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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

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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.

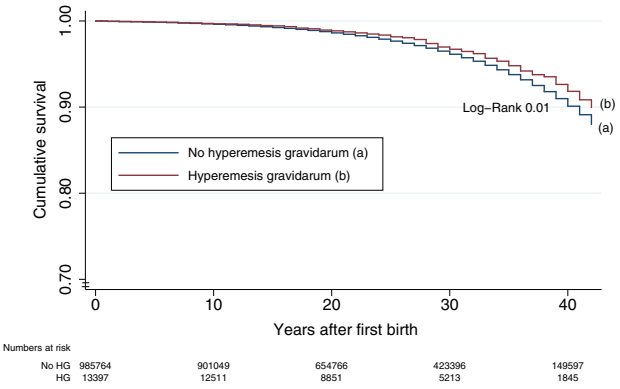

Figure 1. Kaplan–Meier survival curve (all-cause mortality). The time variable is years after first registered birth.

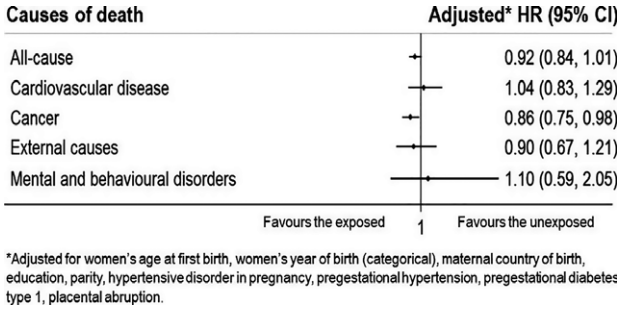

Figure 2. Forest plot of adjusted hazard ratios (HRs) with 95% confidence intervals (CI) in women exposed to hyperemesis gravidarum compared with unexposed women.

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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