Diabetes mellitus, blood glucose and the risk of heart failure: A systematic review and meta-analysis of prospective studies

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KEYWORDS
Diabetes mellitus;
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Abstract *Background and Aim:* The strength of the association between diabetes and risk of heart failure has differed between previous studies and the available studies have not been summarized in a meta-analysis. We therefore quantified the association between diabetes and blood glucose and heart failure in a systematic review and meta-analysis.
Methods and results: PubMed and Embase databases were searched up to May 3rd 2018. Prospective studies on diabetes mellitus or blood glucose and heart failure risk were included. A random effects model was used to calculate summary relative risks (RRs) and 95% confidence intervals (CIs). Seventy seven studies were included. Among the population-based prospective studies, the summary RR for individuals with diabetes vs. no diabetes was 2.06 (95% CIs: 1.73 –2.46, I^2 = 99.8%, n = 30 studies, 401495 cases, 21416780 participants). The summary RR was 1.23 (95% CI: 1.15–1.32, I^2 = 78.2%, n = 10, 5344 cases, 91758 participants) per 20 mg/dl increase in blood glucose and there was evidence of a J-shaped association with nadir around 90 mg/dl and increased risk even within the pre-diabetic blood glucose range. Among the patient-based studies the summary RR was 1.69 (95% CI: 1.57–1.81, I^2 = 85.5%, $p_{heterogeneity}$ < 0.0001) for diabetes vs. no diabetes (n = 41, 100284 cases and >613925 participants) and 1.25 (95% CI: 0.89–1.75, I^2 = 95.6%, $p_{heterogeneity}$ < 0.0001) per 20 mg/dl increase in blood glucose (1016 cases, 34309 participants, n = 2). In the analyses of diabetes and heart failure there was low or no heterogeneity among the population-based studies that adjusted for alcohol intake and physical activity and among the patient-based studies there was no heterogeneity among studies with ≤10 years follow-up.
Conclusions: These results suggest that individuals with diabetes are at an increased risk of developing heart failure and there is evidence of increased risk even within the pre-diabetic range of blood glucose.

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Introduction

Cardiovascular disease is the leading cause of death globally, accounting for 17.9 million deaths in 2015 [1]. In the US 670 000 incident heart failures occurred in 2006 and approximately 5.8 million persons lived with heart failure [2]. The economic costs due to heart failure have been estimated at 39 billion US dollars [2]. Mortality in heart failure remains high, ranging from 20 to 40% in spite of advances in the management of heart failure [3,4]. Lifestyle factors may be important determinants of heart failure and established or suspected risk factors include age, coronary heart disease, valvular heart disease, left ventricular hypertrophy, atrial fibrillation, hypertension, family history of cardiovascular disease, high heart rate, low physical activity, smoking, and general and abdominal adiposity [5e9].

In addition, a number of population-based cohort studies have investigated the association between diabetes and heart failure [8e34] and most of these reported an increased risk of heart failure among diabetes patients [8e15,17e20,22e34], with only a few reporting no association [16,21] and one study reporting an association among women, but not in men [24]. However, large differences have been observed in the size of the risk estimates with relative risks (RRs) ranging from 1.20 to 2.95 among the published studies [8e34]. The reasons for the variation in the strength of the association between studies are not clear, but it may include differences in the sample size, geographic location, or study quality of the studies, differences in the adjustment for covariates as well as differences in the age of the participants in the various studies. A number of studies [35e66] have also investigated the association between diabetes and heart failure in various patient groups (individuals who had other specific diseases) and all [35e52,54e61,63e66] except for two [53,62] found a statistically significant positive association, however, again there were considerable differences in the strength of the RRs reported, which ranged from 1.34 to 10.96. Both studies reporting on type 1 diabetes and heart failure found an increased risk [33,34]. Of three studies on elevated blood glucose or prediabetes and risk of heart failure [67e69], two found positive associations [67,68], while one study showed no clear association [69]. Of the studies that investigated the association between blood glucose and heart failure in general population studies [16,70e78] and patient-based studies [38,79], most found positive associations as well, however, the strength of the association has varied considerably between studies. In addition, the shape of the doseeresponse relationship between blood glucose and heart failure has differed between studies with some studies reporting a linear association [72,78] while other studies reported U-shaped [75] or J-shaped associations [77]. We conducted a systematic review and meta-analysis of prospective studies on diabetes mellitus and blood glucose and the risk of heart failure to 1) clarify the strength of the associations, 2) clarify whether fasting blood glucose in the pre-diabetic range is associated with heart failure and 3) identify sources of heterogeneity by conducting subgroup and sensitivity analyses.

Methods

Search strategy and inclusion criteria

We searched the Pubmed, and Embase databases up to July 20th 2017 for eligible studies and the search was later updated to May 3rd 2018. The search terms used are found in the Supplementary Text. We followed standard criteria for reporting meta-analyses [80]. In addition, we searched the reference lists of the identified publications for further studies.

Study selection

We included published prospective cohort studies, nested caseecontrol studies within cohorts and randomized trials that investigated the association between diabetes mellitus and the risk of heart failure. Adjusted estimates of the RR had to be available with the 95% confidence intervals (CIs) in the publication. The literature screening was done by MN, SS, TF, and DA. A list of the excluded studies can be found in Supplementary Table 1.

Data extraction

The following data were extracted from each study: The first author's last name, publication year, country where the study was conducted, the name of the study, study period, sample size, number of cases and participants, subgroup, RRs and 95% CIs for persons with diabetes compared to persons without diabetes and variables that were adjusted for or matched for in the analysis. One investigator extracted the data (DA), and it was checked for accuracy by another investigator (SS).

Statistical methods

We calculated summary RRs and 95% CIs of heart failure for individuals with diabetes mellitus compared to individuals without diabetes mellitus and for elevated blood glucose as a continuous measure using the random-effects model by DerSimonian and Laird [81], which takes into account both within and between study variation (heterogeneity). The average of the natural logarithm of the RRs was estimated and the RR from each study was weighted using random effects weights. Studies from the general population were analysed separately from studies in patient-based populations. When RRs were reported separately for different subgroups, but not overall for the whole study population we pooled the subgroup-specific RRs using a fixed effects model to obtain a pooled estimate which was used for the main analysis. For the linear doseeresponse analysis we used the method by Greenland and Longnecker [82] and computed study-specific linear trends and 95% CIs from the natural log of the RRs and 95%

CIs across categories of blood glucose. For the linear dose**e**response analysis we excluded the lowest category of blood glucose when the second lowest category was used as a reference category, while for the nonlinear dose**e**response analysis the RR estimates were converted using the method by Hamling and colleagues [83]. In a sensitivity analysis, the linear dose**e**response analysis was repeated using the converted RR estimates. Fractional polynomial models were used for the nonlinear dose**e**response analysis and we determined the best fitting fractional polynomial regression model, defined as the one with the lowest deviance. A likelihood ratio test was used to test for nonlinearity [84].

Heterogeneity between studies was evaluated using Q and I^2 statistics [85]. I^2 is a measure of how much of the heterogeneity is due to between study variation rather than chance. I^2-values of 25%, 50% and 75% indicates low, moderate and high heterogeneity respectively. We conducted main analyses (all studies combined) and stratified by study characteristics such as sex, duration of follow-up, geographic location, number of cases, study quality and by adjustment for confounding and potential mediating factors to investigate potential sources of heterogeneity. Study quality was assessed using the Newcastle Ottawa scale which rates studies according to selection, comparability and outcome assessment with a score range from 0 to 9 [86]. Studies with a score <4, 4**e**6, and ≤7 were considered to be of low, medium and high quality. Publication bias was assessed using Egger's test [87] and Begg-Mazumdar's test [88] and by inspection of funnel plots. The trim and fill method by Duval et al [89] was used as a sensitivity analysis to assess the potential influence of publication bias on the results. Sensitivity analyses (influence analyses) excluding one study at a time were conducted to investigate the robustness of the findings. The statistical analyses were conducted using the software package Stata, version 13.1 software (StataCorp, Texas, US).

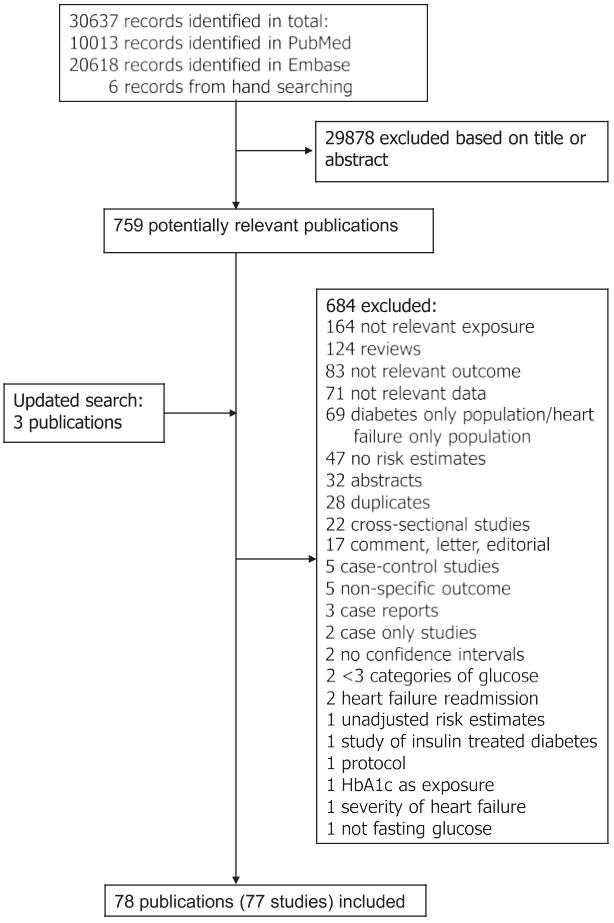

Figure 1 Flow-chart of study selection.

Results

A total of 77 prospective studies (78 publications) [8**e**79, 90**e**95] were included in the systematic review and meta-analysis of diabetes mellitus and blood glucose and risk of heart failure (Fig. 1, Supplementary Table 2**e**5).

Thirty population-based prospective studies (26 publications, 26 risk estimates) [8**e**30,33,90,91] wereincluded in the meta-analysis of diabetes mellitus and heart failure incidence including 401 495 heart failure cases and 21 416 780 participants (Fig. 2, Supplementary Table 2). One publication contained data from four cohort studies [28], another publication contained data from two cohort studies [33] and a third publication contained data from five cohort studies [31] and the latter publication was included only in the analysis stratified by whether the outcome was heart failure with reduced or preserved ejection fraction. Two publications (six cohort studies, two risk estimates) were included in the subgroup analysis of heart failure of diabetes mellitus and heart failure with reduced or preserved ejection fraction [27,31]. Eighteen studies were from the North America, eleven studies were from Europe and one study was from Asia. The summary RR of heart failure for individuals with diabetes mellitus versus individuals without diabetes mellitus was 2.06 (95% CIs: 1.73**e**2.46, I^2 = 99.8%, $p_{heterogeneity}$<0.0001) (Fig. 2). There was no evidence of publication bias with Egger's test = 0.60 or Begg's test = 0.22 (Supplementary Fig. 1). The summary RR ranged from 2.01 (95% CI: 1.68**e**2.41) when excluding the study by Karppi et al. [91] to 2.10 (95% CI: 1.75**e**2.51) when excluding the study by Aronow et al. [11] in sensitivity analyses excluding one study at a time (Supplementary Fig. 2). Inclusion of one additional study that reported on diabetes and heart failure mortality [32] did not materially alter the association, summary RR = 2.03 (95% CI: 1.70**e**2.41, I^2 = 99.8%, $p_{heterogeneity}$<0.0001). Two cohort studies [67,68] were included in a categorical analysis of blood glucose of ≤100 mg/dl compared to <100 mg/dl in relation to heart failure and the summary RR was 1.73 (95% CI: 1.43**e**2.09, I^2 = 0%, $p_{heterogeneity}$ = 0.86). Only one study [69] was identified on prediabetes and risk of heart failure and found no association, thus a meta-analysis was not possible. Only two prospective studies [33,34] were included in the analysis of type 1 diabetes and risk of heart

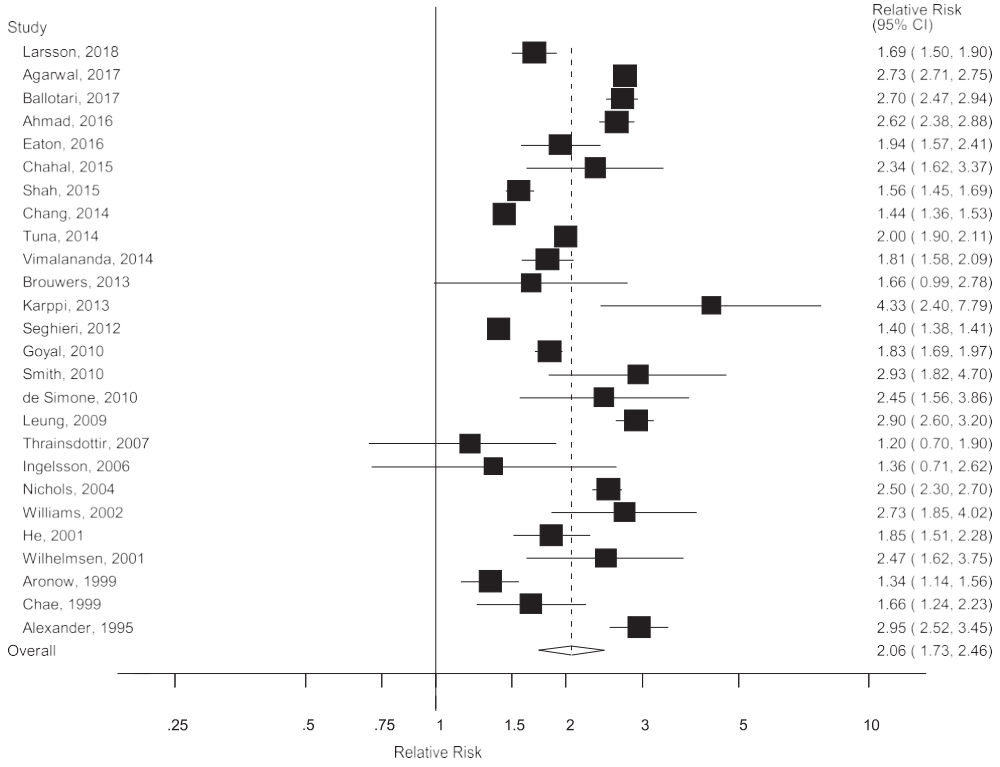

Figure 2 Diabetes mellitus and heart failure in the general population.

failure incidence (6655 cases and 271113 participants) and the summary RR was 3.64 (95% CI: 2.11**e**6.28, I^2 = 0%, $p_{heterogeneity}$ = 0.03) (Supplementary Fig. 3).

Ten population-based cohort studies [16,70**e**78] were included in the meta-analysis of blood glucose and the risk of heart failure including 5344 cases and 91758 participants (Supplementary Table 3). Six studies were from North America, three from Europe and one was an international study. The summary RR per 20 mg/dl increase in blood glucose was 1.23 (95% CI: 1.15**e**1.32, I^2 = 78.2%, $p_{heterogeneity}$<0.0001) (Fig. 3a). There was no evidence of publication bias with Egger's test, p = 0.59, or with Begg's test, p = 0.59 (Supplementary Fig. 4). The summary RR ranged from 1.20 (95% CI: 1.13**e**1.28) when excluding the study by Ogunmoroti et al. [78] to 1.25 (95% CI: 1.17**e**1.34) when excluding the study by Butler et al. in sensitivity analyses excluding one study at a time [73] (Supplementary Fig. 5). In a sensitivity analysis using the converted RR estimates rather than excluding the reference category, when the reference category was not the lowest category, the summary RR per 20 mg/dl (1.11 mmol/l) was 1.18 (95% CI: 1.08**e**1.29, I^2 = 82.1%, $p_{heterogeneity}$<0.0001) (Supplementary Fig. 6). There was evidence of a nonlinear J-shaped association between blood glucose and heart failure, $p_{nonlinearity}$<0.0001, with increased risk at a blood glucose concentration of 70 mg/dl (3.89 mmol/l) compared to 90 mg/dl (5.00 mmol/l) (summary RR = 1.40, 95% CI: 1.00**e**1.95), and from 110 mg/dl (6.11 mmol/l) and above with a dose**e**response relationship of increased risk with increasing blood glucose concentration (Fig. 3b, Supplementary Table 6).

Forty one cohort studies (36 publications, 36 risk estimates) [35**e**66, 92**e**95] were included in the meta-analysis of diabetes mellitus and heart failure risk among patient populations including 100 284 cases and >613 925 participants (Fig. 3, Supplementary Table 4). One publication included data from 4 studies [42] and another publication included data from 3 studies [58]. Eighteen studies were from America, twelve from Europe, four from Asia, two from Australia, one from Israel and two publications contained data from international studies (including data from four cohort studies). The summary RR was 1.69 (95% CI: 1.57**e**1.81, I^2 = 85.5%, $p_{heterogeneity}$<0.0001) for individuals with diabetes compared to individuals without diabetes (Fig. 4). There was evidence of publication bias with Begg's test, p = 0.03, but not with Egger's test, p = 0.15 (Supplementary Fig. 7), however, when excluding three outlying and small studies [54,60,63] with HRs of 4.72, 5.71 and 10.96 Begg's test was attenuated, p = 0.11, and the results remained similar, summary RR = 1.67 (95% CI: 1.56**e**1.79, I^2 = 86.0%, $p_{heterogeneity}$<0.0001). Alternatively, when excluding nine studies with <100 heart failure cases the test for publication bias was also attenuated, Begg's test, p = 0.16, but the results were similar, summary RR = 1.64 (95% CI: 1.52**e**1.76, I^2 = 88.1%, $p_{heterogeneity}$<0.0001). When using the trim and fill method there was 11 studies added to the analysis and the association was attenuated, but

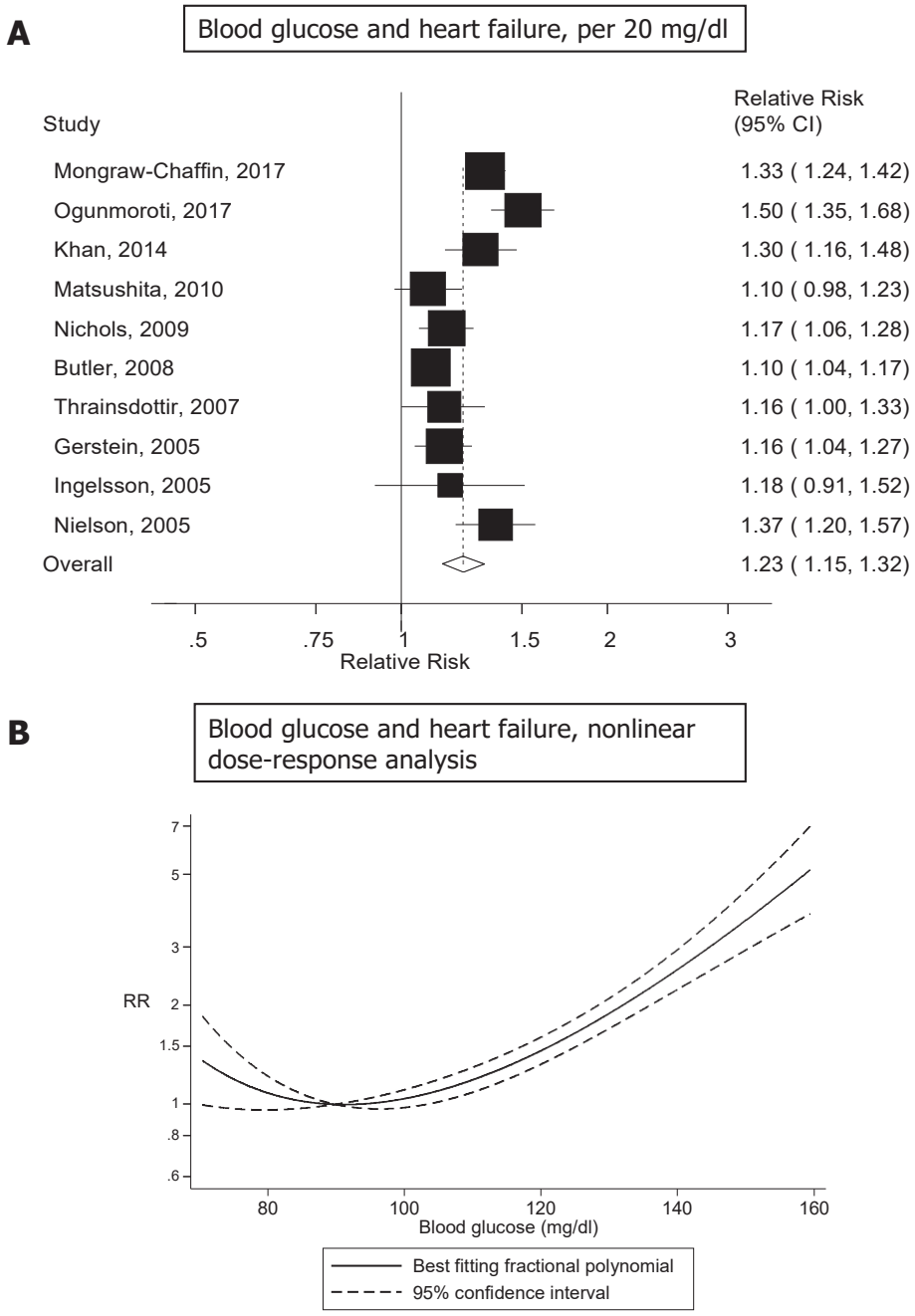

Figure 3 Blood glucose and heart failure in the general population.

remained significant, summary RRZ1.55 (95% CI: 1.45**e**1.66). The summary RR ranged from 1.65 (95% CI: 1.54**e**1.77) when excluding the study by Aksnes et al. [56] to 1.71 (95% CI: 1.58**e**1.85) when excluding the study by Desta et al. [95] in sensitivity analyses excluding one study at a time (Supplementary Fig. 8). Comparing specific patient groups which had comorbid diabetes to those without diabetes, the summary RR was 1.87 (95% CI: 1.53**e**2.27, I^2 Z 0%, $p_{heterogeneity}$ Z 0.71) for patients with atrial fibrillation, 1.64 (95% CI: 1.50**e**1.79, I^2 Z 91.1%, $p_{heterogeneity}$<0.0001) for coronary heart disease patients, 3.29 (95% CI: 0.54**e**19.98, I^2 Z 69.1%, $p_{heterogeneity}$ Z 0.07) for dialysis patients, 2.00 (95% CI: 1.50**e**2.67, I^2 Z 66.1%, $p_{heterogeneity}$ Z 0.05) for patients with hypertension, and 1.85 (95% CI: 1.60**e**2.14, I^2 Z 0%, $p_{heterogeneity}$ Z 0.87) for patients with left ventricular dysfunction (Fig. 3).

Two cohort studies [38,79] were included in the meta-analysis of blood glucose and heart failure risk among patient populations including 1016 cases and 34 309 participants (Fig. 5, Supplementary Table 5). The summary RR per 20 mg/dl increase in blood glucose was 1.25 (95% CI: 0.89 **e**1.75, I^2 Z 95.6%, $p_{heterogeneity}$<0.0001) among patient populations.

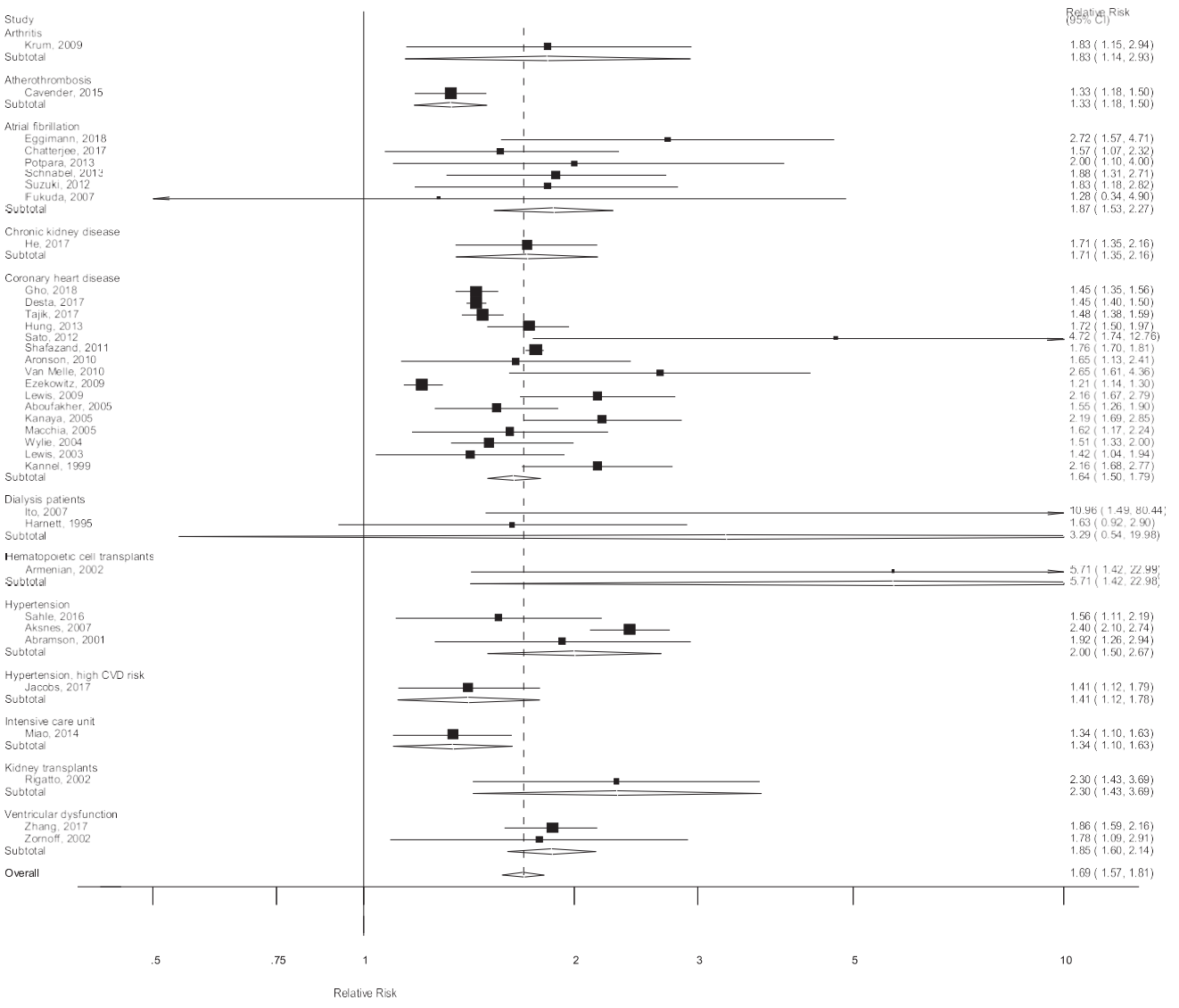

Figure 4 Diabetes mellitus and heart failure in patient populations.

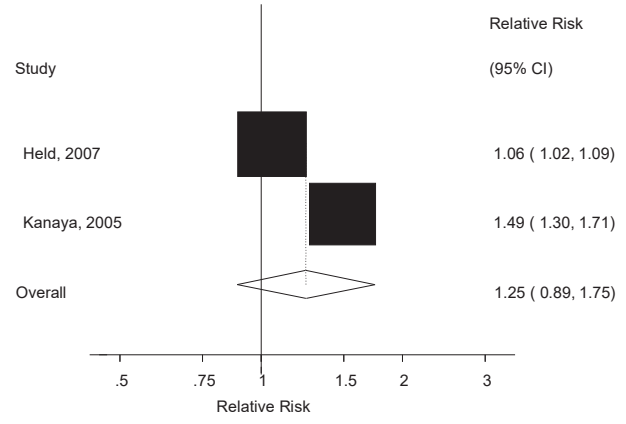

Figure 5 Blood glucose and heart failure in patient populations, per 20 mg/dl.

Subgroup and sensitivity analyses

There were positive associations between diabetes mellitus and heart failure in the population-based studies in all subgroup analyses defined by sex, subtype of heart failure (with reduced or preserved ejection fraction), duration of follow-up, geographic location, number of cases, study quality and adjustment for confounding and potentially mediating factors (including age, alcohol, smoking, BMI, physical activity, resting heart rate, hypertension, blood pressure, serum cholesterol, coronary heart disease, valvular heart disease, atrial fibrillation, and left ventricular hypertrophy) (Supplementary Table 7). With meta-regression analyses there was no indication of heterogeneity between subgroups (Supplementary Table 7). Although heterogeneity in general was very high, there was less

heterogeneity among the studies with adjustment for intake of alcohol, physical activity and resting heart rate (Supplementary Table 7). Similar positive associations were observed across all subgroups among the patient-based studies on diabetes and heart failure risk (Supplementary Fig. 8). There was some indication of heterogeneity between the studies with <200 cases and studies with ≥500 cases ($p_{heterogeneity}$ = 0.01) and between the subgroups of studies that adjusted for hypertension ($p_{heterogeneity}$ = 0.02) and left ventricular hypertrophy ($p_{heterogeneity}$ = 0.03) with weaker associations among larger than smaller studies, and among studies with adjustment for hypertension, but a stronger association among studies with adjustment for left ventricular hypertrophy. There was less heterogeneity among studies with a longer duration of follow-up, among the Asian and Australian studies, and among the studies with adjustment for alcohol, physical activity, resting heart rate, hypertension, blood pressure and left ventricular hypertrophy (Supplementary Table 8).

The mean (median) study quality scores were 7.6 (8.0) in the analysis of the population-based studies (Supplementary Table 9) and 6.9 (7.0) in the patient-based studies (Supplementary Table 10) on diabetes mellitus and the risk of heart failure.

Discussion

This systematic review and meta-analysis suggests that a diabetes diagnosis is associated with a 2-fold increase in the risk of heart failure in the general population and a 69% increase in the relative risk of heart failure in patient-based studies. Type 1 diabetes was associated with a 3.6-fold increase in the risk of heart failure. In addition, there was a 23% increase in the relative risk of heart failure per 20 mg/dl increase in blood glucose among the population-based studies. There was some evidence of a nonlinear J-shaped association between blood glucose and risk of heart failure with an increased risk at 70 mg/dl of blood glucose compared to 90 mg/dl (reference), however, there was evidence of increased risk even in the pre-diabetic blood glucose range with RRs of 1.19 and 1.46 at a blood glucose of 110 and 120 mg/dl and further increases with higher levels of blood glucose. The positive associations between diabetes and heart failure risk were observed both in men and women, and was consistent across geographic locations. The results were robust in numerous subgroup and sensitivity analyses.

Several mechanisms could explain the increased risk of heart failure observed in individuals with diabetes mellitus. Diabetes increases the risk of hypertension [96,97], coronary heart disease [98] and atrial fibrillation [99] which are strong risk factors for heart failure [8,10,27]. In addition, diabetes is related to the development of a special cardiomyopathy often referred to as diabetic cardiomyopathy [100,101], which is characterized by microangiopathy, myocardial fibrosis, and autonomic neuropathy [102] and makes the heart unable to pump effectively. Excess circulating glucose and free fatty acids lead to lipid accumulation not only in adipose tissue, but also in the heart [103]. Cardiomyocytes are not able to store excess lipids, which then cause cellular damage by lipotoxicity. Lipid fragments which are insufficiently processed lead to activation of inflammatory signaling pathways, which interfere with insulin signaling causing insulin resistance [104] and further limits cardiac glucose supply causing a shift towards fatty acid oxidation. Cardiomyocytes subjected to hyperglycemia and subsequent oxidative stress display swollen mitochondria, reduced mitochondrial number, defective myofibrils and intercalated discs [105]. Accumulation of lipids in the heart [106], collagen deposition and fibrosis [107,108] and/or hyperinsulinemia due to insulin resistance [109] contributes to increased risk of hypertrophy of the heart observed in diabetes patients [110]. Both type 1 and type 2 diabetes-induced hyperglycemia can result in myocardial fibrosis, mitochondriopathy, myocyte hypertrophy, and deranged myofibrils, and all of these structural changes may result in heart failure if not treated [105].

Limitations of the present systematic review and meta-analysis includes potential confounding, misclassification of diabetes and heart failure diagnoses, heterogeneity between studies, and the possibility of publication bias affecting the results. Persons with diabetes oftentimes have less healthy lifestyles than persons without diabetes, including higher BMI, less physically activity and they may be more likely to smoke, and have unhealthy diets. Several of the included studies adjusted for the most important confounding factors and the results persisted across all subgroup analyses including those with adjustment for alcohol intake, smoking, adiposity and physical activity, and we did not find evidence of heterogeneity between these subgroups. Residual confounding is possible, but to be able to fully explain the observed associations, the unmeasured confounding factor would have to be strongly associated with both diabetes and heart failure and to be largely independent of the other factors adjusted for in the multivariable models. Diabetes mellitus was assessed by self-report of diagnosis in most studies, thus it is likely that there is underestimation of the number of subjects with diabetes as diabetes diagnoses tend to be under-diagnosed [111], however, because we only included cohort studies any such misclassification would most likely lead to an underestimation of the association between diabetes mellitus and heart failure. Any under-ascertainment or misclassification of heart failure diagnoses would for the same reason most likely lead to an underestimation of the association between diabetes mellitus and heart failure. There was very high heterogeneity in the overall analysis and this persisted across many of the subgroup analyses, but lower heterogeneity was observed among the studies with adjustment for alcohol intake, physical activity and resting heart rate. In the analysis of patient-based studies there was lower heterogeneity among studies with a longer duration of follow-up, among Asian and Australian studies, and among studies with adjustment for alcohol, physical activity, resting heart rate, hypertension, blood pressure or left ventricular hypertrophy. As all the included studies reported risk estimates in the direction of increased risk the observed heterogeneity appeared to be

more driven by differences in the effect sizes rather than differences in the presence or absence of an association. Although there was some indication of publication bias in the analysis of diabetes and heart failure risk in the patient-based studies, we found that this appeared to be driven by three outlying studies or nine rather small studies with <100 cases, and when these studies were excluded the tests for publication were attenuated, but the results were not materially altered. Alternatively, when using the trim and fill method to evaluate the potential impact of publication bias on the results the association was only slightly weaker, but it remained statistically significant.

The present meta-analysis has several strengths such as inclusion of only prospective studies in the analyses (which avoids recall bias and reduces the potential for selection bias), and the very large sample size including >401 000 cases, >21.4 million participants in the population-based studies and >100 000 cases and >600 000 participants in the patient-based studies, which contributed to a robust estimate of the association between diabetes mellitus and risk of heart failure. The ample statistical power also made it possible to conduct several subgroup and sensitivity analyses and the results persisted in these additional analyses and in addition, the quality of the included studies was high. The positive association between diabetes and risk of heart failure was observed in both men and women and in American, European and Asian studies and there was no heterogeneity by sex or geographic location.

Worldwide the number of persons living with diabetes is projected to increase from 422 million in 2014 to 700 million by 2025, and may in addition to the obesity epidemic [5] contribute to additional cases of heart failure if the current trends continue. Given that there was evidence of increased risk of heart failure even within the pre-diabetic range of fasting blood glucose the current findings may have important clinical and public health implications, however, there is a need for further confirmation by additional large-scale cohort studies. Healthy diets and lifestyles that reduce the risk of diabetes which emphasize a high intake of whole grains and less red and processed meat and sugar-sweetened beverages [112**e**114], smoking cessation [115], physical activity [116] and weight control [117] may reduce the risk of heart failure both directly and indirectly [5,118**e**121] and this may have benefits for the prevention of many other diseases as well [98,122**e**125]. Any further studies might want to further assess the dose**e**response relationship between fasting blood glucose and heart failure risk and to clarify whether the increased heart failure risk in individuals with diabetes may be modified by a healthy lifestyle or medication use.

Conclusion

In conclusion, this meta-analysis suggests that individuals with diabetes from the general population have a 2-fold increase in the relative risk of developing heart failure compared to individuals without diabetes, while individuals with diabetes who also have other chronic diseases have a 69% increase in the relative risk of heart failure compared to individuals without diabetes. In addition, a 20 mg/dl increase in blood glucose was associated with a 23% increase in the risk of heart failure and there was evidence of increased even within the pre-diabetic range of blood glucose concentrations.

Contribution

DA designed the research, conducted the statistical analyses and wrote the first draft of the paper. MN, SS, TF and DA conducted the literature screening. All authors interpreted the data, revised the subsequent drafts for important intellectual content, read and approved the final manuscript. D. Aune takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest

The authors declare that there is no duality of interest associated with this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.numecd.2018.07.005.

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