511.
[8] M.F. Piepoli, A.W. Hoes, S. Agewall, C. Albus, C. Brotons, A.L. Catapano, et al., European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR), Eur. J. Prevent. Cardiol. 23 (2016) Np1-np96.
[9] A. Vikanes, A.M. Grjibovski, S. Vangen, P. Magnus, Variations in prevalence of hyperemesis gravidarum by country of birth: a study of 900,074 pregnancies in Norway, 1967–2005, Scand. J. Public Health 36 (2008) 135–142.
[10] F.P. McCarthy, J.E. Lutomski, R.A. Greene, Hyperemesis gravidarum: current perspectives, Int. J. Women's Health 6 (2014) 719–725.
[11] M.N. Niemeijer, I.J. Grooten, N. Vos, J.M. Bais, J.A. van der Post, B.W. Mol, et al., Diagnostic markers for hyperemesis gravidarum: a systematic review and metaanalysis, Am. J. Obstet. Gynecol. 211 (2014) 150.e1-15.
[12] N.M. Lee, S. Saha, Nausea and vomiting of pregnancy, Gastroenterol. Clin. North Am. 40 (2011) 309–334.
[13] M.F. Verberg, D.J. Gillott, N. Al-Fardan, J.G. Grudzinskas, Hyperemesis gravidarum, a literature review, Hum. Reprod. Update 11 (2005) 527–539.
[14] O. Sanu, R.F. Lamont, Hyperemesis gravidarum: pathogenesis and the use of antiemetic agents, Expert Opin. Pharmacother. 12 (2011) 737–748.
[15] T.J. Roseboom, A.C. Ravelli, J.A. van der Post, R.C. Painter, Maternal characteristics largely explain poor pregnancy outcome after hyperemesis gravidarum, Eur. J. Obstet. Gynecol. Reprod. Biol. 156 (2011) 56–59.
[16] A. Vikanes, A.M. Grjibovski, S. Vangen, N. Gunnes, S.O. Samuelsen, P. Magnus, Maternal body composition, smoking, and hyperemesis gravidarum, Ann. Epidemiol. 20 (2010) 592–598.
[17] L. Fiaschi, C. Nelson-Piercy, L.J. Tata, Hospital admission for hyperemesis gravidarum: a nationwide study of occurrence, reoccurrence and risk factors among 8.2 million pregnancies, Hum. Reprod. 31 (2016) 1675–1684.
[18] L. Fiaschi, C. Nelson-Piercy, J. Gibson, L. Szatkowski, L.J. Tata, Adverse maternal and birth outcomes in Women admitted to hospital for hyperemesis gravidarum: a population-based cohort study, Paediatr. Perinat. Epidemiol. 32 (2018) 40–51.
[19] J. Zhang, W.W. Cai, Severe vomiting during pregnancy: antenatal correlates and fetal outcomes, Epidemiology 2 (1991) 454–457.
[20] M. Bolin, H. Akerud, S. Cnattingius, O. Stephansson, A.K. Wikstrom, Hyperemesis gravidarum and risks of placental dysfunction disorders: a population-based cohort study, BJOG 120 (2013) 541–547.
[21] K. Bjartveit, I. Stensvold, P.G. Lund-Larsen, T. Gjervig, O. Kruger, P. Urdal, [Cardiovascular screenings in Norwegian counties. Background and implementation. Status of risk pattern during the period 1986-90 among persons aged 40-42 years in 14 counties], Tidsskr. Nor. Laegeforen. 111 (1991) 2063–2072.
[22] G. Wøien, O. Øyen, S. Graff-Iversen, 22 år med hjerte- og karundersøkelser i norske fylker. Bør vi være tilfreds med utviklingen risikofaktorene har hatt? Norsk Epidemiologi 7 (1997) 255–266.
[23] Norwegian Institute of Public Health, Age 40 Program 1985-1999, 2015. https://www.fhi.no/globalassets/migrering/dokumenter/pdf/rapport-40-aringsundersokelsene.pdf.
[24] L.M. Irgens, Medical birth registry–an essential resource in perinatal medical research, Tidsskr. Nor. Laegeforen. 122 (2002) 2546–2549.
[25] A. Vikanes, P. Magnus, S. Vangen, S. Lomsdal, A.M. Grjibovski, Hyperemesis gravidarum in the Medical Birth Registry of Norway – a validity study, BMC Pregnancy Childbirth 12 (2012) 115.
[26] Statistics Norway, Norwegian Standard Classification of Education, 2003. http://www.ssb.no/a/english/publikasjoner/pdf/nos_c751_en/nos_c751_en.pdf.
[27] M.L. LeFevre, Low-dose aspirin use for the prevention of morbidity and mortality from preeclampsia: U.S. Preventive Services Task Force recommendation statement, Ann. Intern. Med. 161 (2014) 819–826.
[28] N. Auger, W.D. Fraser, M. Schnitzer, L. Leduc, J. Healy-Profitos, G. Paradis, Recurrent pre-eclampsia and subsequent cardiovascular risk, Heart 103 (2017) 235–243.
[29] A. Castles, E.K. Adams, C.L. Melvin, C. Kelsch, M.L. Boulton, Effects of smoking during pregnancy. Five meta-analyses, Am. J. Prev. Med. 16 (1999) 208–215.
[30] D.M. Burns, Epidemiology of smoking-induced cardiovascular disease, Prog. Cardiovasc. Dis. 46 (2003) 11–29.
[31] F.N. Moth, T.R. Sebastian, J. Horn, J. Rich-Edwards, P.R. Romundstad, B.O. Asvold, Validity of a selection of pregnancy complications in the Medical Birth Registry of Norway, Acta Obstet. Gynecol. Scand. 95 (2016) 519–527.
[32] K. Klungsoyr, Q.E. Harmon, L.B. Skard, I. Simonsen, E.T. Austvoll, E.R. Alsaker, et al., Validity of pre-eclampsia registration in the medical birth registry of norway for women participating in the norwegian mother and child cohort study, 1999–2010, Paediatr. Perinat. Epidemiol. 28 (2014) 362–371.
[33] K.J. Rothman, S. Greenland, T.L. Lash, Modern Epidemiology, third ed., Lippincott Williams & Wilkins, Philadelphia, USA, 2008.
[34] B.G. Nordestgaard, A. Langsted, S. Mora, G. Kolovou, H. Baum, E. Bruckert, et al., Fasting is not routinely required for determination of a lipid profile: clinical and laboratory implications including flagging at desirable concentration cutpoints-A joint consensus statement from the European Atherosclerosis Society and European Federation of Clinical Chemistry and Laboratory Medicine, Clin. Chem. 62 (2016) 930–946.
[35] Statistics Norway, Immigrants and Norwegian-born to immigrant parents, 2017. https://www.ssb.no/statistikkbanken/selecttable/hovedtabellHjem.asp?KortNavnWeb=innvbef&CMSSubjectArea=befolkning&PLanguage=1&checked=true.
[36] K.F. Vandraas, A.V. Vikanes, S. Vangen, P. Magnus, N.C. Stoer, A.M. Grjibovski, Hyperemesis gravidarum and birth outcomes-a population-based cohort study of 2.2 million births in the Norwegian Birth Registry, BJOG 120 (2013) 1654–1660.
[37] M.D. Wong, M.F. Shapiro, W.J. Boscardin, S.L. Ettner, Contribution of major diseases to disparities in mortality, N. Engl. J. Med. 347 (2002) 1585–1592.
[38] A. Bokslag, P.W. Teunissen, C. Franssen, F. van Kesteren, O. Kamp, W. Ganzevoort, et al., Effect of early-onset preeclampsia on cardiovascular risk in the fifth decade of life, Am. J. Obstet. Gynecol. (2017) Epub ahead of print.
[39] J.T. Drost, G. Arpaci, J.P. Ottervanger, M.J. de Boer, J. van Eyck, Y.T. van der Schouw, A.H. Maas, Cardiovascular risk factors in women 10 years post early preeclampsia: the Preeclampsia Risk EValuation in FEMales study (PREVFEM), Eur. J. Prevent. Cardiol. 19 (2012) 1138–1144.
[40] I.V. Alsnes, I. Janszky, M.R. Forman, L.J. Vatten, I. Okland, A population-based study of associations between preeclampsia and later cardiovascular risk factors, Am. J. Obstet. Gynecol. 211 (2014) 657.e1-7.
[41] E.B. Magnussen, L.J. Vatten, G.D. Smith, P.R. Romundstad, Hypertensive disorders in pregnancy and subsequently measured cardiovascular risk factors, Obstet. Gynecol. 114 (2009) 961–970.
[42] A.L. Berends, C.J. de Groot, E.J. Sijbrands, M.P. Sie, S.H. Benneheij, R. Pal, et al., Shared constitutional risks for maternal vascular-related pregnancy complications and future cardiovascular disease, Hypertension 51 (2008) 1034–1041.
[43] N.I. Parikh, M. Norberg, E. Ingelsson, S. Cnattingius, R.S. Vasan, M. Domellof, et al., Association of pregnancy complications and characteristics with future risk of elevated blood pressure: the Vasterbotten intervention program, Hypertension 69 (2017) 475–483.
[44] E. Bartsch, K.E. Medcalf, A.L. Park, J.G. Ray, Clinical risk factors for pre-eclampsia determined in early pregnancy: systematic review and meta-analysis of large cohort studies, BMJ 353 (2016) i1753.
[45] S. Fossum, A.V. Vikanes, O. Naess, L. Vos, T. Grotmol, S. Halvorsen, Hyperemesis gravidarum and long-term mortality: a population-based cohort study, BJOG 124 (2017) 1080–1087.