



## Research article

# Melatonin receptor 1B gene rs10830963 C/G polymorphism associated with type 2 diabetes mellitus: An updated meta-analysis of 13,752 participants

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## ABSTRACT

**Background and aims:** It has been indicated that *Melatonin receptor 1B (MTNR1B)* gene rs10830963 C/G polymorphism was associated with the increased type 2 diabetes mellitus (T2DM) risk. Nevertheless, due to the inconsistent results among the individual studies on this topic, no consensus has been reached now. Hence, the present meta-analysis was conducted to illuminate the potential association of human *MTNR1B* gene rs10830963 C/G polymorphism and T2DM.

**Methods and results:** There were 13,752 participants from 7 studies in the present meta-analysis. The pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were assessed by using the fixed or random effects models. A significant association between *MTNR1B* gene rs10830963 C/G polymorphism and T2DM was found under recessive (OR: 1.148, 95% CI: 1.052–1.253,  $P = 0.002$ ), homozygous (OR: 1.197, 95% CI: 1.023–1.401,  $P = 0.025$ ), and additive (OR: 1.067, 95% CI: 1.017–1.120,  $P = 0.008$ ) genetic models.

**Conclusions:** *MTNR1B* gene rs10830963 C/G polymorphism was significantly related to T2DM in the Chinese population. The persons with G allele of the *MTNR1B* gene rs10830963 C/G polymorphism might be the T2DM susceptible population.

## 1. Introduction

T2DM is a metabolic disorder syndrome mainly characterized by hyperglycemia, which is formed by insulin resistance and pancreatic beta cell defect. T2DM is the third chronic disease that seriously threatens human life and health after cardiovascular disease and tumor, and its morbidity and fatality rate are increasing. The diabetes prevalence in Chinese adults increased from 0.67% in 1980 to 10.9% in 2013 to 12.8% in 2017 [1]. The exact pathogenesis of T2DM has not been clarified yet. T2DM has obvious genetic tendency and significant genetic heterogeneity.

Melatonin (MT) is a kind of indole hormone commonly found in living organisms. It is mainly secreted by the pineal gland in human body, and it regulates many important physiological functions such as circadian rhythm, sleep, endocrine, immune and anti-aging [2]. The action of MT is mediated by melatonin receptor 1 (Mella, MT1) and melatonin receptor 2 (Mellb, MT2), both of which are G protein coupled receptors [3]. MT1 is

encoded by *MTNR1A* gene and MT2 is encoded by *MTNR1B* gene. *MTNR1B* gene might mediate the inhibitory effect of MT on insulin secretion through MT signaling pathway, thus participate in the T2DM pathogenetic process. It was reported that *MTNR1B* gene polymorphisms was associated with the fasting blood glucose (FBG) level and T2DM pathogenesis in the European population for the first time in 2008 [4]. The human *MTNR1B* gene, located in 11q21-q22, contains 2 exons and 1 intron, and encodes 362 amino acids, of which the full length is 13159bp. The *MTNR1B* gene was mainly expressed in the retina, brain, and pancreas islet. *MTNR1B* belongs to G-protein coupled receptors and is structurally an intramembrane protein. Melatonin is a neuroendocrine hormone that acts on pancreatic islet cells, resulting in a decrease in cAMP concentration, which is contrary to the pancreas' function, and the insulin secretion is inhibited. After melatonin binds to the receptor, the secretion cycle occurs synchronously with the circadian rhythm. It is speculated that the inhibition of secretion of pancreatic islet cells by these endocrine neurons may lead to the circadian transmission of insulin

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release. There is abundant evidence that the disruption of the insulin release circadian rhythm in the rodent and human islet cells is associated with metabolic disease [5, 6, 7, 8].

The *MTNR1B* gene has a conserved sequence at the splicing site. In this case, the intron changes during splicing, leading to potential functional and structural changes in the *MTNR1B* gene. The *MTNR1B* gene rs10830963 C/G polymorphism is located in the intron [9]. The risk allele G of *MTNR1B* gene rs10830963 C/G polymorphism leads to the *MTNR1B* gene overexpression in the pancreatic islet cells, which contributes to the decreased insulin secretion, elevated FBG level and results in the T2DM occurrence.

Multiple studies on the correlation between *MTNR1B* gene rs10830963 C/G polymorphism and T2DM in the Chinese population have been performed, but no consensus has been reached up to now. In 2009, Rönn et al. reported that the *MTNR1B* gene rs10830963 C/G polymorphism increased the T2DM risk in a Shanghai population and the G allele was the risk allele [10]. Analogously, in 2010, Kan et al. found that the common variant of the *MTNR1B* gene rs10830963 C/G polymorphism confers the T2DM risk in another Shanghai Chinese population and the G allele was associated with the increased T2DM risk [11]. Discriminatively, in 2011, Ling et al. reported that there was no significant association between rs10830963 polymorphism and T2DM risk in another Shanghai Han population [12]. In 2015, Shi et al. replicated the same conclusion in a Gansu Baoan population [13].

For the sake of determining whether the *MTNR1B* gene rs10830963 C/G polymorphism was correlated with T2DM susceptibility, the current meta-analysis including 13,752 participants from 7 researches was carried out (Supplements S1).

## 2. Materials and methods

### 2.1. Publication search and inclusion criteria

The words as “type 2 diabetes mellitus”, “Melatonin receptor 1B”, “*MTNR1B*”, “rs10830963”, “polymorphism”, and “gene” were adopted to search the papers. The studies were retrieved from such electronic databases as the Weipu (VIP) database, WanFang database, the China National Knowledge Infrastructure, the Web of Science, and PubMed. The last search was updated on February 22, 2022. The selected papers were published between 2009 and 2016.

The subsequent recruitment standard should be followed by the selected studies in this meta-analysis. The studies selected should: a) evaluate the association of T2DM with *MTNR1B* gene rs10830963 C/G polymorphism; b) In regard to the T2DM diagnosis criteria: typical diabetic symptoms (polyuria, polydipsia, polyphagia, unexplained weight loss) plus random blood glucose  $\geq 11.1$  mmol/L, or plus blood glucose  $\geq 11.1$  mmol/L 2h after glucose load or plus fasting blood glucose  $\geq 7.0$  mmol/L, or plus glycated hemoglobin A1c (HbA1c)  $\geq 6.5\%$ . If the patients have no typical diabetic symptoms, they should be retested in another day. c) The selected researches ought to be the case-control or cohort studies. The exclusive criteria included the subsequent items: (1) the repeated literatures published by the same research group could only be used once. For the repeated studies, only the studies with large sample size were selected; (2) the literature in which the original research data were not available and the authors were not available by contact.

### 2.2. Data extraction

According to standard operating procedures, three investigators were involved in the data collection process. The data was parallelly collected by two of them. They collected the data independently. In the data collection process, if there was dispute between them, they would consult with the third investigator and resolve the disagreement together. The collected data should include these items as the name of the first author, year of publication, region of study, ethnicity of the study populations,

the CC, CG, GG genotype counts of the *MTNR1B* gene rs10830963 C/G polymorphism in the case group and control group, the methods for genotyping, sample size in the two groups, and the *P* value for judging whether the genotype distribution of the control group conformed to the Hardy Weinberg equilibrium (HWE) or not.

### 2.3. Statistical analyses

In the current research, the software as the Stata 12.0 and Review Manager 5.3 were used to perform the statistical analyses. The relationship of *MTNR1B* gene rs10830963 C/G polymorphism with T2DM was assessed by using the pooled odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). Six genetic models including allelic (G allele vs. G allele + C allele), recessive (GG vs. CC + CG), dominant (CC vs. GG + CG), heterozygous (CG vs. CC), homozygous (GG vs. CC), and additive (G allele vs. C allele) were used in the statistical analyses process.

The heterogeneity from these selected studies was assessed in terms of the  $P_{heterogeneity}$  and  $I^2$  results [14]. Under the condition of  $P_{heterogeneity} > 0.05$ , the data would be analyzed by using the fixed effects models. If not, the data would be analyzed by utilizing the random effects models [15].

The combined ORs were assessed through the Z test. In order to evaluate the HWE, the Fisher's exact test was performed by using the open source software R [16]. The publication bias was diagnosed by using the funnel plot under the recessive genetic model. The symmetry of the funnel plot was evaluated by the Egger linear regression and Begg's test under the additive genetic model [17].  $P < 0.05$  means the significant difference in all these tests items.

## 3. Results

### 3.1. Studies and populations

The included data consist of 6,576 T2DM cases and 7,176 controls which were extracted from 7 studies (Table 1) [10-13,18-20]. After an initiatory investigation, 16 papers were found out. Among these papers, 7 papers met the conditions of this meta-analysis. A manuscript deviating from HWE was not ruled out [12]. Four eliminated studies were not correlated with the *MTNR1B* rs10830963 C/G mutation or T2DM. Five manuscripts were eliminated for their reviews character (Supplement S2).

### 3.2. Pooled analyses

A significant association between *MTNR1B* gene rs10830963 C/G polymorphism and T2DM was found under recessive (OR: 1.148, 95% CI: 1.052–1.253,  $P = 0.002$ ), homozygous (OR: 1.197, 95% CI: 1.023–1.401,  $P = 0.025$ ), and additive (OR: 1.067, 95% CI: 1.017–1.120,  $P = 0.008$ ) genetic models. No significant association between *MTNR1B* gene rs10830963 C/G polymorphism and T2DM was found under the allelic (OR: 1.038, 95% CI: 0.994–1.084,  $P = 0.093$ ), dominant (OR: 0.950, 95% CI: 0.885–1.020,  $P = 0.160$ ), or heterozygous (OR: 1.016, 95% CI: 0.943–1.096,  $P = 0.672$ ) genetic models (Table 2, Figures 1, 2, 3, 4, 5, and 6).

## 4. Publication bias diagnostics

Since the studies with negative results might not be published or retrieved, the publication bias might occur and affect the research results, the publication bias analysis is then conducted. On the funnel plot for the recessive genetic model, the publication bias was not significant (Figure 7). Furthermore, for the additive genetic model, no significant publication bias was uncovered through the Egger's test ( $T = 1.72$ ,  $P = 0.146$ ) (Figure 8).

**Table 1.** The studies characteristics included in this meta-analysis.

Author	Year	Region	Ethnicity	T2DM			Control			Matching criteria	Genotyping method	sample size (T2DM/control)	$P_{HWE}$
				CC	CG	GG	CC	CG	GG				
Ling Y [12]	2011	Shanghai	Han	403	538	177	404	590	167	Sex, ethnicity	Spectroscopy	1118/1161	0.039*
Kan MY [11]	2010	Shanghai	Han	585	960	367	675	989	350	Sex, BMI,WHR,DBP,LDL-C,ethnicity,	PCR-RFLP	1912/2041	0.707
Gao KP [18]	2016	Guangdong	Han	243	347	134	280	350	129	Smoking, ethnicity	Taqman	724/759	0.274
Ronn T [10]	2009	Shanghai	Han	371	553	241	374	558	173	Age, sex, BMI, ethnicity	iPLEX	1165/1105	0.139
Shi XE [13]	2015	Gansu	Baoan	80	100	44	144	208	52	Age, sex, BMI,height, ethnicity	MALDI-TOF-MS	224/404	0.084
Liang SQ [19]	2010	Jilin	Han	15	47	29	25	46	18	Age, sex, DBP, TC, TG, BMI, ethnicity	PCR-RFLP	91/89	0.705
Tam CH [20]	2010	Hongkong	Han	448	633	261	523	789	332	Ethnicity	PCR-RFLP	1342/1644	0.273

\* $P < 0.05$ .

Abbreviations: *MTNR1B*: melatonin receptor 1B; T2DM: type 2 diabetes mellitus; sample size (T2DM/control) size: the total number of T2DM or control group; WHR: waist hip rate; BMI: body mass index; TC: total cholesterol; TG: triglyceride; DBP: diastolic blood pressure; PCR-RFLP: Polymerase chain reaction-restricted fragment length polymorphism; iPLEX: mult iplex PCR; MALDI-TOF-MS: Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry.

**Table 2.** The current meta-analysis results under the six genetic models.

Genetic models	Pooled OR (95% CI)	Z	P	Studies number	T2D size	control size	$P_{heterogeneity}(I^2\%)$
Allelic genetic model $\nabla$	1.038 (0.994–1.084)	1.68	0.093	7	6576	7176	0.617 (0%)
Recessive genetic model $\nabla$	1.148 (1.052–1.253)	3.10	0.002*	7	6576	7176	0.061 (50.3%)
Dominant genetic model $\nabla$	0.950 (0.885–1.020)	1.41	0.160	7	6576	7176	0.154 (35.9%)
Heterozygous genetic model $\nabla$	1.016 (0.943–1.096)	0.42	0.672	7	6576	7176	0.264 (21.7%)
Homozygous genetic model $\Delta$	1.197 (1.023–1.401)	2.24	0.025*	7	6576	7176	0.045* (53.4%)
Additive genetic model $\nabla$	1.067 (1.017–1.120)	2.65	0.008*	7	6576	7176	0.063 (49.9%)

\* $P < 0.05$ .

$\nabla$ : the “fixed effects model” was applied to compute the pooled OR under the allelic, recessive, dominant, heterozygous and additive genetic models.

$\Delta$ : the “random effects model” was applied to compute the pooled OR under the homozygous genetic models.

Abbreviations: CI: confidence interval; OR: odds ratio; T2D size: the total number of T2DM cases; control size: the total number of control group; Allelic genetic model: G allele vs. G allele + C allele; Recessive genetic model: GG vs. CC + CG; Dominant genetic model: CC vs. GG + CG; Heterozygous genetic model: CG vs. CC; Homozygous genetic model: GG vs. CC; Additive genetic model: G allele vs. C allele.

#### 4.1. Sensitivity analysis

After removing any of the individual studies from the meta-analysis, the primary outcome was not influenced under the additive genetic model. It was suggested that the outcome from the current meta-analysis was relatively stable (Figure 9).

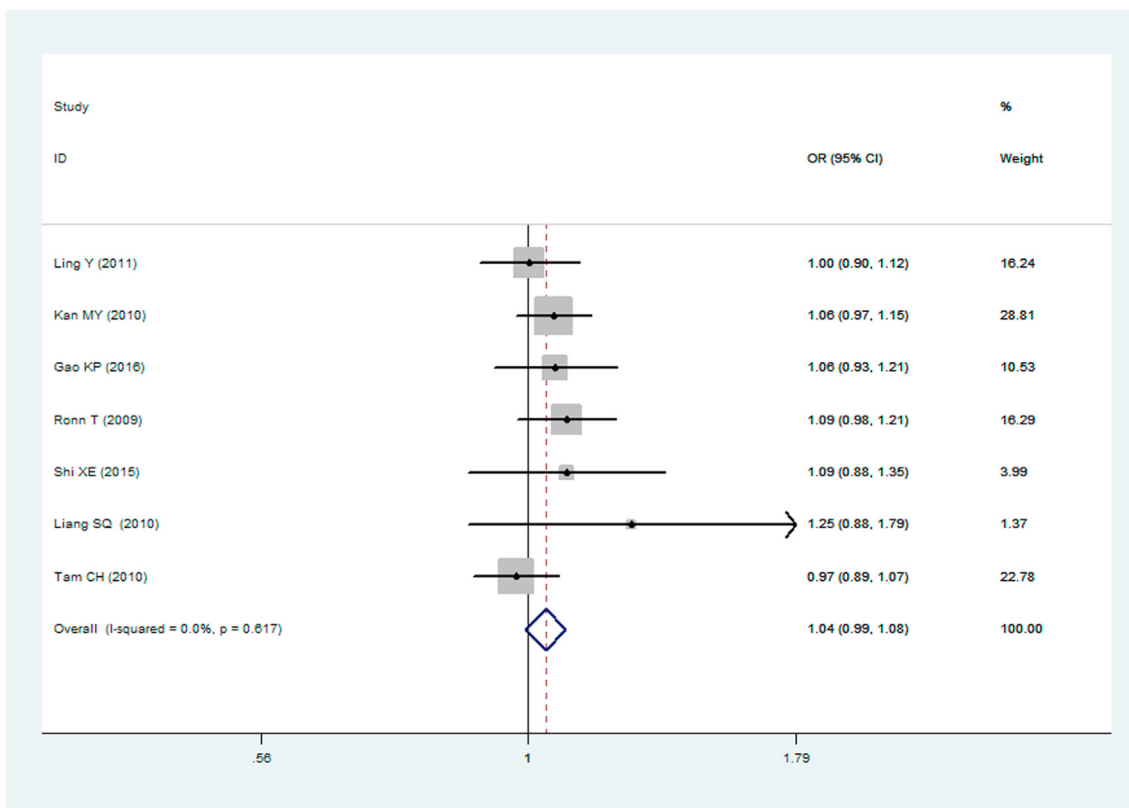
## 5. Discussion

In the present meta-analysis, *MTNR1B* gene rs10830963 C/G polymorphism was found to be significantly associated T2DM risk under the recessive (OR: 1.148), homozygous (OR: 1.197), and additive (OR: 1.067) genetic models.

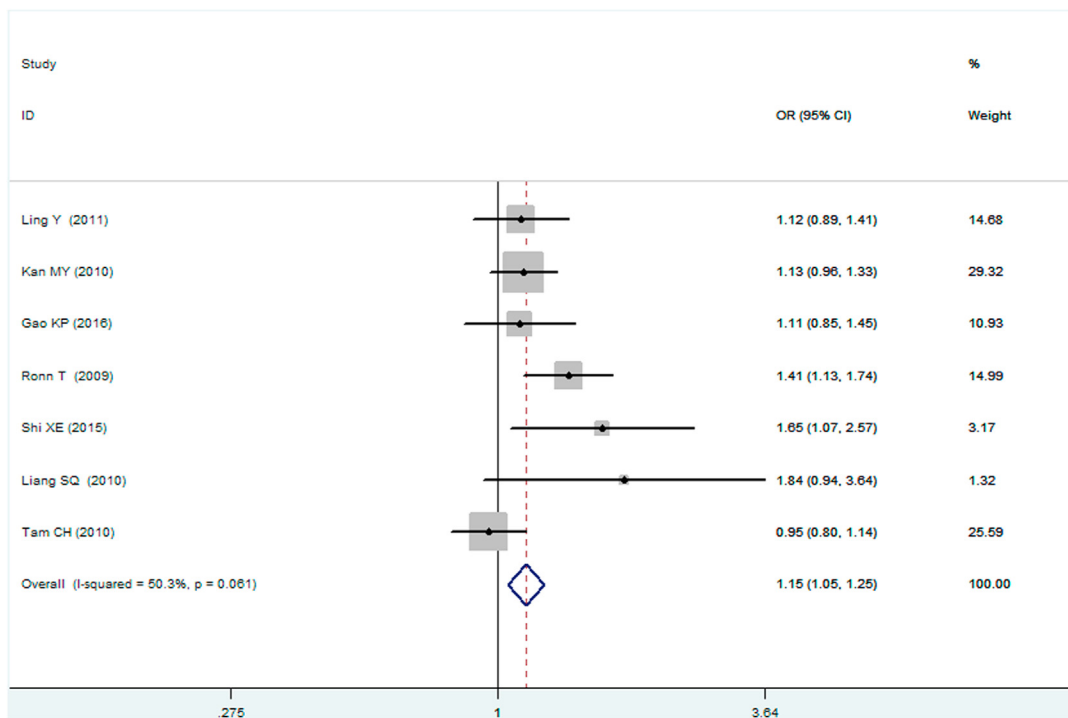
T2DM is a polygenic, multi-factorial disease with high genetic heterogeneity. Insulin resistance and pancreatic beta cell dysfunction are the main characteristics of T2DM. MT is a neuroendocrine hormone secreted by the pineal gland, which plays a regulatory role in biological circadian rhythm, sexual maturation and reproductive immune response, tumor, aging, and so on. Hence, it has a wide range of physiological and pharmacological effects. MT not only regulates sleep, but also insulin secretion. Shorter or less quality sleep can lead to reduced glucose tolerance, increasing the risk of type 2 diabetes. The level of MT secretion is just opposite to the rule of insulin secretion, indicating that MT may have an inhibitory effect on insulin release [21]. *MTNR1B* is conjugated to

inhibitory G protein, and MT activation of *MTNR1B* will block the activation of adenylate cyclase (AC). Activation of AC is the primary activation mechanism of endocrine hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin-promoting polypeptide (GIP). GLP-1 and GIP are incretin which can promote the islet  $\beta$  cells to secrete the insulin and inhibit the islet  $\alpha$  cells to secrete the glucagon. Furthermore, MT might inhibit the release of insulin through the *MTNR1B* mediated cyclic guanine nucleotide pathway [22]. Therefore, the risk allele G of rs10830963 increases the overexpression of *MTNR1B* mRNA in islet cells, which results in the elevated fasting glucose and leads to the T2DM occurrence. In 2009, Lyssenko et al. found that each G allele of rs10830963 polymorphism increased FBG by 0.07 mmol/L and was associated with reduced  $\beta$ -cell function which increased the T2DM risk [23]. The out of balance of glycometabolism steady state and the elevated FBG level are the symbols of T2DM occurrence as they could continuously affect the pancreatic islet  $\beta$  cells function and reduce the insulin secretion. In short, the correlation of rs10830963 C/G polymorphism and T2DM is probably due to the MT overexpression or the increased MT activity which leads to the decreased insulin level, increased FBG level and the T2DM occurrence [4].

The potential therapy significance of *MTNR1B* gene rs10830963 C/G polymorphism on the T2DM was presented as the follows. First, as the MT has the negative impact on the T2DM development, the antagonist targeting on the MT2 in the  $\beta$  cells might be effective.



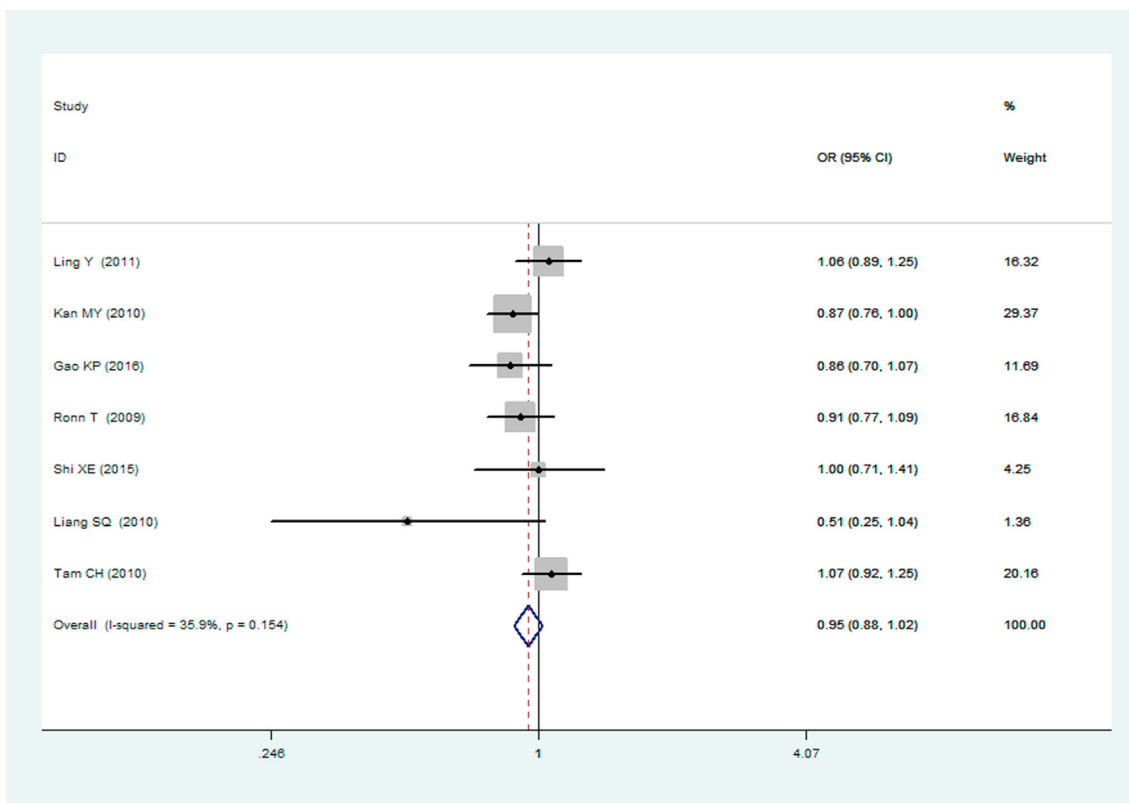
**Figure 1.** Forest plot of T2DM associated with *MTNR1B* gene rs10830963 C/G polymorphism under an allelic genetic model (i.e. G allele vs. G allele + C allele of *MTNR1B* gene rs10830963 C/G polymorphism).



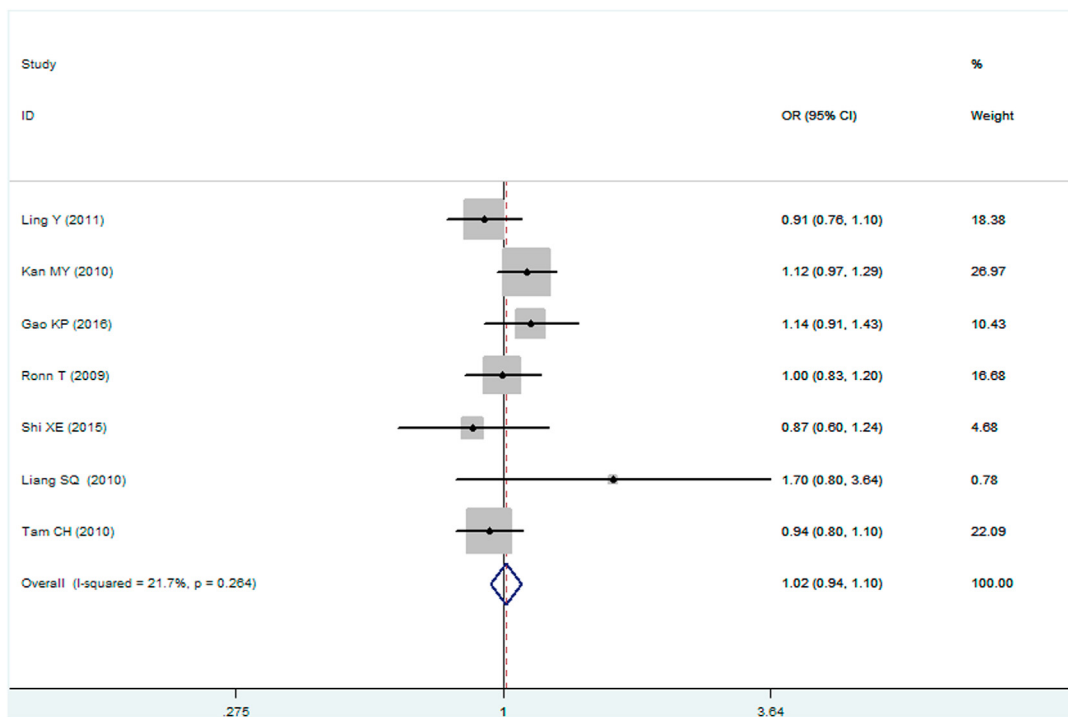
**Figure 2.** Forest plot of T2DM associated with *MTNR1B* gene rs10830963 C/G polymorphism under a recessive genetic model (i.e. GG VS. CC + CG of *MTNR1B* gene rs10830963 C/G polymorphism).

Secondly, the individuals carrying the G risk allele of *MTNR1B* gene rs10830963 C/G polymorphism might have the lower curative effects on the GLP-1 analogues and the inhibitors of the substance promoting

the GLP-1 degradation. Hence, recognizing these individuals would be like to provide a more accurate T2DM diagnosis and treatment methods [23].



**Figure 3.** Forest plot of T2DM associated with *MTNR1B* gene rs10830963 C/G polymorphism under a dominant genetic model (i.e. CC VS. GG + CG of *MTNR1B* gene rs10830963 C/G polymorphism).



**Figure 4.** Forest plot of T2DM associated with *MTNR1B* gene rs10830963 C/G polymorphism under a heterozygous genetic model (i.e., CG vs. CC of *MTNR1B* gene rs10830963 C/G polymorphism).

Similar meta-analyses on the relevance of T2DM risk with *MTNR1B* gene rs10830963 C/G polymorphism were performed previously. In 2019, Shen et al. carried out a meta-analysis to evaluate whether there

was a significant association between *MTNR1B* gene rs10830963 C/G polymorphism and T2DM risk [24]. They found that the *MTNR1B* gene rs10830963 C/G variant was significantly correlated with T2DM

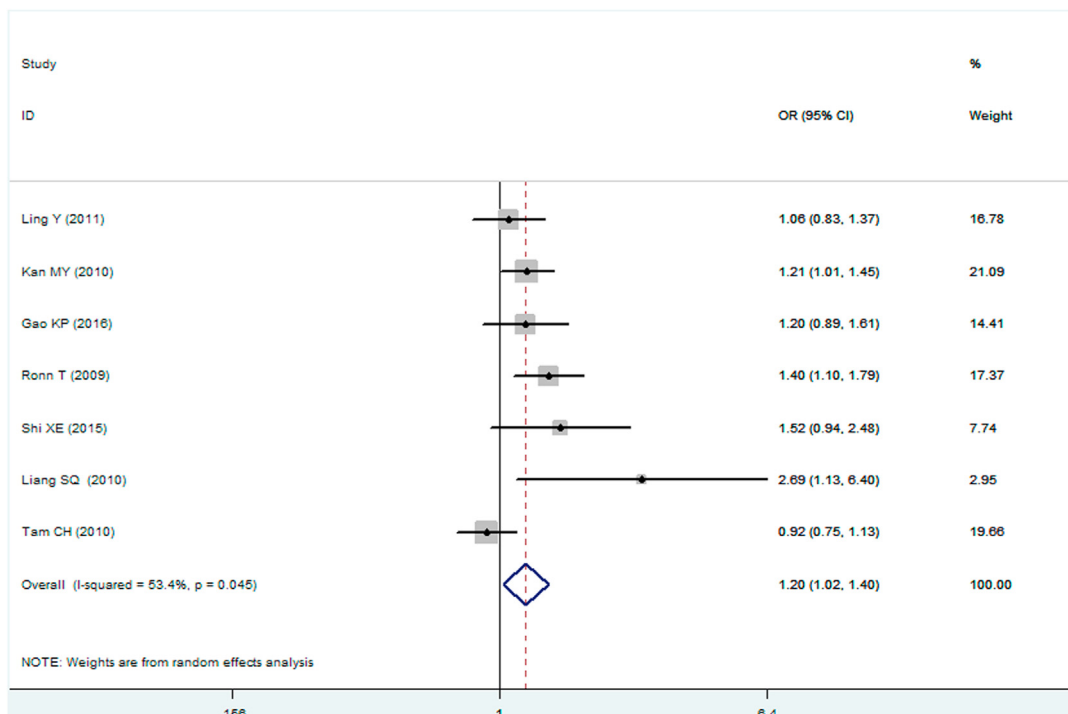


Figure 5. Forest plot of T2DM associated with *MTNR1B* gene rs10830963 C/G polymorphism under a homozygous genetic model (i.e., GG vs. CC of *MTNR1B* gene rs10830963 C/G polymorphism).

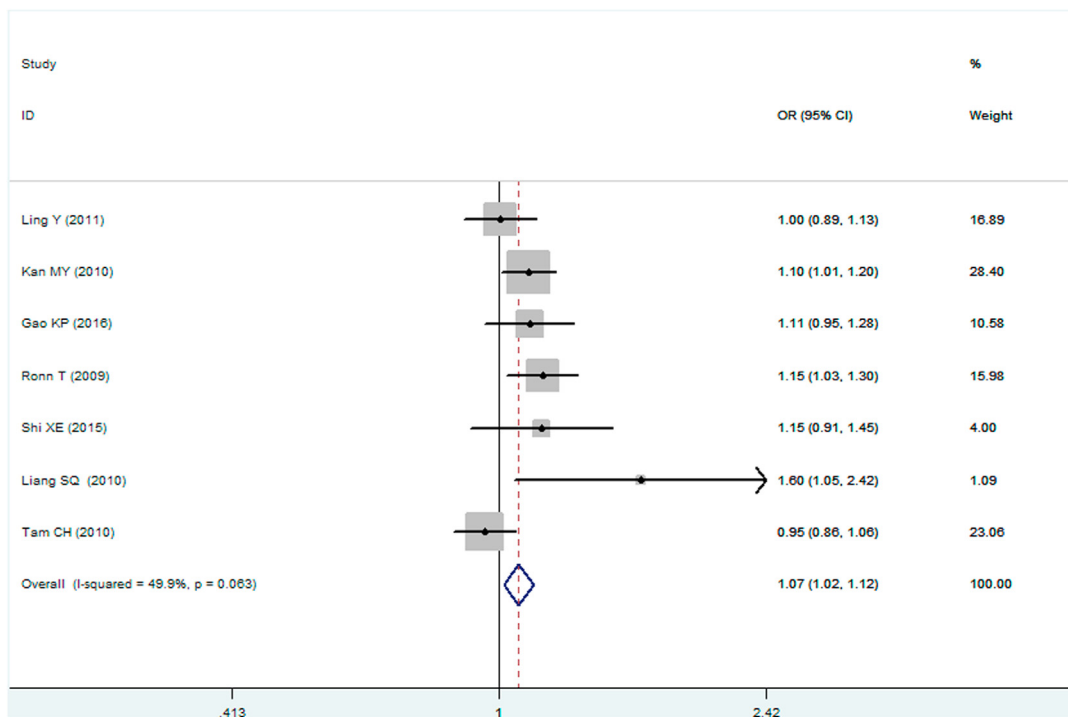
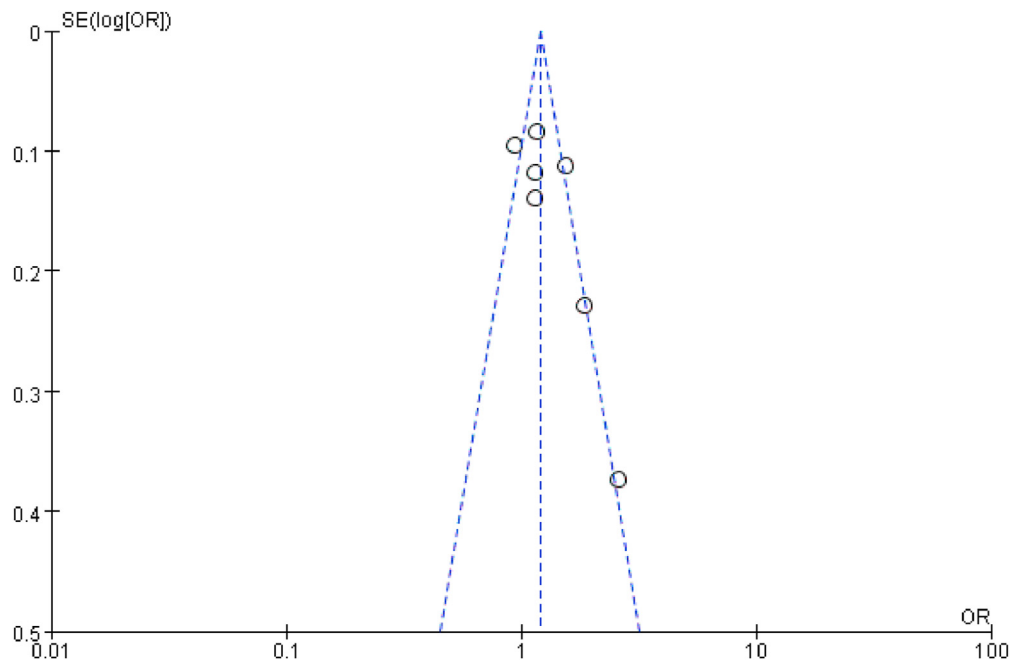


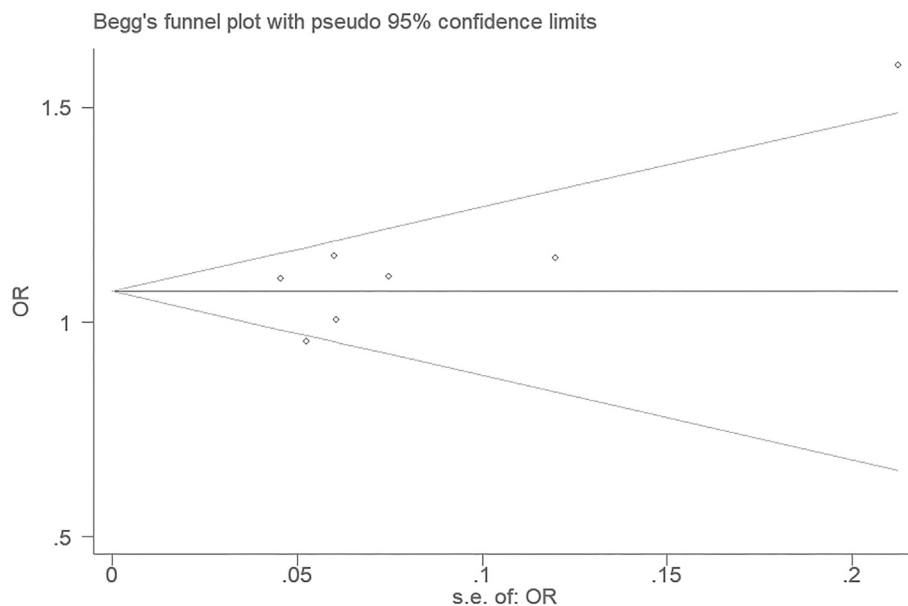
Figure 6. Forest plot of T2DM associated with *MTNR1B* gene rs10830963 C/G polymorphism under an additive genetic model (i.e., G allele vs. C allele of *MTNR1B* gene rs10830963 C/G polymorphism).

susceptibility in South Asians, but not in East Asians. However, they mixed the Chinese population with other population and only 5 Chinese studies were involved to assess this relationship. Consequently, Shen's meta-analysis might not be as objective as the present research because

they neglected the ethnicity difference. In 2021, Feng et al. also performed a meta-analysis to assess the correlation of *MTNR1B* rs10830963 C/G mutation and T2DM risk in a Chinese population [25]. Although they found a significant association between them, only 6 individual



**Figure 7.** The funnel plot for studies of the association of T2DM and *MTNR1B* gene rs10830963 C/G polymorphism under a recessive genetic model (i.e. GG VS.CC + CG of *MTNR1B* gene rs10830963 C/G polymorphism). The horizontal and vertical axes correspond to the OR on log scale and SE (logOR), respectively. OR: odds ratio; SE: standard error.



**Figure 8.** The Begg's funnel plot for studies of the association of T2DM and *MTNR1B* gene rs10830963 C/G polymorphism under an additive genetic model (i.e., G allele vs. C allele of *MTNR1B* gene rs10830963 C/G polymorphism). The horizontal and vertical axes correspond to the OR on log scale and SE (logOR), respectively. OR: odds ratio; SE: standard error.

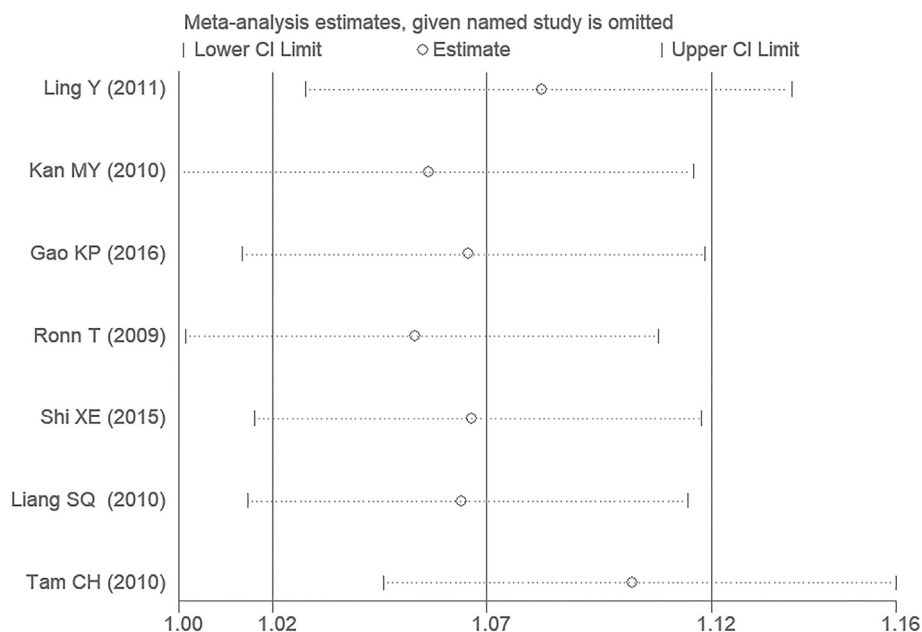
studies were contained in their meta-analysis. Hence, the conclusion deduced from their meta-analysis might not be as entire as that from the current meta-analysis.

Some limitations still existed inevitably in this current meta-analysis. There were not sufficient large-scale researches to estimate the correlation between the *MTNR1B* gene rs10830963 C/G polymorphism and T2DM yet. Moreover, environmental factors such as too much diet intake, too little physical exercise, and chronic tension and anxiety were closely linked to the T2DM onset. Other genes polymorphism as *NEUROD1* gene Ala45Thr polymorphism, *GHRL* gene Leu72Met polymorphism and *SUM O 4* gene M55V polymorphism might influence the T2DM development

[26,27,28]. In the present research, the correlation of the *MTNR1B* rs10830963 C/G mutation and T2DM was assessed. Otherwise, there's another mutation, i.e., *MTNR1B* gene rs1387153 C/T polymorphism which was associated with the T2DM risk [29].

In all, *MTNR1B* gene rs10830963 C/G mutant was significantly associated with T2DM risk in the Chinese population. The persons carrying the G allele of *MTNR1B* gene rs10830963 C/G polymorphism might be easier to suffer from T2DM than the persons carrying the C allele. Larger scale researches on the correlation of *MTNR1B* gene rs10830963 C/G polymorphism and T2DM should be performed to further elucidate this correlation.





**Figure 9.** The sensitivity analysis on the association of T2DM and *MTNR1B* gene rs10830963 C/G polymorphism under an additive genetic model (i.e., G allele vs. C allele of *MTNR1B* gene rs10830963 C/G polymorphism).

## Declarations

### Author contribution statement

Yan-yan Li: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Hui Wang: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Yang-yang Zhang: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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### Data availability statement

Data included in article/supp. material/referenced in article.

### Declaration of interest's statement

The authors declare no conflict of interest.

### Additional information

Supplementary content related to this article has been published online at <https://doi.org/10.1016/j.heliyon.2022.e11786>.

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