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A Meta-Analysis on the Prevalence and Risk of Gestational Diabetes Mellitus in the Context of COVID-19

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Abstract

Background: The objectives of this study are: 1) to compare the prevalence of gestational diabetes mellitus (GDM) among pandemic and pre-pandemic cohorts, 2) to evaluate the risk of GDM among pregnant women who tested positive and negative for coronavirus disease 2019 (COVID-19), and 3) to evaluate the risk of COVID-19 among pregnant women diagnosed with and without GDM.

Methods: A literature search was carried out in PubMed and Cochrane library databases with relevant keywords from its inception till March 2024. Observational studies that 1) evaluated the prevalence of GDM during pandemic and pre-pandemic period, and 2) investigated the GDM and COVID-19 status among pregnant women were included.

Results: The analysis revealed that the prevalence of GDM was significantly increased by 17% (odds ratio (OR), 1.17; 95% confidence interval (CI), 1.12 to 1.23; $P < 0.00001$) during the pandemic period compared to pre-pandemic period and the odds of pregnant women with GDM tested positive for COVID-19 were 1.28-fold greater (OR, 1.28; 95% CI, 1.13 to 1.44; $P < 0.0001$) than the odds of pregnant women with GDM tested negative for COVID-19. However, the analysis also revealed that pregnant women with COVID-19 were less likely (OR, 0.02; 95% CI, 0.01 to 0.02; $P < 0.00001$) to be diagnosed with GDM when compared to pregnant women with COVID-19 and without GDM.

Conclusion: The present study suggests that GDM acts as a risk factor for COVID-19 infection among pregnant women. This might be due to the hypothesis that altered sense of taste is associated among pregnant women with GDM and COVID-19 due to the taste receptor polymorphisms which regulates the innate immunity downstream signaling. However, molecular studies were needed to validate this hypothesis and evaluate the therapeutic role of taste receptors in the management of COVID-19 and GDM.

Keywords: Gestational diabetes mellitus; SARS-CoV-2; Coronavirus disease 2019; Meta-analysis; Long COVID

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), declared as a global pandemic by World Health Organization (WHO) on March 11, 2020, caused adverse effects and disrupted global economy, health-care systems, leading to long COVID symptoms such as taste dysfunction and dysregulation of immune system and immunological memory [1-3]. Several studies have observed the indirect impact of the pandemic on maternal health-care services such as reduced hospital visits for routine and unscheduled pregnancy care, limited physical activity due to the pandemic lockdowns and adverse pregnancy outcomes [1-4]. Evidence from the previous observational studies reported that there was an increased prevalence of gestational diabetes mellitus (GDM) among pregnant women during the pandemic period along with the rising risk factors of obesity/overweight, reduced outdoor physical activities, dietary, behavioral (mental health problems), lifestyle changes and taste dysfunction during the COVID-19 pandemic period [4, 5]. Interestingly, studies also demonstrated that there is a significant prevalence of taste dysfunction among individuals with confirmed COVID-19 [6, 7] and the type 2 taste receptor R family member 38 (TAS2R38) proline-alanine-valine (PAV) taster allele was significantly associated with COVID-19 [8]. Previous studies hypothesized that single nucleotide polymorphisms (SNPs) in extra-oral type 2 taste receptors (TAS2Rs) found in respiratory tract regulate innate immunity through facilitating the release of anti-viral nitric oxide (NO) which causes intra-cellular damage of microbes, removal of pathogens by increasing ciliary beat frequency and muco-ciliary clearance [9-11]. Further, NO release from the ciliated epithelial cells prevents viral RNA replication by inhibiting the binding of spike proteins of coronavirus with angiotensin converting enzyme 2 [9-11]. In addition, studies showed that adverse pregnancy outcomes such as gestational diabetes mellitus (GDM) might be influenced by maternal immune dysregulation and GDM also influences neonatal innate immunity [5, 12]. Although chloroquine (or hydroxychloroquine), an agonist of TAS2Rs (bitter taste receptors) was used for a brief period in the management of COVID-19, it was discontinued due to its potential adverse events [10, 11, 13]. Moreover, our previous analysis has suggested that SNPs in taste receptor genes such as TAS2R subtypes (type 2 taste receptor R family member 9 (TAS2R9)), transient receptor potential cation channel subfamily M member 5 (TRPM5) were significantly associated with increased risk of GDM susceptibility and pregnant women with GDM had an im-

paired sweet, salt and bitter taste stimuli perception due to SNPs in taste receptor genes [5]. Further, expression of TRPM5 and TAS2R9 in pancreatic beta cells potentially regulates glucose and insulin homeostasis [5]. However, the meta-analyses published in 2021 were conducted with studies published until January 2021 and reported inconsistent results regarding the association between the COVID-19 pandemic and GDM [1-3]. Hence, the objectives of this study are 1) to compare the prevalence of GDM among pandemic and pre-pandemic cohorts, 2) to evaluate the risk of GDM among the pregnant women who tested positive and negative for COVID-19, and 3) to evaluate the risk of COVID-19 among pregnant women diagnosed with and without GDM, with additional studies published until March 2024.

Material and Methods

This meta-analysis was registered in International Prospective Register of Systematic Reviews (PROSPERO) (Reg. No. CRD42024521805) and prepared following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines. Institutional review board/ethical clearance is not applicable as this is a meta-analysis conducted from the previously published observational studies.

Search strategy

A literature search was carried out in PubMed and Cochrane library databases with keywords such as "(severe acute respiratory syndrome coronavirus 2) OR (SARS-CoV-2) OR (coronavirus disease 2019) OR (COVID-19) AND (gestational diabetes mellitus)" from its inception till March 2024. Further citation searches were carried out to identify relevant studies. Observational studies that 1) evaluated the prevalence of GDM during pandemic and pre-pandemic period and 2) investigated the GDM and COVID-19 status among pregnant women were included. Articles that are not relevant to our study, not in English language, case reports, not have sufficient data and without control groups, review articles, editorials, erratums, book chapters, guidelines and research letters were excluded. The screening of title and abstract was carried out to identify the relevant articles. Further, the full texts of the identified studies were reviewed for inclusion based on the inclusion criteria and further the patient/population, intervention, comparison, outcomes (PICO) inclusion criteria were listed in the Supplementary Material 1 (www.jofem.org). The definitions of pandemic, pre-pandemic cohorts, COVID-19 and GDM diagnostic criteria were based on the respective included studies.

Data extraction and quality assessment

Data extraction was carried out in excel spreadsheet. Data regarding the study design, population, number of pregnant women diagnosed with GDM during the pandemic and pre-pandemic period, number of pregnant women with confirmed COVID-19 infection diagnosed with and without GDM, number of pregnant women with GDM tested positive and negative for COVID-19 were extracted from the respective studies wherever applicable. Quality assessment of the included studies was carried out using the Newcastle-Ottawa scale (NOS) for case-control and cohort studies. NOS comprises three domains: selection domain, comparability domain and outcome/exposure domain. The studies were categorized into good quality (defined as three or four stars in the selection domain, one or two stars in the comparability domain, two or three stars in the outcome and three or four stars in the exposure domain), fair quality (defined as two stars in the selection domain, one or two stars in the comparability domain, two or three stars in the outcome domain and two stars in the exposure domain), and poor quality (defined as zero or one star in the selection domain, zero stars in the comparability domain and zero or one star in the outcome/exposure domain) according to Agency for Health Research and Quality (AHRQ) standards.

Statistical analysis

Statistical analysis was done in RevMan software (Version 5.4; Cochrane collaboration). Pooled odds ratios (ORs) with 95% confidence intervals (CIs) were estimated from random effects meta-analysis models and P-value less than 0.05 was considered statistically significant. Heterogeneity was assessed by the I^2 statistic and Chi-squared test, where a P value of less than 0.1 was considered statistically significant. Publication bias was assessed by visual inspection of funnel plot and leave-one out sensitivity analysis.

Results

Of the 21,178 records identified through database searches, 63 studies were included in the meta-analysis. Figure 1 depicts the process of selection of articles. Across the included studies representing more than 18 countries, a total of 164,578 pregnant women diagnosed with GDM among 2,452,025 pregnant women during the COVID-19 pandemic and 212,952 pregnant women diagnosed with GDM among 3,145,914 pregnant women during the pre-pandemic period were reported. Further, among 21,254 pregnant women with confirmed COVID-19 infection, 2,591 pregnant women diagnosed with GDM were compared with 18,663 pregnant women without GDM. In addition, the study also included 1,142 pregnant women tested positive for COVID-19 among 8,886 pregnant women with GDM and 106,405 pregnant women tested negative for COVID-19 among the 880,342 pregnant women with GDM. The characteristics of the included studies are shown in Table 1 [4, 14-75] and Supplementary Table 1 (www.jofem.org).

Comparison of GDM prevalence during pandemic and pre-pandemic period

Twenty-six studies comprising 5,597,939 pregnant women categorized into pandemic cohort and pre-pandemic cohort

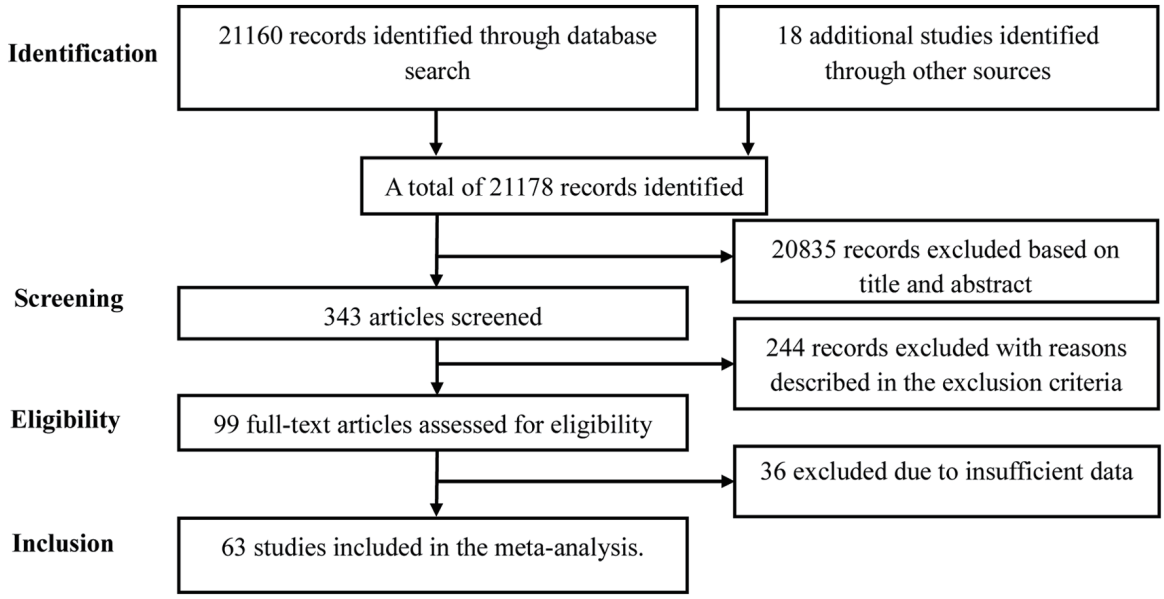

Figure 1. Flowchart summarizing the selection process.

were included in our meta-analysis. The random effects meta-analysis model revealed that the prevalence of GDM was significantly increased by 17% during the COVID-19 pandemic period when compared to the pre-pandemic period (OR, 1.17; 95% CI, 1.12 to 1.23; $P < 0.00001$) with heterogeneity of $I^2 = 96\%$ ($P < 0.00001$) as shown in Figure 2. Methodological quality assessment of the included studies by NOS suggested an overall good quality for the 26 studies and visual inspection of the funnel plot shows low publication bias (Supplementary Figure 1, www.jofem.org). The fixed effects meta-analysis model (OR, 1.15; 95% CI, 1.14 to 1.16; $P < 0.00001$) and the leave-one out sensitivity analysis (ORs were in the range of 1.16 to 1.19) showed no significant difference from the overall effect measure estimated from the random effects meta-analysis model (Supplementary Table 2, www.jofem.org).

COVID-19 as a risk factor for GDM

Thirty-seven studies comprising 21,254 pregnant women confirmed with COVID-19 infection were included in the meta-analysis. The random effects meta-analysis models revealed that the odds of pregnant women with COVID-19 infection associated with GDM were less compared to pregnant women with COVID-19 infection associated without GDM (OR, 0.02; 95% CI, 0.01 to 0.02; $P < 0.00001$) with heterogeneity of $I^2 = 97\%$ ($P < 0.00001$) as shown in Figure 3. Methodological quality assessment of included studies by NOS suggested that four studies were of poor quality, one was of fair quality and remaining 32 studies were of good quality. Visual inspection of funnel plot shows low publication bias (Supplementary Figure 2, www.jofem.org). The stratification analysis by eliminating the poor-quality studies (OR = 0.02), fixed effects meta-analysis model (OR, 0.02; 95% CI, 0.02 to 0.03; $P < 0.00001$) and the leave-one out sensitivity analysis (OR = 0.02) showed no significant difference from the overall effect measure estimated from the random effects meta-analysis model (Supplementary Table 2, www.jofem.org). However, limitations such as small differences and high heterogeneity need to be considered.

GDM as a risk factor for COVID-19

Twenty-one studies comprising 889,228 pregnant women with GDM tested positive and negative for COVID-19 were included in the meta-analysis. The random effects model showed that the odds of pregnant women with GDM diagnosed as positive for COVID-19 were 1.28-fold greater than the odds of pregnant women with GDM tested negative for COVID-19 (OR, 1.28; 95% CI, 1.13 to 1.44; $P < 0.0001$) with heterogeneity of $I^2 = 35\%$ ($P = 0.06$) as shown in Figure 4. Methodological quality assessment of the included studies by NOS suggested an overall good quality and visual inspection of the funnel plot shows low publication bias (Supplementary Figure 3, www.jofem.org). The fixed effects meta-analysis model (OR, 1.31; 95% CI, 1.23 to 1.40; $P < 0.00001$) and the leave-one out sensitivity analysis (ORs were in the range of 1.24 to 1.30) showed no significant difference from the overall effect measure estimated from the random effects meta-analysis model (Supplementary Table 2, www.jofem.org).

Discussion

The meta-analysis showed that the prevalence of GDM has increased by 17% during the pandemic period compared to pre-pandemic period and the odds of pregnant women with GDM tested positive for COVID-19 were 1.28-fold greater than the odds of pregnant women with GDM tested negative for COVID-19. These findings suggest that pregnant women with

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study	Study design (country)	Total study population	Study period		Overall quality
			Pre-pandemic cohort (years)	Pandemic cohort (years)	
Comparison of GDM prevalence during pandemic and pre-pandemic cohorts					
Gu, 2020 [14]	Cohort (China)	582	January to February 2019	January to February 2020	Good
Justman, 2020 [15]	Cohort (Israel)	1,352	March to April 2019	March to April 2020	Good
Pariente, 2020 [16]	Cohort (Israel)	346	November 2016 to April 2017	March 18 to April 29, 2020	Good
Molina-Vega, 2021 [17]	Cohort (Spain)	492	September 1, 2019 to November 30, 2019	September 1, 2020 to November 30, 2020	Good
Chelu, 2022 [18]	Cohort (Romania)	17,230	2017 to 2019	2020 and 2021	Good
Collins-Smith, 2022 [19]	Cohort (USA)	20,548	April to July, 2018 and 2019	April to July 2020	Good
Gurol-Urganci, 2022 [20]	Cohort (UK)	948,020	March 23, 2019 to February 22, 2020	March 23, 2020 to February 22, 2021	Good
Handley, 2022 [21]	Cohort (USA)	31,474	March 10 to December 31, 2018 and 2019	March 10 to December 31, 2020	Good
He, 2022 [22]	Cohort (China)	140,844	2015 to 2019	2020	Good
Keating, 2022 [23]	Case-control (Ireland)	3,890	April 1 to June 30, 2019	April 1 to June 30, 2020	Good
La Verde, 2022 [24]	Cohort (Italy)	1,295	June 11, 2019 to March 9, 2020	March 10, 2020 to December 1, 2020	Good
Liu, 2022 [25]	Cohort (China)	3,272	June 2020 to July 2020	October 2020 to December 2020	Good
Ornaghi, 2022 [26]	Cohort (Italy)	3,666	March 1 to November 30, 2019	March 1 to November 30, 2020	Good
Yin, 2022 [27]	Cohort (China)	53,680	January to February, 2019	January to February, 2020 and 2021	Good
Zanardo, 2022 [28]	Case-control (Italy)	1,170	2019	2020	Good
Zheng, 2022 [29]	Cohort (China)	6,611	January 23 to July 31, 2019	January 23 to July 31, 2020	Good
Ansari, 2023 [30]	Cohort (Iran)	5,711	March to May 2019	March to May 2020	Good
Auger, 2023 [31]	Cohort (Canada)	569,686	January 1, 2014 to February 29, 2020 and August 23, 2019 to February 29, 2020	March 1, 2020 to March 31, 2021	Good
Boguslawski, 2023 [32]	Cohort (USA)	1,680	March 1, 2019 to August 31, 2019	March 1, 2020 to August 31, 2020	Good
Gharacheh, 2023 [33]	Cohort (Iran)	1,208,671	February 30 to August 30, 2019	February 30 to August 30, 2020	Good
Gholami, 2023 [34]	Cohort (Iran)	2,371,332	February 2019 to February 30, 2020	March 1, 2020 to March 1, 2021	Good
Meloncelli, 2023 [35]	Cohort (Australia)	57,891	July 1 to December 31, 2019	July 1 to December 31, 2020	Good
Raischer, 2023 [36]	Cohort (Israel)	4,765	April to September 2019	April to September 2020	Good
Rhou, 2023 [37]	Cohort (Australia)	28,207	January 1, 2018 to January 31, 2020	February 1, 2020 to January 31, 2022	Good
Garrow, 2024 [4]	Cohort (USA)	69,824	May 1, 2018 to March 11, 2020	March 12, 2020 to December 2022	Good
Zare, 2024 [38]	Cohort (Iran)	6,856	February 18, 2019 to February 17, 2020	February 18, 2020 to February 17, 2021	Good

Table 1. Characteristics of Studies Included in the Meta-Analysis - *(continued)*

Study	Study design (country)	Total study population	Study period	No. of pregnant women with GDM and with COVID-19 (total GDM/total COVID-19)	Overall quality
COVID-19 as a risk factor for GDM					
Adhikari, 2020 [39]	Cohort (USA)	3,374	March 18 to August 22, 2020	14/252	Good
Gulersen, 2020 [40]	Cohort (USA)	100	April 9, 2020 to April 27, 2020	1/50	Good
Kayem, 2020 [41]	Cohort (France)	617	March 1 to April 14, 2020	71/617	Good
Knight, 2020 [42]	Cohort (UK)	427	March 1 to April 14, 2020	50/427	Good
Panagiotakopoulos, 2020 [43]	Cohort (USA)	105	March 1 to May 30, 2020	16/105	Fair
Patberg, 2021 [44]	Cohort (USA)	133	March 31 to June 17, 2020	5/77	Good
Prabhu, 2020 [45]	Cohort (USA)	675	March 22 to March 24, 2020	6/70	Good
Sakowicz, 2020 [46]	Cohort (USA)	1,418	April 8 to May 31, 2020	6/101	Good
Yang, 2020 [47]	Cohort (China)	11,078	January 13 to March 18, 2020	3/65	Good
Yazihan, 2020 [48]	Case-control (Turkey)	187	June 14 to August 28, 2020	1/95	Good
Aydin, 2021 [49]	Cohort (Turkey)	167	April to December 2020	3/163	Good
Epelboin, 2021 [50]	Cohort (France)	244,645	March to June 2020	139/874	Good
Gupta, 2021 [51]	Cohort (India)	3,165	September 1 to November 30, 2020	16/108	Good
Hcini, 2021 [52]	Cohort (French Guiana)	507	June 16 to August 16, 2020	13/137	Good
Hill, 2021 [53]	Cohort (USA)	218	April 10 to June 15, 2020	9/218	Good
Katz, 2021 [54]	Case-control (USA)	1,454	March 19 to May 31, 2020	33/490	Good
Siddiqui, 2021 [55]	Cohort (India)	100	May 25 to September 3, 2020	4/100	Poor
Almaghrabi, 2022 [56]	Cohort (Saudi arabia)	31	2021	9/31	Good
Damar Cakirca, 2022 [57]	Cohort (Turkey)	75	April to August 2020	3/75	Poor
Eskanazi, 2022 [58]	Cohort (18 countries*)	2,071	March 2020 to February 2021	75/672	Good
Ferrara, 2022 [59]	Cohort (USA)	44,318	March 1, 2020 to March 16, 2021	104/1,101	Good
Kleinwechter, 2022 [60]	Cohort (Germany and Austria)	2819	April 3, 2020 to August 24, 2021	140/1,490	Good
Kurian, 2022 [61]	Cohort (India)	856	August 1, 2020 to July 31, 2021	120/856	Good
Minisha, 2022 [62]	Cohort (Qatar)	500	March 2020 to March 2021	202/500	Good
Monod, 2022 [63]	Case-control (Italy)	159	January to February 2022	15/65	Good
Ortqvist, 2022 [64]	Cohort (Sweden and Norway)	188,822	March 2020 to January 2021 (Sweden) and March 2020 to August 2021 (Norway)	172/2,222	Good
Radan, 2022 [65]	Case-control (Switzerland)	224	May 2020 to July 2021	26/75	Good
Radan, 2022 [66]	Cohort (Switzerland)	153	May 2020 to July 2021	30/153	Poor
Simon, 2022 [67]	Cohort (France)	510,387	March to December 2020	498/2,927	Good
Vikas, 2022 [68]	Cohort (India)	49	3 months during COVID-19 pandemic	4/49	Poor
Vousden, 2022 [69]	Cohort (UK)	4,436	March 1, 2020 to October 31, 2021	439/4,436	Good
Ziert, 2022 [70]	Cohort (Germany)	1,485	April 3, 2020 to April 24, 2021	144/1,485	Good
Cundubey, 2023 [71]	Case-control (Turkey)	463	March 2020 to March 2022	13/56	Good
Libretti, 2024 [72]	Case-control (Italy)	168	March 2020 to March 2023	23/168	Good
Xiao, 2023 [73]	Case-control (China)	198	December 1, 2022 to January 31, 2023	20/89	Good
Zehra, 2023 [74]	Case-control (Pakistan)	246	April 1, 2020 to January 31, 2022	59/244	Good
Yi, 2024 [75]	Cohort (China)	611	December 7, 2019 to April 30, 2023	105/611	Good

Table 1. Characteristics of Studies Included in the Meta-Analysis - *(continued)*

Study	Study design (country)	Total study population	Study period	No. of pregnant women		Overall quality
				Total GDM/total COVID-19 positive	Total GDM/total COVID-19 negative	
GDM as a risk factor for COVID-19						
Adhikari, 2020 [39]	Cohort (China)	3,374	March 18 to August 22, 2020	14/252	207/3,122	Good
Gulersen, 2020 [40]	Cohort (USA)	100	April 9, 2020 to April 27, 2020 and November 2019 (controls)	1/50	7/50	Good
Patberg, 2020 [44]	Cohort (USA)	133	March 31, 2020 to June 17, 2020	5/77	0/56	Good
Prabhu, 2020 [45]	Cohort (USA)	675	March 22, 2020 to March 24, 2020	6/70	54/605	Good
Sakowicz, 2020 [46]	Cohort (USA)	1,418	April 8, 2020 to May 31, 2020	6/101	87/1,317	Good
Yang, 2020 [47]	Cohort (China)	11,078	January 13 to March 18, 2020	3/65	1,207/11,013	Good
Yazihan, 2020 [48]	Case-control (Turkey)	187	June 14, 2020 to August 28, 2020	1/95	2/92	Good
Epelboin, 2021 [50]	Cohort (France)	244,645	March to June 2020	139/874	29,251/243,771	Good
Gupta, 2021 [51]	Cohort (India)	3,165	September 1, 2020 to November 30, 2020	108/16	334/3,057	Good
Hcini, 2021 [52]	Cohort (French Guiana)	507	June 16 to August 16, 2020	13/137	30/370	Good
Hill, 2021 [53]	Cohort (USA)	218	April 10 to June 15, 2020	4/49	47/413	Good
Katz, 2021 [54]	Case-control (USA)	1,454	March 19 to May 31, 2020	33/490	67/964	Good
Eskanazi, 2022 [58]	Cohort (18 countries*)	2,071	March 2020 to February 2021	75/672	119/1,399	Good
Monod, 2022 [63]	Case-control (Italy)	159	January 2020 to February 2022	15/65	18/94	Good
Ortqvist, 2022 [64]	Cohort (Sweden and Norway)	188,822	March 2020 to January 2021 (Sweden) and March 2020 to August 2021 (Norway)	172/2,222	5,648/105,477	Good
Radan, 2022 [65]	Case-control (Switzerland)	224	May 2020 to July 2021	26/75	24/149	Good
Simon, 2022 [67]	Cohort (France)	510,387	March to December, 2020	498/2,927	69,130/507,460	Good
Cundubey, 2023 [71]	Case-control (Turkey)	463	March 2020 to March 2022	13/56	88/407	Good
Libretti, 2023 [72]	Case-control (Italy)	168	March 2020 to March, 2023	23/168	9/170	Good
Xiao, 2023 [73]	Case-control (China)	198	December 1, 2022 to January 31, 2023	20/89	21/109	Good
Zehra, 2023 [74]	Case-control (Pakistan)	246	April 1 to January 31, 2022	59/244	55/247	Good

COVID-19: coronavirus disease 2019; GDM: gestational diabetes mellitus; USA: United States of America; UK: United Kingdom; *18 countries = Argentina, Brazil, Egypt, France, Ghana, India, Indonesia, Italy, Japan, Mexico, Nigeria, North Macedonia, Pakistan, Russia, Spain, Switzerland, the United Kingdom, and the United States.

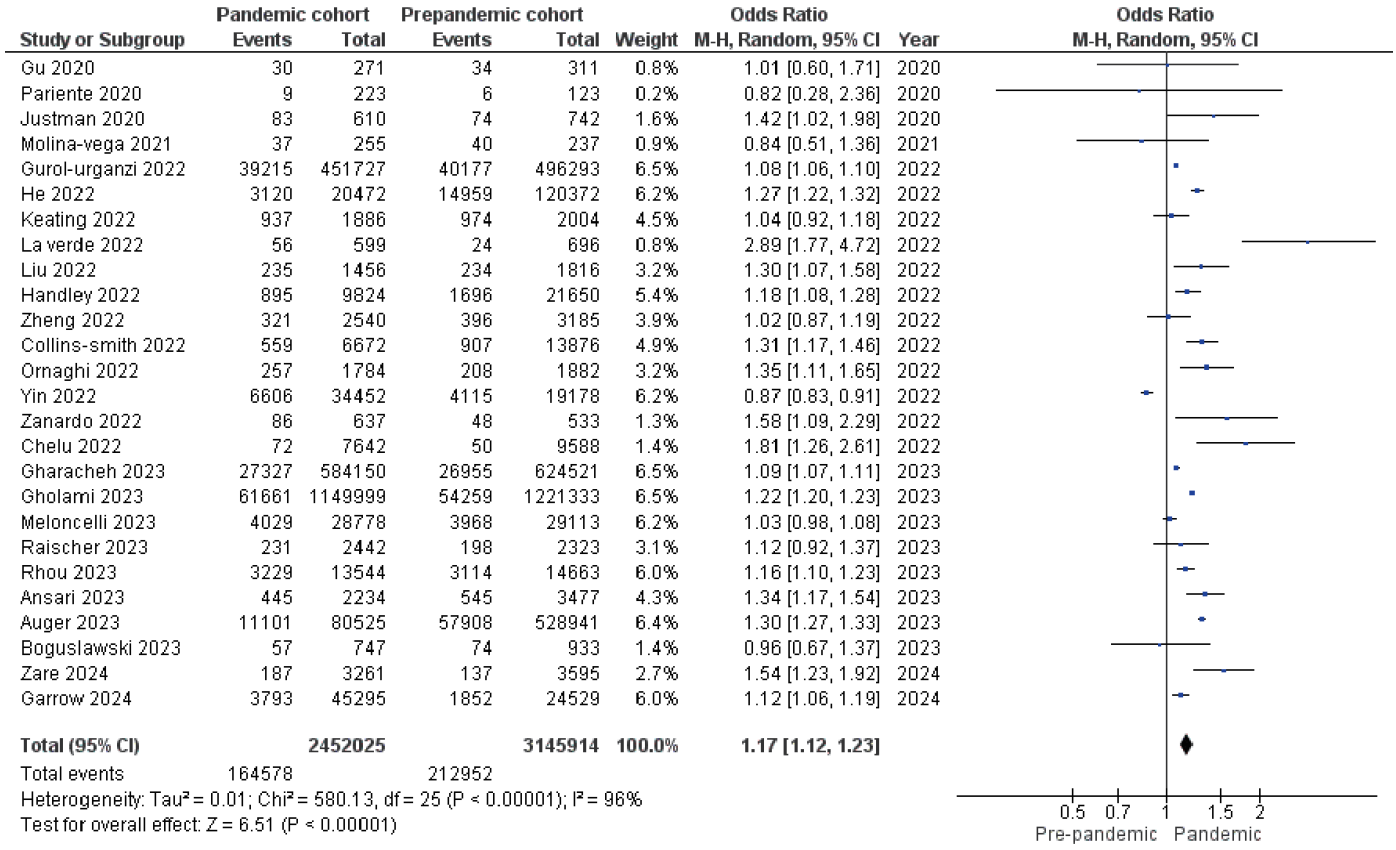

Figure 2. Forest plot shows the random effects meta-analysis model comparing the prevalence of GDM among pregnant women during pandemic and pre-pandemic period. COVID-19: coronavirus disease 2019; GDM: gestational diabetes mellitus.

GDM have increased risk of COVID-19 infections among GDM cohorts (pregnant women diagnosed with GDM) which is consistent with the results reported by our previous meta-analysis [76-78] and contradictory to the results reported by the previous meta-analysis [1-3]. Further, this is in consistent with the previous observational studies that the prevalence of GDM was increased during the pandemic period compared to the pre-pandemic period [33, 34] and contradictory to the overall decreased prevalence of GDM from 2019 to 2021, although the prevalence of GDM increased during the most severe period of the pandemic [27]. The increased odds of pregnant women with GDM tested positive for COVID-19 were consistent with the previous observational studies that the occurrence of GDM was significantly higher among pregnant women with COVID-19 compared to pregnant women without COVID-19 [64, 67]. This might be due to the lockdown restrictions, restricted physical activity, maternal stress, dietary changes, behavioral changes and taste dysfunction associated with COVID-19. However, the results also showed that the odds of pregnant women with confirmed COVID-19 infection associated with GDM were significantly less compared to pregnant women with COVID-19 infection associated without GDM among COVID-19 cohorts (pregnant women tested positive for COVID-19). This is contradictory to the previous reports that pregnant women who are overweight or obese and with GDM were more likely to have severe COVID-19 infection and more likely to be tested positive for COVID-19 infection respectively [64, 69]. This might be due to the decreased frequency of visits to the hospitals and outdoor activities due to fear of infections and lockdown restrictions [1-4].

Further, stratification analysis by regions specified by WHO showed that the prevalence of GDM was significantly increased among regions such as Europe and Central Asia, Middle East and North Africa, and North America during the pandemic period (Supplementary Figure 4, www.jofem.org). In addition, stratification analysis by incomes specified by WHO revealed that the prevalence of GDM was significantly increased among lower middle income countries and high income countries but not in upper middle income countries during the pandemic period (Supplementary Figure 5, www.jofem.org). These might be due to the reports that socio-economic determinants of health play a pivotal role in the increased prevalence of GDM [4, 16]. In addition, stratification analysis for cohort studies showed significant association but no significant association was found in case-control studies (Supplementary Figures 6, 7, www.jofem.org).

Regarding COVID-19 as a risk factor for GDM, stratification analysis by cohort studies, case-control studies, WHO regions and incomes was consistent with the finding that pregnant women with COVID-19 were less likely to be diagnosed with GDM among COVID-19 cohorts (Supplementary Fig-

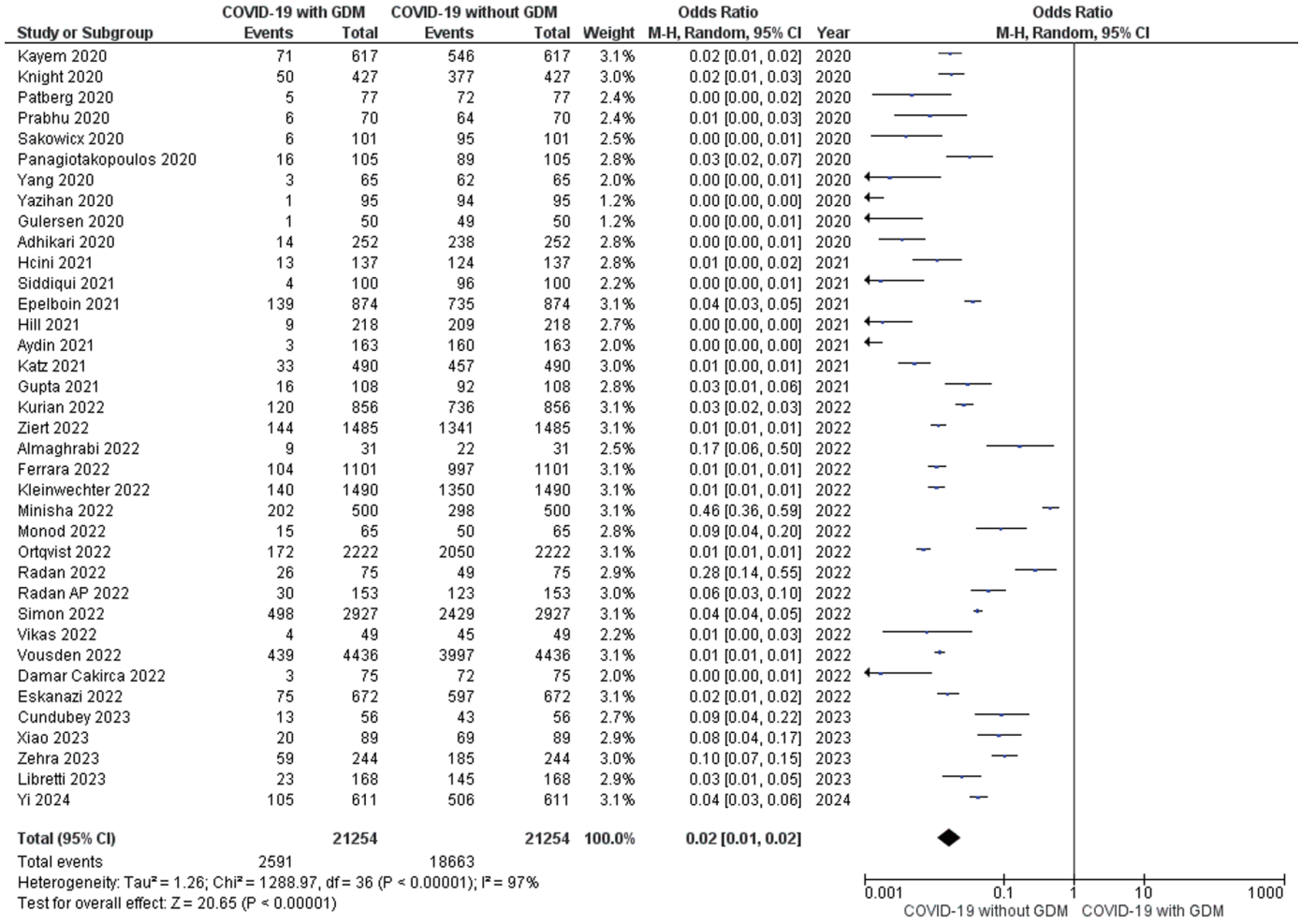

Figure 3. Forest plot shows the random effects meta-analysis model evaluating the risk of COVID-19 for the diagnosis of GDM among pregnant women diagnosed with GDM and without GDM. COVID-19: coronavirus disease 2019; GDM: gestational diabetes mellitus.

ures 8-12, www.jofem.org).

Regarding GDM as a risk factor for COVID-19, stratification analysis by WHO regions showed that the odds of pregnant women with GDM tested positive for COVID-19 were significantly higher among regions such as Europe and Central Asia when compared to pregnant women with GDM tested negative for COVID-19 but no significant association was found among East Asia and Pacific, North America, and South Asia (Supplementary Figure 13, www.jofem.org). Stratification analysis by incomes specified by WHO revealed that the odds of pregnant women tested positive for COVID-19 were significantly higher in high income countries when compared to pregnant women with GDM tested negative for COVID-19 but no significant association was found among lower middle income countries and upper middle income countries (Supplementary Figure 14, www.jofem.org). In addition, stratification analysis for cohort studies showed significant association but no significant association was found in case-control studies (Supplementary Figures 15, 16, www.jofem.org).

In summary, the underlying mechanism behind the increased prevalence of GDM and its associated risk with COVID-19 infection was not exactly known, but the available evidence suggests that disruption of maternity health-care services, reduced health seeking behavior due to the fear of COVID-19 infection or restricted visitations in hospitals due to COVID-19 burden, unequal distribution of tele-health services and nutrition counseling, perceived maternal psychological stress due to financial burdens and social isolation, physical inactivity, dietary and behavioral lifestyle changes might have contributed to the increased prevalence of GDM during the COVID-19 pandemic [1-4, 16]. The increased risk of COVID-19 among pregnant women with GDM (GDM cohorts) might be explained by the hypothesis that taste dysfunction (one of the long COVID pathology) and altered taste perception towards impaired sweet, salt and fat taste stimuli downstream signaling among pregnant women with GDM due to SNPs in taste receptors such as TAS2R subtypes and TRPM5 correlates with the impaired innate immunity regulated by the taste receptor polymorphisms against respiratory infections such as COVID-19 [9-12]. Thus, the increased prevalence of

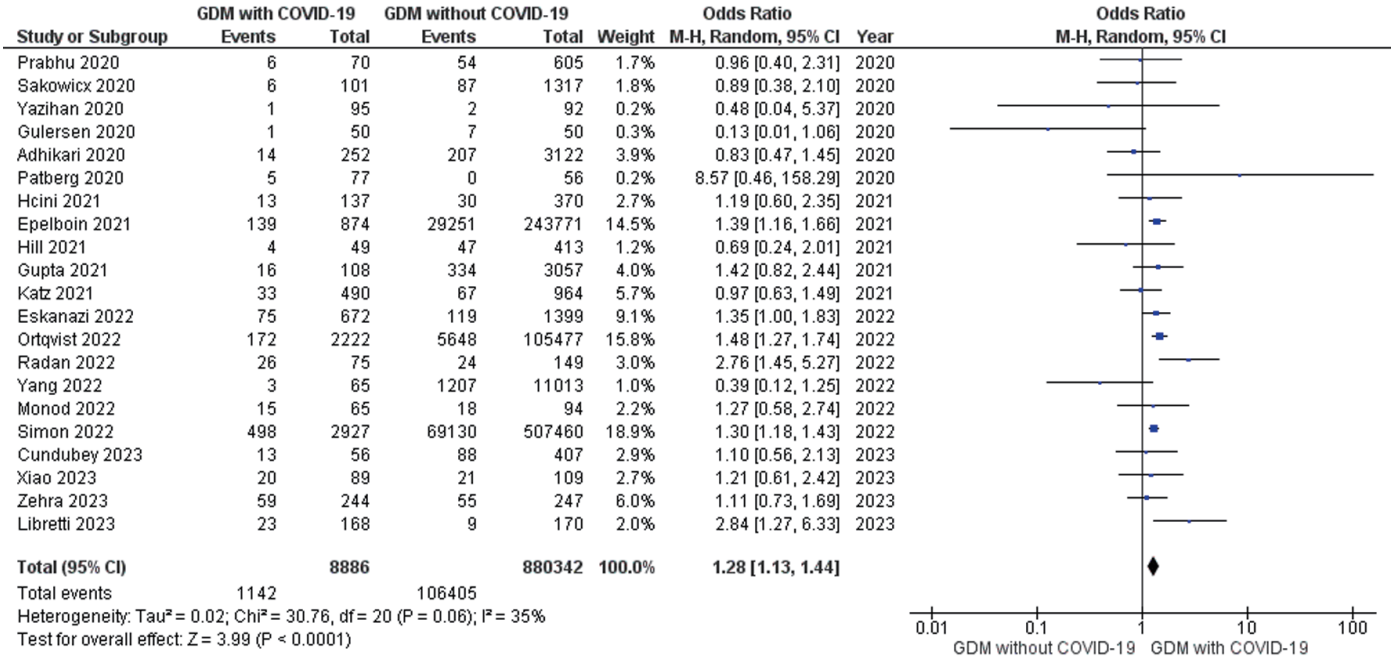

Figure 4. Forest plot shows the random effects meta-analysis model evaluating the risk of GDM for the diagnosis of COVID-19 among pregnant women tested positive and negative for COVID-19. COVID-19: coronavirus disease 2019; GDM: gestational diabetes mellitus.

gestational diabetes among pregnant women during the COVID-19 pandemic might be related to the taste dysfunction due to COVID-19 infection [10-12]. However, molecular studies were needed to validate this hypothesis and evaluate the role of taste receptor polymorphisms and its downstream signaling pathways in the management of COVID-19 and GDM.

Strengths and limitations

Some limitations need to be considered when interpreting these results such as high heterogeneity, retrospective nature of the included studies, different definitions of the study period, lack of stratification analysis regarding asymptomatic COVID-19, severity and timing of COVID-19 infection, timing of GDM diagnosis, different diagnostic criteria for GDM, gestational weight gain, maternal comorbidities, social determinants of health and the literature search was restricted to English language. The high heterogeneity might be due to the different consideration of pandemic and pre-pandemic period among the included studies, different diagnostic criteria for GDM, different region and study population. Additionally, sensitivity analysis showed no credible differences from the overall effect measures (Supplementary Table 2, www.jofem.org). The information regarding the missing data due to reasons specified in the respective included studies were incorporated into the assessment of overall quality of studies by NOS and stratification analysis by excluding the overall poor and fair quality of studies reveals no significant difference from the overall effect measures and several stratification analysis based on different regions, incomes, case-control and cohort studies were shown in the Supplementary Table 2 and Supplementary Figures 4-16 (www.jofem.org). Nevertheless, the present study provides a comprehensive analysis regarding the impact of COVID-19 pandemic on pregnant women with GDM as a full text article compared to the abstracts presented by the author in International Diabetic Federation Congress 2023. Further, the current evidence could aid clinicians and policymakers in the development of more efficient strategies and modify implementation of programs in combating the risk of GDM among pregnant women during future potential pandemics.

Conclusion

The results suggest that there was an increased prevalence of GDM during the COVID-19 pandemic period compared to pre-pandemic period and there was an increased odds of pregnant women with GDM tested positive for COVID-19. This suggests that dysregulated immune mechanisms among pregnant women with GDM might predispose to COVID-19 infections. The etiology might be the taste receptor polymorphisms or other molecular mechanisms yet to be hypothesized which regulates the innate immunity against respiratory infections such as COVID-19. However, the results also suggest that GDM was less likely to be diagnosed among pregnant women with COVID-19 infection. Moreover, molecular studies were needed to evaluate the therapeutic role of taste receptors in the management of COVID-19 and GDM. The present analysis highlights the need for future studies to evaluate the pathophysiological mechanisms of COVID-19 and the impact of associated risk factors on pregnant women with GDM.

Supplementary Material

Suppl 1. PICO definitions for Inclusion criteria.

Supplementary Table 1. Characteristics of participants of the included studies.

Supplementary Table 2. Leave-one out sensitivity analysis.

Supplementary Figure 1. Funnel plot (random (A) and fixed (B) effects models) for the comparison of GDM prevalence during pandemic and pre-pandemic cohorts.

Supplementary Figure 2. Funnel plots (random (A) and fixed (B) effects models) regarding COVID-19 as a risk factor for GDM.

Supplementary Figure 3. Funnel plot (random (A) and fixed (B) effects models) regarding GDM as a risk factor for COVID-19.

Supplementary Figure 4. Forest plot shows the random effects meta-analysis model comparing the prevalence of GDM during pandemic and pre-pandemic period stratified by WHO specified regions.

Supplementary Figure 5. Forest plot shows the random effects meta-analysis model comparing the prevalence of GDM during pandemic and pre-pandemic period stratified by WHO specified countries based on income levels and economies.

Supplementary Figure 6. Forest plot shows the random effects meta-analysis model comparing the prevalence of GDM during pandemic and pre-pandemic period stratified by including only cohort studies.

Supplementary Figure 7. Forest plot shows the random effects meta-analysis model comparing the prevalence of GDM during pandemic and pre-pandemic period stratified by Case-control studies only.

Supplementary Figure 8. Forest plot shows the random effects meta-analysis model evaluating the risk of COVID-19 for the diagnosis of GDM among pregnant women stratified by WHO specified regions. The study Eskanazi et. al., 2022 excluded as it involves 18 countries.

Supplementary Figure 9. Forest plot shows the random effects meta-analysis model evaluating the risk of COVID-19 for the diagnosis of GDM among pregnant women stratified by WHO specified countries with different incomes and economies. The study Eskanazi et. al., 2022 excluded as it involves 18 countries.

Supplementary Figure 10. Forest plot shows the random effects meta-analysis model evaluating the risk of COVID-19 for the diagnosis of GDM among pregnant women stratified by cohort studies only.

Supplementary Figure 11. Forest plot shows the random effects meta-analysis model evaluating the risk of COVID-19 for the diagnosis of GDM among pregnant women stratified by case-control studies only.

Supplementary Figure 12. Forest plot shows the random effects meta-analysis model evaluating the risk of COVID-19 for the diagnosis of GDM among pregnant women stratified by overall high quality studies only.

Supplementary Figure 13. Forest plot shows the random effects meta-analysis model evaluating the risk of GDM for the diagnosis of COVID-19 among pregnant women stratified by WHO specified regions. The study Eskanazi et. al., 2022 excluded as it involves 18 countries.

Supplementary Figure 14. Forest plot shows the random effects meta-analysis model evaluating the risk of GDM for the diagnosis of COVID-19 among pregnant women stratified by WHO specified countries with different incomes and economies. The study Eskanazi et. al., 2022 excluded as it involves 18 countries.

Supplementary Figure 15. Forest plot shows the random effects meta-analysis model evaluating the risk of GDM for the diagnosis of COVID-19 among pregnant women stratified by cohort studies only.

Supplementary Figure 16. Forest plot shows the random effects meta-analysis model evaluating the risk of GDM for the diagnosis of COVID-19 among pregnant women stratified by case-control studies only.

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Conflict of Interest

The author has no relevant financial or non-financial interests to disclose. The author has no competing interest.

Informed Consent

Not applicable.

Author Contributions

Conceptualization, study selection, study screening, quality assessment, data extraction, statistical analysis, original draft, revisions and preparation of final version for submission of the manuscript were carried out by the author Vishnu Shivam.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

AHRQ: Agency for Health Research and Quality; 95% CI: 95% confidence interval; COVID-19: coronavirus disease 2019; GDM: gestational diabetes mellitus; OR: odds ratio; PAV: proline-alanine-valine; PICO: patient/population, intervention, comparison, outcomes; PROSPERO: International Prospective Register of Systematic Reviews; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TAS2Rs: type 2 taste receptors; TAS2R38: type 2 taste receptor R family member 38; TAS2R9: type 2 taste receptor R family member 9; TRPM5: transient receptor potential cation channel subfamily M member 5; WHO: World Health Organization

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