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REVIEW ARTICLE

# RISK FACTORS OF HYPEREMESIS GRAVIDARUM: META-ANALYSIS FROM RETROSPECTIVE COHORT STUDIES

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**ABSTRACT**

*Hyperemesis gravidarum (HG) is a pregnancy condition characterized by prolonged and severe nausea and vomiting of pregnancy, which causes dehydration and weight loss that requires extensive medical care and hospital admission. Studies of hyperemesis were limited in statistical power and generalizability as a result of being facility-based and relatively small in size. This study aimed to investigate the factors associated with HG among pregnant women. It systematically reviews articles published in PubMed, EMBASE, and Science Direct databases. Statistical analysis was carried out by Review Manager 5.3 (RevMan 5.3). Three hundreds and eighteen studies were found in the databases, and 6 of them met the qualifications. The results of this meta-analysis suggested that mothers with female baby (OR= 1.25; 95% CI: 1.20-1.31), with a previous history of HG (OR= 5.38; 95% CI: 1.10-26.36), multiparity (OR = 1.07; 95% CI: 0.94-1.22), with more than 1 fetus (OR= 2.13; 95%CI: 1.95-2.33), and underweight (OR= 1.19; 95%CI: 1.10-1.28) have higher risk to HG compared to those with male baby, without previous history of HG, primipara, single fetus, and normal BMI respectively. In addition, smoking mothers have a lower risk of HG compared to those who have never had a cigarette (OR= 0.69; 95%CI: 0.31-1.54). Finally, it suggested that mothers with female baby, history of previous HG, multiparity, underweight, and multi-baby are risk factors of HG. Meanwhile, smoking is perceived to be protective factors of HG.*

***Keywords***: *cohort, hyperemesis gravidarum, nausea, risk factors, vomiting of pregnancy.*

## INTRODUCTION

Nausea and vomiting of pregnancy (NVP) is a frequent symptom that affects up to 70% of pregnant women[1]. It is common and usually begins at 6–8 weeks of gestation and generally resolves by 16–20 weeks[2]. The tenth edition of International Statistical Classification of Disease and Related Health Problems defines hyperemesis gravidarum (HG) as persistent and excessive vomiting starting before the end of the 22nd week of gestation and further subdivides the condition into mild and severe, with severe being associated with metabolic disturbances, such as carbohydrate depletion, dehydration, or electrolyte imbalance[3]. According to a study by Rosebo[illegible]n et al. (2011)[4], hyperemesis gravidarum occurs in 0.5–3% of pregnancies and is the most frequent reason for hospitalization in the first half of the pregnancy.

Women with HG are at risk of problems, such as hematemesis and dehydration, which can cause dizziness and syncope. Women with HG are at increased risk of developing secondary depression and anxiety usually subsides with nausea/vomiting remission by the third trimester of pregnancy. A Norwegian cohort study of 2,270,363 births found a decreased risk of very preterm birth (<32 weeks gestation) born to women without HG[5-10]. Compared to unexposed newborns, HG is related with minor reductions in 21.4 g and gestational length (0.5 days). It has been linked to an increase in the number of low birth weight and small for gestational age newborns[9,11-14].

Hyperemesis patients commonly have multiple pregnancies and molar pregnancies[14]. Other risk factors for hyperemesis include older maternal age, genetic susceptibility, high parity, ethnicity, marital status, smoker, unplanned pregnancies, depression or psychiatric illness, less socioeconomic status, previous history of hyperemesis, pre-existing diabetes, high body mass index, asthma, hyperthyroid disorders, female fetus, dysmenorrhea, urinary tract infections, peptic ulceration, and other gastrointestinal disorders[15-18].

Hyperemesis gravidarum is associated with adverse pregnancy outcomes. It is a frequent pregnancy complication that has been linked to a variety of risk factors, such as trophoblastic infection, HG from a previous pregnancy, and fetal anomalies such triploid, trisomy 21, and hydrops fetal[19]. This is mostly explained by differences in maternal features. Given the impact of the early environment on later health, studies that aim to assess the maternal risk

factors of hyperemesis gravidarum need to be given high priority. Therefore, the current study aimed to assess the maternal factors associated with the hyperemesis gravidarum among pregnant women.

## METHODS

This study employed meta-analysis according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

### Inclusion and exclusion criteria

We included studies describing or reporting any diagnostic criteria for HG. Only observational, peer-reviewed English-language published studies were included, without any limitation in the date of publication and geographical location. Studies were eligible for inclusion if they reported that the sample was characterized or diagnosed with HG and if they reported an association focusing on risk factors for etiology of hyperemesis gravidarum and representing the general population of pregnant women.
Studies written in any language other than English were excluded. RCTs, experimental animal studies, reviews, meta-analyses, case reports, letters, commentaries, research protocols, and editorials were also excluded.

### Search strategy

Studies by an electronic search of PubMed, EMBASE and Science Direct, defining published articles in the targeted journals were detected. The following filters were used: "hyperemesis gravidarum"[MeSH Terms] OR ("hyperemesis"[All Fields] AND "gravidarum"[All Fields] OR "hyperemesis gravidarum"[All Fields]) OR "Morning Sickness"[Mesh] OR "Nausea"[Mesh] OR "Vomiting"[Mesh] OR "hyperemesis"[tiab] AND "gravidarum"[tiab] OR "hyperemesis gravidarum"[tw]. "risk factors"[MeSH Terms] OR ("risk"[All Fields] AND "factors"[All Fields]) OR "risk factors"[All Fields] OR "determinants" [All Fields] OR "Epidemiologic Factors"[Mesh] OR "predictors" [All Fields] OR "associated factors"[Mesh] OR "associated risk factors" [All Fields].

### Study selection

Based on eligibility and exclusion criteria, the titles and abstracts were independently reviewed by researchers, and full texts of potentially relevant studies were obtained for further assessment. Disagreements among reviewers were resolved by consensus.

### Data extraction

Data extraction for eligible studies was independently performed by authors using a predesigned piloted extraction form. Data extraction for each study included: first author, year of publication, study location, study design, sample size, duration of the study, and results of the risk factors analyzed in aOR with 95% Confidence Intervals.

### Quality assessment

The quality of the included studies was evaluated by the authors using the Newcastle Ottawa Scale (NOS) for non-randomized studies. The NOS checklist assesses the quality of studies across three categories: selection of the study groups; comparability of the groups; and ascertainment of either the exposure or outcome of interest for cohort studies. The minimum score of the NOS "star system" is 0 and the maximum score is 9. We rated the quality of the studies according to the number of stars; low scores indicated low quality and a high risk of bias. The studies with a score of <6 stars were considered low quality; studies with a score of 6-7 stars were considered moderate quality, and studies with a score of >7 stars were considered high quality. Information on the quality assessment of the included studies is provided in table 2.

### Statistical Analysis

By utilizing Review Manager (REVMAN) 5, statistical analysis was performed to inspect the determinants of HG. Extracted data, including the hazard ratio and CI 95% were transferred into REVMAN. The effect size was calculated as an adjusted odds ratio (aOR) with a confidence interval of 95% and a two-sided p-value less than 0.05, signifying a statistical significance difference between groups. The pooled odds ratio was utilized to estimate the association between risk factors and HG. The heterogeneity between studies was measured statistically by using the intuitive index ($I^2$). An intuitive index is a total variation across studies that describe the percentage because of heterogeneity instead of the error of the sample[20,21]. An $I^2$ value of more than 50% indicates a substantial heterogeneity level[21]. Random effect analysis models are used if heterogeneity is detected by more than 50%[22]. Publication bias was assessed by funnel plot asymmetry test. The symmetrically distributed shape of funnel plots indicates no potential publication bias; otherwise, the asymmetrical shape of funnel plots signifies potential publication bias[23].

## RESULTS

A total of 318 studies were identified through a systematic search. After the exclusion of duplicates (n 127), the remaining 191 studies were screened. After exclusions of the title or abstract of the paper, or of review articles, and not English-language papers, 11 full-text studies remained to be assessed. Out of these, 5 studies were excluded because not cohort studies and the effect size unmatched with others variable resulting in 6 studies for inclusion in this meta-analysis. Figure 1 shows the Prisma flow diagram of the selection process.

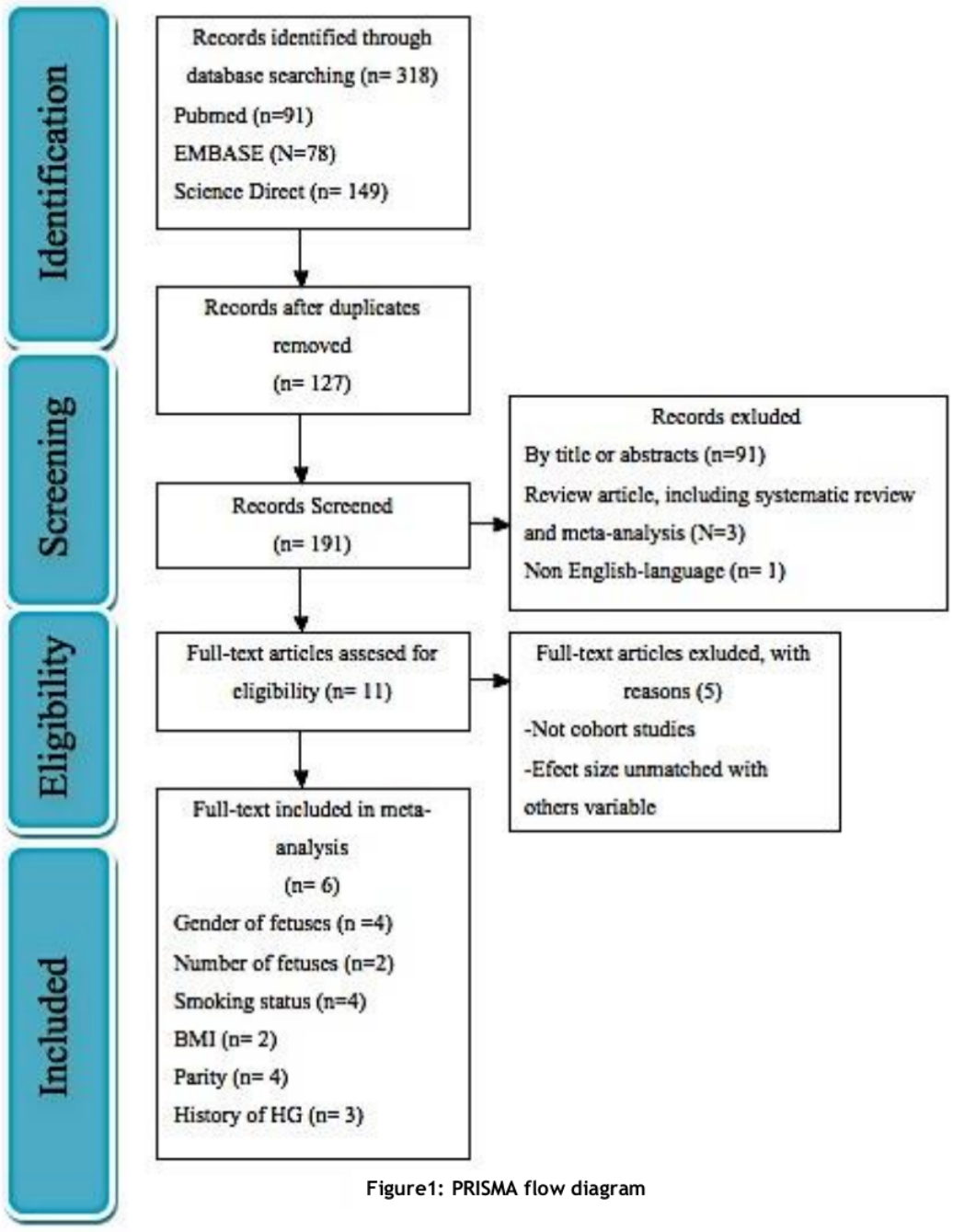


**Figure1: PRISMA flow diagram**

### Characteristics of the included studies

A summary of the characteristics and findings of the included studies is presented in Table 1. The 6 included studies were published between 2005 and 2021. Three studies were conducted in Norway, one in the UK, one in South Korea, and one in Finland. All were cohort-designed studies. Two were population-based retrospective cohort studies[24,25], one had been derived from the Korean National Health Insurance (KNHI) claims database[26], one from patient discharge data linked to a birth cohort data set[35], one from hospital records of admissions and outpatient appointments[27], and two from a health care register[28,29]. The total sample sizes of the studies included in this meta-analysis were 1,375,809 pregnant women. Studies used diverse definitions for HG. One study utilized the 8th version of International Classification of Disease (ICD)[29], three studies used the 10th version[26–28], and two studies used a definition proposed by MoBa data[24,25]. Relatively, in terms of the total quality score according to our definition, 2 studies were of high quality, and 4 were moderate (Table 2).

### Risk Factors of HG among Pregnant Women

The results of meta-analysis for the association between some of the risk factors and HG among pregnant women are summarized in Table 3 and presented as a forest plot in Fig.2. Mothers with a female baby were more likely to experience HG compared to those who have a male baby (OR= 1.25; 95%CI: 1.20–1.31). Mothers with a previous history of HG in their past pregnancy also experienced the same compared to those without previous history of HG (OR= 5.38; 95% CI: 1.10–26.36). Mothers with multiparity had more risk of HG than those with primipara (OR = 1.07; 95% CI: 0.94–1.22). Underweight mothers also had more risk to HG compared to those with normal BMI (OR= 1.19; 95% CI: 1.10–1.28). Mothers with more than 1 fetus also had more risk to HG than single fetus mothers (OR= 2.13; 95% CI: 1.95–2.33). And lastly, oddly mothers with current smoking status had a lower risk of HG compared to those who never smoked (OR= 0.69; 95% CI: 0.31–1.54). Some of the results were statistically significant (gender of fetuses, number of fetuses, and BMI) and used random effects (gender of fetuses, history of HG, parity, and smoking status).

### Publication Bias

We assessed the funnel plot in analysis, and overall, it did not show any substantial asymmetry (Fig. 3) although some of it had a significant difference value of standard errors indicating the difference in sample size.

All figures and tables were presented in appendices.

## DISCUSSION

Although there is a rapidly growing interest in assessing the risk factors of HG in pregnant women, it remains unclear with certain risk factors influencing the incidence of HG in pregnant women. In addition, to our knowledge, this meta-analysis is currently the only one to discuss this issue. However, some previous systematic reviews have been published to discuss the same matter. One of them is published in 2010 by Fan and Jacobsen40. This study includes 43 studies, suggesting that low pre-pregnancy weight, helicobacter pylori infection, a history of hyperemesis gravidarum in the previous pregnancy, and carrying a female fetus appear to be risk factors for hyperemesis gravidarum. The associations between HG and maternal age, gravidity, and parity, have not been studied. This study included 6 cohort studies involving 1,375,809 pregnant women with sufficient statistical power. It was designed to summarize the epidemiologic evidence on the association of some risk of HG in pregnant women. A complete and systematic literature search was performed. An improved understanding of this issue may have prominent clinical implications, especially the modifiable risk factors, e.g. BMI and smoking status for preconception counseling for women or therapy for women currently suffering from HG.

The current study found that women who have female infants, are underweight, have multiparity, have more than one fetus, and have HG in the previous pregnancy exhibit considerably elevated odds of HG. Meanwhile, smoking status decreases the risk of HG among pregnant women. It affirms the finding that women with HG in one pregnancy are more likely to report HG in subsequent pregnancies[19,31]. The low pre-pregnancy BMI of the mother increases the risk of hyperemesis gravidarum[32,33]. HG in previous pregnancies is a significant risk factor for HG in the present pregnancy[34,35]. There found a report of a female predominance among the offspring of mothers with HG[36]. Compared to singleton pregnancy, multiple fetuses are associated with a statistically significant increased risk of hyperemesis[14,38]. Contrary to the previous research, this study suggested that smoking decreases HG. It affirms that maternal smoking was associated with decreased risk HG[38]. The quality of the cohort data in primary studies may not be accurate for some variables, especially for a sensitive behavior, such as smoking, and would affect the results of these risk factors influencing HG. Another plausible reason is that the prevalence of smoking respondents in studies population that suggest lower risk is much lower than those in other studies that suggest higher risk. However, this study suggested to carefully consider that many complication could occur during pregnancy because of smoking, such as sudden infant death

syndrome, asthma, stillbirth, low birth weight, and obesity amongst infants[39].

**Strengths and limitations**

This study included a large number of participants, thus providing sufficient statistical power to address the risk factors of HG among pregnant women. However, further evaluation needs to be performed due to the potential bias and evidence of heterogeneity. Furthermore, the evaluation of the eligibility of the identified studies was based on predefined criteria and conducted independently by the researchers. In addition, our meta-analysis did not only cover one risk factor of HG but considered six. Several limitations also need to be acknowledged: first of all, the number of primary studies included in this study is limited; secondly, we did not conduct a subgroup analysis which might help the figuration of more significant factors regarding HG. In addition, the literature search was carried out only over three databases written in English, which potentially missed relevant information. We were also aware that there might be other risk factors of HG, were not covered in this study because of the lack of statistical data. Lastly, estimation was highly heterogenous ($I^2$: from 75% to 100%), except for the estimated associations with BMI ($I^2$ = 0%) and the number of fetuses ($I^2$ = 46%). However, we only included cohort-design studies, which reduced recall and selection bias.

## CONCLUSION

In conclusion, this study demonstrated that the existing evidence is sufficient to determine the risk factors of HG among pregnant women. While the research activity regarding HG is intense, studies with more determinants are highly required. It suggested future studies with more determinants of HG, especially on modifiable determinants, appropriate design, using pregnancy and birth data, preferably not self-reported, examining various confounders and adjusting for them in multivariable models. Future high-quality research may likely challenge the current conclusions.

**Conflict of interests**

The authors declare no potential conflict of interest.

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Appendix

**Table 1a. Summary of the characteristics of the studies included**

| No | Author (Year) | Study Location | Study Design | Sample Size (Deliveries/ Pregnancies | Duration | Outcome |
|---|---|---|---|---|---|---|
| **1.** | Fiaschi et al. (2016) | UK | Cohort | 8,215,538 | 1997-2012 | • **Number of fetuses**<br>1 Ref<br>>3 2.33 1.99–2.72<br>• **Parity**<br>Primipara ref<br>Multi 0.90 (0.89–0.91)<br>• **Gender**<br>Singleton male Ref<br>Singleton female 1.23 (1.22–1.25)<br>Multiple males 2.02 (86.3–2.18)<br>Multiple females 2.41 (2.24–2.59)<br>Multiple mixed 2.43 (2.28–2.60)<br>• **History of HG** 4.74 (4.46–5.05) |
| **2.** | Kim et al. (2021) | South Korea | Cohort | 216,373 | 2013-2015 | • **Parity**<br>Primipara ref<br>Multipara 1.18 (1.06-1.30)<br>• Neonatal gender-female 1.34 (1.23-1.46)<br>• **Smoking history**<br>Never Ref<br>Current 0.77 (0.58-1.02)<br>• **Pre-pregnancy BMI (kg/m2)**<br>>18.5 (1.16 (1.03-1.31)<br>Normal Ref<br>>25 1.04 (0.87- 1.24) |
| **3.** | Kjeldgaard et al. (2017) | Norway | Cohort | 81,786 | 1998-2008 | • **Parity**<br>Primipara Ref<br>Multipara 1.43 (1.20-1.69)<br>• **Pre-pregnancy BMI** 1.02 (1.00-1.04)<br>• **Smoking Status**<br>No Ref<br>Yes 0.46 (0.37-0.56)<br>• **Sex of the child**<br>Boy Ref<br>Girl 1.50 (1.28-1.76) |

Table 1b. Summary of the characteristics of the studies included

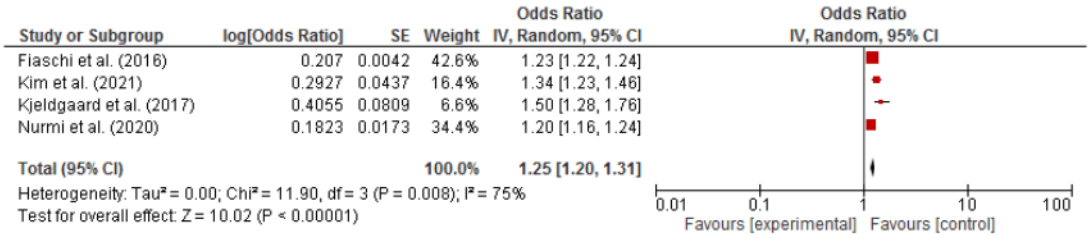
| | | | | | | |
|---|---|---|---|---|---|---|
| **4.** | **Kjeldgaard-2 et al. (2017)** | **Norway** | **Cohort** | **92,947** | **1998-2008** | • **Parity**<br>**Primi Ref**<br>**Multi 0.97 (0.92-1.02)**<br>• **Smoking Status**<br>**No Ref**<br>**.Yes 1.48 (1.42-1.56)**<br>• **History of HEG**<br>**No Ref**<br>**Yes 1.26 (1.19-1.33)** |
| **5.** | Nurmi et al. (2020) | Finland | Cohort | 437,465 | 2005-2017 | • **Pre-pregnancy BMI**<br><18.5 1.21 (1.10-1.34)<br>18.5-24.9 Ref<br>25-29.9 1.15 (1.09-1.21)<br>30-34.9 1.33 (1.24-1.43)<br>>35 1.41 (1.28-1.56)<br>• **Smoking Status**No Ref<br>Stop 0.70 (0.64-0.76)<br>Current 0.44 (0.40-0.48)<br>• **Number of fetus**<br>1 Ref<br>>2 2.04 (1.83-2.28)<br>• **Sex the fetus**<br>Male Ref<br>Female 1.20 (1.16-1.24) |
| **6.** | Trogstad et al. (2005) | Norway | Cohort | 547,238 | 1967-1998 | • **History of HEG** 26.08 (23.94-28.42)<br>**No** Ref<br>**Yes** 26.08 (23.94-28.42) |

Table 2. Summary of the quality assessment of the included studies

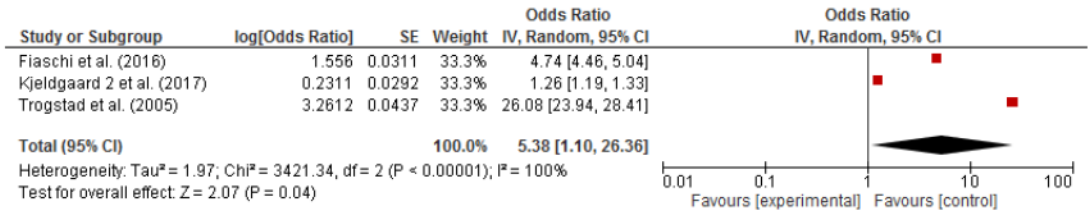
| No | Studies | Selection | | | | Comparability | Outcome | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Representativeness of the exposed cohort | Selection of the non exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | Comparability of cohorts on the basis of the design or analysis controlled for confounders | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts | Total score/ Quality |
| 1 | Fiaschi et al. (2016) | b1 | a1 | a1 | b0 | b1 | b1 | a1 | a1 | 7 |
| 2 | Kim et al. (2021) | b1 | a1 | b1 | b0 | b1 | a1 | a1 | a1 | 7 |
| 3 | Kjeldgaard et al. (2017) | a1 | a1 | a1 | b1 | b1 | b1 | a1 | a1 | 8 |
| 4 | Kjeldgaard-2 et al. (2017) | a1 | a1 | a1 | b1 | b1 | b1 | a1 | a1 | 8 |
| 5 | Nurmi et al. (2020) | a1 | a1 | a1 | b0 | b1 | b1 | a1 | a1 | 7 |
| 6 | Trogstad et al. (2005) | a1 | a1 | a1 | b0 | b1 | b1 | a1 | a1 | 7 |

Table 3. Summary of pooled meta-analysis of the association between risk factors and HG among pregnant women

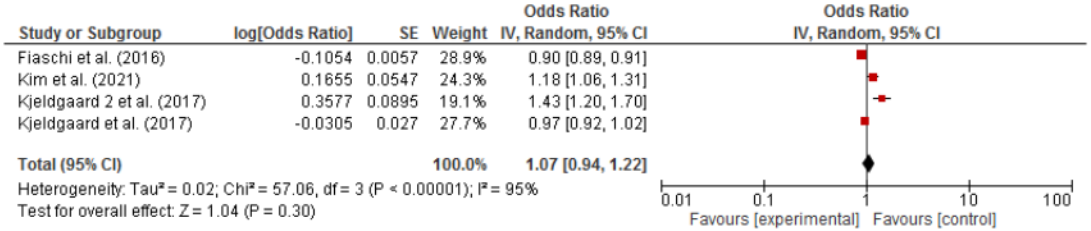
| Risk Factors | Number of Included Studies | Sample sizes | Pooled aOR (95%) | p-value | Heterogeneity | $I^2$ | p-value |
|---|---|---|---|---|---|---|---|
| **Gender of fetuses** | 4 | 8,987,164 | 1.25 (1.20-1.31) | <0.00001 | Random | 75% | 0.008 |
| **History of HG** | 3 | 8,855,723 | 5.38 (1.10-26.36) | 0.04 | Random | 100% | <0.00001 |
| **Parity** | 4 | 8,606,644 | 1.07 (0.94-1.22) | 0.30 | Random | 95% | <0.00001 |
| **Smoking Status** | 4 | 828,571 | 0.69 [0.31-1.54] | 0.37 | Random | 100% | <0.00001 |
| **Number of fetuses** | 2 | 8,653,003 | 2.13 (1.95-2.33) | <0.00001 | Fixed | 46% | 0.17 |
| **BMI** | 2 | 653,838 | 1.19 (1.10-1.28) | <0.00001 | Fixed | 0% | 0.59 |



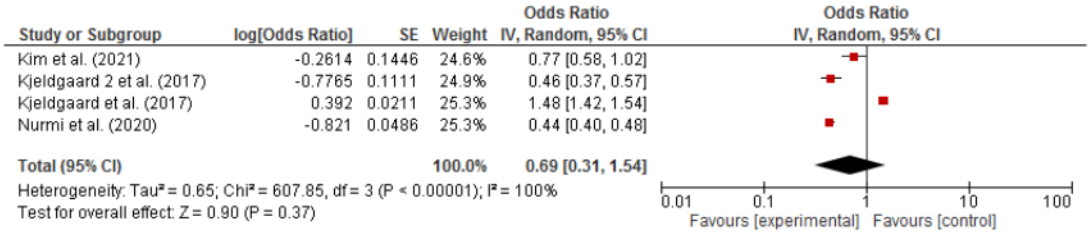

Gender of fetuses



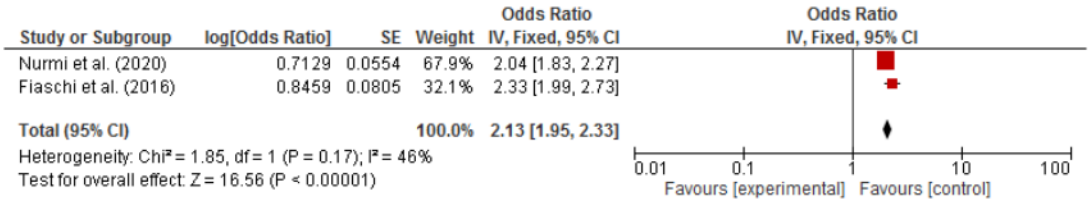

History of HG



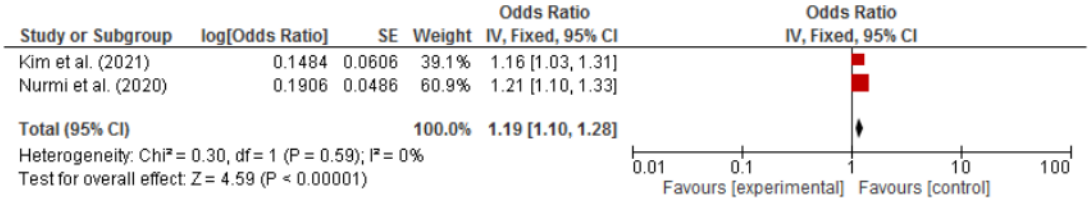

Parity




Smoking Status

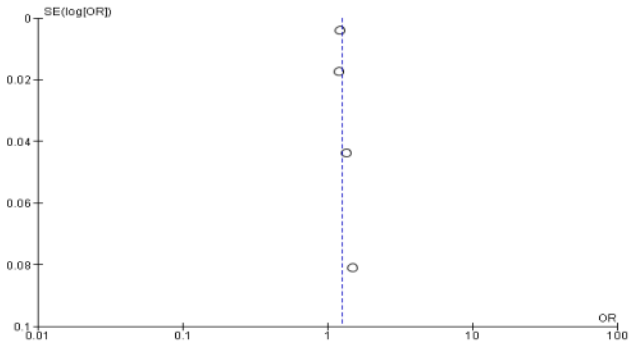



Number of fetuses

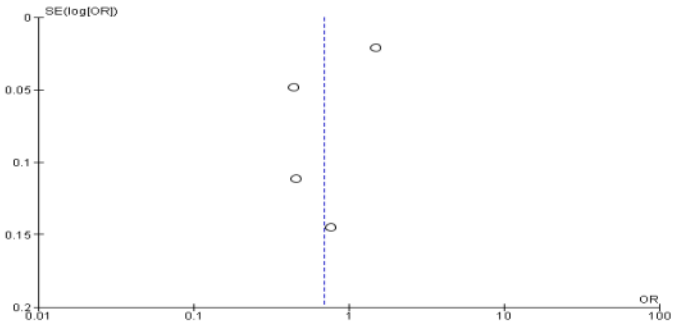



BMI (underweight)

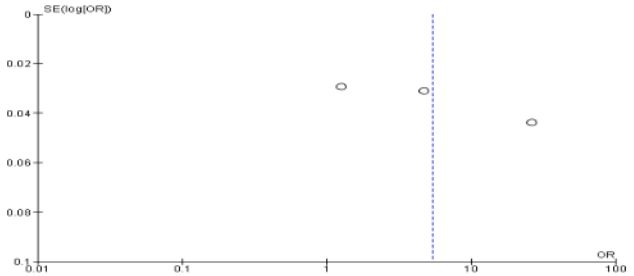
Fig. 2 Forest plot for risk factors of HG among pregnant women



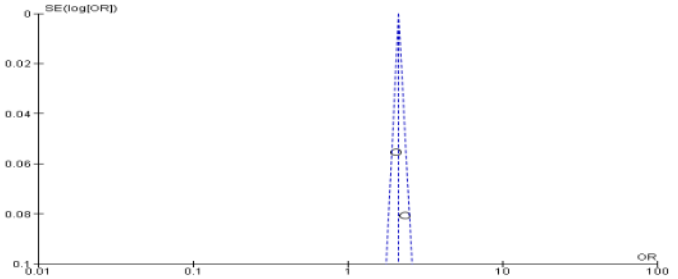

Gender of fetuses



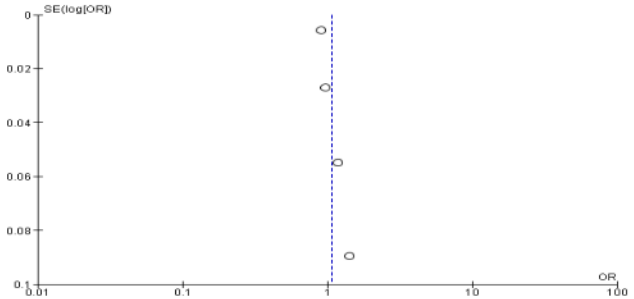

Smoking Status




History of HG

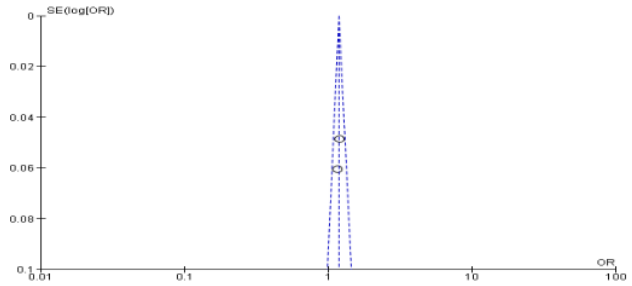



Number of fetuses




Parity

Fig. 3 Funnel plot for risk factors of HG among pregnant women




BMI

Fig. 3 Funnel plot for risk factors of HG among pregnant women

# RISK FACTORS OF HYPEREMESIS GRAVIDARUM: META-ANALYSIS FROM RETROSPECTIVE COHORT STUDIES

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