

RESEARCH

Testosterone level and risk of type 2 diabetes in men: a systematic review and meta-analysis

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Abstract

Background: Type 2 diabetes is a risk factor for testosterone deficiency and impaired sex steroid status. Some studies also investigated the association of testosterone level with diabetes risk in men, but reported controversial findings. To clarify this issue, we conducted a systematic review and meta-analysis.

Methods: PubMed, EMBASE and Web of Science were searched for eligible cohort or nested case–control studies published up to August 15, 2017. Meta-analysis was used to calculate the pooled relative risk (RR) of type 2 diabetes associated with higher testosterone level.

Results: Thirteen cohort or nested case–control studies with 16,709 participants were included. Meta-analysis showed that higher total testosterone level could significantly decrease the risk of type 2 diabetes in men (RR=0.65; 95% CI 0.50–0.84; $P=0.001$), and higher free testosterone level could also decrease the risk of type 2 diabetes in men (RR=0.94; 95% CI 0.90–0.99; $P=0.014$). After excluding two studies that did not calculate RRs by quartiles of testosterone levels, both higher total testosterone and free testosterone levels could decrease the risk of type 2 diabetes in men, and the pooled RRs were 0.62 (95% CI 0.51–0.76; $P<0.001$) and 0.77 (95% CI 0.61–0.98; $P=0.03$), respectively.

Conclusion: This meta-analysis suggests that higher testosterone level can significantly decrease the risk of type 2 diabetes in men. Therefore, combined with previous researches, the findings above suggest a reverse-causality scenario in the relation between testosterone deficiency and risk of type 2 diabetes in men.

Key Words

- ▶ testosterone
- ▶ type 2 diabetes
- ▶ meta-analysis

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Introduction

Diabetes is a public health issue, and there are over 0.4 billion people suffering from diabetes over the world, and its prevalence is still increasing remarkably every year (1). Type 2 diabetes mellitus (T2DM) is the major type of diabetes, which is associated with numerous complications including cardiovascular disease, peripheral neuropathy, stroke, infection, chronic renal failure, retinopathy and so on (2). Therefore, it is evident that both the treatment and the prevention of diabetes are critical. To compensate for progressive β -cell failure, standard treatment for T2DM includes lifestyle modification,

oral hypoglycemic agents and insulin therapy. Besides, current pharmaceutical paradigm for T2DM is limited because they fail to maintain stable glucose control; furthermore, oral medications are associated with adverse effects that are involved in hypoglycemia, weight gain and the loss of bone (3). Therefore, further studies of the pathogenesis and risk factors of T2DM are still necessary to cope with the epidemic of T2DM.

There is evidence to indicate that endogenous sex hormones play a vital role in the pathogenesis of T2DM (4). Some studies proposed that testosterone was possibly

linked with T2DM risk (5). The study by Rohwer and coworkers found that low testosterone level was associated with higher risk for T2DM among men but lower risk for T2DM among women (6). Elabbay and coworkers found T2DM patients tended to have significantly lower testosterone level when compared with non-diabetic individuals (7). However, evidence is less convincing and somewhat controversial for the impact of testosterone on T2DM risk among men. The study by Lakshman and coworkers reported that free testosterone level was not associated with risk of T2DM among men (8). Another study by Holmboe and coworkers also found that low testosterone level were not a risk factor for T2DM (9). Therefore, it is still unclear whether circulating testosterone level has an obvious impact on T2DM risk among men. There is also short of a comprehensive estimation of the relationship between circulating testosterone level and T2DM risk in men. Therefore, the objective of this study was to investigate whether circulating testosterone level was associated with T2DM risk in men.

Materials and methods

Search strategy and selection criteria

PubMed, EMBASE and Web of Science were searched to identify eligible studies. We searched databases from January 1980 to August 15, 2017. We employed the following keywords and MeSH searches: (testosterone or hypogonadism) and (diabetes or diabetic or type 2 diabetes mellitus or T2DM) and longitudinal or prospective or nested or cohort. We did not use the language restriction. For more eligible studies, we retrieved the reference lists of relevant articles or reviews.

We used the following predefined inclusion criteria: (1) cohort or nested case-control studies; (2) studies assessing T2DM risk associated with testosterone level in men; (3) the outcomes of interest were the risk estimates of T2DM associated with total or free testosterone, such as hazard ratio (HR), relative risk (RR) and odds ratio (OR). In this meta-analysis, to make it more comprehensive, we evaluated the risk of T2DM associated with total testosterone and free testosterone separately.

Data extraction and quality assessment

Using a predesigned form, the data were extracted independently by two authors from each study. We resolved the disagreements by discussion among all authors.

Data extracted from eligible studies mainly contained the first authors' name, publication year, study design, country, number of participants, duration of follow-up, types of testosterone, risk estimates and confounding factors used for adjustment analysis. If the study provided both unadjusted and adjusted risk estimates, we only used the latter one in our meta-analysis.

The study quality was assessed using the Newcastle Ottawa Scale (NOS) (10). According to its criteria, bias risk of included studies was assessed on selection of participants, comparability between groups (exposed and non-exposed participants), and the ascertainment of outcomes. Those three domains were scored by four stars, three stars and two stars, respectively. Studies with total stars of less than 6 were deemed to low-quality studies. Studies with 6 or more stars were regarded as moderate to high-quality studies.

Statistical analysis

Meta-analysis was used to calculate the pooled RRs of T2DM associated with testosterone. The I^2 and the Cochran's Q statistic were used to evaluate the heterogeneity (11, 12). For the Q statistic, $P < 0.10$ suggested statistically significant heterogeneity. I^2 more than 50% also suggested substantial heterogeneity among included studies. Random-effect meta-analysis was used when substantial heterogeneity existed (13); otherwise, fixed-effect meta-analysis was used when heterogeneity was not significant (14). To explore the effects of individual study on the overall results, we also performed a sensitivity analysis by excluding studies by turns. Sensitivity analyses were also carried out by excluding two studies without RRs calculated by quartiles or tertiles of testosterone levels. Publication bias was evaluated by funnel plot and Egger's test (15). We used Stata (version 12.0) to perform this meta-analysis. The P value < 0.05 was considered significant difference.

Results

Study selection and characteristics

We identified 572 articles from literature search (Fig. 1). After reading titles and abstracts, most of them were excluded because some studies were not cohort or nested case-control studies or because the exposures or outcomes were not relevant to our analysis, leaving 36 articles to the stage of detailed evaluation. Then 24 studies were

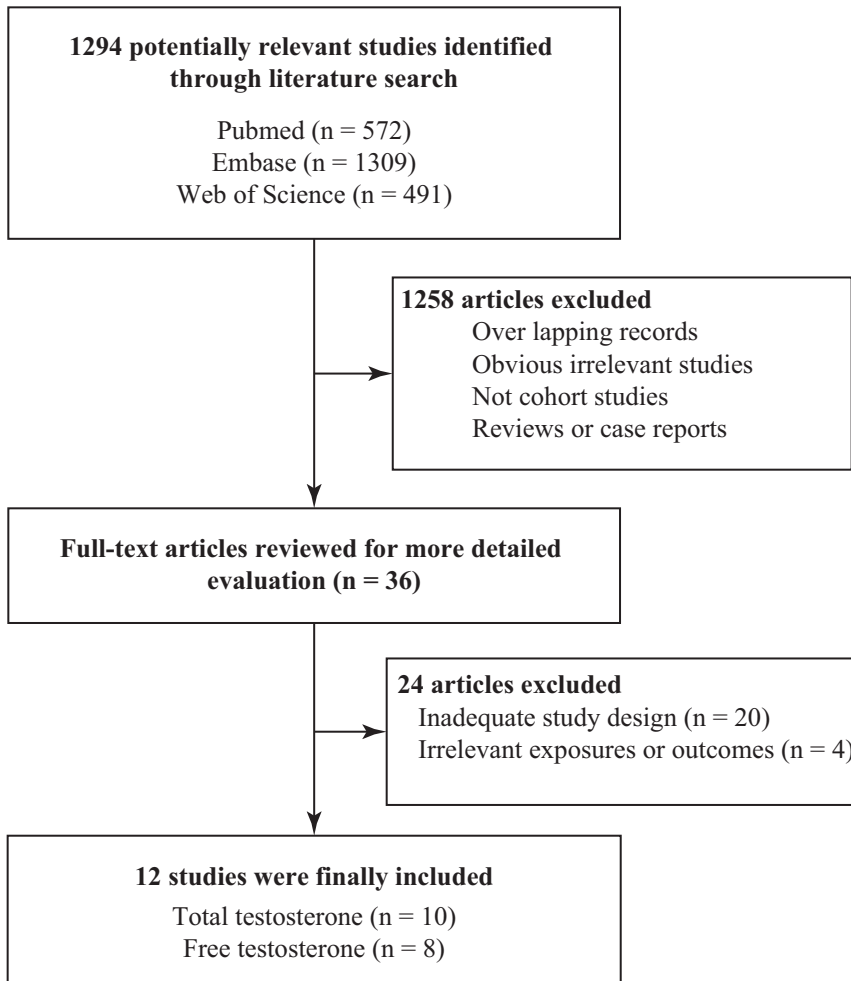


Figure 1
Flowchart of study selection in the meta-analysis.

excluded after reading their full-texts (16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38). Finally, 12 studies were included into our meta-analysis (9, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49). There were a total of 16,709 participants.

We summarized and listed the main characteristics of the included studies in Table 1. These included studies were published between 1996 and 2016, and all of them were published in English. All studies were done in developed countries, and only one study was performed in developing countries (Table 1). The time of follow-up ranged from 4.7 to 29 years. Ten studies reported RRs of T2DM associated with higher level of total testosterone, and 8 studies reported RRs of T2DM associated with higher level of free testosterone (Table 1). Ten of those 12 studies reported RRs calculated by quartiles or tertiles of testosterone levels, but two studies reported RRs calculated by some increment of testosterone levels (47, 49). Each study adjusted for a wide range of confounding factors, such as age, smoking, estradiol and so on. The quality of

those studies was shown in Table 1, and all studies had a high quality (Table 1).

Meta-analysis

Obvious heterogeneity was observed among those 10 studies on total testosterone ($I^2=64.6\%$), and random-effect meta-analysis was utilized. Meta-analysis of those studies suggested that high level of total testosterone significantly decreased risk of T2DM among men (RR=0.65; 95% CI 0.50–0.84, $P=0.001$; Fig. 2A). After excluding one study without RRs calculated by quartiles of testosterone levels, meta-analysis of those 9 left studies found that there was still an obvious association between high total testosterone level and decreased risk of T2DM among men (RR=0.62; 95% CI 0.51–0.76; $P<0.001$; Fig. 2B). In the sensitivity analysis by excluding studies by turns, the pooled RRs were not significantly altered by any single study (Fig. 3), suggesting no obvious impact of individual study on the overall results.

Table 1 The main characteristics of the included studies in the meta-analysis.

Study	Design	Country	Groups of participants (mean age, years)	Types of testosterone	Follow-up	Confounding factors	Quality
Jasuja <i>et al.</i> (46)	Prospective cohort	USA	1031 men without diabetes at baseline which were from Framingham Heart Study (FHS) generation 2 study (59 years)	TT	6.8	Age, smoking, BMI, SHBG, and estradiol	8
Soriguer <i>et al.</i> (45)	Prospective cohort	Spain	368 men without diabetes at baseline, including 57 incident T2DM cases and 311 non-diabetic controls during follow-up (38 years)	ft	11	Age and waist circumference	8
Schipf <i>et al.</i> (44)	Prospective cohort	Germany	1339 men without T2DM at baseline, including 68 incident T2DM cases and 1271 non-diabetic controls during follow-up (50 years)	TT	5	Age, waist circumference, smoking	8
Lakshman <i>et al.</i> (43)	Prospective cohort	USA	1128 men without T2DM at baseline, including 90 incident T2DM cases and 1038 non-diabetic controls during follow-up (54 years)	TT; ft	13	Age, BMI, smoking, high blood pressure, alcohol intake, and physical activity	8
Vikan <i>et al.</i> (42)	Prospective cohort	Norway	1454 men without T2DM at baseline, including 76 incident T2DM cases and 1378 non-diabetic controls during follow-up (59 years)	TT; ft	9.1	Age, HDL cholesterol, systolic blood pressure, and waist circumference	8
Oh <i>et al.</i> (40)	Prospective cohort	USA	294 men without T2DM at baseline, including 26 incident T2DM cases and 268 non-diabetic controls during follow-up (68 years)	TT	8	Baseline age, BMI, and systolic blood pressure	7
Laaksonen <i>et al.</i> (41)	Prospective cohort	Finland	702 men without diabetes at baseline, including 57 incident T2DM cases and 645 non-diabetic controls during follow-up (51 years)	TT; ft	11	Age, presence of cardiovascular disease, smoking, alcohol consumption, waist, concentrations of insulin, glucose, and triglycerides, blood pressure, etc.	8
Haffner <i>et al.</i> (39)	Nested case-control	USA	176 incident diabetes male cases during follow-up and 352 matched non-diabetic men (46 years)	TT; ft	5	Age, age, diastolic blood pressure, serum cholesterol, smoking, fasting glucose, body mass index, etc.	7

(Continued)

Table 1 Continued

Study	Design	Country	Groups of participants (mean age, years)	Types of testosterone	Follow-up	Confounding factors	Quality
Joyce <i>et al.</i> (47)	Prospective cohort	USA	852 men without diabetes at baseline, including 112 incident T2DM cases and 740 non-diabetic controls during follow-up (76 years)	ft	9.8	Age, race, site, alcohol consumption, current smoking status, and BMI	8
Salminen <i>et al.</i> (49)	Prospective cohort	Finland	430 men without diabetes at baseline, including 30 incident T2DM cases and 400 non-T2DM controls during follow-up (72 years)	TT; ft	9	BMI, fasting blood glucose, cardiovascular diseases and sex hormone-binding globulin	8
Holmboe <i>et al.</i> (9)	Prospective cohort	Denmark	5187 men without diabetes at baseline, including 211 incident T2DM cases and 4976 non-diabetic controls during follow-up (not available)	TT; ft	29	BMI, study, alcohol consumption and exercise with age as the underlying time scale	9
Hu <i>et al.</i> (48)	Nested case-control	China	145 incident T2DM men during follow-up and 145 matched non-T2DM men (61 years)	TT	5	BMI, systolic blood pressure, diastolic blood pressure, current smoking, alcohol use, hypertension, exercise frequency, family history of T2DM, etc.	9

BMI, body mass index; ft, free testosterone; T2DM, type 2 diabetes mellitus; TT, total testosterone.

Heterogeneity was not observed among those 8 studies on free testosterone ($I^2=17.9\%$), and fixed-effect meta-analysis was utilized. Meta-analysis of those studies suggested that high level of free testosterone was significantly associated with decreased risk of T2DM in men (RR=0.94; 95% CI 0.90–0.99; $P=0.014$; Fig. 4A). After excluding two studies without RRs calculated by quartiles of testosterone levels, meta-analysis of those 6 left studies found that high free testosterone level could decrease the risk of T2DM in men (RR=0.77, 95% CI 0.61–0.98; $P=0.03$; Fig. 4B).

Funnel plot suggested no obvious tendency of publication bias in the meta-analysis of the association between total testosterone level and T2DM in men (Fig. 5, $P=0.17$).

Discussion

Our study is the first meta-analysis of cohort studies to investigate the association between circulating

testosterone level and T2DM risk in men. Twelve studies were finally included, and the findings suggested that high total testosterone level was significantly associated with decreased risk of T2DM in men (RR=0.65; 95% CI 0.50–0.84; $P=0.001$). In addition, high free testosterone level was also significantly associated with decreased risk of T2DM in men (RR=0.94; 95% CI 0.90–0.99; $P=0.014$). Sensitivity analyses also found that high testosterone level was significantly associated with decreased risk of T2DM among men. The findings above suggest that testosterone has an important protective effect against T2DM among men, and men with higher testosterone level have a decreased risk for T2DM than those with lower testosterone level.

The findings of our meta-analysis indicate that male persons with a low testosterone level are predisposed to T2DM. Some mechanisms or hypotheses have been proposed to explain the association between testosterone and diabetes (50, 51). Firstly, the key role of insulin resistance in the pathogenesis of T2DM has been well

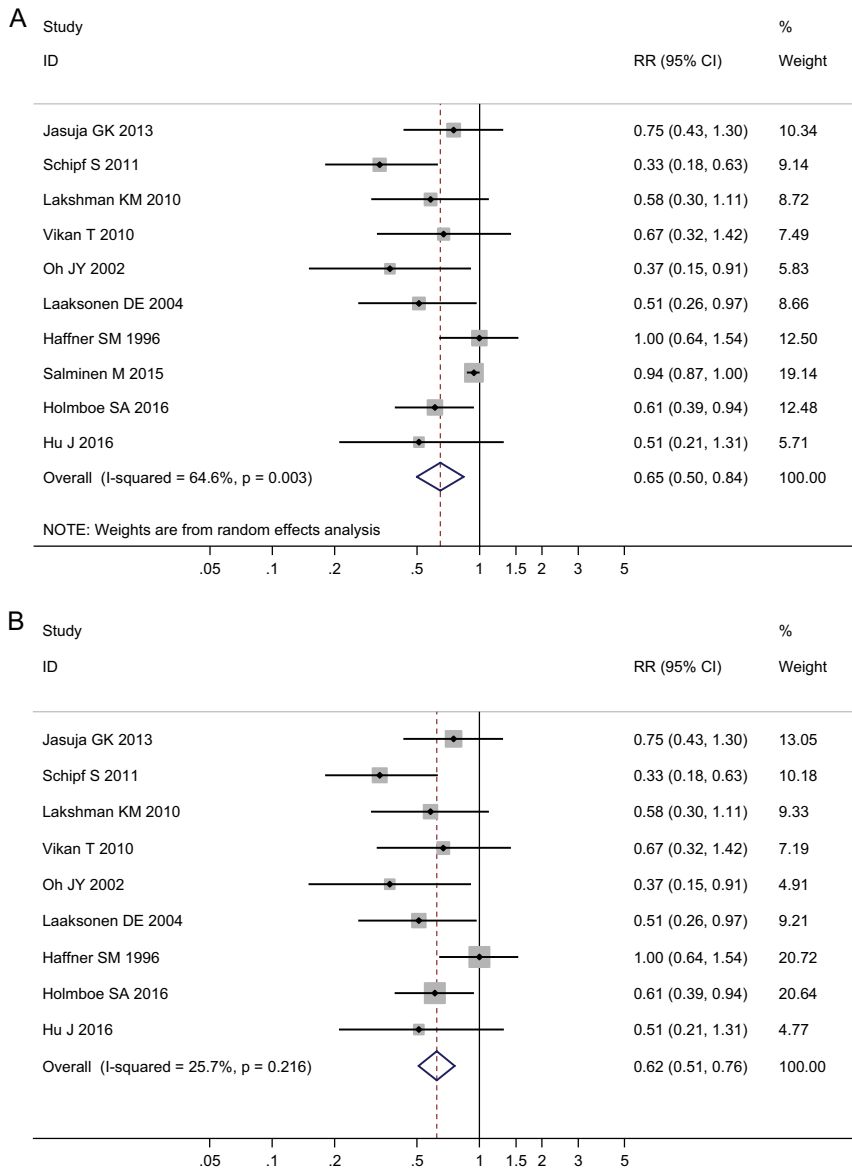


Figure 2 Forest plots in the meta-analysis of the association between total testosterone level and T2DM in men. (A) Meta-analysis showed that high total testosterone level could obviously decrease the risk of T2DM among men (RR, relative risk; 95% CI, 95% confidence interval). (B) Forest plot in the meta-analysis of 9 studies reporting RRs of T2DM calculated by quartiles or tertiles of total testosterone levels.

established. Previous studies have proven the inverse association between testosterone and insulin resistance, and individuals with testosterone deficiency have higher level of insulin resistance, which can further result in increased risk of T2DM (52, 53). An experimental study also supports that testosterone deficiency can increase fasting glucose associated with hepatic and extra-hepatic insulin resistance in adult male rats (54). Secondly, testosterone can regulate the expressions of important genes involved in insulin signaling and glucose uptake, such as glucose transporter-4 (GLUT4) (55, 56). Testosterone can increase the expression of GLUT4 in the muscle cells and adipocytes, and lower expression GLUT4 caused by testosterone deficiency decreases glucose transport and insulin responsiveness, which may finally

cause T2DM. In one study, testicular feminized mice with testosterone deficiency have a reduced GLUT4 level in muscle and a decreased glycolytic enzyme activity in muscle, liver and abdominal adipose tissues (57). Thirdly, obesity caused by testosterone deficiency is another possible explanation. An experimental study by Fan and coworkers revealed that androgen receptor (AR) played an important role in modulating fat accumulation in male mice, and elimination of the effect of testosterone through AR knockout in mice promoted the development of obesity, which could further contribute to diabetes (58). Finally, abnormalities in lipid metabolism are also involved in the pathogenesis of diabetes, which are associated with impaired insulin responsiveness and abnormalities in glucose control (59). The dysregulated lipid metabolism

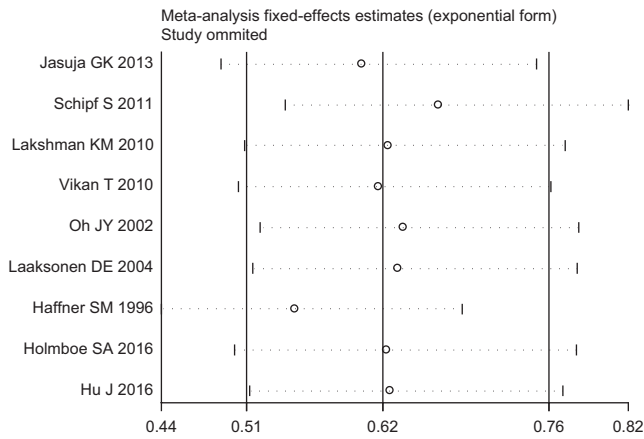


Figure 3
Sensitivity analysis by excluding studies by turns suggested that the pooled RRs were not significantly altered by any single study.

caused by testosterone deficiency may result in decreased insulin sensitivity and increase the risk of T2DM (60, 61). However, the precise molecular mechanisms underlying the link of testosterone to T2DM are still not well defined.

The relationship between testosterone deficiency and diabetic predisposition implies that supplementation of testosterone may be a prophylactic means for T2DM in specific persons. A study by Canguven and coworkers found that testosterone therapy could decrease the levels of glycated hemoglobin, total cholesterol and triglycerides in elderly hypogonadal men, which might reduce the risk of diabetes in those individuals (62). It is not a unique instance, but has its counterpart. Permpongkosol and coworkers also reported that testosterone replacement could significantly decreased body fat and glycated hemoglobin in men with hypogonadism (63). An observational study by Yassin *et al.* found that testosterone

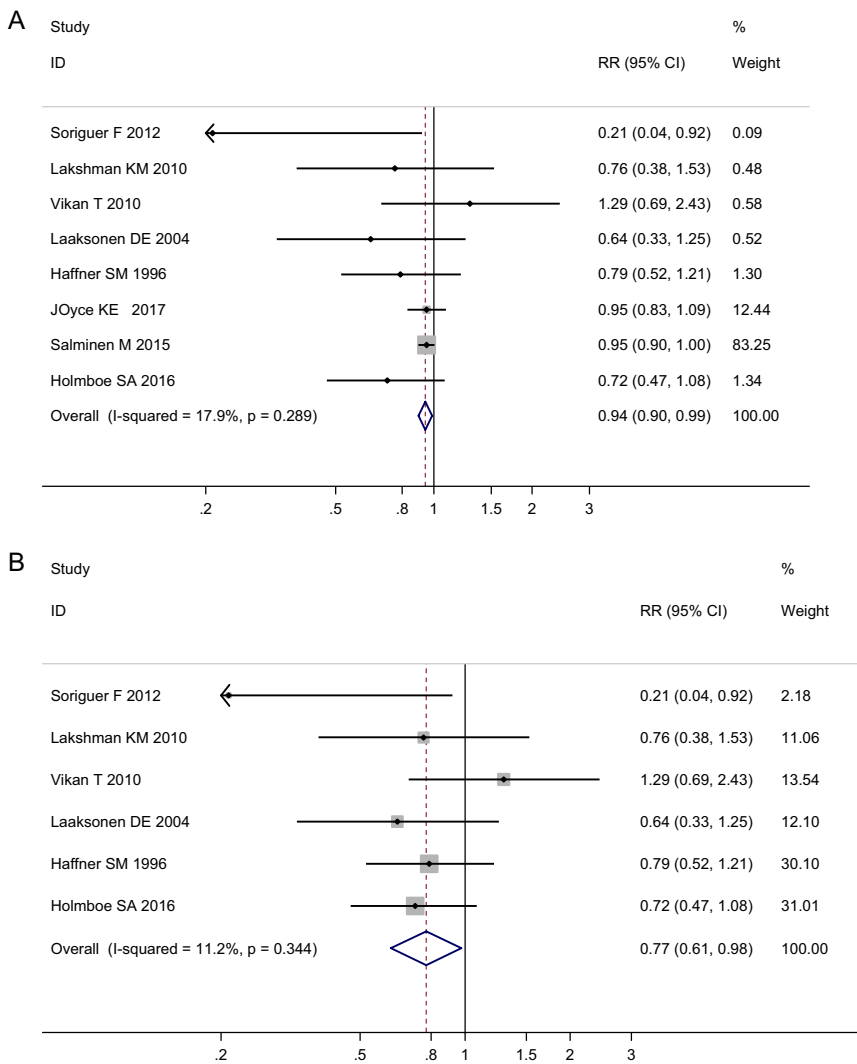


Figure 4
Forest plots in the meta-analysis of the association between free testosterone level and T2DM in men. (A) Meta-analysis showed that high free testosterone level could obviously decrease the risk of T2DM among men. (B) Forest plot in the meta-analysis of 6 studies reporting RRs of T2DM calculated by quartiles or tertiles of free testosterone levels.

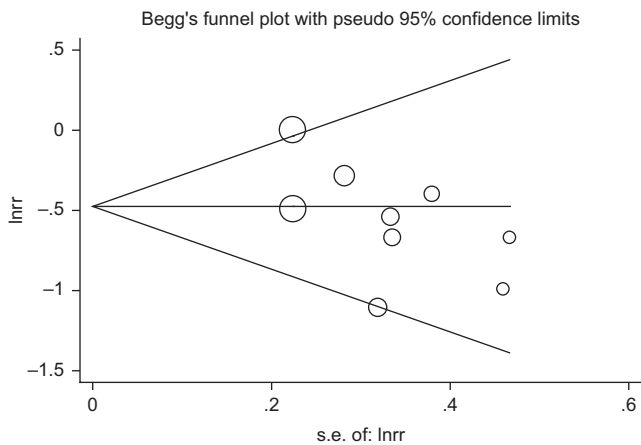


Figure 5
Funnel plot in the meta-analysis of the association between total testosterone and risk of T2DM in men.

application could decrease the levels of fasting glucose and HbA1c in hypogonadal elderly men (64). An experimental study using male mouse model of T2DM found that testosterone supplementation could improve glucose homeostasis (65). A clinical trial in men with lowered bioavailable testosterone level and T2DM found that testosterone therapy improved body composition and decreased HDL cholesterol level (66). Another study reported that testosterone therapy could reduce insulin resistance and improve glycemic control in hypogonadal men with type 2 diabetes (67). A recent clinical trial found that testosterone treatment in men with T2DM increased insulin sensitivity and reduced diabetic chronic inflammation (68). Though the above-mentioned findings strongly suggest that testosterone supplementation has a protective role against diabetes, more clinical trials are still needed to confirm this scenario, to determine the dosage and the approaches.

To summarize, our findings from the meta-analysis provide strong epidemiologic evidence for testosterone deficiency as an important risk factor of T2DM in men. As many observational studies have found that testosterone deficiency is very prevalent in male T2DM patients and also associated with poorer outcomes of diabetes (69, 70, 71, 72), our research has a broad and bright clinical utilization in the future.

A previous systematic review published in 2006 also assessed the association between testosterone and diabetes (4). The systematic review above mainly included retrospective case-control or cross-sectional studies and included only two nested case-control studies, which was unable to evaluate the causal relationship between testosterone and T2DM. Compared with the

previous systematic review, our study only included prospective cohort or nested case-control studies, which could assess the causal relationship between risk factor and diseases. We finally included 13 cohort or nested case-control studies, and the sample size of the pooled subjects was large enough to allow a reliable assessment of the causal relationship between testosterone and risk of T2DM in men. The pooled results in our meta-analysis provided strong epidemiological evidence for the causal relationship between testosterone and T2DM. Moreover, in the sensitivity analyses, the consistent and obvious links of testosterone with T2DM further strengthened the epidemiological evidence for testosterone as a protective factor against T2DM in men. The results of the present meta-analysis are very helpful to define the causal association between testosterone deficiency and T2DM.

Thus, there are many studies might support that testosterone deficiency leads to T2DM as described earlier. However, other studies suggest that T2DM is a risk factor for testosterone deficiency and impaired sex steroid status (73). One large prospective study showed that the development of T2DM is a major driver of the age-related testosterone decline (74). Treatment of hypogonadal men concomitant with T2DM with rosiglitazone caused an increase in serum testosterone levels (75). Another study demonstrated a significant reduction in total and free testosterone levels in men after glucose ingestion (76). Therefore, it seems that both insulin resistance and glucose itself may induce hypotestosteronaemia in patients with diabetes. About the impact of insulin resistance on testosterone, one longitudinal study indicated a negative correlation between changes in insulin resistance and alterations in testosterone levels in diabetic men over time (77). IL-6 and TNF- α , two major inflammatory cytokines related to insulin resistance in T2DM, are able to reduce the production of testosterone from Leydig cells (79). In addition, TNF- α and IL-1 β have been shown to suppress secretion of hypothalamic gonadotropin-releasing hormone in experimental animals (80). Hence, there appears to be a bidirectional link between lower testosterone levels and T2DM, and a reverse-causality scenario exists in the relation between testosterone deficiency and T2DM risk in men.

Several limitations of the meta-analysis should be considered. Firstly, in the meta-analysis on the impact of total testosterone on T2DM risk among men, there was obvious heterogeneity which may be a result of the different study design, different statistical analysis or different characteristics of recruited subjects. Secondly, there were no uniform criteria for high or low testosterone

levels among those included studies. At present, the adequate cut-off value in defining low testosterone level is still unclear, which needs to be defined in future research. Finally, most of our included studies were from European countries and USA, and only one study was conducted in Asia. Therefore, given above limitations, the findings from the present meta-analysis should be treated with caution.

In conclusion, this meta-analysis suggests that higher testosterone level can significantly decrease the risk of T2DM in men, and testosterone is an important protective factor against T2DM in men. Besides, more researches are recommended to evaluate the effect of testosterone supplementation in reducing T2DM risk in individuals with testosterone deficiency and to assess the effect of testosterone treatment in improving clinical outcomes among male patients with T2DM.

Declaration of interest

The authors declare no conflict of interest. They are all responsible for the content of the paper.

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Author contribution statement

Qiu-ming Yao, Bin Wang and Xiao-fei An designed the study. Qiuming Yao and Bin Wang extracted the data. Qiuming Yao and Bin Wang performed the analyses. Qiuming Yao wrote the draft. Jinan Zhang and Liumei Ding revised it critically.

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