

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055374
Article Type:	Original research
Date Submitted by the Author:	11-Jul-2021
Complete List of Authors:	Yang, Zhi; Chengdu Fifth People's Hospital, Department of Radiology Xu, Rong; Sichuan University West China Second University Hospital Wang, Jia-rong; Sichuan University West China Second University Hospital Xu, Hua-yan; Sichuan University West China Second University Hospital Fu, Hang; Sichuan University West China Second University Hospital Xie, Ling-jun; Sichuan University West China Second University Hospital Yang, Meng-xi Zhang, Lu; Sichuan University West China Second University Hospital Wen, Ling-yi; Sichuan University West China Second University Hospital Liu, Hui; Sichuan University West China Second University Hospital Li, Hong; Sichuan University West China Second University Hospital Yang, Zhi-gang; Sichuan University, Guo, Ying-kun ; Sichuan University West China Second University Hospital, 3. Department of Radiology
Keywords:	DIABETES & ENDOCRINOLOGY, RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

**Title page :**

**Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis**

Zhi Yang<sup>1,2\*</sup>, MS; Rong Xu<sup>1\*</sup>, MS; Jia-rong Wang<sup>1</sup>, MD; Hua-yan Xu<sup>1</sup>, MD; Hang Fu<sup>1</sup>, MS; Ling-jun Xie<sup>1</sup>, MS; Meng-xi Yang<sup>4</sup>, MS; Lu Zhang<sup>1</sup>, MS; Ling-yi Wen<sup>1</sup>, MD; Hui Liu<sup>1</sup>, MS; Hong Li<sup>3</sup>, MD; Zhi-gang Yang<sup>4†</sup>, MD; Ying-kun Guo<sup>1†</sup>, MD

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, China.
2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
3. Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu, China.
4. Department of Radiology, West China Hospital, Sichuan University, Chengdu, China.

**\* These authors contributed equally to this work and should be considered the co-first authors.**

**† Guarantor and correspondent:**

**These two authors contributed equally to this work and should be considered corresponding authors.**

**Zhigang Yang, PhD, MD**

Department of Radiology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, No.37 Guoxue Xiang, Chengdu, 610041, China

Tel: +86-28-85423817(O)

E-mail: yangzg666@163.com

**Yingkun Guo, MD**

Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3 South Renmin Road, Chengdu, 610041, China

Tel: +86-28-85503275(O)

E-mail: gykpanda@163.com

## Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

### ABSTRACT

**Aim/Introduction:** Prior studies demonstrated that myocardial fibrosis assessed by late gadolinium-enhanced (LGE) MRI is associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) or major adverse cardiac events (MACE) in patients with diabetes. However, the results of these studies were controversial and limited. Therefore, we performed this meta-analysis assessing the associations of myocardial fibrosis detected by LGE with the risk of MACCE and MACE in patients with diabetes.

**Materials And Methods:** We selected studies using MEDLINE, EMBASE and Cochrane by Ovid on December 2019. Pooled hazard ratios (HR), and 95% confidence intervals (CI) by random-effects model to assess the relationship of myocardial fibrosis and risk of MACCE or MACE in patients with diabetes. Results: Eight studies with 1121 patients were included in this meta-analysis, and follow-up of patients ranged from 17 to 70 months. The presence of myocardial fibrosis detected by LGE was associated with an increased risk for MACCE (HR: 2.58; 95%CI 1.42-4.71; P=0.002) and MACE (HR: 5.28; 95%CI 3.20-8.70; P=0.000) in patients with diabetes. In a subgroup meta-analysis, ischemic fibrosis detected by LGE was associated with MACCE/MACE (HR 3.75, 95%CI 2.11-6.69; P=0.000) in patients with diabetes. In diabetic patients with preserved ejection fraction, the association between myocardial fibrosis detected by LGE and MACCE/MACE remained significant (HR: 3.98; 95%CI 2.22-7.25; P=0.000).

**Conclusions:** This study demonstrated that myocardial fibrosis detected by LGE conferred an increase in the risk of MACCE/MACE in patients with diabetes and may be an imaging biomarker for risk stratification.

**Keywords:** Magnetic Resonance Imaging, Diabetes, Meta-analysis, Systemic review

### Strengths and limitations of this study:

The presence of myocardial fibrosis detected by LGE-MRI in patients with diabetes was markedly associated with an important and increased risk of MACCE/MACE.

The prevalence of myocardial fibrosis detected by LGE among patients with diabetes is higher than that among nondiabetic patients.

Diabetes duration plays a central role in the assessment of cardiovascular risk, but the incremental value of diabetes duration to the prevalence and incidence of LGE was not revealed in this article.

### INTRODUCTION

Diabetes is becoming a global healthcare problem, and it is estimated that there will be 693 million individuals with diabetes by 2045.<sup>1</sup> Patients with diabetes have a higher prevalence of myocardial fibrosis

1  
2  
3 than their nondiabetic counterparts as a result of microvascular and macrovascular dysfunction, even  
4 when asymptomatic.<sup>2-5</sup> Moreover, the presence of myocardial fibrosis is associated with diabetic  
5 cardiomyopathy.<sup>6-8</sup> In addition, myocardial fibrosis can increase the risk of left ventricular (LV)  
6 dysfunction and heart failure with preserved ejection fraction in patients with diabetes.<sup>9 10</sup> Therefore, it  
7 is important to detect myocardial fibrosis by noninvasive imaging technology for risk stratification in the  
8 clinical routine.  
9  
10

11  
12 Among detectors of myocardial fibrosis, late gadolinium-enhanced magnetic resonance imaging (LGE-  
13 MRI) is the most reliable tool for identifying and quantifying myocardial fibrosis in vivo.<sup>11-13</sup>  
14 Furthermore, LGE-MRI is noninvasive and can easily discriminate between ischemic and nonischemic  
15 fibrosis without ionizing radiation.<sup>3</sup> Furthermore, recent guidelines suggested that MRI may be  
16 considered an imaging technique for stratifying cardiovascular risk in patients with diabetes.<sup>14 15</sup> This  
17 highlights the role of LGE-MRI in risk stratification of patients with diabetes.  
18  
19

20  
21 Approximately 19% of asymptomatic patients with diabetes have myocardial fibrosis upon LGE-MRI.<sup>2</sup>  
22 Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict  
23 major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial  
24 fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.<sup>2 3 16-21</sup> In addition, most  
25 previous studies were single-center studies and have been limited by small numbers of events.  
26 Consequently, we performed a meta-analysis to assess the association of LV myocardial fibrosis detected  
27 by late gadolinium enhancement (LGE) with future MACCE and MACE in patients with diabetes.  
28  
29  
30

## 31 32 **METHODS**

33 This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of  
34 Observational Studies in Epidemiology (MOOSE) statement.<sup>22 23</sup>  
35

### 36 **Patient and Public Involvement**

37 No patient involved.  
38

### 39 **Data Sources and Searches**

40 We searched the Ovid MEDLINE, Ovid EMBASE and Ovid Cochrane Library databases to find eligible  
41 studies in December 2019. The search strategy included the following keywords: “diabetes”, “diabetes  
42 mellitus”, “MR”, “cardiac magnetic resonance”, “CMR”, “gadolinium”, “LGE”, “prognosis”,  
43 “diagnosed”, “predictor”, and “death”. The details of the search strategy used for Ovid are available in  
44 Supplemental Table S1. In addition, only articles published in peer-reviewed journals and in the English  
45 language were included.  
46

### 47 **Study Selection**

48 All articles were independently screened by two reviewers using the following inclusion criteria, and any  
49 disagreement was resolved by consensus. The inclusion criteria were as follows: the design was  
50 prospective or retrospective cohort study; the populations were patients with diabetes, and exposure of  
51 myocardial fibrosis was detected by LGE-MRI; the outcomes used composite endpoints including all-  
52 cause mortality, cardiac and cerebrovascular disease, late coronary revascularization, and hospitalization  
53 for unstable angina; the study reported the hazard ratio (HR) and 95% confidence intervals (CI) and had  
54  $\geq 12$  months of follow-up. We excluded reviews, abstracts, animal studies, case reports, and cross-  
55 sectional studies. Additionally, if the cases were reported more than once, we included the study with the  
56 most comprehensive information. Moreover, to obtain eligible studies, two reviewers independently  
57  
58  
59  
60

1  
2  
3 screened the title first, then the abstract, and finally the full text.

#### 4 **Data Extraction and Quality Assessment**

5 We extracted the following demographic data from each included study: author, year of publication,  
6 sample size, study design, age, LGE status, follow-up duration, outcome, and HR (95% CI). Additionally,  
7 we extracted the adjustment HR if the study reported the HR with adjustment models.  
8

9 All of the included studies were prospective or retrospective cohort designs, and we used the Newcastle  
10 Ottawa Scale (NOS) to judge the study quality, which is usually used for evaluating the quality of cohort  
11 studies in meta-analyses.<sup>24,25</sup> The scale uses a maximum of 9 points involving 3 factors: patient selection  
12 (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).<sup>26</sup> We delimited the quality of  
13 studies as low (0 to 3 scores), moderate (4 to 6 scores), and high (7 to 9 scores).  
14

#### 15 **Data Synthesis and Analysis**

16 In this meta-analysis, the outcome measure was the occurrence of future adverse cardiac and/or  
17 cerebrovascular events among diabetes patients with LGE compared to those without LGE. We defined  
18 the primary endpoint as MACCE, including myocardial infarction (MI), all-cause mortality, coronary  
19 and carotid revascularization, heart failure, ventricular arrhythmias, unstable angina, cardiac and  
20 cerebrovascular death, and cerebrovascular disease. The secondary end points were MACE, including  
21 all-cause mortality, cardiac death, MI, heart failure, unstable angina, and ventricular arrhythmias.  
22 Additionally, the pattern of myocardial fibrosis was classified as ischemic fibrosis or nonischemic  
23 fibrosis as described previously.<sup>3</sup>  
24  
25  
26  
27  
28

29 We pooled the adjusted HR with its 95% CI using a random-effects model. In addition, we calculated  
30 the annualized event rates (AERs) by dividing the total events by the median follow-up periods. To  
31 analyze the heterogeneity of the included studies, we used forest plots and the  $I^2$  statistic.<sup>27</sup> We assigned  
32  $I^2$  values of 0 ~ 25%, ~ 50%, ~ 75% for low, medium, and high heterogeneity of studies, respectively.  
33  
34  
35

36 Considering the heterogeneity of the included studies, we conducted sensitivity analyses by omitting 1  
37 article to assess the influence of a single study. In particular, subgroup analyses were performed by  
38 outcome and the pattern of myocardial fibrosis. Additionally, a funnel plot was used to assess the  
39 publication bias of the included studies.<sup>28</sup> The analyses were performed with Stata version 12 (StataCorp).  
40  $P$  values were two sided, with a level of 0.05 considered significant.  
41

## 42 **RESULTS**

### 43 **Literature Search**

44 Based on the selection strategy, we found 2134 citations. Of these, 151 duplicate studies were excluded.  
45 After screening the title and abstract, 12 articles remained for assessment of the full text. Four studies<sup>29-</sup>  
46 <sup>32</sup> were excluded for the following reasons: studies without our outcome of interest, study populations  
47 did not meet our inclusion criteria, and studies did not report the HR. Ultimately, 8 studies<sup>2,3,16-21</sup> fulfilled  
48 our inclusion criteria and were included in this meta-analysis (Fig. 1).  
49

### 50 **Study Characteristics**

51 In aggregate, 8 studies included a total of 1121 patients with diabetes (median age ranging from 52 to  
52 67; 67% were men) who underwent LGE-MRI and whose follow-up ranged from 17 to 70 months.  
53 Across the 8 studies, 6 articles<sup>2,17-21</sup> reported the duration of diabetes, and the mean duration of diabetes  
54 was 15 years. A total of 6 studies<sup>2,3,16,19-21</sup> reported the LV ejection fraction, and the mean LV ejection  
55 fraction was 57.78%. The presence of LGE was evaluated by visual analysis in 6 publications.<sup>2,3,18-21</sup> All  
56 of the included studies reported multiple clinical outcomes. The main characteristics of the included  
57  
58  
59  
60

articles are shown in Table 1.

Among the 8 selected studies, 6 studies<sup>16-21</sup> (75%) were conducted in a single center (Germany, n=2; USA, n=2; Japan, n=2), and 2 studies<sup>2,3</sup> were performed in multiple centers (USA, n=1; Europe, n=1). Five articles<sup>2,3,17,20,21</sup> (62.5%) reported adjusted HR. Six studies<sup>2,16,18-21</sup> reported patients with ischemic fibrosis, and the remaining 2 studies<sup>3,17</sup> reported patients with ischemic and nonischemic fibrosis.

Of the 8 eligible studies, 7 received 7 to 9 scores, and the mean NOS score was 7.5. Overall, the aforementioned analysis showed that the included articles had high quality (Table 1). Among the identified studies, there was no risk of publication bias assessed by visual analysis of the funnel plot (Supplemental Fig. S1).

### **Prevalence of LGE and AERs**

Across the 8 studies, the prevalence of myocardial fibrosis detected by LGE ranged from 15% to 62%, and the prevalence of LGE in the total sample was 38.09% (n=427). Furthermore, a total of 164 events occurred in the diabetes group (n=1121) during the median follow-up of 3.4 years. Patients with diabetes had AERs for MACCE of 4.3%. However, only 3 studies<sup>2,19,21</sup> reported a total of 301 patients with diabetes. Among these patients, 19.27% (n=58) had myocardial fibrosis detected by LGE, with 27 events occurring over a median follow-up of 3.9 years. The AERs of patients with diabetes and LGE was 11.94%.

### **MACCE and MACE**

A total of 8 studies reported the outcome of MACCE or MACE, and the presence of myocardial fibrosis detected by LGE was a strong predictor of MACCE and MACE in patients with diabetes (random-effects HR 3.87, 95% CI 2.58-5.80; P=0.000) (Fig. 2). Low heterogeneity ( $I^2=15.1\%$ , P=0.311) existed in the meta-analysis. In addition, sensitivity analysis performed by excluding 1 study each time found that the HR values were not significantly changed.

In the analysis of the outcome of MACCE, 3 articles<sup>17,20,21</sup> were included in this subgroup meta-analysis, including 64 participants with LGE and 165 diabetes without LGE, with a total of 64 MACCE outcomes during the follow-up period. Myocardial fibrosis detected by LGE was associated with an increased risk of MACCE in patients with diabetes. The pooled random-effects HR was 2.58 (95% CI 1.42-4.71; P=0.002), with no evidence of heterogeneity ( $I^2=14.1\%$ ; P=0.312) (Fig. 2).

To explore the association between myocardial fibrosis and the outcome of MACE in patients with diabetes, we included 5 articles<sup>2,3,16,18,19</sup> that provided a subgroup meta-analysis. The results showed that the presence of LGE in diabetes was associated with a significantly higher risk of MACE. As in the discovery analyses, the pooled HR was 5.28 (95% CI 3.20-8.70; P=0.000) with no significant heterogeneity ( $I^2=0\%$ ; P=0.643) from random effects (Fig. 2).

To further verify the robustness of the results, we grouped all included studies by adjusted or non-adjusted HR. In patients with diabetes, myocardial fibrosis detected by LGE was associated with an increased risk of MACCE and MACE in a subgroup meta-analysis with or without adjusted HR. The pooled HRs were 3.52 (random-effects, 95% CI 2.02-6.16;  $I^2=35.8\%$ ) and 4.63 (random-effects, 95% CI 2.35-9.14;  $I^2=0\%$ ), respectively. There was no significant heterogeneity among the studies (Supplemental Fig. S2).



To evaluate the pattern of myocardial fibrosis effects, we further calculated a pooled HR by source of diabetes with different patterns of myocardial fibrosis. In patients with diabetes, ischemic fibrosis detected by LGE was significantly associated with increased MACCE and MACE (random-effects HR 3.75, 95% CI 2.11-6.69;  $I^2=38.3\%$ ). Furthermore, all myocardial fibrosis detected by LGE in patients with diabetes may increase the risk of MACCE and MACE (random-effects HR 4.27, 95% CI 2.17-8.37;  $I^2=0\%$ ) (Supplemental Fig. S3).

To confirm whether there were similar results in patients with preserved LV ejection fraction, we conducted a subgroup meta-analysis with 6 studies. Among individuals with diabetes and LV ejection fraction > 50%, the presence of myocardial fibrosis assessed by LGE was significantly associated with MACCE and MACE. The pooled HR was 3.98 (95% CI 2.22-7.25;  $P=0.000$ ) with random effects, and there was medium heterogeneity among the studies ( $I^2=37.9\%$ ;  $P=0.153$ ) (Fig. 3).

## DISCUSSION

In this meta-analysis, the prevalence of myocardial fibrosis assessed by LGE was increased in patients with diabetes, occurring in 38.09% of them. In addition, the presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted. Specifically, myocardial fibrosis detected by LGE has a higher predictive value for the occurrence of future MACE than MACCE in patients with diabetes. Furthermore, myocardial fibrosis by LGE may be an imaging biomarker for predicting adverse outcomes in patients with diabetes.

In our meta-analysis, the results supported previous studies showing that participants with diabetes have a higher presence of myocardial fibrosis detected by LGE. Importantly, in our included studies, the presence of myocardial fibrosis in symptomatic patients with diabetes was higher than that in asymptomatic patients with diabetes.<sup>2 3 17</sup> Given that more than 38.09% of patients with diabetes have myocardial fibrosis detected by LGE in our meta-analysis, it indicated that LGE is very important for screening myocardial fibrosis in diabetes. Current guidelines recommend that MRI may be a risk tool in asymptomatic patients with diabetes at moderate or high risk of cardiovascular disease.<sup>14</sup> However, the value of MRI in routine clinical stratification of cardiovascular risk is unclear. Notably, in our meta-analysis, focal myocardial fibrosis detected by LGE did seem to predict a higher occurrence MACCE/MACE in the future, and the AERs for MACCE/MACE in patients with diabetes and LGE was 11.94%. Additionally, the presence of myocardial fibrosis indicated a 8-fold higher risk for death/MI even in asymptomatic patients with diabetes.<sup>2</sup> It must be noted that other techniques, such as ECG, have lower accuracy and sensitivity for detecting myocardial fibrosis than LGE.<sup>33 34</sup> Thus, this finding highlighted the value of LGE for screening for cardiovascular risk in patients with diabetes.

The risk of myocardial fibrosis in patients with diabetes is increased and likely multifactorial. First, patients with diabetes have a higher risk for coronary artery disease and myocardial dysfunction.<sup>35-37</sup> Moreover, hyperglycemic metabolism, microvascular disease, and cardiac autonomic neuropathy are involved in the mechanisms of myocardial fibrosis.<sup>4 38 39</sup> However, many studies have shown that patients with diabetes have a high incidence of obesity, visceral fat, hyperlipidemia, and insulin resistance, which may impair myocardial function.<sup>6 40 41</sup> Furthermore, the multiple risk factors described above should increase the myocardial fibrosis burden. In addition, myocardial fibrosis is widespread in subjects with

1  
2  
3 diabetes and may be associated with a high risk for cardiovascular disease.  
4  
5

6 Although the focal myocardial fibrosis translates to an adverse outcome in future is not fully clear, several  
7 potential mechanisms may lead to MACCE/MACE. First, patients with diabetes are more inclined to  
8 develop myocardial fibrosis, and myocardial fibrosis is associated with ventricular arrhythmia and heart  
9 failure.<sup>3 42-44</sup> Second, patients with diabetes and myocardial fibrosis usually have a greater burden of  
10 microvascular complications, such as myocardial ischemia, which confers an increased risk of  
11 MACCE/MACE.<sup>16 45</sup> Additionally, the myocardial fibrosis detected by LGE, especially subendocardial  
12 fibrosis, indicates more severe coronary calcium and atherosclerotic disease, which denotes a higher risk  
13 of MACE.<sup>46 47</sup> Furthermore, subjects with diabetes had higher LV and left atrial remodeling due to  
14 myocardial fibrosis.<sup>9 43 48</sup> For these reasons, the myocardial fibrosis detected by LGE indeed has clinical  
15 relevance.  
16  
17  
18  
19

20 As previously described, LGE-MRI has become a powerful noninvasive imaging method for the  
21 assessment of myocardial fibrosis.<sup>11</sup> Unfortunately, our meta-analysis demonstrated that the presence of  
22 myocardial fibrosis derived from LGE conferred an HR of 3.87 for future MACCE/MACE in individuals  
23 with diabetes, and the risk increased with ischemic myocardial fibrosis. It must be indicated that two  
24 studies<sup>20 21</sup> were included in our meta-analysis, which showed that ischemic myocardial fibrosis detected  
25 by LGE did not increase the rate of MACCE. This might be explained by the following reasons, such as  
26 limited patients and the patients having a high prevalence of cardiovascular disease. Indeed, detecting  
27 myocardial fibrosis can be used to clinically assess myocardial damage and to stratify cardiovascular risk  
28 in participants with diabetes. To date, only one study, which screened for asymptomatic diabetes by LGE,  
29 showed that diabetes with ischemic myocardial fibrosis conferred an 8-fold higher risk for all-cause  
30 mortality and MI.<sup>2</sup> The prevalence of myocardial fibrosis detected by LGE among patients with diabetes  
31 is higher than that among nondiabetic patients.<sup>3 30</sup> Therefore, patients with diabetes and myocardial  
32 fibrosis might need aggressive management of cardiac and cerebrovascular risk factors.  
33  
34  
35  
36  
37

38 However, our meta-analysis has some limitations. First, in our meta-analysis, 2 studies<sup>20 21</sup> were from the  
39 same group of patients but reported different outcomes. However, when we excluded either of the above  
40 articles, the pooled HR and heterogeneity did not change significantly. Second, the incidence of  
41 myocardial fibrosis in patients with diabetes was not community-based epidemiology research. The  
42 prevalence of myocardial fibrosis, therefore, may be higher in this study, which pooled studies including  
43 high-risk or average-risk populations with diabetes. Third, a previous study found that women with  
44 diabetes had a higher risk for MACCE than men with diabetes.<sup>49</sup> However, this study was not designed  
45 to evaluate sex differences in the effect of myocardial fibrosis on MACCE/MACE in patients with  
46 diabetes. Fourth, most studies selected in this meta-analysis reported adjusted HRs, and various  
47 adjustments for adverse outcomes among the selected studies may affect the pooled results. However,  
48 the heterogeneity among the selected studies was low, and publication bias did not exist. This might  
49 strengthen the clinical meaning of the pooled result. Finally, the incremental value of diabetes duration  
50 to the prevalence and incidence of LGE was not revealed. However, diabetes duration plays a central  
51 role in the assessment of cardiovascular risk.<sup>14 50</sup> Hence, a prospective study that evaluates the association  
52 between diabetes duration and myocardial fibrosis and determines the best time to screen myocardial  
53 fibrosis by LGE-CMR for risk stratification in patients with diabetes is needed.  
54  
55  
56  
57  
58  
59  
60

## CONCLUSIONS

In patients with diabetes, the presence of myocardial fibrosis detected by LGE-MRI was markedly associated with an important and increased risk of MACCE/MACE. Myocardial fibrosis may be a risk marker for improving risk stratification in patients with diabetes. This meta-analysis highlights the role of LGE-MRI in helping identify high-risk diabetic patients in routine clinical practice.

## REFERENCE

- 1 Cho NH, Shaw JE, Karuranga S, *et al.* IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes research and clinical practice* 2018;138:271-81.
- 2 Elliott MD, Heitner JF, Kim H, *et al.* Prevalence and prognosis of unrecognized myocardial infarction in asymptomatic patients with diabetes: A two-center study with up to 5 years of follow-up. *Diabetes Care* 2019;42:1290-6.
- 3 Giusca S, Kelle S, Nagel E, *et al.* Differences in the prognostic relevance of myocardial ischaemia and scar by cardiac magnetic resonance in patients with and without diabetes mellitus. *European heart journal cardiovascular Imaging* 2016;17:812-20.
- 4 Jia G, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to This Clinical Entity. *Circulation research* 2018;122:624-38.
- 5 Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular mechanisms and therapeutic opportunities. *Journal of molecular and cellular cardiology* 2016;90:84-93.
- 6 Marwick TH, Ritchie R, Shaw JE, *et al.* Implications of Underlying Mechanisms for the Recognition and Management of Diabetic Cardiomyopathy. *Journal of the American College of Cardiology* 2018;71:339-51.
- 7 Adegate E, Singh J. Structural changes in the myocardium during diabetes-induced cardiomyopathy. *Heart failure reviews* 2014;19:15-23.
- 8 Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia- and insulin-resistance-induced heart disease. *Diabetologia* 2018;61:21-8.
- 9 Storz C, Hetterich H, Lorbeer R, *et al.* Myocardial tissue characterization by contrast-enhanced cardiac magnetic resonance imaging in subjects with prediabetes, diabetes, and normal controls with preserved ejection fraction from the general population. *European heart journal cardiovascular Imaging* 2018;19:701-8.
- 10 Armstrong AC, Ambale-Venkatesh B, Turkbey E, *et al.* Association of Cardiovascular Risk Factors and Myocardial Fibrosis With Early Cardiac Dysfunction in Type 1 Diabetes: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care* 2017;40:405-11.
- 11 Mewton N, Liu CY, Croisille P, *et al.* Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *Journal of the American College of Cardiology* 2011;57:891-903.
- 12 Hiromi Hashimura FK, Hatsue Ishibashi-Ueda, Yoshiaki Morita, *et al.* Radiologic-Pathologic Correlation of Primary and Secondary Cardiomyopathies:MR Imaging and Histopathologic Findings in Hearts from Autopsy and Transplantation. *Radiographics* 2017;37:719-36.
- 13 Iles LM, Ellims AH, Llewellyn H, *et al.* Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. *European heart journal*

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- cardiovascular Imaging* 2015;16:14-22.
- 14 Cosentino F, Grant PJ, Aboyans V, *et al.* 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European heart journal* 2020;41:255-323.
- 15 Jensen MT, Fung K, Aung N, *et al.* Changes in Cardiac Morphology and Function in Individuals With Diabetes Mellitus: The UK Biobank Cardiovascular Magnetic Resonance Substudy. *Circulation Cardiovascular imaging* 2019;12:e009476.
- 16 Heydari B, Juan YH, Liu H, *et al.* Stress Perfusion Cardiac Magnetic Resonance Imaging Effectively Risk Stratifies Diabetic Patients with Suspected Myocardial Ischemia. *Circulation: Cardiovascular Imaging* 2016;9:e004136.
- 17 Kwong RY, Sattar H, Wu H, *et al.* Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation* 2008;118:1011-20.
- 18 Yoon YE, Kitagawa K, Kato S, *et al.* Prognostic significance of unrecognized myocardial infarction detected with MR imaging in patients with impaired fasting glucose compared with those with diabetes. *Radiology* 2012;262:807-15.
- 19 Yoon YE, Kitagawa K, Kato S, *et al.* Prognostic value of unrecognized myocardial infarction detected by late gadolinium-enhanced MRI in diabetic patients with normal global and regional left ventricular systolic function. *European radiology* 2013;23:2101-8.
- 20 Bamberg F, Parhofer KG, Lochner E, *et al.* Diabetes mellitus: Long-term prognostic value of whole-body MR imaging for the occurrence of cardiac and cerebrovascular events. *Radiology* 2013;269:730-7.
- 21 Bertheau RC, Bamberg F, Lochner E, *et al.* Whole-Body MR Imaging Including Angiography: Predicting Recurrent Events in Diabetics. *European radiology* 2016;26:1420-30.
- 22 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* 2000;283:2008-12.
- 23 Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84.
- 24 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology* 2010;25:603-5.
- 25 Zeng X, Zhang Y, Kwong JS, *et al.* The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *Journal of evidence-based medicine* 2015;8:2-10.
- 26 Mantovani A, Byrne CD, Bonora E, *et al.* Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis. *Diabetes Care* 2018;41:372-82.
- 27 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine* 2002;21:1539-1558
- 28 Liu JL. The role of the funnel plot in detecting publication and related biases in meta-analysis. *Evidence-based dentistry* 2011;12:121-2
- 29 Reinstadler SJ, Stiermaier T, Eitel C, *et al.* Relationship between diabetes and ischaemic injury among patients with revascularized ST-elevation myocardial infarction. *Diabetes, Obesity and Metabolism* 2017;19:1706-13.

- 1  
2  
3  
4 30 Lindman BR, Davila-Roman VG, Mann DL, *et al.* Cardiovascular phenotype in HFpEF patients  
5 with or without diabetes: a RELAX trial ancillary study. *Journal of the American College of*  
6 *Cardiology* 2014;64:541-9.
- 7  
8 31 Eitel I, Hintze S, De Waha S, *et al.* Prognostic impact of hyperglycemia in nondiabetic and  
9 diabetic patients with ST-elevation myocardial infarction: Insights from contrast-enhanced  
10 magnetic resonance imaging. *Circulation: Cardiovascular Imaging* 2012;5:708-18.
- 11  
12 32 Donnino R, Patel S, Nguyen AH, *et al.* Comparison of quantity of left ventricular scarring and  
13 remodeling by magnetic resonance imaging in patients with versus without diabetes mellitus and  
14 with coronary artery disease. *American Journal of Cardiology* 2011;107:1575-8.
- 15  
16 33 Ramos R, Albert X, Sala J, *et al.* Prevalence and incidence of Q-wave unrecognized myocardial  
17 infarction in general population: Diagnostic value of the electrocardiogram. The REGICOR study.  
18 *International journal of cardiology* 2016;225:300-5.
- 19  
20 34 Barbier CE, Bjerner T, Johansson L, *et al.* Myocardial scars more frequent than expected:  
21 magnetic resonance imaging detects potential risk group. *Journal of the American College of*  
22 *Cardiology* 2006;48:765-71.
- 23  
24 35 Bertoni AG, Goff Jr DC, D'Agostino Jr RB, *et al.* Diabetic cardiomyopathy and subclinical  
25 cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care*  
26 2006;29:588-94.
- 27  
28 36 Shivu GN, Phan TT, Abozguia K, *et al.* Relationship between coronary microvascular  
29 dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. *Circulation*  
30 2010;121:1209-15.
- 31  
32 37 Campbell DJ, Somaratne JB, Jenkins AJ, *et al.* Impact of type 2 diabetes and the metabolic  
33 syndrome on myocardial structure and microvasculature of men with coronary artery disease.  
34 *Cardiovascular diabetology* 2011;10:80.
- 35  
36 38 Tarquini R, Lazzeri C, Pala L, *et al.* The diabetic cardiomyopathy. *Acta diabetologica*  
37 2011;48:173-81.
- 38  
39 39 Gao Y, Yang ZG, Ren Y, *et al.* Evaluation of myocardial fibrosis in diabetes with cardiac  
40 magnetic resonance T1-mapping: Correlation with the high-level hemoglobin A1c. *Diabetes*  
41 *research and clinical practice* 2019;150:72-80.
- 42  
43 40 Turkbey EB, Backlund JY, Genuth S, *et al.* Myocardial structure, function, and scar in patients  
44 with type 1 diabetes mellitus. *Circulation* 2011;124:1737-46.
- 45  
46 41 Ng ACT, Strudwick M, van der Geest RJ, *et al.* Impact of Epicardial Adipose Tissue, Left  
47 Ventricular Myocardial Fat Content, and Interstitial Fibrosis on Myocardial Contractile Function.  
48 *Circ Cardiovasc Imaging* 2018;11:e007372.
- 49  
50 42 Anselmino M, Matta M, D'Ascenzo F, *et al.* Catheter ablation of atrial fibrillation in patients with  
51 diabetes mellitus: a systematic review and meta-analysis. *Europace* 2015;17:1518-25.
- 52  
53 43 Gulsin GS, Kanagala P, Chan DCS, *et al.* Differential left ventricular and left atrial remodelling in  
54 heart failure with preserved ejection fraction patients with and without diabetes. *Therapeutic*  
55 *Advances in Endocrinology and Metabolism* 2019;10:2042018819861593.
- 56  
57 44 Mordi I, Bezerra H, Carrick D, *et al.* The Combined Incremental Prognostic Value of LVEF, Late  
58 Gadolinium Enhancement, and Global Circumferential Strain Assessed by CMR. *JACC*  
59 *Cardiovascular imaging* 2015;8:540-9.
- 60  
61 45 Sandesara PB, O'Neal WT, Kelli HM, *et al.* The Prognostic Significance of Diabetes and  
62 Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- Diabetes Care* 2018;41:150-5.
- 46 Schelbert EB, Cao JJ, Sigurdsson S, *et al.* Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. *Jama* 2012;308:890-6.
- 47 Acharya T, Aspelund T, Jonasson TF, *et al.* Association of Unrecognized Myocardial Infarction With Long-term Outcomes in Community-Dwelling Older Adults: The ICELAND MI Study. *JAMA Cardiol* 2018;3:1101-6.
- 48 Cao Y, Zeng W, Cui Y, *et al.* Increased myocardial extracellular volume assessed by cardiovascular magnetic resonance T1 mapping and its determinants in type 2 diabetes mellitus patients with normal myocardial systolic strain. *Cardiovascular diabetology* 2018;17:7.
- 49 Wang H, Ba Y, Cai R-C, *et al.* Association between diabetes mellitus and the risk for major cardiovascular outcomes and all-cause mortality in women compared with men: a meta-analysis of prospective cohort studies. *BMJ open* 2019;9:e024935.
- 50 Dabelea D, Stafford JM, Mayer-Davis EJ, *et al.* Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood. *Jama* 2017;317:825-35.

### Figure legend

Figure 1. Flow chart of literature and study selection.

Figure 2. Forest plot and pooled estimates of the effect of myocardial fibrosis detected by LGE on the risk of MACCE or MACE. LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, hazard ratios; CI, confidence interval.

Figure 3. Forrest plots of 6 studies for pooled HR for MACCE and MACE in patients with diabetes with normal LV ejection fraction and myocardial fibrosis detected by LGE. HR, Hazard Ratios; LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; CI, confidence interval.

**Table legend**

Table 1. Description of the Studies Included in the Meta-Analysis

**Supplement legend**

Supplement Table S1. The exact search strategy was used in OvidSP.

Supplement Figure S1. Funnel plots of 8 eligible studies.

Supplement Figure S2. Forrest plots of pooled HR for MACCE and MACE in adjusted or not adjusted HR studies. HR, Hazard Ratios; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, Hazard Ratios; CI, confidence interval.

Supplement Figure S3. Forrest plots of selected studies for pooled HR for MACCE and MACE in patients with diabetes and different pattern of myocardial fibrosis detected by LGE. HR, Hazard Ratios; LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; CI, confidence interval.

**Notes**

**Funding**

This work was supported by the National Natural Science Foundation of China (No. 81771887, 81771897, 81971586 , 81901712); the Program for Young Scholars and Innovative Research Team in Sichuan Province (No. 2017TD0005) of China; and 1-3-5 project for disciplines of excellence, West China Hospital, Sichuan University (No.ZYGD18013).

**Compliance with ethical standards**

Not applicable.

**Conflict of interest**

The authors report no conflicts of interest.

**Authors' contributions**

Zhi Yang and Rong Xu conceived of this study, and participated in its design and coordination and drafted the manuscript, Zhi-gang Yang and Ying-kun Guo helped to draft the manuscript. Other participated in the design of the study and helped with the statistical analysis. All authors read and approved this manuscript.

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information.

For peer review only

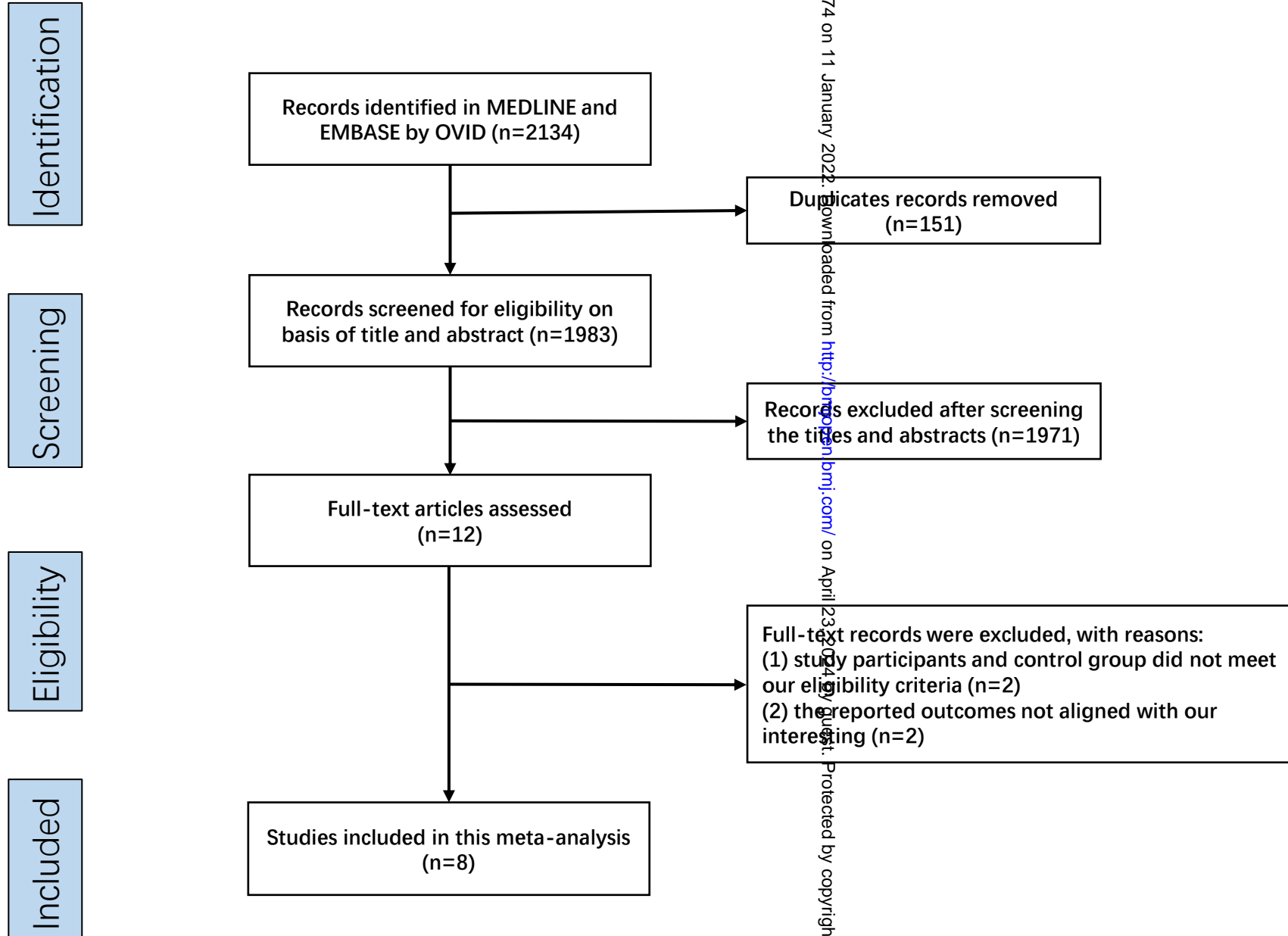
Table 1 Description of the Studies Included in the Meta-Analysis

First Author, Year	Journal	Patients	HbA1c, %	LGE Definition	DM (type)	Mean age (years)	Duration of Diabetes (years)	LVEF (%)	Follow-up duration (months)	Major LGE(%)	Total events	Adjusted HR	Fibrosis type	Type design	Outcome	NO S	
Bertheau RC,2016	Eur Radiol Circ	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	8	YES	Ischemic	Prospective, single-centre	MAC CE	7
Heydari B,2016	Cardiovascular Imaging	173	7.9±1.8	2 SD	NA	61.7±1.9	NA	51.8±1.6	34.8±3.0	109	88	21	NO	Ischemic	Prospective, single-centre	MAC E	7
Elliott MD,2019	Diabetes Care	120	NA	visual	1 and 2	52±13	17±11	63±9	46 (33-64)	65	23	19	YES	Ischemic	Prospective, two-centre	MAC E	9
Yoon YE,2013	Eur Radiol	120	7.4±1.5	visual	2	67±9	11±11	63±6	27 (7-112)	83	18	10	NO	Ischemic	Retrospective, single-centre	MAC E	7
Giusca S,2016	Eur Heart J Cardiovascular	328	NA	visual	NA	67±11	NA	57.7±1.6	35 (23-51.6)	250	176	26	YES	Ischemic and nonischemic	Prospective, multicentre	MAC E	8

bmjopen-2021-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

sc Imaging																	
Bambe rg F,2013	Radiolog y	61	7.2 (6.5- 7.9)	1 and 2 visual	67.5(56 .7-71.8)	19(14- 28)	56(46- 61)	70 (57- 72)	31	17	18	YES	Ischemic and nonische mic	Prospectiv e, single- centre	MAC CE	7	
Kwong RY,20 08	Circulati on	107	7.3±1. 6	2 SD NA	59±12	10.7± 8.5	NA	17 (6- 57)	67	30	38	YES	Ischemic and nonische mic	Prospectiv e, single- centre	MAC CE	9	
Yoon YE,20 12	Radiolog y	151	7.4±1. 6	visual	NA	67±9	14±11	NA	30(6- 103)	113	58	24	NO	Ischemic centre	Retrospect ive, single- centre	MAC E	6

Columns represent n(%) or mean±SD or median (IQR); DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NOS, Newcastle-Ottawa Scale; HR, hazard ratio; NR, not reported; MACCE, major adverse cardiac and cerebrovascular events; MACCE, major adverse cardiac events.

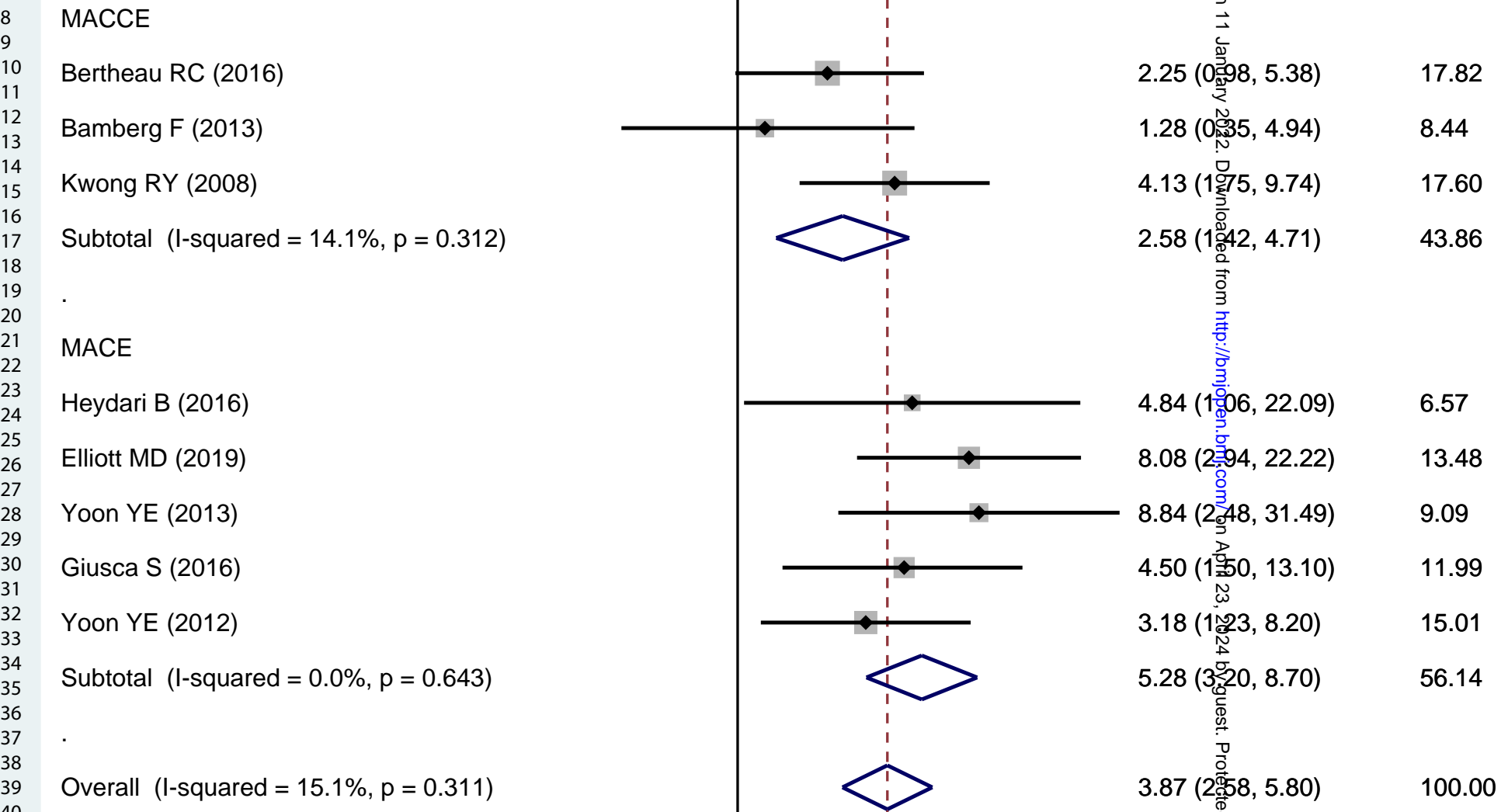


-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1 Study %  
 2  
 3 ID HR (95% CI) Weight



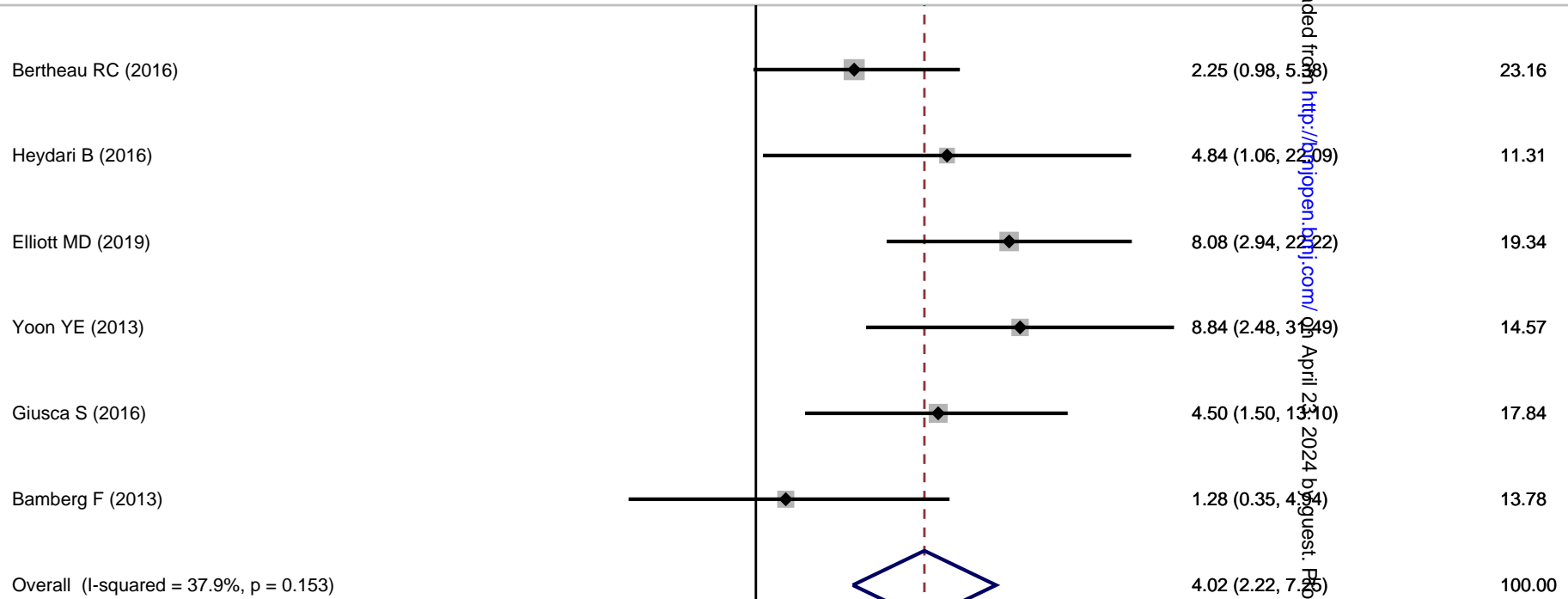
NOTE: Weights are from random effects analysis

.0318 1 31.5

55374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

Study				%
ID		HR (95% CI)		Weight



NOTE: Weights are from random effects analysis

.0318 1 31.5

### Supplement legend

Supplement Table S1. The exact search strategy was used in OvidSP.

Supplement Figure S1. Funnel plots of 8 eligible studies.

Supplement Figure S2. Forrest plots of pooled HR for MACCE and MACE in adjusted or not adjusted HR studies. HR, Hazard Ratios; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, Hazard Ratios; CI, confidence interval.

Supplement Figure S3. Forrest plots of selected studies for pooled HR for MACCE and MACE in patients with diabetes and different pattern of myocardial fibrosis detected by LGE. HR, Hazard Ratios; LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; CI, confidence interval.

bmjopen-2021-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.**Supplement Table S1**

Search methodology

Search strategies

- 
- 1 diabetes. ab, kw, ti.
  - 2 diabetes mellitus. ab, kw, ti.
  - 3 "diabetic\*". ab, kw, ti.
  - 4 1 or 2 or 3
  - 5 mri. ab, kw, ti.
  - 6 MR. ab, kw, ti.
  - 7 "magnetic resonance imag\*". ab, kw, ti.
  - 8 cardiac magnetic resonance. ab, kw, ti.
  - 9 cmr. ab, kw, ti.
  - 10 late gadolinium enhancement. ab, kw, ti.
  - 11 lge. ab, kw, ti.
  - 12 delayed gadolinium enhancement. ab, kw, ti.
  - 13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
  - 14 prognosis. sh.
  - 15 diagnosed. tw.
  - 16 cohort:.mp.
  - 17 predictor:.mp.
  - 18 death.mp.
  - 19 exp \*models, statistical/
  - 20 14 or 15 or 16 or 17 or 18 or 19
  - 21 4 and 13 and 20
  - 22 limit 21 to English language [Limit not valid in CDSR, CCA, CLCMR; records were retained]

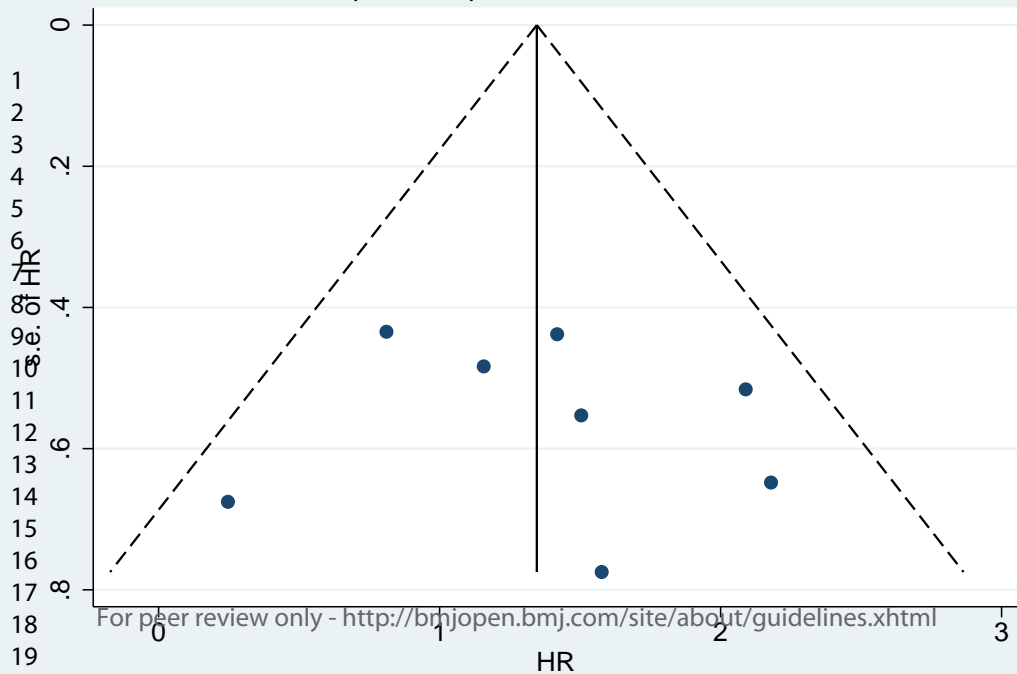


1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

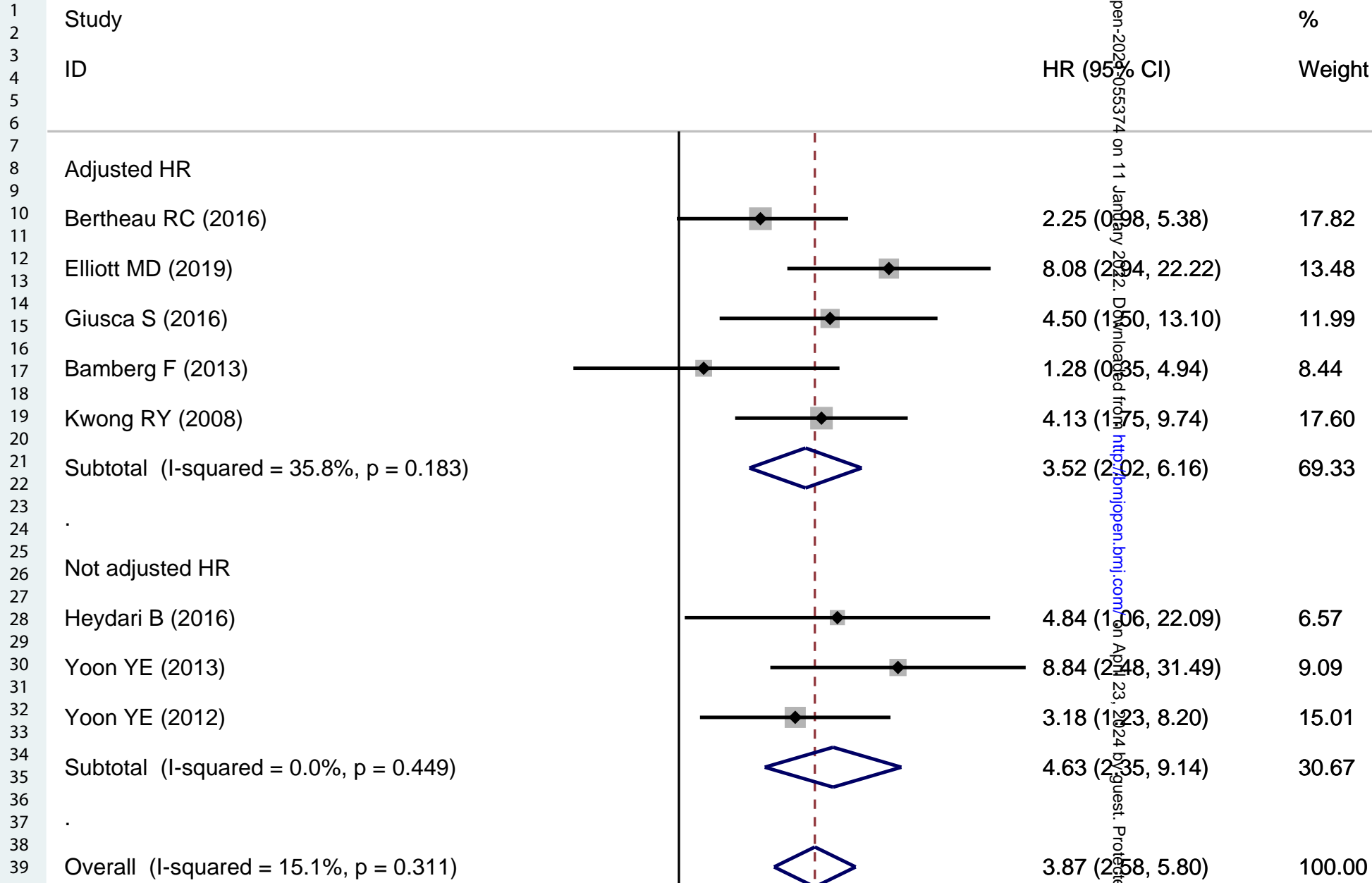
- 23 limit 22 to human [Limit not valid in CDSR, CCA, CLCMR; records were retained]
  - 24 limit 23 to clinical study [Limit not valid in CDSR, CCA, CLCMR, Embase; records were retained]
  - 25 limit 24 to journal article [Limit not valid in CDSR, CCA, Embase; records were retained]
  - 26 limit 25 to (embase or medline) [Limit not valid in CDSR, CCA, CLCMR, Ovid MEDLINE(R); records were retained]
- 

1 to 26 were performed in OvidSP platform.

For peer review only



1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.



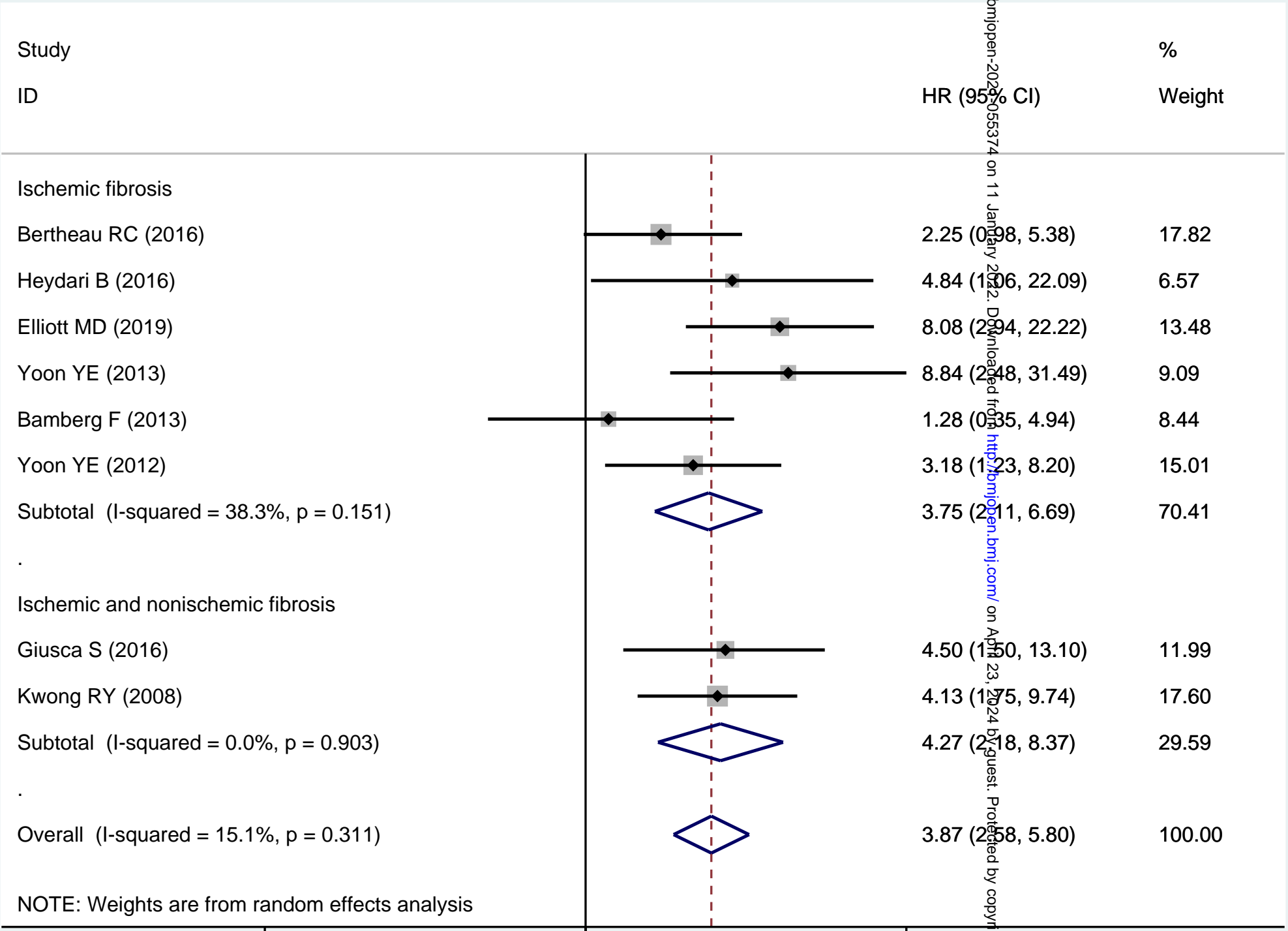
NOTE: Weights are from random effects analysis

.0318

1

31.5

1 1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.



NOTE: Weights are from random effects analysis

0.0318

1

31.5



## PRISMA 2020 Checklist

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

Section and Topic	Item #	Checklist item	Location where item is reported
<b>TITLE</b>			
Title	1	Identify the report as a systematic review.	1
<b>ABSTRACT</b>			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
<b>INTRODUCTION</b>			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	2,3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	2,3
<b>METHODS</b>			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3,4
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4,5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5,6
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5,6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	4,5,6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	4
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	4
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	4
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5,6
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	4,5,6



**PRISMA 2020 Checklist**

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47

136/bmjopen-2021-055374 on 21 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

Section and Topic	Item #	Checklist item	Location where item is reported
<b>RESULTS</b>			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	5
Study characteristics	17	Cite each included study and present its characteristics.	5
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	4,5,6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	5
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	5,6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	5,6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	5,6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	5,6
<b>DISCUSSION</b>			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	6,7
	23b	Discuss any limitations of the evidence included in the review.	7
	23c	Discuss any limitations of the review processes used.	7
	23d	Discuss implications of the results for practice, policy, and future research.	7
<b>OTHER INFORMATION</b>			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	3
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	3
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	3
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	11,12
Competing interests	26	Declare any competing interests of review authors.	12
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	12

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71  
 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>  
 For more information, visit: <http://www.prisma-statement.org/>

# BMJ Open

## Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055374.R1
Article Type:	Original research
Date Submitted by the Author:	17-Sep-2021
Complete List of Authors:	<p>Yang, Zhi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education; Chengdu Fifth People's Hospital, Department of Radiology</p> <p>Xu, Rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Wang, Jia-rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Xu, Hua-yan; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Fu, Hang; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Xie, Ling-jun; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Yang, Meng-xi ; Sichuan University West China Hospital, Department of Radiology</p> <p>Zhang, Lu; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Wen, Ling-yi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Liu, Hui; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Li, Hong; Sichuan University West China Second University Hospital, Key Laboratory of Obstetrics&amp;Gynecology and Pediatric Disease and Birth Defects of Ministry of Education</p> <p>Yang, Zhi-gang; Sichuan University West China Hospital, Department of Radiology</p> <p>Guo, Ying-kun ; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and</p>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

	Related Diseases of Women and Children of Ministry of Education
<b>Primary Subject Heading</b> :	Radiology and imaging
<b>Secondary Subject Heading</b> :	Diabetes and endocrinology, Cardiovascular medicine
<b>Keywords</b> :	RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, DIABETES & ENDOCRINOLOGY

SCHOLARONE™  
Manuscripts





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

**Title page :****Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis**

Zhi Yang<sup>1,2\*</sup>, MS; Rong Xu<sup>1\*</sup>, MS; Jia-rong Wang<sup>1</sup>, MD; Hua-yan Xu<sup>1</sup>, MD; Hang Fu<sup>1</sup>, MS; Ling-jun Xie<sup>1</sup>, MS; Meng-xi Yang<sup>4</sup>, MS; Lu Zhang<sup>1</sup>, MS; Ling-yi Wen<sup>1</sup>, MD; Hui Liu<sup>1</sup>, MS; Hong Li<sup>3</sup>, MD; Zhi-gang Yang<sup>4†</sup>, MD; Ying-kun Guo<sup>1†</sup>, MD

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
3. Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

**\* These authors contributed equally to this work and should be considered the co-first authors.**

**† Guarantor and correspondent:**

**These two authors contributed equally to this work and should be considered corresponding authors.**

**Zhigang Yang, PhD, MD**

Department of Radiology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, No.37 Guoxue Xiang, Chengdu, 610041, China

Tel: +86-28-85423817(O)

E-mail: yangzg666@163.com

**Yingkun Guo, MD**

Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3 South Renmin Road, Chengdu, 610041, China

Tel: +86-28-85503275(O)

E-mail: gykpanda@163.com

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

### ABSTRACT

**Objective** To performed this meta-analysis assessing the associations of myocardial fibrosis detected by late gadolinium-enhanced (LGE) MRI with the risk of major adverse cardiac and cerebrovascular events (MACCE) and major adverse cardiac events (MACE) in patients with diabetes.

**Design** Systematic review and meta-analysis u the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

**Data sources** We selected studies using MEDLINE, EMBASE and Cochrane by Ovid on 27 August 2021.

**Eligibility criteria for selecting studies** Prospective or respective cohort studies if they reported the hazard ratio (HR) and 95% confidence intervals (CI) for MACCE/MACE in patients with both type 1 and 2 diabetes and LGE compared with those without LGE, and articles published in the English language.

**Data extraction and synthesis** Two review authors independently extracted data and assessed the quality of study. Pooled hazard ratios (HR), and 95% confidence intervals (CI) by random-effects model. Heterogeneity were assessed using forest plots and the  $I^2$  statistic.

**Results** Eight studies with 1121 patients with both type 1 and type 2 diabetes were included in this meta-analysis, and follow-up of patients ranged from 17 to 70 months. The presence of myocardial fibrosis detected by LGE was associated with an increased risk for MACCE (HR: 2.58; 95%CI 1.42-4.71; P=0.002) and MACE (HR: 5.28; 95%CI 3.20-8.70; P=0.000) in patients with diabetes. In a subgroup meta-analysis, ischemic fibrosis detected by LGE was associated with MACCE (HR 3.75, 95%CI 2.11-6.69; P=0.000) in patients with diabetes. In diabetic patients with preserved ejection fraction, the association between myocardial fibrosis detected by LGE and MACCE remained significant (HR: 3.98; 95%CI 2.22-7.25; P=0.000).

**Conclusions** This study demonstrated that myocardial fibrosis detected by LGE conferred an increase in the risk of MACCE/MACE in patients with diabetes and may be an imaging biomarker for risk stratification.

**Keywords:** Magnetic Resonance Imaging, Diabetes, Meta-analysis, Systemic review

### Strengths and limitations of this study:

This meta-analysis focuses on the relationship between LGE and MACCE/MACE in patients with diabetes, and the distribution of ischemic LGE seems to increase the unfavorable prognosis.

This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

All included studies were not community-based epidemiology research, and came from developed

1  
2  
3 countries.

4 Additionally, most studies selected in this meta-analysis reported adjusted HRs may lead to bias.  
5  
6

## 7 INTRODUCTION

8 Diabetes is becoming a global healthcare problem, and it is estimated that there will be 693 million  
9 individuals with diabetes by 2045.<sup>1</sup> Patients with diabetes have a higher prevalence of myocardial fibrosis  
10 than their nondiabetic counterparts as a result of microvascular and macrovascular dysfunction, even  
11 when asymptomatic.<sup>2-5</sup> Moreover, the presence of myocardial fibrosis is associated with diabetic  
12 cardiomyopathy.<sup>6-8</sup> In addition, myocardial fibrosis can increase the risk of left ventricular (LV)  
13 dysfunction and heart failure with preserved ejection fraction in patients with diabetes.<sup>9 10</sup> Therefore, it  
14 is important to detect myocardial fibrosis by noninvasive imaging technology for risk stratification in the  
15 clinical routine.  
16  
17  
18  
19

20 Among detectors of myocardial fibrosis, late gadolinium-enhanced magnetic resonance imaging (LGE-  
21 MRI) is the most reliable tool for identifying and quantifying myocardial fibrosis in vivo that allows  
22 discriminate between ischemic and nonischemic fibrosis without ionizing radiation.<sup>11-13</sup> LGE-MRI, a  
23 promising technique, can provides more histological information over with unenhanced cardiac MRI, to  
24 illuminate the complex pathophysiologic pathways of myocardial viability.<sup>3</sup> Furthermore, recent  
25 guidelines suggested that MRI may be considered an imaging technique for stratifying cardiovascular  
26 risk in patients with diabetes.<sup>14 15</sup> This maybe highlights the role of LGE-MRI in risk stratification of  
27 patients with diabetes.  
28  
29  
30  
31

32 Approximately 19% of asymptomatic patients with diabetes have myocardial fibrosis upon LGE-MRI.<sup>2</sup>  
33 Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict  
34 major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial  
35 fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.<sup>2 3 16-21</sup> In addition, most  
36 previous studies were single-center studies and have been limited by small numbers of events.  
37 Consequently, we performed a meta-analysis to assess the association of LV myocardial fibrosis detected  
38 by late gadolinium enhancement (LGE) with future MACCE and MACE in patients with diabetes.  
39  
40  
41

## 42 METHODS

43 This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of  
44 Observational Studies in Epidemiology (MOOSE) statement.<sup>22 23</sup>

### 45 Data Sources and Searches

46 We searched the Ovid MEDLINE, Ovid EMBASE and Ovid Cochrane Library databases to find eligible  
47 studies in December 2019. The search strategy included the following keywords: “diabetes”, “diabetes  
48 mellitus”, “MR”, “cardiac magnetic resonance”, “CMR”, “gadolinium”, “LGE”, “prognosis”,  
49 “diagnosed”, “predictor”, and “death”. The details of the search strategy used for Ovid are available in  
50 Supplemental Table S1-S3. In addition, only articles published in peer-reviewed journals and in the  
51 English language were included.  
52  
53

### 54 Study Selection

55 All articles were independently screened by two reviewers (ZY, RX) using the following inclusion  
56 criteria, and any disagreement was resolved by consensus. The inclusion criteria were as follows: the  
57 design was prospective or retrospective cohort study; the populations were patients with diabetes, and  
58  
59  
60

1  
2  
3 exposure of myocardial fibrosis was detected by LGE-MRI; the outcomes used composite endpoints  
4 including all-cause mortality, cardiac and cerebrovascular disease, late coronary revascularization, and  
5 hospitalization for unstable angina; the study reported the hazard ratio (HR) and 95% confidence  
6 intervals (CI) and had  $\geq 12$  months of follow-up. We excluded reviews, abstracts, animal studies, case  
7 reports, and cross-sectional studies. Additionally, if the cases were reported more than once, we included  
8 the study with the most comprehensive information. Moreover, to obtain eligible studies, two reviewers  
9 independently screened the title first, then the abstract, and finally the full text.

### 12 **Data Extraction and Quality Assessment**

13 We extracted the following demographic data from each included study: author, year of publication,  
14 sample size, study design, age, LGE status, follow-up duration, outcome, and HR (95% CI). Additionally,  
15 we extracted the adjustment HR if the study reported the HR with adjustment models.

16 All of the included studies were prospective or retrospective cohort designs, and we used the Newcastle  
17 Ottawa Scale (NOS) to judge the study quality, which is usually used for evaluating the quality of cohort  
18 studies in meta-analyses.<sup>24,25</sup> The scale uses a maximum of 9 points involving 3 factors: patient selection  
19 (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).<sup>26</sup> We delimited the quality of  
20 studies as low (0 to 3 scores), moderate (4 to 6 scores), and high (7 to 9 scores).

### 24 **Data Synthesis and Analysis**

25 In this meta-analysis, the outcome measure was the occurrence of future adverse cardiac and/or  
26 cerebrovascular events among diabetes patients with LGE compared to those without LGE. We defined  
27 the primary endpoint as MACCE, including myocardial infarction (MI), all-cause mortality, coronary  
28 and carotid revascularization, heart failure, ventricular arrhythmias, unstable angina, cardiac and  
29 cerebrovascular death, and cerebrovascular disease. The secondary end points were MACE, including  
30 all-cause mortality, cardiac death, MI, heart failure, unstable angina, and ventricular arrhythmias.  
31 Additionally, the pattern of myocardial fibrosis was classified as ischemic fibrosis or nonischemic  
32 fibrosis as described previously.<sup>3</sup>

33 We pooled the adjusted HR with its 95% CI using a random-effects model. In addition, we calculated  
34 the annualized event rates by dividing the total events by the median follow-up periods. To analyze the  
35 heterogeneity of the included studies, we used forest plots and the  $I^2$  statistic.<sup>27</sup> We assigned  $I^2$  values of  
36 0 ~ 25%, ~ 50%, ~ 75% for low, medium, and high heterogeneity of studies, respectively. Considering  
37 the heterogeneity of the included studies, we conducted sensitivity analyses by omitting 1 article to assess  
38 the influence of a single study. In particular, subgroup analyses were performed by outcome and the  
39 pattern of myocardial fibrosis. Additionally, a funnel plot was used to assess the publication bias of the  
40 included studies.<sup>28</sup> The analyses were performed with Stata version 12 (StataCorp). *P* values were two  
41 sided, with a level of 0.05 considered significant.

### 50 **Patient and Public Involvement**

51 No patient involved.

## 52 **RESULTS**

### 54 **Literature Search**

55 Based on the selection strategy, we found 4520 citations. Of these, 349 duplicate studies were excluded.  
56 After screening the title and abstract, 14 articles remained for assessment of the full text. Four studies<sup>29-  
57 32</sup> were excluded for the following reasons: studies without our outcome of interest, study populations  
58 did not meet our inclusion criteria, and studies did not report the HR. Ultimately, 8 studies<sup>2,3,16-21</sup> fulfilled  
59  
60

our inclusion criteria and were included in this meta-analysis (Fig. 1).

### Study Characteristics

In aggregate, 8 studies included a total of 1121 patients with diabetes (median age ranging from 52 to 67; 67% were men) who underwent LGE-MRI and whose follow-up ranged from 17 to 70 months. Across the 8 studies, 6 articles<sup>2 17-21</sup> reported the duration of diabetes, and the mean duration of diabetes was 15 years. A total of 6 studies<sup>2 3 16 19-21</sup> reported the LV ejection fraction, and the mean LV ejection fraction was 57.78%. The presence of LGE was evaluated by visual analysis in 6 publications.<sup>2 3 18-21</sup> All of the included studies reported multiple clinical outcomes. The main characteristics of the included articles are shown in Table 1.

Among the 8 selected studies, 6 studies<sup>16-21</sup> (75%) were conducted in a single center (Germany, n=2; USA, n=2; Japan, n=2), and 2 studies<sup>2 3</sup> were performed in multiple centers (USA, n=1; Europe, n=1). Five articles<sup>2 3 17 20 21</sup> (62.5%) reported adjusted HR. Six studies<sup>2 16 18-21</sup> reported patients with ischemic fibrosis, and the remaining 2 studies<sup>3 17</sup> reported patients with ischemic and nonischemic fibrosis.

Of the 8 eligible studies, 7 received 7 to 9 scores, and the mean NOS score was 7.5. Overall, the aforementioned analysis showed that the included articles had high quality (Table 1). Among the identified studies, there was no risk of publication bias assessed by visual analysis of the funnel plot (Supplemental Fig. S1).

### Prevalence of LGE and annualized event rates

Across the 8 studies, the prevalence of myocardial fibrosis detected by LGE ranged from 15% to 62%, and the prevalence of LGE in the total sample was 38.09% (n=427). Furthermore, a total of 164 events occurred in the diabetes group (n=1121) during the median follow-up of 3.4 years. Patients with diabetes had annualized event rates for MACCE of 4.3%.

Additionally, 3 studies<sup>2 19 21</sup> reported a total of 301 patients with diabetes, and 19.27% (n=58) patients with diabetes had LGE. These patients which with patients and LGE, with 27 events occurring over a median follow-up of 3.9 years. The annualized event rates of patients with diabetes and LGE was 11.94%.

### MACCE and MACE

A total of 8 studies reported the outcome of MACCE or MACE, and the presence of myocardial fibrosis detected by LGE was a strong predictor of MACCE and MACE in patients with diabetes (random-effects HR 3.87, 95% CI 2.58-5.80; P=0.000) (Fig. 2). Low heterogeneity ( $I^2=15.1%$ , P=0.311) existed in the meta-analysis. In addition, sensitivity analysis performed by excluding 1 study each time found that the HR values were not significantly changed.

In the analysis of the outcome of MACCE, 3 articles<sup>17 20 21</sup> were included in this subgroup meta-analysis, including 64 participants with LGE and 165 diabetes without LGE, with a total of 64 MACCE outcomes during the follow-up period. Myocardial fibrosis detected by LGE was associated with an increased risk of MACCE in patients with diabetes. The pooled random-effects HR was 2.58 (95% CI 1.42-4.71; P=0.002), with no evidence of heterogeneity ( $I^2=14.1%$ ; P=0.312) (Fig. 2).

To explore the association between myocardial fibrosis and the outcome of MACE in patients with diabetes, we included 5 articles<sup>2 3 16 18 19</sup> that provided a subgroup meta-analysis. The results showed that the presence of LGE in diabetes was associated with a significantly higher risk of MACE. As in the

1  
2  
3 discovery analyses, the pooled HR was 5.28 (95% CI 3.20-8.70; P=0.000) with no significant  
4 heterogeneity ( $I^2=0\%$ ; P=0.643) from random effects (Fig. 2).  
5  
6

7 To further verify the robustness of the results, we grouped all included studies by adjusted or non-  
8 adjusted HR. In patients with diabetes, myocardial fibrosis detected by LGE was associated with an  
9 increased risk of MACCE and MACE in a subgroup meta-analysis with or without adjusted HR. The  
10 pooled HRs were 3.52 (random-effects, 95% CI 2.02-6.16;  $I^2=35.8\%$ ) and 4.63 (random-effects, 95% CI  
11 2.35-9.14;  $I^2=0\%$ ), respectively. There was no significant heterogeneity among the studies (Supplemental  
12 Fig. S2).  
13  
14

15 To evaluate the pattern of myocardial fibrosis effects, we further calculated a pooled HR by source of  
16 diabetes with different patterns of myocardial fibrosis. In patients with diabetes, ischemic fibrosis  
17 detected by LGE was significantly associated with increased MACCE and MACE (random-effects HR  
18 3.75, 95% CI 2.11-6.69;  $I^2=38.3\%$ ). There is no study in our meta-analysis reported the relationship  
19 between non-ischemic fibrosis and risk of MACCE and MACE; hence, we cannot perform a meta-  
20 analysis to assess the relationship between non-ischemic fibrosis and MACCE/MACE. Furthermore, all  
21 myocardial fibrosis detected by LGE in patients with diabetes may increase the risk of MACCE and  
22 MACE (random-effects HR 4.27, 95% CI 2.17-8.37;  $I^2=0\%$ ) (Supplemental Fig. S3).  
23  
24  
25  
26  
27

28 To confirm whether there were similar results in patients with preserved LV ejection fraction, we  
29 conducted a subgroup meta-analysis with 6 studies. Among individuals with diabetes and LV ejection  
30 fraction > 50%, the presence of myocardial fibrosis assessed by LGE was significantly associated with  
31 MACCE and MACE. The pooled HR was 3.98 (95% CI 2.22-7.25; P=0.000) with random effects, and  
32 there was medium heterogeneity among the studies ( $I^2=37.9\%$ ; P=0.153) (Fig. 3).  
33  
34  
35

## 36 DISCUSSION

37 In this meta-analysis, the prevalence of myocardial fibrosis assessed by LGE was increased in patients  
38 with diabetes, occurring in 38.09% of them. In addition, the presence of myocardial fibrosis assessed by  
39 LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction  
40 persisted. Moreover, the distribution of ischemic LGE seems to increase the unfavorable prognosis;  
41 however, in this study, non-ischemic LGE and MACCE/MACE in patients who with diabetes were not  
42 obtained. Specifically, ischemic myocardial fibrosis detected by LGE has a higher predictive value for  
43 the occurrence of future MACE than MACCE in patients with diabetes. Furthermore, myocardial fibrosis  
44 by LGE may be an imaging biomarker for predicting adverse outcomes in patients with diabetes.  
45  
46  
47  
48

49 In our meta-analysis, the results supported previous studies showing that participants with diabetes have  
50 a higher presence of myocardial fibrosis detected by LGE. Importantly, in our included studies, the  
51 presence of myocardial fibrosis in symptomatic patients with diabetes was higher than that in  
52 asymptomatic patients with diabetes.<sup>2 3 17</sup> Current guidelines recommend that MRI may be a risk tool in  
53 asymptomatic patients with diabetes at moderate or high risk of cardiovascular disease.<sup>14</sup> However, the  
54 value of MRI in routine clinical stratification of cardiovascular risk is unclear. Notably, in our meta-  
55 analysis, focal myocardial fibrosis detected by LGE did seem to predict a higher occurrence  
56 MACCE/MACE in the future, and the annualized event rates for MACCE/MACE in patients with  
57 diabetes and LGE was 11.94%. Additionally, the presence of myocardial fibrosis indicated a 8-fold  
58  
59  
60

1  
2  
3 higher risk for death/MI even in asymptomatic patients with diabetes.<sup>2</sup> It must be noted that other  
4 techniques, such as ECG, have lower accuracy and sensitivity for detecting myocardial fibrosis than  
5 LGE.<sup>33,34</sup> Thus, this finding maybe highlighted the value of LGE for screening for cardiovascular risk in  
6 symptomatic patients with diabetes.  
7  
8

9  
10 The risk of myocardial fibrosis in patients with diabetes is increased and likely multifactorial. First,  
11 patients with diabetes have a higher risk for coronary artery disease and myocardial dysfunction.<sup>35-37</sup>  
12 Moreover, hyperglycemic metabolism, microvascular disease, and cardiac autonomic neuropathy are  
13 involved in the mechanisms of myocardial fibrosis.<sup>4,38,39</sup> However, many studies have shown that patients  
14 with diabetes have a high incidence of obesity, visceral fat, hyperlipidemia, and insulin resistance, which  
15 may impair myocardial function.<sup>6,40,41</sup> Furthermore, the multiple risk factors described above should  
16 increase the myocardial fibrosis burden. In addition, myocardial fibrosis is widespread in subjects with  
17 diabetes and may be associated with a high risk for cardiovascular disease.  
18  
19

20  
21 Although the focal myocardial fibrosis translates to an adverse outcome in future is not fully clear, several  
22 potential mechanisms may lead to MACCE/MACE. First, patients with diabetes are more inclined to  
23 develop myocardial fibrosis, and myocardial fibrosis is associated with ventricular arrhythmia and heart  
24 failure.<sup>3,42-44</sup> Second, patients with diabetes and myocardial fibrosis usually have a greater burden of  
25 microvascular complications, such as myocardial ischemia, which confers an increased risk of  
26 MACCE/MACE.<sup>16,45</sup> Additionally, the myocardial fibrosis detected by LGE, especially subendocardial  
27 fibrosis, indicates patients with diabetes has had a subendocardial infarction in the past, which denotes a  
28 higher risk of MACE in the future.<sup>46,47</sup> Furthermore, subjects with diabetes had higher LV and left atrial  
29 remodeling due to myocardial fibrosis.<sup>9,43,48</sup> For these reasons, the myocardial fibrosis detected by LGE  
30 indeed has clinical relevance.  
31  
32  
33  
34  
35

36 As previously described, LGE-MRI has become a powerful noninvasive imaging method for the  
37 assessment of myocardial fibrosis.<sup>11</sup> Unfortunately, our meta-analysis demonstrated that the presence of  
38 myocardial fibrosis derived from LGE conferred an HR of 3.87 for future MACCE/MACE in individuals  
39 with diabetes, and the risk increased with ischemic myocardial fibrosis. It must be indicated that two  
40 studies<sup>20,21</sup> were included in our meta-analysis, which showed that ischemic myocardial fibrosis detected  
41 by LGE did not increase the rate of MACCE. This might be explained by the following reasons, such as  
42 limited patients and the patients having a high prevalence of cardiovascular disease. Indeed, detecting  
43 myocardial fibrosis can be used to clinically assess myocardial damage and to stratify cardiovascular risk  
44 in participants with diabetes. To date, only one study, which screened for asymptomatic diabetes by LGE,  
45 showed that diabetes with ischemic myocardial fibrosis conferred an 8-fold higher risk for all-cause  
46 mortality and MI.<sup>2</sup> The prevalence of myocardial fibrosis detected by LGE among patients with diabetes  
47 is higher than that among nondiabetic patients.<sup>3,30</sup> Therefore, patients with diabetes and myocardial  
48 fibrosis might need aggressive management of cardiac and cerebrovascular risk factors.  
49  
50  
51  
52  
53

54 However, our meta-analysis has some limitations. First, in our meta-analysis, 2 studies<sup>20,21</sup> were from the  
55 same group of patients but reported different outcomes. However, when we excluded either of the above  
56 articles, the pooled HR and heterogeneity did not change significantly. Second, the incidence of  
57 myocardial fibrosis in patients with diabetes was not community-based epidemiology research. The  
58 prevalence of myocardial fibrosis, therefore, may be higher in this study, which pooled studies including  
59  
60



1  
2  
3 high-risk or average-risk populations with diabetes. Third, a previous study found that non-ischemic LGE  
4 is associated with increased myocardial mass, increased myocardial extracellular volume and impaired  
5 diastolic parameters.<sup>49</sup> However, this study was not designed to evaluate the effect of non-ischemic  
6 myocardial fibrosis on MACCE/MACE in patients with diabetes. Further studies are needed to establish  
7 those non-ischemic LGE lesions and their prognosis. Fourth, most studies selected in this meta-analysis  
8 reported adjusted HRs, and various adjustments for adverse outcomes among the selected studies may  
9 affect the pooled results. However, the heterogeneity among the selected studies was low, and publication  
10 bias did not exist. This might strengthen the clinical meaning of the pooled result. Finally, the incremental  
11 value of diabetes duration to the prevalence and incidence of LGE was not revealed. However, diabetes  
12 duration plays a central role in the assessment of cardiovascular risk.<sup>14 50</sup> Hence, a prospective study that  
13 evaluates the association between diabetes duration and myocardial fibrosis and determines the best time  
14 to screen myocardial fibrosis by LGE-CMR for risk stratification in patients with diabetes is needed.  
15  
16  
17  
18  
19

## 20 CONCLUSIONS

21 In patients with diabetes, the presence of myocardial fibrosis detected by LGE-MRI was markedly  
22 associated with an important and increased risk of MACCE/MACE. Myocardial fibrosis may be a risk  
23 marker for improving risk stratification in patients with diabetes. This meta-analysis highlights the role  
24 of LGE-MRI in helping identify high-risk diabetic patients in clinical practice.  
25  
26  
27

## 28 REFERENCE

- 29  
30 1 Cho NH, Shaw JE, Karuranga S, *et al.* IDF Diabetes Atlas: Global estimates of diabetes  
31 prevalence for 2017 and projections for 2045. *Diabetes research and clinical practice*  
32 2018;138:271-81.
- 33 2 Elliott MD, Heitner JF, Kim H, *et al.* Prevalence and prognosis of unrecognized myocardial  
34 infarction in asymptomatic patients with diabetes: A two-center study with up to 5 years of  
35 follow-up. *Diabetes Care* 2019;42:1290-6.
- 36 3 Giusca S, Kelle S, Nagel E, *et al.* Differences in the prognostic relevance of myocardial ischaemia  
37 and scar by cardiac magnetic resonance in patients with and without diabetes mellitus. *European*  
38 *heart journal cardiovascular Imaging* 2016;17:812-20.
- 39 4 Jia G, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to  
40 This Clinical Entity. *Circulation research* 2018;122:624-38.
- 41 5 Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular  
42 mechanisms and therapeutic opportunities. *Journal of molecular and cellular cardiology*  
43 2016;90:84-93.
- 44 6 Marwick TH, Ritchie R, Shaw JE, *et al.* Implications of Underlying Mechanisms for the  
45 Recognition and Management of Diabetic Cardiomyopathy. *Journal of the American College of*  
46 *Cardiology* 2018;71:339-51.
- 47 7 Adegate E, Singh J. Structural changes in the myocardium during diabetes-induced  
48 cardiomyopathy. *Heart failure reviews* 2014;19:15-23.
- 49 8 Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia- and insulin-  
50 resistance-induced heart disease. *Diabetologia* 2018;61:21-8
- 51 9 Storz C, Hetterich H, Lorbeer R, *et al.* Myocardial tissue characterization by contrast-enhanced  
52 cardiac magnetic resonance imaging in subjects with prediabetes, diabetes, and normal controls  
53  
54  
55  
56  
57  
58  
59  
60

- with preserved ejection fraction from the general population. *European heart journal cardiovascular Imaging* 2018;19:701-8.
- 10 Armstrong AC, Ambale-Venkatesh B, Turkbey E, *et al.* Association of Cardiovascular Risk Factors and Myocardial Fibrosis With Early Cardiac Dysfunction in Type 1 Diabetes: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care* 2017;40:405-11.
- 11 Mewton N, Liu CY, Croisille P, *et al.* Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *Journal of the American College of Cardiology* 2011;57:891-903.
- 12 Hiromi Hashimura FK, Hatsue Ishibashi-Ueda, Yoshiaki Morita, *et al.* Radiologic-Pathologic Correlation of Primary and Secondary Cardiomyopathies:MR Imaging and Histopathologic Findings in Hearts from Autopsy and Transplantation. *Radiographics* 2017;37:719-36.
- 13 Iles LM, Ellims AH, Llewellyn H, *et al.* Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. *European heart journal cardiovascular Imaging* 2015;16:14-22.
- 14 Cosentino F, Grant PJ, Aboyans V, *et al.* 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European heart journal* 2020;41:255-323.
- 15 Jensen MT, Fung K, Aung N, *et al.* Changes in Cardiac Morphology and Function in Individuals With Diabetes Mellitus: The UK Biobank Cardiovascular Magnetic Resonance Substudy. *Circulation Cardiovascular imaging* 2019;12:e009476.
- 16 Heydari B, Juan YH, Liu H, *et al.* Stress Perfusion Cardiac Magnetic Resonance Imaging Effectively Risk Stratifies Diabetic Patients with Suspected Myocardial Ischemia. *Circulation: Cardiovascular Imaging* 2016;9:e004136.
- 17 Kwong RY, Sattar H, Wu H, *et al.* Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation* 2008;118:1011-20.
- 18 Yoon YE, Kitagawa K, Kato S, *et al.* Prognostic significance of unrecognized myocardial infarction detected with MR imaging in patients with impaired fasting glucose compared with those with diabetes. *Radiology* 2012;262:807-15.
- 19 Yoon YE, Kitagawa K, Kato S, *et al.* Prognostic value of unrecognized myocardial infarction detected by late gadolinium-enhanced MRI in diabetic patients with normal global and regional left ventricular systolic function. *European radiology* 2013;23:2101-8.
- 20 Bamberg F, Parhofer KG, Lochner E, *et al.* Diabetes mellitus: Long-term prognostic value of whole-body MR imaging for the occurrence of cardiac and cerebrovascular events. *Radiology* 2013;269:730-7.
- 21 Bertheau RC, Bamberg F, Lochner E, *et al.* Whole-Body MR Imaging Including Angiography: Predicting Recurrent Events in Diabetics. *European radiology* 2016;26:1420-30.
- 22 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *Jama* 2000;283:2008-12.
- 23 Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84.
- 24 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of

- 1  
2  
3 nonrandomized studies in meta-analyses. *European journal of epidemiology* 2010;25:603-5.
- 4  
5 25 Zeng X, Zhang Y, Kwong JS, *et al.* The methodological quality assessment tools for preclinical  
6 and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a  
7 systematic review. *Journal of evidence-based medicine* 2015;8:2-10.
- 8  
9 26 Mantovani A, Byrne CD, Bonora E, *et al.* Nonalcoholic Fatty Liver Disease and Risk of Incident  
10 Type 2 Diabetes: A Meta-analysis. *Diabetes Care* 2018;41:372-82.
- 11  
12 27 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine*  
13 2002;21:1539-1558
- 14  
15 28 Liu JL. The role of the funnel plot in detecting publication and related biases in meta-analysis.  
16 *Evidence-based dentistry* 2011;12:121-2
- 17  
18 29 Reinstadler SJ, Stiermaier T, Eitel C, *et al.* Relationship between diabetes and ischaemic injury  
19 among patients with revascularized ST-elevation myocardial infarction. *Diabetes, Obesity and*  
20 *Metabolism* 2017;19:1706-13.
- 21  
22 30 Lindman BR, Davila-Roman VG, Mann DL, *et al.* Cardiovascular phenotype in HFpEF patients  
23 with or without diabetes: a RELAX trial ancillary study. *Journal of the American College of*  
24 *Cardiology* 2014;64:541-9.
- 25  
26 31 Eitel I, Hintze S, De Waha S, *et al.* Prognostic impact of hyperglycemia in nondiabetic and  
27 diabetic patients with ST-elevation myocardial infarction: Insights from contrast-enhanced  
28 magnetic resonance imaging. *Circulation: Cardiovascular Imaging* 2012;5:708-18.
- 29  
30 32 Donnino R, Patel S, Nguyen AH, *et al.* Comparison of quantity of left ventricular scarring and  
31 remodeling by magnetic resonance imaging in patients with versus without diabetes mellitus and  
32 with coronary artery disease. *American Journal of Cardiology* 2011;107:1575-8.
- 33  
34 33 Ramos R, Albert X, Sala J, *et al.* Prevalence and incidence of Q-wave unrecognized myocardial  
35 infarction in general population: Diagnostic value of the electrocardiogram. The REGICOR study.  
36 *International journal of cardiology* 2016;225:300-5.
- 37  
38 34 Barbier CE, Bjerner T, Johansson L, *et al.* Myocardial scars more frequent than expected:  
39 magnetic resonance imaging detects potential risk group. *Journal of the American College of*  
40 *Cardiology* 2006;48:765-71.
- 41  
42 35 Bertoni AG, Goff Jr DC, D'Agostino Jr RB, *et al.* Diabetic cardiomyopathy and subclinical  
43 cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care*  
44 2006;29:588-94.
- 45  
46 36 Shivu GN, Phan TT, Abozguia K, *et al.* Relationship between coronary microvascular  
47 dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. *Circulation*  
48 2010;121:1209-15.
- 49  
50 37 Campbell DJ, Somaratne JB, Jenkins AJ, *et al.* Impact of type 2 diabetes and the metabolic  
51 syndrome on myocardial structure and microvasculature of men with coronary artery disease.  
52 *Cardiovascular diabetology* 2011;10:80.
- 53  
54 38 Tarquini R, Lazzeri C, Pala L, *et al.* The diabetic cardiomyopathy. *Acta diabetologica*  
55 2011;48:173-81.
- 56  
57 39 Gao Y, Yang ZG, Ren Y, *et al.* Evaluation of myocardial fibrosis in diabetes with cardiac  
58 magnetic resonance T1-mapping: Correlation with the high-level hemoglobin A1c. *Diabetes*  
59 *research and clinical practice* 2019;150:72-80.
- 60  
40 Turkbey EB, Backlund JY, Genuth S, *et al.* Myocardial structure, function, and scar in patients  
with type 1 diabetes mellitus. *Circulation* 2011;124:1737-46.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 41 Ng ACT, Strudwick M, van der Geest RJ, *et al.* Impact of Epicardial Adipose Tissue, Left Ventricular Myocardial Fat Content, and Interstitial Fibrosis on Myocardial Contractile Function. *Circ Cardiovasc Imaging* 2018;11:e007372.
  - 42 Anselmino M, Matta M, D'Ascenzo F, *et al.* Catheter ablation of atrial fibrillation in patients with diabetes mellitus: a systematic review and meta-analysis. *Europace* 2015;17:1518-25.
  - 43 Gulsin GS, Kanagala P, Chan DCS, *et al.* Differential left ventricular and left atrial remodelling in heart failure with preserved ejection fraction patients with and without diabetes. *Therapeutic Advances in Endocrinology and Metabolism* 2019;10:2042018819861593.
  - 44 Mordi I, Bezerra H, Carrick D, *et al.* The Combined Incremental Prognostic Value of LVEF, Late Gadolinium Enhancement, and Global Circumferential Strain Assessed by CMR. *JACC Cardiovascular imaging* 2015;8:540-9.
  - 45 Sandesara PB, O'Neal WT, Kelli HM, *et al.* The Prognostic Significance of Diabetes and Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction. *Diabetes Care* 2018;41:150-5.
  - 46 Schelbert EB, Cao JJ, Sigurdsson S, *et al.* Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. *Jama* 2012;308:890-6.
  - 47 Acharya T, Aspelund T, Jonasson TF, *et al.* Association of Unrecognized Myocardial Infarction With Long-term Outcomes in Community-Dwelling Older Adults: The ICELAND MI Study. *JAMA Cardiol* 2018;3:1101-6.
  - 48 Cao Y, Zeng W, Cui Y, *et al.* Increased myocardial extracellular volume assessed by cardiovascular magnetic resonance T1 mapping and its determinants in type 2 diabetes mellitus patients with normal myocardial systolic strain. *Cardiovascular diabetology* 2018;17:7.
  - 49 Bojer AS, Sørensen MH, Vejstrup N, *et al.* Distinct non-ischemic myocardial late gadolinium enhancement lesions in patients with type 2 diabetes. *Cardiovasc Diabetol* 2020;19(1):184.
  - 50 Dabelea D, Stafford JM, Mayer-Davis EJ, *et al.* Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood. *Jama* 2017;317:825-35.

#### Figure legend

Figure 1. Flow chart of literature and study selection.

Figure 2. Forest plot and pooled estimates of the effect of myocardial fibrosis detected by LGE on the risk of MACCE or MACE. LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, hazard ratios; CI,

1  
2  
3  
4 confidence interval.  
5  
6  
7  
8

9 Figure 3. Forest plots of 6 studies for pooled HR for MACCE and MACE in patients with diabetes  
10 with normal LV ejection fraction and myocardial fibrosis detected by LGE. HR, Hazard Ratios;  
11 LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events;  
12 MACE, major adverse cardiac events; CI, confidence interval.  
13  
14  
15  
16  
17  
18  
19  
20  
21

## 22 **Table legend**

23  
24  
25  
26  
27 Table 1. Description of the Studies Included in the Meta-Analysis  
28  
29  
30  
31

## 32 **Supplement legend**

33  
34  
35  
36  
37 Supplement Table S1. The exact search strategy was used in OvidSP.  
38  
39  
40  
41

42  
43 Supplement Figure S1. Funnel plots of 8 eligible studies.  
44  
45  
46  
47

48 Supplement Figure S2. Forest plots of pooled HR for MACCE and MACE in adjusted or not  
49 adjusted HR studies. HR, Hazard Ratios; MACCE, major adverse cardiac and cerebrovascular  
50 events; MACE, major adverse cardiac events; HR, Hazard Ratios; CI, confidence interval.  
51  
52  
53  
54  
55  
56  
57

58 Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCE and MACE in  
59  
60

1  
2  
3  
4 patients with diabetes and different pattern of myocardial fibrosis detected by LGE. HR, Hazard  
5  
6 Ratios; LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular  
7  
8 events; MACE, major adverse cardiac events; CI, confidence interval.  
9  
10  
11  
12  
13

#### 14 **Notes**

#### 17 **Author affiliations**

- 19 1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women  
20 and Children of Ministry of Education, Sichuan University West China Second University  
21 Hospital, Chengdu, China.
- 22 2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
- 23 3. Key Laboratory of Obstetrics&Gynecology and Pediatric Disease and Birth Defects of Ministry  
24 of Education, Sichuan University West China Second University Hospital, Chengdu, China.
- 25 4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

#### 37 **Funding**

38  
39  
40 This work was supported by the National Natural Science Foundation of China (No. 81771887,  
41 81771897, 81971586 , 81901712); the Program for Young Scholars and Innovative Research Team  
42 in Sichuan Province (No. 2017TD0005) of China; and 1-3-5 project for disciplines of excellence,  
43 West China Hospital, Sichuan University (No.ZYGD18013).  
44  
45  
46  
47  
48  
49  
50  
51

#### 52 **Compliance with ethical standards**

53  
54 Not applicable.  
55  
56  
57  
58  
59  
60

**Conflict of interest**

The authors report no conflicts of interest.

**Authors' contributions**

Zhi Yang and Rong Xu conceived of this study, and participated in its design and coordination and drafted the manuscript. Contribution to the conceptualization and design: Jia-rong Wang, Hua-yan Xu, Hang Fu, Ling-jun Xie and Meng-xi Yang. Data analysis and interpretation: Lu Zhang, Ling-yi Wen, Hui Liu and Hong Li. Obtaining funding: Zhi-gang Yang and Ying-kun Guo. Zhi-gang Yang and Ying-kun Guo interpreted the results, critically revised the manuscript, and helped to and approved the final version. All authors read and approved this manuscript.

**Patient consent for publication**

Not required.

**Ethics approval**

Ethics approval was not required for this meta-analysis.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Data availability statement**

No additional data are available.

Table 1 Description of the Studies Included in the Meta-Analysis

First Author, Year	Journal	Patients	HbA <sub>1c</sub> , %	LGE Definition	DM (type)	Mean age (years)	Duration of Diabetes (years)	LVEF (%)	Follow-up duration (months)	Major LGE(%)	Total events	Adjusted HR	Fibrosis type	Type design	Outcome	NO S	
Bertheau RC,2016	Eur Radiol Circ	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	8	YES	Ischemic	Prospective, single-centre	MAC CE	7
Heydari B,2016	Cardiovascular Imaging	173	7.9±1.8	2 SD	NA	61.7±1.9	NA	51.8±1.6	34.8±3.0	109	88	21	NO	Ischemic	Prospective, single-centre	MAC E	7
Elliott MD,2019	Diabetes Care	120	NA	visual	1 and 2	52±13	17±11	63±9	46 (33-64)	65	23	19	YES	Ischemic	Prospective, two-centre	MAC E	9
Yoon YE,2013	Eur Radiol	120	7.4±1.5	visual	2	67±9	11±11	63±6	27 (7-112)	83	18	10	NO	Ischemic	Retrospective, single-centre	MAC E	7
Giusca S,2016	Eur Heart J Cardiova	328	NA	visual	NA	67±11	NA	57.7±1.6	35 (23-51.6)	250	176	26	YES	Ischemic and nonischemic	Prospective, multicentre	MAC E	8



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

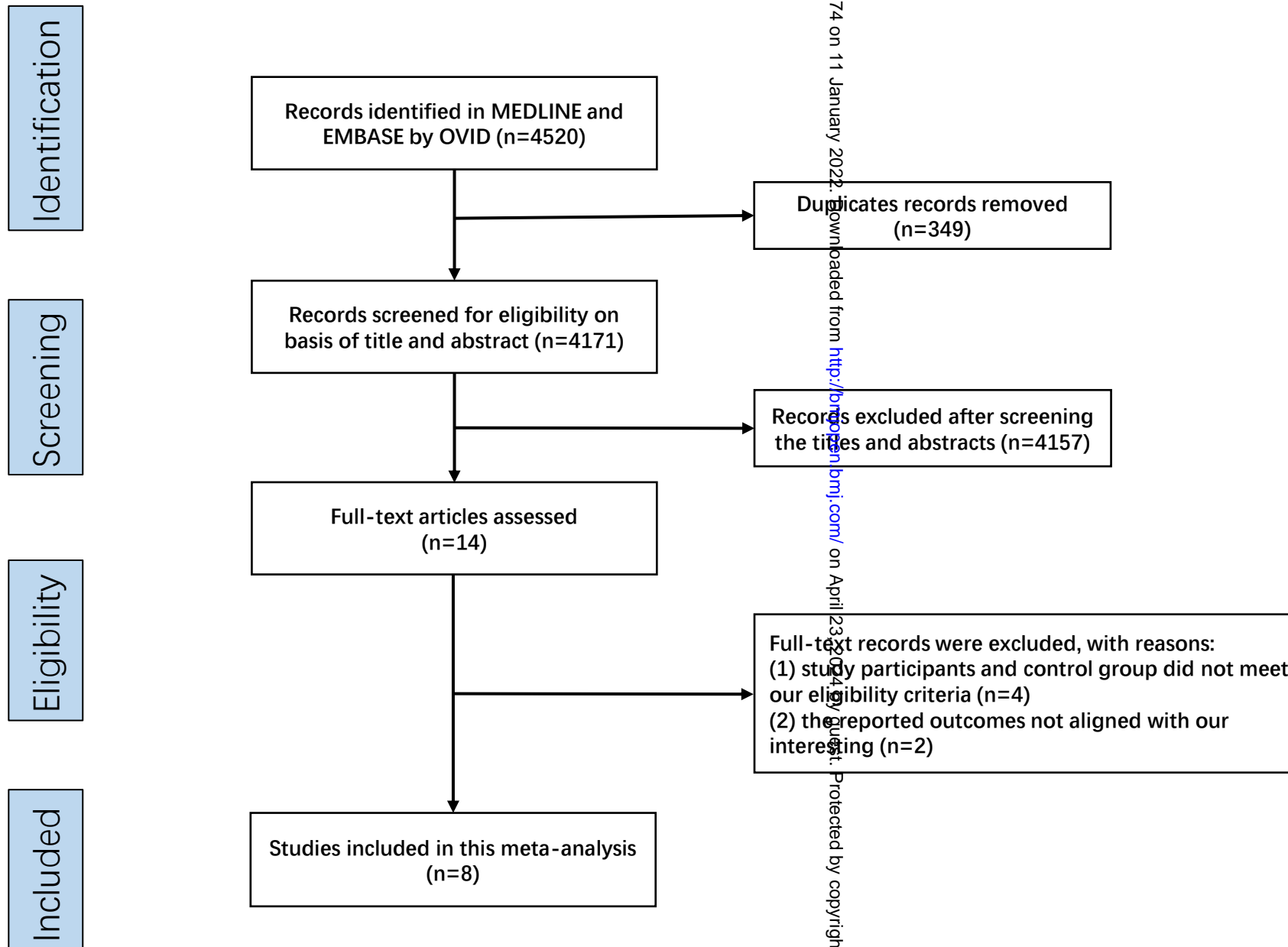
sc  
Imaging

Bamberg, 2013	Radiology	61	7.2 (6.5-7.9)	1 visual	2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	18	YES	Ischemic and nonischemic	Prospective, single-centre	MACCE	7
Kwong, 2008	Circulation	107	7.3±1.6	2 SD	NA	59±12	10.7±8.5	NA	17 (6-57)	67	30	38	YES	Ischemic and nonischemic	Prospective, single-centre	MACCE	9
Yoon, 2012	Radiology	151	7.4±1.6	visual	NA	67±9	14±11	NA	30(6-103)	113	58	24	NO	Ischemic	Retrospective, single-centre	MACCE	6

Columns represent n(%) or mean±SD or median (IQR); DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NOS, Newcastle-Ottawa Scale; HR, hazard ratio; NR, not reported; MACCE, major adverse cardiac and cerebrovascular events; MACCE, major adverse cardiac events.

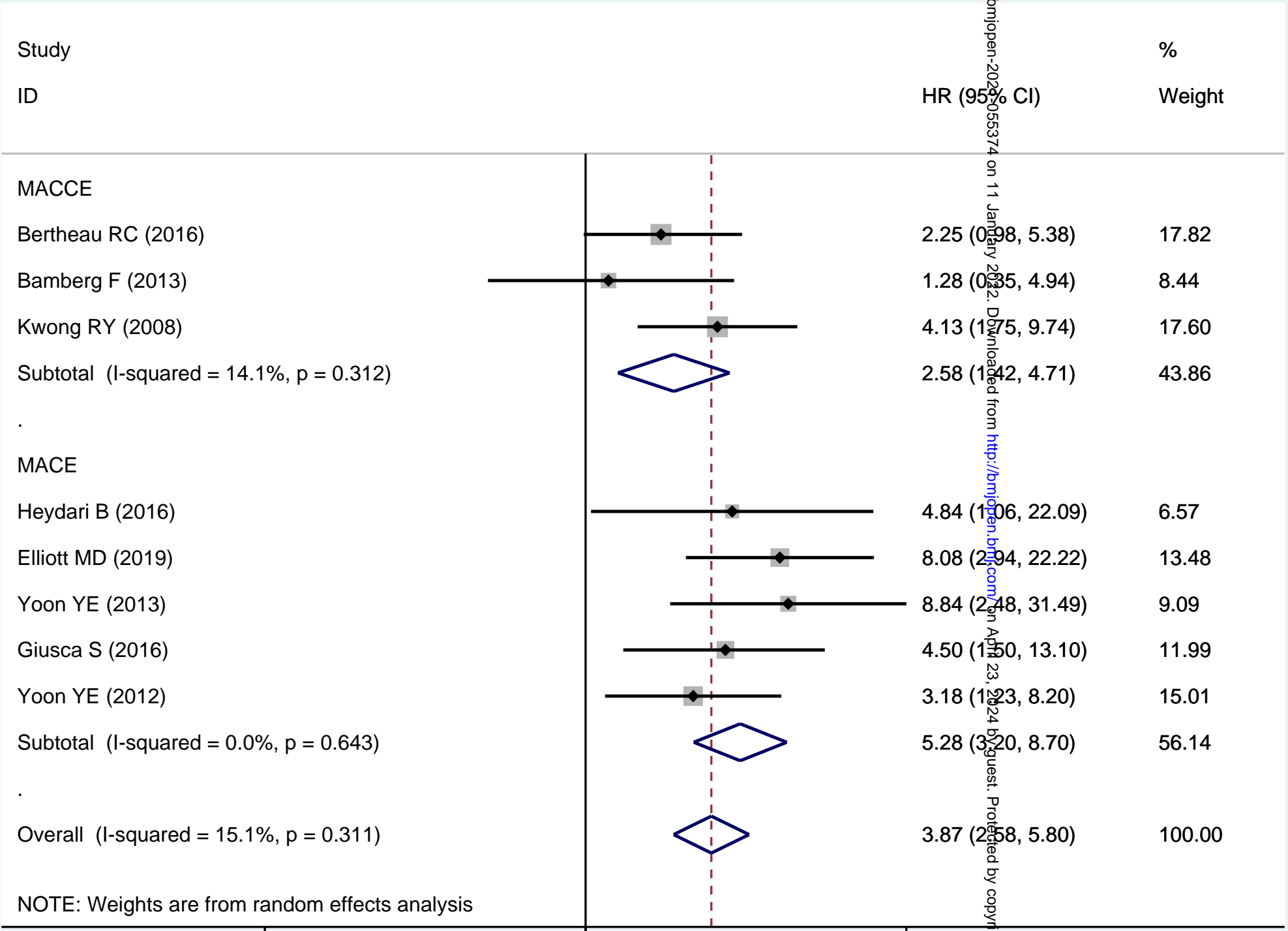
bmjopen-2021-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

11055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48



NOTE: Weights are from random effects analysis

0.0318

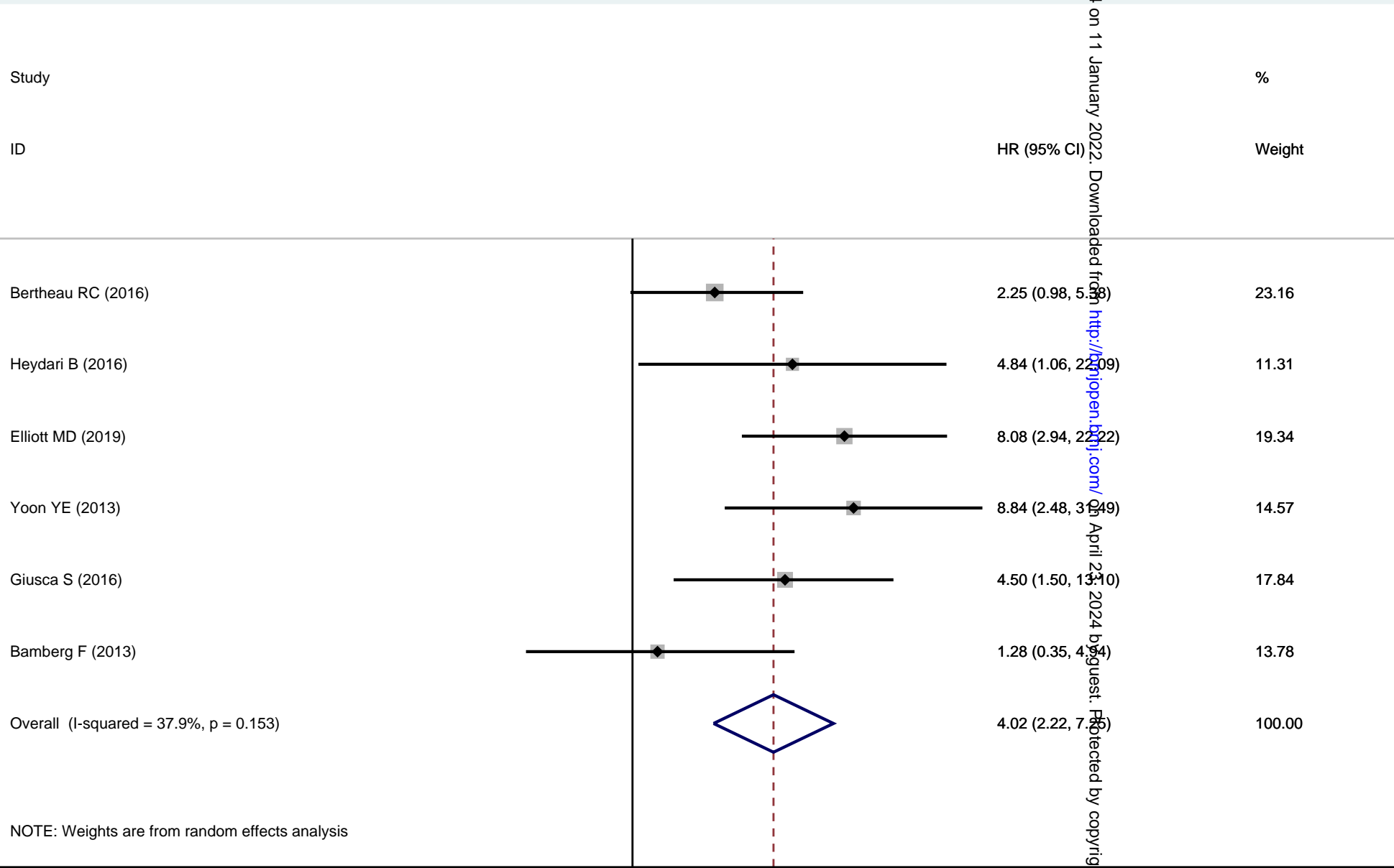
1

31.5

1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

55374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41



NOTE: Weights are from random effects analysis

.0318

1

31.5

## Supplement legend

Supplement Table S1. The exact search strategy was used in OvidSP.

Supplement Table S2. The exact search strategy was used in PubMed.

Supplement Table S3. The exact search strategy was used in Cochrane Library.

Supplement Figure S1. Funnel plots of 8 eligible studies.

Supplement Figure S2. Forest plots of pooled HR for MACCE and MACE in adjusted or not adjusted HR studies. HR, Hazard Ratios; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, Hazard Ratios; CI, confidence interval.

Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCE and MACE in patients with diabetes and different pattern of myocardial fibrosis detected by LGE. HR, Hazard Ratios; LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; CI, confidence interval.

## Supplement Tabe S1-1

Search methodology

Search strategies

---

1 diabetes. ab, kw, ti.

2 diabetes mellitus. ab, kw, ti.

3 "diabetic\*". ab, kw, ti.

4 1 or 2 or 3

5 mri. ab, kw, ti.

6 MR. ab, kw, ti.

7 "magnetic resonance imag\*". ab, kw, ti.

8 cardiac magnetic resonance. ab, kw, ti.

9 cmr. ab, kw, ti.

1  
2  
3  
4  
5 10 late gadolinium enhancement. ab, kw, ti.  
6

7  
8 11 lge. ab, kw, ti.  
9

10  
11 12 delayed gadolinium enhancement. ab, kw, ti.  
12

13 13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12  
14

15  
16 14 prognosis. sh.  
17

18  
19 15 diagnosed. tw.  
20

21  
22 16 cohort:.mp.  
23

24  
25 17 predictor:.mp.  
26

27  
28 18 death.mp.  
29

30  
31 19 exp \*models, statistical/  
32

33  
34 20 14 or 15 or 16 or 17 or 18 or 19  
35

36  
37 21 4 and 13 and 20  
38

39  
40 22 limit 21 to English language [Limit not valid in CDSR, CCA, CLCMR; records were retained]  
41  
42  
43  
44  
45  
46

1  
2  
3  
4  
5 23 limit 22 to human [Limit not valid in CDSR, CCA, CLCMR; records were retained]  
6

7  
8 24 limit 23 to journal article [Limit not valid in CDSR, CCA, Embase; records were retained]  
9

10 25 limit 24 to (embase or medline) [Limit not valid in CDSR, CCA, CLCMR, Ovid MEDLINE(R); records were retained]  
11

12  
13 

---

14 1 to 25 were performed in OvidSP platform.  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46



## Supplement Table S1-2

Search methodology

Search strategies

---

1 diabetes[Title/Abstract]

2 "diabetes mellitus"[Title/Abstract]

3 "diabetic\*"[Title/Abstract]

4 1 or 2 or 3

5 mri[Title/Abstract]

6 MR[Title/Abstract]

7 "magnetic resonance imag\*"[Title/Abstract]

8 "Magnetic Resonance Imaging"[MeSH Terms]

9 "cardiac magnetic resonance"[Title/Abstract]

1  
2  
3  
4  
5 10 cmr[Title/Abstract]  
6

7  
8 11 "late gadolinium enhancement" [Title/Abstract]  
9

10  
11 12 LGE[Title/Abstract]  
12

13 13 "delayed gadolinium enhancement"[ Title/Abstract]  
14

15  
16 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13  
17

18 15 prognosis[ MeSH Terms]  
19

20  
21 16 diagnosed[Title/Abstract]  
22

23  
24 17 cohort:[MeSH Terms]  
25

26 18 "predictor\*" [Title/Abstract]  
27

28  
29 19 death[MeSH Terms]  
30

31 20 models, statistical[MeSH Terms]  
32

33  
34 21 15 or 16 or 17 or 18 or 19 or 20  
35

36  
37 22 4 and 14 and 21  
38  
39  
40  
41  
42  
43  
44  
45  
46

1  
2  
3  
4  
5 23 "english and humans"[Filter]  
6  
7

8 24 22 and 23  
9

10 25 journal article[Filter]  
11  
12

13 26 24 and 25  
14

---

15  
16 1 to 26 were performed in PubMed.  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

## Supplement Tabe S1-3

Search methodolog

Search strategies

---

1 diabetes:ti,ab,kw

2 "diabetes mellitus":ti,ab,kw

3 "diabetic\*":ti,ab,kw

4 1 or 2 or 3

5 mri:ti,ab,kw

6 MR:ti,ab,kw

7 "magnetic resonance imag\*":ti,ab,kw

8 "Magnetic Resonance Imaging"[MeSH Terms]

9 "cardiac magnetic resonance":ti,ab,kw

1  
2  
3  
4  
5 10 cmr:ti,ab,kw  
6

7  
8 11 "late gadolinium enhancement" :ti,ab,kw  
9

10  
11 12 LGE:ti,ab,kw  
12

13 13 "delayed gadolinium enhancement":ti,ab,kw  
14

15  
16 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13  
17

18 15 prognosis[ MeSH Terms]  
19

20  
21 16 diagnosed:ti,ab,kw  
22

23 17 cohort:[MeSH Terms]  
24

25  
26 18 "predictor\*":ti,ab,kw  
27

28  
29 19 death[MeSH Terms]  
30

31 20 models, statistical[MeSH Terms]  
32

33  
34 21 15 or 16 or 17 or 18 or 19 or 20  
35

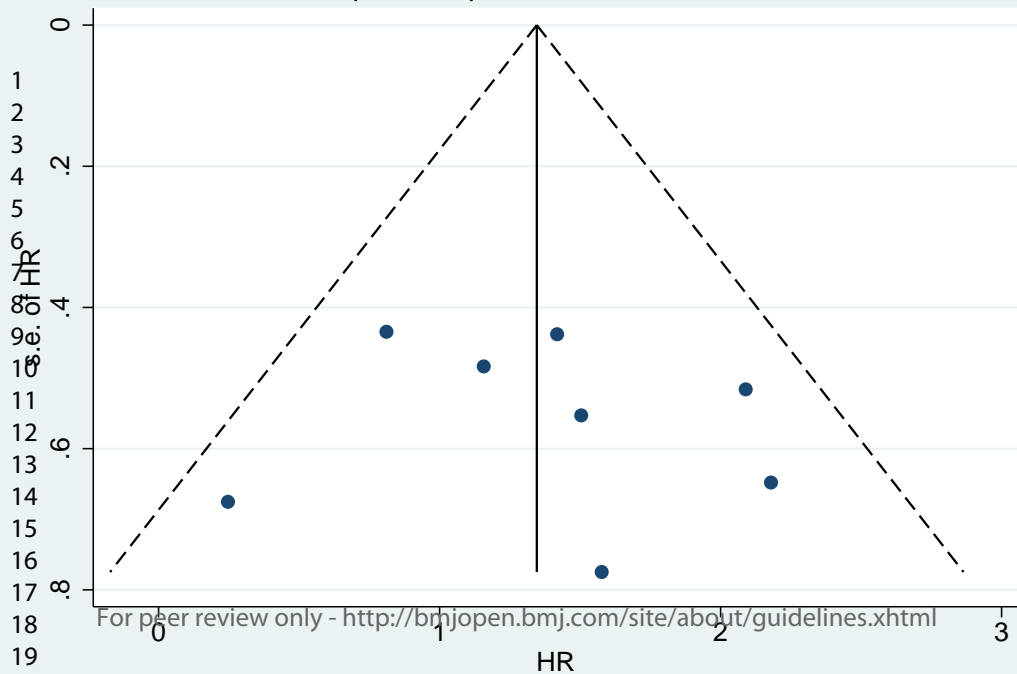
36  
37 22 4 and 14 and 21  
38  
39  
40  
41  
42  
43  
44  
45  
46

---

1 to 26 were performed in Cochrane Library.

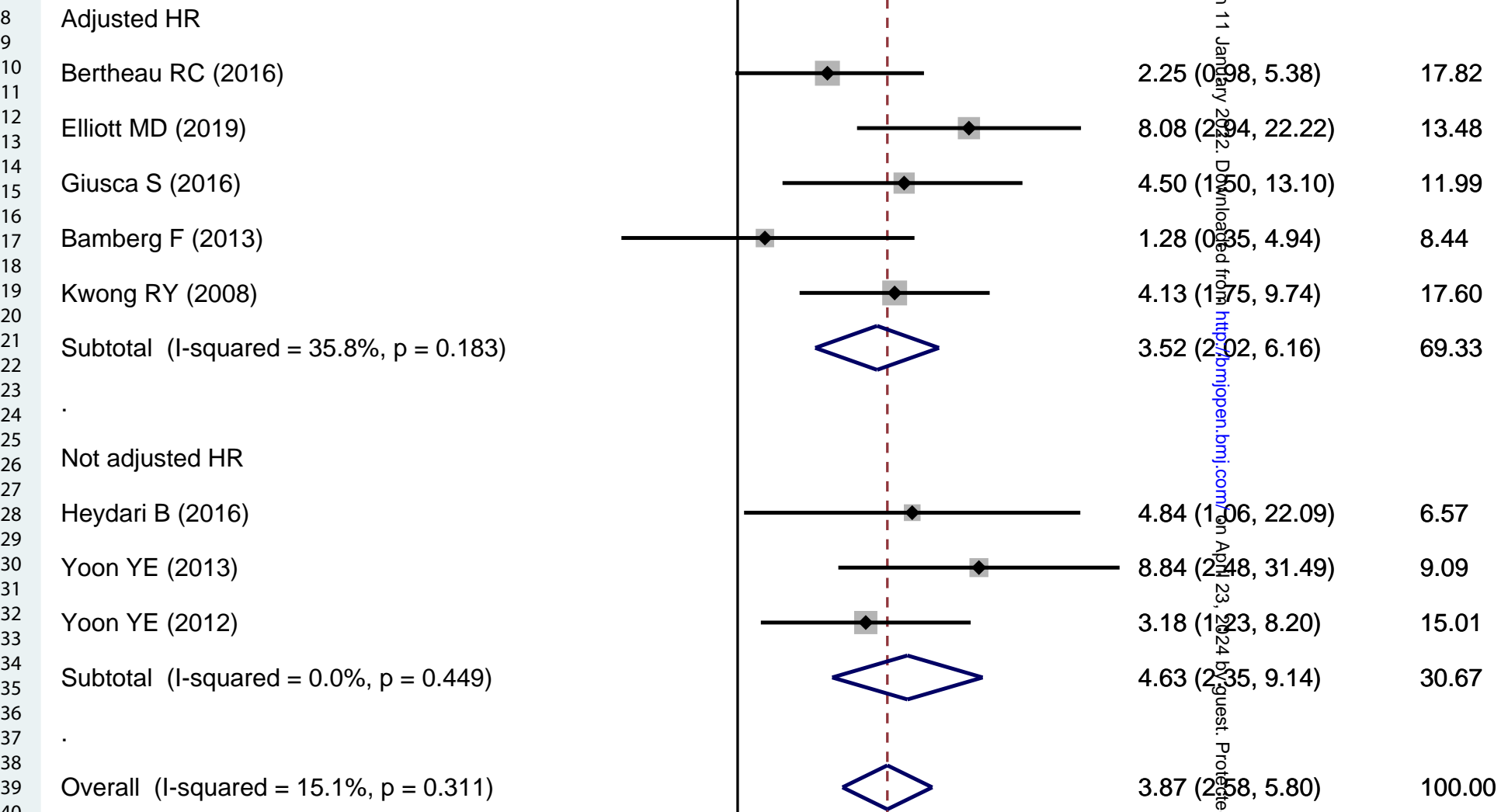
For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46



1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1 Study %  
 2  
 3 ID HR (95% CI) Weight  
 4  
 5  
 6

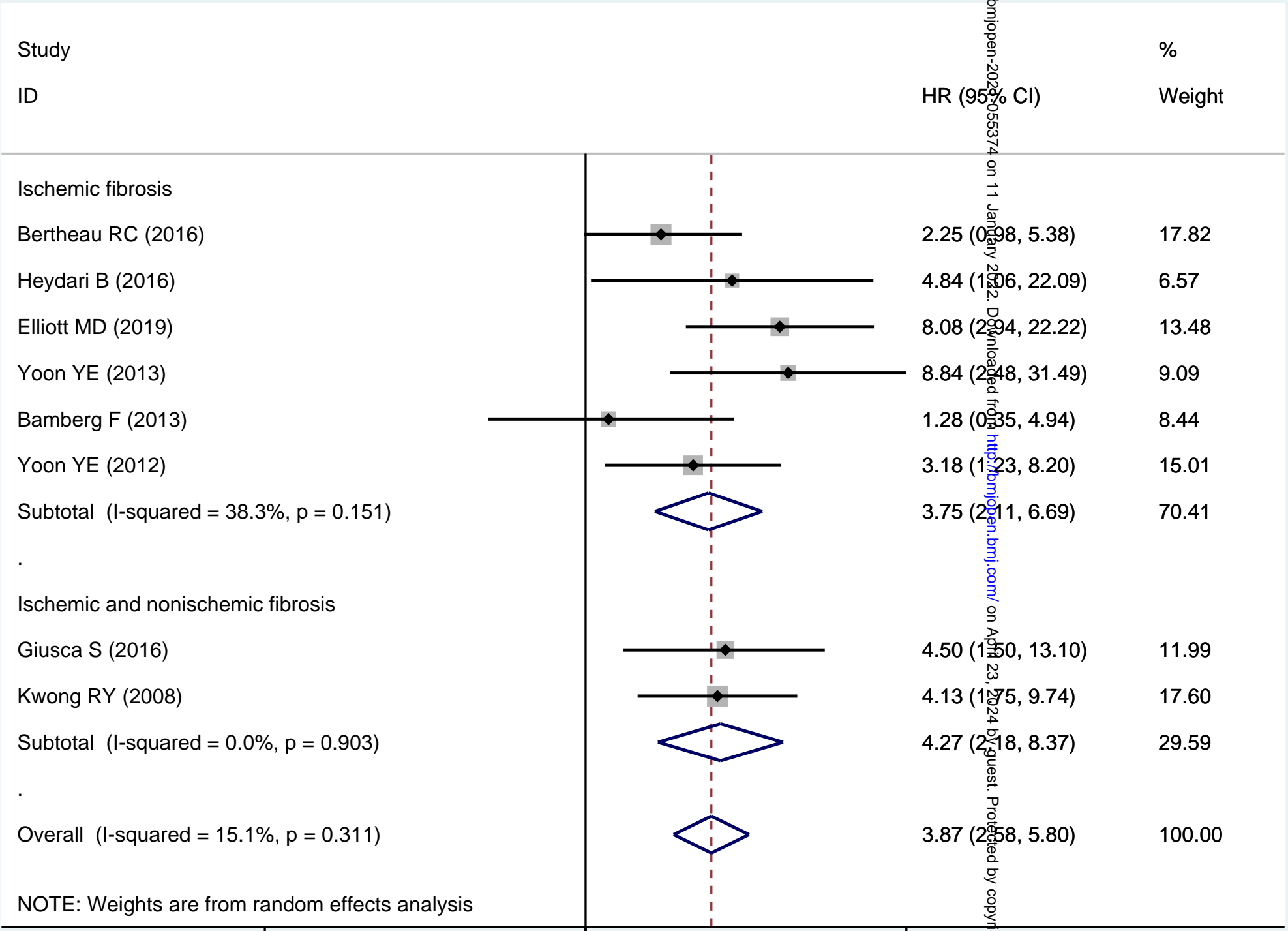


NOTE: Weights are from random effects analysis

44  
 45 .0318 1 31.5  
 46 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>  
 47  
 48



1 1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.



NOTE: Weights are from random effects analysis

0.0318

1

31.5

## MOOSE Checklist

### Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Corresponding Author :

Yingkun Guo, MD, PHD

Department of Radiology, Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education; West China Second University Hospital, Sichuan University,

Address: 20# South Renmin Road, Chengdu, Sichuan 610041, China.

Phone No: +86-18980006572

Fax No: +86 28-85502946(H)

Email Address: gykpanda@163.com

Criteria	Brief description of how the criteria were handled in the meta-analysis
<b>Reporting of background should include</b>	
√ Problem definition	Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.
√ Hypothesis statement	LGE is associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) or major adverse cardiac events (MACE) in patients with diabetes.
√ Description of study outcomes	MACCE/MACE
√ Type of exposure or intervention used	LGE-MRI
√ Type of study designs used	We included case-control studies, prospective cohort studies, retrospective studies, and randomized controlled studies.
√ Study population	Patients with diabetes.

<b>Reporting of search strategy should include</b>		
√	Qualifications of searchers	The credentials of the two investigators ZY and RX are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	See the section of “Data Sources and Searches” in the article.
√	Databases and registries searched	PubMed and EMBASE, Cochrane Library
√	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list is available upon request.
√	Method of addressing articles published in languages other than English	Articles published in the English language were included.
√	Method of handling abstracts and unpublished studies	Only studies published in peer-reviewed journals were included.
√	Description of any contact with authors	Not.
<b>Reporting of methods should include</b>		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and HR (95% CI).
√	Assessment of confounding	We extracted the adjustment HR if the study reported the HR with adjustment models.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
√	Assessment of heterogeneity	To analyze the heterogeneity of the included studies, we used forest plots and the I <sup>2</sup> statistic.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 1 summary table detailing the search strategy used for database search, 1 flow chart, 1 summary

		table, 4 forest plots, 1 funnel plots.
	<b>Reporting of results should include</b>	
√	Graph summarizing individual study estimates and overall estimate	Figure 1
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Figure 2
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, $I^2$ values and results of sensitivity analyses.
	<b>Reporting of discussion should include</b>	
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
√	Justification for exclusion	We excluded reviews, abstracts, animal studies, case reports, and cross-sectional studies.
√	Assessment of quality of included studies	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
	<b>Reporting of conclusions should include</b>	
√	Consideration of alternative explanations for observed results	In this article, we discussed the potential reasons that patients with diabetes have more myocardial fibrosis than who without diabetes. In addition, we discussed the myocardial fibrosis detected by LGE-MRI may increase the risk of MACCE/MACE, and the limitations of our study.
√	Generalization of the conclusions	The presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted.
√	Guidelines for future research	Myocardial fibrosis detected by LGE-MRI may be a risk marker for improving risk stratification in patients with diabetes.
√	Disclosure of funding source	This work was supported by the National Natural Science Foundation of China (No. 81771887, 81771897, 81971586, 81901712); the Program for Young Scholars and Innovative Research Team in Sichuan Province (No. 2017TD0005) of China; and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (No.ZYGD18013).

# BMJ Open

## Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055374.R2
Article Type:	Original research
Date Submitted by the Author:	08-Nov-2021
Complete List of Authors:	<p>Yang, Zhi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education; Chengdu Fifth People's Hospital, Department of Radiology</p> <p>Xu, Rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Wang, Jia-rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Xu, Hua-yan; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Fu, Hang; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Xie, Ling-jun; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Yang, Meng-xi ; Sichuan University West China Hospital, Department of Radiology</p> <p>Zhang, Lu; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Wen, Ling-yi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Liu, Hui; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Li, Hong; Sichuan University West China Second University Hospital, Key Laboratory of Obstetrics&amp;Gynecology and Pediatric Disease and Birth Defects of Ministry of Education</p> <p>Yang, Zhi-gang; Sichuan University West China Hospital, Department of Radiology</p> <p>Guo, Ying-kun ; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and</p>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

	Related Diseases of Women and Children of Ministry of Education
<b>Primary Subject Heading</b> :	Radiology and imaging
<b>Secondary Subject Heading</b> :	Diabetes and endocrinology, Cardiovascular medicine
<b>Keywords</b> :	RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, DIABETES & ENDOCRINOLOGY

SCHOLARONE™  
Manuscripts

BMJ Open: first published as 10.1136/bmjopen-2021-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

**Title page :****Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis**

Zhi Yang<sup>1,2\*</sup>, MS; Rong Xu<sup>1\*</sup>, MS; Jia-rong Wang<sup>1</sup>, MD; Hua-yan Xu<sup>1</sup>, MD; Hang Fu<sup>1</sup>, MS; Ling-jun Xie<sup>1</sup>, MS; Meng-xi Yang<sup>4</sup>, MS; Lu Zhang<sup>1</sup>, MS; Ling-yi Wen<sup>1</sup>, MD; Hui Liu<sup>1</sup>, MS; Hong Li<sup>3</sup>, MD; Zhi-gang Yang<sup>4†</sup>, MD; Ying-kun Guo<sup>1†</sup>, MD

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
3. Key Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

**\* These authors contributed equally to this work and should be considered the co-first authors.**

**† Guarantor and correspondent:**

**These two authors contributed equally to this work and should be considered corresponding authors.**

**Zhigang Yang, PhD, MD**

Department of Radiology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, No.37 Guoxue Xiang, Chengdu, 610041, China

Tel: +86-28-85423817(O)

E-mail: yangzg666@163.com

**Yingkun Guo, MD**

Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3 South Renmin Road, Chengdu, 610041, China

Tel: +86-28-85503275(O)

E-mail: gykpanda@163.com



## Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

### ABSTRACT

**Objective** This meta-analysis assessed the associations of myocardial fibrosis detected by late gadolinium-enhanced (LGE) MRI with the risk of major adverse cardiac and cerebrovascular events (MACCEs) and major adverse cardiac events (MACEs) in patients with diabetes.

**Design** This systematic review and meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

**Data sources** We retrieved studies from the MEDLINE, Embase and Cochrane by Ovid databases on 27 August 2021.

**Eligibility criteria for selecting studies** Prospective or retrospective cohort studies were included if they reported the hazard ratio (HR) and 95% confidence intervals (CI) for MACCEs/MACEs in patients with either type 1 or 2 diabetes and LGE compared with patients without LGE and if the articles were published in the English language.

**Data extraction and synthesis** Two review authors independently extracted data and assessed the quality of the included studies. Pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were analysed using a random effects model. Heterogeneity was assessed using forest plots and the  $I^2$  statistic.

**Results** Eight studies with 1121 patients with type 1 or type 2 diabetes were included in this meta-analysis, and the follow-up of patients ranged from 17 to 70 months. The presence of myocardial fibrosis detected by LGE was associated with an increased risk for MACCEs (HR: 2.58; 95% CI 1.42-4.71;  $P=0.002$ ) and MACEs (HR: 5.28; 95% CI 3.20-8.70;  $P<0.0001$ ) in patients with diabetes. Subgroup analysis revealed that ischaemic fibrosis detected by LGE was associated with MACCEs (HR 3.75, 95% CI 2.11-6.69;  $P<0.0001$ ) in patients with diabetes. In diabetic patients with preserved ejection fraction, the association between myocardial fibrosis detected by LGE and MACCEs remained significant (HR: 3.98; 95% CI 2.22-7.25;  $P<0.0001$ ).

**Conclusions** This study demonstrated that ischaemic myocardial fibrosis detected by LGE conferred an increased risk of MACCEs/MACEs in patients with diabetes and may be an imaging biomarker for risk stratification.

**Keywords:** Magnetic Resonance Imaging, Diabetes, Meta-analysis, Systemic review

### Strengths and limitations of this study:

This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

Myocardial fibrosis was proven to be a reliable prognostic predictor via subgroup analyses based on preserved left ventricular ejection fraction (LVEF), ischaemic LGE, MACCEs or MACEs.

All included studies were not community-based epidemiology research and came from developed countries.

1  
2  
3 Reduced LVEF and nonischaemic subgroup analyses were not performed due to the limited number of  
4 related studies.

## 6 INTRODUCTION

7 Diabetes is becoming a global health care problem, and it is estimated that there will be 693 million  
8 individuals with diabetes by 2045.<sup>1</sup> Patients with diabetes have a higher prevalence of myocardial fibrosis  
9 than their nondiabetic counterparts as a result of macrovascular dysfunction, even when they are  
10 asymptomatic.<sup>2-5</sup> Moreover, the presence of myocardial fibrosis is associated with diabetic  
11 cardiomyopathy.<sup>6-8</sup> In addition, myocardial fibrosis can increase the risk of left ventricular (LV)  
12 dysfunction and heart failure with preserved ejection fraction in patients with diabetes.<sup>9 10</sup> Therefore, it  
13 is important to detect myocardial fibrosis by noninvasive imaging technology for risk stratification.  
14  
15

16  
17 Among detectors of myocardial fibrosis, late gadolinium-enhanced magnetic resonance imaging (LGE-  
18 MRI) is the most reliable tool for identifying and quantifying myocardial fibrosis in vivo and allows  
19 discrimination between ischaemic and nonischaemic fibrosis without ionizing radiation.<sup>11-13</sup> LGE-MRI,  
20 a promising technique, can provide more histological information than unenhanced cardiac MRI to  
21 illuminate the complex pathophysiologic pathways of myocardial viability.<sup>3</sup> Furthermore, recent  
22 guidelines suggested that MRI may be considered an imaging technique for stratifying cardiovascular  
23 risk in patients with diabetes.<sup>14 15</sup> This may highlight the role of LGE-MRI in the risk stratification of  
24 patients with diabetes.  
25  
26  
27

28  
29 Approximately 19% of asymptomatic patients with diabetes have myocardial fibrosis upon LGE-MRI.<sup>2</sup>  
30 Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict  
31 major adverse cardiac events (MACEs) in patients with diabetes, the prognostic value of myocardial  
32 fibrosis for major cardiac and cerebrovascular events (MACCEs) is unclear.<sup>2 3 16-21</sup> In addition, most  
33 previous studies were single-centre studies and have been limited by small numbers of events.  
34 Consequently, we performed a meta-analysis to assess the association of LV myocardial fibrosis detected  
35 by late gadolinium enhancement (LGE) with future MACCEs and MACEs in patients with diabetes.  
36  
37  
38

## 39 METHODS

40  
41 This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of  
42 Observational Studies in Epidemiology (MOOSE) statement.<sup>22 23</sup>  
43

### 44 Data Sources and Searches

45 We searched the Ovid MEDLINE, Ovid Embase and Ovid Cochrane Library databases to find eligible  
46 studies on August 27, 2021. The search strategy included the following keywords: “diabetes”, “diabetes  
47 mellitus”, “MR”, “cardiac magnetic resonance”, “CMR”, “gadolinium”, “LGE”, “prognosis”,  
48 “diagnosed”, “predictor”, and “death”. The details of the search strategy used for Ovid are available in  
49 Supplemental Tables S1-S3. In addition, only articles published in peer-reviewed journals and published  
50 in the English language were included.  
51

### 52 Study Selection

53  
54 All articles were independently screened by two reviewers (ZY, RX), and any disagreement was resolved  
55 by consensus. The inclusion criteria were as follows: the design was a prospective or retrospective cohort  
56 study; the populations were patients with diabetes, and exposure to myocardial fibrosis was detected by  
57 LGE-MRI; the outcomes used composite endpoints including all-cause mortality, cardiac and  
58 cerebrovascular disease, late coronary revascularization, and hospitalization for unstable angina; the  
59  
60

1  
2  
3 study reported the hazard ratio (HR) and 95% confidence intervals (CI) and had  $\geq 12$  months of follow-  
4 up. We excluded reviews, abstracts, animal studies, case reports, and cross-sectional studies.  
5 Additionally, if the cases were reported more than once, we included the study with the most  
6 comprehensive information. The reviewers independently screened the titles first, then the abstracts, and  
7 finally the full texts.  
8  
9

### 10 **Data Extraction and Quality Assessment**

11 We extracted the following data from each included study: author, year of publication, sample size, study  
12 design, age, LGE status, follow-up duration, outcome, and HR (95% CI). Additionally, we extracted the  
13 adjusted HR if the study reported the HR with adjustment models.  
14

15 All of the included studies were prospective or retrospective cohort designs, and we used the Newcastle  
16 Ottawa Scale (NOS) to judge the quality of the studies, as this tool is usually used for evaluating the  
17 quality of cohort studies in meta-analyses.<sup>24 25</sup> The scale uses a maximum of 9 points involving 3 factors:  
18 patient selection (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).<sup>26</sup> We  
19 categorized the quality of studies as low (0 to 3 scores), moderate (4 to 6 scores), and high (7 to 9 scores).  
20  
21

### 22 **Data Synthesis and Analysis**

23 In this meta-analysis, the outcome measure was the prevalence of future adverse cardiac and/or  
24 cerebrovascular events among diabetes patients with LGE compared to those without LGE. We defined  
25 the primary endpoint as MACCEs, including myocardial infarction (MI), all-cause mortality, coronary  
26 and carotid revascularization, heart failure, ventricular arrhythmias, unstable angina, cardiac and  
27 cerebrovascular death, and cerebrovascular disease. The secondary endpoints were MACEs, including  
28 all-cause mortality, cardiac death, MI, heart failure, unstable angina, and ventricular arrhythmias.  
29 Additionally, the pattern of myocardial fibrosis was classified as ischaemic fibrosis or nonischaemic  
30 fibrosis as described previously.<sup>3</sup>  
31  
32

33  
34 We pooled the adjusted HRs with 95% CIs using a random effects model. In addition, we calculated the  
35 annualized event rates by dividing the total events by the median follow-up periods. To analyse the  
36 heterogeneity of the included studies, we used forest plots and the  $I^2$  statistic.<sup>27</sup> We assigned  $I^2$  values of  
37 0 ~ 25%, ~ 50%, ~ 75% for low, medium, and high heterogeneity of studies, respectively. Considering  
38 the heterogeneity of the included studies, we conducted sensitivity analyses by omitting 1 article to assess  
39 the influence of a single study. In particular, subgroup analyses were performed by outcome and the  
40 pattern of myocardial fibrosis. Additionally, a funnel plot was used to assess the publication bias of the  
41 included studies.<sup>28</sup> The analyses were performed with Stata version 12 (StataCorp). *P* values were two  
42 sided, with a level of 0.05 considered significant.  
43  
44

### 45 **Patient and Public Involvement**

46 No patient involved.  
47

## 48 **RESULTS**

### 49 **Literature Search**

50 Based on the selection strategy, we found 4520 citations. Of these, 349 duplicate studies were excluded.  
51 After screening the title and abstract, 14 articles remained for assessment of the full text. Six studies<sup>29-34</sup>  
52 were excluded for the following reasons: studies without our outcome of interest, study populations did  
53 not meet our inclusion criteria, and studies did not report the HR. Ultimately, 8 studies<sup>2 3 16-21</sup> fulfilled  
54 our inclusion criteria and were included in this meta-analysis (Fig. 1).  
55  
56  
57  
58

### 59 **Study Characteristics**

1  
2  
3 In aggregate, 8 studies were analysed, including a total of 1121 patients with diabetes (median age  
4 ranging from 52 to 67; 67% were men) who underwent LGE-MRI and whose follow-up duration ranged  
5 from 17 to 70 months. Across the 8 studies, 6 articles<sup>2 17-21</sup> reported the duration of diabetes, and the  
6 mean duration of diabetes was 15 years. A total of 6 studies<sup>2 3 16 19-21</sup> reported the LV ejection fraction,  
7 and the mean LV ejection fraction was 57.78%. The presence of LGE was evaluated by visual analysis  
8 in 6 studies.<sup>2 3 18-21</sup> All of the included studies reported multiple clinical outcomes. The main  
9 characteristics of the included articles are shown in Table 1.  
10  
11  
12

13  
14 Among the 8 selected studies, 6 studies<sup>16-21</sup> (75%) were conducted in a single centre (Germany, n=2;  
15 USA, n=2; Japan, n=2), and 2 studies<sup>2 3</sup> were performed in multiple centres (USA, n=1; Europe, n=1).  
16 Five articles<sup>2 3 17 20 21</sup> (62.5%) reported adjusted HRs. Six studies<sup>2 16 18-21</sup> reported patients with ischaemic  
17 fibrosis, and the remaining 2 studies<sup>3 17</sup> reported patients with ischaemic and nonischaemic fibrosis.  
18  
19

20 Of the 8 eligible studies, 7 received NOS scores between 7 and 9, and the overall mean NOS score was  
21 7.5. Overall, the aforementioned analysis showed that the included articles had high quality (Table 1).  
22 Among the identified studies, there was no risk of publication bias according to a visual analysis of the  
23 funnel plot (Supplemental Fig. S1).  
24

#### 25 **Prevalence of LGE and annualized event rates**

26 Across the 8 studies, the prevalence of myocardial fibrosis detected by LGE ranged from 15% to 62%,  
27 and the prevalence of LGE in the total sample was 38.09% (n=427). Furthermore, a total of 164 events  
28 occurred in the diabetes group (n=1121) during the median follow-up of 3.4 years. Patients with diabetes  
29 had annualized event rates for MACCEs of 4.3%.  
30  
31

32  
33 Additionally, 3 studies<sup>2 19 21</sup> reported a total of 301 patients with diabetes, and 19.27% (n=58) of patients  
34 with diabetes had LGE. Twenty-seven events occurred in these diabetic patients with LGE over a median  
35 follow-up of 3.9 years. The annualized event rate of patients with diabetes and LGE was 11.94%.  
36

#### 37 **MACCEs and MACEs**

38 A total of 8 studies reported the outcome of MACCEs or MACEs, and the presence of myocardial fibrosis  
39 detected by LGE was a strong predictor of MACCEs and MACEs in patients with diabetes (random  
40 effects HR 3.87, 95% CI 2.58-5.80; P<0.0001) (Fig. 2). There was low heterogeneity (I<sup>2</sup>=15.1%, P=0.311)  
41 in the meta-analysis. In addition, sensitivity analysis performed by excluding 1 study at a time did not  
42 reveal any significant changes in the HR values.  
43  
44

45  
46 In the analysis of the outcome of MACCEs, 3 articles<sup>17 20 21</sup> were included in this subgroup analysis,  
47 including 64 participants with LGE and 165 diabetes without LGE, with a total of 64 MACCEs during  
48 the follow-up period. Myocardial fibrosis detected by LGE was associated with an increased risk of  
49 MACCEs in patients with diabetes. The pooled HR obtained via the random effects model was 2.58  
50 (95% CI 1.42-4.71; P=0.002), with no evidence of heterogeneity (I<sup>2</sup>=14.1%; P=0.312) (Fig. 2).  
51  
52

53  
54 To explore the association between myocardial fibrosis and the outcome of MACEs in patients with  
55 diabetes, we included 5 articles<sup>2 3 16 18 19</sup> that provided a subgroup outcome analysis of MACEs. The  
56 results showed that the presence of LGE in diabetes was associated with a significantly higher risk of  
57 MACEs. As in the discovery analyses, the pooled HR obtained via the random effects model was 5.28  
58 (95% CI 3.20-8.70; P<0.0001), with no significant heterogeneity (I<sup>2</sup>=0%; P=0.643) (Fig. 2).  
59  
60

To further verify the robustness of the results, we grouped all included studies by adjusted or non-adjusted HR. In patients with diabetes, myocardial fibrosis detected by LGE was associated with an increased risk of MACCEs and MACEs in a subgroup analysis with or without adjusted HR. The pooled HRs obtained via a random effects model were 3.52 (95% CI 2.02-6.16;  $I^2=35.8\%$ ) and 4.63 (95% CI 2.35-9.14;  $I^2=0\%$ ), respectively. There was no significant heterogeneity among the studies (Supplemental Fig. S2).

To evaluate the effects of the myocardial fibrosis pattern, we further calculated a pooled HR by source of diabetes with different patterns of myocardial fibrosis. In patients with diabetes, ischaemic fibrosis detected by LGE was significantly associated with increased MACCEs and MACEs (random effects HR 3.75, 95% CI 2.11-6.69;  $I^2=38.3\%$ ). No study in our meta-analysis reported the relationship between nonischaemic fibrosis and the risk of MACCEs and MACEs alone; hence, we cannot perform a meta-analysis to assess the relationship between nonischaemic fibrosis and MACCEs/MACEs. Furthermore, two studies reported that ischaemic and nonischaemic myocardial fibrosis detected by LGE in patients with diabetes may increase the risk of MACCEs and MACEs, and the pooled HR obtained via the random effects model was 4.27 (95% CI 2.17-8.37;  $I^2=0\%$ ) (Supplemental Fig. S3).

To confirm whether there were similar results in patients with preserved LV ejection fraction, we conducted a subgroup analysis with 6 studies. Among individuals with diabetes and LV ejection fraction > 50%, the presence of myocardial fibrosis assessed by LGE was significantly associated with MACCEs and MACEs. The pooled HR obtained via the random effects model was 3.98 (95% CI 2.22-7.25;  $P=0.000$ ), and there was a medium amount of heterogeneity among the studies ( $I^2=37.9\%$ ;  $P=0.153$ ) (Fig. 3).

## DISCUSSION

In this meta-analysis, the prevalence of myocardial fibrosis (mainly ischaemic fibrosis) assessed by LGE was increased in patients with diabetes, occurring in 38.09% of them, and it was associated with an increased risk for MACCEs and MACEs, even when the LV ejection fraction persisted. Moreover, ischaemic myocardial fibrosis detected by LGE has a higher predictive value for the occurrence of future MACEs than MACCEs in patients with diabetes. However, in this study, the relationship of nonischaemic LGE and MACCEs/MACEs in patients with diabetes was not elucidated. Therefore, ischaemic myocardial fibrosis by LGE may be an imaging biomarker for predicting adverse outcomes in patients with diabetes.

In our meta-analysis, the results supported previous studies showing that participants with diabetes have a higher presence of myocardial fibrosis detected by LGE, especially ischaemic fibrosis. Importantly, in our included studies, the presence of myocardial fibrosis in symptomatic patients with diabetes was higher than that in asymptomatic patients with diabetes.<sup>2 3 17</sup> Current guidelines recommend that MRI may be a risk tool in asymptomatic patients with diabetes at moderate or high risk of cardiovascular disease.<sup>14</sup> However, the value of MRI in routine clinical stratification of cardiovascular risk is unclear. Notably, in our meta-analysis, focal ischaemic myocardial fibrosis detected by LGE did seem to predict a higher occurrence of MACCEs/MACEs in the future, and the annualized event rate for MACCEs/MACEs in patients with diabetes and LGE was 11.94%. Additionally, the presence of

1  
2  
3 ischaemic myocardial fibrosis indicated an 8-fold higher risk for death/MI even in asymptomatic patients  
4 with diabetes.<sup>2</sup> It must be noted that other techniques, such as ECG, have lower accuracy and sensitivity  
5 for detecting myocardial fibrosis than LGE.<sup>35 36</sup> Thus, this finding may highlight the value of LGE for  
6 screening for cardiovascular risk in symptomatic patients with diabetes.  
7  
8

9  
10 The risk of myocardial fibrosis in patients with diabetes is increased, and there are multiple factors that  
11 influence this relationship. First, patients with diabetes have a higher risk for coronary artery disease and  
12 myocardial dysfunction.<sup>37-39</sup> Moreover, hyperglycaemic metabolism, microvascular disease, and cardiac  
13 autonomic neuropathy are involved in the mechanisms of myocardial fibrosis.<sup>4 40 41</sup> However, many  
14 studies have shown that patients with diabetes have a high incidence of obesity, visceral fat,  
15 hyperlipidaemia, and insulin resistance, which may impair myocardial function.<sup>6 42 43</sup> Furthermore, the  
16 multiple risk factors described above should increase the myocardial fibrosis burden. In addition,  
17 myocardial fibrosis is widespread in subjects with diabetes and may be associated with a high risk for  
18 cardiovascular disease.  
19  
20  
21  
22

23 Although focal myocardial fibrosis translates to an adverse outcome in the future and is not fully clear,  
24 several potential mechanisms may lead to MACCEs/MACEs. First, patients with diabetes are more  
25 inclined to develop myocardial fibrosis, and myocardial fibrosis is associated with ventricular arrhythmia  
26 and heart failure.<sup>3 44-46</sup> Second, patients with diabetes and myocardial fibrosis usually have a greater  
27 burden of microvascular complications, such as myocardial ischaemia, which confers an increased risk  
28 of MACCEs/MACEs.<sup>16 47</sup> Additionally, the myocardial fibrosis detected by LGE, especially  
29 subendocardial fibrosis, indicates that patients with diabetes have had a subendocardial infarction in the  
30 past, which denotes a higher risk of MACEs in the future.<sup>48 49</sup> Furthermore, subjects with diabetes had  
31 higher LV and left atrial remodelling due to myocardial fibrosis.<sup>9 45 50</sup> For these reasons, the myocardial  
32 fibrosis detected by LGE has great potential to lead to adverse outcomes in the future.  
33  
34  
35  
36

37 As previously described, LGE-MRI has become a powerful noninvasive imaging method for the  
38 assessment of myocardial fibrosis.<sup>11</sup> Although two studies<sup>20 21</sup> included in our meta-analysis showed that  
39 ischaemic myocardial fibrosis detected by LGE did not increase the rate of MACCEs, our meta-analysis  
40 demonstrated that the presence of ischaemic myocardial fibrosis derived from LGE conferred an HR of  
41 3.75 for future MACCEs/MACEs in individuals with diabetes. This might be explained by the following  
42 reasons: limited patient numbers and a higher prevalence of cardiovascular disease at patient enrolment.  
43 Indeed, detecting myocardial fibrosis can be used to clinically assess myocardial damage and to stratify  
44 cardiovascular risk in participants with diabetes. To date, only one study, which screened for  
45 asymptomatic diabetes by LGE, showed that diabetes with ischaemic myocardial fibrosis conferred an  
46 8-fold higher risk for all-cause mortality and MI.<sup>2</sup> The prevalence of ischaemic myocardial fibrosis  
47 detected by LGE among patients with diabetes is higher than that among nondiabetic patients.<sup>3 30</sup>  
48 Therefore, patients with diabetes and ischaemic myocardial fibrosis might need aggressive management  
49 of cardiac and cerebrovascular risk factors.  
50  
51  
52  
53  
54

55 However, our meta-analysis has some limitations. First, in our meta-analysis, 2 studies<sup>20 21</sup> were from the  
56 same group of patients but reported different outcomes. However, when we excluded either of the above  
57 articles, the pooled HR and heterogeneity did not change significantly. Second, the incidence of  
58 myocardial fibrosis in patients with diabetes was not obtained via community-based epidemiology  
59  
60

1  
2  
3 research. Therefore, the prevalence of myocardial fibrosis may be higher in this study, which pooled  
4 studies including high-risk or average-risk populations with diabetes. Third, a previous study found that  
5 nonischaemic LGE is associated with increased myocardial mass, increased myocardial extracellular  
6 volume and impaired diastolic parameters.<sup>51</sup> However, subgroup analysis was not conducted to evaluate  
7 the effect of nonischaemic myocardial fibrosis on MACCEs/MACEs in patients with diabetes due to a  
8 lack of information. Further studies are needed to establish nonischaemic LGE lesions and their  
9 prognosis. Fourth, most studies selected in this meta-analysis reported adjusted HRs, and various  
10 adjustments for adverse outcomes among the selected studies may affect the pooled results. However,  
11 the heterogeneity among the selected studies was low, and publication bias did not exist. This might  
12 strengthen the clinical meaning of the pooled result. Finally, the incremental value of diabetes duration  
13 to the prevalence and incidence of LGE was not revealed. However, diabetes duration plays a central  
14 role in the assessment of cardiovascular risk.<sup>14 52</sup> Hence, prospective studies that evaluate the association  
15 between diabetes duration and myocardial fibrosis and determine the best time to screen myocardial  
16 fibrosis by LGE-CMR for risk stratification in patients with diabetes are needed.  
17  
18  
19  
20  
21  
22

### 23 CONCLUSIONS

24 In patients with diabetes, the presence of myocardial fibrosis detected by LGE-MRI, especially  
25 ischaemic lesions, was markedly associated with an important and increased risk of MACCEs/MACEs.  
26 Ischaemic myocardial fibrosis is a strong risk marker for improving risk stratification in patients with  
27 diabetes. The value of nonischaemic myocardial fibrosis in predicting MACCEs/MACEs in diabetes  
28 needs to be verified in future studies. This meta-analysis highlights the role of LGE-MRI in helping  
29 predict MACCEs/MACEs in complicated diabetic patients, especially those with cardiac complications  
30 and a high risk for myocardial fibrosis.  
31  
32  
33

### 34 REFERENCES

- 35  
36  
37 1 Cho NH, Shaw JE, Karuranga S, *et al.* IDF Diabetes Atlas: Global estimates of diabetes  
38 prevalence for 2017 and projections for 2045. *Diabetes research and clinical practice*  
39 2018;138:271-81.
- 40  
41 2 Elliott MD, Heitner JF, Kim H, *et al.* Prevalence and prognosis of unrecognized myocardial  
42 infarction in asymptomatic patients with diabetes: A two-center study with up to 5 years of  
43 follow-up. *Diabetes Care* 2019;42:1290-6.
- 44  
45 3 Giusca S, Kelle S, Nagel E, *et al.* Differences in the prognostic relevance of myocardial ischaemia  
46 and scar by cardiac magnetic resonance in patients with and without diabetes mellitus. *European*  
47 *heart journal cardiovascular Imaging* 2016;17:812-20.
- 48  
49 4 Jia G, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to  
50 This Clinical Entity. *Circulation research* 2018;122:624-38.
- 51  
52 5 Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular  
53 mechanisms and therapeutic opportunities. *Journal of molecular and cellular cardiology*  
54 2016;90:84-93.
- 55  
56 6 Marwick TH, Ritchie R, Shaw JE, *et al.* Implications of Underlying Mechanisms for the  
57 Recognition and Management of Diabetic Cardiomyopathy. *Journal of the American College of*  
58 *Cardiology* 2018;71:339-51.
- 59  
60 7 Adegate E, Singh J. Structural changes in the myocardium during diabetes-induced

- 1  
2  
3 cardiomyopathy. *Heart failure reviews* 2014;19:15-23.
- 4  
5 8 Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia- and insulin-  
6 resistance-induced heart disease. *Diabetologia* 2018;61:21-8
- 7  
8 9 Storz C, Hetterich H, Lorbeer R, *et al.* Myocardial tissue characterization by contrast-enhanced  
9 cardiac magnetic resonance imaging in subjects with prediabetes, diabetes, and normal controls  
10 with preserved ejection fraction from the general population. *European heart journal*  
11 *cardiovascular Imaging* 2018;19:701-8.
- 12  
13 10 Armstrong AC, Ambale-Venkatesh B, Turkbey E, *et al.* Association of Cardiovascular Risk  
14 Factors and Myocardial Fibrosis With Early Cardiac Dysfunction in Type 1 Diabetes: The  
15 Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and  
16 Complications Study. *Diabetes Care* 2017;40:405-11.
- 17  
18 11 Mewton N, Liu CY, Croisille P, *et al.* Assessment of myocardial fibrosis with cardiovascular  
19 magnetic resonance. *Journal of the American College of Cardiology* 2011;57:891-903.
- 20  
21 12 Hiromi Hashimura FK, Hatsue Ishibashi-Ueda, Yoshiaki Morita, *et al.* Radiologic-Pathologic  
22 Correlation of Primary and Secondary Cardiomyopathies:MR Imaging and Histopathologic  
23 Findings in Hearts from Autopsy and Transplantation. *Radiographics* 2017;37:719-36.
- 24  
25 13 Iles LM, Ellims AH, Llewellyn H, *et al.* Histological validation of cardiac magnetic resonance  
26 analysis of regional and diffuse interstitial myocardial fibrosis. *European heart journal*  
27 *cardiovascular Imaging* 2015;16:14-22.
- 28  
29 14 Cosentino F, Grant PJ, Aboyans V, *et al.* 2019 ESC Guidelines on diabetes, pre-diabetes, and  
30 cardiovascular diseases developed in collaboration with the EASD. *European heart journal*  
31 2020;41:255-323.
- 32  
33 15 Jensen MT, Fung K, Aung N, *et al.* Changes in Cardiac Morphology and Function in Individuals  
34 With Diabetes Mellitus: The UK Biobank Cardiovascular Magnetic Resonance Substudy.  
35 *Circulation Cardiovascular imaging* 2019;12:e009476.
- 36  
37 16 Heydari B, Juan YH, Liu H, *et al.* Stress Perfusion Cardiac Magnetic Resonance Imaging  
38 Effectively Risk Stratifies Diabetic Patients with Suspected Myocardial Ischemia. *Circulation:*  
39 *Cardiovascular Imaging* 2016;9:e004136.
- 40  
41 17 Kwong RY, Sattar H, Wu H, *et al.* Incidence and prognostic implication of unrecognized  
42 myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical  
43 evidence of myocardial infarction. *Circulation* 2008;118:1011-20.
- 44  
45 18 Yoon YE, Kitagawa K, Kato S, *et al.* Prognostic significance of unrecognized myocardial  
46 infarction detected with MR imaging in patients with impaired fasting glucose compared with  
47 those with diabetes. *Radiology* 2012;262:807-15.
- 48  
49 19 Yoon YE, Kitagawa K, Kato S, *et al.* Prognostic value of unrecognized myocardial infarction  
50 detected by late gadolinium-enhanced MRI in diabetic patients with normal global and regional  
51 left ventricular systolic function. *European radiology* 2013;23:2101-8.
- 52  
53 20 Bamberg F, Parhofer KG, Lochner E, *et al.* Diabetes mellitus: Long-term prognostic value of  
54 whole-body MR imaging for the occurrence of cardiac and cerebrovascular events. *Radiology*  
55 2013;269:730-7.
- 56  
57 21 Bertheau RC, Bamberg F, Lochner E, *et al.* Whole-Body MR Imaging Including Angiography:  
58 Predicting Recurrent Events in Diabetics. *European radiology* 2016;26:1420-30.
- 59  
60 22 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a  
proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE)



- group. *Jama* 2000;283:2008-12.
- 23 Hutton B, Salanti G, Caldwell DM, *et al*. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015;162:777-84.
- 24 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European journal of epidemiology* 2010;25:603-5.
- 25 Zeng X, Zhang Y, Kwong JS, *et al*. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *Journal of evidence-based medicine* 2015;8:2-10.
- 26 Mantovani A, Byrne CD, Bonora E, *et al*. Nonalcoholic Fatty Liver Disease and Risk of Incident Type 2 Diabetes: A Meta-analysis. *Diabetes Care* 2018;41:372-82.
- 27 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine* 2002;21:1539-1558.
- 28 Liu JL. The role of the funnel plot in detecting publication and related biases in meta-analysis. *Evidence-based dentistry* 2011;12:121-2.
- 29 Reinstadler SJ, Stiermaier T, Eitel C, *et al*. Relationship between diabetes and ischaemic injury among patients with revascularized ST-elevation myocardial infarction. *Diabetes, Obesity and Metabolism* 2017;19:1706-13.
- 30 Lindman BR, Davila-Roman VG, Mann DL, *et al*. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. *Journal of the American College of Cardiology* 2014;64:541-9.
- 31 Eitel I, Hintze S, De Waha S, *et al*. Prognostic impact of hyperglycemia in nondiabetic and diabetic patients with ST-elevation myocardial infarction: Insights from contrast-enhanced magnetic resonance imaging. *Circulation: Cardiovascular Imaging* 2012;5:708-18.
- 32 Donnino R, Patel S, Nguyen AH, *et al*. Comparison of quantity of left ventricular scarring and remodeling by magnetic resonance imaging in patients with versus without diabetes mellitus and with coronary artery disease. *American Journal of Cardiology* 2011;107:1575-8.
- 33 Lejeune S, Roy C, Slimani A, *et al*. Diabetic phenotype and prognosis of patients with heart failure and preserved ejection fraction in a real life cohort. *Cardiovasc Diabetol* 2021;20(1):48.
- 34 Kato S, Fukui K, Kodama S, *et al*. Incremental prognostic value of coronary flow reserve determined by phase-contrast cine cardiovascular magnetic resonance of the coronary sinus in patients with diabetes mellitus. *J Cardiovasc Magn Reson* 2020;22(1):73.
- 35 Ramos R, Albert X, Sala J, *et al*. Prevalence and incidence of Q-wave unrecognized myocardial infarction in general population: Diagnostic value of the electrocardiogram. The REGICOR study. *International journal of cardiology* 2016;225:300-5.
- 36 Barbier CE, Bjerner T, Johansson L, *et al*. Myocardial scars more frequent than expected: magnetic resonance imaging detects potential risk group. *Journal of the American College of Cardiology* 2006;48:765-71.
- 37 Bertoni AG, Goff Jr DC, D'Agostino Jr RB, *et al*. Diabetic cardiomyopathy and subclinical cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care* 2006;29:588-94.
- 38 Shivu GN, Phan TT, Abozguia K, *et al*. Relationship between coronary microvascular dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. *Circulation* 2010;121:1209-15.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
- 39 Campbell DJ, Somaratne JB, Jenkins AJ, *et al.* Impact of type 2 diabetes and the metabolic syndrome on myocardial structure and microvasculature of men with coronary artery disease. *Cardiovascular diabetology* 2011;10:80.
- 40 Tarquini R, Lazzeri C, Pala L, *et al.* The diabetic cardiomyopathy. *Acta diabetologica* 2011;48:173-81.
- 41 Gao Y, Yang ZG, Ren Y, *et al.* Evaluation of myocardial fibrosis in diabetes with cardiac magnetic resonance T1-mapping: Correlation with the high-level hemoglobin A1c. *Diabetes research and clinical practice* 2019;150:72-80.
- 42 Turkbey EB, Backlund JY, Genuth S, *et al.* Myocardial structure, function, and scar in patients with type 1 diabetes mellitus. *Circulation* 2011;124:1737-46.
- 43 Ng ACT, Strudwick M, van der Geest RJ, *et al.* Impact of Epicardial Adipose Tissue, Left Ventricular Myocardial Fat Content, and Interstitial Fibrosis on Myocardial Contractile Function. *Circ Cardiovasc Imaging* 2018;11:e007372.
- 44 Anselmino M, Matta M, D'Ascenzo F, *et al.* Catheter ablation of atrial fibrillation in patients with diabetes mellitus: a systematic review and meta-analysis. *Europace* 2015;17:1518-25.
- 45 Gulsin GS, Kanagala P, Chan DCS, *et al.* Differential left ventricular and left atrial remodelling in heart failure with preserved ejection fraction patients with and without diabetes. *Therapeutic Advances in Endocrinology and Metabolism* 2019;10:2042018819861593.
- 46 Mordi I, Bezerra H, Carrick D, *et al.* The Combined Incremental Prognostic Value of LVEF, Late Gadolinium Enhancement, and Global Circumferential Strain Assessed by CMR. *JACC Cardiovascular imaging* 2015;8:540-9.
- 47 Sandesara PB, O'Neal WT, Kelli HM, *et al.* The Prognostic Significance of Diabetes and Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction. *Diabetes Care* 2018;41:150-5.
- 48 Schelbert EB, Cao JJ, Sigurdsson S, *et al.* Prevalence and prognosis of unrecognized myocardial infarction determined by cardiac magnetic resonance in older adults. *Jama* 2012;308:890-6.
- 49 Acharya T, Aspelund T, Jonasson TF, *et al.* Association of Unrecognized Myocardial Infarction With Long-term Outcomes in Community-Dwelling Older Adults: The ICELAND MI Study. *JAMA Cardiol* 2018;3:1101-6.
- 50 Cao Y, Zeng W, Cui Y, *et al.* Increased myocardial extracellular volume assessed by cardiovascular magnetic resonance T1 mapping and its determinants in type 2 diabetes mellitus patients with normal myocardial systolic strain. *Cardiovascular diabetology* 2018;17:7.
- 51 Bojer AS, Sørensen MH, Vejlstup N, *et al.* Distinct non-ischemic myocardial late gadolinium enhancement lesions in patients with type 2 diabetes. *Cardiovasc Diabetol* 2020;19(1):184.
- 52 Dabelea D, Stafford JM, Mayer-Davis EJ, *et al.* Association of Type 1 Diabetes vs Type 2 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage Years and Young Adulthood. *Jama* 2017;317:825-35.

## Figure legend

Figure 1. Flow chart of literature and study selection.

1  
2  
3  
4  
5  
6  
7 Figure 2. Forest plot and pooled estimates of the effect of myocardial fibrosis detected by LGE on  
8  
9 the risk of MACCEs or MACEs. LGE, late gadolinium enhancement; MACCEs, major adverse  
10  
11 cardiac and cerebrovascular events; MACEs, major adverse cardiac events; HR, hazard ratios; CI,  
12  
13 confidence interval.  
14  
15  
16  
17  
18  
19

20 Figure 3. Forest plots of 6 studies for pooled HR for MACCEs and MACEs in patients with  
21  
22 diabetes with normal LV ejection fraction and myocardial fibrosis detected by LGE. HR, hazard  
23  
24 ratio; LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular  
25  
26 events; MACEs, major adverse cardiac events; CI, confidence interval.  
27  
28  
29  
30  
31  
32

### 33 **Table legend**

34  
35  
36  
37  
38 Table 1. Description of the Studies Included in the Meta-Analysis  
39  
40  
41  
42

### 43 **Supplement legend**

44  
45  
46  
47  
48 Supplement Table S1. The exact search strategy was used in OvidSP.  
49  
50  
51  
52

53 Supplement Figure S1. Funnel plots of 8 eligible studies.  
54  
55  
56  
57

58 Supplement Figure S2. Forest plots of pooled HRs for MACCEs and MACEs in adjusted or not  
59  
60

1  
2  
3  
4 adjusted HR studies. HR, hazard ratios; MACCEs, major adverse cardiac and cerebrovascular  
5  
6 events; MACEs, major adverse cardiac events; HR, hazard ratios; CI, confidence interval.  
7  
8  
9

10  
11 Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCEs and MACEs  
12  
13 in patients with diabetes and different patterns of myocardial fibrosis detected by LGE. HR,  
14  
15 hazard ratios; LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and  
16  
17 cerebrovascular events; MACEs, major adverse cardiac events; CI, confidence interval.  
18  
19  
20  
21  
22  
23  
24

## 25 Notes

### 26 Author affiliations

- 27  
28  
29  
30 1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women  
31  
32 and Children of Ministry of Education, Sichuan University West China Second University  
33  
34 Hospital, Chengdu, China.  
35  
36  
37 2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.  
38  
39  
40 3. Key Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of  
41  
42 Ministry of Education, Sichuan University West China Second University Hospital, Chengdu,  
43  
44 China.  
45  
46  
47 4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.  
48  
49  
50  
51  
52

### 53 Funding

54  
55  
56 This work was supported by the National Natural Science Foundation of China (No. 81771887,  
57  
58 81771897, 81971586, 81901712); the Program for Young Scholars and Innovative Research Team  
59  
60

1  
2  
3  
4 in Sichuan Province (No. 2017TD0005) of China; and the 1-3-5 project for disciplines of excellence,  
5  
6 West China Hospital, Sichuan University (No. ZYGD18013).  
7  
8

9 **Compliance with ethical standards**

10  
11 Not applicable.  
12  
13  
14  
15  
16

17 **Conflict of interest**

18  
19 The authors report no conflicts of interest.  
20  
21  
22  
23

24 **Authors' contributions**

25 Zhi Yang and Rong Xu conceived of this study, participated in its design and coordination and  
26 drafted the manuscript. Contribution to the conceptualization and design: Jia-rong Wang, Hua-  
27 yan Xu, Hang Fu, Ling-jun Xie and Meng-xi Yang. Data analysis and interpretation: Lu Zhang,  
28 Ling-yi Wen, Hui Liu and Hong Li. Obtaining funding: Zhi-gang Yang and Ying-kun Guo.  
29 Zhi-gang Yang and Ying-kun Guo interpreted the results, critically revised the manuscript, and  
30 helped to and approved the final version. All authors read and approved this manuscript.  
31  
32  
33  
34  
35  
36

37 **Patient consent for publication**

38  
39 Not required.  
40  
41  
42  
43  
44

45 **Ethics approval**

46  
47 Ethics approval was not required for this meta-analysis.  
48  
49  
50  
51

52 **Provenance and peer review**

53  
54 Not commissioned; externally peer reviewed.  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**Data availability statement**

No additional data are available.

For peer review only

Table 1 Description of the Studies Included in the Meta-Analysis

First Author, Year	Journal	Patients	HbA1c, %	LGE Definition	DM (type)	Mean age (years)	Durations (years)	LVEF (%)	Follow-up duration (months)	Major LGE(+) (%)	Total events	Adjusted HR	Fibrosis type	Type design	Outcome	NO S		
Bertheau RC,2016	Eur Radiol Circ	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	8	YES	Ischaemic	Prospective, single-centre	MACC ES	7	
Heydari B,2016	Cardiovascular Imaging	173	7.9±1.8	2 SD	NA	61.7±1.9	NA	51.8±7.6	34.8±30	10	9	88	21	NO	Ischaemic	Prospective, single-centre	MACE S	7
Elliott MD,2019	Diabetes Care	120	NA	visual	1 and 2	52±13	17±11	63±9	46 (33-64)	65	23	19	YES	Ischaemic	Prospective, two-centre	MACE S	9	
Yoon YE,2013	Eur Radiol Eur	120	7.4±1.5	visual	2	67±9	11±11	63±6	27 (7-112)	83	18	10	NO	Ischaemic	Retrospective, single-centre	MACE S	7	
Giusca S,2016	Heart J Cardiova	328	NA	visual	NA	67±11	NA	57.7±1.6	35 (23-51.6)	25	0	176	26	YES	Ischaemic and	Prospective, single-centre	MACE S	8

bmjopen-2021-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

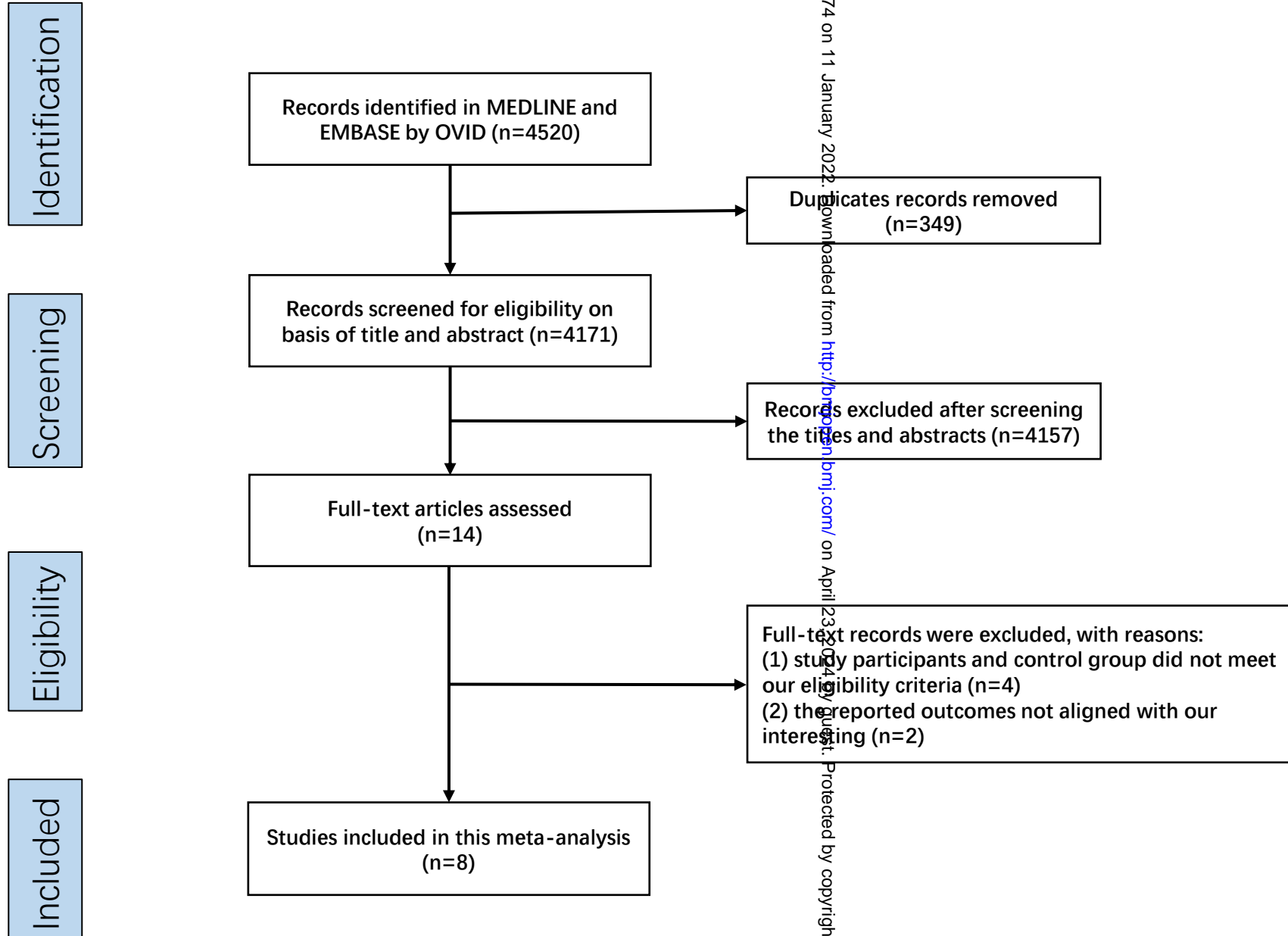
bmjopen-2021-055374 on 11 January 2022. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

sc Imaging														nonischaemic	multicentre		
Bamberg	Radiology	7.2 (6.5-7.9)	1	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	18	YES	Ischaemic	Prospective, single-centre	MACCES	7		
Kwon	Circulation	7.3±1.6	2 SD	10.7±8.5	NA	17 (6-57)	67	30	38	YES	Ischaemic and nonischaemic	Prospective, single-centre	MACCES	9			
Yoon	Radiology	7.4±1.6	visual	67±9	NA	14±11	NA	30(6-103)	11	3	58	24	NO	Ischaemic	Retrospective, single-centre	MACE S	6

Columns represent n(%) or mean±SD or median (IQR); DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NOS, Newcastle–Ottawa Scale; HR, hazard ratio; NR, not reported; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events.



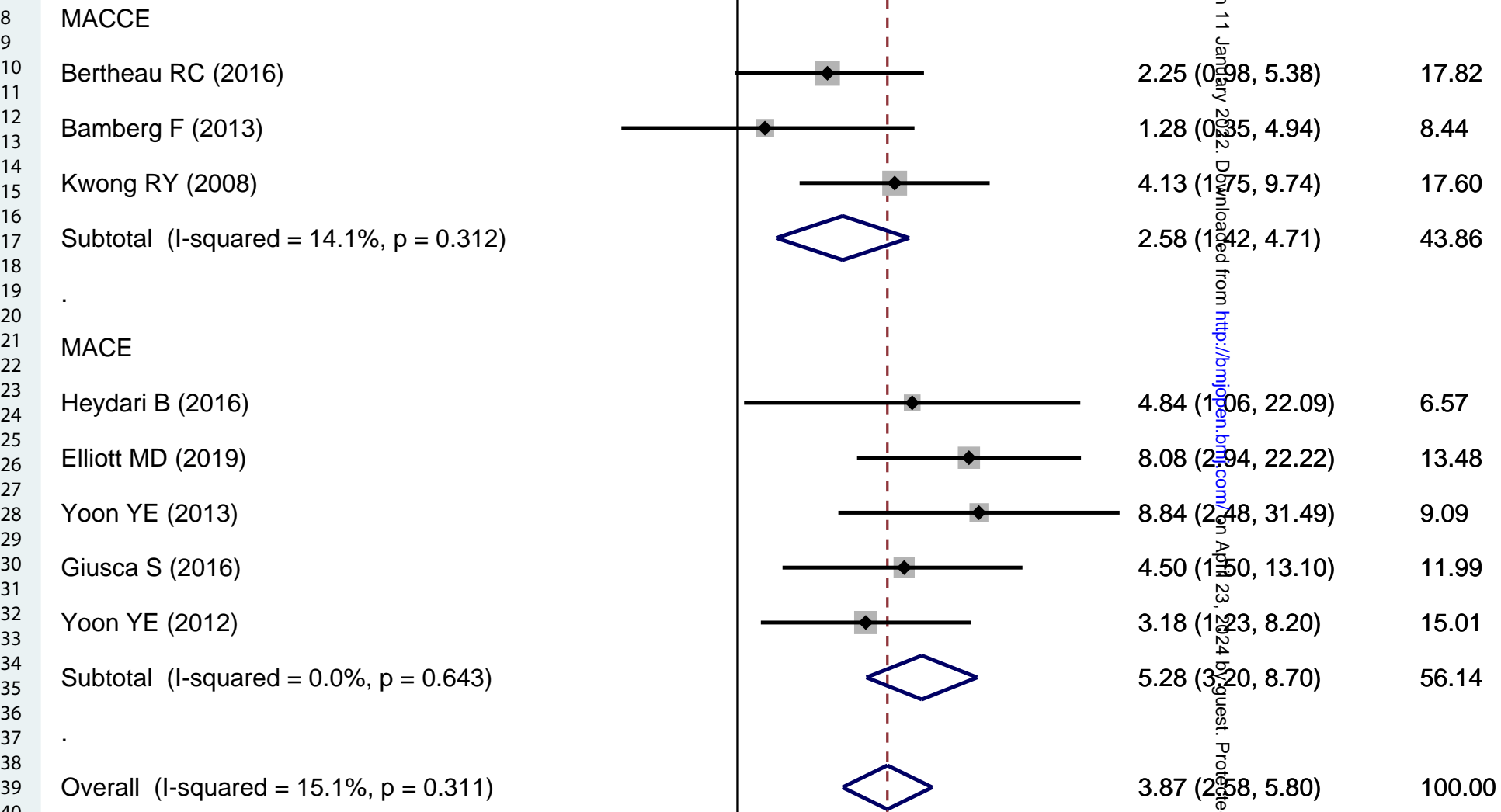


-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1 Study %  
 2  
 3 ID HR (95% CI) Weight



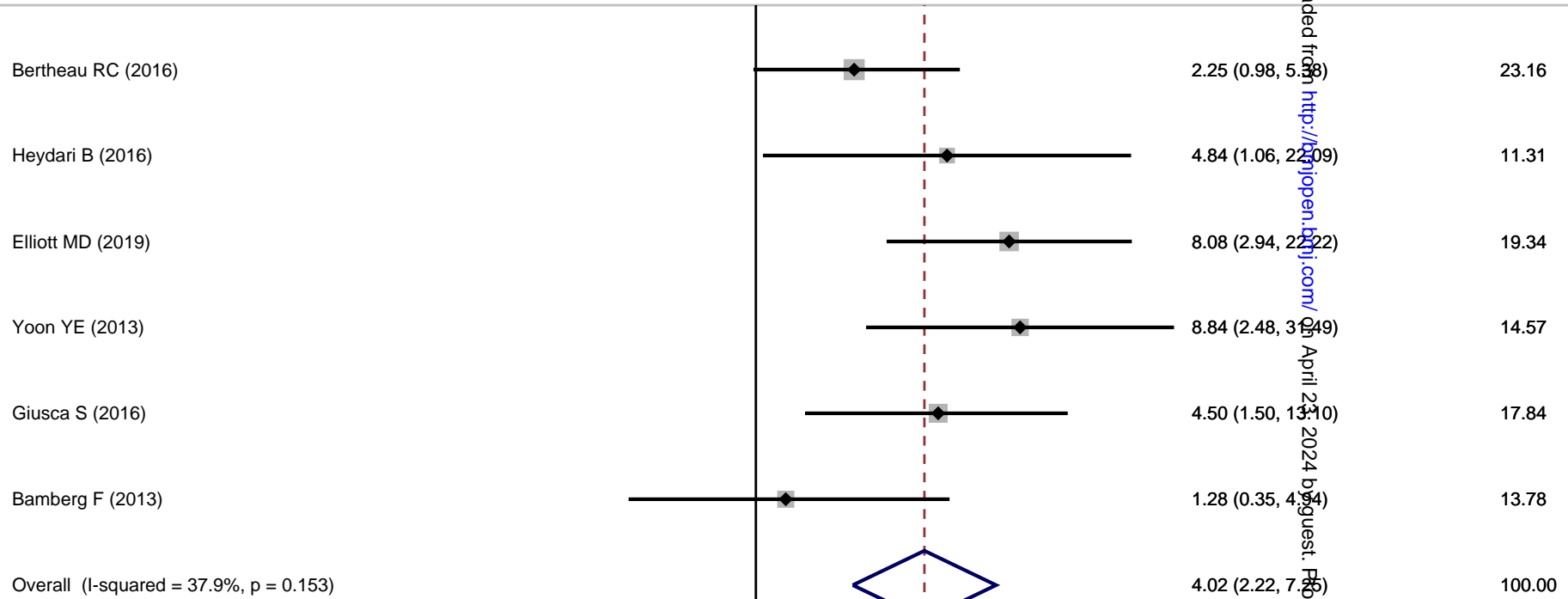
NOTE: Weights are from random effects analysis

.0318 1 31.5

55374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

Study				%
ID		HR (95% CI)		Weight



NOTE: Weights are from random effects analysis

**Supplement legend**

Supplement Table S1. The exact search strategy was used in OvidSP.

Supplement Table S2. The exact search strategy was used in PubMed.

Supplement Table S3. The exact search strategy was used in Cochrane Library.

Supplement Figure S1. Funnel plots of 8 eligible studies.

Supplement Figure S2. Forest plots of pooled HR for MACCE and MACE in adjusted or not adjusted HR studies. HR, Hazard Ratios; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, Hazard Ratios; CI, confidence interval.

Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCE and MACE in patients with diabetes and different pattern of myocardial fibrosis detected by LGE. HR, Hazard Ratios; LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; CI, confidence interval.

## Supplement Tab e S1-1

Search methodology

Search strategies

---

1 diabetes. ab, kw, ti.

2 diabetes mellitus. ab, kw, ti.

3 "diabetic\*". ab, kw, ti.

4 1 or 2 or 3

5 mri. ab, kw, ti.

6 MR. ab, kw, ti.

7 "magnetic resonance imag\*". ab, kw, ti.

8 cardiac magnetic resonance. ab, kw, ti.

9 cmr. ab, kw, ti.

1  
2  
3  
4  
5 10 late gadolinium enhancement. ab, kw, ti.  
6

7  
8 11 lge. ab, kw, ti.  
9

10  
11 12 delayed gadolinium enhancement. ab, kw, ti.  
12

13 13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12  
14

15  
16 14 prognosis. sh.  
17

18  
19 15 diagnosed. tw.  
20

21  
22 16 cohort:.mp.  
23

24  
25 17 predictor:.mp.  
26

27  
28 18 death.mp.  
29

30  
31 19 exp \*models, statistical/  
32

33  
34 20 14 or 15 or 16 or 17 or 18 or 19  
35

36  
37 21 4 and 13 and 20  
38

39  
40 22 limit 21 to English language [Limit not valid in CDSR, CCA, CLCMR; records were retained]  
41  
42  
43  
44  
45  
46

1  
2  
3  
4  
5 23 limit 22 to human [Limit not valid in CDSR, CCA, CLCMR; records were retained]  
6

7  
8 24 limit 23 to journal article [Limit not valid in CDSR, CCA, Embase; records were retained]  
9

10  
11 25 limit 24 to (embase or medline) [Limit not valid in CDSR, CCA, CLCMR, Ovid MEDLINE(R); records were retained]  
12

---

13 1 to 25 were performed in OvidSP platform.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

## Supplement Table S1-2

Search methodology

Search strategies

---

1 diabetes[Title/Abstract]

2 "diabetes mellitus"[Title/Abstract]

3 "diabetic\*"[Title/Abstract]

4 1 or 2 or 3

5 mri[Title/Abstract]

6 MR[Title/Abstract]

7 "magnetic resonance imag\*"[Title/Abstract]

8 "Magnetic Resonance Imaging"[MeSH Terms]

9 "cardiac magnetic resonance"[Title/Abstract]



1  
2  
3  
4  
5 10 cmr[Title/Abstract]  
6

7  
8 11 "late gadolinium enhancement" [Title/Abstract]  
9

10  
11 12 LGE[Title/Abstract]  
12

13 13 "delayed gadolinium enhancement"[ Title/Abstract]  
14

15  
16 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13  
17

18 15 prognosis[ MeSH Terms]  
19

20  
21 16 diagnosed[Title/Abstract]  
22

23  
24 17 cohort:[MeSH Terms]  
25

26 18 "predictor\*" [Title/Abstract]  
27

28  
29 19 death[MeSH Terms]  
30

31 20 models, statistical[MeSH Terms]  
32

33  
34 21 15 or 16 or 17 or 18 or 19 or 20  
35

36  
37 22 4 and 14 and 21  
38  
39  
40  
41  
42  
43  
44  
45  
46

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

23 "english and humans"[Filter]

24 22 and 23

25 journal article[Filter]

26 24 and 25

---

1 to 26 were performed in PubMed.

For peer review only

## Supplement Tabe S1-3

Search methodolog

Search strategies

---

1 diabetes:ti,ab,kw

2 "diabetes mellitus":ti,ab,kw

3 "diabetic\*":ti,ab,kw

4 1 or 2 or 3

5 mri:ti,ab,kw

6 MR:ti,ab,kw

7 "magnetic resonance imag\*":ti,ab,kw

8 "Magnetic Resonance Imaging"[MeSH Terms]

9 "cardiac magnetic resonance":ti,ab,kw

1  
2  
3  
4  
5 10 cmr:ti,ab,kw  
6

7  
8 11 "late gadolinium enhancement" :ti,ab,kw  
9

10 12 LGE:ti,ab,kw  
11

12 13 "delayed gadolinium enhancement":ti,ab,kw  
13  
14

15 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13  
16  
17

18 15 prognosis[ MeSH Terms]  
19  
20

21 16 diagnosed:ti,ab,kw  
22

23 17 cohort:[MeSH Terms]  
24  
25

26 18 "predictor\*":ti,ab,kw  
27  
28

29 19 death[MeSH Terms]  
30

31 20 models, statistical[MeSH Terms]  
32  
33

34 21 15 or 16 or 17 or 18 or 19 or 20  
35

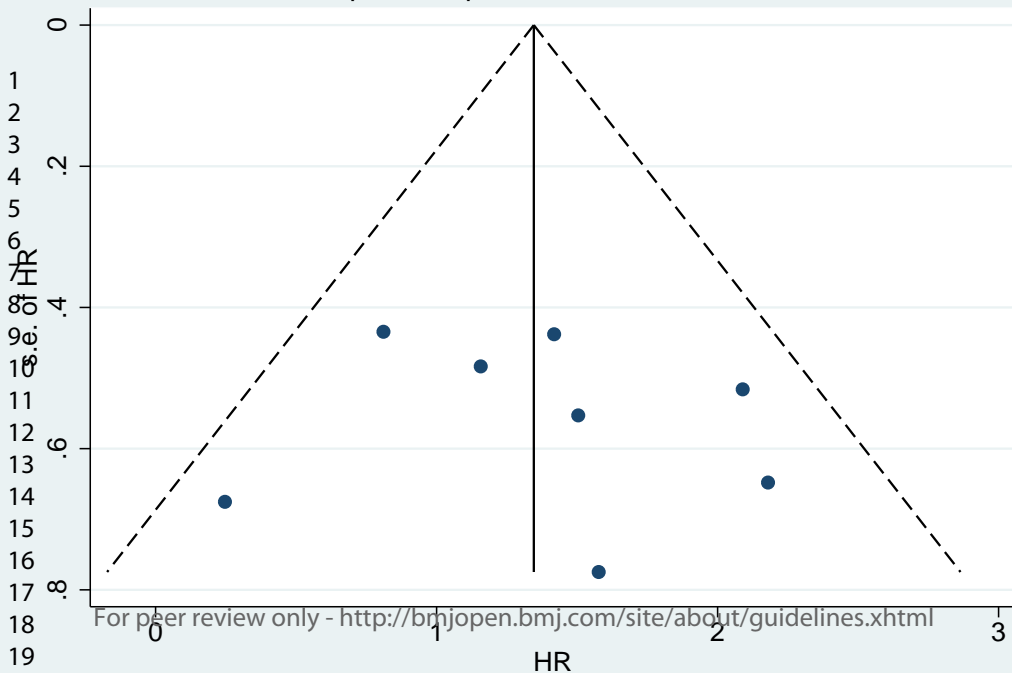
36 22 4 and 14 and 21  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

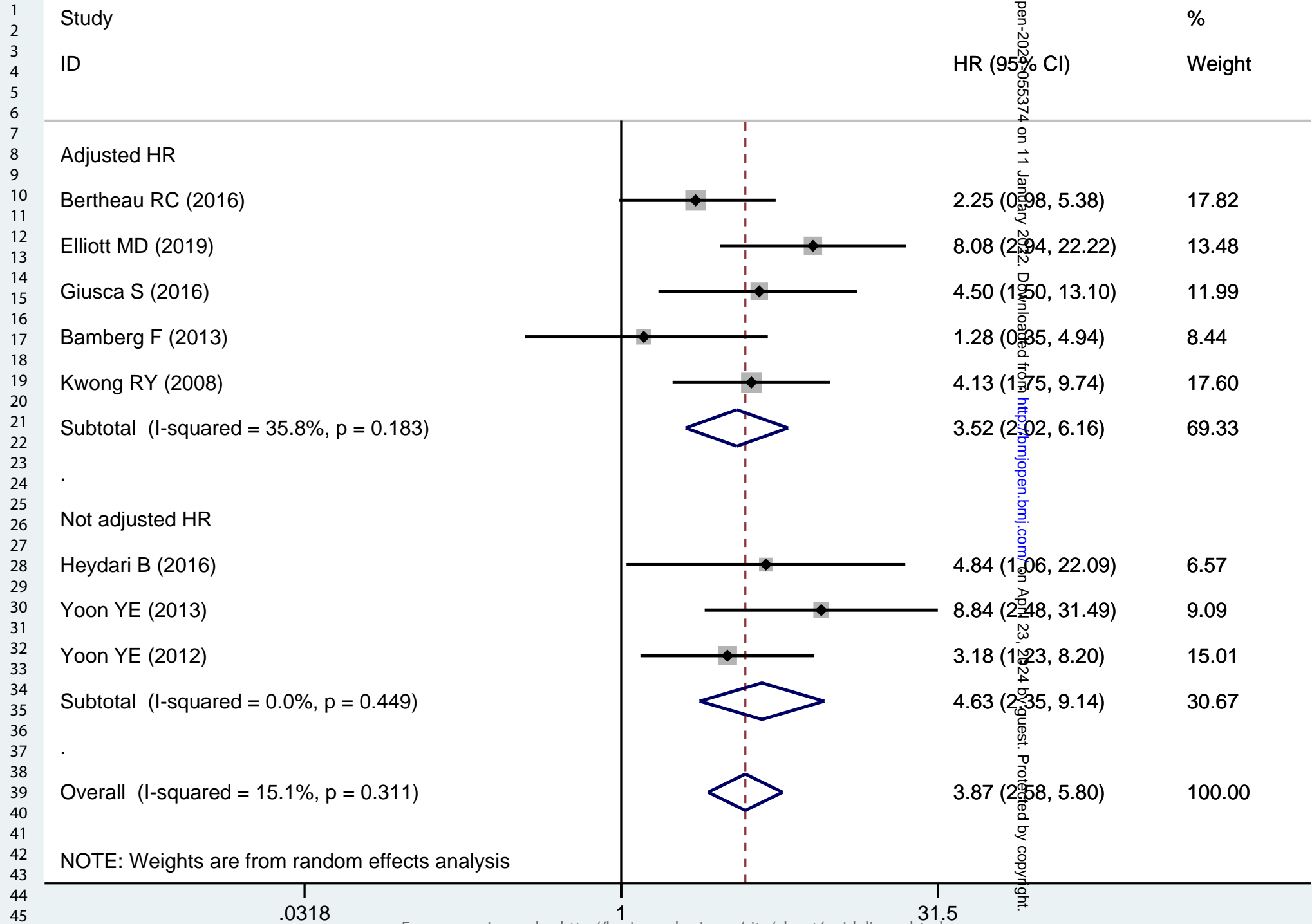
---

1 to 26 were performed in Cochrane Library.

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46





NOTE: Weights are from random effects analysis

.0318

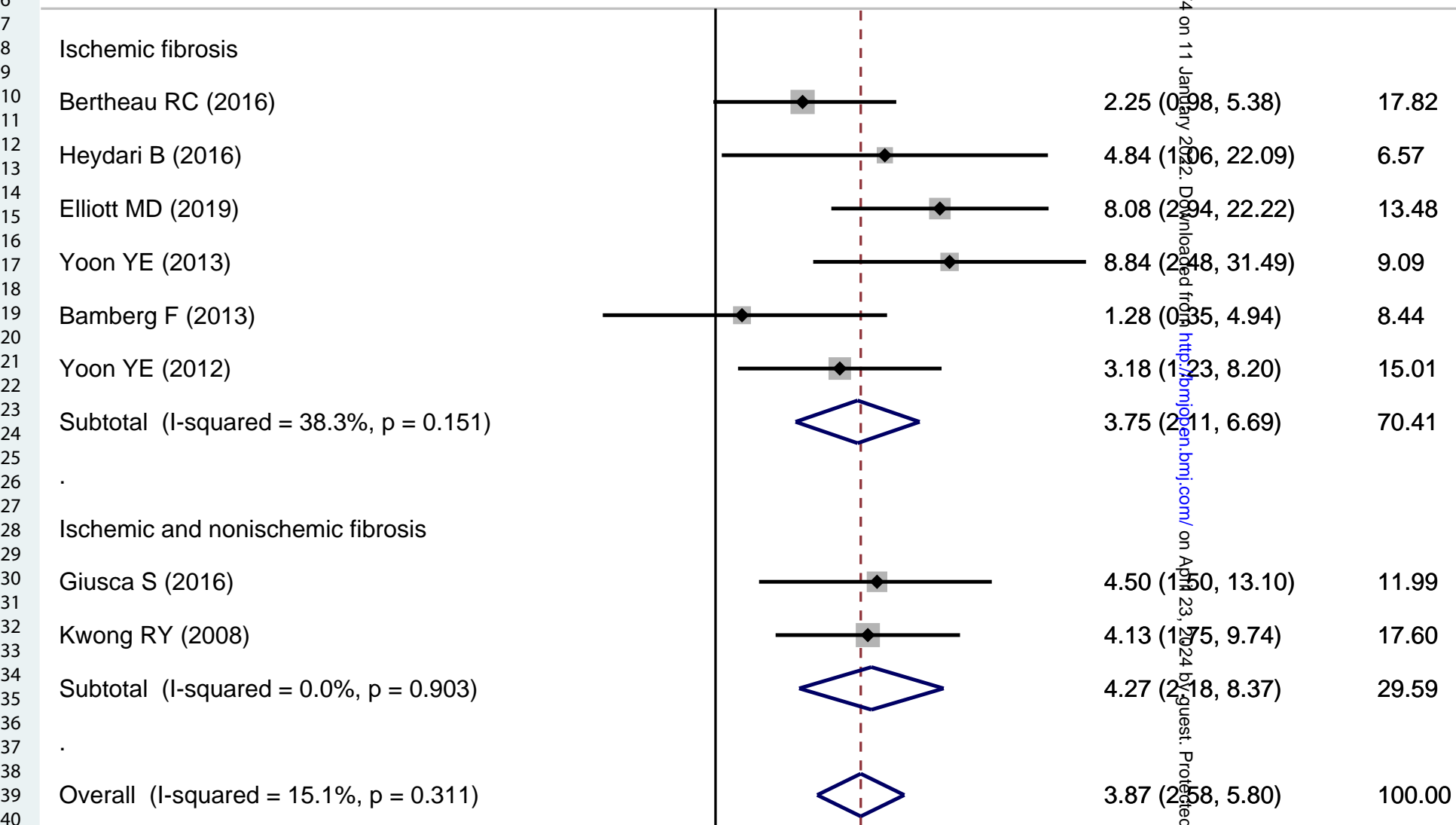
1

31.5

1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1 Study %  
 2  
 3 ID HR (95% CI) Weight



NOTE: Weights are from random effects analysis

.0318 1 31.5



## MOOSE Checklist

### Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Corresponding Author :

Yingkun Guo, MD, PHD

Department of Radiology, Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education; West China Second University Hospital, Sichuan University,

Address: 20# South Renmin Road, Chengdu, Sichuan 610041, China.

Phone No: +86-18980006572

Fax No: +86 28-85502946(H)

Email Address: gykpanda@163.com

Criteria		Brief description of how the criteria were handled in the meta-analysis
<b>Reporting of background should include</b>		
√	Problem definition	Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.
√	Hypothesis statement	LGE is associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) or major adverse cardiac events (MACE) in patients with diabetes.
√	Description of study outcomes	MACCE/MACE
√	Type of exposure or intervention used	LGE-MRI
√	Type of study designs used	We included case-control studies, prospective cohort studies, retrospective studies, and randomized controlled studies.
√	Study population	Patients with diabetes.

<b>Reporting of search strategy should include</b>		
√	Qualifications of searchers	The credentials of the two investigators ZY and RX are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	See the section of “Data Sources and Searches” in the article.
√	Databases and registries searched	PubMed and EMBASE, Cochrane Library
√	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list is available upon request.
√	Method of addressing articles published in languages other than English	Articles published in the English language were included.
√	Method of handling abstracts and unpublished studies	Only studies published in peer-reviewed journals were included.
√	Description of any contact with authors	Not.
<b>Reporting of methods should include</b>		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and HR (95% CI).
√	Assessment of confounding	We extracted the adjustment HR if the study reported the HR with adjustment models.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
√	Assessment of heterogeneity	To analyze the heterogeneity of the included studies, we used forest plots and the $I^2$ statistic.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 1 summary table detailing the search strategy used for database search, 1 flow chart, 1 summary

		table, 4 forest plots, 1 funnel plots.
	<b>Reporting of results should include</b>	
√	Graph summarizing individual study estimates and overall estimate	Figure 1
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Figure 2
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, $I^2$ values and results of sensitivity analyses.
	<b>Reporting of discussion should include</b>	
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
√	Justification for exclusion	We excluded reviews, abstracts, animal studies, case reports, and cross-sectional studies.
√	Assessment of quality of included studies	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
	<b>Reporting of conclusions should include</b>	
√	Consideration of alternative explanations for observed results	In this article, we discussed the potential reasons that patients with diabetes have more myocardial fibrosis than who without diabetes. In addition, we discussed the myocardial fibrosis detected by LGE-MRI may increase the risk of MACCE/MACE, and the limitations of our study.
√	Generalization of the conclusions	The presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted.
√	Guidelines for future research	Myocardial fibrosis detected by LGE-MRI may be a risk marker for improving risk stratification in patients with diabetes.
√	Disclosure of funding source	This work was supported by the National Natural Science Foundation of China (No. 81771887, 81771897, 81971586, 81901712); the Program for Young Scholars and Innovative Research Team in Sichuan Province (No. 2017TD0005) of China; and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (No.ZYGD18013).

# BMJ Open

## Association of myocardial fibrosis detected by late gadolinium-enhanced MRI with clinical outcomes in patients with diabetes: a systematic review and meta-analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-055374.R3
Article Type:	Original research
Date Submitted by the Author:	05-Dec-2021
Complete List of Authors:	<p>Yang, Zhi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education; Chengdu Fifth People's Hospital, Department of Radiology</p> <p>Xu, Rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Wang, Jia-rong; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Xu, Hua-yan; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Fu, Hang; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Xie, Ling-jun; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Yang, Meng-xi ; Sichuan University West China Hospital, Department of Radiology</p> <p>Zhang, Lu; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Wen, Ling-yi; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Liu, Hui; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p> <p>Li, Hong; Sichuan University West China Second University Hospital, Key Laboratory of Obstetrics&amp;Gynecology and Pediatric Disease and Birth Defects of Ministry of Education</p> <p>Yang, Zhi-gang; Sichuan University West China Hospital, Department of Radiology</p> <p>Guo, Ying-kun ; Sichuan University West China Second University Hospital, Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education</p>

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

<b>&lt;b&gt;Primary Subject Heading&lt;/b&gt;:</b>	Radiology and imaging
Secondary Subject Heading:	Diabetes and endocrinology, Cardiovascular medicine
Keywords:	RADIOLOGY & IMAGING, Cardiovascular imaging < RADIOLOGY & IMAGING, Magnetic resonance imaging < RADIOLOGY & IMAGING, DIABETES & ENDOCRINOLOGY

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Association of myocardial fibrosis detected by late gadolinium-enhanced MRI with clinical outcomes in patients with diabetes: a systematic review and meta-analysis

Zhi Yang<sup>1,2\*</sup>, MS; Rong Xu<sup>1\*</sup>, MS; Jia-rong Wang<sup>1</sup>, MD; Hua-yan Xu<sup>1</sup>, MD; Hang Fu<sup>1</sup>, MS; Ling-jun Xie<sup>1</sup>, MS; Meng-xi Yang<sup>4</sup>, MS; Lu Zhang<sup>1</sup>, MS; Ling-yi Wen<sup>1</sup>, MD; Hui Liu<sup>1</sup>, MS; Hong Li<sup>3</sup>, MD; Zhi-gang Yang<sup>4†</sup>, MD; Ying-kun Guo<sup>1†</sup>, MD

1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.
3. Key Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of Ministry of Education, Sichuan University West China Second University Hospital, Chengdu, China.
4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.

\* **These authors contributed equally to this work and should be considered the co-first authors.**

† **Guarantor and correspondent:**

**These two authors contributed equally to this work and should be considered corresponding authors.**

### Zhigang Yang, PhD, MD

Department of Radiology, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, No.37 Guoxue Xiang, Chengdu, 610041, China

Tel: +86-28-85423817(O)

E-mail: yangzg666@163.com

### Yingkun Guo, MD

Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, West China Second University Hospital, Sichuan University, 20# Section 3 South Renmin Road, Chengdu, 610041, China

Tel: +86-28-85503275(O)

E-mail: [gykpanda@163.com](mailto:gykpanda@163.com)

## ABSTRACT

**Objective** This meta-analysis assessed the associations of myocardial fibrosis detected by late gadolinium-enhanced (LGE)-MRI with the risk of major adverse cardiac and cerebrovascular events (MACCEs) and major adverse cardiac events (MACEs) in patients with diabetes.

**Design** Systematic review and meta-analysis reported in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

**Data sources** We searched the MEDLINE, Embase and Cochrane by Ovid databases for studies

published up to Aug 27, 2021.

**Eligibility criteria** Prospective or respective cohort studies were included if they reported the hazard ratio (HR) and 95% confidence intervals (CI) for MACCEs/MACEs in patients with either type 1 or 2 diabetes and LGE-MRI-detected myocardial fibrosis compared with patients without LGE-MRI-detected myocardial fibrosis and if the articles were published in the English language.

**Data extraction and synthesis** Two review authors independently extracted data and assessed the quality of the included studies. Pooled hazard ratios (HR) and 95% confidence intervals (CIs) were analysed using a random effects model. Heterogeneity was assessed using forest plots and  $I^2$  statistics.

**Results** Eight studies with 1121 patients with type 1 or type 2 diabetes were included in this meta-analysis, and the follow-up ranged from 17 to 70 months. The presence of myocardial fibrosis detected by LGE-MRI was associated with an increased risk for MACCEs (HR: 2.58; 95% CI 1.42-4.71;  $P=0.002$ ) and MACEs (HR: 5.28; 95% CI 3.20-8.70;  $P<0.001$ ) in patients with diabetes. Subgroup analysis revealed that ischaemic fibrosis detected by LGE was associated with MACCEs (HR 3.80, 95% CI 2.38-6.07;  $P<0.001$ ) in patients with diabetes.

**Conclusions** This study demonstrated that ischaemic myocardial fibrosis detected by LGE-MRI was associated with an increased risk of MACCEs/MACEs in patients with diabetes and may be an imaging biomarker for risk stratification. Whether LGE-MRI provides incremental prognostic information with respect to MACCEs/MACEs over risk stratification by conventional cardiovascular risk factors requires further study.

**Keywords:** Magnetic Resonance Imaging, Diabetes, Meta-analysis, Systemic review

#### **Strengths and limitations of this study**

\*This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) statement.

\*All included studies were not community-based epidemiology research and came from developed countries.

\*Reduced LVEF and nonischaemic subgroup analyses were not performed due to the limited number of related studies.

#### **INTRODUCTION**

Diabetes is becoming a global health care problem, and it is estimated that there will be 693 million individuals with diabetes by 2045.<sup>1</sup> Patients with diabetes have a higher prevalence of ischemic myocardial fibrosis and non-ischemic myocardial fibrosis than their nondiabetic counterparts, and the mechanism has been confirmed extensively.<sup>2-5</sup> The phenotype of unrecognized ischemic myocardial fibrosis in patients with diabetes was well studied and was associated with 4-8 folds increase in the risk of major adverse cardiac events (MACEs).<sup>2-3</sup> However, even without myocardial ischaemia, hyperglycaemia, oxidative stress, and inflammation may lead to diffuse interstitial and non-ischemic myocardial fibrosis in patients with diabetes.<sup>6-8</sup> In addition, diffuse interstitial myocardial fibrosis can increase the risk of non-ischemic myocardial fibrosis, and was associated with increased risk of left ventricular (LV) dysfunction in patients with diabetes.<sup>9-10</sup> However, Non-ischemic myocardial fibrosis, may be a biomarker for risk stratification, has not been systematically characterized.<sup>3-9</sup>



1  
2  
3  
4  
5 Among detectors of myocardial fibrosis, late gadolinium-enhanced magnetic resonance imaging (LGE-MRI) is the most reliable tool for identifying and quantifying focal myocardial fibrosis in vivo and allows discrimination between ischaemic and nonischaemic fibrosis without ionizing radiation.<sup>11-13</sup> LGE-MRI, a promising technique, can provide more histological information than unenhanced cardiac MRI to illuminate the complex pathophysiologic pathways of myocardial viability.<sup>3</sup> While LGE-MRI is limited by its sensitivity and accuracy for detection of diffuse myocardial fibrosis, the role of T1-mapping MRI technique in quantifying myocardial fibrosis has been validated.<sup>12 13</sup> Furthermore, recent guidelines suggested that MRI may be considered an imaging technique for stratifying cardiovascular risk in patients with diabetes.<sup>14 15</sup> This may highlight the role of LGE-MRI in the risk stratification of patients with diabetes.

18  
19 Approximately 19% of asymptomatic patients with diabetes have myocardial fibrosis upon LGE-MRI.<sup>2</sup> Although several studies have demonstrated that focal myocardial fibrosis detected by LGE-MRI may predict MACEs in patients with diabetes, the prognostic value of focal myocardial fibrosis for major cardiac and cerebrovascular events (MACCEs) is unclear.<sup>3 16-21</sup> In addition, most previous studies were single-centre studies and have been limited by small numbers of events. Consequently, we performed a meta-analysis to assess the association of LV myocardial fibrosis detected by LGE-MRI with future MACCEs and MACEs in patients with diabetes.

## 28 29 **METHODS**

30 This meta-analysis was performed in accordance with the guidelines of the Meta-analysis of  
31 Observational Studies in Epidemiology (MOOSE) statement.<sup>22 23</sup>

### 32 33 **Data Sources and Searches**

34 We searched the Ovid MEDLINE, Ovid Embase and Ovid Cochrane Library databases to find eligible  
35 studies published up to Aug 27, 2021. The search strategy included the following keywords: “diabetes”,  
36 “diabetes mellitus”, “MR”, “cardiac magnetic resonance”, “CMR”, “gadolinium”, “LGE”, “prognosis”,  
37 “diagnosed”, “predictor”, and “death”. The details of the search strategy used for Ovid are available in  
38 Supplemental Tables S1-S3. In addition, only articles published in peer-reviewed journals and published  
39 in the English language were included.

### 40 41 42 **Study Selection**

43 All articles were independently screened by two reviewers (ZY, RX), and any disagreement was resolved  
44 by consensus. The inclusion criteria were as follows: the design was a prospective or retrospective cohort  
45 study; the populations were patients with diabetes, and exposure to myocardial fibrosis was detected by  
46 LGE-MRI; the outcomes used composite endpoints including all-cause mortality, cardiac and  
47 cerebrovascular disease, late coronary revascularization, and hospitalization for unstable angina; the  
48 study reported the hazard ratio (HR) and 95% confidence intervals (CI) and had  $\geq 12$  months of follow-  
49 up. We excluded reviews, abstracts, animal studies, case reports, and cross-sectional studies.  
50 Additionally, if the cases were reported more than once, we included the study with the most  
51 comprehensive information. The reviewers independently screened the titles first, then the abstracts, and  
52 finally the full texts.

### 53 54 55 **Data Extraction and Quality Assessment**

56 We extracted the following data from each included study: author, year of publication, sample size, study  
57 design, age, LGE-MRI-detected myocardial fibrosis status, follow-up duration, outcome, and HR (95%  
58  
59  
60

1  
2  
3 CI). Additionally, we extracted the adjusted HR if the study reported the HR with adjustment models.  
4 All of the included studies were prospective or retrospective cohort designs, and we used the Newcastle  
5 Ottawa Scale (NOS) to judge the quality of the studies, as this tool is usually used for evaluating the  
6 quality of cohort studies in meta-analyses.<sup>24 25</sup> The scale uses a maximum of 9 points involving 3 factors:  
7 patient selection (0 to 4 points), comparability (0 to 2 points), and outcome (0 to 3 points).<sup>26</sup> We  
8 categorized the quality of studies as low (0 to 3 scores), moderate (4 to 6 scores), and high (7 to 9 scores).  
9

### 11 **Data Synthesis and Analysis**

12 In this meta-analysis, the outcome measure was the prevalence of future adverse cardiac and/or  
13 cerebrovascular events among diabetes patients with LGE—MRI-detected myocardial fibrosis compared  
14 with those without LGE-MRI-detected myocardial fibrosis. We defined the primary endpoint as  
15 MACCEs, including myocardial infarction (MI), all-cause mortality, coronary and carotid  
16 revascularization, heart failure, ventricular arrhythmias, unstable angina, cardiac and cerebrovascular  
17 death, and cerebrovascular disease. The secondary endpoints were MACEs, including all-cause mortality,  
18 cardiac death, MI, heart failure, unstable angina, and ventricular arrhythmias. Additionally, the pattern  
19 of myocardial fibrosis was classified as ischaemic fibrosis or nonischaemic fibrosis as described  
20 previously.<sup>3</sup>  
21  
22  
23  
24

25 We pooled the adjusted HRs with 95% CIs using a random effects model. In addition, we calculated the  
26 annualized event rates by dividing the total events by the median follow-up periods. To analyse the  
27 heterogeneity of the included studies, we used forest plots and the  $I^2$  statistic.<sup>27</sup> We assigned  $I^2$  values of  
28 0 ~ 25%, ~ 50%, ~ 75% for low, medium, and high heterogeneity of studies, respectively. Considering  
29 the heterogeneity of the included studies, we conducted sensitivity analyses by omitting 1 article to assess  
30 the influence of a single study. In particular, subgroup analyses were performed by outcome and the  
31 pattern of myocardial fibrosis. Additionally, a funnel plot was used to assess the publication bias of the  
32 included studies.<sup>28</sup> The analyses were performed with Stata version 12 (StataCorp). *P* values were two  
33 sided, with a level of 0.05 considered significant.  
34  
35  
36  
37

### 38 **Patient and Public Involvement**

39 No patient involved.  
40  
41

## 42 **RESULTS**

### 43 **Literature Search**

44 Based on the selection strategy, we found 4520 citations. Of these, 349 duplicate studies were excluded.  
45 After screening the title and abstract, 14 articles remained for assessment of the full text. Six studies<sup>29-34</sup>  
46 were excluded for the following reasons: studies without our outcome of interest, study populations did  
47 not meet our inclusion criteria, and studies did not report the HR. Ultimately, 8 studies<sup>2 3 16-21</sup> fulfilled  
48 our inclusion criteria and were included in this meta-analysis (Fig. 1).  
49  
50

### 51 **Study Characteristics**

52 In aggregate, 8 studies were analysed, including a total of 1121 patients with diabetes (median age  
53 ranging from 52 to 67; 67% were men) who underwent LGE-MRI and whose follow-up duration ranged  
54 from 17 to 70 months. Across the 8 studies, 6 articles<sup>2 17-21</sup> reported the duration of diabetes, and the  
55 mean duration of diabetes was 15 years. A total of 6 studies<sup>2 3 16 19-21</sup> reported the LV ejection fraction,  
56 and the mean LV ejection fraction was 57.78%. The presence of LGE-MRI-detected myocardial fibrosis  
57 was evaluated by visual analysis in 6 studies.<sup>2 3 18-21</sup> All of the included studies reported multiple clinical  
58  
59  
60

1  
2  
3 outcomes. The main characteristics of the included articles are shown in Table 1.  
4

5  
6 Among the 8 selected studies, 6 studies<sup>16-21</sup> (75%) were conducted in a single centre (Germany, n=2;  
7 USA, n=2; Japan, n=2), and 2 studies<sup>2,3</sup> were performed in multiple centres (USA, n=1; Europe, n=1).  
8 Five articles<sup>2,3,17,20,21</sup> (62.5%) reported adjusted HR. Seven studies<sup>2,16-21</sup> reported patients with ischaemic  
9 fibrosis, and the remaining 1 studies<sup>3</sup> reported patients with ischaemic and nonischaemic fibrosis.  
10

11  
12 Of the 8 eligible studies, 7 received NOS scores between 7 and 9, and the overall mean NOS score was  
13 7.5. Overall, the aforementioned analysis showed that the included articles had high quality (Table 1).  
14 Among the identified studies, there was no risk of publication bias according to a visual analysis of the  
15 funnel plot (Supplemental Fig. S1).  
16

### 17 **Prevalence of LGE-MRI-detected myocardial fibrosis and annualized event rates**

18  
19 Across the 8 studies, the prevalence of myocardial fibrosis detected by LGE-MRI ranged from 15% to  
20 62%, and the prevalence of LGE-MRI-detected myocardial fibrosis in the total sample was 38.09%  
21 (n=427). Furthermore, a total of 164 events occurred in the diabetes group (n=1121) during the median  
22 follow-up of 3.4 years. Patients with diabetes had annualized event rates for MACCEs of 4.3%.  
23

24  
25 Additionally, 3 studies<sup>2,19,21</sup> reported a total of 301 patients with diabetes, and 19.27% (n=58) of patients  
26 with diabetes had LGE-MRI-detected myocardial fibrosis. Twenty-seven events occurred in these  
27 diabetic patients with LGE—MRI-detected myocardial fibrosis over a median follow-up of 3.9 years.  
28 The annualized event rate of patients with diabetes and LGE-MRI-detected myocardial fibrosis was  
29 11.94%.  
30

### 31 **MACCEs and MACEs**

32  
33 A total of 8 studies reported the outcome of MACCEs or MACEs, and the presence of myocardial fibrosis  
34 detected by LGE-MRI was a strong predictor of MACCEs and MACEs in patients with diabetes (random  
35 effects HR 3.87, 95% CI 2.58-5.80; P<0.0001) (Fig. 2). There was low heterogeneity (I<sup>2</sup>=15.1%, P=0.311)  
36 in the meta-analysis. In addition, sensitivity analysis performed by excluding 1 study at a time did not  
37 reveal any significant changes in the HR values.  
38

39  
40 In the analysis of the outcome of MACCEs, 3 articles<sup>17,20,21</sup> were included in this subgroup analysis,  
41 including 64 participants with LGE-MRI-detected myocardial fibrosis and 165 without LGE-MRI-  
42 detected myocardial fibrosis, with a total of 64 MACCEs during the follow-up period. Myocardial  
43 fibrosis detected by LGE-MRI was associated with an increased risk of MACCEs in patients with  
44 diabetes. The pooled HR obtained via the random effects model was 2.58 (95% CI 1.42-4.71; P=0.002),  
45 with no evidence of heterogeneity (I<sup>2</sup>=14.1%; P=0.312) (Fig. 2).  
46  
47  
48

49  
50 To explore the association between myocardial fibrosis and the outcome of MACEs in patients with  
51 diabetes, we included 5 articles<sup>2,3,16,18,19</sup> that provided a subgroup outcome analysis of MACEs. The  
52 results showed that the presence of LGE-MRI-detected myocardial fibrosis in diabetes was associated  
53 with a significantly higher risk of MACEs. As in the discovery analyses, the pooled HR obtained via the  
54 random effects model was 5.28 (95% CI 3.20-8.70; P<0.001), with no significant heterogeneity (I<sup>2</sup>=0%;  
55 P=0.643) (Fig. 2).  
56  
57

58  
59 To further verify the robustness of the results, we grouped all included studies by adjusted or non-  
60

1  
2  
3 adjusted HR. In patients with diabetes, myocardial fibrosis detected by LGE-MRI was associated with  
4 an increased risk of MACCEs and MACEs in a subgroup analysis with or without adjusted HR. The  
5 pooled HRs obtained via a random effects model were 3.52 (95% CI 2.02-6.16;  $I^2=35.8\%$ ) and 4.63 (95%  
6 CI 2.35-9.14;  $I^2=0\%$ ), respectively. There was no significant heterogeneity among the studies  
7 (Supplemental Fig. S2).  
8  
9

10  
11 To evaluate the effects of the myocardial fibrosis pattern, we further calculated a pooled HR by source  
12 of diabetes with different patterns of myocardial fibrosis. In patients with diabetes, ischaemic fibrosis  
13 detected by LGE-MRI was significantly associated with increased MACCEs and MACEs (random  
14 effects HR 3.80, 95% CI 2.38-6.07;  $I^2=26.4\%$ ). No study in our meta-analysis reported the relationship  
15 between nonischaemic fibrosis and the risk of MACCEs and MACEs alone; hence, we cannot perform a  
16 meta-analysis to assess the relationship between nonischaemic fibrosis and MACCEs/MACEs.  
17 (Supplemental Fig. S3).  
18  
19

20  
21 To confirm whether there were similar results in patients with preserved LV ejection fraction, we  
22 conducted a subgroup analysis with 6 studies. Among individuals with diabetes and LV ejection fraction  
23  $> 50\%$ , the presence of myocardial fibrosis assessed by LGE-MRI was significantly associated with  
24 MACCEs and MACEs. The pooled HR obtained via the random effects model was 3.98 (95% CI 2.22-  
25 7.25;  $P<0.001$ ), and there was a medium amount of heterogeneity among the studies ( $I^2=37.9\%$ ;  $P=0.153$ )  
26 (Fig. 3).  
27  
28  
29

## 30 DISCUSSION

31  
32 In this meta-analysis, the prevalence of myocardial fibrosis (mainly ischaemic fibrosis) assessed by LGE-  
33 MRI was increased in patients with diabetes, occurring in 38.09% of them, and it was associated with an  
34 increased risk for MACCEs and MACEs, even when the LV ejection fraction persisted. Moreover,  
35 ischaemic myocardial fibrosis detected by LGE-MRI has a higher predictive value for the occurrence of  
36 future MACEs than MACCEs in patients with diabetes. However, in this study, the relationship of  
37 nonischaemic LGE-MRI-detected fibrosis and MACCEs/MACEs in patients with diabetes was not  
38 elucidated. Therefore, ischaemic myocardial fibrosis by LGE-MRI may be an imaging biomarker for  
39 predicting adverse outcomes in patients with diabetes.  
40  
41  
42

43  
44 In our meta-analysis, the results supported previous studies showing that participants with diabetes have  
45 a higher presence of myocardial fibrosis detected by LGE-MRI, especially ischaemic fibrosis.  
46 Importantly, in our included studies, the presence of myocardial fibrosis in symptomatic patients with  
47 diabetes was higher than that in asymptomatic patients with diabetes.<sup>2 3 17</sup> Furthermore, unrecognised  
48 ischaemic myocardial fibrosis in patients with diabetes is considered as a biomarker which is responsible  
49 for poor outcomes, and maybe provides a stronger prognostic value than conventional cardiovascular  
50 risk factors.<sup>2 17</sup> All studies included in our meta-analysis involved patients who had suffered a  
51 unrecognised myocardial infarction, which implied they might represented a higher-risk population.  
52 Current guidelines recommend that MRI may serve as a risk tool in asymptomatic diabetic patients with  
53 moderate or high risk of cardiovascular disease.<sup>14</sup> However, it is unclear whether LGE-MRI-detected  
54 myocardial fibrosis would indicate an increased risk of MACEs in patients with diabetes at low  
55 cardiovascular risk. Notably, in our meta-analysis, focal ischaemic myocardial fibrosis detected by LGE-  
56 MRI did seem to predict a higher occurrence of MACCEs/MACEs, and the annualized event rate for  
57  
58  
59  
60

1  
2  
3 MACCEs/MACEs in patients with diabetes and LGE-MRI-detected myocardial fibrosis was 11.94%.  
4 Additionally, the presence of ischaemic myocardial fibrosis indicated an 8-fold higher risk for death/MI  
5 even in asymptomatic patients with diabetes.<sup>2</sup> Notably, other techniques, such as ECG, have lower  
6 accuracy and sensitivity for detecting myocardial fibrosis than LGE-MRI.<sup>35 36</sup> Thus, this finding may  
7 highlight the value of LGE-MRI for screening for cardiovascular risk in symptomatic patients with  
8 diabetes.  
9  
10

11  
12 The risk of myocardial fibrosis in patients with diabetes is increased, and there are multiple factors that  
13 influence this relationship. First, patients with diabetes have a higher risk for coronary artery disease and  
14 myocardial dysfunction.<sup>37-39</sup> Moreover, hyperglycaemic metabolism, microvascular disease, and cardiac  
15 autonomic neuropathy are involved in the mechanisms of myocardial fibrosis.<sup>4 40 41</sup> However, many  
16 studies have shown that patients with diabetes have a high incidence of obesity, visceral fat,  
17 hyperlipidaemia, and insulin resistance, which may impair myocardial function.<sup>6 42 43</sup> Furthermore, the  
18 multiple risk factors described above should increase the myocardial fibrosis burden. In addition,  
19 myocardial fibrosis is widespread in subjects with diabetes and may be associated with a high risk for  
20 cardiovascular disease.  
21  
22  
23  
24

25 Although focal myocardial fibrosis translates to an adverse outcome in the future and is not fully clear,  
26 several potential mechanisms may lead to MACCEs/MACEs. First, patients with diabetes are more  
27 inclined to develop myocardial fibrosis, and myocardial fibrosis is associated with ventricular arrhythmia  
28 and heart failure.<sup>3 44-46</sup> Second, patients with diabetes and myocardial fibrosis usually have a greater  
29 burden of microvascular complications, such as myocardial ischaemia, which confers an increased risk  
30 of MACCEs/MACEs.<sup>16 47</sup> Additionally, the myocardial fibrosis detected by LGE-MRI, especially  
31 subendocardial fibrosis, indicates that patients with diabetes have had a subendocardial infarction in the  
32 past, which denotes a higher risk of MACEs in the future.<sup>48 49</sup> Furthermore, subjects with diabetes had  
33 higher LV and left atrial remodelling due to myocardial fibrosis.<sup>7 45 50</sup> For these reasons, the myocardial  
34 fibrosis detected by LGE-MRI has great potential to lead to adverse outcomes in the future.  
35  
36  
37  
38  
39

40 As previously described, LGE-MRI has become a powerful non-invasive imaging method for the  
41 assessment of myocardial fibrosis.<sup>11</sup> Although two studies<sup>20 21</sup> included in our meta-analysis showed that  
42 ischaemic myocardial fibrosis detected by LGE-MRI did not increase the rate of MACCEs, our meta-  
43 analysis demonstrated that the presence of ischaemic myocardial fibrosis derived from LGE-MRI  
44 conferred an HR of 3.80 for future MACCEs/MACEs in individuals with diabetes. This might be  
45 explained by the following reasons: limited patient numbers and a higher prevalence of cardiovascular  
46 disease at patient enrolment. Indeed, detecting myocardial fibrosis can be used to clinically assess  
47 myocardial damage and to stratify cardiovascular risk in participants with diabetes. To date, only one  
48 study, which screened for asymptomatic diabetes by LGE-MRI, showed that diabetes with ischaemic  
49 myocardial fibrosis conferred an 8-fold higher risk for all-cause mortality and MI.<sup>2</sup> The prevalence of  
50 ischaemic myocardial fibrosis detected by LGE-MRI among patients with diabetes is higher than that  
51 among nondiabetic patients.<sup>3 30</sup> Although there were several studies have reported the prognostic value  
52 of ischemic myocardial fibrosis detected by LGE-MRI in patients with diabetes, the prognostic value of  
53 non-ischemic myocardial fibrosis has not been studied. Therefore, patients with diabetes and ischaemic  
54 myocardial fibrosis might need aggressive management of cardiac and cerebrovascular risk factors.  
55 Given the scarcity of studies that focused on the prognosis of non-ischemic myocardial fibrosis in patients  
56  
57  
58  
59  
60

with diabetes, more relevant studies are needed.

However, our meta-analysis has some limitations. First, in our meta-analysis, 2 studies<sup>20,21</sup> were from the same group of patients but reported different outcomes. However, when we excluded either of the above articles, the pooled HR and heterogeneity did not change significantly. Second, the incidence of myocardial fibrosis in patients with diabetes was not obtained via community-based epidemiology research. Therefore, the prevalence of myocardial fibrosis may be higher in this study, which pooled studies including high-risk or average-risk populations with diabetes. Third, a previous study found that nonischaemic LGE-MRI-detected myocardial fibrosis is associated with increased myocardial mass, increased myocardial extracellular volume and impaired diastolic parameters.<sup>7</sup> However, subgroup analysis was not conducted to evaluate the effect of nonischaemic myocardial fibrosis on MACCEs/MACEs in patients with diabetes due to a lack of information. Further studies are needed to establish nonischaemic LGE-MRI lesions and their prognosis. Fourth, most studies selected in this meta-analysis reported adjusted HR, and various adjustments for adverse outcomes among the selected studies may affect the pooled results. However, the heterogeneity among the selected studies was low, and publication bias did not exist. This might strengthen the clinical meaning of the pooled result. Finally, the incremental value of diabetes duration to the prevalence and incidence of LGE-MRI-detected myocardial fibrosis was not revealed. However, diabetes duration plays a central role in the assessment of cardiovascular risk.<sup>14, 51</sup> Hence, prospective studies that evaluate the association between diabetes duration and myocardial fibrosis and determine the best time to screen myocardial fibrosis by LGE-MRI for risk stratification in patients with diabetes are needed.

## CONCLUSIONS

In patients with diabetes, the presence of myocardial fibrosis detected by LGE-MRI, especially ischaemic lesions, was markedly associated with an important and increased risk of MACCEs/MACEs. This meta-analysis highlights the potential role of LGE-MRI in helping predict MACCEs/MACEs in complicated diabetic patients, especially those with cardiac complications and a high risk for myocardial fibrosis. Although we reported that ischaemic myocardial fibrosis detected by LGE-MRI is a strong risk marker for improving risk stratification in patients with diabetes, whether LGE-MRI provides incremental prognostic information with respect to MACCEs/MACEs over risk stratification by conventional cardiovascular risk factors requires further study.

## REFERENCES

- 1 Cho NH, Shaw JE, Karuranga S, *et al.* IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes research and clinical practice* 2018;138:271-81.
- 2 Elliott MD, Heitner JF, Kim H, *et al.* Prevalence and prognosis of unrecognized myocardial infarction in asymptomatic patients with diabetes: A two-center study with up to 5 years of follow-up. *Diabetes Care* 2019;42:1290-6.
- 3 Giusca S, Kelle S, Nagel E, *et al.* Differences in the prognostic relevance of myocardial ischaemia and scar by cardiac magnetic resonance in patients with and without diabetes mellitus. *European heart journal cardiovascular Imaging* 2016;17:812-20.
- 4 Jia G, Hill MA, Sowers JR. Diabetic Cardiomyopathy: An Update of Mechanisms Contributing to

- This Clinical Entity. *Circulation research* 2018;122:624-38.
- 5 Russo I, Frangogiannis NG. Diabetes-associated cardiac fibrosis: Cellular effectors, molecular mechanisms and therapeutic opportunities. *Journal of molecular and cellular cardiology* 2016;90:84-93.
- 6 Marwick TH, Ritchie R, Shaw JE, *et al.* Implications of Underlying Mechanisms for the Recognition and Management of Diabetic Cardiomyopathy. *Journal of the American College of Cardiology* 2018;71:339-51.
- 7 Storz C, Hetterich H, Lorbeer R, *et al.* Myocardial tissue characterization by contrast-enhanced cardiac magnetic resonance imaging in subjects with prediabetes, diabetes, and normal controls with preserved ejection fraction from the general population. *European heart journal cardiovascular Imaging* 2018;19:701-8.
- 8 Jia G, Whaley-Connell A, Sowers JR. Diabetic cardiomyopathy: a hyperglycaemia- and insulin-resistance-induced heart disease. *Diabetologia* 2018;61:21-8
- 9 Bojer AS, Sørensen MH, Vejlsstrup N, *et al.* Distinct non-ischemic myocardial late gadolinium enhancement lesions in patients with type 2 diabetes. *Cardiovasc Diabetol* 2020;19(1):184.
- 10 Armstrong AC, Ambale-Venkatesh B, Turkbey E, *et al.* Association of Cardiovascular Risk Factors and Myocardial Fibrosis With Early Cardiac Dysfunction in Type 1 Diabetes: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study. *Diabetes Care* 2017;40:405-11.
- 11 Mewton N, Liu CY, Croisille P, *et al.* Assessment of myocardial fibrosis with cardiovascular magnetic resonance. *Journal of the American College of Cardiology* 2011;57:891-903.
- 12 Hiromi Hashimura FK, Hatsue Ishibashi-Ueda, Yoshiaki Morita, *et al.* Radiologic-Pathologic Correlation of Primary and Secondary Cardiomyopathies:MR Imaging and Histopathologic Findings in Hearts from Autopsy and Transplantation. *Radiographics* 2017;37:719-36.
- 13 Iles LM, Ellims AH, Llewellyn H, *et al.* Histological validation of cardiac magnetic resonance analysis of regional and diffuse interstitial myocardial fibrosis. *European heart journal cardiovascular Imaging* 2015;16:14-22.
- 14 Cosentino F, Grant PJ, Aboyans V, *et al.* 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *European heart journal* 2020;41:255-323.
- 15 Jensen MT, Fung K, Aung N, *et al.* Changes in Cardiac Morphology and Function in Individuals With Diabetes Mellitus: The UK Biobank Cardiovascular Magnetic Resonance Substudy. *Circulation Cardiovascular imaging* 2019;12:e009476.
- 16 Heydari B, Juan YH, Liu H, *et al.* Stress Perfusion Cardiac Magnetic Resonance Imaging Effectively Risk Stratifies Diabetic Patients with Suspected Myocardial Ischemia. *Circulation: Cardiovascular Imaging* 2016;9:e004136.
- 17 Kwong RY, Sattar H, Wu H, *et al.* Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation* 2008;118:1011-20.
- 18 Yoon YE, Kitagawa K, Kato S, *et al.* Prognostic significance of unrecognized myocardial infarction detected with MR imaging in patients with impaired fasting glucose compared with those with diabetes. *Radiology* 2012;262:807-15.
- 19 Yoon YE, Kitagawa K, Kato S, *et al.* Prognostic value of unrecognized myocardial infarction detected by late gadolinium-enhanced MRI in diabetic patients with normal global and regional

- 1  
2  
3 left ventricular systolic function. *European radiology* 2013;23:2101-8.
- 4  
5 20 Bamberg F, Parhofer KG, Lochner E, *et al.* Diabetes mellitus: Long-term prognostic value of  
6 whole-body MR imaging for the occurrence of cardiac and cerebrovascular events. *Radiology*  
7 2013;269:730-7.
- 8  
9 21 Bertheau RC, Bamberg F, Lochner E, *et al.* Whole-Body MR Imaging Including Angiography:  
10 Predicting Recurrent Events in Diabetics. *European radiology* 2016;26:1420-30.
- 11  
12 22 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a  
13 proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE)  
14 group. *Jama* 2000;283:2008-12.
- 15  
16 23 Hutton B, Salanti G, Caldwell DM, *et al.* The PRISMA extension statement for reporting of  
17 systematic reviews incorporating network meta-analyses of health care interventions: checklist  
18 and explanations. *Ann Intern Med* 2015;162:777-84.
- 19  
20 24 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of  
21 nonrandomized studies in meta-analyses. *European journal of epidemiology* 2010;25:603-5.
- 22  
23 25 Zeng X, Zhang Y, Kwong JS, *et al.* The methodological quality assessment tools for preclinical  
24 and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a  
25 systematic review. *Journal of evidence-based medicine* 2015;8:2-10.
- 26  
27 26 Mantovani A, Byrne CD, Bonora E, *et al.* Nonalcoholic Fatty Liver Disease and Risk of Incident  
28 Type 2 Diabetes: A Meta-analysis. *Diabetes Care* 2018;41:372-82.
- 29  
30 27 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in medicine*  
31 2002;21:1539-1558
- 32  
33 28 Liu JL. The role of the funnel plot in detecting publication and related biases in meta-analysis.  
34 *Evidence-based dentistry* 2011;12:121-2
- 35  
36 29 Reinstadler SJ, Stiermaier T, Eitel C, *et al.* Relationship between diabetes and ischaemic injury  
37 among patients with revascularized ST-elevation myocardial infarction. *Diabetes, Obesity and*  
38 *Metabolism* 2017;19:1706-13.
- 39  
40 30 Lindman BR, Davila-Roman VG, Mann DL, *et al.* Cardiovascular phenotype in HFpEF patients  
41 with or without diabetes: a RELAX trial ancillary study. *Journal of the American College of*  
42 *Cardiology* 2014;64:541-9.
- 43  
44 31 Eitel I, Hintze S, De Waha S, *et al.* Prognostic impact of hyperglycemia in nondiabetic and  
45 diabetic patients with ST-elevation myocardial infarction: Insights from contrast-enhanced  
46 magnetic resonance imaging. *Circulation: Cardiovascular Imaging* 2012;5:708-18.
- 47  
48 32 Donnino R, Patel S, Nguyen AH, *et al.* Comparison of quantity of left ventricular scarring and  
49 remodeling by magnetic resonance imaging in patients with versus without diabetes mellitus and  
50 with coronary artery disease. *American Journal of Cardiology* 2011;107:1575-8.
- 51  
52 33 Lejeune S, Roy C, Slimani A, *et al.* Diabetic phenotype and prognosis of patients with heart  
53 failure and preserved ejection fraction in a real life cohort. *Cardiovasc Diabetol* 2021;20(1):48.
- 54  
55 34 Kato S, Fukui K, Kodama S, *et al.* Incremental prognostic value of coronary flow reserve  
56 determined by phase-contrast cine cardiovascular magnetic resonance of the coronary sinus in  
57 patients with diabetes mellitus. *J Cardiovasc Magn Reson* 2020;22(1):73.
- 58  
59 35 Ramos R, Albert X, Sala J, *et al.* Prevalence and incidence of Q-wave unrecognized myocardial  
60 infarction in general population: Diagnostic value of the electrocardiogram. The REGICOR study.  
*International journal of cardiology* 2016;225:300-5.
- 36 Barbier CE, Bjerner T, Johansson L, *et al.* Myocardial scars more frequent than expected:



- 1  
2  
3 magnetic resonance imaging detects potential risk group. *Journal of the American College of*  
4 *Cardiology* 2006;48:765-71.
- 5  
6 37 Bertoni AG, Goff Jr DC, D'Agostino Jr RB, *et al.* Diabetic cardiomyopathy and subclinical  
7 cardiovascular disease: The Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care*  
8 2006;29:588-94.
- 9  
10 38 Shivu GN, Phan TT, Abozguia K, *et al.* Relationship between coronary microvascular  
11 dysfunction and cardiac energetics impairment in type 1 diabetes mellitus. *Circulation*  
12 2010;121:1209-15.
- 13  
14 39 Campbell DJ, Somaratne JB, Jenkins AJ, *et al.* Impact of type 2 diabetes and the metabolic  
15 syndrome on myocardial structure and microvasculature of men with coronary artery disease.  
16 *Cardiovascular diabetology* 2011;10:80.
- 17  
18 40 Tarquini R, Lazzeri C, Pala L, *et al.* The diabetic cardiomyopathy. *Acta diabetologica*  
19 2011;48:173-81.
- 20  
21 41 Gao Y, Yang ZG, Ren Y, *et al.* Evaluation of myocardial fibrosis in diabetes with cardiac  
22 magnetic resonance T1-mapping: Correlation with the high-level hemoglobin A1c. *Diabetes*  
23 *research and clinical practice* 2019;150:72-80.
- 24  
25 42 Turkbey EB, Backlund JY, Genuth S, *et al.* Myocardial structure, function, and scar in patients  
26 with type 1 diabetes mellitus. *Circulation* 2011;124:1737-46.
- 27  
28 43 Ng ACT, Strudwick M, van der Geest RJ, *et al.* Impact of Epicardial Adipose Tissue, Left  
29 Ventricular Myocardial Fat Content, and Interstitial Fibrosis on Myocardial Contractile Function.  
30 *Circ Cardiovasc Imaging* 2018;11:e007372.
- 31  
32 44 Anselmino M, Matta M, D'Ascenzo F, *et al.* Catheter ablation of atrial fibrillation in patients with  
33 diabetes mellitus: a systematic review and meta-analysis. *Europace* 2015;17:1518-25.
- 34  
35 45 Gulsin GS, Kanagala P, Chan DCS, *et al.* Differential left ventricular and left atrial remodelling in  
36 heart failure with preserved ejection fraction patients with and without diabetes. *Therapeutic*  
37 *Advances in Endocrinology and Metabolism* 2019;10:2042018819861593.
- 38  
39 46 Mordi I, Bezerra H, Carrick D, *et al.* The Combined Incremental Prognostic Value of LVEF, Late  
40 Gadolinium Enhancement, and Global Circumferential Strain Assessed by CMR. *JACC*  
41 *Cardiovascular imaging* 2015;8:540-9.
- 42  
43 47 Sandesara PB, O'Neal WT, Kelli HM, *et al.* The Prognostic Significance of Diabetes and  
44 Microvascular Complications in Patients With Heart Failure With Preserved Ejection Fraction.  
45 *Diabetes Care* 2018;41:150-5.
- 46  
47 48 Schelbert EB, Cao JJ, Sigurdsson S, *et al.* Prevalence and prognosis of unrecognized myocardial  
48 infarction determined by cardiac magnetic resonance in older adults. *Jama* 2012;308:890-6.
- 49  
50 49 Acharya T, Aspelund T, Jonasson TF, *et al.* Association of Unrecognized Myocardial Infarction  
51 With Long-term Outcomes in Community-Dwelling Older Adults: The ICELAND MI Study.  
52 *JAMA Cardiol* 2018;3:1101-6.
- 53  
54 50 Cao Y, Zeng W, Cui Y, *et al.* Increased myocardial extracellular volume assessed by  
55 cardiovascular magnetic resonance T1 mapping and its determinants in type 2 diabetes mellitus  
56 patients with normal myocardial systolic strain. *Cardiovascular diabetology* 2018;17:7.
- 57  
58 51 Dabelea D, Stafford JM, Mayer-Davis EJ, *et al.* Association of Type 1 Diabetes vs Type 2  
59 Diabetes Diagnosed During Childhood and Adolescence With Complications During Teenage  
60 Years and Young Adulthood. *Jama* 2017;317:825-35.

## Figure legend

Figure 1. Flow chart of literature and study selection.

Figure 2. Forest plot and pooled estimates of the effect of myocardial fibrosis detected by LGE on the risk of MACCEs or MACEs. LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; HR, hazard ratios; CI, confidence interval.

Figure 3. Forest plots of 6 studies for pooled HR for MACCEs and MACEs in patients with diabetes with normal LV ejection fraction and myocardial fibrosis detected by LGE. HR, hazard ratio; LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events; CI, confidence interval.

## Table legend

Table 1. Description of the Studies Included in the Meta-Analysis

## Supplement legend

Supplement Table S1. The exact search strategy was used in OvidSP.

Supplement Figure S1. Funnel plots of 8 eligible studies.

1  
2  
3  
4  
5  
6  
7 Supplement Figure S2. Forest plots of pooled HRs for MACCEs and MACEs in adjusted or not  
8  
9 adjusted HR studies. HR, hazard ratios; MACCEs, major adverse cardiac and cerebrovascular  
10  
11 events; MACEs, major adverse cardiac events; HR, hazard ratios; CI, confidence interval.  
12  
13  
14  
15  
16

17 Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCEs and MACEs  
18  
19 in patients with diabetes and different patterns of myocardial fibrosis detected by LGE. HR,  
20  
21 hazard ratios; LGE, late gadolinium enhancement; MACCEs, major adverse cardiac and  
22  
23 cerebrovascular events; MACEs, major adverse cardiac events; CI, confidence interval.  
24  
25  
26  
27  
28  
29

### 30 Notes

#### 31 32 Author affiliations

- 33  
34  
35 1. Department of Radiology, Key Laboratory of Birth Defects and Related Diseases of Women  
36  
37 and Children of Ministry of Education, Sichuan University West China Second University  
38  
39 Hospital, Chengdu, China.  
40  
41  
42  
43 2. Department of Radiology, Chengdu Fifth People's Hospital, Chengdu, China.  
44  
45  
46 3. Key Laboratory of Obstetrics & Gynecology and Pediatric Disease and Birth Defects of  
47  
48 Ministry of Education, Sichuan University West China Second University Hospital, Chengdu,  
49  
50  
51 China.  
52  
53  
54 4. Department of Radiology, Sichuan University West China Hospital, Chengdu, China.  
55  
56  
57

#### 58 Funding

1  
2  
3  
4 This work was supported by the National Natural Science Foundation of China (No. 81771887,  
5  
6 81771897, 81971586, 81901712); the Program for Young Scholars and Innovative Research Team  
7  
8 in Sichuan Province (No. 2017TD0005) of China; and the 1·3·5 project for disciplines of excellence,  
9  
10 West China Hospital, Sichuan University (No. ZYGD18013).  
11  
12  
13  
14  
15  
16

### 17 **Competing interests**

18  
19 The authors report no conflicts of interest.  
20  
21  
22  
23

### 24 **Contributors**

25 Zhi Yang and Rong Xu conceived of this study, participated in its design and coordination and  
26 drafted the manuscript. Contribution to the conceptualization and design: Jia-rong Wang, Hua-  
27 yan Xu, Hang Fu, Ling-jun Xie and Meng-xi Yang. Data analysis and interpretation: Lu Zhang,  
28 Ling-yi Wen, Hui Liu and Hong Li. Obtaining funding: Zhi-gang Yang and Ying-kun Guo.  
29 Zhi-gang Yang and Ying-kun Guo interpreted the results, critically revised the manuscript, and  
30 helped to and approved the final version. All authors read and approved this manuscript.  
31  
32  
33  
34  
35  
36

### 37 **Patient consent for publication**

38  
39 Not required.  
40  
41  
42  
43

### 44 **Ethics approval**

45  
46  
47 Ethics approval was not required for this meta-analysis.  
48  
49  
50  
51

### 52 **Provenance and peer review**

53  
54 Not commissioned; externally peer reviewed.  
55  
56  
57  
58  
59

### 60 **Data availability statement**

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

No additional data are available.

For peer review only

Table 1 Description of the Studies Included in the Meta-Analysis

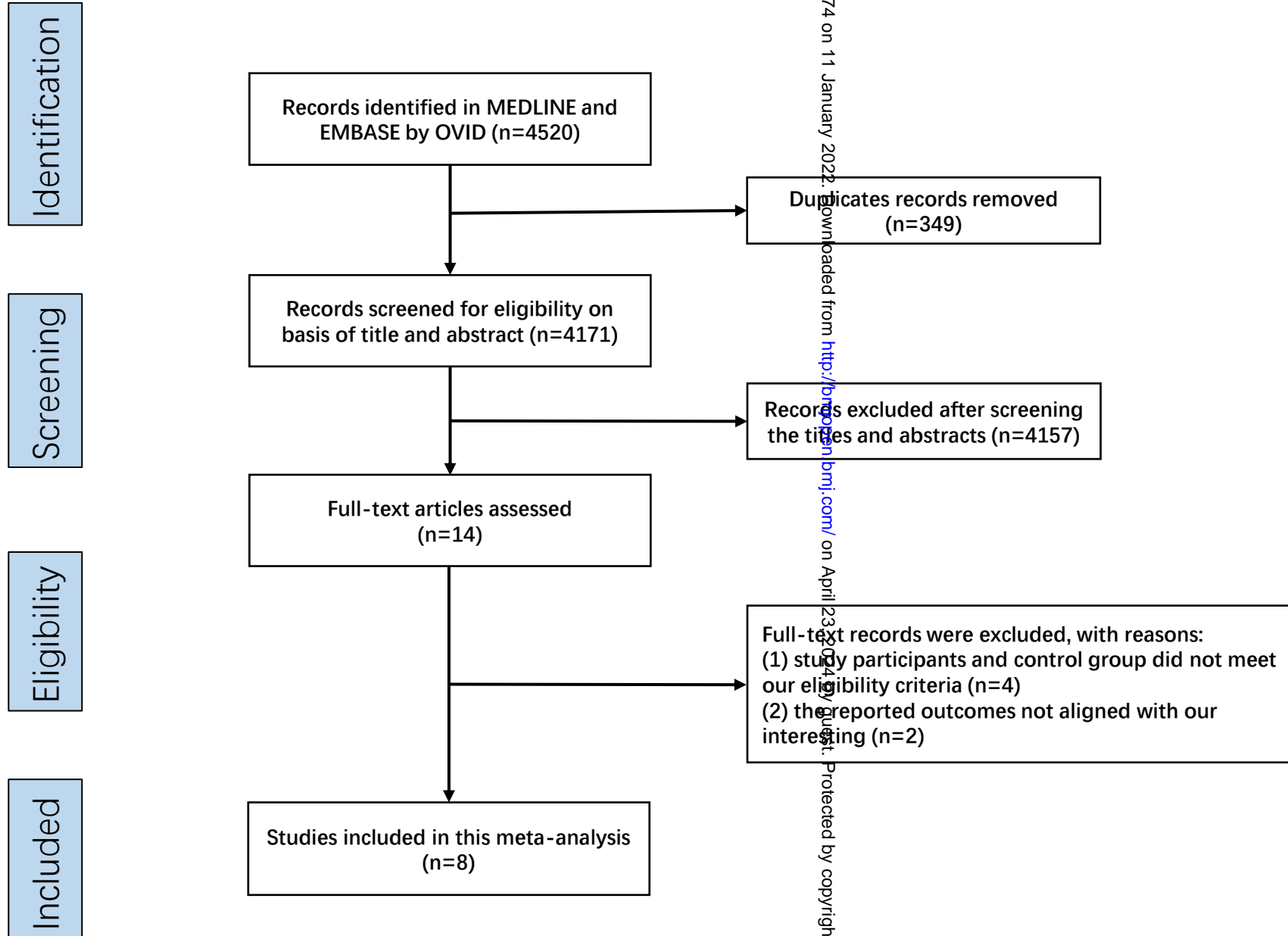
First Author, Year	Journal	Patients	HbA1c, %	LGE Definition	DM (type)	Mean age (years)	Durations (years)	LVEF (%)	Follow-up duration (months)	Major LGE(+) (%)	Total events	Adjusted HR	Fibrosis type	Type design	Outcome	NO S		
Bertheau RC,2016	Eur Radiol Circ	61	7.2 (6.5-7.9)	visual	1 and 2	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	8	YES	Ischaemic	Prospective, single-centre	MACC ES	7	
Heydari B,2016	Cardiovascular Imaging	173	7.9±1.8	2 SD	NA	61.7±1.9	NA	51.8±7.6	34.8±30	10	9	88	21	NO	Ischaemic	Prospective, single-centre	MACE S	7
Elliott MD,2019	Diabetes Care	120	NA	visual	2	52±13	17±11	63±9	46 (33-64)	65	23	19	YES	Ischaemic	Prospective, two-centre	MACE S	9	
Yoon YE,2013	Eur Radiol Eur	120	7.4±1.5	visual	2	67±9	11±11	63±6	27 (7-112)	83	18	10	NO	Ischaemic	Retrospective, single-centre	MACE S	7	
Giusca S,2016	Heart J Cardiova	328	NA	visual	NA	67±11	NA	57.7±1.6	35 (23-51.6)	25	0	176	26	YES	Ischaemic and	Prospective, e,	MACE S	8

bmjopen-2021-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

sc Imaging														nonischaemic	multicentre		
Bamberg	Radiology	7.2 (6.5-7.9)	1	67.5(56.7-71.8)	19(14-28)	56(46-61)	70 (57-72)	31	17	18	YES	Ischaemic	Prospective, single-centre	MACCES	7		
Kwon	Circulation	7.3±1.6	2 SD	10.7±8.5	NA	17 (6-57)	67	30	38	YES	Ischaemic	Prospective, single-centre	MACCES	9			
Yoon	Radiology	7.4±1.6	visual	67±9	NA	14±11	NA	30(6-103)	11	3	58	24	NO	Ischaemic	Retrospective, single-centre	MACE S	6

Columns represent n(%) or mean±SD or median (IQR); DM, diabetes mellitus; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NOS, Newcastle–Ottawa Scale; HR, hazard ratio; NR, not reported; MACCEs, major adverse cardiac and cerebrovascular events; MACEs, major adverse cardiac events.



055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

Identification

Screening

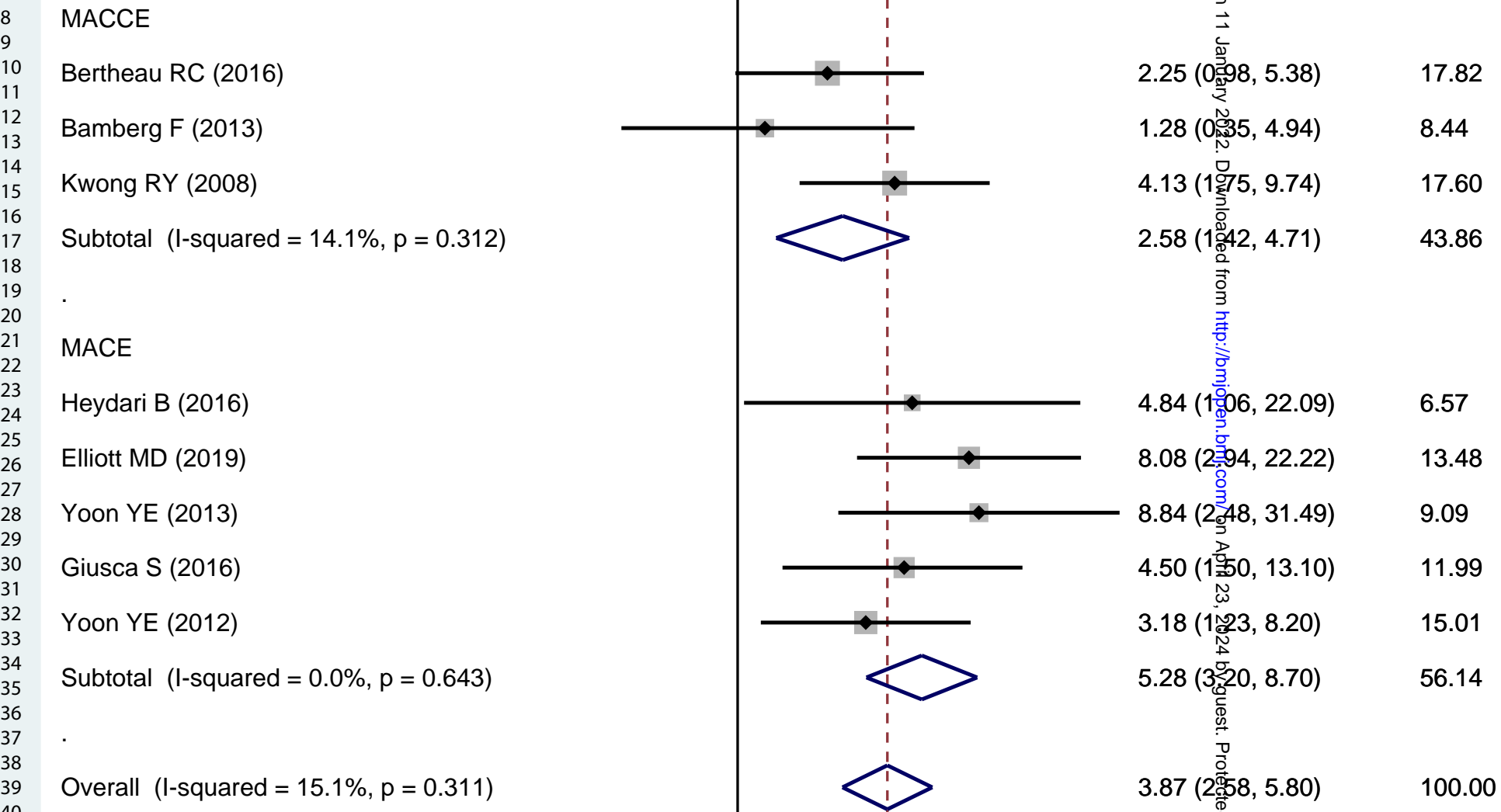
Eligibility

Included



1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from http://bmjopen.bmj.com/ on April 23, 2024 by guest. Protected by copyright.

1 Study %  
 2  
 3 ID HR (95% CI) Weight



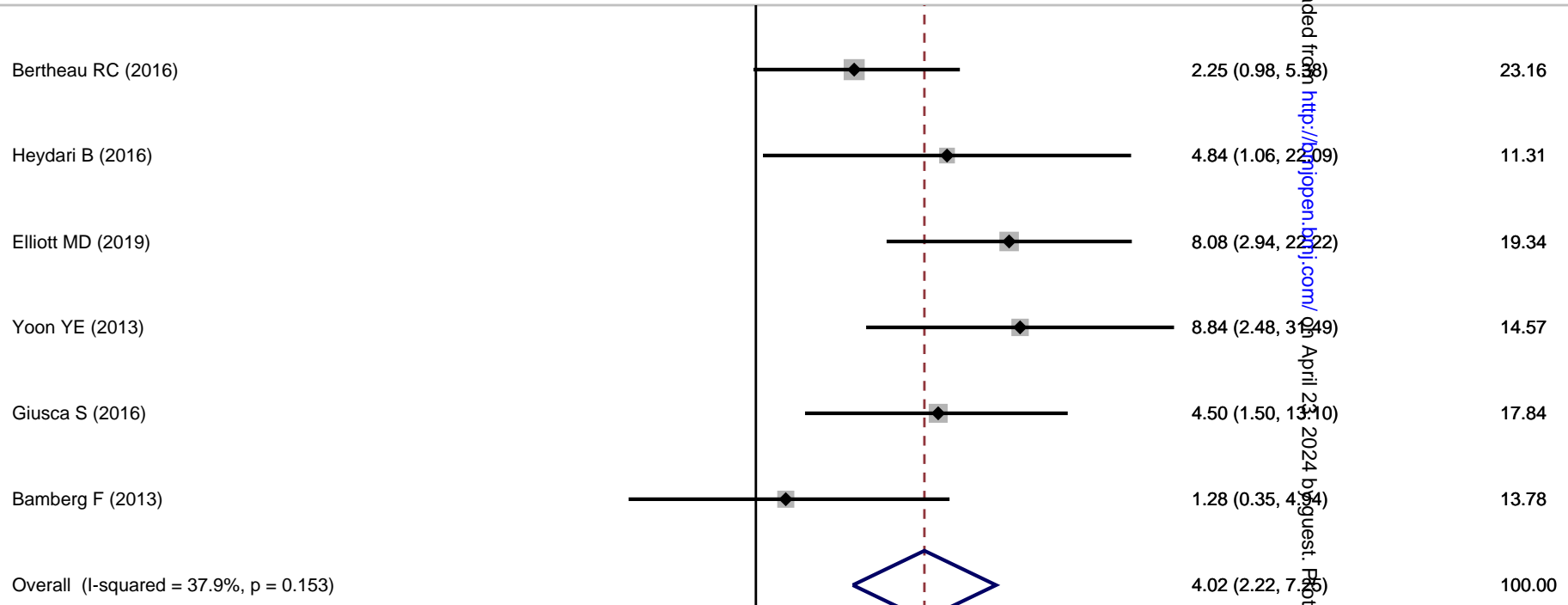
NOTE: Weights are from random effects analysis

.0318 1 31.5

55374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

Study				%
ID		HR (95% CI)		Weight



NOTE: Weights are from random effects analysis

.0318 1 31.5

**Supplement legend**

Supplement Table S1. The exact search strategy was used in OvidSP.

Supplement Table S2. The exact search strategy was used in PubMed.

Supplement Table S3. The exact search strategy was used in Cochrane Library.

Supplement Figure S1. Funnel plots of 8 eligible studies.

Supplement Figure S2. Forest plots of pooled HR for MACCE and MACE in adjusted or not adjusted HR studies. HR, Hazard Ratios; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; HR, Hazard Ratios; CI, confidence interval.

Supplement Figure S3. Forest plots of selected studies for pooled HR for MACCE and MACE in patients with diabetes and different pattern of myocardial fibrosis detected by LGE. HR, Hazard Ratios; LGE, late gadolinium enhancement; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; CI, confidence interval.

## Supplement Tab e S1-1

Search methodology

Search strategies

---

1 diabetes. ab, kw, ti.

2 diabetes mellitus. ab, kw, ti.

3 "diabetic\*". ab, kw, ti.

4 1 or 2 or 3

5 mri. ab, kw, ti.

6 MR. ab, kw, ti.

7 "magnetic resonance imag\*". ab, kw, ti.

8 cardiac magnetic resonance. ab, kw, ti.

9 cmr. ab, kw, ti.

1  
2  
3  
4  
5 10 late gadolinium enhancement. ab, kw, ti.  
6

7  
8 11 lge. ab, kw, ti.  
9

10  
11 12 delayed gadolinium enhancement. ab, kw, ti.  
12

13 13 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12  
14

15  
16 14 prognosis. sh.  
17

18  
19 15 diagnosed. tw.  
20

21  
22 16 cohort:.mp.  
23

24  
25 17 predictor:.mp.  
26

27  
28 18 death.mp.  
29

30  
31 19 exp \*models, statistical/  
32

33  
34 20 14 or 15 or 16 or 17 or 18 or 19  
35

36  
37 21 4 and 13 and 20  
38

39  
40 22 limit 21 to English language [Limit not valid in CDSR, CCA, CLCMR; records were retained]  
41  
42  
43  
44  
45  
46

1  
2  
3  
4  
5 23 limit 22 to human [Limit not valid in CDSR, CCA, CLCMR; records were retained]  
6

7  
8 24 limit 23 to journal article [Limit not valid in CDSR, CCA, Embase; records were retained]  
9

10  
11 25 limit 24 to (embase or medline) [Limit not valid in CDSR, CCA, CLCMR, Ovid MEDLINE(R); records were retained]  
12

---

13 1 to 25 were performed in OvidSP platform.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

## Supplement Table S1-2

Search methodology

Search strategies

---

1 diabetes[Title/Abstract]

2 "diabetes mellitus"[Title/Abstract]

3 "diabetic\*"[Title/Abstract]

4 1 or 2 or 3

5 mri[Title/Abstract]

6 MR[Title/Abstract]

7 "magnetic resonance imag\*"[Title/Abstract]

8 "Magnetic Resonance Imaging"[MeSH Terms]

9 "cardiac magnetic resonance"[Title/Abstract]

1  
2  
3  
4  
5 10 cmr[Title/Abstract]  
6

7  
8 11 "late gadolinium enhancement" [Title/Abstract]  
9

10  
11 12 LGE[Title/Abstract]  
12

13 13 "delayed gadolinium enhancement"[ Title/Abstract]  
14

15  
16 14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13  
17

18 15 prognosis[ MeSH Terms]  
19

20  
21 16 diagnosed[Title/Abstract]  
22

23  
24 17 cohort:[MeSH Terms]  
25

26 18 "predictor\*" [Title/Abstract]  
27

28  
29 19 death[MeSH Terms]  
30

31 20 models, statistical[MeSH Terms]  
32

33  
34 21 15 or 16 or 17 or 18 or 19 or 20  
35

36  
37 22 4 and 14 and 21  
38  
39  
40  
41  
42  
43  
44  
45  
46



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

23 "english and humans"[Filter]

24 22 and 23

25 journal article[Filter]

26 24 and 25

---

1 to 26 were performed in PubMed.

For peer review only

## Supplement Tabe S1-3

Search methodolog

Search strategies

---

1 diabetes:ti,ab,kw

2 "diabetes mellitus":ti,ab,kw

3 "diabetic\*":ti,ab,kw

4 1 or 2 or 3

5 mri:ti,ab,kw

6 MR:ti,ab,kw

7 "magnetic resonance imag\*":ti,ab,kw

8 "Magnetic Resonance Imaging"[MeSH Terms]

9 "cardiac magnetic resonance":ti,ab,kw

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

10 cmr:ti,ab,kw

11 "late gadolinium enhancement" :ti,ab,kw

12 LGE:ti,ab,kw

13 "delayed gadolinium enhancement":ti,ab,kw

14 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15 prognosis[ MeSH Terms]

16 diagnosed:ti,ab,kw

17 cohort:[MeSH Terms]

18 "predictor\*":ti,ab,kw

19 death[MeSH Terms]

20 models, statistical[MeSH Terms]

21 15 or 16 or 17 or 18 or 19 or 20

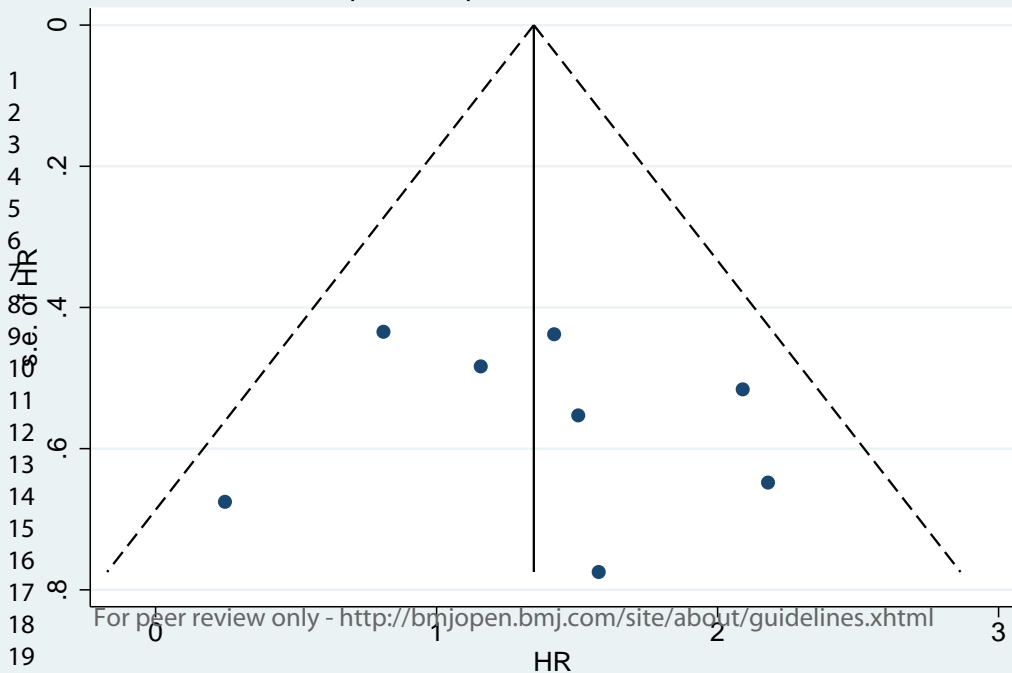
22 4 and 14 and 21

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

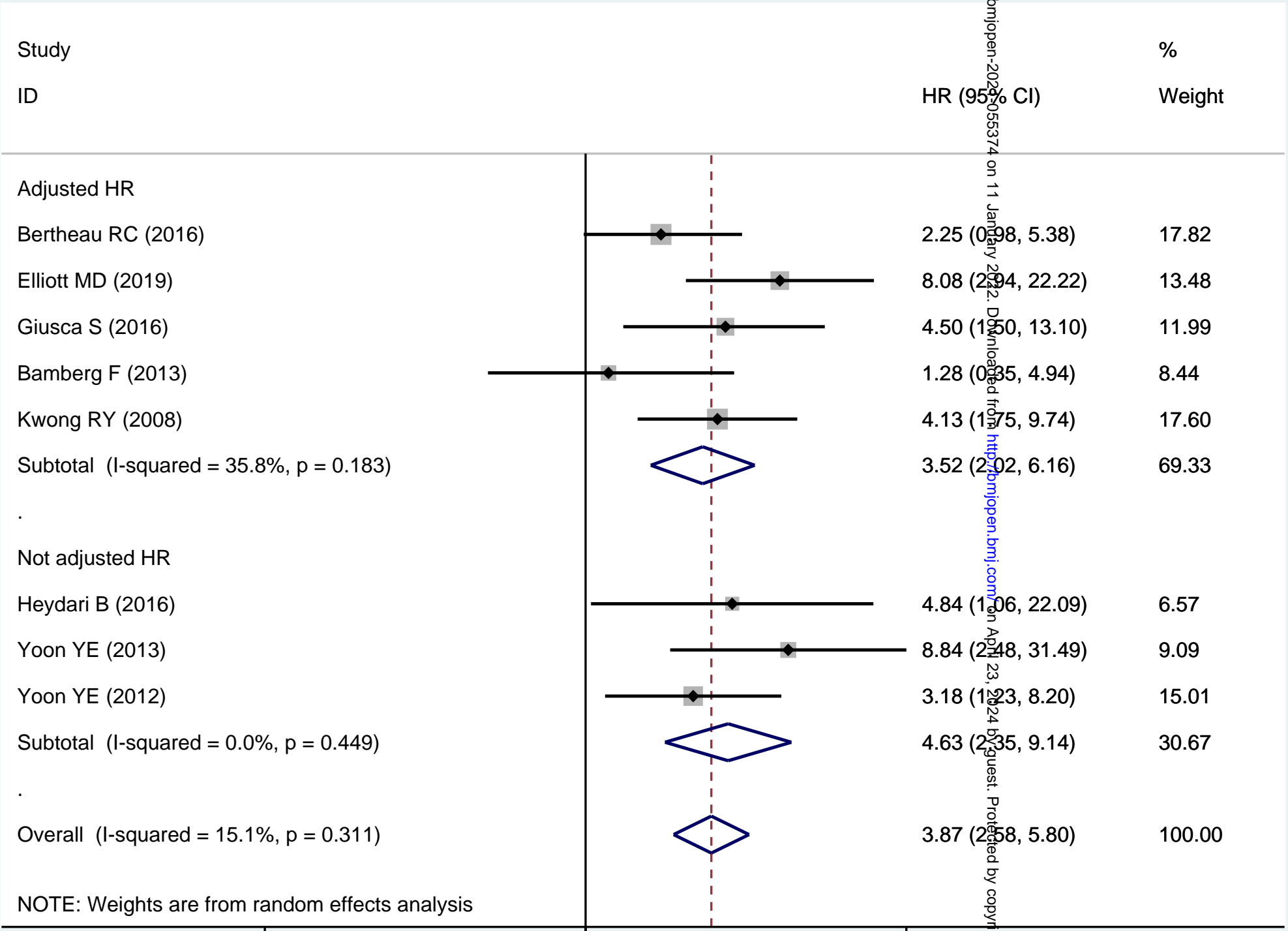
---

1 to 26 were performed in Cochrane Library.

For peer review only



1 136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.



NOTE: Weights are from random effects analysis

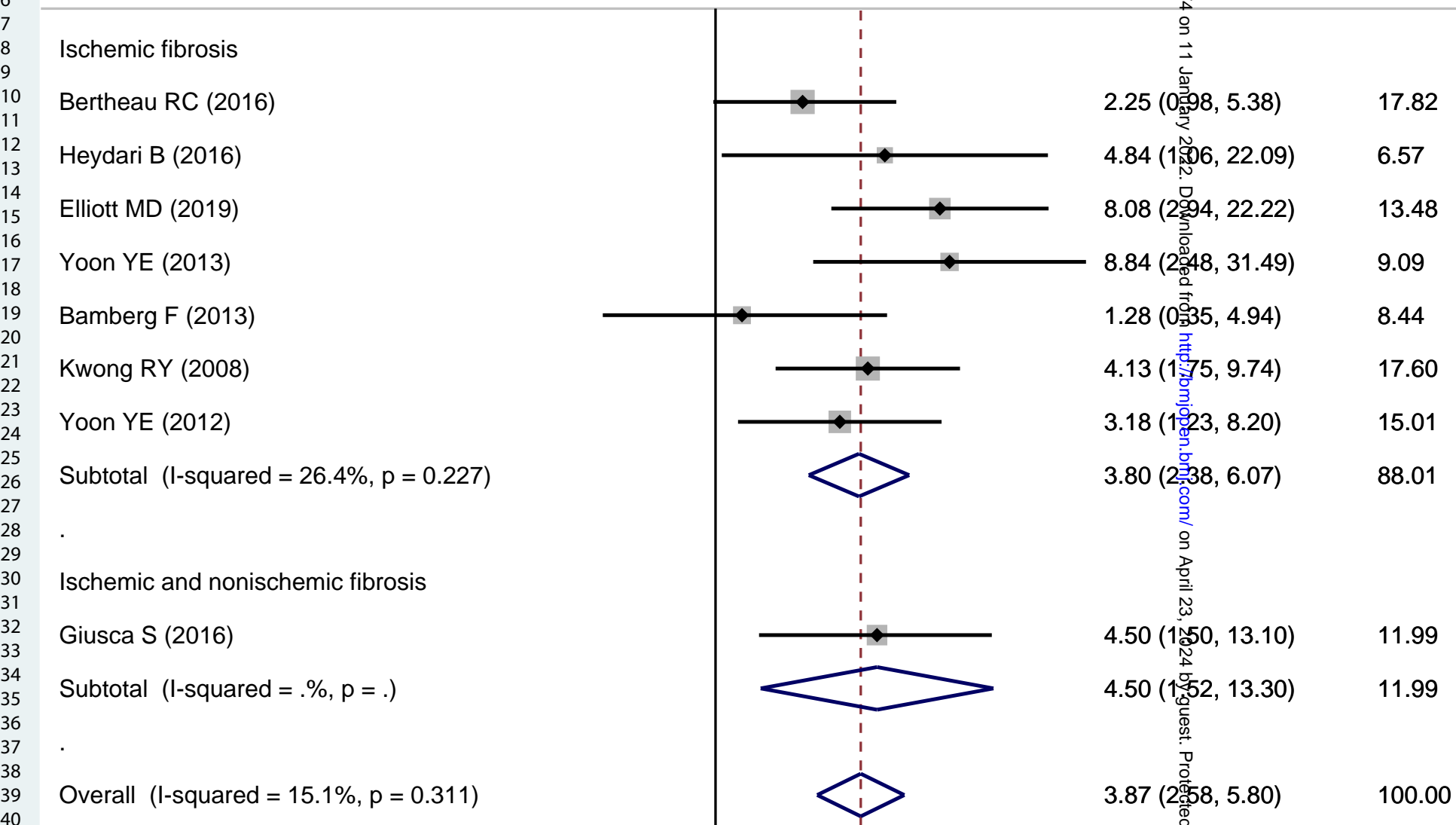
0.0318

1

31.5

1136/bmjopen-2023-055374 on 11 January 2022. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2024 by guest. Protected by copyright.

1 Study %  
 2  
 3 ID HR (95% CI) Weight



NOTE: Weights are from random effects analysis

44  
 45 .0318 1 31.5  
 46 For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

## MOOSE Checklist

### Association of Myocardial Fibrosis Detected by Late Gadolinium-enhanced MRI with Clinical Outcomes of Patients with Diabetes: A Systematic Review and Meta-analysis

Corresponding Author :

Yingkun Guo, MD, PHD

Department of Radiology, Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education; West China Second University Hospital, Sichuan University,

Address: 20# South Renmin Road, Chengdu, Sichuan 610041, China.

Phone No: +86-18980006572

Fax No: +86 28-85502946(H)

Email Address: gykpanda@163.com

Criteria	Brief description of how the criteria were handled in the meta-analysis
<b>Reporting of background should include</b>	
√ Problem definition	Although several studies have demonstrated that myocardial fibrosis detected by LGE-MRI may predict major adverse cardiac events (MACE) in patients with diabetes, the prognostic value of myocardial fibrosis for major cardiac and cerebrovascular events (MACCE) is unclear.
√ Hypothesis statement	LGE is associated with an increased risk for major adverse cardiac and cerebrovascular events (MACCE) or major adverse cardiac events (MACE) in patients with diabetes.
√ Description of study outcomes	MACCE/MACE
√ Type of exposure or intervention used	LGE-MRI
√ Type of study designs used	We included case-control studies, prospective cohort studies, retrospective studies, and randomized controlled studies.
√ Study population	Patients with diabetes.



<b>Reporting of search strategy should include</b>		
√	Qualifications of searchers	The credentials of the two investigators ZY and RX are indicated in the author list.
√	Search strategy, including time period included in the synthesis and keywords	See the section of “Data Sources and Searches” in the article.
√	Databases and registries searched	PubMed and EMBASE, Cochrane Library
√	Search software used, name and version, including special features	We did not employ a search software. EndNote was used to merge retrieved citations and eliminate duplications
√	Use of hand searching	We hand-searched bibliographies of retrieved papers for additional references.
√	List of citations located and those excluded, including justifications	Details of the literature search process are outlined in the flow chart. The citation list is available upon request.
√	Method of addressing articles published in languages other than English	Articles published in the English language were included.
√	Method of handling abstracts and unpublished studies	Only studies published in peer-reviewed journals were included.
√	Description of any contact with authors	Not.
<b>Reporting of methods should include</b>		
√	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Detailed inclusion and exclusion criteria were described in the methods section.
√	Rationale for the selection and coding of data	Data extracted from each of the studies were relevant to the population characteristics, study design, exposure, outcome, and HR (95% CI).
√	Assessment of confounding	We extracted the adjustment HR if the study reported the HR with adjustment models.
√	Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
√	Assessment of heterogeneity	To analyze the heterogeneity of the included studies, we used forest plots and the I <sup>2</sup> statistic.
√	Description of statistical methods in sufficient detail to be replicated	Description of methods of meta-analyses, sensitivity analyses, meta-regression and assessment of publication bias are detailed in the methods.
√	Provision of appropriate tables and graphics	We included 1 summary table detailing the search strategy used for database search, 1 flow chart, 1 summary

		table, 4 forest plots, 1 funnel plots.
	<b>Reporting of results should include</b>	
√	Graph summarizing individual study estimates and overall estimate	Figure 1
√	Table giving descriptive information for each study included	Table 1
√	Results of sensitivity testing	Figure 2
√	Indication of statistical uncertainty of findings	95% confidence intervals were presented with all summary estimates, $I^2$ values and results of sensitivity analyses.
	<b>Reporting of discussion should include</b>	
√	Quantitative assessment of bias	Sensitivity analyses indicate heterogeneity in strengths of the association due to most common biases in observational studies.
√	Justification for exclusion	We excluded reviews, abstracts, animal studies, case reports, and cross-sectional studies.
√	Assessment of quality of included studies	We used the Newcastle Ottawa Scale (NOS) to judge the study quality.
	<b>Reporting of conclusions should include</b>	
√	Consideration of alternative explanations for observed results	In this article, we discussed the potential reasons that patients with diabetes have more myocardial fibrosis than who without diabetes. In addition, we discussed the myocardial fibrosis detected by LGE-MRI may increase the risk of MACCE/MACE, and the limitations of our study.
√	Generalization of the conclusions	The presence of myocardial fibrosis assessed by LGE was associated with an increased risk for MACCE and MACE, even when the LV ejection fraction persisted.
√	Guidelines for future research	Myocardial fibrosis detected by LGE-MRI may be a risk marker for improving risk stratification in patients with diabetes.
√	Disclosure of funding source	This work was supported by the National Natural Science Foundation of China (No. 81771887, 81771897, 81971586, 81901712); the Program for Young Scholars and Innovative Research Team in Sichuan Province (No. 2017TD0005) of China; and 1·3·5 project for disciplines of excellence, West China Hospital, Sichuan University (No.ZYGD18013).