Long-term cardiovascular risk in women with a history of hyperemesis gravidarum

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Doctoral Thesis

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PREFACE

Globally, cardiovascular disease (CVD) is the leading cause of death, for both men and women (1). However, the proportion of deaths due to CVD has declined in many European countries over recent decades (2). In Norway, cancer caused more deaths than CVD in both genders in 2017, when age-standardized rates were considered (3). However, the burden of CVD is not expected to decrease in the near future and CVD will most probably remain an important cause of morbidity and mortality in both genders (4).

Although CVD is more common in men than women when age-standardized rates are considered, in total CVD leads to a larger number of deaths among women compared to men (3). During recent decades, researchers and clinicians have gradually increased their focus on CVD in women. It is of interest in order to prevent CVD, in a public health as well as clinical perspective, to identify people who have an increased risk at an early age. Some pregnancy-related conditions, such as gestational diabetes, preeclampsia and pregnancy-induced hypertension, are known to increase a woman's long-term risk of CVD (5-7). Therefore, these conditions are included as risk factors in both European and American guidelines for CVD prevention in women (8, 9).

Hyperemesis gravidarum is the most common cause of hospitalisation during the first trimester of pregnancy and is characterized by extreme nausea and vomiting in early pregnancy (10). The condition is associated with placental dysfunction disorders, such as pre-eclampsia and placental abruption (11-13). All these pregnancy complications share some characteristics, but whether they also share the increased long-term risk of CVD is not yet known.

In Norway, nationwide health registries and surveys can be used to study large cohorts with long follow-up times. The unique personal identity number in Norway enables linkage between the different data sources. In this study, large population-based cohorts were used to explore long-term cardiovascular risk following hyperemesis gravidarum.

TERMS AND ABBREVATIONS

Terms

Cardiovascular disease:

Cardiovascular disease (CVD) is a systemic disease which can lead to a variety of end-organ manifestations, including coronary heart disease, stroke, heart failure, peripheral vascular disease, aortic aneurysm and arrhythmia. In the included papers, International Classification of Diseases (ICD) – codes for diseases of the circulatory system were used to define CVD (given in table 2, chapter 3.6). The terms ischaemic heart disease and cerebrovascular disease were used to separate between major groups of CVD. Ischaemic heart disease includes all damage due to ischaemia in the myocardium, whereas coronary heart disease in general is understood as diseases of the epicardial coronary arteries. Cerebrovascular diseases are diseases of the vessels in the brain, including ischaemic and haemorrhagic stroke. The introduction of this thesis covers CVD in women overall, focusing on ischaemic heart disease and stroke.

Hyperemesis gravidarum:

Throughout the thesis "hyperemesis gravidarum" is mainly referred to as "hyperemesis". However, "hyperemesis gravidarum" is written when used for the first time in the main sections to increase precision.

Exposed and unexposed:

Hyperemesis gravidarum is termed as exposure in this thesis. The use of the words "exposed" and "unexposed" refers to causal thinking of the effect of an exposure on a studied outcome. However, it is controversial if a disease (hyperemesis) can be classified as an exposure although the term has been used about hyperemesis in this thesis, because of the epidemiological approach to the designs of the included studies. Also, the term "association"' has been applied instead of "cause" throughout the thesis.

Abbreviations

ACME: Automated Classification of Medical Entities

BMI: Body mass index

CI: Confidence interval

CVD: Cardiovascular disease

FS: "Forskning i sykehus" (Research in Hospitals)

GDF15: Growth and differentiation factor 15

hCG: human chorionic gonadotropin

HR: Hazard ratio

ICD: International Classification of Disease

IGFBP7: Insulin-like growth factor binding protein 7

MBRN: Medical Birth Registry of Norway

PCI: Percutaneous coronary intervention

PUQE: Pregnancy-Unique Quantification of Emesis

STEMI: ST-elevation myocardial infarction

LIST OF PAPERS

Paper 1: Hyperemesis gravidarum and long-term mortality: a population-based cohort study

Fossum S, Vikanes ÅV, Næss Ø, Vos L, Grotmol T, Halvorsen S.

BJOG. 2017;124:1080-1087. doi: 10.1111/1471-0528.14454.

Paper 2: Cardiovascular risk profile at the age of 40-45 in women with previous hyperemesis gravidarum or hypertensive disorders in pregnancy: A population-based study

Fossum S, Halvorsen S, Vikanes ÅV, Roseboom TJ, Ariansen I, Næss Ø.

Pregnancy Hypertens. 2018;12:129-135. doi: 10.1016/j.preghy.2018.04.013.

Paper 3: Long-term cardiovascular morbidity following hyperemesis gravidarum: a Norwegian nationwide cohort study

Fossum S, Næss Ø, Halvorsen S, Tell GS, Vikanes ÅV.

Submitted

1.0 INTRODUCTION

1.1 Women and cardiovascular disease

1.1.1 Background

Globally, cardiovascular disease (CVD) was the leading cause of death in both men and women in 2016 (1). In 2015, CVD was the most common cause of death in Europe overall; being responsible for 45% of all deaths (2). In some European countries today, cancer is a more common cause of death than CVD (2). In Norway, cancer caused most deaths in men and women in 2017, when age-standardized rates were considered (3). Due to the reduction in risk factors in the population at large (less smoking, lower cholesterol levels and blood pressure) and better treatments, deaths from CVD are declining in Norway. However, an aging population and improved survival after acute illness may lead to an increased number of people living with CVD. Therefore, primary and secondary prevention as well as identification of individuals at risk are important factors to focus on in order to reduce morbidity and mortality (4).

When age-standardized rates are considered, more men than women are dying from CVD, but given the higher number of elderly women, the total number of deaths due to CVD is higher in women than men for all age groups combined (3). When exploring CVD subgroups, ischemic heart disease occurs 2 to 4 times more frequently in men than women and is reported as a more common cause of death in men (3, 14, 15). In contrast, the differences between genders in regard to stroke incidence and mortality are smaller in all age-groups (3, 16). Among the oldest (>75 years), the age-adjusted mortality rate for stroke is higher for women than men (3).

For most CVDs there are well known differences between men and women in regard to risk factors, symptoms and prognosis (14). Traditionally, women have been underrepresented in studies on CVD (17), but an increased awareness on CVD in women has also resulted in more gender-focused research during recent decades (18).

1.1.2 Symptoms, diagnosis and treatment

Women often present with less specific symptoms of coronary heart disease and stroke compared to men, which can result in delayed diagnosis and treatment (19, 20). Women with myocardial infarction are less likely to report chest pain, and more likely to experience symptoms like dyspnoea, fatigue and pain in the jaw and neck compared to men (19). The underlying pathophysiology may contribute to the difference in clinical presentations, as women are less likely to present with obstructive coronary artery disease than men, but more frequently have vascular dysfunction, coronary artery dissection and spasm (14). Differences in clinical presentation and pathophysiology may lead to less intensive treatment and poorer secondary prevention in women (21). Previous research has shown that in ST-elevation myocardial infarction (STEMI), both genders benefit from early percutaneous coronary intervention (PCI). However, there is conflicting evidence in the setting of a non-STEMI (22). In terms of stroke, women more often experience nausea, headache, dizziness and cognitive dysfunction, compared to men (20). Men are more likely to have ischaemic strokes, while women are at greater risk of subarachnoid haemorrhage (23). Research on differences between genders in pre-hospital delay, diagnosis and treatment for stroke is inconclusive, but post-stroke outcomes seem to be poorer for women than men (23).

1.1.3 Risk factors

Most of the traditional cardiovascular risk factors are the same in men and women. However, several female-specific risk factors and some factors more prevalent in women than men, occur especially with increasing age. Women are on average 7-10 years older than men when they develop ischaemic heart disease, and five years older when they develop stroke (14, 24). Women with CVD tend to have a higher burden of cardiovascular risk factors and comorbidity (25). After the age of 65 years, women are more likely to be hypertensive than men (18). Furthermore, more women than men suffer from autoimmune disorders, for instance rheumatoid arthritis, systemic lupus erythematosus and scleroderma. Moreover, obesity, smoking and diabetes mellitus seem to increase the risk of coronary heart disease more in women

than in men (18). In addition, atrial fibrillation, hypertension and type 2 diabetes mellitus tend to have a greater effect on increasing stroke risk in women compared to men (23).

Several cardiovascular risk factors are unique for women, such as use of combined oral contraceptives, hormonal changes related to menopause, reproductive factors and pregnancy-related conditions can influence risk of stroke and coronary heart disease in women (5, 6, 26-28). Therefore, pregnancy-related conditions, such as preeclampsia and gestational diabetes mellitus, are included in recent European and American cardiovascular prevention guidelines (8, 9).

1.1.4 Evaluation of risk

A number of multivariate risk models are used to estimate the risk of initial CVD events in apparently healthy, asymptomatic individuals, such as the Framingham risk score, QRISK3 and SCORE. Different risk factors are included in each model, and the most common factors included are age, gender, total cholesterol, systolic blood pressure, current smoking and diabetes mellitus (29). In addition, family history of CVD and antihypertensive treatment are included in the Norwegian risk score model, NORRISK 2 (30). Some of the aforementioned gender-specific or female predominant risk factors are mentioned in cardiovascular prevention guidelines, but only a few of them are assessed in risk assessment tools. In NORRISK 2, rheumatoid arthritis is included as an additional factor which increases the long-term cardiovascular risk in addition to the traditional risk factors (30, 31). On the other hand, diabetes mellitus is not included in this model, and these patients should be evaluated in accordance with the disease-specific guidelines for diabetes mellitus. In addition, factors related to reproductive history are not included in the Norwegian risk score system, and therefore also need to be considered individually, together with the traditional cardiovascular risk factors.

The Netherlands was the first country that systematically addressed long-term cardiovascular risk related to pregnancy complications and reproductive factors, and established a national guideline for CVD prevention in women with

a history of preeclampsia (32). Many other countries, including Norway, have recommendations on follow-up after certain pregnancy complications, e.g. preeclampsia and gestational diabetes (33, 34). However, whether adverse pregnancy outcomes should be a part of the traditional cardiovascular risk scores still represents an area of research. A recent Norwegian study found inclusion of pregnancy complications in the cardiovascular risk model (NORRISK II) only to result in small improvements of CVD risk prediction (35). The same conclusion has been drawn from other similar studies, but the authors highlight that hypertensive disorders in pregnancy are associated with increased CVD risk independent of established risk factors and can possibly improve risk prediction in younger individuals (36, 37).

1.2 Hyperemesis gravidarum

1.2.1 Epidemiology

Nausea and vomiting affects up to 80% of all pregnant women and about 1% suffer from extreme symptoms known as hyperemesis gravidarum (hyperemesis) (38, 39). Hyperemesis is the most common cause of hospitalisation in early pregnancy, and associated with large socioeconomic cost (40). The financial burden is related to sick leave, and the level of healthcare provided as the factor with the greatest impact on cost (10, 41).

1.2.2 Definitions

The International Classification of Disease (ICD) is a cornerstone in epidemiological research on morbidity and mortality. The coding system provides an opportunity to assess disease prevalence, incidence and other health problems in the population (42). The Medical Birth Registry of Norway (MBRN) has used ICD-8 and ICD-10. In ICD-8, hyperemesis is defined as "Hyperemesis with mention of neuritis or without mention of neuritis''. ICD-10 defined hyperemesis as ''Excessive vomiting in pregnancy'' and distinguished "mild hyperemesis without metabolic disturbances" from "hyperemesis with metabolic disturbances"; and included that nausea and vomiting had to have started before the 22nd gestational week.

Clinically, hyperemesis is characterised by extreme nausea and vomiting before 20 weeks gestation, resulting in weight loss, dehydration, metabolic disturbances and hospitalisation (43). Hyperemesis is a complex diagnosis and a diagnosis of exclusion. Patients undergo a diagnostic work-up, including laboratory testing and ultrasonography to rule out other causes of nausea and vomiting (40). Hyperemesis is associated with molar pregnancy, multiple gestation and infection with Helicobacter pylori (44). Research on hyperemesis has so far been hampered by the fact that there is no consensus on the definition of hyperemesis (44). In 2002 a scoring system to assess the severity of nausea and vomiting in pregnancy was introduced; the Pregnancy-Unique Quantification of Emesis (PUQE). This scoring system has been validated as a good indicator of symptoms in patients with hyperemesis, and high scores correlate with reduced nutritional intake as well as reduced quality of life (45, 46).

1.2.3 Aetiology and risk factors

The aetiology of hyperemesis remains largely unknown, but is considered to be multifactorial (10, 47). Different underlying mechanisms have been proposed, such as genetic, hormonal and environmental factors (10, 43).

If a woman suffers from hyperemesis in her first pregnancy, her risk of having another pregnancy with hyperemesis is 26 times higher, when compared to women who did not suffer from hyperemesis before (48). If her mother suffered from the condition in one of her pregnancies, the woman is three times more likely to experience hyperemesis in her own pregnancy (49). This may indicate a genetic component, that hyperemesis is inherited along the maternal line. More recent studies have investigated possible genes involved in the aetiology of hyperemesis (50-53). A genome-wide association study identified two genes associated with hyperemesis, growth and differentiation factor 15 (*GDF15)* and insulin-like growth factor binding protein 7 (*IGFBP7)*, both known to be involved in placentation and appetite-regulation (52). The genes identified may play a major role in different aspects of the pathophysiological mechanisms, both endocrine and gastrointestinal pathways.

Human chorionic gonadotropin (hCG) has, until recently, been considered a contributing factor to hyperemesis. Severe nausea and vomiting in pregnancy is associated with conditions with higher levels of hCG such as multiple pregnancies, molar pregnancies and female foetuses (54). However, a systematic review and meta-analysis from 2014 found inconsistent evidence of an association between hyperemesis and hCG (47). Other reproductive hormones, like oestrogen and progesterone, have also been studied in the relation to hyperemesis. Conditions or states associated with higher levels of oestrogen, like low parity, female offspring and high body mass index (BMI) are associated with hyperemesis. The two hormones can alter the gastric rhythm in non-pregnant women and lead to increased nausea and vomiting (10, 45).

The condition is more common among non-Caucasians and non-smokers (38, 55). Young age and low socioeconomic status are also associated with hyperemesis. Several studies have shown an association between hyperemesis and placental dysfunction disorders, such as preeclampsia and placental abruption (11-13). Two recent meta-analyses and systematic reviews identified infection with Helicobacter pylori as a risk factor for hyperemesis (47, 56).

1.2.4 Consequences of hyperemesis for the offspring

Most women with hyperemesis will deliver a healthy child, but there are some possible risks for the baby to be considered. Possible consequences for the unborn child will only be mentioned briefly, as this is beyond the scope of this thesis.

Short-term

Hyperemesis is associated with adverse pregnancy outcomes, such as low birth weight, small-for-gestational-age infants and preterm birth (12, 57). Although low absolute risk, a large British cohort reported that babies to women with hyperemesis were more likely to need resuscitation or neonatal intensive care (12). Not all studies show increased risk of adverse outcomes for women with hyperemesis and reduced maternal weight gain during pregnancy rather than hyperemesis itself has been suggested as a possible explanation (58, 59).

Long-term

Previous research has shown that early life nutrition may have an impact on the long-term health of the growing fetus (60, 61). Several small studies found an increased risk of leukaemia or testicular cancer in the adult offspring of mothers with hyperemesis (62-64), but a large Norwegian study found no such association (65). Recent studies suggest an association between hyperemesis and increased risk of neurodevelopmental delay in children (66, 67). Adverse fetal environment could also have an impact on later metabolic diseases in the offspring (68). Ayyavoo et al. reported lower insulin sensitivity in children born to mothers with severe hyperemesis (69), and Grooten et al. found increased blood pressure at 5-6 years of age in children born to mothers with severe weight loss in pregnancy (70). However, no association between hyperemesis and adolescent metabolic risk factors were found in a large Finnish cohort study (71).

1.2.5 Consequences of hyperemesis for the mother

The majority of women with hyperemesis will recover from their symptoms between 16th and 20th gestational week, but for 22% symptoms can last until delivery (72). There are some possible maternal risks associated with hyperemesis that need to be acknowledged. The maternal short-term consequences will not be discussed in detail, as this is beyond the scope of this thesis.

Short-term

Many mothers with hyperemesis suffer from weight loss, dehydration and metabolic disturbances requiring hospital admission and enteral or intravenous nutrition (10). Although rare, the vomiting and severe nutritional deficiency may lead to neurological complications, including Wernicke's encephalopathy (10). In addition, Vitamin K deficiency, dehydration and immobility may lead to coagulopathy and increased risk of venous thromboembolism in women with hyperemesis (12, 73). Up to two thirds of women with hyperemesis are reported to have gestational transient thyrotoxicosis, although not necessitating treatment (54). Lastly, the condition may lead to significant psychological and emotional distress during as well as long after pregnancy (43, 74).

Approximately 15% of women with hyperemesis have terminated at least one pregnancy due to nausea and vomiting in pregnancy; with inability to care for self or family as main reasons (75).

Long-term

Little is known about the long-term consequences of hyperemesis, and this thesis may contribute to a better understanding of maternal risks following hyperemesis.

Autoimmune disease

One population-based Danish study investigating associations between reproductive factors and the risk of rheumatoid arthritis, found a rate ratio of 1.70 (1.06-2.54) for rheumatoid arthritis in women with a history of hyperemesis (76). Immunological abnormalities and circulating fetal cells in the maternal circulation were proposed as possible mechanisms behind this association. The same research group also found an increased risk of any autoimmune disease among women with a history of hyperemesis, including Graves' disease, pernicious anaemia, Celiac and Crohn's disease (77).

Cancer

Reproductive factors are associated with maternal cancer risk. Parity, early age at first pregnancy and breastfeeding are associated with a reduced risk of breast cancer (78, 79). Also, a history of preeclampsia is associated with a lower risk of maternal breast cancer (78). It has been hypothesised that since hyperemesis was previously found to be associated with hormonal alterations, such as gestational thyrotoxicosis, it impacts on cancer risk later in life. A large Norwegian study from 2015 reported a lower overall cancer risk among women with a history of hyperemesis, but an increased risk of thyroid cancer, which increases with increasing numbers of pregnancies with hyperemesis (80). Some studies, including the aforementioned Norwegian study found no association between hyperemesis and risk of breast cancer (80, 81). Other studies report an increased risk of breast cancer subsequent to hyperemesis (82, 83).

Psychological perspectives

Hyperemesis has historically been thought to be a psychosomatic illness and is still associated with different types of stigmatisation (84). A meta-analysis from 2016, including 12 studies, showed associations between hyperemesis with depression and anxiety in pregnancy, but the study was not able to explore the direction of associations (85). A population-based cohort study from 2017 found women with a lifetime history of depression to have a 50% increase in odds of developing hyperemesis compared to those without, but only 1.2% of women with previous depression developed hyperemesis (86). The same research group found a higher risk of posttraumatic stress symptoms and emotional distress in women up to 18 months after delivery, when having had hyperemesis (87, 88).

1.3 Rationale for the study

Some pregnancy complications, such as preeclampsia and hypertension, are associated with an increased risk of CVD. The hypothesis underlying this study is that hyperemesis could also be associated with an increased risk of CVD. The following observations and associations explain and justify this hypothesis (figure 1):

- Hyperemesis was previously found to be associated with placental dysfunction disorders like preeclampsia and placental abruption (11-13). These conditions are known to increase maternal long-term cardiovascular risk (6, 89).
- Hyperemesis is associated with several traditional cardiovascular risk factors, such as low socioeconomic status, hypertension, diabetes mellitus, hypercholesterolemia and overweight (12, 55, 90, 91).
- An association exists between hyperemesis and later risk of autoimmune diseases (76, 77). Possible underlying mechanisms are not known, but immunological abnormalities or circulating fetal cells in the maternal circulation are suggested to trigger the disease.

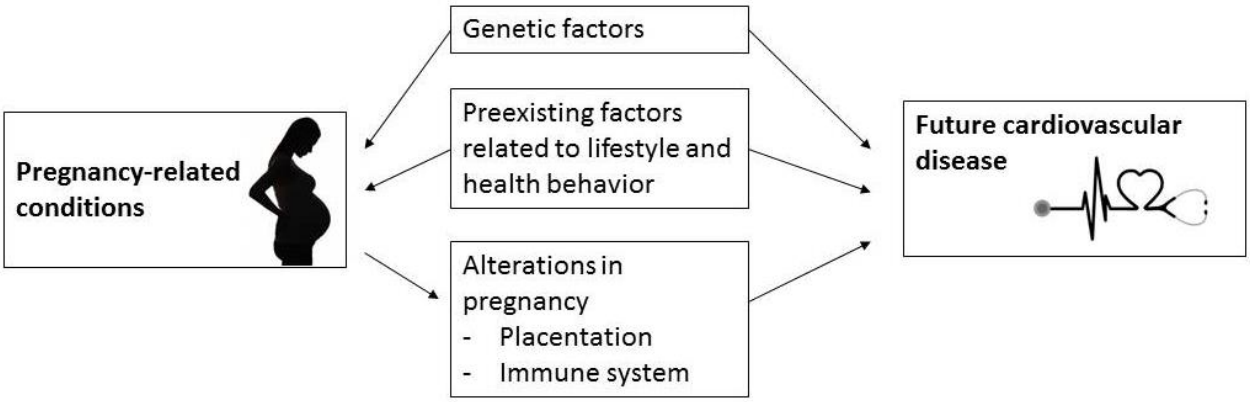

Figure 1. *Possible mechanisms for the association between pregnancy complications and later cardiovascular risk.*

2.0 AIMS OF THE STUDY

General aim

The overall aim for this research project was to assess long-term cardiovascular risk in women with a history of hyperemesis gravidarum.

Specific aims

More specifically, the research questions raised were:

- Is hyperemesis gravidarum associated with increased long-term maternal all-cause mortality or cause-specific mortality? (*Paper I*)
- Is the midlife cardiovascular risk profile among women with a history of hyperemesis gravidarum or hypertensive disorders in pregnancy different from women without such history? (*Paper II*)
- Is hyperemesis gravidarum associated with increased maternal long-term risk of a fatal or nonfatal cardiovascular event? (*Paper III*)

3.0 MATERIAL AND METHODS

Table 1. *Overview of aims as well as material and methods used in the included papers. Each topic is described in more detail throughout this chapter.*

	Paper I	**Paper II**	**Paper III**
Aim	To investigate if HG is associated with increased long-term maternal mortality	To investigate if HG or hypertensive disorders in pregnancy are associated with increased levels of midlife cardiovascular risk factors	To investigate if HG is associated with increased long-term maternal cardiovascular morbidity
Data-sources	The MBRN + The Cause of Death registry	The MBRN + The Age 40 Program	The MBRN + The Cause of Death registry + FS-data
Types of data-sources	Nationwide health registries	Nationwide health registry and health survey	Nationwide health registries and information on hospital discharge
Design	Population-based cohort study	Cross-sectional study	Population-based cohort study
Population	N= 999 161 (13 397 with HG)	N= 178 231 (2140 with HG, 13 348 with hypertensive disorders in pregnancy)	N= 989 473 (13 212 with HG)
Follow-up time	1967-2009	No	1994-2009
Exposure	HG in at least one pregnancy	HG or hypertensive disorder in at	HG in at least one pregnancy

		least one pregnancy	
Primary outcome	All-cause mortality	10 traditional cardiovascular risk factors	Cardiovascular death or hospitalisation with nonfatal stroke, myocardial infarction or angina pectoris
Secondary outcomes	Cardiovascular mortality, deaths due to cancer, external causes or mental and behavioural disorders		Primary outcome without angina pectoris Each of the components in the main outcome
Association measures	Hazard ratios with 95% confidence interval	Odds ratios and β-coefficients with 95% confidence interval	Hazard ratios with 95% confidence interval

HG hyperemesis gravidarum; MBRN Medical Birth Registry of Norway; FS-data "Forskning i sykehus" (Research in Hospitals)

3.1 Data sources

3.1.1 The Medical Birth Registry of Norway

The Medical Birth Registry of Norway (MBRN) was established in 1967 and is the oldest birth registry in the world. All births in Norway are registered within one week after discharge from hospital. This is mandatory, and from 1967 to 2002 all pregnancies ending after week 16 were notified in the MBRN. A notification form is filled in by the midwife or doctor, and contains complete identification of the mother and father, information on mother's health before and during pregnancy, complications during pregnancy and delivery as well as

information on the infant (92, 93). The MBRN has been described in detail elsewhere (92, 93).

3.1.2 The Cause of Death Registry

The Norwegian Cause of Death Registry has a 98% coverage and completeness of the Norwegian population. For all deaths, a death certificate (paper form IS-1025B) with a logical sequence from the underlying to the immediate cause of death must be completed by a medical doctor. A code from the ICD-system is allocated to the diagnosis in the death certificate. The underlying cause of death is identified by the IRIS computer programme with the Automated Classification of Medical Entities (ACME) module, or by assessment of a professional coder. Around 500-700 (1.2-1.7%) death certificates are missing every year in Norway. The Cause of Death Registry used the ICD-7 from 1960 to 1968, ICD-8 from 1969 to 1985, ICD-9 from 1986 to 1995 and ICD-10 codes from 1996 to 2009 (94).

3.1.3 The Age 40 Program

From 1985 to 1999 the Norwegian health authorities conducted a screening program called the Age 40 Program. 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, decreasing over time (95, 96). Altogether, around 600 000 men and women participated in the program. The main aim of this screening program was to investigate midlife cardiovascular factors in the Norwegian population (95-97). The screening included a non-fasting blood sample, measurement of blood pressure, height and weight and filling in a questionnaire. For *Paper II*, some of the traditional cardiovascular risk factors were chosen. A few participants attended the program more than once. If so, only the first visit was used for this study.

3.1.4 Hospital discharge data

All hospitalisations due to CVD or diabetes mellitus have been collected from all Norwegian somatic hospitals from 1994 through 2009. The information has

been retrieved from the Patient Administrative System, with the aid of the FS-system ("Forskning i sykehus", Research in Hospitals). The FS-system contains information on more than 2 million hospitalisations with CVD or diabetes mellitus in more than 600 000 women during this time period (similar numbers for men). The overall objective for establishing this system was to improve the efficiency of research at hospitals and to build a system which facilitates the practical use of scientific findings within hospitals (98). In this thesis, information on hospital discharge data of cardiovascular events (fatal or nonfatal) was used.

3.1.5 Statistics Norway

Statistics Norway is the national statistical institute of Norway and produces official statistics related to the economy, population and society, available to the general public (www.ssb.no). For this research project, information on education and maternal country of birth were obtained from Statistics Norway.

3.2 Linkages

The MBRN was linked to nationwide health registries, health surveys and hospital discharge data. In addition, data from Statistics Norway were used for covariate information. Figure 2 shows the time period with available information from each data source used in the thesis. The personal identification number unique to every Norwegian resident has made linkage of the different data sources possible. To obtain de-identified data, the personal identification numbers were replaced by another code/running-number. The "bridge" between the personal identification numbers and the allocated codes was provided by Statistics Norway and the Norwegian Institute of Public Health. The linkages of the data files were done by the candidate under guidance from the main supervisor.

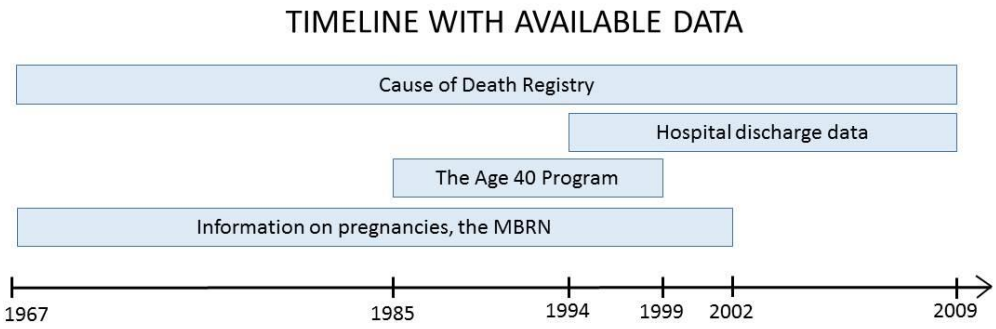

Figure 2. *Years of availability of the data sources used in this thesis.*
MBRN: Medical Birth Registry of Norway

3.3 Study design

3.3.1 Cohort studies: Paper I and III

Paper I and *Paper III* were population-based cohort studies where register data was used to answer the research questions. A cohort study is the archetype for epidemiologic studies and consists of a group of people followed over a specific time period. The question raised in a cohort study is often whether there is an association between the exposure and the disease of interest. The study intends to reveal a causal action of an exposure on the studied outcome. Because of the non-experimental approach, cohort studies can be used to assess the natural or clinical course of a disease (99). When the researcher uses data already collected for other purposes, it is called a retrospective or historical cohort study (100). This is the case when register data is used and the study is performed posthoc.

3.3.2 Cross-sectional study: Paper II

Per definition, all the information in a cross-sectional study refers to the same point in time (99). The study design is often used to measure disease prevalence or characteristics of a population. In *Paper II*, information about the exposure (hyperemesis) was collected from the MBRN several years before the information on cardiovascular risk factors was obtained. As only information on risk factors at a specific time point was available, this study is not a longitudinal, but rather a cross-sectional study with information on the

exposure from the past. This study design can be useful with respect to causal hypotheses.

3.4 Study populations

Paper I

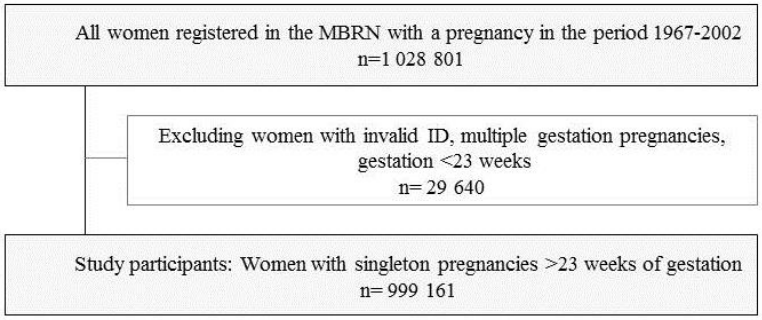

Figure 3. *Simplified flow diagram of the study population in Paper I.*
MBRN: Medical Birth Registry of Norway

The source population in *Paper I* was all women in Norway who were pregnant in the period between 1967 and 2002. The study population comprised women registered in the MBRN with a singleton pregnancy of more than 23 weeks of gestation from 1967 to 2002 (figure 3). Only singleton pregnancies were included, because multiple gestation pregnancies are considered "high-risk-pregnancies" and were not a part of the aim of this research. Women with invalid or missing ID-number or year of birth were also excluded. Because of little missing information on covariates (<1.5%), only complete cases were used in multivariable analyses. The study population consisted of 999 161 women.

Paper II

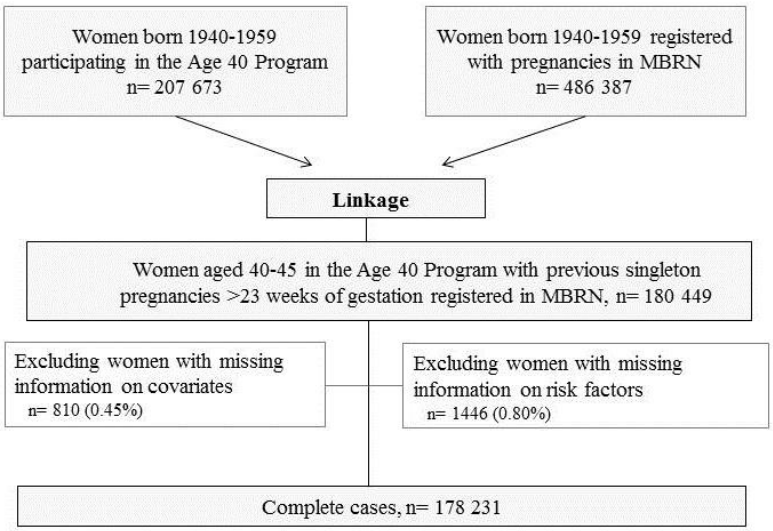

Figure 4. *Simplified flow diagram of the study population in Paper II.*
MBRN: Medical Birth Registry of Norway

The source population in *Paper II* was all women in Norway born in 1940-1959 with a previous pregnancy. The study population comprised women born in 1940-1959 who participated in the Age 40 Program (in 1985-1999) and had a history of a singleton pregnancy of more than 23 weeks gestation registered in the MBRN (figure 4). Women with missing information on some of the studied cardiovascular risk factors were excluded. Less than 0.5% of the women had missing information on sociodemographic variables, these women were also excluded. The study population consisted of 178 231 women. Each woman was only examined once during the Age 40 Program, at an age between 40 to 45 years old.

Paper III

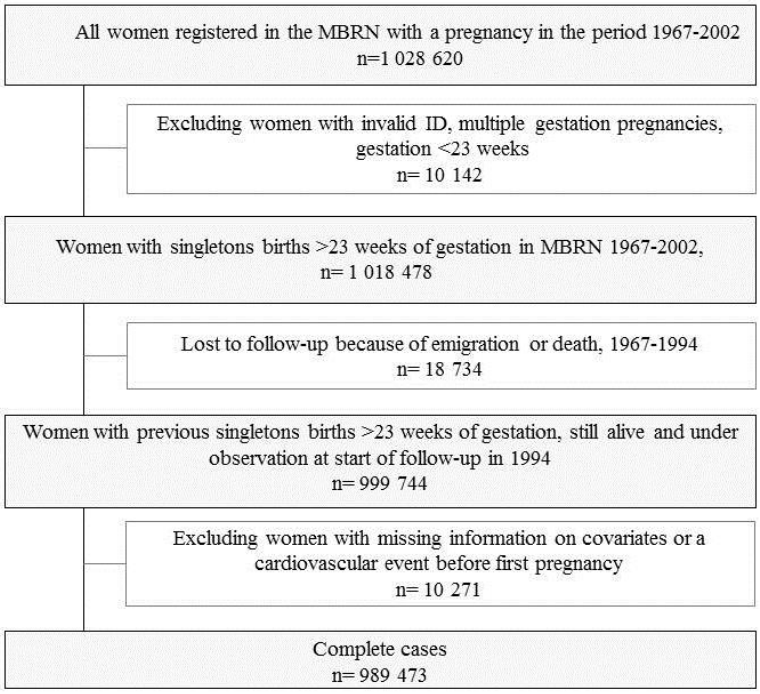

Figure 5. *Simplified flow diagram of the study population in Paper III.*
MBRN: Medical Birth Registry of Norway

The source population in *Paper III* was all women in Norway who were pregnant in the period between 1967 and 2002. The study population comprised women registered in the MBRN with a singleton pregnancy of more than 23 weeks gestation between 1967 and 2002 (figure 5). Women with invalid or missing ID-number or year of birth were excluded. Women who died or emigrated before follow-up started in 1994 (or later if first pregnancy was after 1994) were also excluded. Because of little missing information on covariates (<1.5%), only complete cases were used for analyses. The study population consisted of 989 473 women. Because different data files were used in *Paper I* and *III*, the first boxes in the flow diagrams differ slightly from each other.

3.5 Study variables and definitions

3.5.1 Exposure

Before 1998, maternal diseases during pregnancy were recorded as free text in the antenatal form. A new notification form was introduced in 1998, where check boxes for certain diseases before and during pregnancy were introduced. The textual information on maternal diseases is coded by the staff at the MBRN using ICD-codes.

Hyperemesis gravidarum (hyperemesis) was registered in the MBRN according to ICD-8 until 1998 and from 1999 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) (101). Women with at least one pregnancy complicated with hyperemesis were defined as exposed in all three papers. In addition, a cohort of women with hypertensive disorders in pregnancy was included in *Paper II* to assess the cardiovascular risk profiles among women with known increased long-term risk of CVD in the same population. In this study, hypertensive disorders in pregnancy included gestational hypertension, HELLP syndrome, preeclampsia and eclampsia. Gestational hypertension was defined as at least one measurement of systolic blood pressure ≥140 mmHg and/or 90 mmHg diastolic after the 20th gestational week, without evidence of pre-existing hypertension. The MBRN defines preeclampsia as gestational hypertension combined with proteinuria. After 1998, the MBRN registration form was changed and check boxes for preeclampsia were introduced ("preeclampsia, mild", "preeclampsia, severe", "preeclampsia, before 34 weeks", "gestational hypertension, alone", "eclampsia") (102). The corresponding ICD-codes are shown in table 2.

3.5.2 Covariates

Covariate information was mainly available from the MBRN or from Statistics Norway. Information on maternal health before and during pregnancy was collected from the MBRN and information on socioeconomic status and ethnicity was available from Statistics Norway. If a woman had registered more

than one pregnancy in the MBRN, dichotomous variables based on all pregnancies were created for pre-pregnancy and pregnancy factors (ever/never). In all papers, information on education was obtained from Statistics Norway and used as a proxy for maternal socioeconomic status. Highest attained education was categorized as basic (9 years), secondary (10-12 years) or tertiary (≥13 years), according to the Norwegian Standard Classification of Education (103). In *Paper I* a slightly different categorization was used: ≤10 years of school, 11-13 years, 14-16 years and ≥17 years of school.

3.6 Outcomes and follow-up

Paper I

Information on the studied outcomes was provided from the Cause of Death Registry. Death from CVD, mental and behavioural disorders, external causes and cancer were assessed in addition to all-cause mortality. The corresponding ICD-codes are shown in table 2. Women were followed from their first registered pregnancy in the MBRN until death or censored at the cut-off year of 2009.

Paper II

Information on the studied outcomes was provided from the Age 40 Program. The following cardiovascular risk factors were studied: Family history of coronary heart disease, BMI, smoking, physical activity, systolic and diastolic blood pressure, heart rate, cholesterol, triglycerides, self-reported diabetes mellitus and antihypertensive treatment. This was a cross-sectional study with no follow-up.

Paper III

Information on the studied outcomes was obtained from the Cause of Death Registry and the FS-system (hospital discharge). A cardiovascular event was defined as the occurrence of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalisation with angina pectoris as main or secondary discharge diagnosis. Cardiovascular death was defined as either CVD as the underlying cause of death in the Cause of Death Registry or death within 28 days after hospitalisation with a cardiovascular event. ICD-codes are given in

table 2. Women were followed up with respect to cardiovascular outcomes from 1994 (or their first pregnancy if later than 1994) to 2009.

Table 2. *Summary of ICD-10 codes for exposure and outcome variables used in the thesis.*

Diagnosis	ICD-10 coding
Hyperemesis gravidarum	O21.0, O21.1, O21.9
Hypertensive disorders in pregnancy	O13, O14, O15, O16
Diseases of the circulatory system/CVD Ischaemic heart disease Cerebrovascular disease Other CVD Angina pectoris Myocardial infarction Stroke	I00-I99 I20-I25 I60-I69 (All circulatory system codes exept I20-I25 and I60-I69) I20, I25.1 I21, I22 I60-I61, I63-I64
Mental and behavioural disorders	F00-F99
External causes	V01-Y89
Cancer Tobacco-related Alcohol-related	C00-D48 C33-C34, C00-C16, C32, C25, C64, C67, C53, C18-22, C56, C92 C01-C15, C32, C50, C18-C22

CVD cardiovascular disease; ICD International Classification of Disease

3.7 Statistical methods

Sample size and power calculations were performed before the study started. The sample size was large in all three papers. As an example, 4203 women would have been needed to be included in study II to show a small difference of 1 mmHg in blood pressure, with a power of 90. The database used was much larger than this, comprising more than 178 000 women.

Characteristics of women with and without hyperemesis were presented as number (percentages), mean (standard deviation) or median (percentiles). In *Paper II*, triglycerides had a skewed distribution and were logarithmically transformed to achieve normality. Differences in basic characteristics between the two (or three) cohorts were assessed with t-test (continuous data) or chi-squared test (categorical data). *P-values* below 0.05 were considered statistically significant. In all three papers, included in this thesis, regression models were applied to estimate associations between the exposure

(hyperemesis) and the studied outcomes. In *Paper I* and *Paper III,* Cox proportional regression model for survival data was applied to estimate hazard ratios (HRs) with 95% confidence intervals. The model assumes non-informative censoring and constant HR over time (104). The assumption of proportional hazards was tested using Schoenfield residuals and graphically assessed with log-log plots of survival. Crude, age-adjusted and multivariable-adjusted HRs were estimated. In *Paper* II, linear and logistic regression models were performed for multivariable analyses. In preparation, all variables were checked for deviations from normality, non-linear effects, multicollinearity and homoscedasticity. 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 with 95% confidence interval (CI) were estimated. An estimate with a confidence interval not including one (cox regression or logistic regression) or zero (linear regression) was considered statistically significant. The analyses have been conducted in the statistical software STATA version 14 and 15.

Competing risk

Paper I and *III* investigated cause-specific hazard rates for mortality and morbidity in women with a history of hyperemesis compared to women with previous pregnancies without hyperemesis. In epidemiological follow-up studies, observation of the disease under study may be preceded by other events, which prevents observation of the disease of interest, known as "competing risk" situation (105). The frequency with which the diseased cases occur is measured using either estimates of "risk" or "rate". We have applied Cox regression models to calculate cause-specific HRs for morbidity and mortality. Cause-specific hazards quantify the event rate among the ones at risk of developing the event of interest. Women who die from other causes during follow-up were censored. In studies of all-cause mortality, rates and risks are equivalent, whereas in the setting of competing risk they are not. Therefore, the results in *Paper I* and *III* need to be interpreted as cause-specific HRs and cannot necessarily be interpreted as the cumulative incidence or risk (105).

3.8 Ethics

This PhD project was approved by the Regional Committee for Medical and Health Research Ethics in Norway (2015/1347/REK South-East). In addition, the owners of each register, health survey or hospital discharge data had to give approval for the study and linkages. The participants in the Age 40 Program gave consent to medical research and linkage to other health registries. Due to the large number of women registered in the MBRN, the Cause of Death Registry and the hospital discharge data (FS-data), the ethical committee gave approval for exception from consent from these women.

4.0 SUMMARY OF MAIN RESULTS

4.1 Main results according to paper

Paper I

"Hyperemesis gravidarum and long-term mortality: a population-based cohort study"

Out of 999 161 women with singleton births, 13 397 (1.3%) had hyperemesis. Women with a history of hyperemesis gravidarum were compared to women with previous pregnancies not complicated with hyperemesis. During a median follow-up of 26 years (25 902 036 person-years), 43 470 women died (4.4%). Women exposed to hyperemesis had a lower rate of long-term all-cause mortality compared to women without (crude HR 0.82; 95% CI 0.75-0.90). When adjusting for confounders, this reduction was no longer significant (adjusted HR 0.92; 95% CI 0.84-1.01). With respect to causes of death, women exposed to hyperemesis had a similar rate of cardiovascular death as women not exposed (adjusted HR 1.04; 95% CI 0.83-1.29), but lower long-term rate of death from cancer (adjusted HR 0.86; 95% CI 0.75-0.98).

Paper II

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

Among 178 231 women participating in the Age 40 Program with previous singleton births; 2 140 (1.2%) had experienced hyperemesis and 13 348 (7.5%) hypertensive disorders in pregnancy. Women with each of the pregnancy-related conditions were compared to women with none of the two studied pregnancy-related conditions (reference group). The mean time from first pregnancy to attending the Age 40 Program was 17.9 years. Women who had suffered from hyperemesis were less physically active than the reference group (table 3). They had higher mean BMI, but lower mean systolic blood pressure compared to the reference group. In women with a history of hypertensive disorders in pregnancy, systolic and diastolic blood pressure and BMI were higher compared to the reference group (table 3). They were also more likely to be taking antihypertensive medication and reported more diabetes mellitus in midlife than women in the reference group. Women who had suffered from hyperemesis or hypertensive disorders in pregnancy were less likely to be daily smokers than women without any of the studied pregnancy-related conditions.

Table 3. *A selection of the studied cardiovascular risk factors at the age of 40-45 among women with a history of hyperemesis gravidarum (n=2 140), hypertensive disorders in pregnancy (n= 13 348) or both (n=189), compared to women without such history (n= 162 554).*

	Cardiovascular risk factors Mean (SD) or n (%)					
Pregnancy complications	Body mass index (kg/m2)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Anti-hypertensive treatment, n (%)	Daily smokers, n (%)	Physical inactivity, n (%)
No HG or HT (ref.)	24.2 (3.7)	123.7 (13.6)	74.9 (9.7)	2 128 (1.3)	67 022 (41.2)	33 695 (20.7)
HG	24.4 (3.8)*	122.7 (13.3)*	74.9 (9.7)	32 (1.5)	634 (29.6)*	498 (23.2)*
HT	26.4 (4.9)*	133.4 (16.5)*	80.9 (11.0)*	1 043 (7.8)*	4 177 (31.3)*	2 821 (21.1)
Both HG and HT	26.5 (5.1)*	133.4 (17.6)*	81.3 (12.2)*	24 (12.7)*	47 (24.9)*	45 (23.8)

HG hyperemesis gravidarum; *HT* hypertensive disorders in pregnancy; *SD:* standard deviation
**p-value* <0.01, tested with t- test or chi-squared test

Paper III

"Long-term cardiovascular morbidity following hyperemesis gravidarum: a Norwegian nationwide cohort study"

Among 989 473 women with singleton births included in this nationwide cohort study, 13 212 (1.3%) suffered from hyperemesis. Women with a history of hyperemesis gravidarum were compared to women with previous pregnancies not complicated with hyperemesis. During a median of 15 years of follow-up, a total of 43 482 (4.4%) women experienced a cardiovascular event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke or hospitalisation for angina pectoris). No association was found between hyperemesis and the cardiovascular event rate during follow-up (adjusted HR 1.08; 95% CI 0.99-1.18). In the age-adjusted analysis, the rate of cardiovascular death was lower among women with previous hyperemesis (HR 0.73; 95% CI 0.59-0.91), but the association was no longer significant when adjusting for more potential confounders. Women having suffered from hyperemesis had a higher rate of being hospitalized for angina pectoris during follow-up (adjusted HR 1.28; 95% CI 1.15-1.44) compared to women without hyperemesis.

4.2 Results not included in the papers

Paper I

Hyperemesis is more common among non-smokers (55), but information on smoking habits was unfortunately not registered in the MBRN before 1999. Smoking is a major risk factor for CVD and the inability to adjust for smoking may have led to unmeasured confounding in *Paper I*. To further explore this issue, a sensitivity analysis was conducted exploring a possible impact of unmeasured confounding from smoking on CVD mortality. Percentages of smokers among the exposed and unexposed in a subgroup after 1999 (table S1) were used to investigate differences in rate of dying from CVD related to different smoking habits. Several studies have shown that smokers have twofold hazards of cardiovascular mortality compared with never smokers (106). Based on this information and the distribution of smokers in the subgroup after 1999, a deterministic sensitivity analysis of unmeasured confounding was performed

to explore the possible impact of smoking on the odds ratio of CVD mortality among exposed and unexposed women. The odds ratio of CVD mortality in this study's population can possibly increase from 0.82 (crude, observed odds ratio) to 0.86 (smoking-adjusted odds ratio). This was based on estimation and will be different with other plausible values for the hyperemesis-specific smoking proportion and the smoking related CVD mortality. However, it shows that the lack of adjustment for smoking is likely to influence the results, but not to a great extent.

Paper II

Also in this paper, additional analyses were performed to explore the possible impact of smoking on the studied associations. Information on smoking habits was available from the Age 40 Program. Analyses were stratified on smoking habits (never or daily smokers). All the other nine cardiovascular risk factors were studied for women with a history of hyperemesis, hypertensive disorders in pregnancy, or none of the pregnancy complications of interest. A group of former smokers (n= 40 067) was excluded from these analyses. Women with both hyperemesis and hypertensive disorders in pregnancy were also excluded. 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.

Table 4. *Analyses stratified by smoking status (never or daily smokers). Cardiovascular risk factors among women with hyperemesis gravidarum (n= 1710), hypertensive disorders in pregnancy (n= 10 247) or pregnancies with none of the studied complications (n= 126 018).*

	Stratified analyses			**Full model**
Cardiovascular risk factors	**Never smokers** No HG or HT (n=58 996) HG (n=1 076) HT (n=6 070)	**Daily smokers** No HG or HT (n=67 022) HG (n=634) HT (n=4 177)		**Interaction term**[a] ***p-value***
	β (95%CI)	***β (95% CI)***		
Body mass index (kg/m2) No HG or HT HG HT	 Ref. 0.19 (-0.04, 0.41) 1.95 (1.83, 2.08)	 Ref. 0.32 (0.02, 0.61) 2.38 (2.24, 2.53)		 0.23 <0.01
Systolic blood pressure (mmHg) No HG or HT HG	 Ref. -0.51 (-1.33,0.31)	 Ref. -1.58 (-2.58,-0.57)		 0.38

HT	9.59 (9.16,10.01)	9.00 (8.49, 9.52)		0.07
Diastolic blood pressure (mmHg)				
No HG or HT	Ref.	Ref.		
HG	0.40 (-0.18, 0.98)	-0.24 (-0.95, 0.48)		0.48
HT	6.10 (5.83, 6.38)	5.73 (5.39, 6.07)		0.08
Heart rate (bpm)				
No HG or HT	Ref.	Ref.		
HG	0.36 (-0.31,1.03)	-0.14 (-1.02, 0.74)		0.42
HT	3.13 (2.77, 3.49)	1.80 (1.39, 2.22)		<0.01
Serum total cholesterol (mmol/L)				
No HG or HT	Ref.	Ref.		
HG	0.05 (-0.01, 0.10)	-0.04 (-0.12, 0.04)		0.31
HT	0.14 (0.12, 0.17)	0.15 (0.12, 0.18)		0.50
Triglycerides (mmol/L), median (quartiles)				
No HG or HT	Ref.	Ref.		
HG	0.06 (0.01, 0.11)	0.02 (-0.05, 0.09)		0.55
HT	0.18 (0.16, 0.20)	0.19 (0.16, 0.23)		0.30
	OR (95% CI)	***OR (95%CI)***		
Antihypertensive treatment, n (%)				
No HG or HT	Ref.	Ref.		
HG	1.40 (0.88, 2.22)	0.90 (0.43, 1.90)		0.80
HT	5.86 (5.18, 6.64)	5.46 (4.73, 6.30)		0.04
Physical inactivity, n (%)				
No HG or HT	Ref.	Ref.		
HG	1.27 (1.10, 1.47)	1.12 (0.94, 1.33)		0.81
HT	1.16 (1.08, 1.24)	0.99 (0.93, 1.07)		0.01
Diabetes mellitus, n (%)				
No HG or HT	Ref.	Ref.		
HG	0.83 (0.34, 2.03)	0.60 (0.15, 2.41)		0.63
HT	2.58 (2.01, 3.31)	2.63 (2.00, 3.47)		0.70

HG hyperemesis gravidarum; *HT* hypertensive disorders in pregnancy; *β* β-coefficient; OR Odds ratios; 95% CI 95% confidence interval.

[a] An interaction term (smoking*HG or smoking*HT) was included in each regression model to test for significant interactions

Results: Women with hypertensive disorders in pregnancy had increased cardiovascular risk in both smoking strata, and there was a significant interaction between hypertensive disorders in pregnancy and smoking for BMI, heart rate, current hypertensive treatment and physical inactivity (table 4). There was no statistically significant interaction between hyperemesis and smoking for any of the studied risk factors.

5.0 DISCUSSION

5.1 Main findings

The three papers included in this thesis, provide new knowledge about the potential long-term health consequences for women with a history of hyperemesis gravidarum (hyperemesis). Hyperemesis was not found to be

associated with increased long-term all-cause mortality. Women with a history of hyperemesis did not have increased mortality due to CVD, but were less likely to die from cancer. This was supported by hyperemesis not being associated with an increased rate of nonfatal cardiovascular events during follow-up. However, when exploring each event separately, more women with previous hyperemesis were hospitalized due to angina pectoris compared to those without. Moreover, there were small differences in cardiovascular risk factors at the age of 40-45 between women with a history of hyperemesis and women without such history, except for the lower proportion of daily smokers among women with a history of hyperemesis. Women who had suffered from hyperemesis were less likely to be physically active, had higher BMI and lower systolic blood pressure. Compared to the reference group, women with a history of hypertensive disorders in pregnancy had higher levels of most studied cardiovascular risk factors, except smoking and physical activity.

5.2 Methodological considerations

5.2.1 Study design and study populations

Study design

All three papers use data from registries or health surveys. This provides large study populations and long follow-up time at a low cost and time. The use of registries often reduces bias due to non-response and loss to follow-up. However, there are some limitations in studies relying on existing records, such as missing information of interest or poor data quality. These issues are discussed later in this section.

Study populations

All study populations were large, but the population was relatively young at the end of follow-up in both *Paper I* and *III*. This could reduce the validity of our findings since CVD primarily occurs at an older age, especially in women. However, 25% of the population was >60 years at the end of follow-up. In *Paper III*, additional analyses on women born before 1945 were conducted to explore whether the results changed if only the oldest women were included in the study. The estimates from the sensitivity analysis were similar as in the main

analyses, indicating that the findings remained the same also when the age-distribution was more homogeneous. However, a longer follow-up time would have strengthened the conclusions of *Paper III*.

5.2.2 Random error

Random error is defined as the variability in the data that cannot be readily explained (107).

In epidemiological studies, results are reported using estimates of associations. Often the association is reported as a point estimate with a confidence interval. The confidence interval indicates the precision of the estimate and expresses the statistical variation, or random error, that underlies the estimate (107). The study sample in this thesis is large, which results in less random error and a narrower confidence interval. Another commonly reported measure is the *p-value*. The *p-value* is often used to conclude whether the reported associations are statistically significant or not. Many epidemiologists, however, warn against this dichotomisation of the association as significant or not (108). The *p-value* tests all the assumptions in the model and how the data were generated, not just the often stated null hypothesis. The smaller the *p-value*, the more unusual the data would be if every single assumption was correct, but the value does not tell us which assumption is incorrect (it is not necessarily the hypothesis being tested) (109). Again, a large study sample, which is the case in this thesis, is more likely to result in a small *p-value*. In order to interpret the results accurately, it is of importance to consider the *p-value*, the point estimate, different sources of bias and the clinical implications of the findings, altogether. In the included papers, some findings may have been statistically significant, but the clinical meaning remains less clear.

5.2.3 Bias

Another type of error in epidemiological studies is systematic error, also termed bias. Unlike random errors, systematic errors are not affected by increasing sample size (107).

Selection bias

Problems with selection bias are often absent or small in population-based cohort studies because people are not selected into the study, but participation is often a consequence of mandatory reporting (107). This is the case for the MBRN, the Cause of Death Registry and the FS-data. In the Age 40 program (*Paper II*), the participation rate for women varied between 57% and 91% during the period. The participation rate declined over time and the possibility of selection bias cannot be ruled out in this study.

Information bias

An error due to information bias can arise because the information collected about or from study subjects is erroneous (107). In register based research, there will always be a degree of uncertainty about the data quality. There may be some degree of misclassification, both with respect to the exposure and outcome. This may be a particular problem if the misclassification is differential, meaning that the misclassification is related to other study variables. We have used the MBRN for information on hyperemesis, the Cause of Death Registry for information on fatal outcomes and the FS-system on cardiovascular morbidity. The MBRN and the Cause of Death Registry are considered high quality and almost complete for the Norwegian population (93, 94). Data from the FS-system was quality controlled at almost all Norwegian hospitals in the period of 1995-2003. A random sample of hospitalisations in the FS-system was compared to the original data from the Patient Administrative System at the hospitals. All detected discrepancies were analysed and corrected (110).

The diagnosis of hyperemesis in the MBRN is based upon registration of hyperemesis on the antenatal card, which is retrospectively completed at the point of delivery. There is an increased likelihood of underreporting of many early pregnancy complications in such registries, especially if the condition may lead to an increased chance of early termination of pregnancy. According to the validity study by Vikanes et al., who used strict diagnostic criteria indicating severe hyperemesis, the diagnosis of hyperemesis in the MBRN is less valid for cases of severe hyperemesis (101). Applying less strict diagnostic criteria, implying mild hyperemesis, the study reported a sensitivity and positive

predictive value similar to that reported for rheumatic disease (111) and type I diabetes mellitus (112) in the MBRN. The fact that hyperemesis diagnosis in the MBRN is less valid for severe hyperemesis cases might influence the studied associations and bias the association (if there is one) towards the null value (101). However, the prevalence of hyperemesis in this thesis is 1.2-1.3% and comparable with the prevalence in other populations (39).

There have also been some changes in diagnostic criteria and registration of diagnosis over time, both regarding the exposure and the studied outcomes. The proportion of pregnancies registered with hyperemesis in the MBRN over time is shown in figure 6.

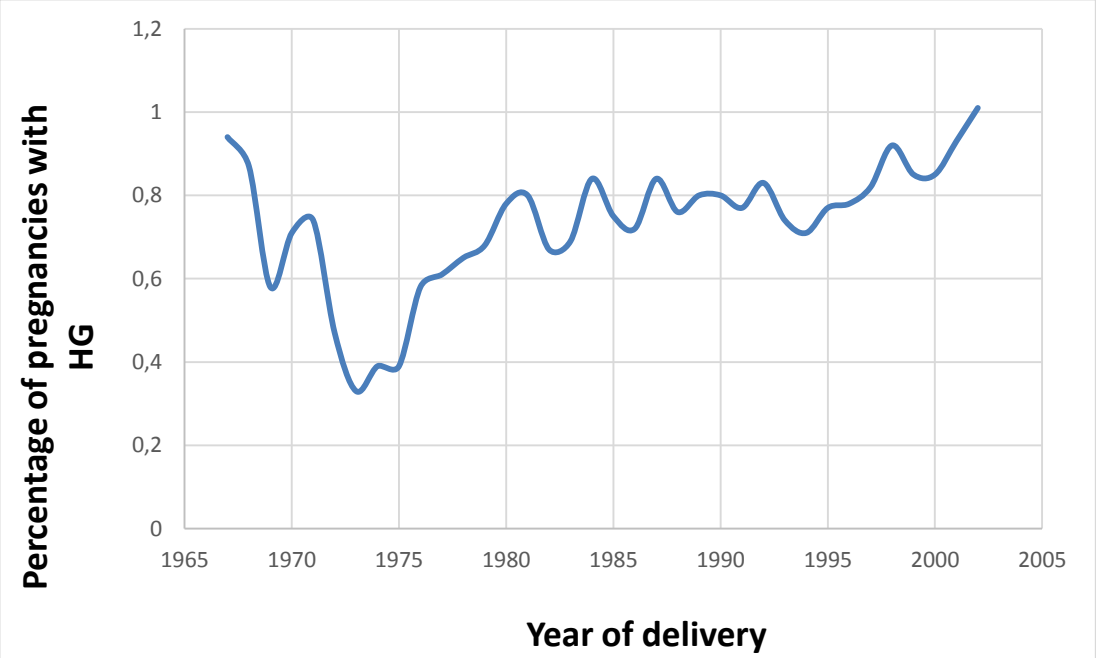

Figure 6. *Percentage of pregnancies with hyperemesis (HG) registered in the Medical Birth Registry of Norway according to year of delivery.*

Confounding

Confounding is an important source of bias in epidemiological research. A confounder is defined as a factor that is a risk factor for both the exposure and the outcome of interest, and the failure of controlling for confounding may lead to biased estimates and wrong conclusions (107). This means that the studied association is actually explained by other variables than the defined exposure.

The current knowledge about risk factors for hyperemesis is inconsistent. Hence, the process of selecting confounders in these studies was difficult. Decisions on available potential confounders were made on the basis of the best available information in the literature. Hyperemesis is associated with young age, parity, pre-gestational hypertension and diabetes mellitus (90, 113). These factors can also influence women's long-term cardiovascular risk (6, 18). Placental dysfunction has been proposed as one of several pathophysiological mechanisms behind hyperemesis. Placental dysfunction disorders, like preeclampsia and placental abruption, are associated with hyperemesis (11-13) and used as a proxy for placental dysfunction in this thesis. These are also conditions associated with increased long-term cardiovascular risk (89, 114). The literature is inconsistent regarding the association between socioeconomic status and hyperemesis (55, 90, 115), but low socioeconomic status is associated with increased morbidity and mortality (116-118). Hyperemesis is more common among non-Caucasians (38), and CVD risk factor burden is higher among ethnic/racial minority women (119). A genetic component is likely in both the risk of hyperemesis and risk of CVD, and in *Paper II* it was possible to adjust for family history of coronary heart disease.

In this work we have mostly adjusted for possible available confounders, using multivariable regression models. Another method used to control for confounding is stratification.

A limitation in retrospective cohort studies is that the researcher only has access to a predefined set of variables and may miss some interesting information. This may lead to unmeasured confounding. Hyperemesis is more common among non-smokers (55), and smoking is an important risk factor for all the studied outcomes. Information on smoking habits was unfortunately not available in the MBRN before 1999 and could not be adjusted for in the analyses. Different types of sensitivity analyses were performed to address this issue, but the exact impact of tobacco smoking on the studied associations is not known. In addition, both high and low pre-pregnant BMI is associated with increased risk of hyperemesis (55), but information on this potential confounder was not registered in the MBRN before 2006. Information on maternal weight loss

during pregnancy and severity of hyperemesis would have strengthened the studies. The possibility of residual confounding from these factors cannot be ruled out. In addition, there may be other, unknown factors influencing the presented estimates.

Immortal person-time

Immortal person-time refers to a period of follow-up during which, by design, the study outcome cannot occur (99). This is a type of bias that can be present in a cohort study when one of the entry criteria into the cohort is dependent on survival. In *Paper II*, the design is a cross-sectional study, but information on exposure (hyperemesis or hypertensive disorders in pregnancy) was collected years before the studied outcome (cardiovascular risk factors). The women had to survive from their registered pregnancy until the time of the health examination to be included in the study, which might introduce immortal time bias. In a theoretical example, women with hyperemesis could have been more likely to die at a younger age, and therefore not reach the age of the health examination. This is however unlikely, as few women in Norway die before the age of 40 and it is unlikely that this had an impact on the studied associations. In addition, *Paper I* revealed no difference in all-cause mortality or CVD mortality according to hyperemesis status.

Left censoring and left truncation

Information on hyperemesis was collected from the MBRN from 1967 and onwards, but follow-up in *Paper III* started in 1994. Women who died or emigrated before start of follow-up were excluded from the study, but information on non-fatal cardiovascular events before 1994 was not available. The lack of information on the occurrence of an event of interest before follow-up is known as left censoring and may introduce bias (120). If the distribution of events before follow-up started differs between women with and without hyperemesis, we may report wrong estimates on the studied associations. On the other hand, cardiovascular events in women are most likely to occur after the age of 50 (121, 122) and 90% of the women in the study were younger than 53 years at start of follow-up making them less likely to have suffered from a cardiovascular event before follow-up started. The fact that women who died

(also from CVD) before start of follow-up were excluded from the study may also introduce bias, known as left truncation. Cardiovascular death among women with and without a history of hyperemesis in this time-period was however assessed in *Paper I* and revealed no difference in CVD deaths between the groups. The bias due to left truncation is therefore likely to be small in the present study.

5.2.4 Age, period and cohort effect

A phenomenon in longitudinal studies in epidemiology is the age, period and cohort effect. This may arise because some factors can change in relation to time during follow-up. Such changes could be related to age, to a specific time period or variations in the risk of health outcome according to the year of birth (cohort effect) (123). Biological changes, changes in the environment and changes in exposure and outcome definitions over time may all lead to such phenomena. This was further explored in *Paper III* because the change from age-adjusted to multivariable-adjusted estimates was mainly due to adjustment for maternal year of birth. Therefore, the difference in estimates of association in different birth cohorts was assessed and the estimates found in different strata varied slightly. This could mean that the association between hyperemesis and later risk of CVD differed over time, either due to changes in registration or diagnostic criteria or other lifestyle changes in the population. However, all the HRs pointed to the same overall result with estimates close to one and negative findings. This small change in estimate may be the consequence of a cohort effect because of heterogeneity in follow-up time for events between young and old segments of the population. On the other hand, the changes across the strata were small, and the influence on the main results was probably of little relevance.

5.2.5 Summary of internal validity

Both random and systematic error can threaten the internal validity and thereby the quality of the study. In this project, the study populations were large, reducing the amount of random error. Systematic errors must always be kept in mind and dealt with throughout a study. The registration in the MBRN, the Cause of Death Registry and FS-system is nationwide and the quality of the

data is considered valid for large scale epidemiological studies. The overall research question in all three papers was the same. When a research question is assessed in different populations, with different designs and sources of bias, it is called triangulation (124). The use of triangulation can strengthen the validity of the study. Moreover, other techniques have been used to increase the internal validity in this thesis. In all three papers, multivariable regression models were conducted to reduce the effect of confounding. Sensitivity analyses have also been conducted to explore the potential effect of other sources of bias or weaknesses in the design of the studies.

5.3 Discussion of main results

The main focus of the discussion will be on the findings related to hyperemesis gravidarum (hyperemesis), but cardiovascular risk following hypertensive disorders in pregnancy will be discussed in relation to these findings.

5.3.1 Mortality and morbidity

Long-term maternal cardiovascular mortality and morbidity following hyperemesis have not been studied before. Cardiovascular mortality and morbidity after hypertensive disorders in pregnancy, including preeclampsia, have been studied extensively and both gestational hypertension and preeclampsia are associated with increased long-term risk of CVD (7, 125). Different mechanisms behind this association have been proposed, including common predisposing risk factors, placental vascular insufficiency, endothelial dysfunction and systemic inflammation (6, 126).

In *Paper I* an age-adjusted HR for all-cause mortality of 0.88 (0.80-0.97) was reported for women with a history of hyperemesis compared to women with pregnancies not complicated by hyperemesis. In this relatively young population of women, the largest proportion of deaths was caused by cancer. Hence, the lower rate of death from cancer among women with a history of hyperemesis may have contributed to lower all-cause mortality. We found little evidence of an association between a history of hyperemesis and increased cardiovascular mortality. The source population in *Paper I* and *III* was the same, and the findings were similar in terms of cardiovascular death. However, the

estimates on cardiovascular mortality were not exactly the same in the two papers. This can be explained by different follow-up times and different definitions of cardiovascular death. In *Paper I,* cardiovascular death was defined as death with CVD as the underlying cause of death registered in the Cause of Death Registry. In *Paper III*, cardiovascular death was defined as death with CVD as the underlying cause of death registered in the Cause of Death Registry or death within 28 days after hospitalisation with a cardiovascular event.

When investigating subgroups of CVD, we found a lower rate of death due to ischaemic heart disease in women with a history of hyperemesis compared to women with pregnancies not complicated with hyperemesis. In contrast, the HR for death from cerebrovascular disease was higher. Although not significant, this difference between the subgroups of CVD may reflect the possible effect of smoking as an unmeasured confounder. Smoking is a well-known risk factor for CVD overall, but may be a stronger risk factor for ischaemic heart disease than for intracranial haemorrhages (127-129). The largest proportion of death due to cerebrovascular disease in the population was caused by intracranial haemorrhages, and the confounding effect of smoking may therefore be smaller in these analyses. However, the number of deaths in each subgroup was small, and the results should be interpreted with caution. Subgroups of CVD were also assessed in the paper on cardiovascular morbidity. The point estimate (HR) for stroke was higher than for myocardial infarction, when women with a history of hyperemesis were compared to women with pregnancies not complicated with hyperemesis. However, the difference was small and the confidence intervals for both HRs include 1.0. Therefore, further investigations are warranted to assess these potential differences in risk of ischaemic heart disease and cerebrovascular disease following hyperemesis.

Furthermore, this thesis reports a higher rate of hospitalisation for angina pectoris among women with a history of hyperemesis, compared to women with previous pregnancies without hyperemesis. The registration of angina pectoris as a discharge diagnosis is however likely to be less accurate than for myocardial infarction (130). The diagnostic criteria for myocardial infarction have changed over time, where troponins were introduced in Norwegian

hospitals in 1999-2001 (131). Women who previously were diagnosed with angina pectoris, may after introduction of troponins have been diagnosed with a myocardial infarction. This would, however, probably not have influenced the difference between the groups. The uncertainty regarding angina pectoris as a discharge diagnosis, may have led to inclusion of events representing non-cardiac chest pain (130). On the other hand, the possibility that women, diagnosed with angina pectoris during the study period, will suffer from a myocardial infarction after years of follow-up cannot be ruled out. Due to these uncertainties regarding the registration of angina pectoris, analyses without angina as a part of the outcome were conducted in *Paper III*.

5.3.2 Placental involvement

There is evidence suggesting that the transportation of fetal cells into the maternal circulation during pregnancy is increased in some pregnancy complications (132). It is for instance well established that cell-free fetal DNA levels are increased in women with preeclampsia (133). Increased levels of cell-free fetal DNA has also been reported in women with hyperemesis and may be a sign of (hyper)activation of the maternal immune system (133). It is suggested that the DNA is derived mainly from the placenta because of the rapid clearance of fetal DNA from maternal blood following delivery, in contrast to other fetal cells that can survive several weeks post-partum (132). Other signs of involvement of the placenta in the aetiology of hyperemesis were highlighted in recent studies by Fejzo et al. (50, 52). This research group assessed a possible genetic component in hyperemesis and reported an association between hyperemesis and two genes (*GDF15* and *IGFBP7*) (52). These genes are both known to be involved in placentation, in addition to appetite regulation and cachexia. Placental dysfunction has also been suggested as an explanation for the reported association between hyperemesis and placental dysfunction disorders, like preeclampsia and placental abruption (13). The authors suggest that the findings of a stronger association between preterm preeclampsia and hyperemesis in the second trimester may be a sign of placental involvement in the aetiology of hyperemesis.

Placental involvement has also been proposed as one of the mechanisms underlying the increased long-term risk of CVD in women with a history of hypertensive disorders in pregnancy. One of the theories relates to the pathophysiology of hypertensive disorders in pregnancy, which is complex. The pathologic vascular lesion of the placenta found in preeclampsia, termed acute atherosis, is similar to that observed in atherosclerosis (125). Furthermore, poor placentation leads to release of inflammatory and antiangiogenic factors. This can cause endothelial dysfunction and impaired hemodynamics in the mother, which can persist up to several years postpartum (134).

Because of this possible relationship between hyperemesis, hypertensive disorders in pregnancy, placentation and later CVD risk, this thesis investigated midlife cardiovascular risk factors in both women with hyperemesis and women with hypertensive disorders in pregnancy.

5.3.3 Hypertension

In *Paper II* slightly lower mean systolic blood pressure was reported in women with a history of hyperemesis compared to the reference group (women with pregnancies without hyperemesis or hypertensive disorders). This difference was 1 mmHg and whether this represents a meaningful difference in systolic blood pressure remains open. Studies on blood pressure lowering for prevention of CVD and death show a continuous log-linear association between blood pressure and vascular events (135). There is clear evidence that lowering blood pressure in people with hypertension reduces the risk of major cardiovascular outcomes and all-cause deaths (136), but the effect of lowering blood pressure in normotensive people is still unclear and might be related to the presence of other cardiovascular risk factors (137). These are however clinical trials studying the effect of lowering blood pressure, and the results cannot necessarily be used to determine a meaningful difference in systolic blood pressure between groups in a general population. A publication from the World Health Organization suggests that every 1 mmHg reduction in the mean population systolic blood pressure could prevent deaths due to coronary heart disease (138).

In comparison, women with hypertensive disorders in pregnancy had almost 10 mmHg higher mean systolic blood pressure than the reference group at this age. This is in line with previous studies (139-142), but we confirm it in a larger population. A recent Norwegian study investigated life course trajectories of cardiovascular risk factors in women with hypertensive disorders in pregnancy (143). The authors concluded that women with hypertensive disorders in pregnancy have adverse cardiovascular risk factor profiles before their first pregnancy, which remain higher compared to other women beyond 50 years of age. Although the current study did not contain longitudinal data, findings from *Paper II* also indicated that the increased risk persisted many years after the hypertensive pregnancy.

In spite of the fact that previous studies have found associations between hyperemesis and pre-existing hypertension and pregnancy-related hypertension (11-13, 90), this study indicates that the mean systolic blood pressure at the age of 40-45 in women with a history of hyperemesis is more similar to women with none of the studied pregnancy complications than women with a history of hypertensive disorders in pregnancy. This finding suggests that the two pregnancy-related conditions are not part of the same disease spectrum. However, neither the possibility of involvement of the placenta in the aetiology of severe hyperemesis, nor the possibility that the two conditions share some pathophysiological mechanisms or characteristics can be ruled out.

5.3.4 Smoking, CVD and cancer

The largest difference between groups reported in *Paper II*, was the difference in smoking habits. An association of hyperemesis with a lower proportion of daily smokers was found. This has been known from previous research (43, 55). The lower rate of cancer deaths, particularly in tobacco-related cancers, as reported in this thesis (*Paper I*), is also in concordance with this finding. A large Scandinavian study from 2015 also reported an inverse association between hyperemesis and risk of some tobacco-related cancers (80). However, if the lower proportion of daily smokers among women with a history of hyperemesis contributed to the lower mortality due to cancer (*Paper I)*, a lower rate of fatal

and nonfatal cardiovascular events following hyperemesis should also have been expected. Instead, a similar rate of both cardiovascular death and the occurrence of a composite of nonfatal or fatal cardiovascular events among women with a history of hyperemesis, compared to women without such history, was found (*Paper I*, *Paper III*). Hence, other mechanisms, in addition to smoking, might be involved in the association between hyperemesis and the lower rate of cancer deaths. Hormonal changes during pregnancy, for instance increased levels of circulating hCG, have been proposed as one explanation for the association between pregnancy factors and subsequent cancer risk (80). The hormone hCG is a complex molecule which is involved in both human pregnancy (for instance placentation) and advanced malignancies (144). Studies have also found other hormones related to pregnancy, like estrogens and progesterone, to be associated with a woman's risk of developing breast cancer (78).

5.3.5 BMI and physical inactivity

Women with a history of hyperemesis had higher mean BMI and reported more physical inactivity at the age of 40-45, compared to women without such history. However, the reported difference in mean BMI was small. As described previously, partly due to a large study sample, a statistically significant result does not necessarily represent a clinically relevant difference. When investigating mean BMI in women with and without a history of hyperemesis, it differed by approximately 0.2 units. Previous studies are inconsistent regarding associations between hyperemesis and pre-pregnancy weight (72, 145, 146). However, a Norwegian study found an association between hyperemesis and both under- and overweight (55). If the latter is the case, this study may not have been able to reveal such an association because mean BMI was used in *Paper II*. The fact that women with a history of hyperemesis were more likely to report physical inactivity, may point in the direction of higher BMI, but again, because of small differences, the practical implications of these findings need to be further studied.

5.3.6 Socioeconomic status and CVD

Differences in health follow a strong social gradient (147). This reflects a person or a group of people's position in society, often related to income, education,

access to resources and control over life. Such conditions have an impact on the person's risk of illness and life expectancy (147). The impact of socioeconomic status on the risk of hyperemesis remains controversial in the literature. In the Norwegian recommendations, low socioeconomic status is mentioned as a risk factor for hyperemesis (113). Some reviews do not mention this factor (10, 43), but others again report no association between hyperemesis and socioeconomic status (148). In *Paper II* a higher level of completed education at the age of 40-45 among women with a history of hyperemesis was found compared to women without this history. In the two other papers, the observed difference between groups in terms of education was modest. Socioeconomic status is an important cardiovascular risk factor (149) and appears to mediate other traditional risk factors for CVD. Modifiable risk factors, like smoking, diet and physical activity follow the educational gradient (150). In all three papers, education has been used as a proxy for socioeconomic status. Information about education is easy to obtain in Norway and is a stable parameter, considered to be more related to lifestyle choices than for instance income and wealth (151). The conflicting results in the literature on the association between hyperemesis and low or high socioeconomic status may, for instance, be explained by different definitions of socioeconomic status. The social inequalities within a population may also differ between countries. In addition, most studies have measured socioeconomic status at start of follow-up (first pregnancy) when women with hyperemesis tend to be at a younger age. This thesis, measured the highest educational level obtained at the end of follow-up (*Papers I* and *III*) or at age of 40-45 (*Paper II*). At this time, women are more likely to have finished their education and this may be a better proxy for socioeconomic status than measurements earlier in life. However, the possibility of residual confounding from factors related to social inequalities cannot be ruled out, as risk of CVD is related to life course socioeconomic position (149, 152).

5.4 Generalisation and interpretation

To our knowledge, these are the first studies to investigate maternal long-term cardiovascular risk following hyperemesis gravidarum (hyperemesis). Almost all findings in this thesis point in the same direction. Women with a history of

hyperemesis did not appear to have increased levels of midlife cardiovascular risk factors or increased cardiovascular morbidity or mortality, compared to women without such a history.

The population-based design makes the results likely to be generalisable to other similar populations. However, because of the homogeneity in ethnicity in this study, the results should not be generalised to other, more ethnically diverse populations. Hyperemesis is more common among non-Caucasian women, who also have an increased burden of CVD (119), and the effect of the ethnic composition in the population on the studied associations is unknown. In addition, the age distribution in the population may have an impact on the generalisability. Different criteria and definitions on hyperemesis and hypertensive disorders in pregnancy will also influence the studied associations. A limitation in all three papers is the registration of hyperemesis in the MBRN. There is a chance that a difference in long-term cardiovascular risk was not detected, because the most severe forms of hyperemesis are missing in the included studies.

Large Norwegian studies investigating pregnancy outcomes following hyperemesis also report negative findings. A study from the Norwegian Mother and Child cohort study (MoBa), concluded that hyperemesis was not associated with adverse pregnancy outcomes (153). The same conclusion was drawn from a large Norwegian study with data from the MBRN (115). However, several other studies report that hyperemesis has a negative impact on fetal heath, both short- and long-term. A systematic review and meta-analysis concluded that hyperemesis is associated with a higher incidence of small-for-gestational-age babies and preterm delivery (57). This should be kept in mind when the findings from the present studies are interpreted. Could there be some characteristics of the Norwegian population which differ from other populations? This divergent finding can possibly be explained by the registration of hyperemesis in Norwegian datasets. Alternatively, differences in lifestyle factors in populations may influence the results, for instance diet or level of physical activity, or treatment and weight gain during pregnancy.

Lifestyle changes over time may also have an impact on the reported findings. For instance, cardiovascular risk factors in *Paper II* were assessed from 1985 to 1999, and lifestyle-changes in the population following this screening program may have resulted in different cardiovascular risk factor levels if the study was conducted today. As an example, smoking habits among women in Norway have changed over the last decades; the amount of tobacco consumed by women peaked in the 1990s and has decreased thereafter (154).

6.0 MAIN CONCLUSIONS

Regarding cardiovascular risk following hyperemesis gravidarum (hyperemesis), the conclusions of the present thesis are as follows:

- Overall, there was no consistent evidence for an association between a history of hyperemesis and increased long-term cardiovascular risk.

- Hyperemesis was not associated with increased maternal long-term all-cause mortality. More specifically, women with hyperemesis did not have increased cardiovascular mortality, but had a lower rate of death from cancer.
- There was no consistent evidence of increased levels of traditional cardiovascular risk factors at the age of 40-45 in women with a history of hyperemesis. In comparison, women with hypertensive disorders in pregnancy seemed to have unfavorable cardiovascular risk profiles in midlife compared to women with uncomplicated pregnancies. The proportion of daily smokers was lower in women with either of the two pregnancy complications.
- Hyperemesis was not associated with increased maternal long-term risk of a fatal or nonfatal cardiovascular event.

7.0 PRACTICAL IMPLICATIONS AND FUTURE PERSPECTIVES

This thesis indicates that women with a history of hyperemesis have a similar long-term risk of CVD as women without such history and may therefore need the same cardiovascular follow-up as women in general. In comparison, this work also suggests that women with a history of hypertensive disorders in pregnancy need special attention on several modifiable cardiovascular risk factors, with increased levels at the age of 40-45 compared to women without such a history. Unmeasured confounding in the studied associations cannot be ruled out completely, especially the lack of ability to adjust for smoking in the analyses may have resulted in an underestimation of associations. Sensitivity analyses have however indicated that this will probably not have a great impact on the studied associations. Furthermore, the large population and long follow-up time decrease the likelihood that hyperemesis is associated with increased risk of premature CVD in this population. In this thesis, cardiovascular risk factors, risk of cardiovascular events and cardiovascular mortality, have been assessed. Information on outcomes was collected from different data sources and in general, all estimates pointed in the same direction of negative findings. This is reassuring for patients with hyperemesis and can help clinicians and researchers with better understanding of the long-term consequences of this complex disease.

This study focused on the maternal long-term cardiovascular risk following hyperemesis. The results need to be confirmed in other populations. Future studies should also distinguish between mild and severe forms of hyperemesis when cardiovascular outcomes are studied. Longer follow-up time with older women is needed to better understand these possible associations. It would be of particular interest to further investigate the reported findings of increased risk of angina pectoris following hyperemesis.

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9.0 ENCLOSED PAPERS 1-3

PAPER I

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Hyperemesis gravidarum and long-term mortality: a population-based cohort study

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Objective To investigate whether exposure to hyperemesis gravidarum (HG) is associated with increased maternal long-term mortality.

Design Population-based cohort study.

Setting Medical Birth Registry of Norway (1967–2002) linked to the Cause of Death Registry.

Population Women in Norway with singleton births in the period 1967–2002, with and without HG. Women were followed until 2009 or death.

Methods Cox proportional hazard regression model was applied to estimate hazard ratios (HRs) with 95% confidence interval (CI).

Main outcome measures The primary outcome was all-cause mortality during follow up. Secondary outcomes were cause-specific mortality (cardiovascular mortality, deaths due to cancer, external causes or mental and behavioural disorders).

Results Of 999 161 women with singleton births, 13 397 (1.3%) experienced HG. During a median follow up of 26 years (25 902 036 person-years), 43 470 women died (4.4%). Women exposed to HG had a lower risk of long-term all-cause mortality compared with women without HG (crude HR 0.82; 95% CI 0.75–0.90). When adjusting for confounders, this reduction was no longer significant (adjusted HR 0.92; 95% CI 0.84–1.01). Women exposed to HG had a similar risk of cardiovascular death as women not exposed (adjusted HR 1.04; 95% CI 0.83–1.29), but a lower long-term risk of death from cancer (adjusted HR 0.86; 95% CI 0.75–0.98).

Conclusion In this large population-based cohort study, HG was not associated with an increased risk of long-term all-cause mortality. Women exposed to HG had no increase in mortality due to cardiovascular disease, but had a reduced risk of death from cancer.

Keywords Cancer, cardiovascular disease, cohort study, hyperemesis gravidarum, long-term mortality.

Tweetable abstract Population-based cohort study: Hyperemesis was not associated with an increased risk of long-term mortality.

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Introduction

Several conditions complicating pregnancies are reported to influence subsequent disease patterns in women. Pregnancy is considered a physiological stress-test especially for the cardiovascular system; an increase in blood volume, heart rate, and cardiac output are necessary changes in normal pregnancies.[1,2] Most women adapt well to the pregnant state, but in some women inadequate adaptation may occur and be a sign of impaired cardiac reserve.[2] Gestational hypertension, pre-eclampsia and placental abruption are all reported to increase the risk of cardiovascular disease (CVD) later in life.[3–7] Moreover, it is well known that gestational diabetes increases the risk of developing type 2 diabetes.[6,8–10] According to the American Heart Association *Guidelines for the prevention of Cardiovascular Disease in Women*, taking a history of pregnancy complications is part of the CVD risk evaluation.[11]

Hyperemesis gravidarum (HG), characterised by extreme nausea and vomiting in early pregnancy,[12] is associated with gestational hypertension, pre-eclampsia as well as placental abruption.[13] The prevalence of HG varies between 0.3 and 3.2%, depending on the maternal country of birth.[14,15] The aetiology is poorly understood, and previous

studies suggest different causal mechanisms, involving placental dysfunction, gastrointestinal pathology, immunologic factors and endocrine and metabolic factors.[16–21] Although HG is the most common reason for hospitalisation during the first trimester,[22] little is known about the long-term consequences of HG exposure. Some studies have reported an association between HG and risk of autoimmune disease later in life.[23,24] A recent study investigating cancer risk after HG exposure reported an inverse association between HG and overall cancer risk.[25] The association between HG and mental health, both as a risk factor and as a consequence of HG, has been disputed.[15,26] The aforementioned possible underlying mechanisms for HG may affect a woman's long-term health and all-cause mortality, but this is still largely unknown.

The main objective of this study was to assess whether women exposed to HG during pregnancy have an increased risk of long-term all-cause mortality compared with women not exposed, using large population-based data with a follow-up time of several decades. Secondly, we explored whether the risk of cardiovascular death and death due to cancer, external causes and psychiatric disorders were higher in women exposed to HG.

Materials and methods

Population

All births in Norway are registered in the Medical Birth Registry of Norway (MBRN). This is mandatory and has to be performed within 1 week after discharge from hospital (the maternal unit). The notification form is filled in by the midwife and the doctor, and contains complete identification of the mother and father, information on mother's health before and during pregnancy, complications during pregnancy and delivery as well as information on the infant.[27] From 1967 to 2002 all pregnancies ending after week 16 were notifiable in the MBRN.[28] By use of a national identification number, each mother was linked to her births for the period 1967–2002. In this study, only women with singleton births after 23 weeks of gestation were included (Figure S1).

Follow up

Data from the MBRN were linked to the Cause of Death Registry through December 2009. The Norwegian Cause of Death Registry has a 98% coverage and completeness of the Norwegian population. For all deaths, a death certificate (paper form IS-1025B) with a logical sequence from the underlying to the immediate cause of death must be completed by a doctor. A code from the International Classification of Disease (ICD) system is allocated to the diagnoses in the death certificate. Subsequently the underlying cause of death is identified by the IRIS computer programme with the Automated Classification of Medical Entities (ACME) module, or by assessment of a professional coder. Around 500–700 (1.2–1.7%) death certificates are missing every year in Norway.[29]

Exposure and outcomes

In the MBRN, women with HG were registered with the ICD-8 codes 638.0 (hyperemesis gravidarum with neuritis) or 638.9 (hyperemesis gravidarum without mention of neuritis) until 1998; from 1999 onwards, HG was registered by the ICD-10 codes O21.0 (mild hyperemesis gravidarum), O21.1 (hyperemesis gravidarum with metabolic disturbances) or O21.9 (vomiting in pregnancy, unspecified).[30] To investigate whether there was a dose–response relationship between exposure and outcome, the consequences of repeated exposure to HG were explored.

The Cause of Death Registry used the ICD-7 from 1960 to 1968, ICD-8 from 1969 to 1985, ICD-9 from 1986 to 1995 and ICD-10 codes from 1996 to 2009. Based on previous research on risk factors and potential consequences of HG, the following outcomes were explored in addition to all-cause mortality (corresponding ICD-10 codes given in brackets for all outcomes): Diseases of the circulatory system (I00-I99), mental and behavioural disorders (F00-F99), external causes (V01-Y89) and cancer (C00-D48).

For subanalyses, CVD was divided into three groups: 'ischaemic heart disease' (I20-25), 'cerebrovascular disease' (I60-69) and 'other CVD' (the remaining circulatory system codes).

Cancer is a very heterogeneous group of diseases, where tobacco smoking and alcohol use are two of the main risk factors.[31] Explorative subanalyses investigating the mortality from tobacco- and alcohol-related cancers were conducted. Tobacco-related cancers comprised lung cancer (C33-34), cancers of the lip, oral cavity and pharynx (C00-14), larynx (C32), oesophagus (C15), stomach (C16), liver (C22), pancreas (C25), kidney (C64), bladder (C67), cervix (C53), colon/rectum (C18-21), ovary (C56) and acute myeloid leukaemia (C92).[32] Alcohol-related cancers included cancer in the oral cavity and pharynx (C01-14), larynx (C32), oesophagus (C15), liver (C22), breast (C50) and colon/rectum (C18-21).[32]

Covariates

Based on prior knowledge[13–15,33] the following covariates were considered as potential confounders: maternal age at first registered pregnancy (continuous), the woman's year of birth (in categories), maternal country of birth, education, parity, hypertensive diseases in pregnancy, placental abruption, pregestational diabetes type 1 and hypertensive disorders before pregnancy.

Hyperemesis gravidarum is associated with expecting a female infant,[34] but whether a female fetus also increases

the severity of HG is not clear.[35–38]Also, the influence of socio-economic status on HG risk is inconsistent in the literature,[33,39,40] but low socio-economic status is associated with increased morbidity and mortality.[41–43]

Age at first birth was the age at the women's first birth registered in the MBRN. As some women may have delivered children before 1967, a parity-variable reflecting the mother's self-reported parity was used. Information on maternal life-time years of education was obtained from Statistics Norway and categorised as: ≤10 years of school, 11–13 years, 14–16 years, ≥17 years of school, missing. Information on maternal country of birth was provided from Statistics Norway and divided into eight categories. For education and maternal country of birth, <2% had missing data, whereas data on maternal age and parity were complete.

Information on gestational hypertension, placental abruption, pre-existing hypertension and diabetes type 1 were obtained from the MBRN. Based on information from each woman's registered pregnancies, dichotomous variables were created (ever/never).

Smoking was not recorded in the MBRN until 1999, and adjustment for this potential confounder was not possible. We compared the smoking habits of hyperemetic and non-hyperemetic women in a subgroup after 1999 to obtain an impression of possible differences between the two groups.

Statistical methods

The analyses were conducted in STATA version 14. The characteristics of women with and without HG were presented as percentages or median (± interquartile range). A Cox proportional hazard regression model was applied to estimate time-to-event outcomes (mortality). Women were followed from their first registered birth until death or censored at the cutoff year of 2009, whichever occurred first. The time-variable in the Cox models was 'time from first birth to death/censored'. Two models were made in addition to the crude analyses: (i) age-adjusted; (ii) adjusted for all available confounders. The fully adjusted model included all conditions associated with both exposure and outcome as confounders, based on prior knowledge.[13–15,33] In our population, not all the listed confounders influenced the estimates, but they were included in the fully adjusted model because of the biological aspects. Age at first registered pregnancy was the strongest confounder. In the fully adjusted model, women with missing information on covariates (1.5% of the total population) were excluded from the analyses. A *P*-value below 0.05 was considered statistically significant.

To investigate the impact of fetal gender and maternal education on risk of all-cause mortality, stratified analyses were conducted.

All data-files were anonymised after linkage. Ethical approval for the study was obtained from the Regional Committee for Medical and Health Research Ethics (2015/1347/REK South-East).

Results

Cohort

In total, 1 028 801 women with a pregnancy between 1967 and 2002 were registered in the MBRN. After excluding women with incorrect registrations, multiple gestation pregnancies and pregnancies with a gestation of <23 weeks, the study population consisted of 999 161 women and more than 2 million pregnancies (Figure S1). Among all women included in this study, 13 397 (1.3%) suffered from HG during at least one pregnancy. Of these, 1173 women experienced HG in more than one pregnancy. The median follow-up time was 26 years (range 0.5–42 years) and total person-years at risk were almost 26 million years (25 902 036). Loss to follow up due to emigration was <3% (26 260 women). Women with HG were more likely to be younger than 30 years at their first registered birth and were more often born in African and Asian countries (Table 1). They were also less likely to be primipara at the end of follow up. In terms of education, modest differences were observed according to HG status. In the subgroup registered after 1999, women with HG were less likely to smoke compared with women without HG (Table S1).

All-cause mortality

Among women exposed to HG, 451 (3.4%) of the women died during follow up, compared with 43 019 (4.4%) of the women not exposed (Table 2). The Kaplan–Meier curve shows the crude overall survival rates during follow up (Figure 1). Cox regression analysis showed that women exposed to HG had a lower risk of long-term all-cause mortality compared with unexposed women [crude hazard ratio (HR) 0.82; 95% confidence interval (CI) 0.75–0.90]. After adjusting for confounders, however, the reduction did not reach the level of statistical significance (adjusted HR 0.92; 95% CI 0.84-1.01) (Table 2).

Among women with repeated exposures to HG (n =1173), 27 (2.3%) died during follow up. Women with HG in two or more pregnancies had a similar risk of long-term all-cause mortality as unexposed women (adjusted HR 0.99; 95% CI 0.68–1.44).

Cause-specific mortality

A total of 7197 (0.7%) women died due to CVD. There was no difference in long-term CVD-mortality between women exposed to HG and women not exposed (Figure 2, Table 2).

Table 1. Characteristics of the study cohort (n = 999 161)

Maternal and pregnancy characteristics	Women with hyperemesis gravidarum (n = 13 397)	Women without hyperemesis gravidarum (n = 985 764)
At baseline		
Median age at first registered pregnancy*	24 (21–27)	25 (21–28)
Age at first registered pregnancy, n (%)		
≤19	1595 (11.9)	118 004 (12.0)
20–24	5718 (42.7)	370 603 (37.6)
25–29	4193 (31.3)	307 118 (31.1)
30–34	1376 (10.3)	129 916 (13.2)
≥35	515 (3.8)	60 123 (6.1)
Pre-gestational diabetes type 1, n (%)	14 (0.1)	1159 (0.1)
Pregestational hypertension, n (%)	65 (0.5)	4419 (0.5)
Education (years), n (%)		
≤10	3392 (25.3)	250 323 (25.4)
11–13	5515 (41.2)	419 582 (42.6)
14–16	3782 (28.2)	260 905 (26.5)
≥17	480 (3.6)	40 280 (4.1)
Missing	228 (1.7)	14 674 (1.4)
Maternal country of birth, n (%)		
Norway	11 658 (87.0)	886 436 (89.9)
Europe	737 (5.5)	58 025 (5.9)
Africa	229 (1.7)	6039 (0.6)
Asia	584 (4.4)	22 574 (2.3)
North America	140 (1.1)	9272 (0.9)
South America	41 (0.3)	2798 (0.3)
Oceania	7 (0.05)	563 (0.06)
Missing	1 (0.01)	57 (0.01)
At end of follow up		
Median age at the end of study*	50 (42–59)	51 (42–61)
Parity by end of follow up,n (%)		
Primipara	1777 (13.3)	203 697 (20.7)
Multipara	11 620 (86.7)	782 067 (79.3)
Pre-eclampsia, pregnancy-related hypertension and eclampsia, n (%)	991 (7.4)	73 927 (7.5)
Placental abruption, *n* (%)	172 (1.3)	11 007 (1.1)

*Median with 25 and 75 quartiles.

During follow up, 23 393 (2.3%) women died from cancer (Table 2). Exposure to HG was associated with a reduced risk of long-term cancer mortality (crude HR 0.78; 95% CI 0.68–0.88), in particular in relation to tobacco-related cancers (Table 2). The estimates remained statistically significant after adjustment for possible confounders (Figure 2, Table 2). There was no difference between groups in death from alcohol-related cancers.

No association was found between exposure to HG and risk of dying from external causes (including accidents and suicide) or mental and behavioural disorders (Table 2).

To further explore the associations between HG and the risk of cardiovascular death, subanalyses differentiating between ischaemic heart disease, cerebrovascular disease and other CVD as causes of death were conducted. The long-term mortality rates from ischaemic heart disease and other CVD were similar in women exposed to HG and those not exposed, but the hazard rate for cerebrovascular disease was higher in the HG-group, although not reaching the level of statistical significance (Table 2).

The risk of death was similar across educational level and fetal gender (Tables S2 and S3).

Discussion

Main findings

To the best of our knowledge this is the first study to investigate maternal long-term mortality after HG exposure. In this large population-based cohort study, exposure to HG was not associated with an increased risk of long-term all-cause mortality, and there was no increase in mortality due to CVD. There was, however, a reduction in mortality from cancer in women exposed to HG.

Strengths and limitations

The MBRN is the oldest birth registry worldwide[27] and provides a unique opportunity to study the long-term impact of HG on mortality. Both the MBRN and the Cause of Death Registry are high-quality health registries with mandatory reporting. Use of a population-based data set rules out the possibility of selection bias. The long follow-up time is a major strength of this study (maximum 42 years), as well as the low percentage of loss to follow up (<3%).

A possible limitation in registry-based research is incorrect or poor registration of HG, partly due to lack of clear diagnostic criteria for HG. In the MBRN there is no information about severity, starting point or duration of HG. Despite these limitations, an assessment study has concluded that MBRN is valid as a database for studies on HG,[30] although the relatively large proportion of false-positive cases found in that study might influence the exposure–outcome associations in terms of reducing the strength of possible associations. HG registration in MBRN is considered valid for use in large-scale epidemiological studies.[30]

The lack of information on smoking habits in MBRN is another limitation in this study. As smoking is associated with a lower risk of HG and increases the risk of CVD,[39,44] it might have influenced the estimates. The proportion of smokers among women in Norway increased in the period after 1965 and peaked in 1975 with 35% smokers.[45] On the

Table 2. Outcomes at the end of follow up in women exposed to hyperemesis gravidarum (n = 13 397) compared with women not exposed (n = 985 764)

Cause of death	Number (%) of deaths according to HG status		Hazard ratio (95% confidence interval) No HG as referent group		
	HG (n = 13 397)	No HG (n = 985 764)	Crude	Age-adjusted	Fully adjusted*
All-cause	451 (3.4)	43 019 (4.4)	0.82 (0.75–0.90)	0.88 (0.80–0.97)	0.92 (0.84–1.01)
Cardiovascular disease (CVD)	79 (0.6)	7118 (0.7)	0.87 (0.70–1.09)	1.00 (0.80–1.25)	1.04 (0.83–1.29)
Ischaemic heart disease	31 (0.2)	3078 (0.3)	0.80 (0.56–1.13)	0.92 (0.65–1.31)	0.96 (0.67–1.37)
Cerebrovascular disease	33 (0.3)	2163 (0.2)	1.19 (0.85–1.68)	1.34 (0.95–1.89)	1.39 (0.98–1.96)
Other CVD	15 (0.1)	1877 (0.2)	0.63 (0.38–1.05)	0.72 (0.43–1.20)	0.74 (0.45–1.23)
Cancer	230 (1.7)	23 163 (2.4)	0.78 (0.68–0.88)	0.83 (0.73–0.95)	0.86 (0.75–0.98)
Tobacco-related cancers	111 (0.8)	12 597 (1.3)	0.69 (0.57–0.84)	0.74 (0.62–0.90)	0.77 (0.64–0.93)
Alcohol-related cancers	97 (0.7)	8061 (0.8)	0.94 (0.77–1.15)	1.01 (0.83–1.24)	1.04 (0.85–1.27)
External causes	46 (0.3)	4122 (0.4)	0.84 (0.63–1.13)	0.84 (0.63–1.12)	0.90 (0.67–1.21)
Mental and behavioural disorders	10 (0.1)	782 (0.1)	0.99 (0.53–1.84)	1.01 (0.54–1.89)	1.10 (0.59–2.05)

HG, hyperemesis gravidarum.
*Adjusted for women's age at first birth, women's year of birth (categorical), maternal country of birth, education, parity, hypertensive disorder in pregnancy, pregestational hypertension, pregestational diabetes type 1, placental abruption.

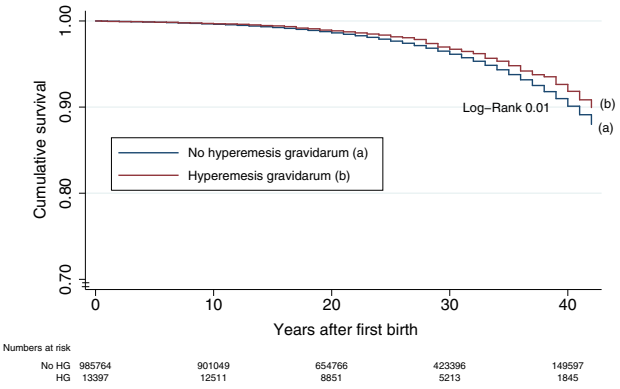

Figure 1. Kaplan–Meier survival curve (all-cause mortality). The time variable is years after first registered birth.

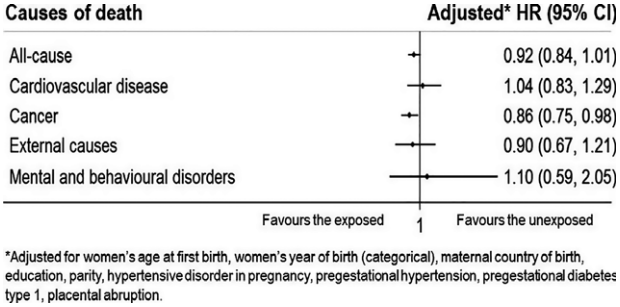

Figure 2. Forest plot of adjusted hazard ratios (HRs) with 95% confidence intervals (CI) in women exposed to hyperemesis gravidarum compared with unexposed women.

other hand, the amount of tobacco consumed by women did not peak until 1990. The impact of tobacco smoking on mortality in this study is unknown. Body mass index (BMI) was not recorded in the MBRN until 2006 and could not be explored in this study. This may be a limitation, as both underweight and obesity have been associated with increased risk of HG.[39]

Comparison with other studies

Bolin et al.[13] reported a doubled risk of pre-eclampsia and a three-fold increased risk of placental abruption after HG exposure, suggesting a possible effect on the placentation. A recent publication showed a skewed placental weight-to-birth weight ratio, possibly reflecting suboptimal placentation, but this was found only in women with HG who were carrying female fetuses.[35] Moreover, HG is reported to be associated with subsequent increased risk of autoimmune diseases.[23,24] A Danish study found a statistically significant association between HG and autoimmune diseases in general and in particular between HG and Sjögren's syndrome, Graves' disease, rheumatoid arthritis, pernicious anaemia, coeliac disease, Crohn's disease, ulcerative colitis and psoriasis.[23] Previous research has also found increased inflammatory markers in women with HG compared with healthy pregnancies.[46–49] Given that several of these conditions associated with HG also are associated with increased risk of CVD, we explored whether HG and CVD-related mortality might be related. Underlying mechanisms could be common genes or common environmental factors, and an inflammation during a restricted time-period could trigger

processes that have an impact on the risk of CVD. In our study, however, we did not find higher CVD mortality in women with HG than in women without HG. In contrast, there was a reduced risk of overall cancer mortality in women exposed to HG. Subanalyses showed lower HR for tobacco-related cancers in the HG-group. This is in line with previous research, but it is not known whether this could be explained by tobacco smoking alone or whether other mechanisms might be involved.[25]

Interpretation

Cardiovascular disease is the leading cause of death among women at large, but for younger women the picture is more heterogeneous. Among women in Norway who died between the age of 50 and 60 years in 2009, 55% of deaths were due to cancer, approximately 11% were caused by CVD, and about 8% were due to external causes.[50] In our sample the larger proportion of deaths caused by cancer reflects the younger population. On the other hand, 25% of the women were older than 61 years at the end of follow up. With almost one million women and a long follow-up time, the lack of any increased risk of death from CVD in our study makes it unlikely that there is any increased risk of premature cardiovascular mortality in women exposed to HG. However, a possible difference in smoking habits in the two groups might have counteracted the effect of HG on cardiovascular mortality, which means the results in our study might be an underestimation.

Subgroup analyses of CVD showed a lower HR for ischaemic heart disease in the hyperemetic women. In contrast, the HR for cerebrovascular disease was higher. Although not significant, this difference between the subgroups may reflect the aforementioned possible effect of smoking as a confounder. Smoking is a well-known risk factor for atherosclerotic disease, in particular coronary heart disease.[44,51,52] In our study population, most of the deaths due to cerebrovascular disease were caused by intracranial haemorrhages, and the effect of smoking as a risk factor for this condition is weaker than for coronary heart disease.[44,53–55] The confounding effect of smoking in these analyses might therefore be smaller.

Regarding the aetiology of HG it has been suggested that hormonal changes could be responsible, in particular increased oestrogen and human chorionic gonadotrophin, both hormones mainly produced by the placenta.[21,56,57] Bearing a female child is associated with increased levels of human chorionic gonadotrophin as well as oestrogen, and has been suggested as an explanation for the almost two-fold increase in risk of HG in women bearing a female child.[34] Whether a female fetus increases the severity of HG, is yet not clear.[35–38] No increased mortality was found in subanalyses stratified on fetal gender in our study. However, this should be interpreted with caution, as we have been able to stratify on fetal gender of the first-born child only, and fetal gender in later pregnancies could have influenced the results.

Another interesting factor is the women's socio-economic status, as previous research is inconsistent regarding the influence of such status on HG risk.[33,39,40] Given the fact that low socio-economic status is associated with increased all-cause mortality,[41–43] it may be considered a confounder in our study. With respect to education, adjustment for education or stratification on education did not influence our results.

Conclusions

In this large population-based cohort study, women exposed to HG in pregnancy neither had an increased risk of long-term all-cause mortality compared with women not exposed, nor an increased risk of death from CVD. HG was, however, associated with a lower risk of death from cancer. In this large study, there was no available information on smoking habits and this will be an interesting topic for future studies regarding risk factors for HG and consequences of the disease. More research is needed to explore potential mechanisms for the lower cancer mortality in women exposed to HG.

Contribution to authorship

SF, ÅVV, ØN and SH designed the study. SF and LV performed the statistical analyses. SF drafted the manuscript and all the other authors critically revised it. All authors approved the final version of the article. SF, ÅVV, ØN and SH 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 full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Disclosure of interests

None declared. Completed disclosure of interests form available to view online as supporting information.

Details of ethics approval

Ethical approval for the study was obtained from the Regional Committee for Medical and Health Research Ethics 11 September 2015 (2015/1347/REK South-East).

Data sharing

No additional data are available.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Study flow diagram.

Table S1. Smoking habits in a subgroup of women with first registered pregnancy after 1999 (n = 96 129).

Table S2. All-cause mortality stratified by educational level.

Table S3. All-cause mortality stratified by fetal gender (gender of first born child if more than one child). ■

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SUPPLEMENTARY TABLES AND FIGURES PAPER I

Table S1. Smoking habits in a subgroup of women with first registered pregnancy after 1999 (n= 96 129).

	Hyperemesis gravidarum (n= 863) Number (%)	**No hyperemesis gravidarum (n=95 266)** Number (%)
Non-smokers	587 (68.0)	53 709 (56.4)
Smokers	119 (13.8)	18 115 (19.0)
Missing	157 (18.2)	23 442 (24.6)

Table S2. All-cause mortality stratified by educational level. Lowest educational level was defined as ≤ 10 years. Highest educational level was defined as ≥ 14 years.

	Hazard ratio (95% confidence interval)		
Educational level	**No HG* as referent group**		
	Crude	**Age-adjusted**	**Fully adjusted****
Low level	0.80 (0.69-0.92)	0.87(0.75-1.01)	0.89 (0.77-1.03)
High level	0.82 (0.75-0.90)	0.88 (0.81-0.97)	0.90 (0.82-0.99)

*HG: hyperemesis gravidarum
** Adjusted for women's age at first birth, women's year of birth (categorical), maternal country of birth, education, parity, hypertensive disorder in pregnancy, pregestational hypertension, pregestational diabetes type 1, placental abruption.

Table S3. All-cause mortality stratified by fetal gender (gender of first born child if more than one child).

Fetal gender	Hazard ratio (95% confidence interval) No HG* as referent group		
	Crude	**Age-adjusted**	**Fully adjusted****
Boy	0.79 (0.69-0.91)	0.86 (0.75-0.98)	0.89 (0.78-1.02)
Girl	0.84 (0.74-0.95)	0.90 (0.80-1.02)	0.93 (0.83-1.07)

*HG: hyperemesis gravidarum

** Adjusted for women's age at first birth, women's year of birth (categorical), maternal country of birth, education, parity, hypertensive disorder in pregnancy, pregestational hypertension, pregestational diabetes type 1, placental abruption.

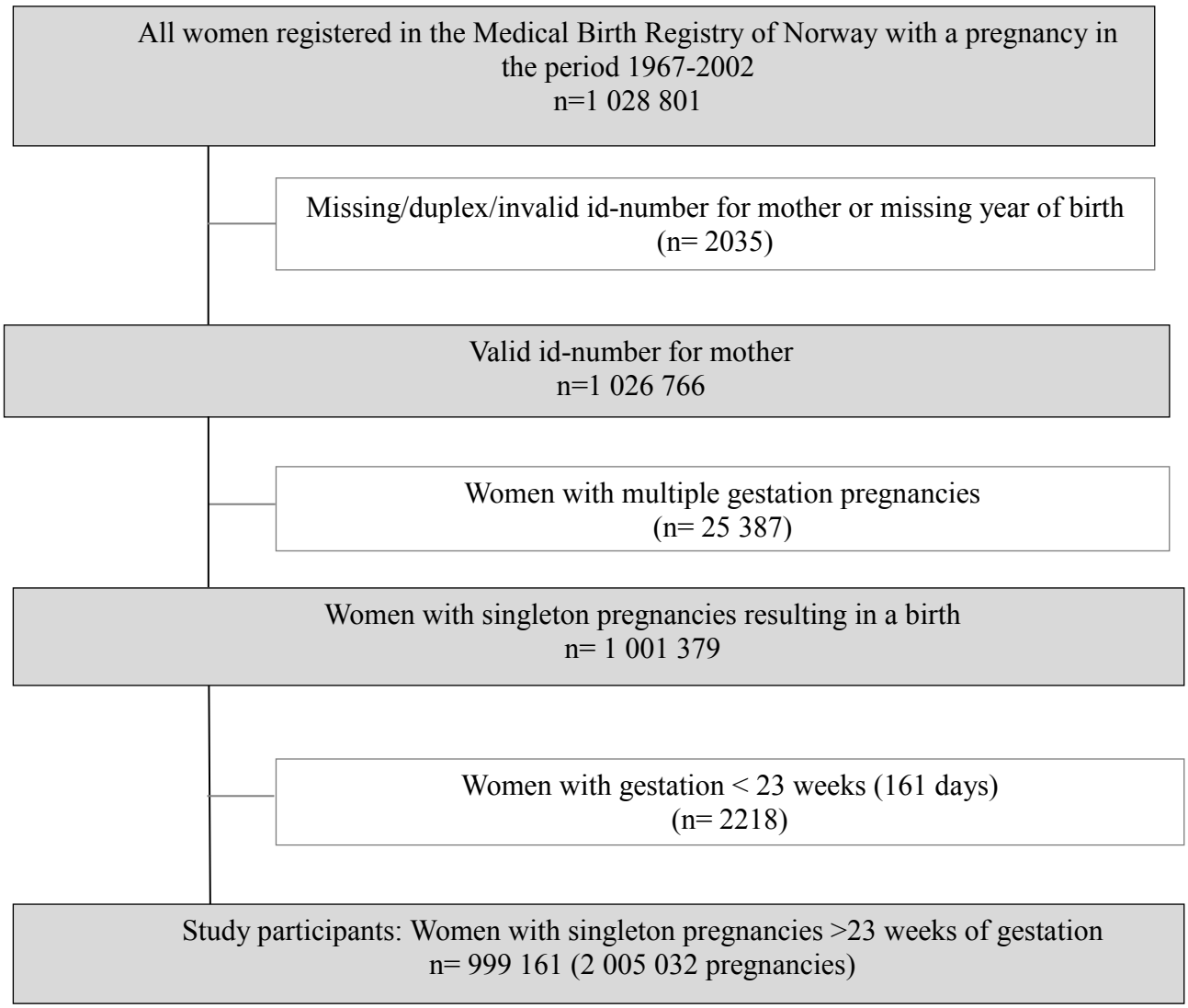

Figure S1 Study flow diagram.

PAPER II

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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

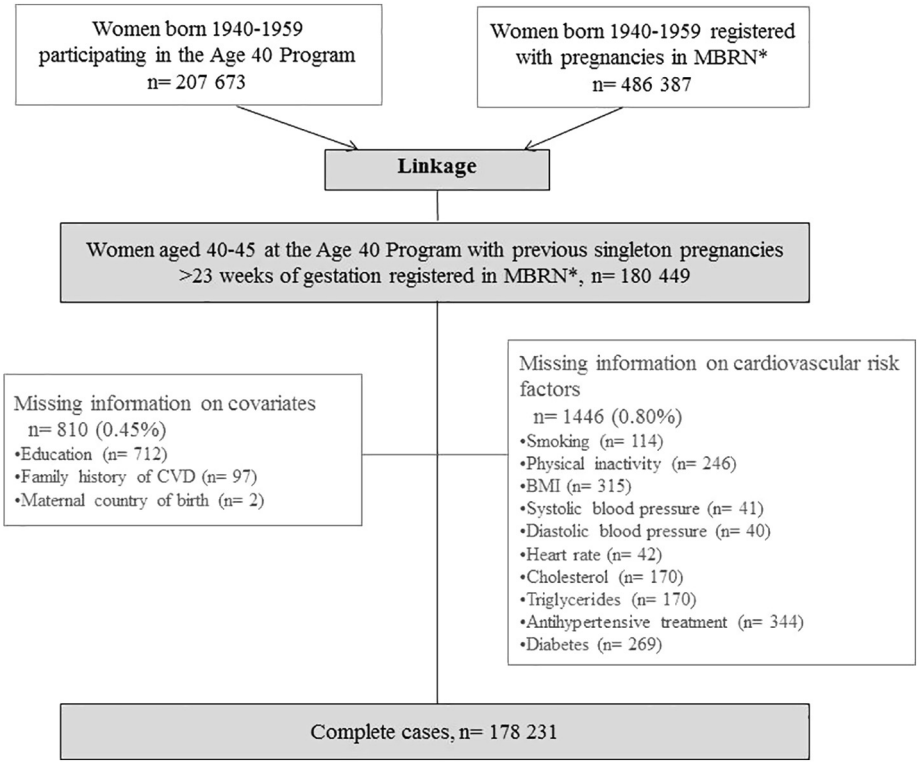

Fig. 1. Participant flow diagram. MBRN: Medical Birth Registry of Norway.

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.

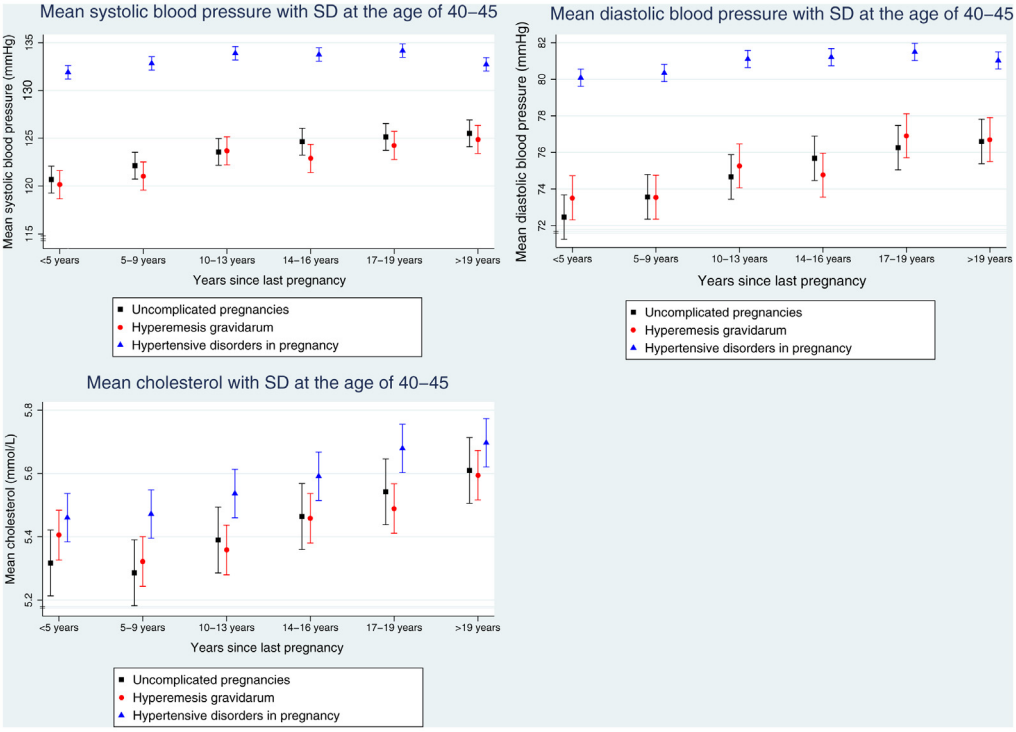

Fig. 2. Cardiovascular risk factors at the age of 40–45: Plot of mean systolic blood pressure, diastolic blood pressure and cholesterol with standard deviations at the age of 40–45 by groups reflecting years since last pregnancy.

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.

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PAPER III (MANUSCRIPT)

Long-term cardiovascular morbidity following hyperemesis gravidarum: a Norwegian nationwide cohort study

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Abstract

Objective: To investigate whether exposure to hyperemesis gravidarum (hyperemesis) is associated with subsequent maternal cardiovascular morbidity.

Design: Nationwide cohort study.

Setting: Medical Birth Registry of Norway (1967-2002) linked to the nationwide Cardiovascular Disease in Norway project 1994-2009 (CVDNOR) and the Cause of Death Registry.

Population: Women in Norway with singleton births from 1967 to 2002, with and without hyperemesis, were followed up with respect to cardiovascular outcomes from 1994 to 2009.

Methods: Cox proportional hazards regression model was applied to estimate hazard ratios (HRs) with 95% confidence interval (CI).

Main outcome measures: The first hospitalisation due to nonfatal stroke, myocardial infarction or angina pectoris, or cardiovascular death.

Results: Among 989 473 women with singleton births, 13 212 (1.3%) suffered from hyperemesis. During follow-up, a total of 43 482 (4.4%) women experienced a cardiovascular event. No association was found between hyperemesis and the risk of a fatal or nonfatal cardiovascular event (adjusted HR 1.08; 95% CI 0.99-1.18). Women with hyperemesis had higher risk of hospitalisation due to angina pectoris (adjusted HR 1.28; 95% CI 1.15-1.44). The risk of cardiovascular death was lower among

hyperemetic women in age-adjusted analysis (HR 0.73; 95% CI 0.59-0.91), but the association was no longer significant when adjusting for possible confounders.

Conclusion: Women with a history of hyperemesis did not have increased risk of a cardiovascular event (nonfatal myocardial infarction or stroke, angina pectoris or cardiovascular death) compared to women without.

Introduction

Both the European and American guidelines for prevention of cardiovascular disease (CVD) in women now include pregnancy-related complications, such as preeclampsia and pregnancy-induced hypertension, as risk factors [1,2]. CVD is the leading cause of death in women [2,3] and early detection of individuals at risk may prevent major cardiovascular events. Pregnancy-related risk factors for CVD provide such an opportunity.

Hyperemesis gravidarum (hyperemesis), characterized by extreme nausea and vomiting in early pregnancy, is the most common reason for hospitalisation in the first trimester of pregnancy and is associated with several risk factors for CVD [4,5]. These include low socioeconomic status, hypertension, hypercholesterolemia, overweight, autoimmune diseases such as rheumatoid arthritis and diabetes mellitus [6-9]. Hyperemesis has also been found associated with placental dysfunction disorders, i.e. preeclampsia and placental abruption [10-12], both known risk factors for CVD later in life [13-15]. Whether women with hyperemesis have a subsequent increased risk of cardiovascular events has to our knowledge not yet been studied.

We therefore aimed to investigate the risk of fatal and nonfatal cardiovascular events during long-term follow-up in women with and without a history of hyperemesis.

Materials and methods

Study population

From 1967 to 2002, all pregnancies ending after week 16 were registered in the Medical Birth Registry of Norway (MBRN) [16]. This registration is mandatory and has to be done within one week after discharge from the delivery unit. Information on maternal health before and during pregnancy, complications during pregnancy and delivery as well as information about the infant are registered. The study population comprised women with singleton births of more than 23 weeks of gestation registered in the MBRN during 1967-2002, being alive in Norway at the start of follow-up (Fig 1).

Fig 1. Flow diagram of the study population. Data on 1 018 478 women with registered pregnancies in the Medical Birth Registry of Norway (MBRN) in 1967-2002 were available. The figure shows how complete cases at start of follow-up were defined.

Exposure

From 1967 to 1998, pregnancy complications were reported in the MBRN 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) [17].

Follow-up

By using the personal identification number unique to every Norwegian resident, data from the MBRN were linked to the Cause of Death Registry and hospital discharge data on cardiovascular events obtained from the Cardiovascular Disease in Norway project (CVDNOR). In CVDNOR (https://cvdnor.b.uib.no/), all hospitalisations due to CVD or diabetes mellitus have been collected from all Norwegian somatic hospitals from 1994 through 2009 (1994 was the first year all hospitals in Norway started to use electronic patient administrative systems). CVDNOR has been described in detail elsewhere [18,19]. Information on death due to CVD during the same time period was obtained from the Norwegian Cause of Death Registry, which has a 98% coverage and completeness of the Norwegian population. For all deaths, a death certificate must be completed by a physician. A code from the ICD system is allocated to the diagnoses in the death certificate [20]. The registry used ICD-9 from 1986 to 1995 and ICD-10 codes from 1996 to 2009. Women with singleton births registered in the MBRN during 1967-1994 were followed with respect to cardiovascular outcomes from 1994 through 2009. Women with singleton births registered in the MBRN during 1994-2002 were followed through 2009.

Outcome

The primary outcome was defined as the occurrence of cardiovascular death, nonfatal myocardial infarction (I21, I22), nonfatal stroke (I60-I61, I63-I64) or hospitalisation due to angina pectoris (I20, I25.1) as main or secondary discharge diagnosis in a time-to-event analysis. Cardiovascular death was defined as CVD (I00-I99) as the underlying

cause of death registered in the Cause of Death Registry or death within 28 days after hospitalisation with a cardiovascular event (I00-I99). Secondary outcome was defined as the primary outcome, excluding angina pectoris. In addition, separate analyses for each component of the primary outcome were conducted.

Covariates

Age at first birth was the woman's age at her first registered birth in the MBRN. Since some women delivered children before 1967, a parity-variable reflecting the mother's self-reported parity was used. Information on maternal country of origin was provided from Statistics Norway.

Information on gestational hypertension, placental abruption, pre-gestational hypertension and pre-gestational diabetes mellitus was obtained from the MBRN. Based on information from each woman's registered pregnancies, dichotomous variables were created (never/ever). Information on smoking and maternal body weight was not available.

Information on maternal highest education at the end of follow-up was obtained from Statistics Norway and categorized as basic (9 years (7 years in the 1960s)), secondary (10-12 years) or tertiary (≥13 years), according to the Norwegian Standard Classification of Education [21].

Statistical methods

The analyses were conducted in STATA version 15. Descriptive statistics of women with and without hyperemesis are presented as median (25 and 75 percentiles) or as

numbers (%). Cox proportional hazards regression model was applied to estimate hazard ratios (HRs) for time-to-event outcomes. Women with previous births, still alive and living in Norway at start of follow-up were followed from 1994 until a CVD event occurred or censored if dead from other causes, emigration or at the cut-off date of December 31st 2009, whichever occurred first. Since angina as a discharge diagnosis may be more prone to bias, we also performed the analyses without angina as a secondary outcome. In addition, the occurrence of a nonfatal myocardial infarction, nonfatal stroke, angina pectoris or cardiovascular death were assessed individually regardless of the order of which the events occurred if a woman had experienced more than one event during follow-up. The time variable in the Cox-models was "years from 1994 (or first pregnancy if later than 1994) to the event of interest/censored". In addition to the crude analyses, age-adjusted (Model 1) and multivariable-adjusted (Model 2) analyses were performed. Based on prior knowledge [4,6,12,22], the following covariates were considered associated with both hyperemesis and the studied outcome, and were included as potential confounders: the woman's age at first pregnancy and year of birth, highest obtained education, country of birth, hypertensive disorders in pregnancy, placental abruption, pre-gestational diabetes and pre-gestational hypertension. Less than 1.5% of the women had missing information on education, information on the other covariates were complete. An estimate with a confidence-interval without one or a *p*-value below 0.05 was considered statistically significant.

Ethical approval for the study was obtained from the Regional Committee for Medical and Health Research Ethics (2015/1347/REK South-East). Due to the large number of women registered in the MBRN and the CVDNOR project, the ethical committee

approved the study, making an exception from the general rule of necessitating consent from all women included. The data was de-identified to preserve the participants' privacy.

Additional analyses

The primary outcome was also assessed in a subgroup of women born before 1945. This group included the oldest women in the study population, aged 50 years or older at start of follow-up. This was done to investigate if the studied associations differed according to if only women at the highest risk of a cardiovascular event in the population were included.

Results

Among 1 018 478 women with singleton births during 1967-2002, 9 044 (0.9%) emigrated and 9 690 (1.0%) died before start of follow-up. Less than 1.5% had missing information on covariates and only complete cases were used for analyses (Fig 1). The study sample comprised 989 473 women, of which 13 212 (1.3%) had suffered from hyperemesis in at least one pregnancy. The median follow-up time was 15 years (range 0-15) and total person-years at risk were 13 527 714. Lost to follow-up because of emigration was 10 360 (1.1%) women and 20 719 (2.1%) women were censored due to death from other causes during follow-up (1994-2009). Women with a history of hyperemesis were younger at their first registered pregnancy and were less often of ethnic Norwegian origin compared to women without hyperemesis. There was no difference between the two exposure groups in the proportion of women with pre-

gestational diabetes mellitus or pre-gestational hypertension. Women with a history of hyperemesis were younger at start of follow-up. At the end of follow-up, women with previous hyperemesis were younger, had obtained a higher level of education and were more often multipara, compared to women without hyperemesis (Table 1).

Table 1 Characteristics of the study cohort: Women in Norway with singleton births from 1967 to 2002 (n= 989 473).

Maternal and pregnancy characteristics	**Women with hyperemesis gravidarum (n= 13 212)**	**Women without hyperemesis gravidarum (n= 976 261)**	***P*-value****
At time of delivery			
Median age at first pregnancy*	24 (21-27)	25 (21-28)	<0.01
Age at first reg. pregnancy, n (%) ≤19 20-24 25-29 30-34 ≥35	 1 574 (11.9) 5 677 (43.0) 4 136 (31.3) 1 333 (10.1) 492 (3.7)	 117 031 (12.0) 368 935 (37.8) 304 875 (31.2) 127 826 (13.1) 57 594 (5.9)	<0.01
Pre-gestational diabetes, n (%)	44 (0.3)	3 672 (0.4)	0.4
Pre-gestational hypertension, n (%)	63 (0.5)	4 386 (0.5)	0.6
Maternal country of origin, n (%) Norway Europe Africa Asia North-America South-America Oceania	 11 565 (87.5) 758 (5.7) 170 (1.3) 507 (3.8) 165 (1.3) 40 (0.3) 7 (0.1)	 880 279 (90.2) 57 747 (5.9) 4 853 (0.5) 19 447 (2.0) 10 931 (1.1) 2 517 (0.3) 487 (0.1)	<0.01
At start of follow-up			
Median age at start of follow-up*	35 (28-45)	37 (29-46)	<0.01
At end of follow-up			
Median age at the end of study*	50 (42-59)	52 (43-61)	<0.01
Min, max age at the end of study	22, 89	19, 91	
Highest obtained education, n (%) Basic Secondary Tertiary	 3 367 (25.5) 5 797 (43.9) 4 048 (30.6)	 248 107 (25.4) 444 304 (45.5) 283 850 (29.1)	<0.01
Parity by end of follow-up, n (%) Primipara Multipara	 1 727 (13.1) 11 485 (86.9)	 201 865 (20.7) 774 396 (79.3)	<0.01
Preeclampsia, pregnancy-related hypertension and eclampsia, n (%)	985 (7.5)	73 581 (7.5)	0.7
Placental abruption, n (%)	169 (1.3)	10 911 (1.1)	0.1

*Median with 25 and 75 percentiles

**Tested with t-test or chi-squared test

Primary outcome

Among women with a history of hyperemesis, 535 (4.1%) experienced at least one cardiovascular event during follow-up, compared to 42 947 (4.4%) of the women without such history (Table 2). In the crude analysis, women with hyperemesis had a lower risk of a cardiovascular event compared to women without such history (Fig 2 and Table 2), but this association was no longer present after adjustment for age and other available confounders (Table 2). When the effect of each confounder was considered individually, we found that the change from Model 1 to Model 2 was mainly driven by the woman's year of birth.

Fig. 2 Event-free survival during follow-up (1994-2009). Women in Norway with a history of hyperemesis gravidarum (n= 13 212) compared to women without such history (n= 976 261).

Table 2 Primary and secondary outcomes during 15 years of follow-up (1994-2009) in women with a history of hyperemesis gravidarum (n= 13 212) compared to women without (n= 976 261) in Norway.

Cardiovascular event	**Number (%) of women with events according to HG status**		**Hazard ratio (95% confidence interval) for CVD event No HG as referent group**		
	HG (n= 13 212)	**No HG (n= 976 261)**	**Crude model**	**Model 1***	**Model 2****
Primary outcome *CVD death, nonfatal MI, nonfatal stroke or hospitalization with angina pectoris*	535 (4.1)	42 947 (4.4)	0.90 (0.83-0.98)	0.98 (0.90-1.07)	1.08 (0.99-1.18)
Main secondary outcome *CVD death, nonfatal MI or nonfatal stroke*	319 (2.4)	29 033 (3.0)	0.80 (0.71-0.89)	0.88 (0.78-0.98)	0.96 (0.86-1.08)
Additional secondary outcomes					
Death from CVD	81 (0.6)	9 333 (1.0)	0.63 (0.51-0.78)	0.73 (0.59-0.91)	0.81 (0.65-1.01)
Angina pectoris	299 (2.3)	20 151 (2.1)	1.08 (0.96-1.21)	1.16 (1.03-1.30)	1.28 (1.15-1.44)
Nonfatal MI	126 (1.0)	11 063 (1.1)	0.83 (0.69-0.99)	0.90 (0.76-1.08)	1.01 (0.84-1.20)
Nonfatal stroke	163 (1.2)	13 038 (1.3)	0.91 (0.78-1.06)	0.99 (0.85-1.15)	1.07 (0.92-1.25)

HG: hyperemesis gravidarum, CVD: cardiovascular disease, MI: myocardial infarction

*Age-adjusted
**Adjusted for woman's age at first birth, woman's year of birth (categorical), country of birth, education, hypertensive disorder in pregnancy, pre-gestational hypertension, pre-gestational diabetes, placental abruption.

Secondary outcomes

After excluding angina as a part of the composite outcome, 319 (2.4%) of the women with a history of hyperemesis had experienced a cardiovascular event (cardiovascular death, nonfatal myocardial infarction or stroke) during follow-up, compared to 29 033 (3.0%) of the women without such history. In the crude analysis there was a lower risk of a cardiovascular event among women with a history of hyperemesis compared to women without hyperemesis, and still significantly lower after adjustment for age, but after adjustment for other available confounders, the association was no longer significant (Table 2).

During follow-up, women with a history of hyperemesis had lower risk of cardiovascular death compared to women without such history (crude HR 0.63; 95% CI 0.51-0.78) (Table 2). The association was still significantly lower after age-adjustment, but after adjustment for other available confounders, the association was no longer significant. The risk of nonfatal myocardial infarction or stroke did not differ according to hyperemesis-status in pregnancy (Table 2). Women with hyperemesis had a higher risk of being hospitalised with angina pectoris, both in the age-adjusted and multivariable-adjusted model (Table 2).

Additional analyses

Among 165 327 women born before 1945 with previous pregnancy, 1743 women had suffered from hyperemesis. During 15 years of follow-up, a total of 23 287 (14.1%)

women experienced a cardiovascular event (primary outcome). In the subgroup of older women those with a history of hyperemesis had similar risk of a cardiovascular event as women without (table 3).

Table 3 Primary outcome during 15 years of follow-up (1994-2009) in women born before 1945 with a history of hyperemesis gravidarum (n= 1 743) compared to women without (n= 163 584) in Norway.

Cardiovascular event	**Number (%) of women with events according to HG status**		**Hazard ratio (95% confidence interval) for CVD event No HG as referent group**		
	HG (n= 1 743)	**No HG (n= 163 584)**	**Crude model**	**Model 1***	**Model 2****
Primary outcome *First hospitalisation with MI, stroke or angina pectoris, or CVD death*	242 (13.9)	23 045 (14.1)	0.98 (0.86-1.11)	1.06 (0.94-1.21)	1.08 (0.95-1.23)

HG: hyperemesis gravidarum, CVD: cardiovascular disease, MI: myocardial infarction
*Age-adjusted
**Adjusted for woman's age at first birth, woman's year of birth (categorical), country of birth, education, hypertensive disorder in pregnancy, pre-gestational hypertension, pre-gestational diabetes, placental abruption.

Discussion

Main findings

In this large nationwide cohort study, we found no evidence of increased risk of a cardiovascular event (nonfatal myocardial infarction or stroke, angina pectoris or cardiovascular death) long-term in women with hyperemesis compared to those without.

Strengths and limitations

A major strength in this study is the large nationwide study population and the long follow-up-time for cardiovascular events. The MBRN and the Cause of Death Registry

have mandatory reporting, and CVDNOR contains information on CVD hospitalisations from all somatic hospitals in Norway in the time-period. Moreover, the linkage of the MBRN to both CVDNOR and the Cause of Death Registry made it possible to include cardiovascular deaths outside hospital and increase the accuracy by defining cardiovascular death as either death within 28 days after discharge with a cardiovascular event or CVD as the underlying cause of death on the death certificate.

The change in estimate from Model 1 to Model 2 was mainly due to the adjustment for maternal year of birth. This change was also found independent of adjustment for age. We assessed the difference in effect estimates in different birth cohorts and found slightly different effect estimates in different strata, but all the HRs pointed to the same overall result with estimates close to one and negative findings. The small change in estimate may be the consequence of a cohort effect [23] because of heterogeneity in follow-up time for events between young and old segments of the population. The lack of information on cardiovascular events in the period before 1994 is another limitation. On the other hand, cardiovascular events in women are most likely to occur after the age of 50 [19,24] and 90% of the women in this study were younger than 53 years at start of follow-up in 1994, making them less likely to have suffered from a cardiovascular event before follow-up started. Moreover, the uncertainty related to angina as a discharge diagnosis may have led to inclusion of events representing non-cardiac chest pain [25]. It is therefore not known whether the increased risk of being hospitalised due to angina pectoris among women with previous hyperemesis indicates an increased risk of later ischemic heart disease or not.

Although incorrect registration is a limitation in all register-based research, hyperemesis in the MBRN has previously been validated and found eligible for large-scale epidemiological studies [17]. Moreover, the MBRN did not contain information on potential confounders, such as smoking-habits or body mass index before 1999 and 2006, respectively. Smoking is associated with a reduced risk of hyperemesis and hyperemesis is associated with both underweight and obesity [7]. We also lacked information on hypertension, diabetes and cholesterol at start of follow-up. The lack of potential confounder control may have contributed to residual confounding. However, we have previously shown that hyperemetic women at the age of 40 have similar cardiovascular risk factor profiles as women without hyperemesis [26].

Comparison with other studies

Few previous studies have explored cardiovascular risk subsequent to hyperemesis. Some large population-based studies have, however, found women with a history of hyperemesis to have increased risk of preeclampsia [10,12] and autoimmune diseases such as rheumatoid arthritis [9,27]. Immunological abnormalities and increase of fetal cells in maternal circulation may reflect possible underlying mechanisms, such as abnormal placentation and increased levels of human chorionic gonadotropin (hCG) [10]. Such mechanisms could also contribute to explain associations between autoimmune disease and hyperemesis.

Hyperemesis during second trimester is found to be strongly associated with preterm pre-eclampsia, placental abruption as well as a giving birth to a small-for-gestational-age baby [12]. Despite the fact that all aforementioned conditions are associated with

increased risk of CVD later in life [13,28], we did not find any evidence of increased risk for cardiovascular events subsequent to hyperemesis. This is, however, in line with findings in our previous articles on midlife cardiovascular risk factors subsequent to hyperemesis, and on risk of cardiovascular death among women with a history of hyperemesis [26, 29]. Compared to our previous paper on long-term mortality following hyperemesis, the slightly lower HR for cardiovascular death in crude and age-adjusted analyses in the present study may be explained by different follow-up time and a broader definition of cardiovascular death. In the previous paper cardiovascular death was defined as CVD as the underlying cause of death registered in the Cause of Death Registry [29]. In the present paper, we defined cardiovascular death as CVD as the underlying cause of death registered in the Cause of Death Registry or death within 28 days after hospitalisation with a cardiovascular event.

Interpretation

Results of the current study indicate that women with a history of hyperemesis do not have higher risk of cardiovascular events later in life, indicating that they may have the same cardiovascular follow-up as the female population in general.

Although the study population was relatively young at the end of follow-up, 25% of the women were above 60 years and it is unlikely that hyperemesis is associated with increased risk of a premature cardiovascular event. This assumption is furthermore supported by the large cohort, number of events and long follow-up time. Additional analyses on women aged 50 years or older at start of follow-up revealed no increase in risk of a cardiovascular event among women with a history of hyperemesis compared to

women without. When conducting sub-analyses, exploring each cardiovascular event separately, we found that hyperemetic women had slightly increased risk of being hospitalised due to angina pectoris. The difference was significant in the adjusted model only, something which makes the interpretation difficult. Moreover, the diagnostic criteria for myocardial infarction have changed over time, and troponins were first introduced in Norwegian hospitals in 1999-2001 [30]. This means that women previously diagnosed with angina, may after introduction of troponins have been diagnosed with a myocardial infarction. This would, however, probably not have changed the results for the primary outcome. It is not known whether women with angina in our study have suffered from a myocardial infarction after follow-up and because of the relatively young population, this could be a topic for future research.

Conclusion

In this large nationwide cohort study, we found no evidence of increased risk of a cardiovascular event (nonfatal myocardial infarction or stroke, angina pectoris or cardiovascular death) in women with a history of hyperemesis compared to women without.

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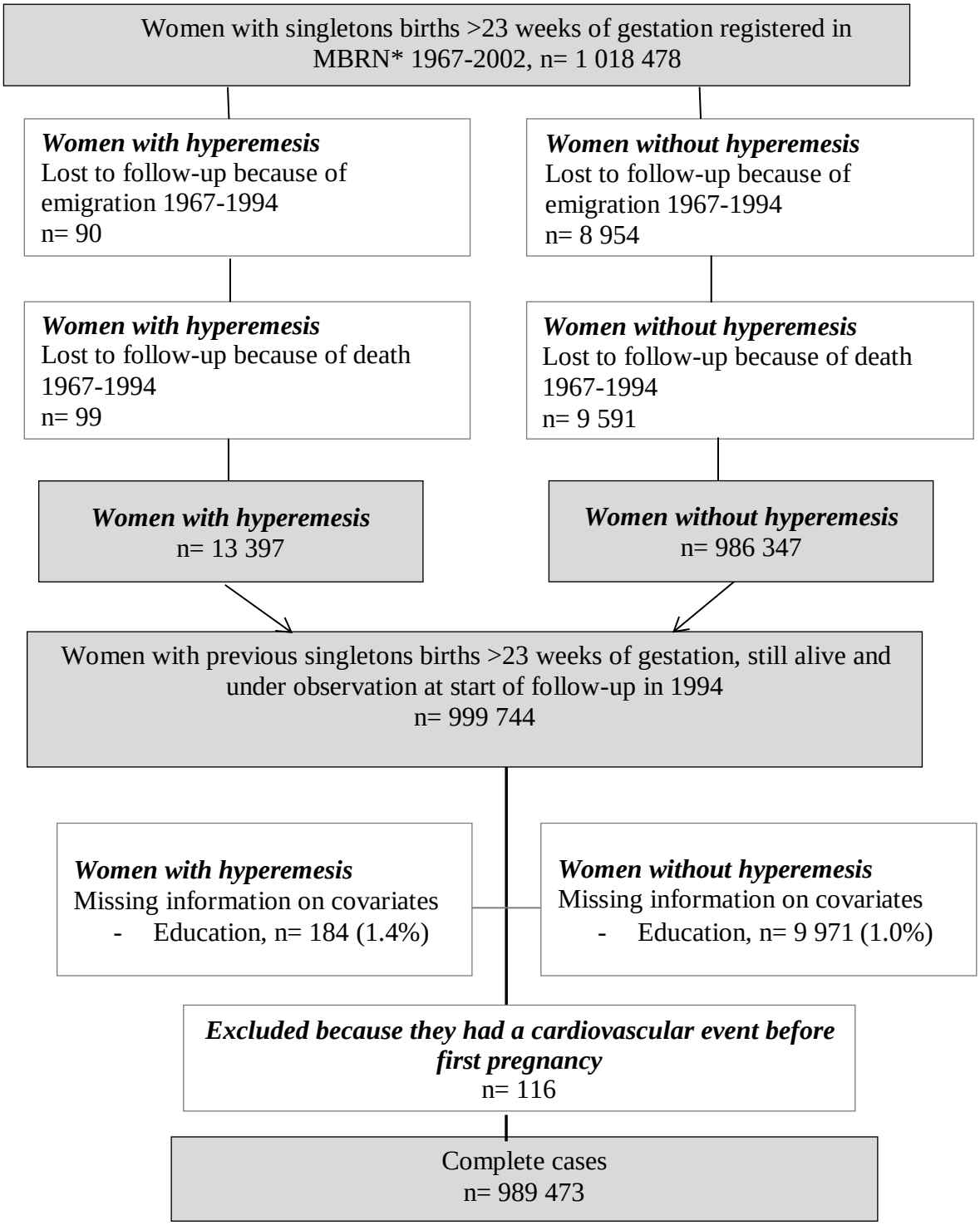
Figure 1


Women with singletons births >23 weeks of gestation registered in MBRN* 1967-2002, n= 1 018 478
Women with hyperemesis
Lost to follow-up because of emigration 1967-1994
n= 90
Women without hyperemesis
Lost to follow-up because of emigration 1967-1994
n= 8 954
Women with hyperemesis
Lost to follow-up because of death 1967-1994
n= 99
Women without hyperemesis
Lost to follow-up because of death 1967-1994
n= 9 591
Women with hyperemesis
n= 13 397
Women without hyperemesis
n= 986 347
Women with previous singletons births >23 weeks of gestation, still alive and under observation at start of follow-up in 1994
n= 999 744
Women with hyperemesis
Missing information on covariates
- Education, n= 184 (1.4%)
Women without hyperemesis
Missing information on covariates
- Education, n= 9 971 (1.0%)
Excluded because they had a cardiovascular event before first pregnancy
n= 116
Complete cases
n= 989 473

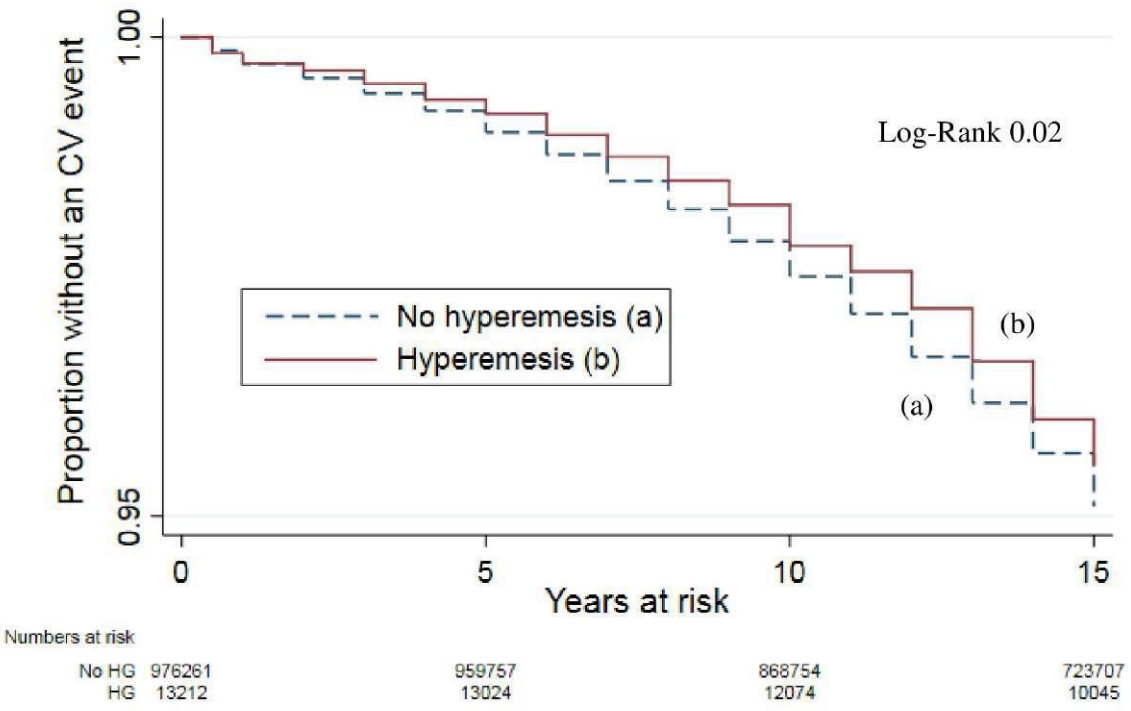

Proportion without an CV event
1.00
0.95
Log-Rank 0.02
No hyperemesis (a)
Hyperemesis (b)
(b)
(a)
0
5
10
15
Years at risk
Numbers at risk
No HG 976261 959757 868754 723707
HG 13212 13024 12074 10045

Figure 2.

10.0 APPENDIX

ANTENATAL FORM (1967-1998) – THE MEDICAL BIRTH REGISTRY OF NORWAY

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

Barnet

Barnet var 1 ☐ Levende født 2 ☐ Dødfødt foster | Født dag, mnd., år | Klokkeslett | Personnr. | Skriv ikke her

1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling | Kjønn 1 ☐ Gutt 2 ☐ Pike

Etternavn, alle fornavn (bare for levendefødte)

Fødested. Navn og adresse på sykehuset/fødehjemmet | Kommune

Faren

Etternavn, alle fornavn | Født dag, mnd., år | Bostedskommune

Moren

Etternavn, alle fornavn. Pikenavn | Født dag, mnd., år

Bosted. Adresse | Kommune

Ekteskapelig status 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt | Ekteskapsår (gifte)

Antall tidligere fødte (før denne fødselen) | Levende fødte | Av disse i live | Dødfødte

Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:

Morens helse før svangerskapet

1 ☐ Normal 2 ☐ Sykdom (spesifiser):

Siste menstruasjons første blødningsdag

Morens helse under svangerskapet

1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):

Ble fødselen provosert

1 ☐ Nei 2 ☐ Ja

Inngrep under fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Inngrepet utført av 1 ☐ Lege 2 ☐ Jordmor

Komplikasjoner i forbindelse med fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Fostervann, placenta og navlesnor

1 ☐ Normalt 2 ☐ Patologisk (spesifiser):

Barnets tilstand

Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja | Apgarscore etter 1 min. | etter 5 min.

For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:

Lengde (i cm) | Hode-omkr. (i cm) | Vekt (i g) | For døde innen 24 timer Livet varte i | Timer | Min

For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen
Dødsårsak:

Seksjon? 1 ☐ Nei 2 ☐ Ja

Alvorlige arvelige lidelser i slekten

1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:

Sted (sykehusets stempel) | Dato | Jordmor | Lege

50 000. 5.96. SEM GRAFISK

DEATH CERTIFICATE (PAPER FORM IS- 1025B)

Sem AS

Fastsatt av Sosialdepartementet 1993 Blankett 1

Legeerklæring om dødsfall/melding om unaturlig dødsfall

Jfr. lov om leger av 13/6 1980 §§ 40 og 41.

Blanketten fylles ut i samsvar med rettledningen på baksiden og leveres rekvirenten (den som har plikt til å melde dødsfallet) i forseglet konvolutt som i byene adresseres til skifteretten og på landet til lensmannen på dødsstedet. Kopi av legeerklæringen sendes den lokale politimyndighet, hvis dødsfallet kan være unaturlig. (Se rettledning på baksiden.)

Avdødes slektsnavn, for- og mellomnavn	Kjønn ☐ 1 M ☐ 2 K	Født dag, mnd., år	Personnr.	Fylles ut av Statistisk Sentralbyrå

Bosted, kommune	gate og husnr.	postadresse	

Dødssted, kommune	Død utenfor institusjon				
	1 ☐ Hjemme	2 ☐ Annet sted	3 ☐ Under transport til sykehus	4 ☐ Død i sykehus eller annen institusjon	

For døde i sykehus eller annen institusjon: Institusjonens navn	Død dag, mnd., år	
Hvis sykehus: Avdeling. For annen institusjon: Type institusjon		

Yrke (eget, eventuelt forsørgerens)	

Ekteskaplig status	For barn døde innen 24 timer etter fødselen, hvor lenge varte livet? Timer	Minutter	
1 ☐ Ugift 2 ☐ Gift 3 ☐ Enke, -mann 4 ☐ Skilt 5 ☐ Separert			

Navn og adresse på den lege som har **behandlet** avdøde under siste sykdom	

Opplysning om dødsårsaken

Alle rubrikker må fylles ut. (Se rettledning på baksiden.)

		Omtrent tid mellom sykdommens begynnelse og døden	
I. Sykdom eller tilstand som direkte (umiddelbart) har ført til døden. (Her skal **ikke** føres dødsmåten f.eks. hjertesvikt, hjertelammelse, asteni, men den sykdom, skade eller komplikasjon som umiddelbart fremkalte døden.)	a)		
	Som skyltdtes (var en følge av)		
Oppgi den eller de sykelige tilstander, skader eller misdannelser som har ført til (lå bak) den dødsårsak som er nevnt ovenfor. Den tilstand som innledet sykdomsforløpet, føres sist.	b)		
	Som skyltdtes (var en følge av)		
	c)		
II. Andre vesentlige tilstander som kan ha bidratt til dødens inntreden, men som ikke står i direkte årsaksforhold til den sykdom eller tilstand som har fremkalt døden.			

Dersom døden skyldtes skade (ulykke) eller følger av denne:	Dato skaden (ulykken) skjedde	Sted ☐ I/ved hjemmet	☐ Annet sted	Yrkesulykke? ☐ Ja ☐ Nei	
	Hvordan skjedde ulykken?				

Spesielle omstendigheter ved dødsfallet/foretatte undersøkelser tyder på (sett kryss)									
☐ Drap	☐ Selvmord	☐ Misbruk av narkotika	☐ Medisinsk feil	☐ Ukjent årsak	☐ Plutselig/ uventet	☐ Dødsfall i fengsel/arrest	☐ Ukjent lik	☐ Yrkessykdom	

Ble det foretatt operasjon? ☐ Ja ☐ Nei	Dato operert	Viktigste funn	

Opplysningene under I bygger på ☐ Obduksjon ☐ Unders. før døden ☐ Syning av liket	Vil den oppgitte dødsårsak senere bli revurdert? ☐ Ja ☐ Nei ☐ Vet ikke	

Undertegnede lege som har synet liket og som har ☐ behandlet den døde under siste sykdom (sett event. kryss), erklærer herved at dødsårsaken er den ovenfor nevnte.	Melding om unaturlig dødsfall er sendt/gitt muntlig til politiet/lensmannen ☐ Ja ☐ Nei Undertegnede lege erklærer herved at det ikke er grunn til å anta at døden er voldt ved en straffbar handling. (Erklæringen gis bare når kremasjon ønskes eller liket føres ut av riket.)
Dato Lege Adresse:	Dato Lege Adresse:

I. Forevist skifteretten/lensmannen og sendes den offentlige lege/politiet på dødsstedet	II. Forevist politiet og sendes den offentlige lege på dødsstedet	III. Off. lege/helseråd (stempel)
Dato For skifteretten/lensmannen Adresse:	Dato For politimesteren Adresse:	

IS-1025 B

Rettledning for legen ved utfylling av meldingen

En dødsmelding er et dokument som har rettslig betydning. Alle opplysninger må derfor gis med største nøyaktighet, og meldingen må fylles ut med tydelig skrift.

For de enkelte rubrikker må følgende iakttas:

Avdødes navn: Både slektsnavn, for- og mellomnavn skrives helt ut. For barn som dør før det har fått navn, oppgis foreldrenes (morens) slektsnavn.

Bosted: Her oppgir hvor den døde var registrert bosatt. Personer som på grunn av utdanning eller arbeid midlertidig oppholder seg borte fra hjemmet, regnes som bosatt på hjemstedet. Personer som dør i sykehus, fengsel o.l., regnes som bosatt der de hadde sitt bosted før anbringelsen. For barn født på sykehus/klinikk, som dør umiddelbart etter fødselen, oppgis foreldrenes (morens) bosted. Personer som ved døden var anbragt i andre institusjoner (aldershjem, skolehjem o.l.) eller i privat pleie, regnes som bosatt der. Norsk personell ved norske diplomatiske stasjoner i utlandet regnes forsatt som bosatt i den kommunen de hadde sitt bosted ved utreisen.

Dødssted: Her oppgis kommune, og det krysses av hvor døden inntrådte (hjemme, annet sted, under transport til sykehus, i sykehus eller annen institusjon). Ved dødsfall i sykehus oppgis sykehusets navn og avdeling, ved dødsfall i annen institusjon oppgis navn, type og postadresse.

Yrke: Oppgis avdødes yrke eller levevei. For yrkesaktive og tidligere yrkesaktive oppgis hovedyrket, for arbeidsløse vanlig yrke. For pensjonister og trygdede oppgis tidligere yrke med tilføyelse «fhv». For forsørgede oppgis forsørgerens, eventuelt forsørgelsesmåten.

Dødsårsaken: (det vises også til særskilt rettledning)

Under Ia) skal føres den sykdom, komplikasjon eller tilstand som **direkte** fremkalte døden. I de fleste tilfelle vil denne umiddelbare dødsårsak skyldes eller være en følge av en eller flere sykdommer, skader eller tilstander. Disse føres under b) og c), og den tilstand som etter legens mening startet årsakskjeden føres sist. Hvis den sykdom eller tilstand som føres opp under Ia) beskriver hendelsesforløpet fullstendig, er det ikke nødvendig å fylle ut b) og c).

Årsakssammenhengen mellom Ia, b og c omfatter ikke bare den etiologiske eller patogenetiske sammenheng, men også sekvenser der grunnlidelsen antas å ha ført til den direkte dødsårsak p.g.a. funksjonsnedsettelse eller andre forstyrrelser.

Under II føres andre vesentlige tilstander som bidro til den dødelige utgang, men som ikke sto i direkte årsaksforhold til den sykdom eller tilstand som fremkalte døden.

Hvis mulig oppgis om tilstanden var akutt eller kronisk og hvor lenge hver tilstand har vart. Ved sykdomsbetegnelser hvor lokalisasjon ikke går fram av sykdommens navn, eks. ved kreft og tuberkulose, må sykdommens anatomiske sete oppgis.

Ved unaturlig død skal legen opplyse om det foreligger drap, selvmord eller ulykke. Utførlige opplysninger om den ytre årsak bes gitt uansett om døden er en umiddelbar følge av skaden eller av den patologiske tilstand som skaden kan ha ført til.

Ved unaturlig død skal legen sende skriftlig melding til politiet/lensmannen på dødsstedet, jfr. § 41 i lov om leger av 13/6 1980 nr. 42 og forskrifter for legens melding om unaturlig dødsfall o.l. Se forøvrig særskilt rettledning nedenfor.

Rettledning for legen ved melding om unaturlig dødsfall

Legeloven § 41 bestemmer at den lege som skal gi erklæring om dødsfall, uten opphold skal underrette politiet dersom det er grunn til å regne med at dødsfallet kan være unaturlig. På samme måte meldes funn av ukjent lik, og dødsfall i fengsel eller i politi- eller militærarrest. Unnlatelse av å melde fra er straffbar. Meldeplikten går foran taushetsplikt.

Melding til politiet om unaturlig dødsfall skal først skje muntlig eller telefonisk så snart som mulig. Deretter skal sendes skriftlig melding. Denne er en kopi av legeerklæringen om dødsfall, for at legene skal slippe et ekstra meldingsskjema. På skjemaet er det en del spørsmål som knytter seg til unaturlig dødsfall. Opplysningene her hører med til den vanlige legeerklæring om dødsfall.

Grensen mellom naturlig og unaturlig død er ikke sparp. Det kan ofte være uklart om et dødsfall er naturlig eller unaturlig. Årsaksforholdene er ofte usikre, og kan hyppig bare bringes på det rene ved etterforskning eller ved sakkyndig likundersøkelse.

Legen behører ikke ta et bestemt standpunkt til om det foreligger naturlig eller unaturlig død, til årsaks- eller skyldforhold e.l. Hans plikt til å gi muntlig melding til politiet inntrer når han skjønner at det kan foreligge unaturlig død. Når han så gir skriflig melding, kan legen gi uttrykk for at svaret er usikkert ved å sette spørsmålstegn istedenfor kryss ved de spørsmål som gjelder unaturlig død eller ved å krysse av i rubrikken for ukjent årsak. Et dødfall vil kunne falle inn under flere rubrikker; et narkotikadødsfall kan samtidig være et selvmord, en ulykke eller et uaktsomt drap, og det kan inntreffe under anholdelse eller i arrestrom.

Har legen gitt muntlig melding, bør i alle tilfeller skriftlig melding sendes, også om dødsfallet ikke lenger antas å være unaturlig.

Oversendelse av dødsmeldinger

Ved begravelse skal skifteretten (lensmannen) etter å ha fylt ut skjema for melding til soknepresten, (jfr. Justisdepartementets rundskriv av 1. desember 1938) sende denne legeerklæring direkte (i posten) til den offentlige lege på dødsstedet.

Ved kremasjon eller hvis liket skal føres ut av riket, skal skifteretten (lensmannen) etter å ha fylt ut skjema for melding til soknepresten (jfr. Justisdepartementets rundskriv av 1. desember 1938) oppfordre rekvirenten til å bringe legeerklæringen videre til politiet, som gir ham (henne) særskilt erklæring om at det fra politiets side ikke er noe til hinder for kremasjon eller at liket føres ut av riket.

Politiet sender deretter legeerklæringen direkte (i posten) til den offentlige lege på dødsstedet.

Den offentlige lege skal sende de dødsmeldingene han mottar til Statistisk Sentralbyrå, postboks 8131 Dep., Oslo. Fra byene skal meldingene sendes den 1. i hver måned, fra landdistriktene kvartalsvis innen 8 dager etter kvartalets utløp (jfr. årlig rundskriv fra Helsedirektøren).

Denne blankett fås ved henvendelse til den offentlige lege, som får det nødvendige antall fra fylkeslegen. Fylkeslegen rekvirerer skjema fra Sosial- og helsedirektoratet, postboks 7000 St. Olavs plass, 0130 OSLO.

Leveringsadresse: Universitets gt. 2.

THE AGE 40 PROGRAM – QUESTIONNAIRE 1997-1999

Spørreskjemaet er en viktig del av helseundersøkelsen. Vennligst fyll ut skjemaet på forhånd og ta det med til helseunder søkelsen. Dersom enkelte spørsmål er uklare, lar du dem stå ubesvart til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen. *Alle svar vil bli behandlet strengt fortrolig.*

Det utfylte skjemaet vil bli lest av en maskin. Bruk blå eller sort farge ved utfylling. Det er viktig at du går fram slik:

- i de små boksene setter du kryss for det svaret som passer best for deg
- i de store boksene skriver du tall eller blokkbokstaver – NB! innenfor rammen for boksen.

Eksempler:
Avkryssing: [X] Tall: 1 2 3 4 5 6 7 8 9 0 Bokstaver: A B C

Med vennlig hilsen

Statens helseundersøkelser ♥ Kommunehelsetjenesten

1. EGEN HELSE

Hvordan er helsen din nå? *(Sett bare ett kryss)*

Dårlig	Ikke helt god	God	Svært god
☐ 1	☐ 2	☐ 3	☐ 4

Har du, eller har du hatt:	JA	NEI	Alder første gang	
Hjerteinfarkt	☐	☐		år
Angina pectoris (hjertekrampe)	☐	☐		år
«Hjerneslag/hjerneblødning («drypp»)	☐	☐		år
Astma	☐	☐		år
Diabetes (sukkersyke)	☐	☐		år

Får du smerter eller ubehag i brystet når du:	JA	NEI
Går i bakker, trapper eller fort på flat mark?	☐	☐

Hvis du får slike smerter, pleier du da å:

Stoppe?	Saktne farten?	Fortsette i samme takt?
☐ 1	☐ 2	☐ 3

	JA	NEI
Dersom du stopper, forsvinner smertene da etter mindre enn 10 minutter?	☐	☐
Kan slike smerter like gjerne opptre mens du er i ro?	☐	☐

2. HVORLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst?	☐	☐	☐	☐
Trygg og rolig?	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom?	☐	☐	☐	☐
	1	2	3	4

3. SYKDOM I FAMILIEN

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?	☐	☐	☐
Har en eller flere foreldre/søsken hatt:			
Hjerteinfarkt *før* de fylte 60 år?	☐	☐	☐
Hjerneslag/hjerneblødning *før* de fylte 70 år?	☐	☐	☐

4. MUSKEL/SKJELETT-PLAGER

	JA	NEI
Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende?	☐	☐

Hvis NEI, gå til avsnitt 5. SOSIALE FORHOLD.
Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?	JA	NEI
Nakke	☐	☐
Skuldre (aksler)	☐	☐
Albuer	☐	☐
Håndledd/hender	☐	☐
Bryst, mage	☐	☐
Øvre del av ryggen	☐	☐
Korsryggen	☐	☐
Hofter	☐	☐
Knær	☐	☐
Ankler, føtter	☐	☐

Hvor lenge har plagene vart sammenhengende?
Svar for det området hvor plagene har vart lengst.

Hvis under 1 år, oppgi antall mnd. ..... *Antall mnd.*

Hvis 1 år eller mer, oppgi antall år ..... *Antall år*

Har plagene redusert din arbeidsevne det siste året?
Gjelder også hjemmearbeidende. Sett bare ett kryss.

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐ 1	☐ 2	☐ 3	☐ 4

	JA	NEI	Ikke i arbeid
Har du vært sykmeldt pga. disse plagene det siste året?	☐	☐	☐
Har plagene ført til redusert aktivitet i fritida?	☐	☐	

5. SOSIALE FORHOLD

Mottar du nå noen av følgende ytelser?	JA	NEI
Syketrygd (sykmeldt)	☐	☐
Attføringspenger	☐	☐
Uførepensjon (hel eller delvis)	☐	☐
Arbeidsledighetstrygd	☐	☐

Er husarbeid i hjemmet hovedyrket ditt? *(Svar NEI hvis lønnet arbeid utenom husarbeid er 18 timer eller mer pr. uke)*	JA	NEI
	☐	☐

6. UTDANNING

Hvilken utdanning er den høyeste du har fullført?
Sett bare ett kryss.

- Mindre enn 7 år grunnskole ☐
- Grunnskole 7-10 år, framhaldsskole, folkehøgskole ☐ 1
- Realskole, middelskole, yrkesskole, 1-2 årig videregående skole ☐ 2
- Artium, øk.gymnas, allmennfaglig retning i videregående skole ☐ 3
- Høgskole/universitet, mindre enn 4 år ☐ 4
- Høgskole/universitet, 4 år eller mer ☐ 5

7. KOST

Hvor ofte bruker du disse matvarene?
Sett kryss i de rutene som beskriver ditt forbruk best.

	Flere g. daglig	Daglig	1-6 g. pr uke	1-3 g. pr mnd	Sjelden eller aldri
Fisk (middag, pålegg)	☐	☐	☐	☐	☐
Frukt/grønt	☐	☐	☐	☐	☐
Helmelk, kefir, yoghurt	☐	☐	☐	☐	☐
Lettmelk, lettyoghurt	☐	☐	☐	☐	☐
Skummet melk (sur/søt)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Hva slags smør eller margarin bruker du vanligvis PÅ BRØDET?
Sett kryss i den ruta som passer best.

- Bruker ikke smør/margarin ☐ 1
- Meierismør ☐ 2
- Hard margarin ☐ 3
- Bløt (soft) margarin ☐ 4
- Smør/margarin blanding ☐ 5
- Lettmargarin/lettsmør (Brelett) ☐ 6

Hva slags fett bruker du/dere vanligvis TIL MATLAGING?
Sett kryss i den ruta som passer best.

- Smør/margarin ☐ 1
- Myk (soft) margarin/olje ☐ 2
- Bare olje ☐ 3
- Vet ikke ☐ 4

8. KAFFE / TE / ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?
Sett 0 hvis du ikke drikker kaffe/te daglig.

Antall kopper daglig

Kokekaffe	Annen kaffe	Te
☐☐	☐☐	☐☐

	JA	NEI
Er du total avholdsmann/-kvinne?	☐	☐

Hvor mange ganger i måneden drikker du vanligvis alkohol? *Regn ikke med lettøl.*
Sett 0 hvis mindre enn 1 gang i mnd. ..... *Antall ganger* ☐☐

Hvor mange glass øl, vin eller brennevin drikker du VANLIGVIS i løpet av to uker?
Regn ikke med lettøl. Sett 0 hvis du ikke drikker alkohol.

Glass øl	Glass vin	Glass brennevin
☐☐	☐☐	☐☐

9. RØYKING

Hvor lenge er du vanligvis daglig tilstede i røykfylt rom? ..... *Antall hele timer* ☐☐
Sett 0 hvis du ikke oppholder deg i røykfylt rom.

Røyker du selv:

	JA	NEI
Sigaretter daglig?	☐	☐
Sigarer/sigarillos daglig?	☐	☐
Pipe daglig?	☐	☐

Aldri røykt daglig ..... (Sett kryss) ☐

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? ..... *Antall år* ☐☐

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? ..... *Antall sigaretter* ☐☐

Hvor gammel var du da du begynte å røyke daglig? ..... *Alder i år* ☐☐

Hvor mange år til sammen har du røykt daglig? ..... *Antall år* ☐☐

10. MOSJON

Hvordan har din fysiske aktivitet i fritiden vært det siste året?
Tenk deg et ukentlig gjennomsnitt for året.
Arbeidsvei regnes som fritid. Besvar begge spørsmålene.

	Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)*	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	☐ 1	☐ 2	☐ 3	☐ 4

Bevegelse og kroppslig anstrengelse i din fritid. Hvis aktiviteten varierer meget f.eks. mellom sommer og vinter, så ta et gjennomsnitt. Spørsmålet gjelder bare det siste året.
Sett kryss i den ruta som passer best.

- Leser, ser på fjernsyn eller annen stillesittende beskjeftigelse? ☐ 1
- Spaserer, sykler eller beveger deg på annen måte minst 4 timer i uka? ☐ 2
  (Her skal du også regne med gang eller sykling til arbeidsstedet, søndagsturer m.m.)
- Driver mosjonsidrett, tyngre hagearbeid e.l.? ☐ 3
  (Merk at aktiviteten skal vare minst 4 timer i uka)
- Trener hardt eller driver konkurranseidrett regelmessig og flere ganger i uka? ☐ 4

11. ENDRING AV HELSEVANER

Dette gjelder din interesse for å endre helsevaner. Røykespørsmålet besvares bare av dem som røyker.

	Spise sunnere		Trimme mer		Slutte å røyke	
	JA	NEI	JA	NEI	JA	NEI
Har du de siste 12 mnd. forsøkt å:	☐	☐	☐	☐	☐	☐
Om 5 år, tror du at du har endret vaner på noen av disse områdene?	☐	☐	☐	☐	☐	☐

	Høyeste vekt	Laveste vekt
Anslå din høyeste og laveste vekt i løpet av de siste 5 år. *(Hele kg)* *(Se bort fra vekt under svangerskap)*	☐☐☐	☐☐☐

VEND!

12. MEDISIN MOT HØYT BLODTRYKK

Bruker du medisin mot høyt blodtrykk?

Nå	Før, men ikke nå	Aldri brukt
☐ 1	☐ 2	☐ 3

Hvis du bruker medisin nå, hvilke(t) merke(r) bruker du?

Ikke skriv i disse rutene

13. MEDISIN MOT HØYT KOLESTEROL

	JA	NEI
Bruker du kolesterolsenkende medisiner NÅ?	☐	☐

Hvis NEI, gå til 14. ETTERUNDERSØKELSE.

Hvor gammel var du da du begynte med kolesterolsenkende medisiner? ..... *Alder i år*

Hvis du bruker kolesterolsenkende medisiner, hva var grunnen til at du begynte med slik medisin?
(Sett kryss i de rutene som passer for deg.)

	JA	NEI
Hjerteinfarkt	☐	☐
Angina pectoris (hjertekrampe, brystkrampe)	☐	☐
Høyt innhold av kolesterol i blodet	☐	☐
Hjertesykdom i familien (foreldre, søsken)	☐	☐
Hjerneslag/hjerneblødning/ «drypp»	☐	☐
Dårlig blodsirkulasjon i bena (åreforkalkning, «røykeben»)	☐	☐
Andre årsaker	☐	☐

Skriv hvilke årsaker her:

Ikke skriv i disse rutene

	JA	NEI
Jeg er usikker på årsaken	☐	☐

Hvilke kolesterolsenkende medisiner bruker du NÅ og hvilken dose bruker du?

Hvilke(t) merke(r) bruker du? — Samlet dose på ett døgn

mg

mg

mg

Ikke skriv i disse rutene

14. ETTERUNDERSØKELSE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker du da å bli henvist til?
Oppgi legens navn:

Ikke skriv i disse rutene

15. TIL KVINNER SOM DELTAR I HELSE-UNDERSØKELSEN

Hvor gammel var du da du fikk menstruasjon aller første gang? ..... *Alder i år*

	JA	NEI
Har du for tiden regelmessig menstruasjon? *Regn den for regelmessig hvis den ikke har vært borte mer enn 3 mnd. sammenhengende siste år.*	☐	☐

Til deg som svarte JA: Omtrent hvor mange dager etter starten på siste menstruasjon skjer helseundersøkelsen? *(Sett bare ett kryss)*

Under 8 ☐ 8-14 ☐ 15-21 ☐ Mer enn 21 dager ☐

Hvis du for tiden ikke har regelmessig menstruasjon, ber vi deg fylle ut nedenfor *(Sett bare ett kryss)*

Menstruasjonen sluttet av seg selv for minst 6 mnd. siden (overgangsalder)	☐ 1
Menstruasjonen sluttet etter underlivs-operasjon, strålebehandling eller cellegift	☐ 2
Usikker på om menstruasjonen har sluttet (mulig overgangsalder)	☐ 3
Gravid i mindre enn 6 måneder	☐ 4
Gravid i 6 måneder eller mer	☐ 5
Har nylig født eller ammer, og har ikke fått menstruasjonen tilbake	☐ 6
Helt uregelmessige menstruasjoner, med svært korte eller svært lange pauser	☐ 7
Ingen eller uregelmessig menstruasjon på grunn av hormonbehandling	☐ 8
Har aldri hatt menstruasjoner	☐ 9

Hvis du ikke lenger har menstruasjon, hvor gammel var du da den sluttet? ..... *Alder i år*

Hvor mange barn (levende barn) **har du født?** *Antall barn*

Hvor lenge har du ammet dine barn til sammen?
(f.eks. 3 barn: 1 + 6 + 10 = 17 måneder) ..... *Antall mnd.*

Bruker du nå, eller har du tidligere brukt	Nå	Før, men ikke nå	Aldri
P-pille (*også minipille*) eller p-sprøyte	☐	☐	☐
Vanlig spiral	☐	☐	☐
Hormonspiral (pris ca. kr. 1000)	☐	☐	☐
Østrogen/progesteron *(tabletter, plaster, sprøyte)*	☐	☐	☐
Østrogen *(krem eller stikkpiller)*	☐	☐	☐

Til deg som bruker p-pille, hormonspiral (ikke vanlig spiral) eller hormoner i overgangsalderen NÅ:
Hvilke(t) merke(r) bruker du?

Ikke skriv i disse rutene

Omtrent hvor lenge har du brukt det du bruker nå?

Antall år *Hvis mindre enn ett år: .....Måneder*

Takk for utfyllingen!
Nok en gang:
Velkommen til undersøkelsen!

IE 3213201 - 30.000 - Beyer-Hecos 11/98 (ID.NR. 1/98)

ERRATA

LIST OF CORRECTIONS

ERRATA

Regarding Paper III (manuscript), “Long-term cardiovascular morbidity following hyperemesis gravidarum: A Norwegian nationwide cohort study”:

The first sentence in the additional analyses section in materials and methods (page 9 in the manuscript) was incorrect.

Incorrect: The primary outcome was also assessed in a subgroup of women born after 1945.

Corrected: The primary outcome was also assessed in a subgroup of women born before 1945.

The first sentence in the additional analyses section in results (page 13 in the manuscript) was incorrect.

Incorrect: Among 165 327 women born after 1945 with a previous pregnancy, 1743 women had suffered from hyperemesis.

Corrected: Among 165 327 women born before 1945 with a previous pregnancy, 1743 women had suffered from hyperemesis.

The legend of table 3 (page 14 in the manuscript) was incorrect.

Incorrect: Primary outcome during 15 years of follow-up (1994-2009) in women born after 1945 with a history of hyperemesis gravidarum (n= 1 743) compared to women without (n= 163 584) in Norway.

Corrected: Primary outcome during 15 years of follow-up (1994-2009) in women born before 1945 with a history of hyperemesis gravidarum (n= 1 743) compared to women without (n= 163 584) in Norway.