Endokrynologia Polska
DOI: 10.5603/EP.a2017.0045
Tom/Volume 68; Numer/Number 5/2017
ISSN 0423–104X

Melatonin receptor 1B gene polymorphism rs10830963 and gestational diabetes mellitus among a Chinese population — a meta-analysis of association studies

Polimorfizm rs10830963 w genie receptora melatoniny 1B a cukrzyca ciążowa w populacji chińskiej — metaanaliza badań

Xiao-lin Lu[1], Xiu-ying Yao[2], Xin-li Liu[2], Yu-Xin[1], Lin-lin Zhao[2], Zhen Wang[1], Ming-ming Cui[1], Li-hua Wu[1], Shao-fang Shangguan[1], Shao-yan Chang[1], Ting Zhang[1], Li Wang[1]

[1]Beijing Municipal Key Laboratory of Child Development and Nutriomics, Capital Institute of Pediatrics, Beijing 100020, China
[2]Department of Obstetrics and Gynecology, PLA army general hospital 263th Clinical Department, Beijing 100024, China

Abstract

Introduction: Studies have been conducted to investigate the association between rs10830963 of *MTNR1B* and the risk of gestational diabetes mellitus (GDM), but with inconclusive results. We aimed to clarify these controversies, especially with regard to the association in the Chinese population.

Material and methods: A systemic literature reference search inclusive to August 12, 2016 yielded 35 articles, from which 11 studies met the inclusion criteria for the final meta-analysis, including 3889 patients with GDM and 6708 controls.

Results: We found statistically significant associations between rs10830963 and GDM using odds ratios (ORs) and 95% confidence intervals (CIs) [GG genotype vs. CC genotype: OR = 1.70, 95% CI: 1.38–2.10; G allele vs C allele: OR = 1.27, 95% CI: 1.20–1.36; GG+CG vs. CC (dominant model): OR = 1.31, 95% CI: 1.20–1.44; GG vs CG+CC (recessive model): OR = 1.41, 95% CI: 1.26–1.58]. In subgroup analyses stratified by ethnicity, we also observed rs10830963 to be associated with significantly increased risk of GDM in all genetic models in the Chinese population.

Conclusions: Our meta-analysis indicated that the rs10830963 polymorphism might serve as a risk factor of GDM in the Chinese population. **(Endokrynol Pol 2017; 68 (5): 550–560)**

Key words: *single nucleotide polymorphism, melatonin receptor 1B gene, gestational diabetes mellitus, meta-analysis*

Streszczenie

Wstęp: Wyniki dotychczas badań przeprowadzonych w celu ustalenia związku między polimorfizmem rs10830963 w genie *MTNR1B* a ryzykiem cukrzycy ciążowej (*gestational diabetes mellitus*, GDM) nie pozwoliły na sformułowanie jednoznacznych wniosków. Niniejsze badanie przeprowadzono w celu wyjaśnienia tych kontrowersji, zwłaszcza w odniesieniu do występowania tych związków w populacji chińskiej.

Materiał i metody: W wyniku przeszukania w sposób systematyczny piśmiennictwa obejmującego okres do 12 sierpnia 2016 roku wytypowano 35 artykułów, spośród których 11 badań spełniało kryteria włączenia do metaanalizy. Obejmowały one 3889 chorych z GDM i 6708 osób kontrolnych.

Wyniki: Autorzy stwierdzili statystycznie istotny związek między polimorfizmem rs10830963 a GDM, obliczając ilorazy szans (*odds ratio*, OR) i 95-procentowe przedziały ufności (*confidence interval*, CI) [genotyp GG *vs.* genotyp CC: OR = 1,70; 95% CI: 1,38–2,10; allel G *vs.* allel C: OR = 1,27; 95% CI: 1,20–1,36; GG+CG vs CC (model dominujący): OR = 1,31; 95% CI: 1,20–1,44; GG *vs.* CG+CC (model recesywny): OR = 1,41; 95% CI: 1,26–1,58]. W analizach podgrup wydzielonych na podstawie pochodzenia etnicznego również stwierdzono, że polimorfizm rs10830963 wiąże się z istotnie wyższym ryzykiem GDM we wszystkich modelach genetycznych w populacji chińskiej.

Wnioski: Przeprowadzona przez autorów metaanaliza wskazuje, że polimorfizm rs10830963 może być uważany za czynnik ryzyka GDM w populacji chińskiej. **(Endokrynol Pol 2017; 68 (5): 550–560)**

Słowa kluczowe: *polimorfizm pojedynczego nukleotydu, gen receptora melatoniny 1B, cukrzyca ciążowa, metaanaliza*

Introduction

Gestational diabetes mellitus (GDM), defined as glucose intolerance of variable degree with onset or first recognition during pregnancy, is among the most common metabolic disorders during pregnancy. The prevalence of GDM, with a rising trend globally, varies by area and ethnic population. During the last decade, the prevalence of GDM among western countries varied from 1–3% to 8–18% [1, 2]. For Asian females, including the

Ting Zhang, Li Wang, Beijing Municipal Key Laboratory of Child Development and Nutriomics, Capital Institute of Pediatrics, Beijing 100020, China tel: +86-10-85695585. Fax: +86-10-85631504. e-mail: lily_wang@yeah.net; zhangtingcv@126.com

Chinese Han population, the prevalence of GDM was hypothesised to be higher than in Caucasian females [3].

Studies have shown that GDM is strongly associated with both maternal and offspring adverse health outcomes, including macrosomia, stillbirths, and neonatal metabolic disturbances. Pregnant women with GDM are more likely to be affected with type 2 diabetes mellitus (T2DM) and develop multiple cancers in the years following pregnancy [4]. With the increasing incidence and severe consequence of GDM, it has become a growing health concern.

GDM, caused by environmental and genetic factors, as well as gene-environment interactions, shares similar pathophysiological features to T2DM, such as glucose intolerance, insulin resistance, and impaired pancreatic β-cell function [5–7]. Furthermore, several studies have revealed that women with GDM history are more likely to develop T2DM. In addition, women with a family history of T2DM may be more predisposed to develop GDM than those without a GDM history [1, 6]. These studies suggest that susceptible genes are involved in T2DM and probably also contribute to the genetic aetiology of GDM.

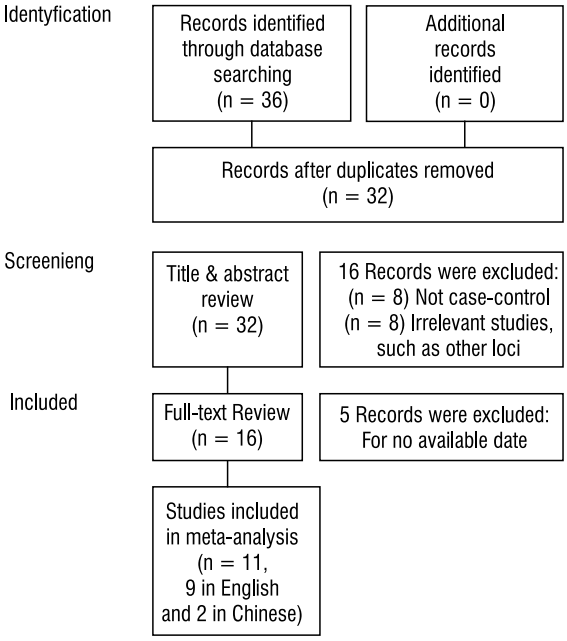


Figure 1. *Flow diagram of the selected studies and specific reasons for exclusion from the present meta-analysis*

Rycina. 1. *Diagram przedstawiający wybór badań i przyczyny wykluczenia niektórych badań z metaanalizy*

Table I. ***Characteristics of included studies***

Tabela I. ***Charakterystyka włączonych badań***

Author	Year	Ethnicity	GDM			Control			Diagnostic criteria	Genotyping method
			Sample size	Age mean ± SD	Pregravid BMI mean ± SD	Sample size	Age mean ± SD	Pregravid BMI mean ± SD		
Deng	2011	Chinese	87	31.8 ± 4.6	23.6 ± 3.0	91	29.7 ± 3.5	21.5 ± 2.4	OGTT confirmed	Sequencing
Wang	2011	Chinese	725	30.00 (28.00, 3.00)*	21.48 (19.57, 23.62)*	1039	32.00 (30.00, 35.00)*	21.72 (19.89, 24.04)	GDM per ADA criteria	TaqMan
Kim	2011	Korean	928	33.17 (22–52)*	23.32 ± 4.01	990	32.24 (23–44)*	21.40 ± 2.93	OGTT confirmed	TaqMan
Vlassi	2012	Greek	77	35.45 ± 4.44	25.83 ± 5.13	98	31.39 ± 5.25	26.76 ± 6.26	GDM per ADA criteria	Applied Biosystems SNaPshot
Qi	2013	Chinese	110	28.75 ± 3.19	NA	110	28.17 ± 2.43	NA	GDM per ADA criteria	PCR-SSCP
Li	2013	Chinese	350	32.42 ± 4.87	25.34 ± 5.27	480	31.98 ± 5.21	24.69 ± 4.61	GDM per IADPSG criteria	PCR-RFLP
Stuebe	2014	Caucasian	56	NA	NA	843	NA	NA	OGTT confirmed	Sequenom iPLEX platform
		African-American	24	NA	NA	362	NA	NA	OGTT confirmed	Sequenom iPLEX platform
Wang	2014	Chinese	184	28.2 ± 3.8	21.2 ± 1.8	235	27.9 ± 4.1	20.7 ± 1.4	OGTT confirmed	PCR-SSCP
Vejrazkova	2014	Czechs	485	34.1 ± 6.12	24.3 ± 4.93	422	34.8 ± 15.09	23.7 ± 4.18	WHO guidelines	TaqMan
Junior	2015	Euro-Brazilian	183	32 (28–36)*	32.0 (27.7–36.4)*	183	29 (27–33)*	25.4 (22.5–28.3)*	GDM per ADA criteria	TaqMan
Liu	2016	Chinese	674	31.6#	24.41#	690	32.1	25.12	OGTT confirmed	TaqMan

*The results are presented as median (interquartile-range); # The results are presented as mean only; OGTT, the oral glucose tolerance test; ADA, the American Diabetes Association; IADPSG, the International Association of Diabetes in Pregnancy Study Groups

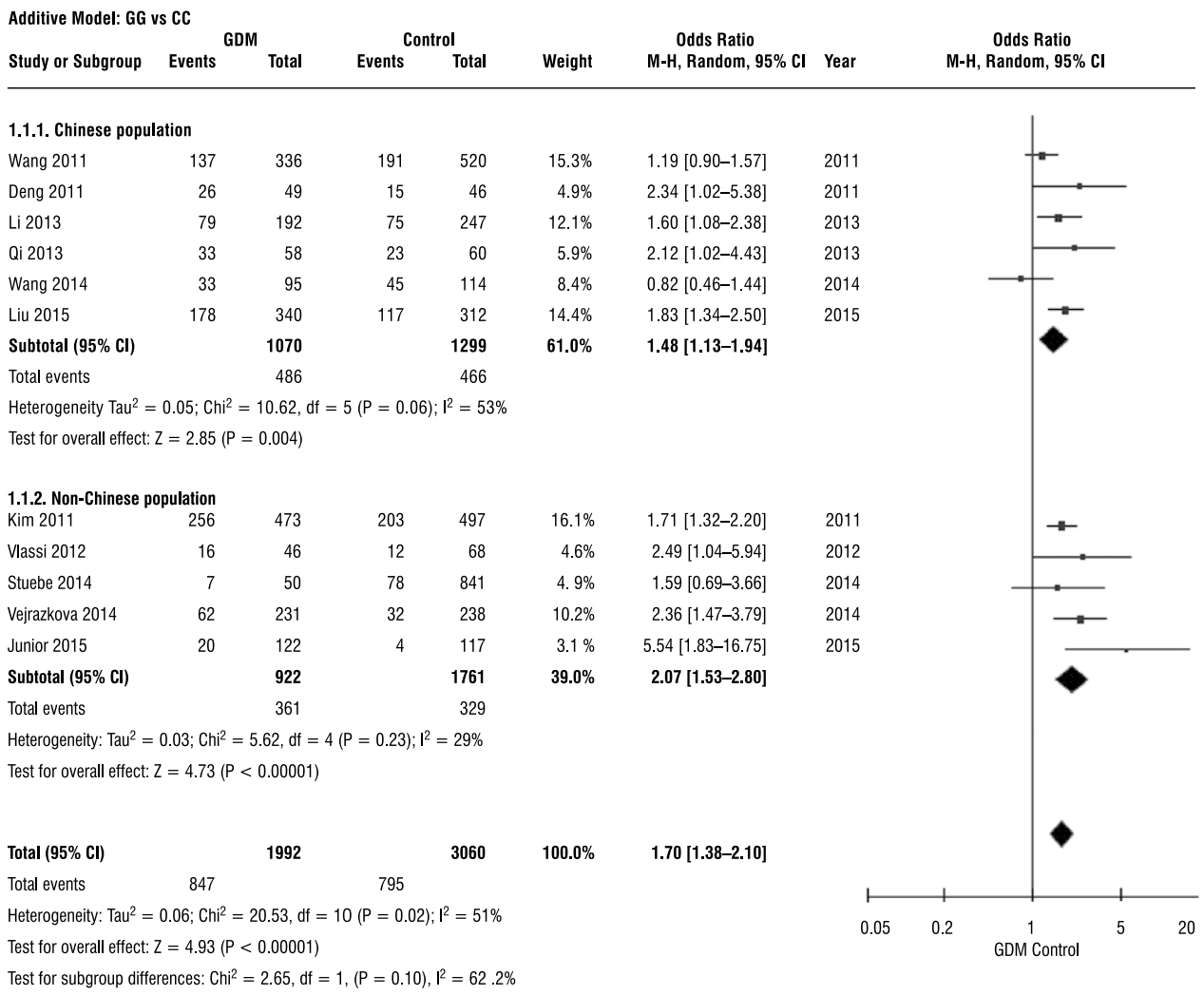


Figure 2. *Forest plots of the association between the rs10830963 polymorphism in* MTNR1B *and risk of GDM in the homozygote GG genotype comparison*

Rycina 2. *Wykresy typu forest plot przedstawiające związek między polimorfizmem rs10830963 w genie* MTNR1B *a ryzykiem GDM w porównaniu homozygot GG*

Melatonin receptor 1B (*MTNR1B*) gene, as a novel diabetogenic gene, is located on human chromosome 11q21–22 [8–11] and encodes MTNR1B protein, which belongs to the G protein-coupled receptor family and plays an inhibitory role in insulin secretion [12]. Knockout mice of *MTNR1B* were found to have significantly decreased fasting glucose levels [13].

Recently, considerable efforts have been devoted to exploring the relationships between the *MTNR1B* polymorphisms and GDM. Among them, rs10830963, an intron SNP of *MTNR1B*, has been studied in depth. Because there is controversy among previous studies over the association between the rs10830963 polymorphism and the incidence of GDM and the lack of sufficient evidence about this variation on GDM, we performed a meta-analysis to explore the association between the rs10830963 polymorphism in the *MTNR1B* gene and GDM risk around the world, especially in the Chinese Han population.

Material and methods

Literature search strategy

We conducted a systemic search on PubMed, Embase, and China National Knowledge Infrastructure (CNKI) databases up to August 12, 2016 using the following keywords: (1) "Melatonin receptor 1B" or "MTNR1B"; (2) "gestational diabetes mellitus" or "GDM" or "pregnancy diabetes mellitus"; and (3) "polymorphism" or "variant" or "genotype". The literature search was restricted to studies published in English or Chinese. In addition, all references of articles retrieved were hand-searched for additional articles relevant to this topic. For articles by the same author using the same case series, we selected the study with the largest sample size.

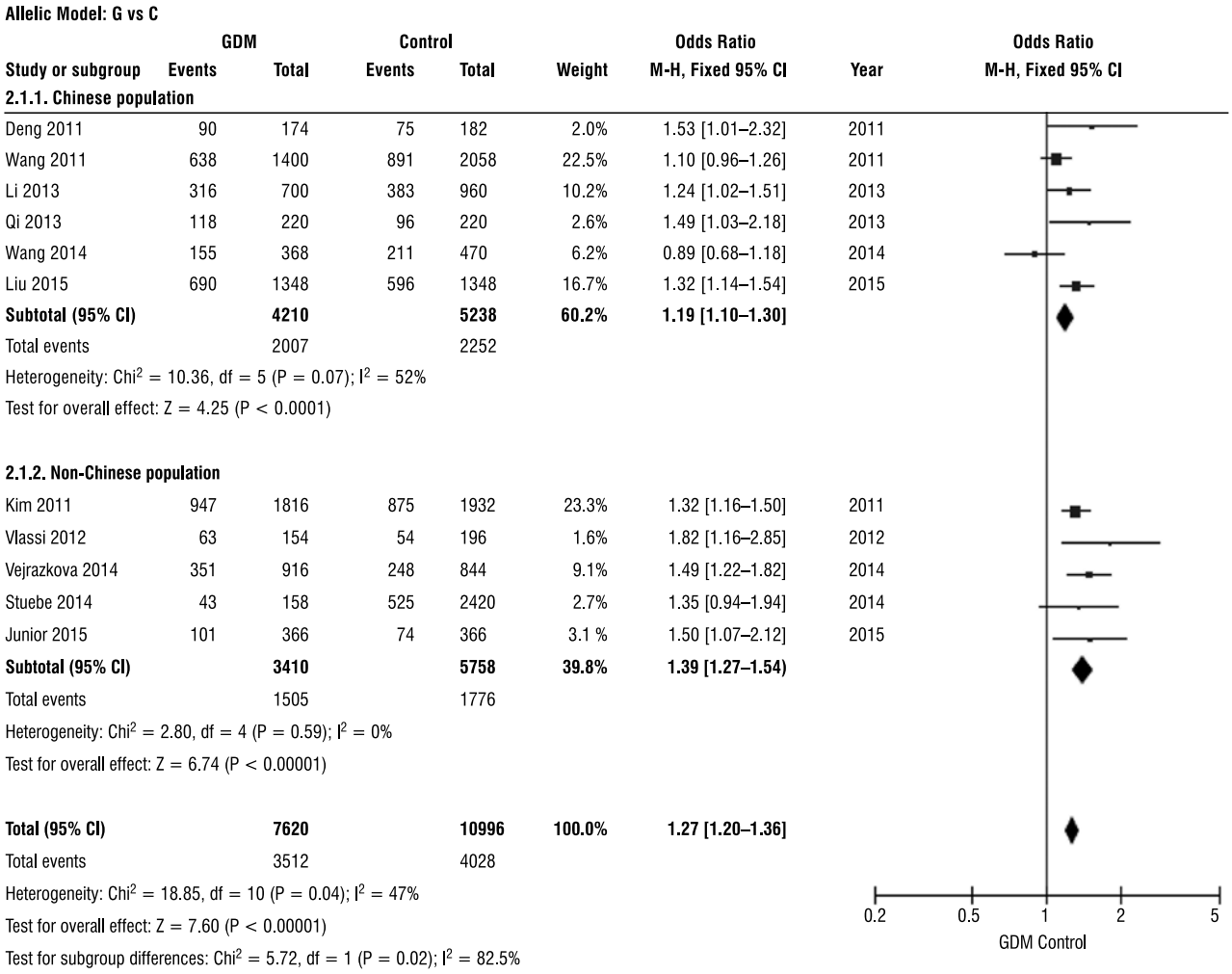


Figure 3. *Forest plots of the association between the rs10830963 polymorphism in* MTNR1B *and risk of GDM in the allele comparison*
Rycina 3. *Wykresy typu forest plot przedstawiające związek między polimorfizmem rs10830963 w genie* MTNR1B *a ryzykiem GDM w porównaniu alleli*

Eligible studies and data extraction

Eligible studies had to meet the following criteria: (1) original papers containing independent data, (2) all patients met the diagnostic criteria for GDM, (3) papers were case–control studies, (4) investigations evaluated the relationship between rs10830963 and GDM susceptibility, and (5) sufficient available published data for odds ratio (OR) estimation with 95% confidence interval (CI) and *P*-value. The major reasons for excluding studies were: (1) overlapping data, (2) design other than a case-control study, and (3) no available data reported.

Two reviewers (Lu and Wu) blindly performed data extraction separately for all selected publications. For each of the included articles, we extracted the first author's name, publication year, study population (ethnicity), definition and numbers of cases and controls, mean age of cases and controls, body mass index (BMI), frequency of genotypes, Hardy-Weinberg equilibrium status, and genotyping method. For studies that included subjects of different ethnic groups, we extracted data for each one. Further discussion among all authors resolved any disagreement by consensus on a given extracted item.

Statistical methods

Summary statistics were performed with Review Manager 5.1 software (RevMan 5.1. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2011). Calculating OR and 95% CI measured the strength of association between polymorphism rs10830963 and GDM risk. The statistical significance of the pooled OR was determined with the Z-test. The pooled ORs and 95% CIs were calculated, respectively, by comparisons between the GDM group and control group using the following genetic models: (1) allelic model (G vs. C); (2) additive model (GG vs. CC); (3) dominant model (GG+GC vs. CC); and (4) recessive model (GG vs. GC+CC). For each genetic comparison,

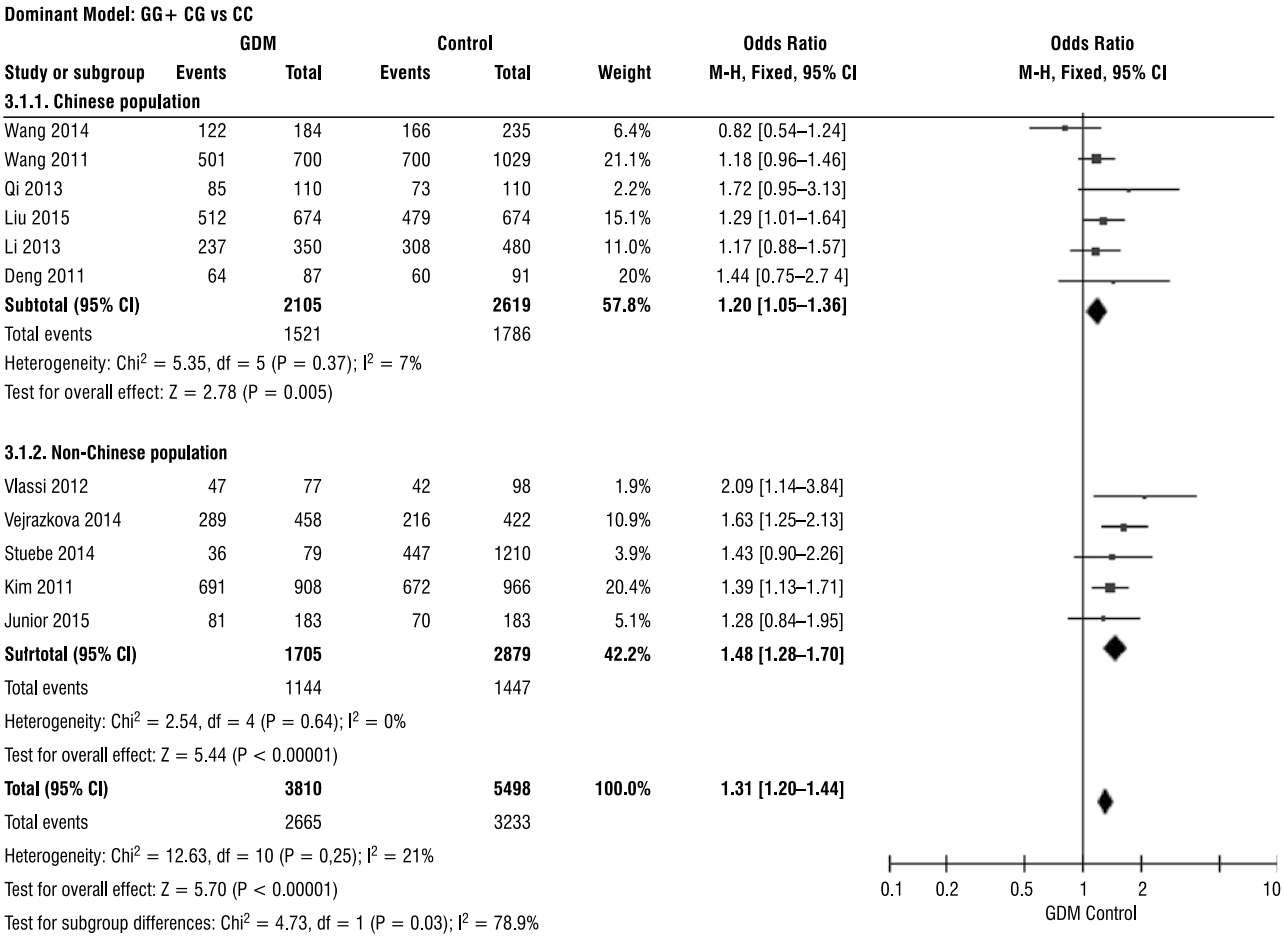


Figure 4. *Forest plots of the association between the rs10830963 polymorphism in* MTNR1B *and risk of GDM in the dominant genetic model comparison*

Rycina 4. *Wykresy typu forest plot przedstawiające związek między polimorfizmem rs10830963 w genie* MTNR1B *a ryzykiem GDM w porównaniu dominujących modeli genetycznych*

subgroup analysis according to background ethnicity was carried out in the Chinese to estimate the ethnic-specific OR.

For evaluating possible heterogeneity across the studies, a statistical test for heterogeneity was performed by a Chi-square-based Q-test. Statistical heterogeneity was assessed by I^2 measurement. A random-effect model was adopted when the effects were assumed to be homogenous ($I^2 > 50\%$ and $p < 0.05$). Otherwise, a fixed-effect model was adopted [14]. Two-sided *P* value less than 0.05 was considered statistically significant.

Results

Characteristics of included studies

We initially identified 35 eligible references. Among these, we excluded 24 studies because of unmatched search criteria, such as not a case-control study, other loci besides rs10830963, or overlapping publications. Finally, 11 studies with 3889 GDM cases and 6708 controls were included in the meta-analysis, and half of the articles focused on the association in the Chinese population [15–25]. Figure 1 shows details of the study selection process.

Association of MTNR1B rs10830963 Polymorphism with GDM

As shown in Figure 2, the heterogeneities for the overall data are small, and p values were all greater than 0.05 in all comparisons except for the GG genotype ($I^2 = 51\%$, $p = 0.02$). Moreover, according to the stratified analysis of ethnicity, we found that the heterogeneities in the Chinese population subgroup were all small and that there was no significant heterogeneity for any model comparison. This suggests that ethnicity may be a substantial factor contributing to heterogeneity. According to the heterogeneity for comparisons of each model in the overall analysis, we adopted a random-effect model to analyse the GG genotype comparison model. Other comparisons without heterogeneities were analysed using the fixed-effect model.

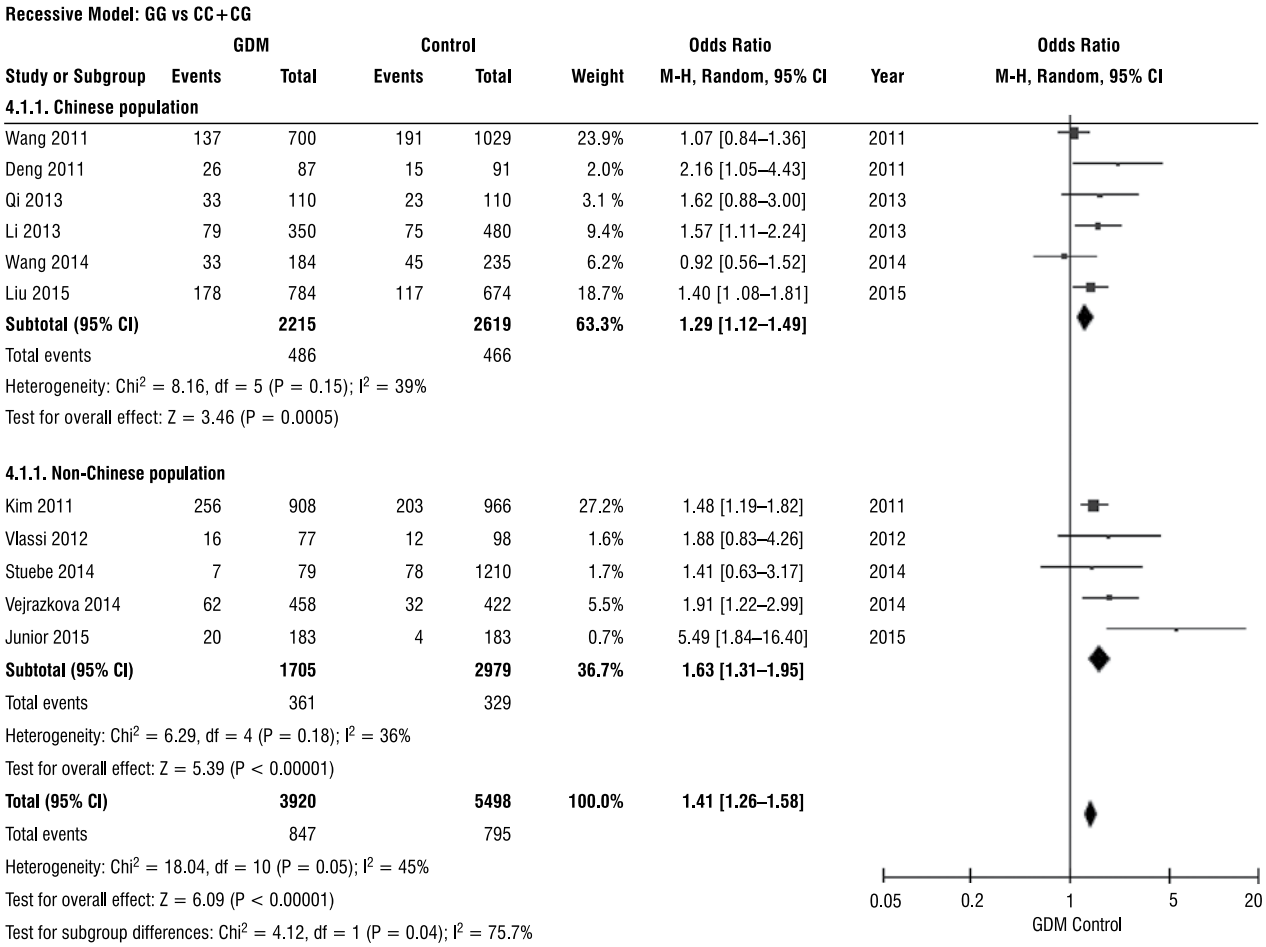


Figure 5. *Forest plots of the association between the rs10830963 polymorphism in* MTNR1B *and risk of GDM in the recessive genetic model comparison*

Rycina 5. *Wykresy typu forest plot przedstawiające związek między polimorfizmem rs10830963 w genie* MTNR1B *a ryzykiem GDM w porównaniu recesywnych modeli genetycznych*

In general, we observed positive evidence of notable associations between the increased risk of GDM and the variant in multiple genetic models when all the eligible studies were pooled into the meta-analysis. Using the fixed effect model, the pooled OR of the G allele was 1.27 (95% CI = 1.20–1.36, p < 0.00001, Figure 3), and the corresponding results of the dominant and recessive genetic models were 1.31 (95% CI = 1.20–1.44, p < 0.00001, Figure 4) and 1.41 (95% CI = 1.26–1.58, p < 0.00001, Figure 5), respectively. Therefore, because of the significant heterogeneity, the association for the GG genotype on GDM was analysed using the random effect model, and the pooled OR value was 1.70 (95% CI = 1.38–2.10, p < 0.00001, Figure 2). In addition, the association between heterozygote CG genotype and GDM was statistically significant, with the pooled OR being 1.20 (95% CI = 1.09–1.33, p = 0.0003, Figure 6).

According to the stratified overall analysis of ethnicity, the Chinese were associated with GDM susceptibility in all genetic models except for the heterozygote CG genotype comparison. To test and verify these significant associations in the Chinese population, we excluded the participants from the Wang (2011) project [18], who weighed the most in each meta-analysis. After the exclusion, we reassessed the meta-analyses. The results remained significant with pooled OR of 1.62, 1.25, 1.20, and 1.42 for the homozygote genotype, allele, dominant genetic model, and recessive genetic model comparisons, respectively (Supplementary Figure 1).

Publication bias

We explored publication bias using funnel plots (Figure 7). The shapes of the funnel plots did not reveal any evidence of obvious visual asymmetry.

Discussion

It is widely believed that GDM shares similar risk factors with T2DM, and women with a GDM history tend to

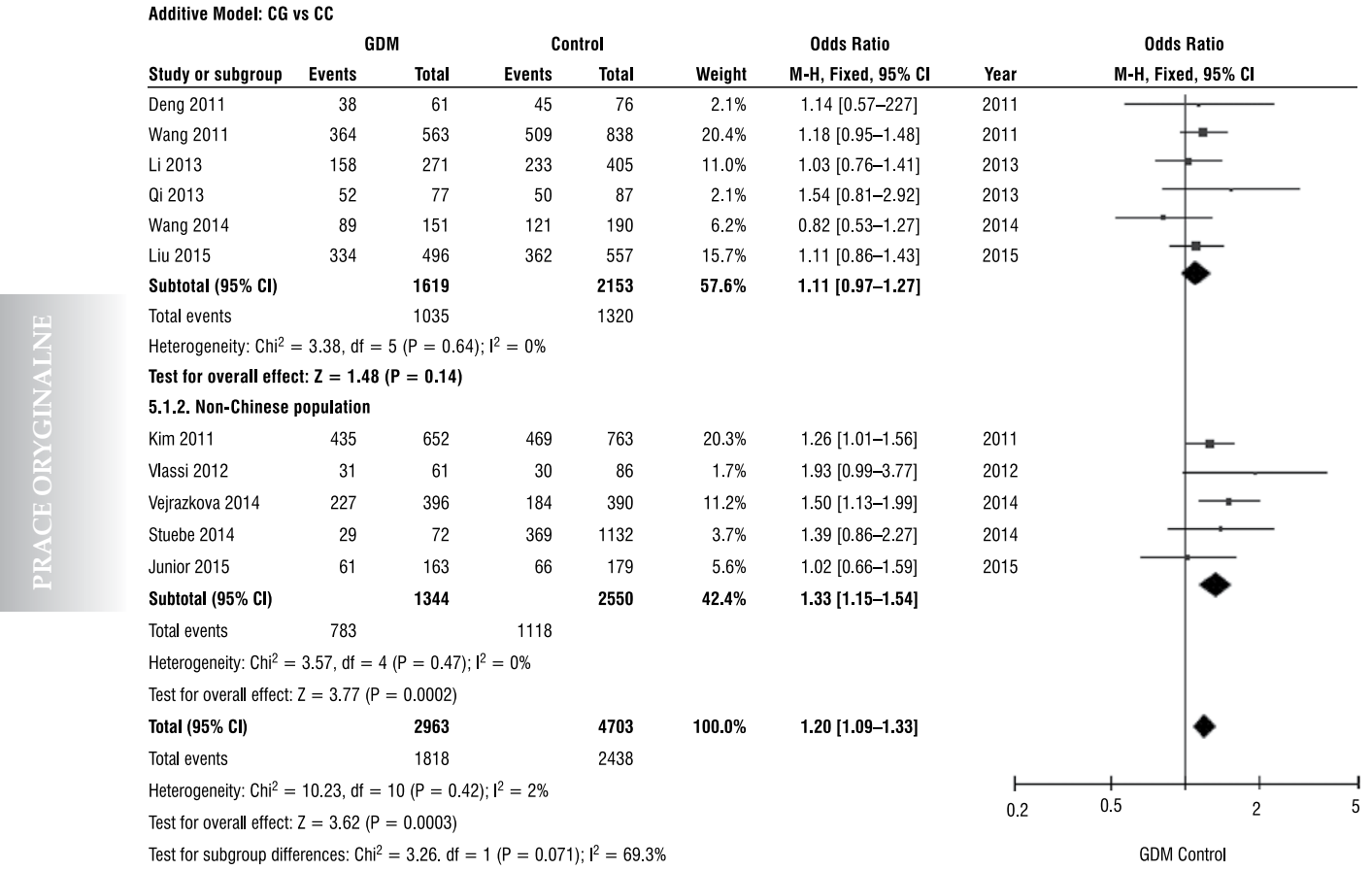


Figure 6. *Forest plots of the association between the rs10830963 polymorphism in* MTNR1B *and risk of GDM in the heterozygote GC genotype comparison*

Rycina 6. *Wykresy typu forest plot przedstawiające związek między polimorfizmem rs10830963 w genie* MTNR1B *a ryzykiem GDM w porównaniu heterozygot GC*

have an increased risk of T2DM [1, 26]. We conducted a meta-analysis to investigate the potential association between the rs10830963 polymorphism in *MTNR1B*, a genetic variant of a known T2DM loci, and GDM risk. Our results confirmed significant associations of GDM with the rs10830963 polymorphism in the overall population, and especially in the Chinese population. To the best of our knowledge, this study is the first meta-analysis to assess the relationship between the rs10830963 polymorphism and GDM susceptibility in Chinese people.

Despite accumulating evidence recognising multiple risk factors of GDM, the causes underlying the development and progression of GDM have not been fully elucidated. GDM only affects a small proportion of pregnant women, although pregnancy is characterised by progressive insulin resistance and is prone to abnormal glucose tolerance [27, 28]. Normally, the elevated insulin secretion by pancreatic islet β-cells compensates for elevated insulin resistance, but GDM could develop when a genetic predisposition of pancreatic islet β-cell impairment is unmasked by increased insulin resistance during pregnancy [27, 29]. Several studies using the genome-wide association study (GWAS), a powerful method for the detection of genetic contributions to polygenic diseases, suggest that inherited abnormalities of certain genes related to pancreatic islet β-cell function, including *MTNR1B*, are probably implicated in the aetiology of GDM [10, 30].

However, because GWAS has been shown to produce false associations [31], other types of association studies are a useful tool to identify genetic factors conferring susceptibility to diseases. A few genetic association studies have been conducted in various populations to assess possible associations of GDM with the genetic variation of rs10830963. Because original genetic association studies are generally believed to have shortcomings, such as inadequate statistical power, population stratification, and publication bias, we conducted the current meta-analysis to obtain a more comprehensive and intrinsic result of the relationship between the polymorphism of this loci and GDM risk.

The strength of the present study is the systematic way in which we have summarised results of the

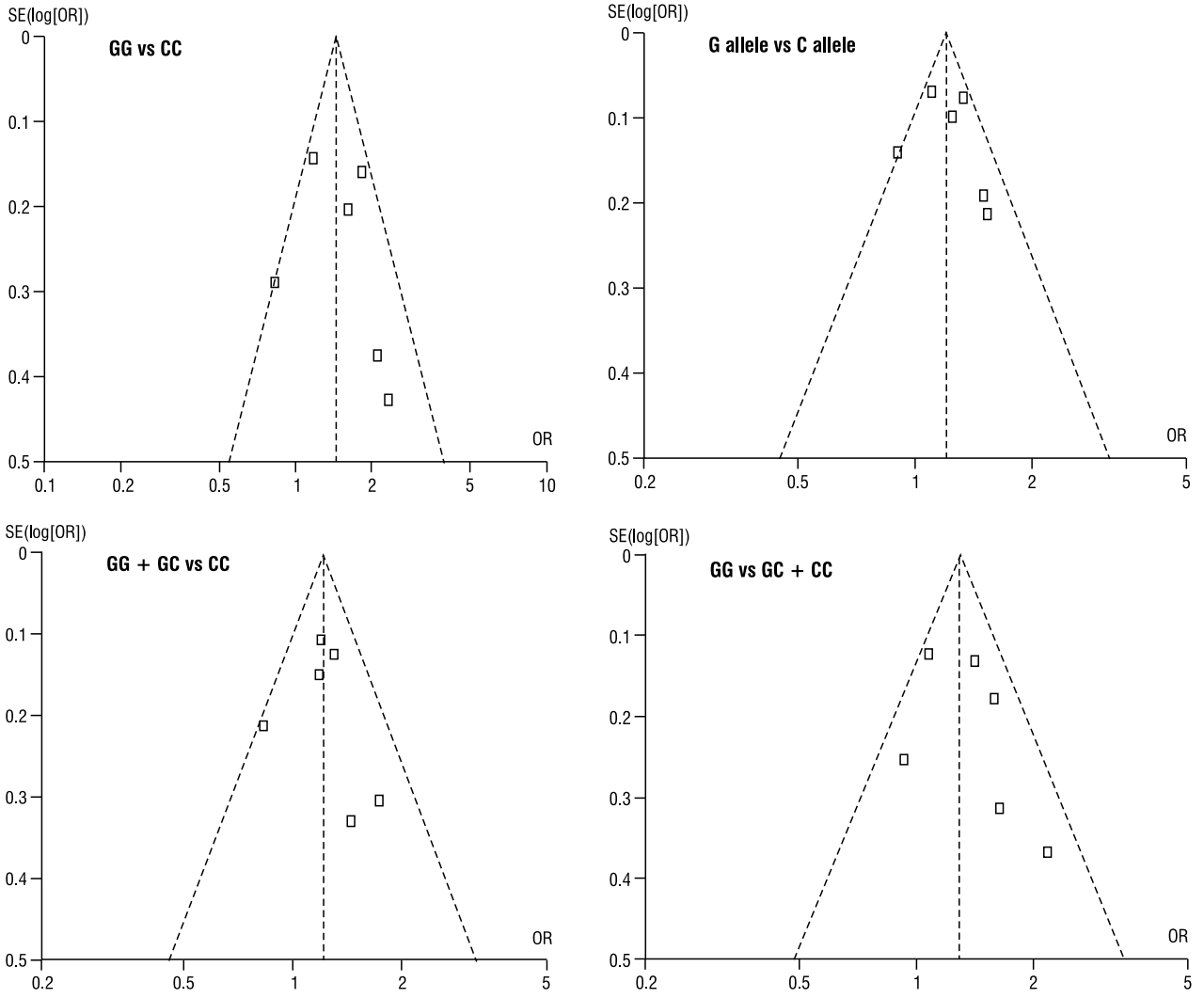


Figure 7. *Funnel plots for all comparisons in the Chinese population. The shapes of the funnel plots did not reveal any evidence of obvious visual asymmetry. SE — standard error; OR — odds ratio*

Rycina 7 *Wykresy lejkowe dla wszystkich porównań w populacji chińskiej. Kształt wykresów lejkowych nie wykazuje żadnych widocznych cech asymetrii. SE — błąd standardowy; OR — iloraz szans*

eligible studies for the SNP–GDM association. Our results indicate that the rs10830963 polymorphism of *MTNR1B* is a risk factor for GDM, and we found significant associations in all genetic models including the heterozygote CG genotype comparison. Our conclusion is consistent with former meta-analyses by Liu and Zhang [25, 32]. Regarding the population that mainly contributes to the between-study heterogeneity, we performed stratified analyses by ethnicity to evaluate the heterogeneity between studies. Consistent with the results in the overall population, we observed significant associations for the polymorphism in almost all genetic models in the Chinese population. Our results confirmed the earlier finding of a positive association in several studies, with the exception of the study by Wang et al. [18]. The difference in Wang's study could be accounted for by various degrees of clinical heterogeneity, which are induced by the different severities of GDM, comorbidities, and functional status of patients. It should also be noted that consensus of the diagnostic criteria of the current GDM definition differed in the included studies.

In addition, our results of the overall population differed from the Chinese population, which showed no significant association of heterozygote CG genotype frequency of the rs10830963 polymorphism with GDM risk in the Chinese population. The difference may be due to the relatively small number of participants. Only six studies were included in the Chinese meta-analysis. Therefore, additional studies are warranted to further validate ethnic differences of the effect of this polymorphism on GDM risk.

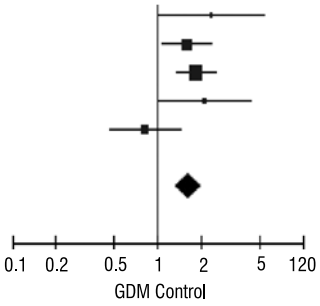
MTNR1A and MTNR1B, both high-affinity receptors of melatonin, are expressed in α-cells and β-cells of the

GG vs CC

	GDM		Control			Odds Ratio	Odds Ratio
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Deng 2011	26	49	15	46	5.2%	2.34 [1.02–5.38]	
Li 2013	79	192	75	247	27.5%	1.60 [1.08–2.38]	
Liu 2015	178	340	117	312	41.4%	1.83 [1.34–2.50]	
Qi 2013	33	58	23	60	6.9%	2.12 [1.02–4.43]	
Wang 2014	33	95	45	114	19.0%	0.82 [0.46–1.44]	
Total (95% CI)		**734**		**779**	**100.0%**	**1.62 [1.32–2.00]**	
Total events	349		275				

Heterogeneity: $Chi^2 = 7.51$, df = 4 (P = 0.11); $I^2 = 47\%$

Test for overall effect: Z = 4.58 (P < 0.00001)

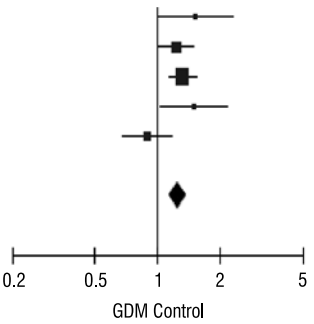


G allele vs C allele

	GDM		Control			Odds Ratio	Odds Ratio
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Deng 2011	90	174	75	182	5.4%	1.53 [1.01–2.32]	
Li 2013	316	700	383	960	27.0%	1.24 [1.02–1.51]	
Liu 2015	690	1348	596	1348	44.4%	1.32 [1.14–1.54]	
Qi 2013	118	220	96	220	6.8%	1.49 [1.03–2.18]	
Wang 2014	155	368	211	470	16.4%	0.89 [0.68–1.18]	
Total (95% CI)		**2810**		**3180**	**100.0%**	**1.25 [1.13–1.39]**	
Total events	1369		1361				

Heterogeneity: $Chi^2 = 8.02$, df = 4 (P = 0.09); $I^2 = 50\%$

Test for overall effect: Z = 4.32 (P < 0.0001)

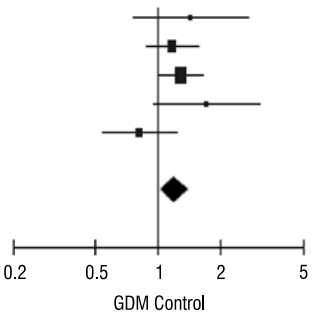


GG+GC vs CC

	GDM		Control			Odds Ratio	Odds Ratio
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Deng 2011	64	87	60	91	5.5%	1.44 [0.75–2.74]	
Li 2013	237	350	308	480	29.9%	1.17 [0.88–1.57]	
Liu 2015	512	674	479	674	41.1%	1.29 [1.01–1.64]	
Qi 2013	85	110	73	110	5.9%	1.72 [0.95–3.13]	
Wang 2014	122	184	166	235	17.5%	0.82 [0.54–1.24]	
Total (95% CI)		**1405**		**1590**	**100.0%**	**1.20 [1.03–1.41]**	
Total events	1020		1086				

Heterogeneity $Chi^2 = 5.34$, df = 4 (P = 0.25); $I^2 = 25\%$

Test for overall effect: Z = 2.30 (P = 0.02)

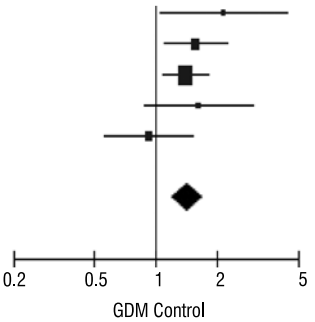


GG vs CG+CC

	GDM		Control			Odds Ratio	Odds Ratio
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Fixed, 95% CI**	**M-H, Fixed, 95% CI**
Deng 2011	26	87	15	91	5.0%	2.16 [1.05–4.43]	
Li 2013	79	350	75	480	23.9%	1.57 [1.11–2.24]	
Liu 2015	178	784	117	674	47.4%	1.40 [1.08–1.81]	
Qi 2013	33	110	23	110	7.9%	1.62 [0.88–3.00]	
Wang 2014	33	184	45	235	15.8%	0.92 [0.56–1.52]	
Total (95% CI)		**1515**		**1590**	**100.0%**	**1.42 [1.19–1.70]**	
Total events	349		275				

Heterogeneity: $Chi^2 = 4.71$, df = 4 (P = 0.32); $I^2 = 15\%$

Test for overall effect: Z = 3.88 (P = 0.0001)



Supplementary Figure 1. *Meta-analyses in Chinese without the Wang 2011 project*

Rycina dodatkowa 1. *Metaanaliza populacji chińskiej z pominięciem projektu badawczego Wanga z 2011 r.*

pancreatic islets, respectively [33]. The GWAS method has recently shown that the MTNR1B/MT2 receptor may be involved in the pathogenesis of type 2 diabetes mellitus. MTNR1B down-regulates glucokinase expression and glucose-stimulated insulin secretion. An increased expression of MTNR1B on β-cells leads to impaired insulin secretion. Regarding this evidence, and comparing with MTNR1A, we suggest that aberrant MTNR1B expression is involved in the pathogenesis of GDM. Although rs10830963 SNP is in the intron of the *MTNR1B* gene, the significant association found for this SNP with GDM suggests that the variation plays a key role in the regulation of MTNR1B expression. Previous studies have shown that the G allele of rs10830963 polymorphism in the *MTNR1B* exhibits a higher expression of this melatonin receptor on the β-cells as compared with that of the C allele. Further studies are required to confirm this association.

Some limitations of this study should be addressed, to understand the results. First, the small sample size of subgroup analysis may not have enough statistical power, so further studies with a larger sample size of target ethnic groups are required. Second, publication bias is a concern in all meta-analyses. Negative studies are less likely to be published or are underreported in published articles, potentially leading to an overestimation of the association. Finally, the integral outcomes were originated in individually unadjusted ORs, while models should be adjusted by potentially confounding factors, including age, nutritional status, and environmental factors.

Conclusions

This study confirms the association of rs10830963 in *MTNR1B* with GDM risk. Our results suggest that the variation might increase the incidence of GDM, especially in the Chinese population. Our study provides important clues on the aetiology of GDM, although further studies focusing on the affected pathway are still required.

Grants

This project was supported by the National Natural Science Foundation of China (grant numbers 81370967) and Beijing Natural Science Foundation (7132036).

Author contributions

Xiao-lin Lu and Xiu-Ying Yao prepared the manuscript; Xin-Li Liu, Zhen Wang, and Li-hua Wu searched the literature; Yu Xin and Lin-lin Zhao analysed the data; Ming-ming Cui, Shao-yan Chang, and Shao-fang Shangguan revised critical data; Li Wang and Ting Zhang designed the study.

Compliance with ethical standards

Funding: The National Natural Science Foundation of China (grant numbers 81370967) and Beijing Natural Science Foundation (7132036) funded this project.

Conflicts of Interest: The authors declare no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Ben-Haroush A, Yogev Y, Hod M. Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. Diabet Med. 2004; 21(2): 103–113, indexed in Pubmed: 14984444.
2. Poomalar GK. Changing trends in management of gestational diabetes mellitus. World J Diabetes. 2015; 6(2): 284–295, doi: 10.4239/wjd.v6.i2.284, indexed in Pubmed: 25789109.
3. Yew TW, Khoo CM, Thai AhC, et al. The Prevalence of Gestational Diabetes Mellitus Among Asian Females is Lower Using the New 2013 World Health Organization Diagnostic Criteria. Endocr Pract. 2014; 20(10): 1064–1069, doi: 10.4158/EP14028.OR, indexed in Pubmed: 24936548.
4. Tong GX, Cheng J, Chai J, et al. Association between gestational diabetes mellitus and subsequent risk of cancer: a systematic review of epidemiological studies. Asian Pac J Cancer Prev. 2014; 15(10): 4265–4269, doi: 10.7314/apjcp.2014.15.10.4265, indexed in Pubmed: 24935382.
5. Valizadeh M, Alavi N, Mazloomzadeh S, et al. The risk factors and incidence of type 2 diabetes mellitus and metabolic syndrome in women with previous gestational diabetes. Int J Endocrinol Metab. 2015; 13(2): e21696, doi: 10.5812/ijem.21696, indexed in Pubmed: 25892996.
6. Kim C, Newton KM, Knopp RH. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. Diabetes Care. 2002; 25(10): 1862–1868, doi: 10.2337/diacare.25.10.1862, indexed in Pubmed: 12351492.
7. Wung SF, Lin PC. Shared genomics of type 2 and gestational diabetes mellitus. Annu Rev Nurs Res. 2011; 29: 227–260, indexed in Pubmed: 22891507.
8. Rönn T, Wen J, Yang Z, et al. A common variant in MTNR1B, encoding melatonin receptor 1B, is associated with type 2 diabetes and fasting plasma glucose in Han Chinese individuals. Diabetologia. 2009; 52(5): 830–833, doi: 10.1007/s00125-009-1297-8, indexed in Pubmed: 19241057.
9. Bouatia-Naji N, Bonnefond A, Cavalcanti-Proença C, et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat Genet. 2009; 41(1): 89–94, doi: 10.1038/ng.277, indexed in Pubmed: 19060909.
10. Zhao Qi, Xiao J, He J, et al. Cross-sectional and longitudinal replication analyses of genome-wide association loci of type 2 diabetes in Han Chinese. PLoS One. 2014; 9(3): e91790, doi: 10.1371/journal.pone.0091790, indexed in Pubmed: 24637646.
11. Xia Q, Chen ZX, Wang YC, et al. Association between the melatonin receptor 1B gene polymorphism on the risk of type 2 diabetes, impaired glucose regulation: a meta-analysis. PLoS One. 2012; 7(11): e50107, doi: 10.1371/journal.pone.0050107, indexed in Pubmed: 23226241.
12. Ramracheya RD, Muller DS, Squires PE, et al. Function and expression of melatonin receptors on human pancreatic islets. J Pineal Res. 2008; 44(3): 273–279, doi: 10.1111/j.1600-079X.2007.00523.x, indexed in Pubmed: 18194202.
13. Mühlbauer E, Gross E, Labucay K, et al. Loss of melatonin signalling and its impact on circadian rhythms in mouse organs regulating blood glucose. Eur J Pharmacol. 2009; 606(1-3): 61–71, doi: 10.1016/j.ejphar.2009.01.029, indexed in Pubmed: 19374844.
14. Melsen WG, Bootsma MCJ, Rovers MM, et al. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect. 2014; 20(2): 123–129, doi: 10.1111/1469-0691.12494, indexed in Pubmed: 24320992.
15. Deng ZF, Chen YH, Xiang MH, et al. et al.. Association of genetic variant rs10830963 of melatonin receptor 1B gene in women with gestational diabetes mellitus Clin J Preinat Med. 2011; 14(11): 666–9.
16. Kim JY, Cheong HS, Park BL, et al. Melatonin receptor 1 B polymorphisms associated with the risk of gestational diabetes mellitus. BMC Med Genet. 2011; 12: 82, doi: 10.1186/1471-2350-12-82, indexed in Pubmed: 21658282.
17. Vlassi M, Gazouli M, Paltoglou G, et al. The rs10830963 variant of melatonin receptor MTNR1B is associated with increased risk for gestational diabetes mellitus in a Greek population. Hormones (Athens). 2012; 11(1): 70–76, indexed in Pubmed: 22450346.

18. Wang Y, Nie M, Li W, et al. Association of six single nucleotide polymorphisms with gestational diabetes mellitus in a Chinese population. PLoS One. 2011; 6(11): e26953, doi: 10.1371/journal.pone.0026953, indexed in Pubmed: 22096510.
19. Qi JHG, Wang J. Correlation study between single nucleotide polymorphism of melatonin receptor 1B gene and gestational diabetes mellitus. CHINA MEDICAL HERALD. 2013; 10(3): 4–6.
20. Li C, Qiao B, Zhan Y, et al. Association between genetic variations in MTNR1A and MTNR1B genes and gestational diabetes mellitus in Han Chinese women. Gynecol Obstet Invest. 2013; 76(4): 221–227, doi: 10.1159/000355521, indexed in Pubmed: 24157813.
21. Stuebe AM, Wise A, Nguyen T, et al. Obesity and diabetes genetic variants associated with gestational weight gain. Am J Obstet Gynecol. 2010; 203(3): 283.e1–283.17, doi: 10.1016/j.ajog.2010.06.069, indexed in Pubmed: 20816152.
22. Wang XD, Bao LS. Association between gene polymorphism of melatonin receptor 1B and gestational diabetes mellitus Chin J Diabetes. 2014;22(398-400.
23. Vejrazkova DLP, Vankova M, Bradnova O, et al. MTNR1B genetic variability is associated with gestational diabetes in Czech women. Diabetologia 2014;57. ; 1(SUPPL.1): S448.
24. Junior JP, Frigeri HR, Dos Santos-Weiss ICR, et al. The MTNR1B gene polymorphism rs10830963 is associated with gestational diabetes in a Brazilian population. Gene. 2015; 568(1): 114–115, doi: 10.1016/j.gene.2015.05.024, indexed in Pubmed: 25982863.
25. Liu Q, Huang Z, Li H, et al. Relationship between melatonin receptor 1B (rs10830963 and rs1387153) with gestational diabetes mellitus: a case-control study and meta-analysis. Arch Gynecol Obstet. 2016; 294(1): 55–61, doi: 10.1007/s00404-015-3948-y, indexed in Pubmed: 26563312.
26. Bellamy L, Casas JP, Hingorani AD, et al. Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet. 2009; 373(9677): 1773–1779, doi: 10.1016/S0140-6736(09)60731-5, indexed in Pubmed: 19465232.
27. Lambrinoudaki I, Vlachou SA, Creatsas G. Genetics in Gestational Diabetes Mellitus: Association with Incidence, Severity, Pregnancy Outcome and Response to Treatment. Current Diabetes Reviews. 2010; 6(6): 393–399, doi: 10.2174/157339910793499155.
28. Watanabe RM. Inherited destiny? Genetics and gestational diabetes mellitus. Genome Med. 2011; 3(3): 18, doi: 10.1186/gm232, indexed in Pubmed: 21457499.
29. Zhang C, Bao W, Rong Y, et al. Genetic variants and the risk of gestational diabetes mellitus: a systematic review. Hum Reprod Update. 2013; 19(4): 376–390, doi: 10.1093/humupd/dmt013, indexed in Pubmed: 23690305.
30. Kwak SH, Kim SH, Cho YM, et al. A genome-wide association study of gestational diabetes mellitus in Korean women. Diabetes. 2012; 61(2): 531–541, doi: 10.2337/db11-1034, indexed in Pubmed: 22233651.
31. McCarthy MI, Abecasis GR, Cardon LR, et al. Genome-wide association studies for complex traits: consensus, uncertainty and challenges. Nat Rev Genet. 2008; 9(5): 356–369, doi: 10.1038/nrg2344, indexed in Pubmed: 18398418.
32. Zhang Y, Sun CM, Hu XQ, et al. Relationship between melatonin receptor 1B and insulin receptor substrate 1 polymorphisms with gestational diabetes mellitus: a systematic review and meta-analysis. Sci Rep. 2014; 4: 6113, doi: 10.1038/srep06113, indexed in Pubmed: 25146448.
33. Pandi-Perumal SR, Trakht I, Srinivasan V, et al. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. Prog Neurobiol. 2008; 85(3): 335–353, doi: 10.1016/j.pneurobio.2008.04.001, indexed in Pubmed: 18571301.