



Type 2 diabetes mellitus does not increase the risk of multiple myeloma: a systematic review and meta-analysis

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Background: Epidemiological studies have shown that patients with type 2 diabetes mellitus (T2DM) are at a higher risk of secondary tumors. However, no consensus has been made about whether T2DM can increase the risk of multiple myeloma (MM).

Methods: We searched the databases of PubMed, Cochrane Library and EMBASE and cross-checked the bibliography. Data quality was assessed using the Newcastle-Ottawa scale (NOS). Heterogeneity was calculated as the odds ratio (OR) using a random-effects model. Data were analyzed using Stata version 12.0 software.

Results: A total of 13 articles were selected into this meta-analysis. Initially, we found that diabetic patients had a higher risk of myeloma than non-diabetic patients (OR =1.60, 95% CI: 1.13–2.26, $I^2=98%$, $P=0.000$). But the data in these articles were highly heterogeneous ($I^2>75%$). Therefore, eight of the included articles showed a moderate heterogeneity ($I^2=71.6%$). We used Galbraith heterogeneity map to analyze the causes of heterogeneity. Two articles with high heterogeneity were excluded. Then, we found the heterogeneity of the left six articles was reduced from moderate to mild ($I^2=45.9%$, $P=0.100$). The final results of this meta-analysis showed that T2DM was not a risk factor for increased incidence of MM (OR =1.05, 95% CI: 0.83–1.33, $I^2=45.9%$, $P=0.100$). Also, the subgroup analysis (case-control studies *vs.* cohort studies) showed no statistical difference (OR =1.19, 95% CI: 0.76–1.85, $I^2=1%$, $P=0.364$; OR =1.00, 95% CI: 0.75–1.33, $I^2=71.2%$, $P=0.031$; respectively).

Conclusions: T2DM is not a risk factor for the increased incidence of MM, a finding that should be validated with more strictly designed randomized controlled trials (RCTs).

Keywords: Meta-analysis; type 2 diabetes mellitus (T2DM); multiple myeloma (MM); carcinogenic risk

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Introduction

Multiple myeloma (MM) is a malignant disease featuring plasma cell proliferation and accounting for about 15% of lymphoid system tumors (1). In recent years, the incidence of MM has increased significantly, making MM the second commonest hematological disease. MM occurs in 1.6% of all cancer cases and about 10% of blood malignancy cases in the United States. In 2015, America estimated 28,850 new cases and more than 11,000 MM-led deaths. Age and race may be risk factors of MM. Over 85% of MM cases are over 65 years, and the incidence in the blacks is twice of that in the whites (2). With new drugs like bortezomib, thalidomide, lenalidomide, as well as autologous stem cell transplantation (ASCT), the median survival period of MM patients has been greatly improved, but there is no doubt that MM relapses in those showing drug resistance (3). Therefore, it is necessary to explore other risk factors that cause the increase in MM incidence.

Recent studies have shown a worldwide increase in the prevalence of diabetes. Of the 400 million people with diabetes worldwide, 85–95% suffer from type 2 diabetes mellitus (T2DM) (4–6). For a long time, there has been speculation about the possible link between T2DM and the risk of cancer, because some cancers are diagnosed more frequently in diabetics than in non-diabetics (7). A number of original studies and meta-analyses have shown that T2DM is associated with an increased risk of cancers in the pancreas, liver, endometrium, breast, colorectum, and bladder, and a decreased risk of prostate cancer (8).

However, the association between T2DM and MM incidence remains controversial (9–12). Therefore, we conducted this meta-analysis to resolve this question.

Methods

Study design and eligibility criteria

Instructed by professional researchers and following the guidelines for the meta-analysis of Observational Studies in Epidemiology (MOOSE), two investigators searched the related database independently (13). In PubMed, Cochrane Library (<https://www.cochranelibrary.com>), and EMBASE databases, the following keywords were searched: diabetes, type 2 diabetes mellitus, and myeloma (the latest search on February 28, 2019) (See appendix for more details about the search procedures). The reference lists were checked to identify relevant studies. All studies that met the inclusion criteria (provided below) were subjected to our meta-

analysis.

The authors (Zhang and Sha) screened publications using the following inclusion criteria: (I) evaluated and clearly defined exposure to T2DM; (II) reported the risk of MM incidence; (III) the type of study was case-control or cohort; (IV) the risk score was reported as hazard ratio (HR), incidence risk ratio, rate ratio (RR), odds ratio (OR), and 95% confidence interval (CI), or the article provided sufficient information to allow the calculation of OR and 95% CI. If multiple publications were generated by the same study, only the most recent was selected. Any disagreement between the two authors was resolved by a third researcher through efficient discussion.

Excluded were studies (I) including patients not diagnosed with T2DM; (II) duplicates within and between the databases; (III) written in reviews, viewpoints, or reports; and (IV) showing insufficient data.

Data extraction

Data were extracted by two investigators (Zhang and Sha), and the differences were reviewed by a third researcher (Liu) and resolved by consensus. An qualified article included the name of the first author, publishing date, country, study period, study type [cohort (CO) or case-control (CC)], sample size (case group and control group), number of cases, OR, 95% CI, adjusted variables, and confounders in the multivariate analysis (see *Tables 1, S1, S2*). If necessary, letters were given to the first authors to acquire the detailed data.

Quality assessment

The methodological scientificity of the included studies was assessed independently by two researchers using the nine-item Newcastle-Ottawa scale (NOS) (http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm) (23). The scale was used for non-randomized case-control and cohort studies, with a maximum of 9. The quality of the included literature was determined by assessing three features: group selection (four questions), comparability (one question), exposure, and outcomes for study participants (three questions). All questions scored 1, except for the comparability between the study groups. In terms of study comparability, a study with a rigorous design or a good control of significant confounding factors was scored separately (maximum 2 points). Any conflicting judgement was resolved by consensus. We considered articles scoring

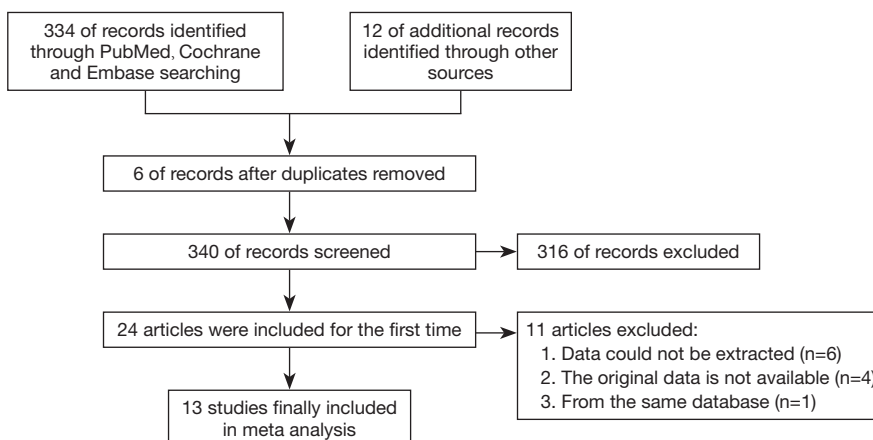


Figure 1 Results of the literature search.

≥ 7 points as high-quality; the others were regarded as low-quality.

Statistical analysis

We evaluated the data heterogeneity using the Cochrane Q test and I^2 , and $P < 0.1$ for the Q statistic or $I^2 > 75\%$ suggested high heterogeneity (24,25). If significant heterogeneity existed, the random-effects model (DerSimonian-Laird method) was applied; otherwise, a fixed-effects model (Mantel-Haenszel method) was utilized (26). In each round of sensitivity analysis, one study was excluded to test its impact on the stability of the overall results. Publication bias was evaluated by the Begg's funnel plot and Egger's linear regression test with a funnel plot. If $P < 0.05$, it indicated the existence of publication bias (27). Data were analyzed using Stata version 12.0 software (StataCorp LP, College Station, TX, USA), and P value < 0.05 was regarded as statistically significant.

Results

Characteristics and quality of included studies

A total of 334 pieces of literature were found after the literature search. The searching processes (including reasons for exclusion) are listed in *Figure 1*. All included studies were written in English. In the end, 13 studies were deemed suitable and selected for meta-analysis, including 5 case-control studies and 8 cohort studies, with a total of 2,135,496 case groups and 31,861,710 control groups (9-12,14-22). The main characteristics of the included studies are shown

in *Table 1* (see *Tables S1* and *S2* for relevant information). Of the 13 studies, seven showed an increased risk of MM in patients with T2DM; one showed the opposite relationship; the remaining five showed no significant association. Three reviewers reached an agreement in scoring study quality, including 6 points for 3 articles, 7 points for 7 articles, and 8 points for 3 articles (see *Tables 2* and *3* for details). Hence, 10 studies were of high quality, and 3 were of low quality.

Quality control

Overall, the risk of myeloma was higher in patients with diabetes (OR =1.60, 95% CI: 1.13–2.26, $I^2=98\%$, $P=0.000$) (*Figure 2*). As shown in *Figure 2*, I^2 value was 98%, indicating a high heterogeneity in the data of the included studies. So, a random-effects model was adopted for statistical analysis. First, through the first round of sensitivity analysis, we excluded three studies with high heterogeneity (9,11,14). The remaining studies showed a high heterogeneity ($I^2=81.5\%$, greater than 75%). Therefore, we conducted a second sensitivity analysis and excluded another study with high heterogeneity (12). I^2 dropped to 71.5%, indicating a moderate heterogeneity. After the third round of sensitive analysis, a study with a greater impact on heterogeneity was further eliminated (19). In the end, eight studies were left for meta-analysis (*Figure 3*), but I^2 rose to 73.3% (*Figure S1*). Next, Galbraith heterogeneity map was used to further detect the possible sources of heterogeneity (*Figure 4*). Finally, six studies were included in this meta-analysis, because none of them significantly influenced the pooled OR and 95% CIs. Therefore, our results were expected to be comparatively reliable and stable (*Figure 5*). The six

Table 1 Summary of include studies

Reference	Design	Cases	Controls	Summary of findings
Atchison <i>et al.</i> (9)	CO	594,815	3,906,763	Increased risk of MM in patients with DM
Boursi <i>et al.</i> (10)	CC	138	746	Decreased risk of MM in patients with DM
Carstensen <i>et al.</i> (14)	CO	56,889	4,579,016	Increased risk of MM in patients with DM
Dankner <i>et al.</i> (11)	CO	159,104	1,618,849	Increased risk of MM in patients with DM
Fortuny <i>et al.</i> (15)	CC	84	590	Increased risk of MM in patients with DM
Gini <i>et al.</i> (16)	CO	32,247	46,735	No association between MM and DM
Harding <i>et al.</i> (12)	CO	872,706	20,295,817	Increased risk of MM in patients with DM
Khan <i>et al.</i> (17)	CO	3,307	53,574	No association between MM and DM
Khan <i>et al.</i> (18)	CO	11,139	382,338	No association between MM and DM
Liu <i>et al.</i> (19)	CO	380,196	495,625	Increased risk of MM in patients with DM
La Vecchia <i>et al.</i> (20)	CC	1,067	16,758	No association between MM and DM
Vineis <i>et al.</i> (21)	CC	175	4,212	Increased risk of MM in patients with DM
Wotton <i>et al.</i> (22)	CC	23,629	460,687	No association between MM and DM

CO, cohort; CC, case-control; MM, multiple myeloma; DM, diabetes mellitus.

Table 2 Quality assessment of cohort studies using the Newcastle-Ottawa Quality Assessment Scale

Study (reference)	Exposed populations represent or to some extent represent communities	The non-exposed and exposed groups came from the same population	Ascertainment of exposure (secure record or structured interview)	Demonstration that outcome of interest was not present at start of study	The exposed and non-exposed groups were matched and/or adjusted for factors	Outcome defined with independent validation	Follow-up long enough for outcomes to occur	The loss of follow-up rate is within the range of bias	Overall score
Atchison <i>et al.</i> (9)	1	1	1	1	2	1	1	0	8
Carstensen <i>et al.</i> (14)	1	1	1	1	1	1	1	0	7
Dankner <i>et al.</i> (11)	1	1	1	1	1	1	1	0	7
Gini <i>et al.</i> (16)	1	1	1	1	1	1	1	0	7
Harding <i>et al.</i> (12)	1	0	1	1	1	1	1	0	6
Khan <i>et al.</i> (18)	1	1	0	1	2	1	1	0	7
Khan <i>et al.</i> (17)	1	1	0	1	1	1	1	0	6
Liu <i>et al.</i> (19)	1	1	1	1	2	1	1	0	8

A study could be awarded a maximum of one star for each item except for the item control for important factor or additional factor. The definition/explanation of each column of the Newcastle Ottawa Quality Assessment Scale is available from (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). One means study adequately fulfilled a quality criterion (two for cohort fully matched and adjusted), 0 means it did not. Quality scale does not imply that items are of equal relevant importance

Table 3 Quality assessment of case-control studies using the Newcastle-Ottawa Quality Assessment Scale

Study (reference)	Case defined with independent validation	Representativeness of the cases	Selection of controls from community	Statement that controls have no history of outcome	Cases and controls matched and/or adjusted by factors	Ascertain exposure by blinded structured interview	Same method of ascertainment for cases and controls	Same response rate for both groups	Overall score
Boursi <i>et al.</i> (10)	1	1	1	1	1	1	1	0	7
Fortuny <i>et al.</i> (15)	1	1	1	1	1	1	1	0	7
La Vecchia <i>et al.</i> (20)	1	1	1	1	0	0	1	1	6
Vineis <i>et al.</i> (21)	1	1	1	1	2	0	1	0	7
Wotton <i>et al.</i> (22)	1	1	1	1	2	1	1	0	8

A study could be awarded a maximum of one star for each item except for the item control for important factor or additional factor. The definition/explanation of each column of the Newcastle Ottawa Quality Assessment Scale is available from (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). One means study adequately fulfilled a quality criterion (two for cohort fully matched and adjusted), 0 means it did not. Quality scale does not imply that items are of equal relevant importance.

studies were submitted to a fixed-effects model.

Association between diabetes and MM

As shown in *Figure 6*, the incidence of concomitant myeloma in diabetic patients was only 1.05 times higher than that of non-diabetic patients (OR =1.05, 95% CI: 0.83–1.33, $I^2=45.9\%$, $P=0.100$), with no significant difference. A subgroup analysis found that the risk of myeloma detected by case-control studies was higher than that detected by the cohort studies (OR =1.19, 95% CI: 0.76–1.85, $I^2=1\%$, $P=0.364$; OR =1.00, 95% CI: 0.75–1.33, $I^2=71.2\%$, $P=0.031$, respectively) (*Figure 7*), but this difference was not significant.

Sensitivity analysis and publication bias

The sensitivity analysis was implemented to evaluate the contribution of every study to the pooled estimation. Seven studies were omitted, and the pooled OR was reevaluated based on the remaining studies that showed a low heterogeneity (*Figures 2, 6*). Begg's and Egger's tests were utilized to evaluate the publication bias and the funnel plots were displayed in *Figure 8*. In the pooled analysis of OR, the P values of Begg's and Egger's tests were all above 0.05, indicating that no publication bias existed in this study and our findings were statistically robust.

Discussion

Since 1980, the age-standardized prevalence of diabetes has increased by little or remained unchanged among adults in each country. But the number of diabetic adults has grown by four folds as the global population explodes (28). Diabetes frequently arises from immune and hormonal abnormalities (29). Malignant tumors are associated with T2DM-favoring conditions (30). Therefore, more and more researchers are concerned about whether patients with T2DM are confronted with a higher risk of second cancer. Previously, Castillo *et al.* conducted a meta-analysis in which adjusted OR value was used to evaluate the relationship between T2DM and the risk of non-Hodgkin's lymphoma, leukemia and myeloma (31). Up to now, no independent study has been conducted to clarify the relationship between T2DM and MM. Based on the data from previous studies, our meta-analysis found that T2DM is not a risk factor of MM. Although only six studies were included in this analysis, their inner consistency made our

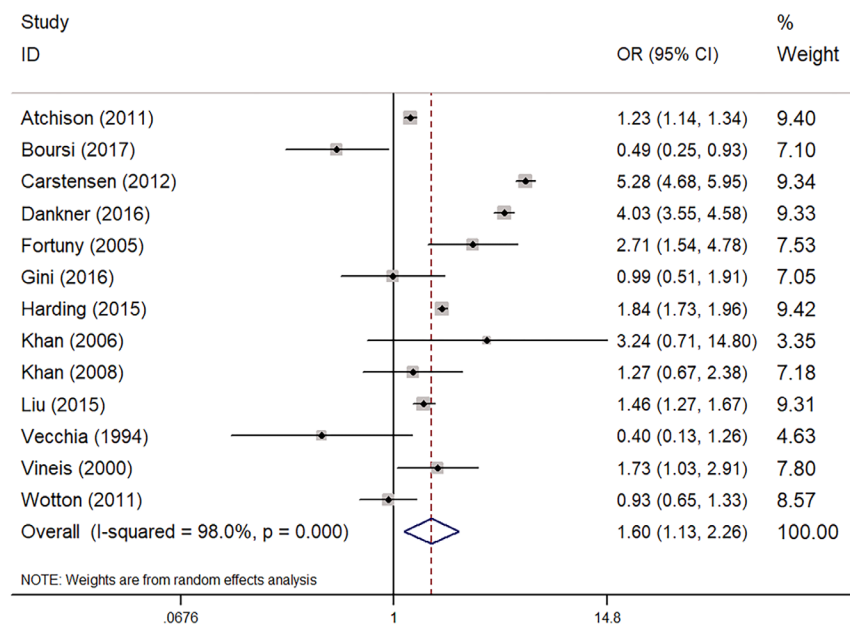


Figure 2 Odds ratio (OR) of myeloma for patients with diabetes compared with control subjects (patients without diabetes).

findings reliable.

Many factors, like congenital genetic defects and controllable environmental assaults, can increase the risk of MM. T2DM is more common in people aged over 40, especially those obese. Obesity is a risk factor for MM. To a certain extent, patients with T2DM should have a higher incidence of MM. But we found that T2DM does not serve as a risk factor for myeloma. We hypothesize that this may be related to the use of hypoglycemic drugs.

As we all know, metformin is the first choice for T2DM. A population-based observational study showed that patients who used single metformin presented a lower incidence of cancer (5.4% vs. 8.1%) than those who used other hypoglycemic drugs (16). Long-term use of metformin also lowers the morbidity and mortality of cancers in patients with diabetes (32). At the same time, metformin can prolong the progress of monoclonal gammopathy of undetermined significance (MGUS) to MM to a certain extent (10). Besides, metformin can curb the transition of MGUS to MM (33). The reason may be that metformin activates the AMPK pathway, inhibits gluconeogenesis, and induces glucose into muscle cells, all helpful to reduce circulating glucose and insulin (34). Cancer cells usually require high levels of glucose uptake, but metformin can reduce

circulating glucose (35). At the same time, metformin can lead to weight loss (36). All these mechanisms are beneficial to reduce the risk of MM in patients with T2DM.

However, in addition to metformin, many other hypoglycemic drugs are also commonly used for T2DM. Insulin and insulin-like growth factors promote tumor development by stimulating epithelial cell proliferation (37,38). The use of insulin is more common in patients with poor blood glucose control or compliance. Sulfonylureas increases circulating insulin level, probably resulting in cancer. Hsieh *et al.* showed that metformin reduced the risk of cancer by 25% compared to sulfonylureas (39). These differences in the relationship between drugs and cancer risk mean that we need to be cautious with our findings.

Studies have shown that the incidence of MM varies with race, with Asians showing a lower incidence than Caucasians (40). Since the beginning of 2007, genome-wide association studies (GWAS) have found more than 70 susceptible loci of T2DM, such as KCNJ11, TCF7L2, IRS1, MTNR1B, PPARG2, IGF2BP2, CDKN2A, HHEX, FTO, etc. (41). A recent study explored the relationship between common T2DM-related variants and the risk of MM, demonstrating that T2DM-related variant genes KCNQ1, CDKM2A-2B, IGF-1, and MADD were linked to

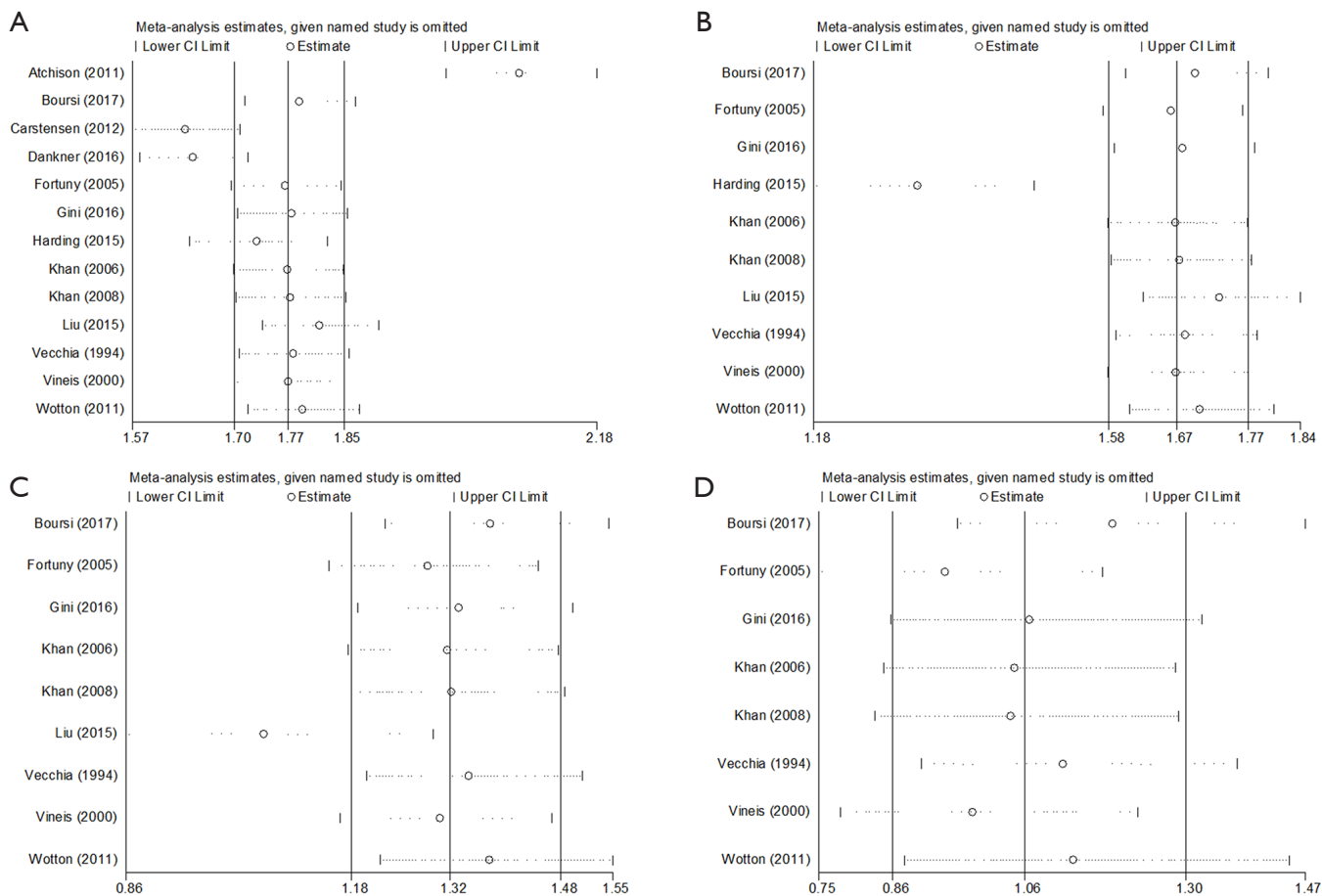


Figure 3 Sensitivity analysis of each included study. (A) The first analysis; (B) the second analysis; (C) the third analysis; (D) the fourth analysis.

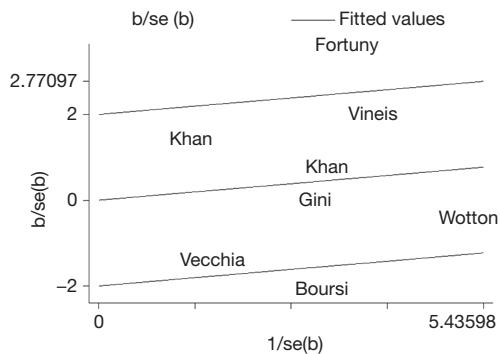


Figure 4 Galbraith heterogeneity of each included study.

the increase in MM incidence, and that *KCNJ11*, *THADA*, *LTA*, and *FTO* genes were associated with the decrease in MM incidence. These genes may influence the risk of MM

through non-insulin-related mechanisms (42). Therefore, for newly diagnosed T2DM, relevant genetic testing may be required.

MM risk in the case-control studies was significantly lower than that in the cohort studies, presumably due to the error caused by the relatively small number of cases and recall bias. After all, some patients have a vague definition of diabetes, and they do not consider that an increase in blood glucose without drug control (which has reached the diagnostic criteria for diabetes and is temporarily regulated by diet and exercise) also supports the diagnosis of diabetes. These biases could increase or decrease the risk of parallel occurrence of diabetes and myeloma.

In this study, some limitations might exist. Firstly, our search was limited to published studies (with unpublished or ongoing studies not included), and the articles published in

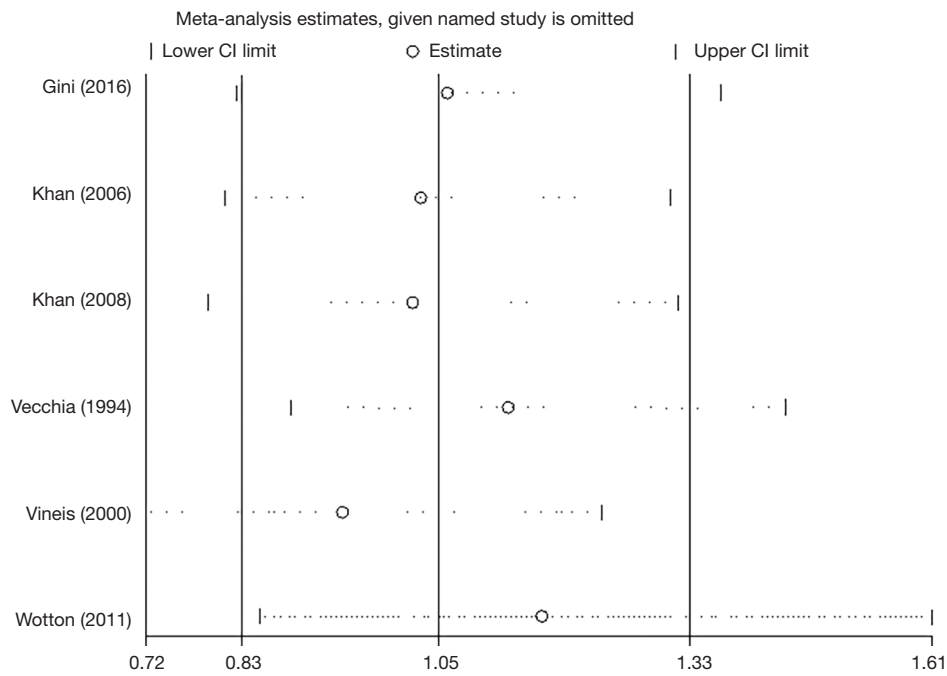


Figure 5 Sensitivity analysis of each included study.

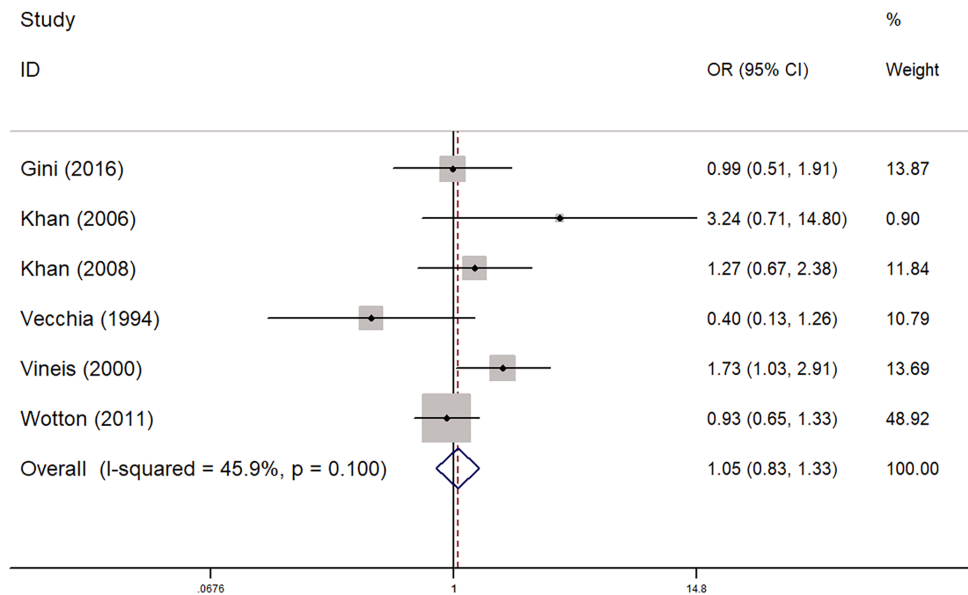


Figure 6 Odds ratio (OR) of myeloma for patients with diabetes compared with control subjects (patients without diabetes).

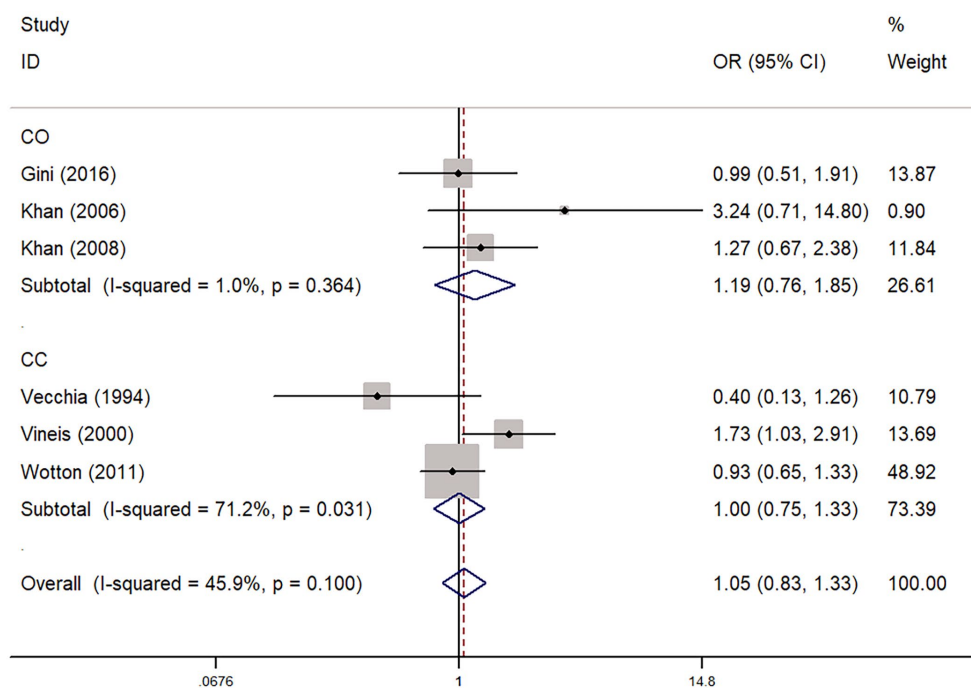


Figure 7 Odds ratio (OR) of myeloma for patients with diabetes in different study types.

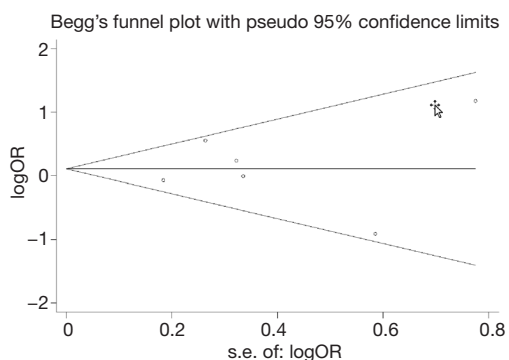


Figure 8 Begg's funnel plots of the publication bias.

English. Secondly, the study included people from different regions, the gender distribution was uneven among the study groups, and the observation time for diabetes was not consistent. Thirdly, data were missing during the extraction of MM patients. All these limitations should be overcome in future better-designed studies.

Conclusions

This meta-analysis showed that T2DM is not a risk factor of MM. More large-scale, prospective randomized controlled

studies are needed to verify the association between the two.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr.2020.03.36>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Main characteristics of cohort studies evaluating the association between T2DM and the incidence of MM

Author	Year	Country	Study design	Study period	Age (year)	DM assessment	MM assessment	Source of cohort	Total N [N of case]	Adjusted variables	OR	95% CI	NOS
Atchison <i>et al.</i> (9)	2011	US	CO	1969–1996	18–100	Hospital discharge records	hospital records and Social Security Administration mortality files	Veterans Affairs Hospital	4,501,578 [4,641]	Age, year, race, number of hospital visits	1.23	1.14–1.34	8
Carstensen <i>et al.</i> (14)	2012	Danish	CO	1995–2009	>30	The National Diabetes Register	The Danish Cancer Registry	Entire Danish population	4,635,905 [4,618]	Age, year, sex	5.28	4.68–5.95	7
Dankner <i>et al.</i> (11)	2016	Israelis	CO	2002–2012	21–89	Meet the 6 criteria in the paper	The Israel National Cancer Registry	The largest health maintenance organization	1,777,953 [1,167]	Age, ethnicity, and socioeconomic status	4.03	3.55–4.58	7
Gini <i>et al.</i> (16)	2016	Northern Italy	CO	2002–2009	40–84	Meet the 3 criteria in the paper	Cancer registry	Population-based	32,247 [15]	Age, sex	0.99	0.51–1.91	7
Harding <i>et al.</i> (12)	2015	Australian	CO	1997–2008	>30	The National Diabetes Services Scheme	Australian Cancer Database	The National Diabetes Services Schem	872,706 [1,013]	Age, sex, year	1.84	1.73–1.96	6
Khan <i>et al.</i> (18)	2006	Japan	CO	1988–1997	40–79	Self-administered questionnaire	Population-based and hospital-based cancer registries	The Japan Collaborative Cohort (JACC) Study	56,881 [12]	Age, BMI, smoking, drinking	3.24	0.71–14.80	7
Khan <i>et al.</i> (17)	2008	European	CO	1992–2000	>30	Self-reported	Histologically confirmed	23 study centers in ten European countries	393,477 [281]	Age, sex, region	1.27	0.67–2.38	6
Liu <i>et al.</i> (19)	2015	Sweden	CO	1964–2010	>39	Swedish Hospital Discharge Register, the Outpatient Register and the primary health care in Stockholm and Skåne County	The nationwide Swedish Cancer Register	Several national Swedish registers	380,196 [432]	Age, sex, year, region, socioeconomic status	1.46	1.27–1.67	8

Table S2 Main characteristics of case-control studies evaluating the association between T2DM and the incidence of MM

Author	Year	Country	Study design	Study period	DM assessment	MM assessment	Source of case, N	Source of control, N	Adjusted variables	OR	95% CI	NOS
Boursi <i>et al.</i> (10)	2017	UK	CC	1995–2013	General practitioners diagnosed	READ codes	The Health Improvement Network, 138	The health improvement network, 746	Age, sex, year	0.49	0.25–0.93	7
Fortuny <i>et al.</i> (15)	2005	Spain	CC	1998–2002	Personal interviews	Histology, immunohistochemistry test and flow cytometry	At four centres in Spain, 84	At four centres in Spain, 590	Age, gender, study centre	2.71	1.54–4.78	7
La Vecchia <i>et al.</i> (20)	1994	Northern Italy	CC	1983–1992	Self-administered questionnaire	The National Cancer Institute	Greater Milan area, 1,067	Greater Milan area, 16,758	Age, sex, education, smoking, BMI	0.40	0.13–1.26	6
Vineis <i>et al.</i> (21)	2000	Italy	CC	1990–1993	Personal interviews	Cancer registry and hospital records	11 Italian areas, 175	11 Italian areas, 4,212	Age, sex, centre	1.73	1.03–2.91	7
Wotton <i>et al.</i> (22)	2011	UK	CC	1993–2008	Records from National Health Service hospital and ORLS	Records from National Health Service hospital and ORLS	Oxford Record Linkage Study (ORLS), 23,629	Oxford Record Linkage Study (ORLS), 460,687	Age, sex, calendar year of first recorded admission and district of residence	0.93	0.65–1.33	8

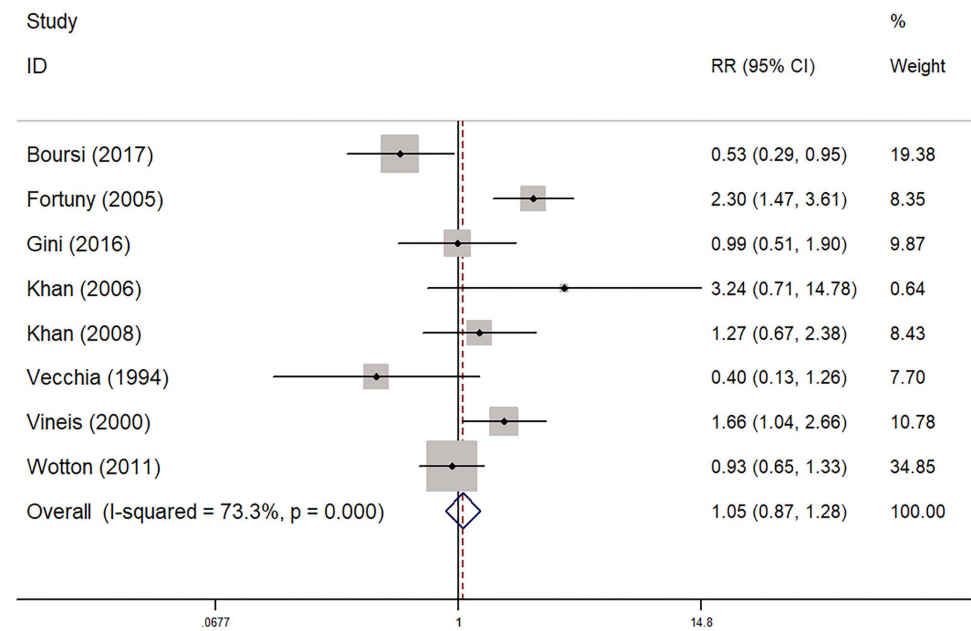


Figure S1 Sensitivity analysis of each included study.