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Systematic Review

Pre-Pregnancy Body Mass Index and the Risk of Hyperemesis Gravidarum: A Systematic Review and Meta-Analysis

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Abstract

Background: Hyperemesis gravidarum (HG) is an infrequent and severe occurrence of nausea and/or vomiting during pregnancy, with a prevalence ranging from 0.3% to 2%. Until now, no meta-analytic study has been undertaken to assess the correlation between pre-pregnancy body mass index (BMI) and the likelihood of HG. Consequently, this meta-analysis was carried out to examine the connection between BMI and HG risk. **Methods**: For this systematic review and meta-analysis, we conducted a thorough search of electronic bibliographic databases such as PubMed, Web of Science, Scopus, and Science Direct until May 2022. The outcomes were presented utilizing a random-effects model. Heterogeneity was assessed using the chi-square test and I^2 statistic. Potential publication bias was examined using Begg's test. Additionally, we evaluated the quality of studies using the Newcastle Ottawa Scale. **Results**: In total, seven studies were included in the present meta-analysis such as six cohort studies and one cross-sectional study. In this meta-analysis, 3,573,663 participants were involved. Based on the results, the underweight was a risk factor for HG (odds ratio (OR) = 1.91, 95% confidence interval (CI): 1.21, 2.61). There was not significant association between overweigh and HG (OR = 1.23, 95% CI: 0.96, 1.50). In addition, there was not significant association between obesity and HG (OR = 0.88, 95% CI: 0.42, 1.34). Heterogeneity was seen among the included studies. **Conclusions**: An apparent association between pre-pregnancy BMI and the risk of HG has been observed. However, further investigation is necessary, as the mechanisms and the connection to GDF15 are not yet clear. The most supported public health advice is to attain a healthy BMI before conception. Additionally, the oversight of confounding variables should be taken into account, highlighting the need for comprehensive consideration in future studies.

Keywords: body mass index; hyperemesis gravidarum; nausea; meta-analysis

1. Introduction

Nausea and vomiting are prevalent symptoms in the initial stages of pregnancy, being self-limiting and reported by approximately 80% of pregnant women [1]. Hyperemesis gravidarum (HG) represents an intense form of pregnancy-related vomiting, characterized by its relative rarity, with prevalence ranging between 0.3% and 2% [2]. The diagnosis of HG is established when nausea and vomiting reach such severity that women experience difficulty in consuming food and/or beverages normally, leading to conditions like alkalosis, dehydration, and hypokalemia, along with a significant reduction in daily activity [3]. Persistent vomiting and nausea can lead to a reduction in the absorption of essential nutrients, potentially resulting in the development of anemia in individuals [4].

While the exact cause of HG remains unknown, various associated factors have been identified, indicating that the etiology of HG is likely multifactorial [5]. Certain studies have proposed hormonal changes, including elevated levels of human chorionic gonadotropin, a rapid increase in estrogen levels, hyperthyroidism, deficiency in adrenocorticotropic hormone, adrenal insufficiency, an imbalance between luteinizing hormone and prolactin, and an elevated level of GDF15, as potential contributors to the etiology of HG [3,6,7].

Recent epidemiological studies have indicated an association between low pre-pregnancy body mass index (BMI) and HG [8]. Until now, no meta-analytic study has been undertaken to explore the connection between pre-pregnancy BMI and the risk of HG. Therefore, the objective of this study is to conduct a meta-analysis specifically focused on determining the association between pre-pregnancy BMI and the risk of HG.

2. Materials and Methods

Our meta-analysis was conducted following the 2020 PRISMA statement [9]. The PRISMA diagram provides details on the number of retrieved sources, the number of excluded sources, and the reasons for exclusion in order to maintain transparency in the reporting of this meta-analysis (Fig. 1). Moreover, we registered the study protocol at the

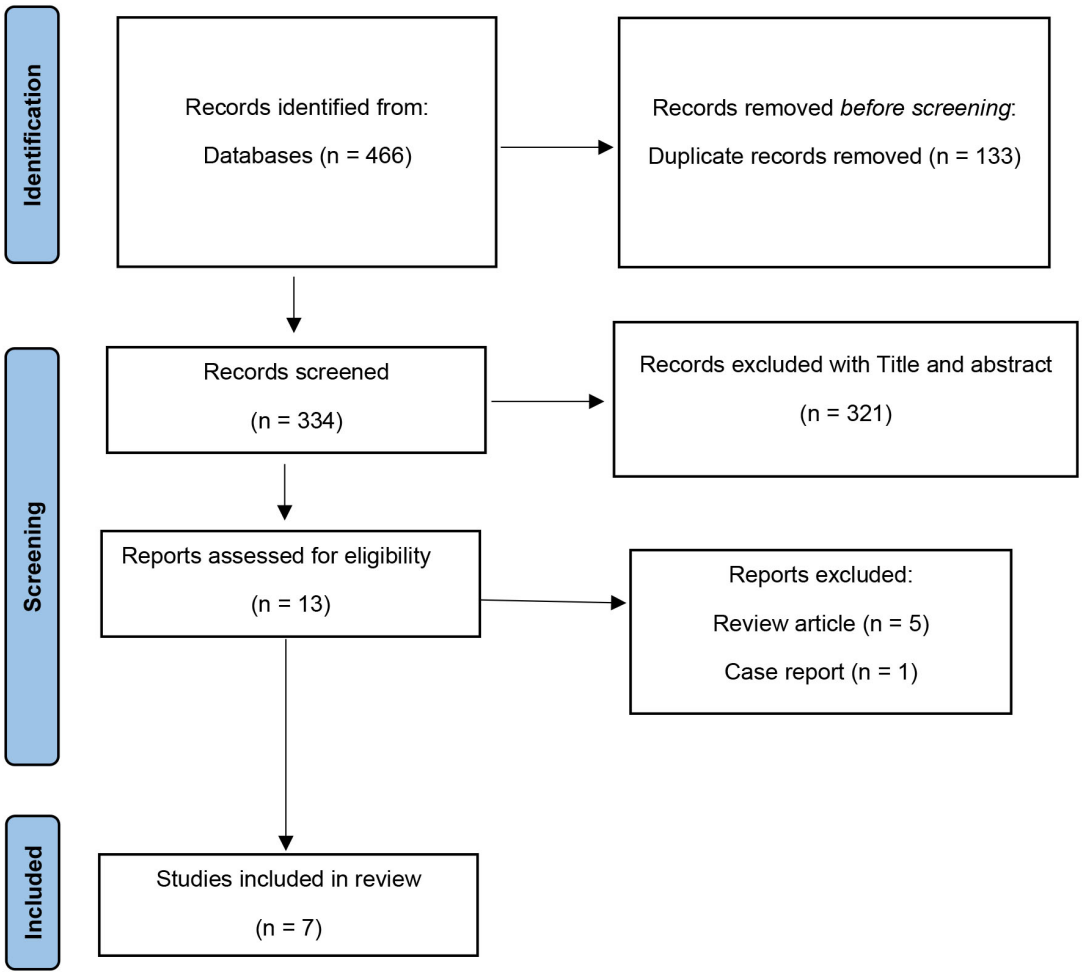

Fig. 1. Diagram of information through the different phases of the meta-analysis.

International Prospective Register of Systematic Reviews (PROSPERO) with register number CRD42023492488, Date: 22/12/2023.

2.1 Strategy Search

The search strategy employed a combination of keywords, including 'hyperemesis gravidarum', 'hyperemesis gravid', 'pernicious vomiting of pregnancy', and 'body mass index', 'BMI', 'body size', 'obese', 'obesity', 'overweight', or 'underweight'. Electronic bibliographic databases such as PubMed, Web of Science, Scopus, and Science Direct were searched from their inception until May 2022. Additionally, a thorough investigation of the reference lists of identified papers was carried out to ensure the inclusion of any relevant sources missed during the initial database searches.

2.2 Inclusion and Exclusion Criteria

In this study, only original research articles, specifically case-control and cohort studies, were included, while other types of articles such as letters to the editor, case reports, and systematic reviews were excluded. The inclusion criteria encompassed studies that concentrated on exploring the causal associations between pre-pregnancy BMI and the risk of HG, including patients. There were no restrictions on the language or publication date of the retrieved sources. Additionally, only peer-reviewed articles, whether published or in-press, were considered for inclusion.

2.3 Study Selection and Data Extraction

Two authors (EJ and AMS) conducted independent reviews of the studies to ensure they met the inclusion criteria for this meta-analysis. Any disagreements were resolved through discussions among the authors. The information extracted from the included articles included details such as the name of the first author and publication year, country, study design, participant age (in years), sample size, and the effect measure along with its corresponding 95% confidence interval (CI).

2.4 Definition

In accordance with the World Health Organization (WHO) classification, a normal weight BMI falls within the range of 18.5 to 24.9 kg/m^2. Underweight is defined as a

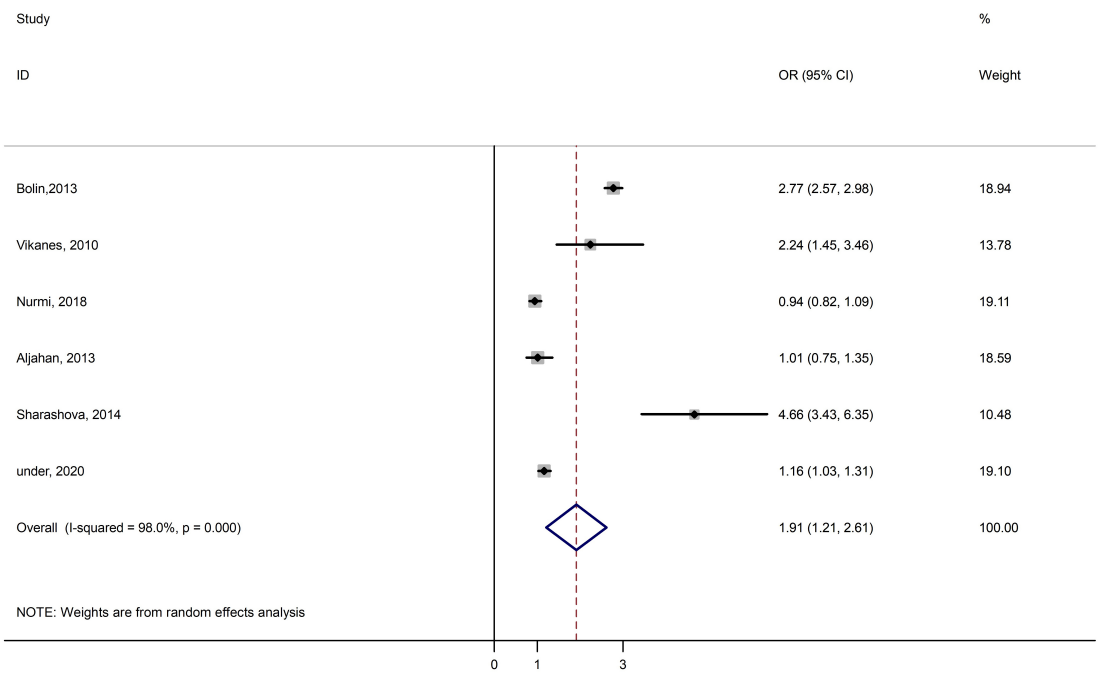

Fig. 2. The association between underweight and the risk of hyperemesis gravidarum.

BMI less than 18.5 kg/m^2, overweight ranges from 25 to 29.9 kg/m^2, and obesity is identified with a BMI greater than 30 kg/m^2 [10].

2.5 Quality of the Study

The quality of the studies was evaluated using the Newcastle Ottawa Scale (NOS) [11], a 9-item scale specifically designed for non-randomized case-control and cohort studies. The NOS assesses aspects such as the selection of cases and controls (including definition and representativeness), comparability of cases and controls, and exposure. Studies with a score of $\geq$7 were categorized as high quality, while those with a score below 7 were considered medium or low quality.

2.6 Heterogeneity Assessment and Publication Bias

Between-study heterogeneity was assessed using the I^2 statistic [12] and chi-square. Additionally, the potential for publication bias was examined using Begg's tests [13].

2.7 Statistical Analysis

For the meta-analysis, a random-effect model was employed, and the effect size was determined using the odds ratio (OR). In addition to the odds ratio, the 95% confidence interval (CI) for the odds ratio was also calculated. All statistical analyses were conducted using STAT Version 14 (StataCorp, College Station, TX, USA). The significance level for all analyses was adjusted to 0.05. Due to the limited number of included studies, a subgroup analysis was not conducted to investigate the impact of confounding factors.

3. Results

A total of 467 articles were identified, with 261 retrieved from electronic databases and 206 obtained through the review of reference lists. No articles were found through conference database searches. After screening titles and abstracts, 133 duplicate and 322 irrelevant articles were excluded. Following a thorough examination of full texts, five articles were further excluded as they did not meet the inclusion criteria, specifically, their BMI categorization did not align with WHO categorization (Fig. 1). Ultimately, seven studies were included in the present meta-analysis, comprising six cohort studies [5,8,14–17] and one cross-sectional study [18]. In this meta-analysis, 3,573,663 participants were involved (Table 1, Ref. [5,8,14–18]).

The association between being underweight and the risk of HG is presented in Fig. 2. Based on the results, the underweight was a risk factor for HG (OR = 1.91, 95% CI: 1.21, 2.61). There was not significant association between overweigh and HG (OR = 1.23, 95% CI: 0.96, 1.50). In addition, there was not significant association between obesity and HG (OR = 0.88, 95% CI: 0.42, 1.34). Heterogeneity was seen among the included studies (Figs. 2,3,4). Only one study reported findings based on relative risk (RR) [17]. They showed that pre-pregnancy underweight is a risk factor for HG (RR = 1.19, 95% CI: 1.14, 1.24) and obesity is a protective factor (RR = 0.93, 95% CI: 0.89, 0.97). There was not significant association between pre-pregnancy overweight and HG (RR = 1.0, 95% CI: 0.97, 1.03).

The presence of publication bias by Begg's test was conducted. There was no evidence of publication bias

Table 1. Summary results of the included studies.

First author, year	Country	Design	Sample size	Estimate	Adjustment	HG criteria	Outcome BMI		Age (year)	Quality
Bolin, 2013 [14]	Sweden	Cohort	1,156,050	Odds ratio	Crude	Medical Birth Registry	Underweight/ overweight/obese	Measured	Not reported	High
Cedergren, 2008 [16]	Sweden	Cohort	1,692,329	Relative risk	Adjusted	Hospitalized due to HG	Obesity	Measured	Not reported	High
Vikanes, 2010 [8]	Norway	Cohort	33,467	Odds ratio	Adjusted/Crude	Hospitalized before week 25	Underweight/ overweight/obese	Not reported	Not reported	High
Alijahan, 2013 [18]	Iran	Cross-sectional	8270	Odds ratio	Crude	Hospitalized due to severe vomiting during pregnancy	Underweight/ overweight/obese	Self-reported	18–35	Low
Sharashova, 2014 [15]	Russia	Cohort	29,709	Odds ratio	Crude	Records	Underweight/ overweight/obese	Measured	27.1	High
Nurmi, 2020 [5]	Finland	Cohort	437,465	Odds ratio	Adjusted/Crude	patient registry for inpatients	Underweight/ overweight/obese	Medical record	Not reported	High
Kim, 2020 [17]	Korea	Cohort	216,373	Odds ratio	Adjusted/Crude	Hospitalization for HG	Underweight/obese	Measured	30.59	High

HG, Hyperemesis gravidarum; BMI, body mass index.

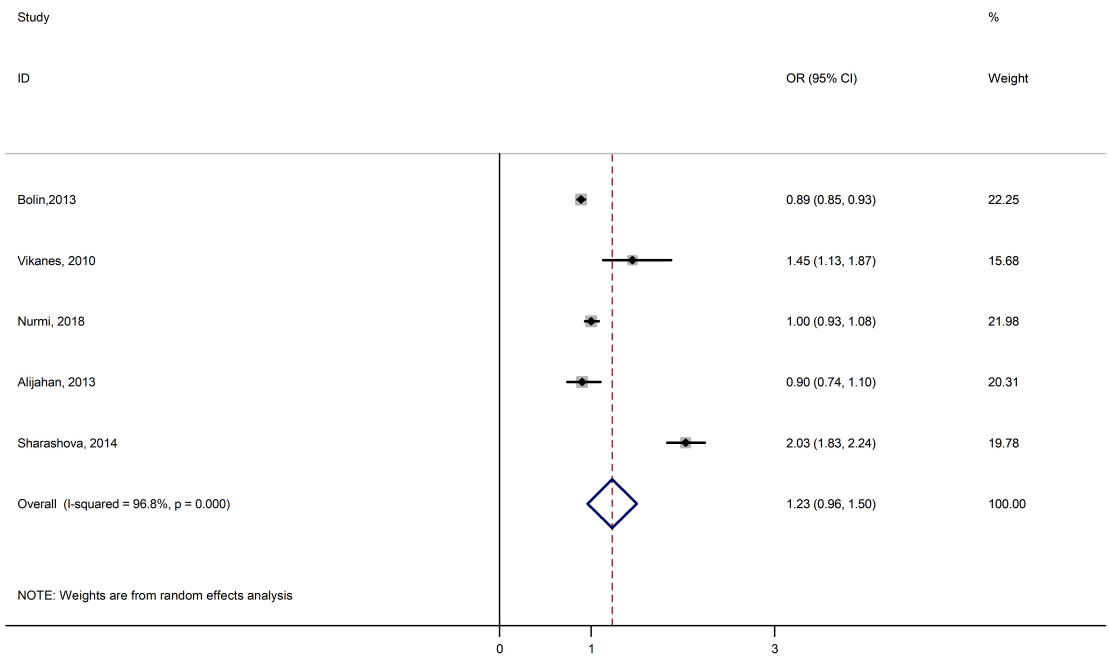

Fig. 3. The association between overweight and the risk of hyperemesis gravidarum.

among the included studies reporting the association between underweight and the risk of HG (p = 0.851), overweight (p = 0.327), and obesity (p = 0.850), respectively.

According to the NOS checklist, there were five studies with high quality and one study with low quality (Tables 1,2, Ref. [5,8,14–18]).

4. Discussion

In this initial systematic review, we systematically examined evidence from epidemiological studies exploring the relationship between pre-pregnancy BMI and HG. Our findings indicate that a low pre-pregnancy BMI is associated with an elevated risk of HG. However, pre-pregnancy overweight and obesity do not seem to have a significant impact on the occurrence of HG.

A woman's overall health is affected by her body weight, and pre-pregnancy BMI serves as a marker that reflects an individual's nutritional status and weight [19]. In pregnancy, both obesity and maternal overweight elevate the risk of complications such as gestational diabetes, hypertension, thromboembolic diseases, cesarean delivery, and fetal death [20]. Nevertheless, the impact of low maternal weight on obstetric outcomes remains unclear. Certain studies have indicated an elevated risk of preterm birth, low birth weight, and prenatal loss in underweight women [21]. Conversely, interpregnancy weight gain is linked to an increased risk of developing gestational diabetes, pre-eclampsia, and delivering a large-for-gestational age neonate. On the other hand, interpregnancy weight loss is associated with a reduced risk of delivering a large-for-gestational age neonate [22,23].

Hyperemesis is often diagnosed regarding with percent of weight loss, 5% is a common cut-off. In underweight women a smaller absolute weight loss (in kilos) would amount to larger percent weight loss [24]. Thus, they may be diagnosed with HG more often than a woman with a high body weight (Most likely underweight women have less nutritional reserves and need treatment sooner than women with higher body weight, this may also impact how these women are hospitalized and as such defined as hyperemesis). Although it is a clinical relevant finding that obese women have an increased risk and as such also merits antiemetic and nutritional treatment to improve the health of their pregnancy [25].

Women with HG admitted in the second trimester face an elevated risk, including more than double the risk of preterm pre-eclampsia, triple the risk of placental abruption, and a 39% increased risk of delivering a small for gestational age (SGA) birth [14]. Therefore, it is crucial to identify various risk factors associated with HG, such as the hereditary factors [8], Helicobacter pylori infection [26], psychological stress [27], mechanical causes with decreased gastrointestinal motility, Asian and Caucasian populations [28], trophoblastic diseases of pregnancy [29], female fetus [29], and ethnicity [27,30]. However, the nature of this phenomenon, whether it is a cause or an effect of HG, requires further exploration and discussion [31].

On the contrary, factors such as smoking history [32], alcohol consumption [17], older age (35 years), and carrying male fetuses are identified as protective factors against HG. The results of this meta-analysis suggest an association between low pre-pregnancy BMI and HG. It's worth noting that the study by Kosus *et al*. [24] reported conflicting

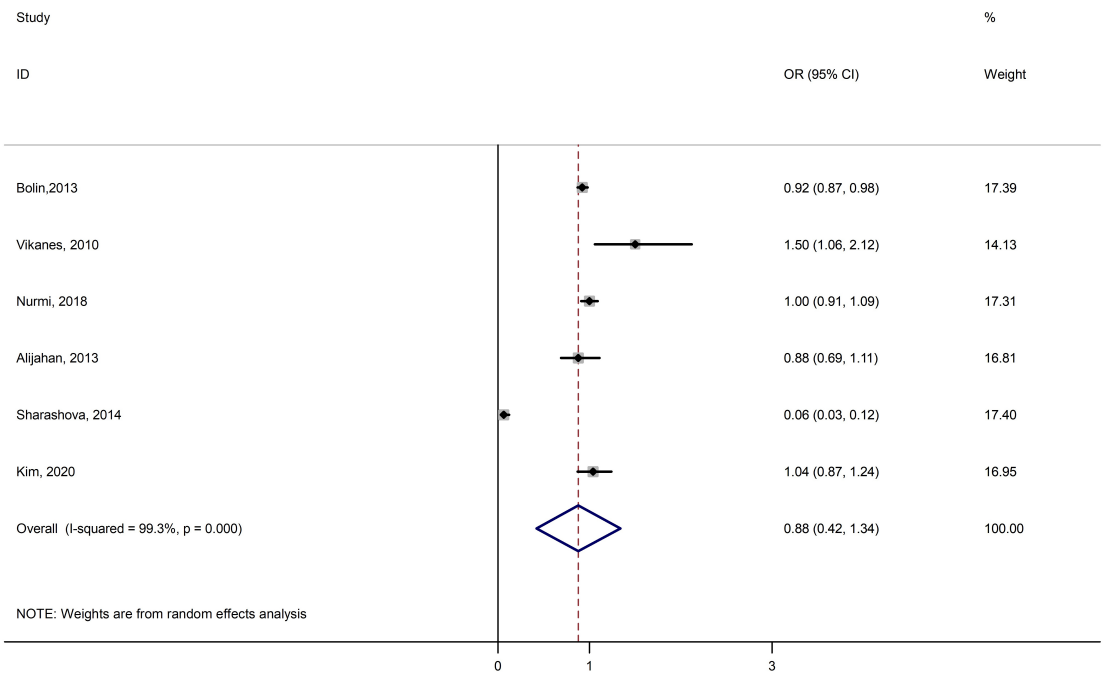

Fig. 4. The association between obesity and the risk of hyperemesis gravidarum.

Table 2. Score of Quality of studies based on the Newcastle Ottawa Scale (NOS).

First author, Year	Selection	Comparability	Exposure	Total quality score
Bolin, 2013 [14]	3	1	3	7
Cedergren, 2008 [16]	3	2	3	8
Vikanes, 2010 [8]	4	2	3	9
Alijahan, 2013 [18]	2	1	2	5
Sharashova, 2014 [15]	3	1	3	7
Nurmi, 2020 [5]	4	2	3	9
Kim, 2020 [17]	4	2	3	9

Low quality ($<$7 points), and high quality ($\geq$7 points).

findings, indicating that patients with HG had significantly higher levels of visceral adipose tissue and pre-pregnancy BMI compared to the control group.

Two mechanisms have been suggested for the cause of increased HG in pre-pregnancy underweight women, both of which depend on serum leptin levels: (1) Leptin secreted from the placenta by a hypothalamic receptor reduces appetite (weight loss) followed by nausea and vomiting [33]. (2) Leptin may increase the secretion of human chorionic gonadotropin, which plays a critical role in the pathogenesis of HG [34]. It is plausible that having fewer fat deposits may not be sufficient to counteract the circulating placental factors contributing to HG. Additionally, estrogen is proposed as another potential cause. Some theories suggest that women with pre-pregnancy underweight may have lower levels of circulating estrogen before pregnancy, leading to an exaggerated response to the increase in hormonal levels during the first trimester [17,35]. A recent study by Fejzo *et al.* [3] revealed elevated levels of GDF15, one of the most abundant peptides secreted from human trophoblast organoids, in women suffering from HG. This implies that GDF15 may play a role in the pathophysiology of HG [3].

In a study by Cedergren *et al.* [16], the risk of HG was 40% higher in women with a BMI of less than 20 kg/m^2 compared to those with a BMI between 20 and 24.9. This study also revealed that obese women had a lower risk of exposure to antiemetics in early pregnancy than women of ideal weight, and obesity was associated with a reduced risk of HG requiring hospitalization [16]. Additionally, Matsuo *et al.* [36] reported an increased risk of HG in women with a BMI of less than 19.93. It is noteworthy that one of the studies, conducted by Vikanes *et al.* [8], used a different cut-off point of 18.5, aligning with the WHO's definition of underweight. This study found a higher risk of HG in underweight women compared to the other two studies [8]. These findings are consistent with the results of the present study.

Women with BMI abnormalities may require additional healthcare resources during pregnancy [14]. How-

ever, it is important to note that there is no definitive treatment for HG. In outpatient women, recommended approaches include intermittent infusion of 5% dextrose, Ringer's lactate serum, anti-nausea medications, diet modification, avoidance of stimulant foods, and the use of pyridoxine and phenothiazine [37]. There are multiple treatments for HG. Treatments can be divided into 3 categories: first-line: ginger, second-line: vitamin B6, antihistamines, dopamine and antagonists, and third-line such as corticosteroids, transdermal clonidine, gabapentin with severity of symptoms and response to prior therapies guiding decision-making on treatment [1].

If nausea and vomiting persist, along with weight loss exceeding 5% of total body weight and the occurrence of metabolic disorders, hospitalization is recommended [38]. Additionally, alternative non-pharmacological therapies, including ginger, acupuncture, and acupressure (with pressure applied to the PC-6 point in the middle of the arm), have been suggested for HG, although their efficacy is limited [39].

There are several limitations in this study is the need for more control over confounding variables in some studies. (a) Only in 3 of the 6 included studies was the adjust form used to control confounding variables, which can cause bias in the results. (b) Another limitation of this study was the lack of measurement of the severity of HG in studies. (c) There was the high heterogeneity among included studies. (d) Many women with HG do not wish to be admitted to hospital and are managed as an outpatient due to caring commitments and other demands and confounding variables and (e) It is possible that those who are already underweight are more likely to seek help and hospitalization for HG, if they lose weight. Whereas weight loss and poor appetite for those in the overweight/obesity category is often minimized and overlooked. However, the present meta-analysis with 3,573,663 participants showed an association between pre-pregnancy BMI and HG risk.

5. Conclusions

An apparent association between pre-pregnancy BMI and the risk of HG has been observed. However, further investigation is necessary, as the mechanisms and the connection to GDF15 are not yet clear. The most supported public health advice is to attain a healthy BMI before conception. Additionally, the oversight of confounding variables should be taken into account, highlighting the need for comprehensive consideration in future studies.

Abbreviations

HG, Hyperemesis Gravidarum; BMI, Body Mass Index; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis; WHO, World Health Organization; CI, Confidence Interval; NOS, Newcastle Ottawa Scale; OR, Odds Ratio; RR, Relative Risk.

Availability of Data and Materials

Access to data is possible with permission from the responsible author (AMS).

Author Contributions

Conceptualization: EJ and AMS; methodology, EJ and AMS; software, SK; investigation, EJ; data curation, SA and AMS; writing—original draft preparation, EJ, SK, AMS and SA; writing-review and editing, AMS; supervision, EJ; project administration, SK. All authors have read and agreed to the published version of the manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of Hamadan University of Medical Sciences (ID: IR.UMSHA.REC.1400.277).

Acknowledgment

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.ceog5104082.

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