Acta Manilana 72 (2024), 18-32

ISSN: 0065-1370

Acta Manilana

journal homepage: https://actamanilana.ust.edu.ph/

Association of *MTNR1B* rs10830963 C>G Polymorphism with the risk of Gestational Diabetes Mellitus: An Updated Meta-analysis

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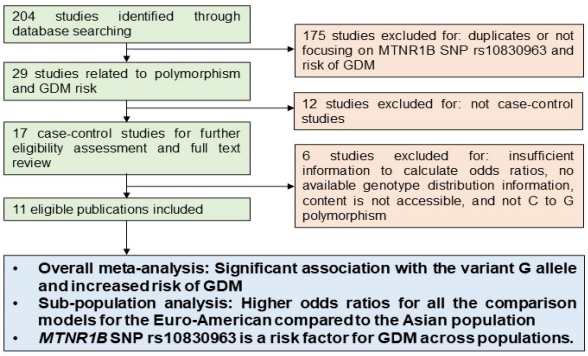
Graphical Abstract



Abstract

Gestational diabetes mellitus (GDM) is one of the metabolic disorders of pregnancy that result in short- and long-term adverse outcomes to both the mothers and her offspring. Among the factors linked to GDM susceptibility, genetic variations such as single nucleotide polymorphisms (SNPs) are the most implicated. Several case-control association studies have reported that the G allele of SNP rs10830963 in the melatonin receptor 1B (*MTNR1B*) is associated with higher GDM risk, however others reported insignificant associations. Previous meta-analyses also showed inconsistent findings. Herein, we performed a comprehensive literature search and meta-analysis to clarify the role of the SNP on GDM risk. Pooled odds ratios (ORs) with 95% CI were calculated to measure the strength of the association. Meta-analysis of the overall population using 11 eligible studies with a total of 4760 GDM cases and 5345 controls revealed significant association with the variant G allele and increased risk of GDM (CC vs. CG: OR = 1.28, 95% CI = 1.17−1.41, P < 0.001; CC vs. GG: OR = 1.92, 95% CI = 1.49−2.49, P < 0.001; C vs. G: OR = 1.30, 95% CI = 1.16−1.46, P < 0.001).

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DOI: https://doi.org/10.53603/actamanil.72.2024.aryw4782

Date Received: 10 January 2024
Date Revised: 16 February 2024
Date Accepted: 19 February 2024

In the subpopulation analysis, similar results were observed in Asians (CC vs. CG: OR = 1.26, 95% CI = 1.07−1.49, P = 0.005; CC vs. GG: OR = 1.66, 95% CI = 1.26−2.19, P < 0.001; C vs. G: OR = 1.30, 95% CI = 1.12−1.50, P < 0.001) with notably lower OR for CC vs GG. For the Euro-American population, higher ORs were noted for all the comparison models (CC vs. CG: OR = 1.40, 95% CI = 1.15−1.70, P = 0.005; CC vs. GG: OR = 2.84, 95% CI = 2.05−3.93, P < 0.001; C vs. G: OR = 1.37, 95% CI = 1.19−1.58, P < 0.001). Overall, the results suggest that the *MTNR1B* SNP rs10830963 is a risk factor for GDM across all populations with increased susceptibility observed among Euro-Americans.

Keywords: rs10830963; single nucleotide polymorphism; type 2 diabetes; gestational diabetes; melatonin receptor 1B; meta-analysis

Introduction

Normal pregnancy in women is known to be associated with metabolic changes such as increased adipose deposition and aggravated insulin resistance. These physiological abnormalities may result in gestational diabetes mellitus (GDM), a condition characterized by inability of the body to produce enough insulin to regulate blood sugar levels during pregnancy [1-2]. In a meta-analysis by Saeedi et al. [3], the GDM prevalence rate worldwide is at 14.7% following the International Association of Diabetes and Pregnancy Study Groups criteria. In the Philippines, a slightly smaller prevalence rate at 14% has been reported. A study in 2018 which utilized a more limited population scope (University of Santo Tomas Hospital – Clinical Division) showed GDM had a prevalence rate of 7.5% [4-5]. In terms of the unwanted outcomes, GDM can cause adverse effects such as pre-eclampsia, premature birth, and large birth weight babies, which can increase the risk of delivery complications [6]. The risk of developing type 2 diabetes mellitus for both the mother and baby is also higher among GDM patients [7]. Therefore, it is important to identify potential risk factors for GDM prior to pregnancy.

Among the known risk factors for GDM include obesity, a family history of diabetes, and increased maternal age [8-9]. Several studies have also shown that genetic factors have major roles in GDM susceptibility. Recent genome-wide association studies in various populations found that genetic variants near or within the melatonin receptor 1B (*MTNR1B*), a 22 kb-gene located on chromosome 11q21 to 11q22, were strongly linked to GDM [10-11]. More than 60 single nucleotide polymorphisms (SNPs) have been reported in *MTNR1B*, including SNP rs10830963, a C>G substitution found in the unique intron between the two exons of the gene [12].

Due to the functional effects of SNP rs10830963 C>G, several association studies have been conducted to determine its association with the risk of developing GDM. Some genotype-phenotype studies have shown that the G allele of SNP rs10830963 is associated with higher *MTNR1B* transcript levels and increased insulin resistance leading to increased GDM risk, however others reported either insignificant or much weaker associations in terms of the odds ratio values [13-16]. Previous meta-analyses, which included studies published up until 2017, have been recommended to update the statistical power of their findings [17-18]. From 2018 to 2022, more case-control studies have been published with inconsistent results and conclusions.

Therefore, an updated meta-analysis with a larger sample size and with the inclusion of more Asian samples [16, 19] and Arabian populations [20] is warranted to further clarify the role of SNP rs10830963 C>G as a predisposing factor in the development of GDM.

Materials and methods

Study Selection. A comprehensive literature search was conducted for genetic association studies on single nucleotide polymorphism (SNP) rs10830963 and gestational diabetes mellitus (GDM) published prior to January 2023 using Google Scholar, PubMed, Medline, ScienceDirect, Cochrane Library and SpringerLink databases. The keywords used were "gestational diabetes mellitus", "melatonin receptor 1B" or "*MTNR1B*", "single nucleotide polymorphisms" or "variants" or "SNP", "rs10830963", and "association" as well as their combinations. The primary keywords used to retrieve journal articles were "*MTNR1B*", and "gestational diabetes mellitus". The Boolean operator "and" was utilized to combine keywords during the search strategy.

Studies were required to meet the following inclusion criteria: (1) it must be a case-control study; 2) studies must be published before January 2023; (3) literatures must be focused on the association between SNP rs10830963 C>G polymorphism and GDM susceptibility; (4) there are definite diagnostic criteria for GDM; and (5) there is an available genotype distribution information and odds ratios with 95% confidence interval (CI). Review papers, commentary articles, previous meta-analyses, non-English and non-accessible publications, and articles with incomplete raw data or duplicate data and irrelevant information to *MTNR1B* genetic polymorphisms and GDM were excluded.

Data Extraction. The titles and abstracts of potential articles obtained during the literature search were screened and reviewed by three independent reviewers (S Gutierrez, M Magdalaga, O Albuaimi, and J Manzano) according to the selection criteria. Discrepancies were resolved through consensus and group discussion. Data was extracted by the reviewers from the screened articles were as follows: name of the first author, year of publication, country, ethnicity of population, country of origin of the cases and controls, number of GDM cases and controls, mean age of GDM cases and controls, genotypic distribution data, allelic distribution data or frequency, and significant results of the association studies. Hardy-Weinberg equilibrium (HWE) *p*-values for controls were calculated.

Statistical Analysis. A meta-analysis was conducted to investigate the association between *MTNR1B* SNP rs10830963 and GDM in the overall population. The reviewers also performed subgroup analysis in the Asian and Euro-American subpopulations. Due to lack of data on American population with only one study, we opted to combine both European and American (Western) populations. Odds ratios (ORs) with respective confidence intervals (CIs) were calculated to determine the strength of the associations through comparison of the minor (G) and the major (C) alleles, and genotypes. Three comparison models were generated – homozygous contrast (CC vs GG), heterozygous contrast (CC vs CG), and allelic contrast (C vs G). Data analysis was performed using Review Manager (RevMan) Statistical Software (version 5.4.1; Cochrane Collaboration, Oxford, England).

The Chi-square (X^2) test was utilized to calculate the heterogeneity of the gathered studies in terms of the degree of association. In addition, the I^2 statistic was used to compute the percentage of variation in the results caused by the heterogeneity instead of utilizing the sampling error ($I^2 > 50\%$, significant heterogeneity) [21]. If the variation was found to be heterogeneous, a random-effects model will be used to pool the OR; otherwise, a fixed-effect model was adopted [22]. In the case of the fixed-effect models, a fixed population effect is assumed and the true effect size for all the studies is considered statistically identical which means the effect size variation between studies is due to within-studies estimation error. For random-effects models, it is presumed that the effect sizes are sampled from a population of effect sizes and that the true effect sizes are warranted to vary due to differences in the mixes of participants across all studies [23-24]. The pooled ORs were evaluated using Z-test for overall effect (p-value < 0.05, statistically significant).

The Chi-square (X^2) test was also used to compute the statistical difference between the controls and patients with GDM in terms of their genotypic and allelic frequencies. The genotypic distribution was analyzed to determine conformity with HWE using Microsoft Excel.

Results

Study Selection and Characteristics of Eligible Studies. The flow diagram of the selection process for the included studies is summarized in Figure 1. A total of 204 studies were initially identified through database searching, 107 of which were obtained from Google Scholar, 34 from SpringerLink and 63 from PubMed. Titles of the studies were screened, and 175 publications were excluded for duplicates or not focusing on rs10830963 polymorphism and risk of GDM. The remaining 29 studies were further evaluated based on study design and 12 were excluded because these were not case-control studies. Of the remaining 17 studies, 6 were excluded due to lack of insufficient data to calculate odds ratios and genotypic distribution, inaccessible content, and different SNP which was C to T and not C to G was used. Overall, a total of 11 publications were included in this meta-analysis.

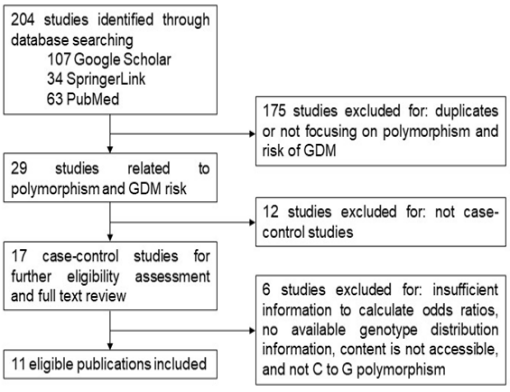

Figure 1. Flow diagram of the selection process of eligible studies.

Table 1. Characteristics of included studies showing the year of publication, ethnicity of subjects, country of origin, mean age of subjects, Hardy-Weinberg Equilibrium (HWE) p-value for controls, and their findings.

Authors	Year	Ethnicity of subjects	Country of study	P_{HWE} for controls	Association between rs10830963 and increased GDM risk
Kim et al. [25]	2011	Asian	South Korea	0.8197	Significant association
Wang et al. [13]	2011	Asian	China	0.9720	No significant association
Vlassi et al. [26]	2012	European	Greece	0.0697	Significant association
Li et al. [27]	2013	Asian	China	0.9651	Significant association
Vejrazkova et al. [28]	2014	European	Czech Republic	0.5819	Significant association
Junior et al. [29]	2015	American	Brazil	0.2802	Significant association
Liu et al. [14]	2016	Asian	China	0.0703	Significant association but relatively weak (OR < 1, 95% CI)
Tarnowski et al. [15]	2017	European	Poland	0.2832	Significant association
Li et al. [19]	2018	Asian	China	0.7931	Significant association
Alharbi et al. [20]	2019	Asian	Saudi Arabia	0.0002	Significant association
Liu et al. [16]	2022	Asian	China	0.3127	Significant association

In Table 1, the main characteristics of the included publications (n=11) are presented. All the genotypic frequency distributions of the polymorphism in controls agreed with the Hardy-Weinberg equilibrium (HWE) except for the study of Alharbi et al. [20]. In terms of significant findings, only the study of Wang et al. [13] concluded insignificant association between rs10830963 C>G polymorphism and increased risk of GDM. Meanwhile, Liu et al. [14] indicated significant association yet with a weak OR value of less than 1 (95% CI).

Meta-analysis of the overall population. In this meta-analysis, a total of 4760 GDM cases and 5345 controls were used from the 11 studies. The genotypic and allelic frequencies of both GDM cases and controls were calculated and combined in Table 2. For the GDM cases, the highest genotypic frequency was observed in the heterozygous wild-type (CG) with 48% while the lowest in the homozygous mutant type (GG) with 24%. A similar scenario was noted in the controls with the heterozygous wild-type having the highest frequency (47%) and lowest in the homozygous mutant type (19%). Additionally, the wild-type allele (C) showed higher frequency for both cases and controls with 52% and 57%, respectively.

To identify the statistical difference between the genotypic and allelic frequencies in GDM cases and controls, we performed chi-square test (X^2) which revealed the significant difference between the two groups for both genotype ($p < 0.0001$) and allelic frequencies ($p < 0.0001$).

Table 2. Genotypic and allelic frequencies in the overall population for both cases and controls. The X^2 and *p*-values **are also shown.**

Variable	GDM no. (%)	Control no. (%)	X^2, *p*-value
Genotype			
CC	1314 (0.28)	1775 (0.33)	
CG	2284 (0.48)	2534 (0.47)	$X^2 = 60.0304$, $p < 0.0001$
GG	1162 (0.24)	1036 (0.19)	
Allele			
C	4912 (0.52)	6107 (0.57)	$X^2 = 62.2637$, $p < 0.0001$
G	(0.48)	4583 (0.43)	

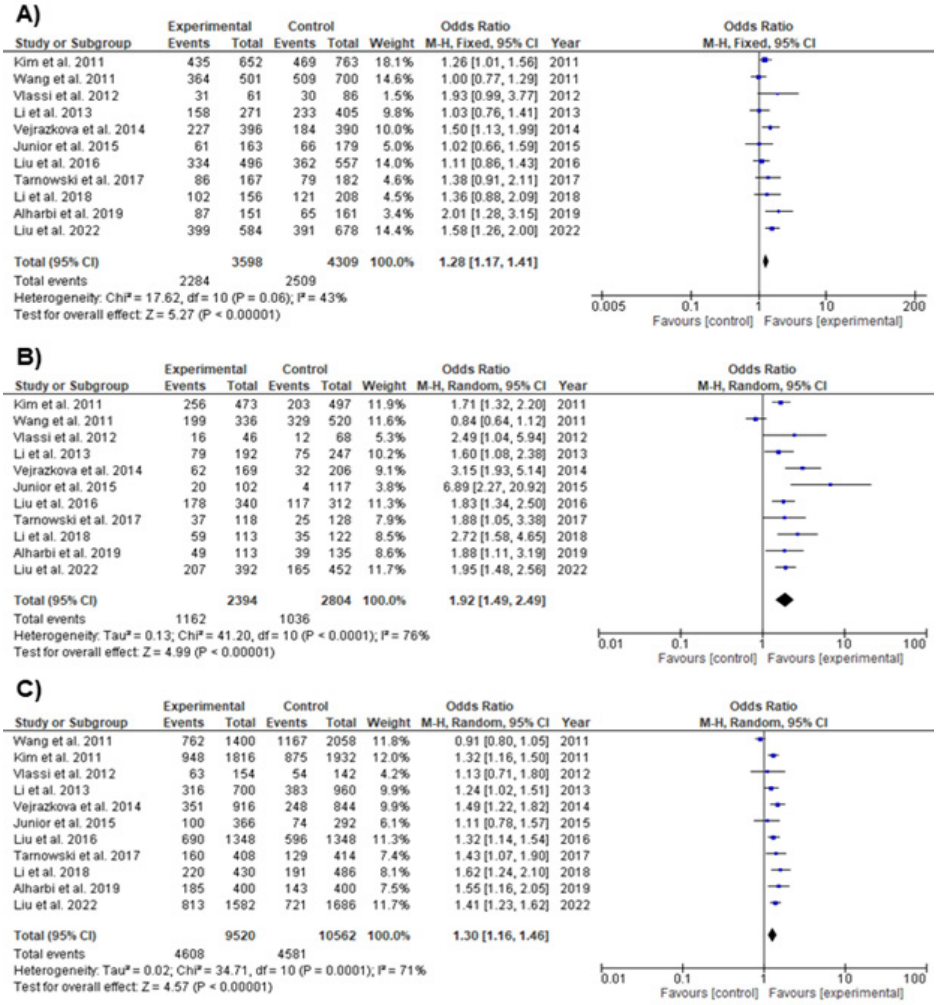

Figure 2. Meta-analysis of the overall population: (a) comparison of CC vs. CG genotypes; (b) comparison of CC vs. GG genotypes; and (c) comparison of C vs G alleles.

The GDM group deviated from HWE ($P_{HWE} < 0.05$) and this departure from HWE has been implicated in many case-control studies as possible genetic association between the SNP and GDM risk. Additionally, case groups do not need to agree with HWE and may be due to lack of fit test [30].

In the meta-analysis of the overall population with 11 studies, the association between rs10830963 C>G polymorphism and GDM risk was statistically tested. Individual and overall odds ratios (ORs) and its corresponding 95% confidence intervals (CI), as well as the p-values for the overall effect, are shown in Figure 2.

To determine the association between *MTNR1B* SNP rs10830963 and GDM risk, odds ratios for the genotypic and allelic frequencies from the combined eleven studies were calculated. The wild-type genotype (CC) and major allele (C) served as baselines for comparison thus generating three comparison models – heterozygous contrast (CC vs CG), homozygous contrast (CC vs GG), and allelic contrast (G vs C). Due to the significant heterogeneity (I^2 > 50%) found in both homozygous and allelic contrast models, a random-effects model was used. Fixed-effects model was used in the heterozygous contrast model. As shown in Figure 2, the pooled data revealed significant association between rs10830963 and GDM susceptibility in the three models (CC vs. CG: OR = 1.28, 95% CI = 1.17−1.41, P < 0.001; CC vs. GG: OR = 1.92, 95% CI = 1.49−2.49, P < 0.001; C vs. G: OR = 1.30, 95% CI = 1.16−1.46, P < 0.001). The highest OR was observed in the homozygous dominant contrast model (CC vs GG).

Subgroup analysis of the Asian population. To further identify the relevance of SNP rs10830963 C>G as a predisposing factor to increased GDM susceptibility, the Asian (or Eastern) population with seven studies and the Euro-American (or Western) population with four studies were subjected to stratified (or subgroup) analysis. The American population was merged with European data as only one study was included for the earlier.

In the subgroup analysis for the Asian population, there were 3838 GDM cases and 4435 controls. The combined genotypic and allelic frequencies are shown in Table 3. Similar to the data from the overall population, the highest genotypic frequencies were observed in the heterozygous wild-type with 49% and 48% for the GDM and control groups, respectively. However, the lowest genotypic frequency was observed in the homozygous wild-type (24%) for the cases while in the homozygous mutant (22%) for the controls. The wild-type allele frequency (56%) was also higher for the control group, but higher frequency was observed in the mutant allele (1%) for GDM cases. Chi-square test (X^2) revealed significant differences between the genotypic ($p < 0.0001$) and allelic frequencies ($p < 0.0001$) in the GDM and control groups.

For the stratified analysis, the same comparison models in the overall population were utilized. A random-effects model was used for the models (I^2 > 50%). Similar to the overall population, there were also significant associations between rs10830963 and GDM risk in the Asian population in these models (CC vs. CG: OR = 1.26, 95% CI = 1.07−1.49, P = 0.005; CC vs. GG: OR = 1.66, 95% CI = 1.26−2.19, P < 0.001; C vs. G: OR = 1.30, 95% CI = 1.12−1.50, P < 0.001) (Figure 3). Notably, there was a less OR value in the homozygous contrast model (CC vs GG) among Asians compared with the overall pooled data.

Table 3. Genotypic and allelic frequencies in the Asian population.

Variable	GDM no. (%)	Control no. (%)	X^2, *p*-value
Genotype			
CC	932 (0.24)	1322 (0.30)	
CG	1879 (0.49)	2150 (0.48)	X^2 = 44.9194, p < 0.0001
GG	1027 (0.27)	963 (0.22)	
Allele			
C	3742 (0.49)	4794 (0.54)	X^2 = 46.2476, p < 0.0001
G	3934 (0.51)	4076 (0.46)	

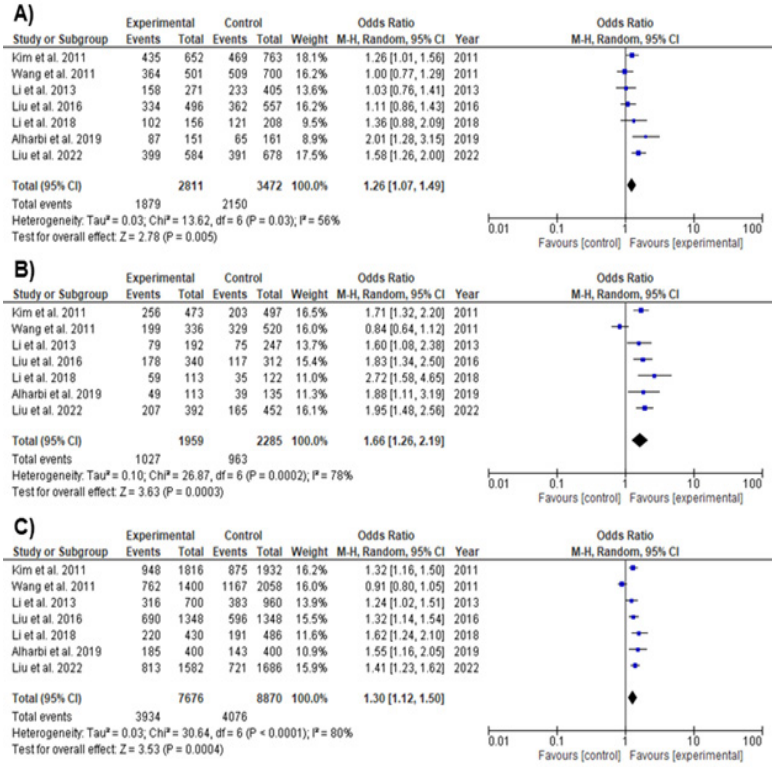

Figure 3. Subgroup analysis of the Asian population: (a) comparison of CG vs GG genotypes; (b) comparison of CC vs GG genotypes; and (c) comparison of C vs G alleles.

Subgroup analysis of the Euro-American population. To assess the effect of rs10830963 to GDM susceptibility among Euro-Americans, subgroup analysis was performed with 922 GDM cases and 910 controls. The highest genotypic frequency for the GDM cases was observed in the heterozygous wild-type with 44%, followed by the homozygous wild-type with 41%. However, homozygous wild-type (CG) had the highest genotypic frequency for the control group (53%) (Table 4). Significant difference exists between the genotypic ($p < 0.0001$) and allelic ($p < 0.0001$) frequencies in the GDM and controls. Both groups agreed with HWE ($P_{HWE} > 0.05$).

Table 4. Genotypic and allelic frequencies in the Euro-American population.

Variable	GDM no. (%)	Control no. (%)	X^2, *p*-value
Genotype			
CC	382 (0.41)	478 (0.53)	
CG	405 (0.44)	359 (0.39)	$X^2 = 31.8894$, $p < 0.0001$
GG	135 (0.15)	73 (0.08)	
Allele			
C	1170 (0.63)	1315 (0.72)	$X^2 = 32.5297$, $p < 0.0001$
G	674 (0.37)	505 (0.28)	

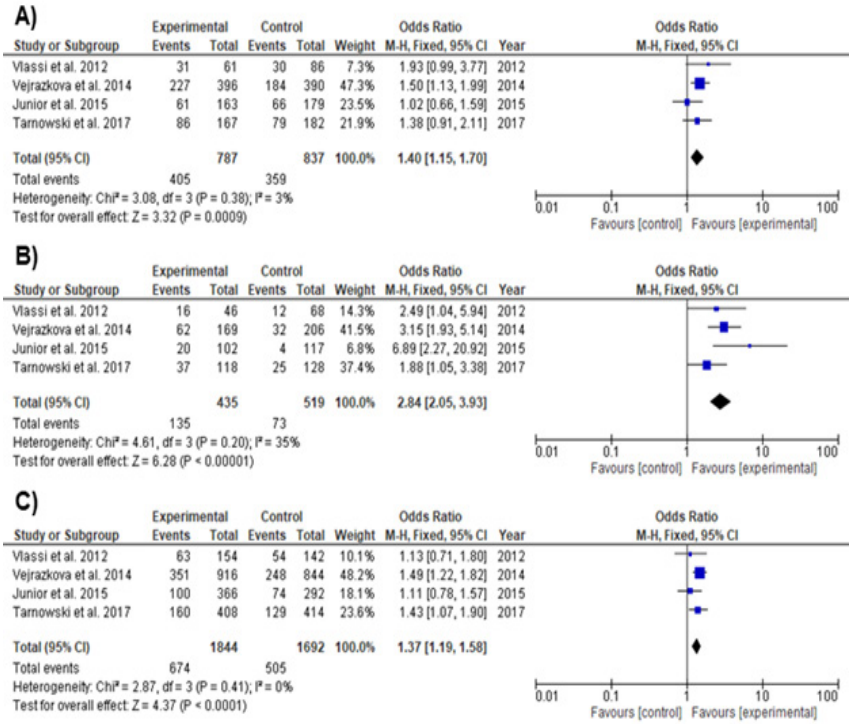

Figure 4. Subgroup analysis of the Euro-American population: (a) comparison of CG vs GG genotypes; (b) comparison of CC vs GG genotypes; and (c) comparison of C vs G alleles.

For the Euro-American population, the same three models for homozygous contrast, heterozygous contrast, and allelic contrast were used. Fixed-effects model was used in all the models (I^2 > 50%). Stronger significant associations were determined for the Euro-American subpopulation in terms of the computed odds ratios (CC vs. CG: OR = 1.40, 95% CI = 1.15−1.70, P = 0.005; CC vs. GG: OR = 2.84, 95% CI = 2.05−3.93, P < 0.001; C vs. G: OR = 1.37, 95% CI = 1.19−1.58, P < 0.001) (Figure 4). The highest OR difference between the Euro-American subgroup and the Asian population was reported in the homozygous contrast model (CC vs GG) with almost 1.5x higher risk for Euro-Americans with genotype GG compared to the baseline genotype CC.

Discussion

Gestational diabetes mellitus (GDM) is known to predispose patients to type 2 following other short- and long-term adverse pregnancy outcomes [31]. Moreover, GDM can also increase the risk of the mother to develop hypertension, dyslipidemia, obesity and other cardiovascular diseases [18]. Although family history, lifestyle, and other environmental factors have been reported to be associated with GDM, enormous studies have indicated the key role of genetic factors in increasing GDM susceptibility [32-34].

Genome-wide association studies and candidate gene-based association case-control studies have shown that genetic variants, such as single nucleotide polymorphisms (SNPs), are implicated in the etiology and pathophysiology of GDM. These SNPs were shown to eventually lead to impairment of β-cells, resistance to insulin, and/or abnormal uptake and utilization of glucose [10, 35-36].

In our present study, we report the significant association of *MTNR1B* SNP rs10830963 C>G with increased risk of GDM, especially among Euro-Americans (Figure 3 and 4).

MTNR1B is a gene that codes for MT2 protein, which is a G-protein coupled 7-transmembrane receptor and is considered as a high-affinity melatonin receptor [37-38]. Melatonin acts as a neurohormone and a ligand to this receptor which regulates the circadian rhythm via photoperiodic switching from the eyes to the central nervous system and this rhythm modulates insulin levels in the body [39]. Several experimental studies have shown that the variant G allele caused an increased *MTNR1B* expression compared to that of the wild-type C allele. Therefore, it has been suggested that the increased expression of *MTNR1B* may alter the normal insulin regulatory functions of the melatonin-MT2 receptor complex [40]. Putative mechanisms of the downregulation of insulin secretion include modified disposition index and impaired β-cells thereby leading to acute insulin response as observed in type 2 diabetes patients with genetic variations in the *MTNR1B* gene [40-42]. It is also proposed that increased *MTNR1B* expression may lead to decreased intracellular cyclic adenosine monophosphate levels in β cells and eventually downregulate glucose-stimulated insulin release [17]. In our meta-analysis, *MTNR1B* SNP rs10830963 C>G was shown to be associated with increased incidence of GDM, especially among Euro-Americans (Figure 4).

Previous meta-analyses have been conducted and showed inconsistent results. Zhang et al. [9] reported significant association between *MTNR1B* rs10830963 C>G and GDM incidence for CG vs GG model (OR = 1.24, 95% CI = 1.14-1.35). However, only 5 studies with a total of 2122 GDM cases and 2664 controls were utilized, and subgroup analysis was not performed. In the updated meta-analyses of Huang et al. [17] and Bai et al. [18], only studies published up to 2017 were included. Since then, there have been more case-control studies published. Our updated meta-analysis showed that publications from 2018 to 2022 accounted for 22.3%, 28.8%, and 27.3% of the pooled data for the homozygous contrast (CC vs CG), homozygous contrast (CC vs GG), and allelic contrast (G vs C) models, respectively (Figure 2).

In addition, Bai et al. [18] reported significant association between *MTNR1B* rs10830963 C>G and GDM risk in the overall population with 3296 GDM cases and 3709 controls. Similar results were reported for both Asian and European populations. However, this study concluded that Euro-Americans with *MTNR1B* SNP rs10830963 C>G may have much greater susceptibility to GDM compared to Asians. The study also recommended increasing the sample size to strengthen the statistical power of the data. In the present meta-analysis, a higher number of GDM cases (n = 4760) and controls (n = 5345) were used, and we report similar significant association for the overall population.

The current meta-analysis offers an updated statistical power in terms of the association between *MTNR1B* SNP rs10830963 C>G and GDM risk. However, some limitations should be acknowledged such as the limited number of studies for the American population which might restrict the statistical power of the data for the stratified analysis, especially the Euro-American subgroup. We also acknowledge that the majority of the studies included in the meta-analysis showed significant associations. However, the inclusion of more recent studies contributed to the updated statistical data of our meta-analysis.

We also recommend further analysis on the effect of the SNP rs10830963 on indices and tests implicated in GDM pathogenesis such as β-cell function and insulin responses and sensitivity.

Conclusion

In summary, this current meta-analysis suggests that the *MTNR1B* SNP rs10830963 C>G may increase the risk of developing GDM in both Asian (Western) and Euro-American (Western) populations. Euro-Americans with rs10830963 C>G polymorphism appear to be more susceptible to GDM compared to Asians. However, studies with much larger samples especially among Americans, more diverse populations such as African and South American populations, and further functional experimental investigations on the effect of the SNP to pathologic hallmarks of GDM across populations are warranted.

Acknowledgment

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization, methodology, data collection, data analysis and interpretation, original draft preparation, review and editing of the draft, J.A.H.M, S.M.G., M.T.M. Methodology, data collection, data analysis and interpretation, original draft preparation, review and editing of the draft, O.A.A. Conceptualization, data analysis and interpretation, review and editing of the draft, supervision, J.D.A.R. All authors have read and agreed to the final version of the manuscript.

Funding

None.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

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