Incidence and risk factors of hyperemesis gravidarum: A national register-based study in Finland, 2005–2017

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Abstract

Introduction: Hyperemesis gravidarum is the most common reason for hospitalization in early pregnancy in pregnancies resulting in delivery. Several associative factors indicate that the etiology is likely to be multifactorial. To assess this, we used a unique procedure to compare hyperemetic pregnancies to non-hyperemetic pregnancies both with different women and the same women's different pregnancies.

Material and methods: Data about all pregnancies resulting in delivery in Finland in 2005–2017 were retrieved from health care registers. Women who had hyperemesis gravidarum diagnosis in any pregnancy in the Finnish Hospital Discharge Register were chosen as cases (n = 9315) and other women (n = 428 150) as the reference group. Incidence of hyperemesis gravidarum was calculated and associations between hyperemesis and maternal, environmental and pregnancy-related factors were analyzed in a novel setting by comparing case women's pregnancies diagnosed with hyperemesis to 1) reference group women's pregnancies and 2) case women's non-hyperemetic pregnancies.

Results: Out of the 437 465 women who had at least one pregnancy resulting in delivery during the study period, 9315 women had at least one hyperemetic pregnancy. Total number of pregnancies resulting in delivery was 741 387 and 9549 of those were diagnosed with hyperemesis gravidarum, thus the incidence of hyperemesis gravidarum was 1.3%. In comparison 1), case women's hyperemetic pregnancies vs reference group's pregnancies, younger maternal age, higher gravidity, underweight and overweight were associated with increased risk of hyperemesis; in contrast, in comparison 2), case women's hyperemetic pregnancies vs their non-hyperemetic pregnancies, higher age and obesity were associated with higher risk of hyperemesis, whereas the risk was lower as gravidity and parity increased. In both comparisons, smoking was associated with lower risk, whereas higher municipality population, assisted reproductive technology, multiple gestation and female sex of the fetus were associated with increased risk of hyperemesis.

Conclusions: Our novel study setting provided new insights about risk factors: hyperemetic pregnancies differ both from pregnancies of women who had never been diagnosed with

hyperemesis and from hyperemetic women's non-hyperemetic pregnancies. Incidence of hyperemesis gravidarum in Finland was comparable to other countries.

Keywords

Hyperemesis gravidarum, nausea, vomiting, pregnancy, prenatal care, pregnancy complications, incidence

Abbreviations

ART, assisted reproductive technology; BMI, body mass index; CI, confidence interval; FMBR, Finnish Medical Birth Register; HG, hyperemesis gravidarum; ICD, International Classification of Diseases; OR, odds ratio.

Key message

The incidence of hyperemesis gravidarum (HG) in Finland is 1.3%. A novel comparison setting revealed that pregnancies diagnosed with HG differ not only from pregnancies of women never diagnosed with HG but also from HG patients' other, non-HG pregnancies.

Introduction

Hyperemesis gravidarum (HG) refers to intractable, severe nausea and vomiting of pregnancy.[1,2] Even though approximately 70%, or up to 91% of pregnant women experience nausea and vomiting to some degree during the first trimester of pregnancy, HG is a relatively rare condition with an incidence between 0.3% and 3.6%, or even up to 10.8% of all pregnancies.[3,4] Commonly used criteria for hospital care of HG are persistent vomiting, weight loss of more than 5% of pre-pregnancy weight and ketonuria,[5] although universally accepted diagnostic criteria for HG remain to be defined.[2,6] In Finland, HG is diagnosed according to the International Classification of Diseases (ICD).[7,8] There are currently no official hospitalization criteria or clinical guidelines for diagnosis or treatment of HG in Finland, but the primary Finnish medical journal Duodecim has described the above-mentioned criteria and treatment protocols based on intravenous hydration, parenteral nutrition and antiemetics.[9,10]

Etiology of HG remains unknown, but several associative factors have been identified, suggesting that the etiology of HG is multifactorial. Young maternal age,[11] under- or overweight,[12] assisted reproductive technology (ART),[13] multiple pregnancy[11,14] and female fetus[14,15] have been associated with increased risk, smoking is associated with lower risk,[11,12] and results about gravidity and parity are inconclusive.[11,13,16,17]

The objective of our study was to estimate the incidence of HG in Finland, thus far unknown, as well as to evaluate annual variation in incidences. Furthermore, we used a unique procedure to analyze maternal, environmental and pregnancy-related factors associated with HG to test the hypothesis of multifactorial etiology of HG in the Finnish population.

Material and methods

The data were compiled using Finnish health care registers. All Finnish citizens and permanent residents have their unique personal identity code which is included in all health care registers and permits linking data between registers. The information of pregnancies resulting in delivery between years 2005 and 2017 was drawn from the Finnish Medical Birth Register (FMBR). All women who had pregnancies resulting in delivery between years 2005 and 2017 in the FMBR

were included in the study (n = 437 465) (Figure 1). Women who had HG diagnosis (ICD-10 diagnosis codes O21, O21.0, O21.1, O21.2, O21.8 and O21.9) in any pregnancy in the Finnish Hospital Discharge Register, including pregnancies not resulting in delivery, were chosen as cases (n = 9315) and women without HG diagnosis in any pregnancy as the reference group (n = 428 150). The register encompasses both outpatient data and hospitalizations, and the ICD-10 diagnosis codes as defined by the World Health Organization[7,8] are used in providing clinical diagnosis of HG in Finland. Five pregnancies with another cause of vomiting than HG (four cases of gallstones and one case of pancreatitis) were excluded. Pregnancies with HG diagnosis and resulting in delivery (n = 9549) were compared to pregnancies without HG diagnosis resulting in delivery: first, the reference group women's pregnancies (n = 723 453) and second, the case women's non-HG pregnancies (n = 8385). To compare with our earlier results concerning recurrence of HG in subsequent pregnancies in 2004–2011,[18] the same calculations were performed in the present data set. The number of deliveries among women whose first pregnancy resulting in delivery during the study period was diagnosed with HG and the number of deliveries among women whose first pregnancy resulting in delivery during the study period was not diagnosed with HG were calculated.

Incidence of HG was calculated by comparing the number of pregnancies with HG diagnosis resulting in delivery to the number of all pregnancies resulting in delivery during the study period according to the time of delivery. Further, annual variation of incidence was calculated. To estimate the number of terminated HG pregnancies, pregnancy termination data were retrieved from the Register of Induced abortions. Termination dates and pregnancy weeks were compared with HG diagnosis dates from the Hospital Discharge Register to determine whether a terminated pregnancy included an HG diagnosis.

The data of maternal, environmental and pregnancy-related factors were drawn from FMBR and included maternal age in years (20 or younger; 21–25; 26–30; 31–35; 36–40 and 41 or older), gravidity (number of pregnancies, including the present), parity (number of deliveries, including the present), pre-pregnancy body mass index (BMI) (< 18.5 kg/m^2; 18.5–24.9 kg/m^2; 25–29.9 kg/m^2; 30–34.9 kg/m^2 and ≥ 35 kg/m^2), smoking (no; yes, but quit during the first trimester; yes, continued smoking after the first trimester), marital status (living/not living with partner), socioeconomic status based on official classification of maternal occupation, standard

classification by Statistics Finland (upper level white-collar workers, eg specialists and management level; lower level white-collar workers, eg office staff; blue-collar workers, eg manual laborers; at home; other), municipality population (< 10 000 inhabitants; 10 000–99 999 inhabitants; ≥ 100 000 inhabitants), ART (no/yes), number of fetuses (one; two or more) and sex of fetuses in singleton pregnancies (one male; one female) and multiple pregnancies (all male; all female; both sexes).

Statistical analysis

The annual incidences of HG were compared with Poisson regression and incidence rate ratio with 95% confidence interval (CI) was calculated. The associations between HG and associative factors (age, gravidity, parity, pre-pregnancy BMI, smoking, marital status, socioeconomic status, municipality population, ART, number and sex of fetuses) were analyzed using logistic regression with generalized estimating equation to account for the repeated pregnancies of the women. Factors with a *P* value < .10 in the univariable analysis were included in the multivariable model with the exception of socioeconomic status which was excluded from the multivariable analysis due to high proportion of missing data. Missing data were in general rare and not imputed. Results are expressed using odds ratios (OR) with 95% confidence intervals. Statistical analysis was performed using SAS System for Windows, version 9.4 (SAS Institute Inc., Cary, NC).

Ethical approval

The data were compiled with permission of the Finnish Institute for Health and Welfare (THL/658/5.05.00/2012; THL/372/5.05.00/2018). Ethical committee of Hospital District of Southwest Finland (43/180/2011) approved the study plan.

Results

During the study period, there were in total 741 387 pregnancies resulting in delivery and of those 9549 pregnancies had a HG diagnosis. The incidence of HG in all pregnancies resulting in delivery was thus 1.3%. In singleton pregnancies, the incidence was 1.3% as well (9051 of 730

717 pregnancies), and in multiple pregnancies, the incidence was 2.9% (305 of 10 670 pregnancies). The annual incidence varied between 1.2% and 1.5% and had a minor increasing trend of 0.01% per year (incidence rate ratio for 1-year increase = 1.01, $P < 0.001$, 95 % CI; 1.00 to 1.02), or 1 case/10 000 deliveries during the study period (Figure 2). There were 5756 case women who had more than one delivery during the study period, and 3047 of them (53%) had HG in their first pregnancy resulting in delivery during the study period; 2709 women (47%) did not. The women whose first pregnancy resulting in delivery included an HG diagnosis had 4301 deliveries during the study period after their first delivery (1.4 deliveries/woman) and the women whose first pregnancy resulting in delivery did not include an HG diagnosis had 4318 deliveries (1.6 deliveries/woman). 5366 case women had more than one pregnancy resulting in delivery with HG in at least one of them, permitting the analysis of recurrence of HG in the pregnancies following their first pregnancy diagnosed with HG and resulting in delivery. These women had 5066 pregnancies resulting in delivery following their first pregnancy diagnosed with HG and resulting in delivery, and 1125 of these pregnancies were diagnosed with HG. The recurrence rate of HG in subsequent pregnancies was thus 22%. There were 80 214 terminated pregnancies in 2005–2017, 509 of which included an HG diagnosis, and the incidence of HG in terminated pregnancies was thus 0.6%. Combined incidence of HG in pregnancies resulting in delivery and terminated pregnancies was 1.2%.

When comparing the case women's pregnancies diagnosed with HG and resulting in delivery (n = 9549) to the reference women's pregnancies resulting in delivery (n = 723 453), young maternal age (25 years or younger compared to reference group 26–30 years), higher gravidity, underweight, overweight, obesity, living alone, low socioeconomic status, living in larger municipalities, ART, multiple gestation and female sex of the fetus (both in singleton and multiple pregnancies) were associated with higher risk of HG. Higher maternal age (31 years or older compared to reference group 26–30 years) and smoking were associated with lower risk of HG. Parity was not associated with HG in univariable analysis and was excluded from the multivariable model due to collinearity with gravidity. (Table 1, Figure 3)

When comparing the case women's pregnancies diagnosed with HG and resulting in delivery (n = 9549) to their non-HG pregnancies resulting in delivery (n = 8385), higher maternal age (31 years or older compared to reference group 26–30 years), obesity (BMI $\geq$ 35 kg/m^2), living in

larger municipalities, ART, multiple gestation and female sex of the fetus were associated with higher risk of HG. Younger maternal age (25 years or younger compared to reference group 26–30 years), higher gravidity and higher parity, as well as smoking, when continued in the third trimester, and certain maternal occupation categories (blue collar worker, at home, or other compared to the reference category, upper level white-collar), were associated with lower risk of HG. Marital status was not associated with HG pregnancies. (Table 1, Figure 3)

Discussion

Our study was the first to investigate the incidence of HG in Finland. We found an average incidence of 1.3%, which fell inside the range observed in earlier register-based studies in various countries, between 0.3% and 3.6%.[1,3] Reasons behind the small observed annual increase of one case/10,000 deliveries are not known, and future follow-up of the incidence will be of interest. Recurrence of HG in subsequent pregnancies resulting in delivery, 22%, was comparable to our earlier results in a smaller data set, 24%.[18] As for associative factors, the HG pregnancies resulting in delivery differed both from pregnancies of women with no HG diagnosis and from the HG women's non-HG pregnancies resulting in delivery. The latter finding was a novel one. In both comparisons, living in larger municipalities, ART, multiple gestation and female sex of the fetus were associated with higher and smoking with lower risk of HG, whereas results about age, gravidity, parity, BMI, marital status and socioeconomic status differed between the comparisons.

Main strengths of our study are the high quality and coverage of the register-based data. In Finland, HG is mainly treated in hospitals and specialized clinics; Finland does not have a system based on independent general practitioners (private practitioners/family doctors), but instead primary health care is organized in health care centers. Women with HG are referred to specialized obstetric clinics, which are part of services provided by hospital districts. The health care registers are collected systematically throughout the country into centralized registers, data provision is obligatory and all hospitals use the same data collection protocols established by the Finnish Institute for Health and Welfare.[19] Validation studies have shown a high level of accountability and coverage of the register data.[20] Our population-level dataset with HG diagnoses including both outpatient data and hospitalizations, and during a 13-year study period, provided a good basis for analyses. As the Hospital Discharge Register permitted excluding all

HG patients from the reference group by defining the cases by the presence of HG diagnosis in any pregnancy, whether or not the pregnancy resulted in delivery, our study setting ensured an optimal reference group for the comparisons: none of the women in the reference group had had HG diagnosis in any of their pregnancies resulting in delivery in 2005–2017, nor in their pregnancies not resulting in delivery, nor in their earlier pregnancies. In our earlier study concerning recurrence of HG[18] we analyzed data of 1836 Finnish women diagnosed with HG, but as the data included only HG patients, and no reference women, and as the data collection period was short, the dataset was thereafter extended to its present range. Our data collection strategy permitted us to compare the case women's pregnancies resulting in delivery and diagnosed with HG not only to reference women's pregnancies resulting in delivery, but also to the case women's non-HG pregnancies resulting in delivery, enabling us to separately evaluate the effect of the associative factors both between different women and between the same women's different pregnancies. This grouping enabled us to find pertinent results which would have been unseen in a different setup.

The most important limitation in register-based data is the possibility that some severe vomiting cases may not have been diagnosed, if, for example, those women did not seek medical care, or if the symptoms had resolved by the time the women had an appointment. Thus, some HG cases may have been missed and the observed incidence can be considered a lower limit of the real incidence. The incidence of HG in terminated pregnancies was low. The relatively short duration of terminated pregnancies may lead to underdiagnosing of HG if the pregnancy is terminated before the HG symptoms become severe enough to call for outpatient treatment or hospitalization, and thus the most reliable way for calculating the incidence appears to be to use only pregnancies resulting in delivery. Further, taking spontaneous abortions into account in calculating the incidence would be of interest, but as there is no information about the spontaneous abortions, and the FMBR only includes pregnancies resulting in delivery, their effect could not be estimated in the present study setting. In addition, registers are not optimal for some research questions. For instance, to assess the study subjects' socioeconomic status, we used maternal occupation as a surrogate variable, although even if a person is registered eg as unemployed in the data, she may not have low income or other socioeconomic problems. Similarly, we used data about living with or without a partner to assess psychosocial support, even though living alone does not exclude the possibility of other support networks. Keeping

these limitations in mind, we chose these variables, since in a large scale, such as our dataset, they can be assumed to reflect the conditions reasonably well.

Our results fill an important gap concerning the incidence of HG in the Finnish population. One earlier study included data about HG in Finland in 1986, reporting that the proportion of women hospitalized due to HG was 0.7%, but the number of HG cases was only 62 women and only hospitalized patients were included,[21] and thus that study could not provide a full estimation of incidence. In Sweden and Norway, two Scandinavian countries fairly comparable with Finland, incidences between 0.9% and 1.1% have been reported using data of singleton births derived from the Swedish and Norwegian Medical Birth Registers.[22,23] In other countries, both low, eg 0.5% in the USA[24] and high incidences, eg 4.5% in Kuwait[25] have been reported. The different incidences probably stem from various reasons, such as varying symptom severity, different reporting, diversity in diagnostic criteria or data systems and cultural or genetic differences.[26] In Finland, the ICD-10 classification[7,8] is used, permitting compilation of diagnoses in centralized, nation-wide registers. Consensus about the definition of HG had not been reached until 2019, when the first consensus definition was presented in the Third International Colloquium on Hyperemesis Gravidarum (unpublished), and different inclusion and exclusion criteria have been implemented.[2,6] For instance, patients with late-onset HG symptoms are often excluded and thus typically only cases in early pregnancy are evaluated, and the cutoff to determine early pregnancy fluctuates considerably: some authors have referred to the entire first trimester,[27] others have set the limit earlier in the first trimester, eg to gestational week ten,[26] or extended the limit until gestational week 24[11] or 25[12] while others, like us, have not limited the timing of the symptoms.[13] In the Swedish and Norwegian register studies, O21.2 and O21.8 diagnoses were excluded,[22,23] whereas we included both. Our decision to include O21.2 diagnoses was based on our observation that even though the O21.2 diagnostic code criteria state symptoms starting after 22 completed weeks of gestation, it was not uncommon to receive this diagnosis even in cases when another O21 diagnosis was present earlier in the same pregnancy. Similarly, another cause of vomiting was sometimes not stated in association with O21.8 diagnosis, and after consulting with practicing clinicians, we chose to include all O21 diagnostic codes in order not to miss any cases and only excluded pregnancies where another cause of vomiting was found. In addition, this procedure ensured that the women with late onset HG would not end up in the reference group. However, as classification based on these diagnoses does not permit completely certain

identification of real HG pregnancies, it cannot be excluded that some of the pregnancies diagnosed with these diagnosis codes may not have been HG pregnancies and including them can also be considered a limitation. Nonetheless, we have chosen to include them in order to miss as few of the real HG cases as possible, erring rather on the side of inclusion than exclusion.

In our study, case women had their pregnancies resulting in delivery (both HG and non-HG pregnancies) at a younger age compared to the reference women, and the risk of HG appeared to diminish as age increased, the difference being most pronounced in the age group of 20 and younger. This is in line with previous literature.[11] However, when comparing the case women's HG pregnancies resulting in delivery to their non-HG pregnancies resulting in delivery, the relation turned out to be inverse: among the case women, the risk of HG was slightly lower in younger age compared to the reference age group of 26–30 years, and the risk increased after 31 years, being almost double among women 41 years or older. The reason for this phenomenon is not known, but this novel finding contrasts with earlier conceptions about the risk of HG diminishing with age: if a woman has susceptibility to HG, the risk may actually increase as age increases.

Our results shed valuable light on the association of gravidity and parity with HG. In previous studies, conflicting results about the effect of gravidity and parity have been found: some studies have found primiparous women to be at a higher risk of HG,[11,13,16] while others have found higher gravidity to be associated with higher risk.[17] Our results suggest that a crucial difference lies in the reference group: when compared to women who had never been diagnosed with HG, higher gravidity was associated with increased risk of HG. However, when case women's HG pregnancies resulting in delivery were compared to their non-HG pregnancies resulting in delivery, it turned out that the risk of HG diminished incrementally as gravidity and parity increased. The latter finding may indicate that the biochemical reactions leading to HG could be alleviated in subsequent pregnancies. Or, it can also be hypothesized that experiencing HG may affect family planning: women who have experienced recurrent HG after a first HG pregnancy may tend to avoid future pregnancies, or terminate a pregnancy in case of recurring HG, whereas those without recurring HG may end up having more pregnancies. The observed lower number of deliveries among our case women whose first pregnancy resulting in delivery during the study period was diagnosed with HG endorses this hypothesis. As terminated pregnancies are not

included in the FMBR, they remained outside the analysis, and the combined effect of these phenomena could result in the observed lower proportion of HG pregnancies in the higher gravidity categories. Testing these conjectures using the Register of Induced Abortions is not fully possible as the register had no cases where HG was an indication for termination. With the currently available data, the possibility that some HG pregnancies may have been terminated instead of carried out to delivery cannot be excluded. The decreasing risk of HG among women with previous pregnancies could also partly be due to active treatment of symptoms in HG women's subsequent pregnancies: if early symptoms are effectively managed, progression to HG may in some cases be avoided, which could lead to the observed lower risk of HG in the subsequent pregnancies.

In accordance with our results, both low and high BMI[12,28] have been associated with higher risk of HG. In addition, our analysis revealed that the difference in BMI lies predominantly between the case and reference groups: between case and reference groups, underweight, overweight and obesity were associated with HG, whereas only obesity was associated with HG when comparing the case women's HG pregnancies resulting in delivery and their non-HG pregnancies resulting in delivery. There are many factors, such as leptin and ghrelin levels, essential in the regulation of food intake and appetite[29] which may affect an individual woman's BMI and possibly her risk of HG.[30,31] Earlier results about smoking, too, agree with our findings: smokers have been shown to be less susceptible to HG,[11,12,27,32] possibly due to the detrimental effect of smoking on placental function.[33] Psychosocially insecure situations, such as living alone while pregnant, are reported to be associated with an elevated risk of HG,[34] and our results of the case vs reference comparison support this finding. Low socioeconomic status is associated with higher risk of HG according to several studies,[13,32,34,35] and the results are consistent despite methodological diversity: variables such as employment status,[32,34] level of education[35] or average price of housing in home address[13] have been applied for evaluating the socioeconomic status. We used maternal occupation in our analyses, and found the same effect when comparing the case women's HG pregnancies resulting in delivery to reference women's pregnancies resulting in delivery: women with higher-level occupation were at lower risk of HG. However, when comparing the case women's HG pregnancies resulting in delivery to their non-HG pregnancies resulting in delivery, the risk was lowest in those pregnancies when the women were at home. The data does not permit to discern whether this is due to an actual decrease of HG, or decrease of diagnosis, and the high proportion

of missing data in the FMBR concerning maternal occupation obliged us to exclude it from multivariable analysis and suggests that these results should be interpreted with caution. In our data, the women with HG were more often from communities with higher population count. Although one of the basic principles in Finnish health care system is equal access to health care, and referral from primary care to specialized care is equally available across the country, in small rural communities women may live relatively far from their nearest health care unit, potentially leading to limited access to health care and possible underdiagnosing. On the other hand, they may live closer to their relatives, allowing them to cope at home longer before seeking medical help, whereas women who have moved to bigger cities may have smaller support networks, compensated with better health care services availability. In accordance with our results, ARTs,[13] female fetus[14,15] and multiple fetuses[11,14] have been found to be associated to an increased risk of HG.

Conclusion

Incidence of HG in Finland was 1.3% and a small annual increase of 1 case/10 000 deliveries was observed between 2005 and 2017. Our extensive study setting provided detailed answers about risk factors of HG. We found that HG pregnancies differ both from pregnancies of women who have never been diagnosed with HG and from non-HG pregnancies of women who have been diagnosed with HG in at least one pregnancy. In the different comparisons, some factors such as ART, female sex of the fetus and multiple gestation were uniformly associated with higher risk of HG, but unforeseen inverse associations between age and gravidity and HG were found: when compared to reference women's pregnancies resulting in delivery, HG pregnancies resulting in delivery were more common in younger age groups and the risk of HG increased as gravidity increased, whereas when compared to case women's non-HG pregnancies resulting in delivery, HG was more common in the higher age groups and the risk decreased as gravidity increased. Together these results support the multifactorial etiology of HG.

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Tweetable abstract

Hyperemetic pregnancies differ both from pregnancies of women who have never been diagnosed with hyperemesis and from hyperemesis patients' other, non-hyperemetic pregnancies.

Tables

Table 1. Results from multivariable logistic regression. Associations between HG and maternal, environmental and pregnancy-related factors in pregnancies resulting in delivery, in two comparisons: 1) case women's pregnancies diagnosed with HG compared to reference group women's pregnancies and 2) case women's pregnancies diagnosed with HG compared to case women's non-HG pregnancies.

	Case group		**Reference group**	**Comparison 1: case HG vs reference pregnancies**		**Comparison 2: case HG vs case women's non-HG pregnancies**	
	Case women's HG pregnancies n = 9549	**Case women's non-HG pregnancies n = 8385**	**All pregnancies of the reference women, n = 723 453**	**Univariable analysis**	**Multivariable analysis[a]**	**Univariable analysis**	**Multivariable analysis[a]**
	n (%)	n (%)	n (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age (years)							
20 or younger	568 (6.0)	473 (5.6)	29 018 (4.0)	1.41 (1.30–1.52)	1.94 (1.77–2.12)	1.10 (0.98–1.26)	0.88 (0.76–1.02)
21–25	2228 (23.3)	2071 (24.7)	129 956 (18.0)	1.28 (1.23–1.34)	1.44 (1.38–1.52)	0.99 (0.92–1.07)	0.90 (0.83–0.97)
26–30	3176 (33.3)	2949 (35.2)	241 766 (33.4)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
31–35	2449 (25.7)	2077 (24.8)	214 044 (29.6)	0.86 (0.83–0.90)	0.79 (0.75–0.82)	1.10 (1.02–1.18)	1.22 (1.13–1.32)
36–40	960 (10.1)	706 (8.4)	91 792 (12.7)	0.77 (0.72–0.82)	0.66 (0.61–0.70)	1.26 (1.13–1.39)	1.59 (1.42–1.78)
41 or older	168 (1.8)	109 (1.3)	16 877 (2.3)	0.70 (0.61–0.81)	0.56 (0.48–0.66)	1.42 (1.10–1.82)	1.95 (1.50–2.53)
Gravidity (number of pregnancies, current pregnancy included)							
1	3135 (32.9)	1710 (20.4)	233 337 (32.3)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
2	2729 (28.6)	2279 (27.2)	217 204 (30.0)	1.00 (0.97–1.04)	1.11 (1.07–1.15)	0.63 (0.58–0.69)	0.60 (0.55–0.66)
3	1669 (17.5)	1695 (20.2)	129 136 (17.9)	1.02 (0.98–1.07)	1.23 (1.16–1.29)	0.52 (0.47–0.56)	0.47 (0.43–0.52)
4	925 (9.7)	1050 (12.5)	66 150 (9.1)	1.09 (1.03–1.15)	1.41 (1.32–1.51)	0.46 (0.41–0.51)	0.41 (0.36–0.46)
5 or more	1090 (11.4)	1644 (19.6)	77 159 (10.7)	1.15 (1.08–1.22)	1.60 (1.48–1.73)	0.35 (0.31–0.38)	0.28 (0.25–0.31)
Unknown	1	7	467				
Parity (number of pregnancies resulting in delivery, current pregnancy included)							
1	4265 (44.7)	2357 (28.1)	303 018 (41.9)	1 (Ref)		1 (Ref)	
2	3047 (31.9)	3006 (35.9)	244 370 (33.8)	0.98 (0.95–1.00)		0.52 (0.48–0.56)	
3	1367 (14.3)	1599 (19.1)	105 261 (14.6)	0.98 (0.93–1.03)		0.43 (0.40–0.48)	
4	473 (5.0)	703 (8.4)	36 185 (5.0)	0.98 (0.91–1.06)		0.36 (0.32–0.41)	
5 or more	394 (4.1)	713 (8.5)	34 175 (4.7)	0.94 (0.85–1.04)		0.29 (0.25–0.34)	
Unknown	3	7	444				
Pre-pregnancy body mass index (BMI), kg/m^2							
Less than 18.5	432 (4.8)	402 (4.9)	25 449 (3.6)	1.33 (1.22–1.46)	1.21 (1.10–1.34)	0.96 (0.85–1.10)	0.96 (0.83–1.10)
18.5–24.9	5363 (58.23)	4703 (57.8)	435 726 (62.3)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
25–29.9	2076 (22.4)	1812 (22.4)	152 360 (21.8)	1.10 (1.05–1.16)	1.15 (1.09–1.21)	1.00 (0.93–1.07)	1.04 (0.97–1.12)
30–34.9	905 (9.7)	806 (10.0)	57 602 (8.2)	1.25 (1.17–1.34)	1.33 (1.24–1.43)	0.98 (0.89–1.08)	1.07 (0.97–1.19)
35 or more	462 (4.9)	396 (5.0)	28 615 (4.1)	1.29 (1.18–1.42)	1.41 (1.28–1.56)	0.99 (0.86–1.13)	1.16 (1.01–1.33)

Unknown	301	276	23 701				
Smoking during pregnancy							
No	8350 (89.7)	7129 (87.7)	596 643 (84.7)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Yes, but quit in 1st trimester	448 (4.8)	385 (4.7)	40 475 (5.7)	0.80 (0.74–0.87)	0.70 (0.64–0.76)	0.98 (0.86–1.11)	1.05 (0.92–1.21)
Yes, continued after 1st trimester	511 (5.5)	615 (7.6)	67 150 (9.5)	0.57 (0.52–0.62)	0.44 (0.40–0.48)	0.71 (0.64–0.79)	0.85 (0.75–0.96)
Unknown	236	260	19 185				
Marital status							
Living with partner	8516 (93.8)	7546 (93.5)	650 552 (94.5)	1 (Ref)		1 (Ref)	
Living alone	566 (6.2)	520 (6.5)	38 184 (5.5)	1.08 (1.00–1.17)	1.11 (1.03–1.21)	0.96 (0.85–1.08)	1.01 (0.89–1.14)
Unknown	462	324	34 717				
Socioeconomic status							
Upper level white-collar	959 (16.5)	776 (15.1)	102 012 (21.9)	1 (Ref)		1 (Ref)	
White collar	2377 (41.1)	2051 (39.7)	189 595 (40.7)	1.35 (1.25–1.46)		0.92 (0.83–1.02)	
Blue collar	852 (14.7)	800 (15.6)	75 167 (16.1)	1.22 (1.11–1.35)		0.84 (0.74–0.94)	
At home[b]	422 (7.8)	493 (9.4)	25 413 (5.5)	1.81 (1.61–2.03)		0.67 (0.57–0.78)	
Other[c]	1143 (19.9)	1047 (20.2)	73 602 (15.8)	1.65 (1.51–1.80)		0.86 (0.77–0.97)	
Unknown	3711	3303	257 664				
Municipality population							
Fewer than 10 000 inhabitants	1333 (13.9)	1452 (17.5)	122 886 (17.1)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
10 000–99 999 inhabitants	4062 (42.5)	3697 (44.5)	322 268 (44.8)	1.14 (1.07–1.21)	1.19 (1.11–1.27)	1.21 (1.11–1.31)	1.15 (1.06–1.25)
100 000 inhabitants or more	4118 (43.6)	3178 (38.0)	274 496 (38.1)	1.31 (1.23–1.40)	1.47 (1.37–1.57)	1.42 (1.30–1.54)	1.31 (1.20–1.42)
Unknown	35	59	3803				
Assisted reproductive technology (ART)							
No	9223 (96.6)	8251 (98.4)	706 218 (97.6)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Yes	326 (3.4)	134 (1.6)	17 235 (2.4)	1.34 (1.21–1.49)	1.47 (1.33–1.63)	2.19 (1.81–2.64)	1.44 (1.21–1.71)
Number of fetuses							
1 fetus	9244 (96.8)	8310 (99.1)	713 163 (98.6)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
2 or more fetuses	305 (3.2)	75 (0.9)	10 290 (1.4)	2.03 (1.83–2.24)	2.04 (1.83–2.28)	3.31 (2.63–4.15)	2.90 (2.28–3.68)
Sex of the fetus, all pregnancies							
Male	4388 (46.0)	4359 (52.0)	370 094 (51.2)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Female	5161 (54.0)	4026 (48.0)	353 331 (48.8)	1.19 (1.16–1.23)	1.20 (1.16–1.24)	1.24 (1.17–1.32)	1.26 (1.18–1.34)
Unknown			26				
Sex of the fetus, singleton pregnancies							
One fetus, male	4266 (46.1)	4321 (52.0)	364 888 (51.2)	1 (Ref)		1 (Ref)	
One fetus, female	4978 (53.9)	3989 (48.0)	348 249 (48.8)	1.18 (1.15–1.22)		1.24 (1.17–1.32)	
Unknown			26				
Sex of the fetuses, multiple gestation							
>1 fetus, all males	71 (23.3)	31 (41.3)	3445 (33.5)	1 (Ref)		1 (Ref)	
>1 fetus, all females	122 (40.0)	21 (28.0)	3368 (32.7)	1.66 (1.27–2.16)		2.52 (1.39–4.60)	
>1 fetus, both sexes	112 (36.7)	23 (30.7)	3477 (33.8)	1.49 (1.14–1.95)		2.12 (1.16–3.90)	

HG, Hyperemesis gravidarum

[a] Multivariable analysis, included in the model: Age, gravidity, pre-pregnancy BMI, smoking, marital status, municipality population, ART, number of fetuses, sex of the fetus. Socioeconomic status excluded from the multivariable analysis due to high proportion of missing data. Parity excluded from the multivariable analysis due to collinearity with gravidity. Sex of the fetus, singleton pregnancies and sex of the fetuses, multiple gestation excluded from the multivariable analysis due to collinearity with the sex of the fetus in all pregnancies.

[b] Socioeconomic status, At home: Unemployed, retired, stay-at-home mother.

[c] Socioeconomic status, Other: Entrepreneur, student, other.

Figures

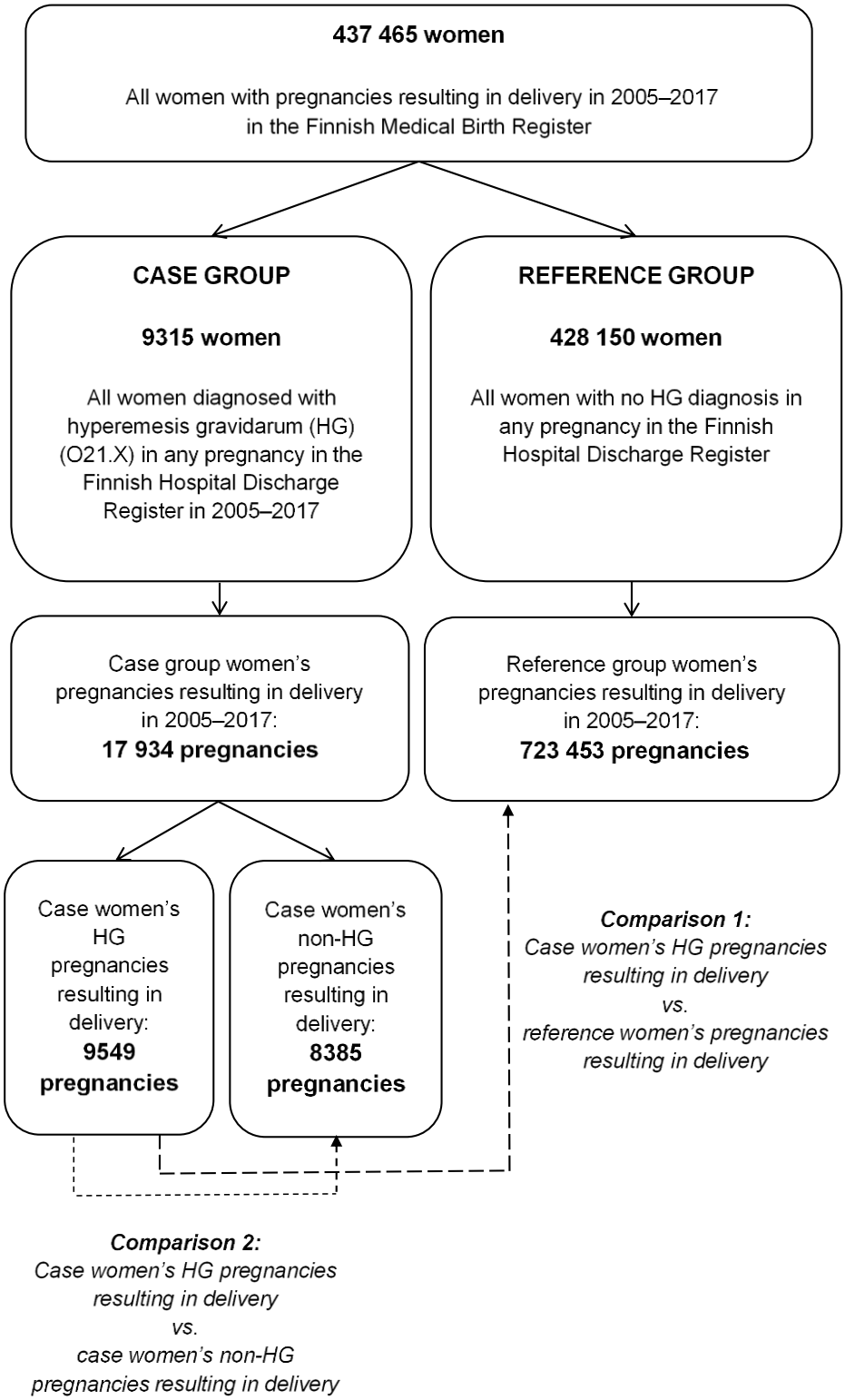

Figure 1. Flowchart of the study.

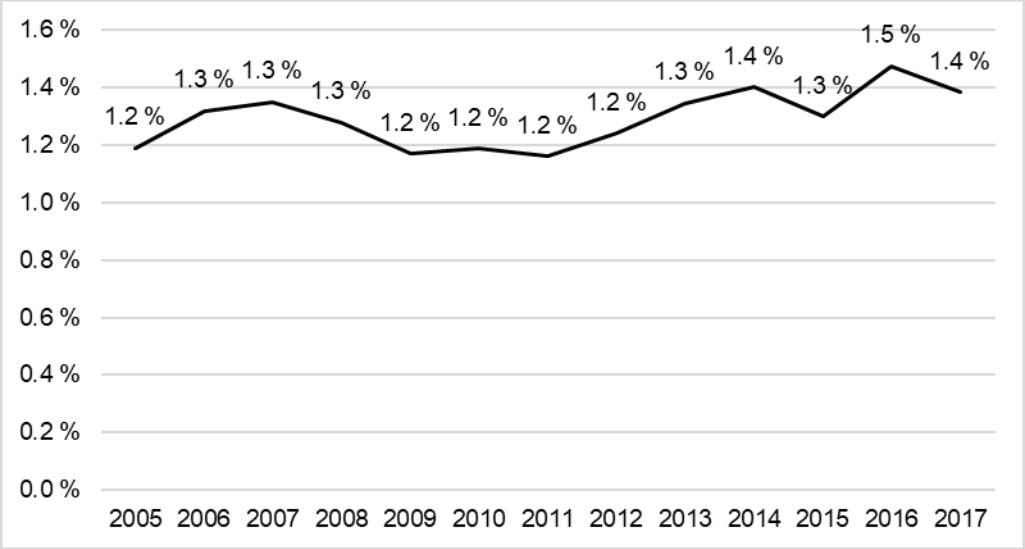

Figure 2. Annual incidences of hyperemesis gravidarum in Finland, 2005–2017.

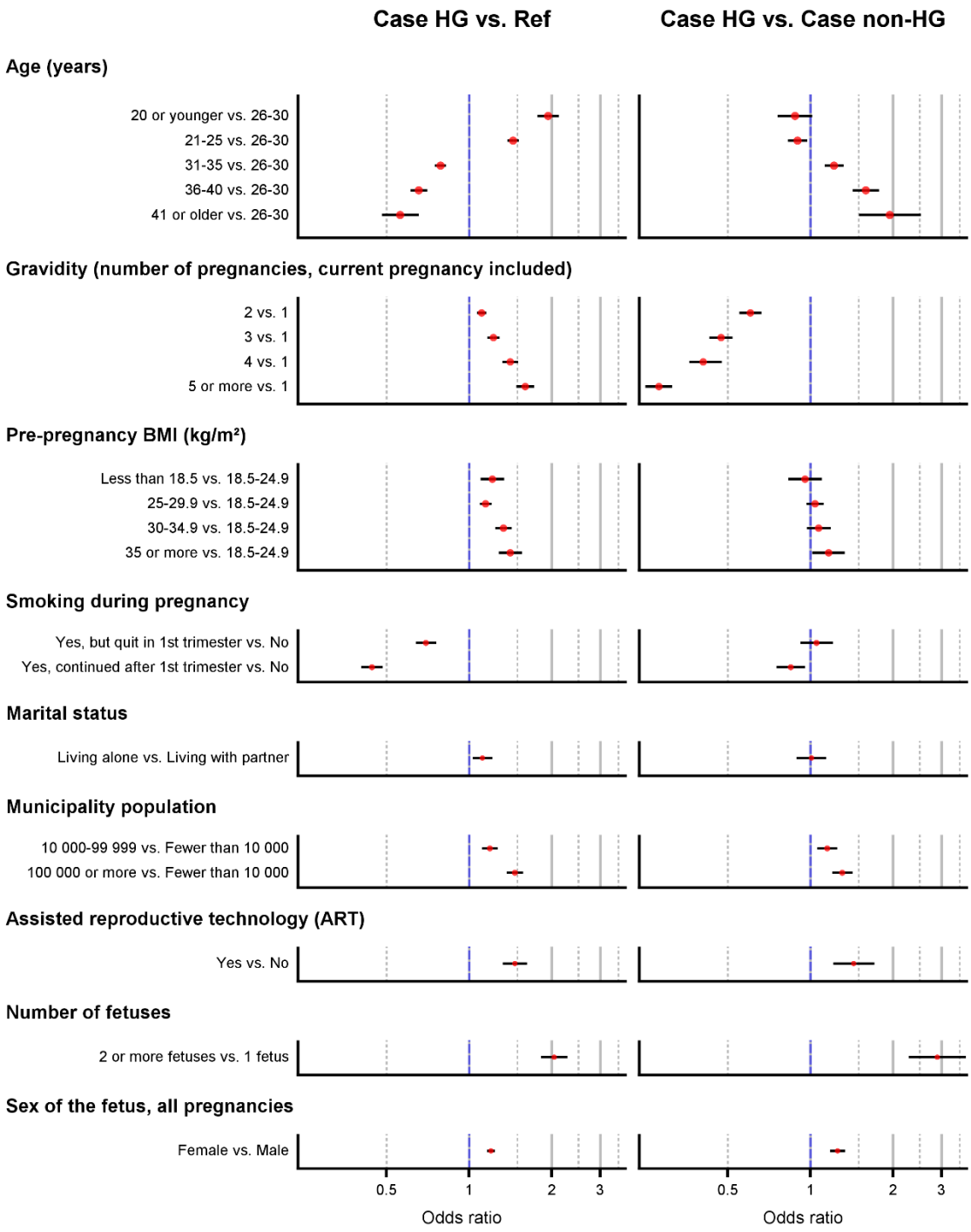

Figure 3. Summary of odds ratios and their 95% confidence intervals from multivariable models for pregnancy comparisons: 1) Case women's HG pregnancies resulting in delivery vs reference women's pregnancies resulting in delivery and 2) Case women's HG pregnancies resulting in delivery vs their non-HG pregnancies resulting in delivery.

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