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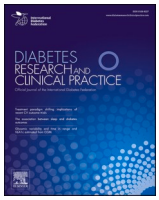

Diabetes and risk of heart failure in people with and without cardiovascular disease: systematic review and meta-analysis

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A B S T R A C T

Background: People with diabetes have an increased risk of heart failure (HF), compared to those without diabetes. However, no comprehensive systematic review and meta-analysis has explored whether these associations could differ in relation to prevalent cardiovascular disease (CVD).
Aims: To estimate the association between diabetes and incident heart failure (HF), compared to without diabetes, in individuals with and without CVD.
Methods: PubMed, Scopus, and Web of Science were searched for observational cohort studies from the earliest dates to 22nd March 2023. A random-effects model calculated the pooled relative risk (RR).
Results: Of 11,609 articles, 31 and 6 studies reported data in people with type 2 diabetes (T2D) and type 1 diabetes (T1D) respectively. Individuals with T2D had an increased risk of HF irrespective of CVD prevalence: 1.61 (95% CI: 1.35–1.92) in those with CVD; 1.78 (1.60–1.99) without CVD; and 2.02 (1.75–2.33) with unspecified CVD prevalence. Meta-regression did not identify a significant difference comparing HF risk in T2D individuals with vs. without CVD ($p = 0.232$).
Conclusion: People with T2D, compared to those without diabetes, have similar increased risk of HF, regardless of CVD prevalence. Strategies proven to lower HF risk in T2D individuals should be prioritized for those with and without CVD.

1. Introduction

Diabetes mellitus and heart failure (HF) tend to exist as common comorbid conditions [1], with approximately 4.3 to 28 % of HF individuals with prevalent type 2 diabetes (T2D) and 12–57 % of T2D individuals presenting with HF [2]. People with diabetes also have an increased risk of HF, which subsequently increases their risk of hospitalizations [3,4] and mortality [5,6] to further burden global economic and healthcare resources [7]. Nearly 537 million adults are currently living with diabetes world-wide, estimated to rise to 643 million by 2030 [8]; HF currently affects 64.3 million people globally [9], predicted to rise by 50 % in the next 20 years [10]. Hence, early prevention and management strategies to lower HF risk in individuals with diabetes is of public health importance [11,12]. This is further reinforced in evidence showing HF as the most common initial presentation of cardiovascular disease (CVD) in people with diabetes [13].

A previous meta-analysis from 2018 [14] showed that persons with diabetes have an increased risk of HF, relative to without diabetes (relative risk, RR: 2.06, 95 % confidence interval, CI: 1.73 to 2.46). However, this study pooled estimates from heterogeneous study designs (e.g., case-control and cohort), which could have led to biased estimates. To address this limitation, a recent 2020 meta-analysis [15], exclusively using data from observational cohort studies, reported that individuals with diabetes have an increased risk of new-onset HF, relative to without diabetes (RR: 2.14; 95 % CI: 1.96 to 2.34). However, the author's included studies that did not adjust for at minimum age and sex, which could have led to biased results. The study also found an attenuated association when restricting the population to individuals with prevalent coronary heart disease (CHD) (RR: 1.94, 95 % CI: 1.77 to 2.12) [15]. It remains unclear whether, and to what extent, the association between diabetes and incident HF could differ in populations with and without broad CVD.

Clarifying this uncertainty is relevant since the presence of CVD could be influencing therapy prescription patterns, i.e. recent evidence shows sodium-glucose co-transporter 2 (SGLT-2) inhibitors are preferentially administered to T2D individuals with, compared to without CVD for CVD and CVD mortality [16]. In addition, compared to those without CVD, individuals with T2D and prevalent CVD tend to present with a different risk factor profile and lower risk factor control [17]. However, whether such differences contribute to HF risk-disparities in

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people with T2D, compared to without diabetes by CVD prevalence remains unclear with sparse evidence. This is important to potentially develop more tailored strategies to lower HF risk accounting for CVD prevalence in people with diabetes [18].

This systematic review and meta-analysis aims to: [1] investigate the association between diabetes (type 2 or type 1) and incident HF, compared to people without diabetes, in individuals with and without CVD; [2] identify the potential sources of heterogeneity by conducting subgroup and sensitivity analysis.

2. Methods

2.1. Databases and search strategy

This study was conducted in accordance with the Preferred Reporting items for Systematic Reviews and Meta-analysis (PRISMA) (**supplemental material**). The protocol is registered at https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=259885. We searched electronic databases (PubMed, Scopus, and Web of Science) for observational cohort studies published from the earliest start database-specific date to 22nd March 2023. We also hand searched the reference lists of relevant systematic reviews and meta-analysis studies to capture additional studies. The search strategy was developed with the assistance of two clinical epidemiologists. The full search strategy is provided in **Supplementary Table S1**.

2.2. Study eligibility

We included observational cohort studies that reported RR (e.g., hazard or rate ratio) with their 95 % CI for the association between diabetes (vs. without diabetes) and incident HF. We included studies that clearly defined the exposure group as 'diabetes', 'type 1 diabetes' or 'type 2 diabetes' and the control group as 'people without diabetes'. We defined T2D as either 'diabetes' or 'T2D' since 80–95 % of individuals with diabetes have T2D [19]. We included studies if the outcome was incident HF and excluded participants with clearly defined prevalent HF at study entry. In studies where the exclusion of HF at baseline was unclear, we included the study. When handling duplicate cohorts with over-lapping study time periods, we included the study with the latest available data. We excluded studies that did not account for at least age and sex as confounding variables, in addition to studies that were not in English language. Three authors thoroughly defined the study inclusion and exclusion criterion, as well as the electronic search strategy. An author independently screened the title, abstracts, and full text articles to identify relevant papers; two additional authors were involved in the screening process to discuss study inclusion in detail against the predefined eligibility criterion in case of uncertainty. Any disagreement was settled among all authors and any discrepancy resolved by consensus.

2.3. Study quality

The Newcastle-Ottawa Scale (NOS) for quality assessment of cohort studies [20] was used to evaluate the risk of bias (**Table S2**). This includes evaluating the selection of study groups (Selection), comparability of groups (Comparability), and ascertainment of the outcome (Outcome) [20]. Studies were considered of low, average, and high-quality studies by scores of 0–4, 4–6, and 7–9 respectively [20]. Three authors assessed the quality of studies, and any ambiguities were resolved through discussion with all other authors.

2.4. Data extraction

We extracted the reported RR and 95 % CI for the risk of incident HF comparing individuals with vs without diabetes, separately by diabetes type. Data extracted from each study included: first author's last name, publication year, sex, diabetes type, CVD prevalence (i.e., cohort with prevalent CVD; without CVD; and unspecified CVD prevalence - defined as a cohort with unstratified or unknown CVD prevalence), mean age, mean year of baseline recruitment, number of participants, incident HF cases, duration of follow-up, continent, country, cohort name, and adjustments for confounding variables – further information found in **Table S3**. An author extracted the data, which was checked for accuracy by all other authors. Study authors were contacted if the full text or study estimates were not available.

2.5. Data analysis

We calculated the pooled estimate of RR with 95 % CI separately for each population (with prevalent CVD, without CVD and unspecified CVD prevalence) using Sidik-Jonkman random-effects model. Heterogeneity was assessed using I^2 statistic, where < 25 %, 25–50 % and 50 % was interpreted as indicative of low, moderate, and high. Associations were stratified by sex to investigate sex-specific differences and a meta-regression was conducted across several risk factors, including mean age, publication year, recruitment year, continent, ascertainment of diabetes and heart failure – further details can be found in **Table S4**.

Funnel plots were used to assess potential small study effects, in addition to the Egger's test. If publication bias was found to be significant, we used the trim-and-fill method based on the Duval and Tweedle non-parametric method [21] to adjust for publication bias.

In a sensitivity analysis, we excluded studies that did not explicitly state HF exclusion at baseline. In addition, we only included studies that defined T2D as 'T2D only', compared to 'diabetes mellitus or T2D' to assess the robustness of our exposure definition. We also excluded duplicate cohorts across all populations vs. each subgroup population to investigate whether our results could be impacted by potential repeated participants.

Two-sided $p < 0.05$ was considered statistically significant. All analyses were conducted using Stata version 17.0 (Stata Corp, Texas, and USA).

3. Results

3.1. Study characteristics

Of the 11,609 studies, 31 articles [6,13,22–50] consisting of 34 cohorts for T2D were identified (prevalent CVD: 11; without CVD: 12; unspecified CVD prevalence: 11) and 6 articles [6,24,27,29,46,51] consisting of 7 cohorts were identified for T1D (prevalent CVD: 1; without CVD: 3; unspecified CVD prevalence: 3) (Fig. 1). The total number of individuals were 501,536 for cohorts of T2D with CVD, 27,855,580 for T2D without CVD, 9,046,486 for T2D with unspecified CVD prevalence; 251,538 for T1D with CVD, 18,580,888 for T1D without CVD, and 3,690,911 for T1D unspecified CVD prevalence (**Table S3**). Of studies investigating T2D, mean age was 57.99, 61.25 and 64.74 in those with CVD, without CVD and unspecified CVD prevalence respectively. Mean baseline recruitment (years) was higher in those with prevalent CVD (2007), compared to without CVD (2004) and unspecified CVD (2001). Most studies were from Europe at 45.45 %, 50.00 % and 54.55 % in those with CVD, without CVD and unspecified CVD prevalence. In T2D, most studies had low risk of bias, with 90.91 %, 91.67 % and 72.73 % reported in populations with CVD, without CVD, and unspecified CVD prevalence. **Table S3** summarises the characteristics of all included studies.

3.2. Meta-analyses

Meta-analysis of the RR (95 % CI) between T2D and HF, compared to people without diabetes, showed similar RR regardless of CVD prevalence (with prevalent CVD: 1.61; 1.35 to 1.92; without prevalent CVD: 1.78; 1.60 to 1.99 and unspecified CVD prevalence: 2.02; 1.75 to 2.33 (Fig. 2). The difference in the association between T2D and HF,

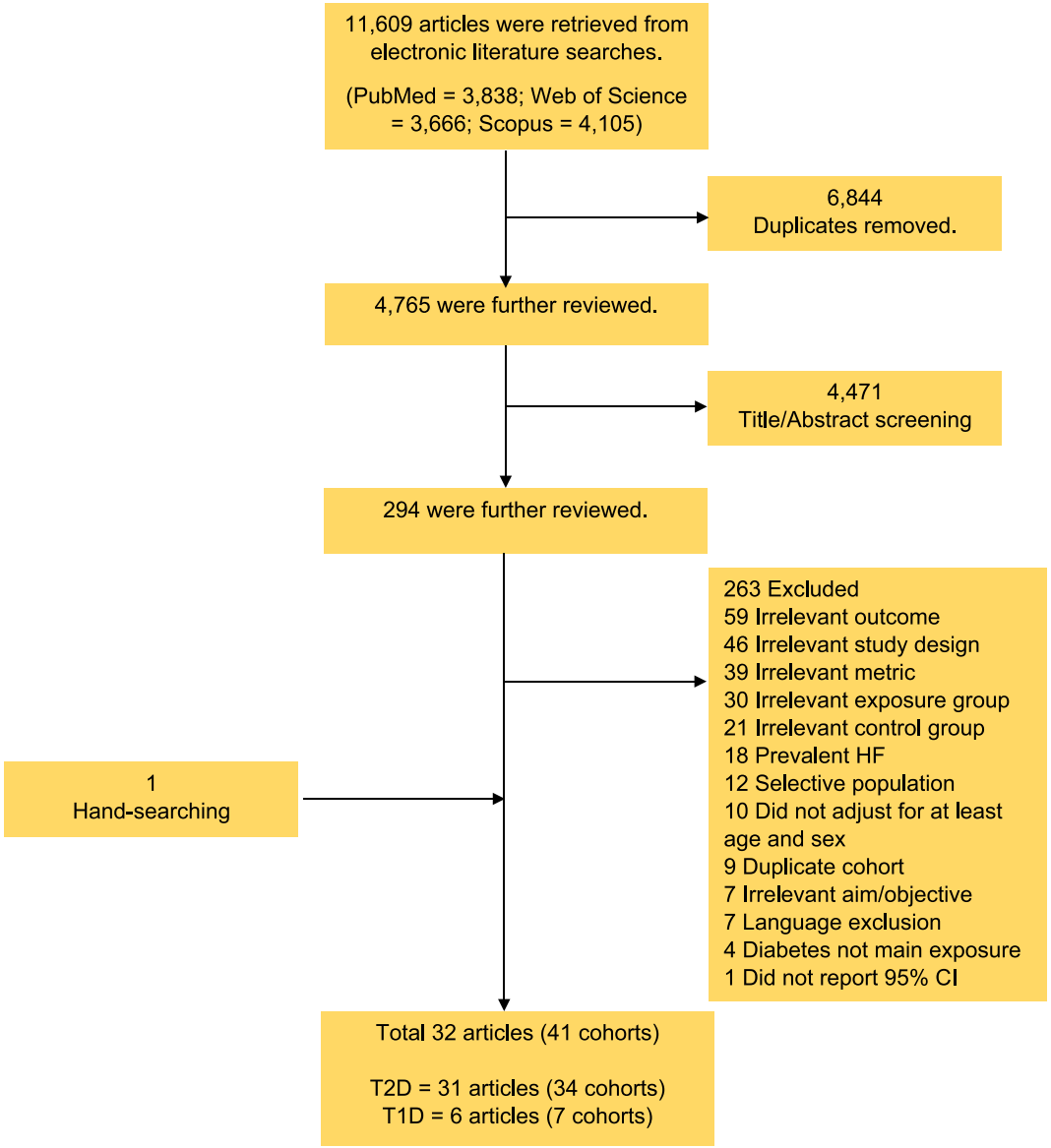

Fig. 1. Flow chart of the study selection process. T2D = type 2 diabetes; T1D = type 1 diabetes; HF = heart failure, CI = confidence interval.

compared to people without diabetes in populations with vs. without CVD was not statistically significant (p = 0.232) (**Table S4**). The I^2 statistic for heterogeneity between studies was 92.73 %, 98.86 %, 99.40 % for cohorts with CVD, without CVD, and unspecified CVD prevalence, respectively, indicative of substantial heterogeneity.

Meta-analysis of the RR (95 % CI) for T1D and HF, compared to people without diabetes, showed 1.59 (1.42 to 1.78) in individuals with prevalent CVD, 2.94 (2.61 to 3.32) without CVD, and 4.11 (2.96 to 6.27) in a cohort with unspecified CVD prevalence (Fig. 3). The I^2 statistic for heterogeneity between studies could not be estimated for T1D studies with prevalent CVD since only one study was available, while it was 8.25 % for T1D studies without CVD and 94.22 % for T1D studies with unspecified CVD prevalence.

3.3. Publication bias

Evidence of publication bias was identified in T2D studies with prevalent CVD, with funnel plot indicating asymmetry and Egger's test being statistically significant (p < 0.001). No indication of publication bias was shown from funnel plots in T2D studies without prevalent CVD and unspecified CVD prevalence, with Egger's tests being statistically non-significant (p = 0.713 and p = 0.519 respectfully) (**Figure S1**). Results following the trim-and-fill method for studies with T2D, suggested that there were no hypothetical unpublished studies in those without CVD and with unspecified CVD prevalence, but 4 studies were identified for those with prevalent CVD (**Table S5**). The Egger's test suggests evidence of publication bias for T1D studies with unspecified CVD prevalence (p = 0.000), but no evidence for T1D studies without CVD (p = 0.337) (**Figure S2** and **Table S6**).

3.4. Meta-regression and subgroup analysis

Meta-regression in T2D individuals without CVD identified a significant association between the RR of HF and continent (p = 0.035); in T2D individuals with prevalent CVD, there was a significant association between RR and diabetes ascertainment (p = 0.007) (**Table S4**). In T2D studies with prevalent CVD, no statistical difference in the association between HF and type of prevalent CVD at baseline was identified (p = 0.565) (**Table S4**). In T2D studies with unspecified CVD prevalence, subgroup analysis by sex found no statistical difference comparing women vs. men (p = 0.931) (**Table S4 and Figure S3**). Due to limited studies, further meta-regression analysis by sex and T1D studies could

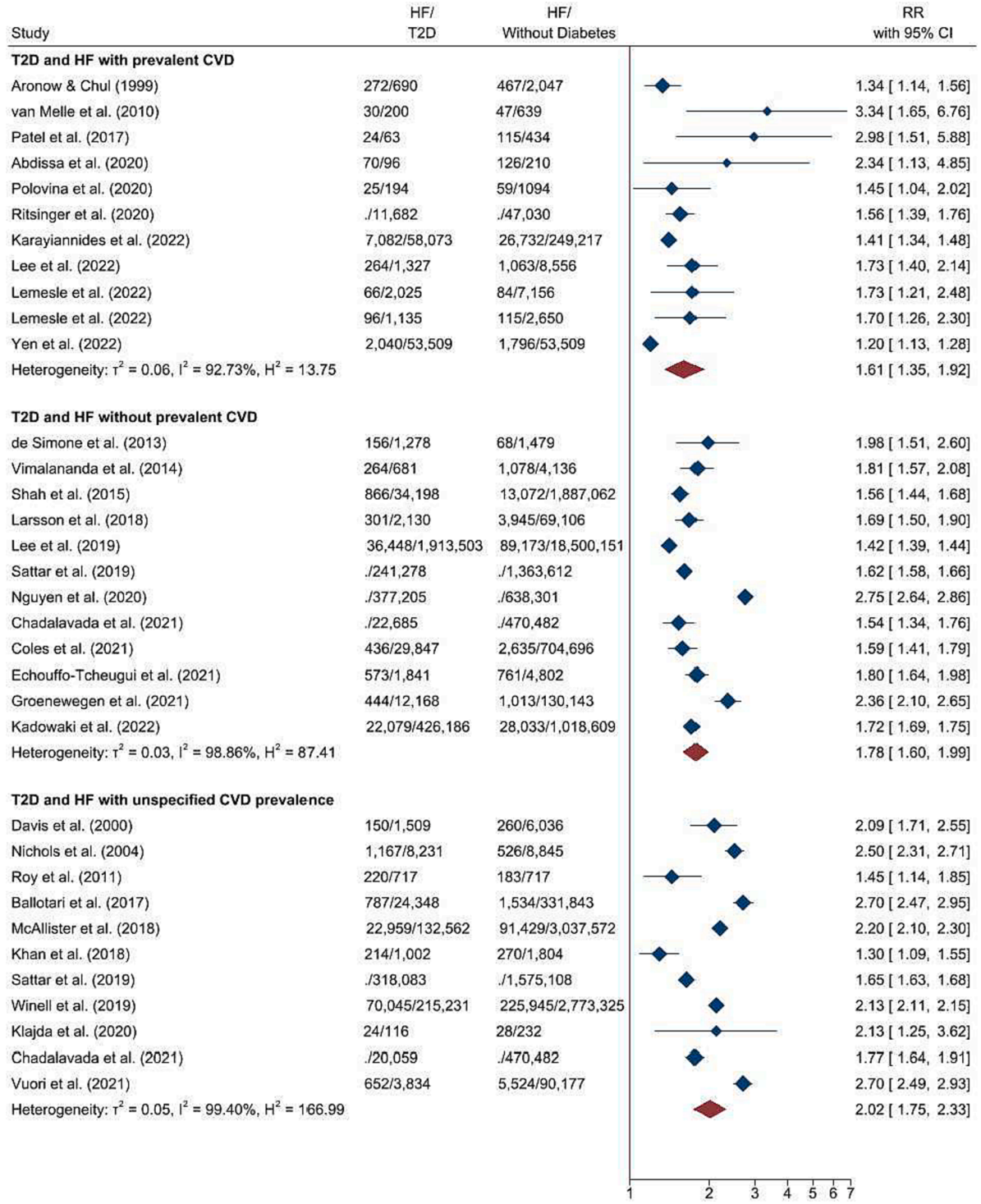

Fig. 2. Forest plot of the association between type 2 diabetes (T2D) and heart failure (HF) in populations with different cardiovascular disease (CVD) prevalence.

not be conducted (<10 studies).

3.5. Sensitivity analysis

For T2D, we excluded studies where HF prevalence at baseline was unclear or uncertain, resulting in marginally heighted estimates in those with and without prevalent CVD, but no difference in RR was identified for studies with unspecified CVD prevalence (**Figure S4**). We also excluded studies that defined T2D as 'diabetes mellitus' and included papers defining T2D as 'T2D' only to assess the robustness of our exposure definition. This notably attenuated the RR of HF for T2D individuals with CVD and without CVD but heightened for studies with unspecified CVD prevalence (**Figure S5**). We also excluded studies [38,46] to investigate whether associations differed due to the possibility of duplicate participants for which our findings were robust (T2D individuals with vs. without CVD, p = 0.189) (**Table S4**).

4. Discussion

This systematic review and meta-analysis found that individuals with

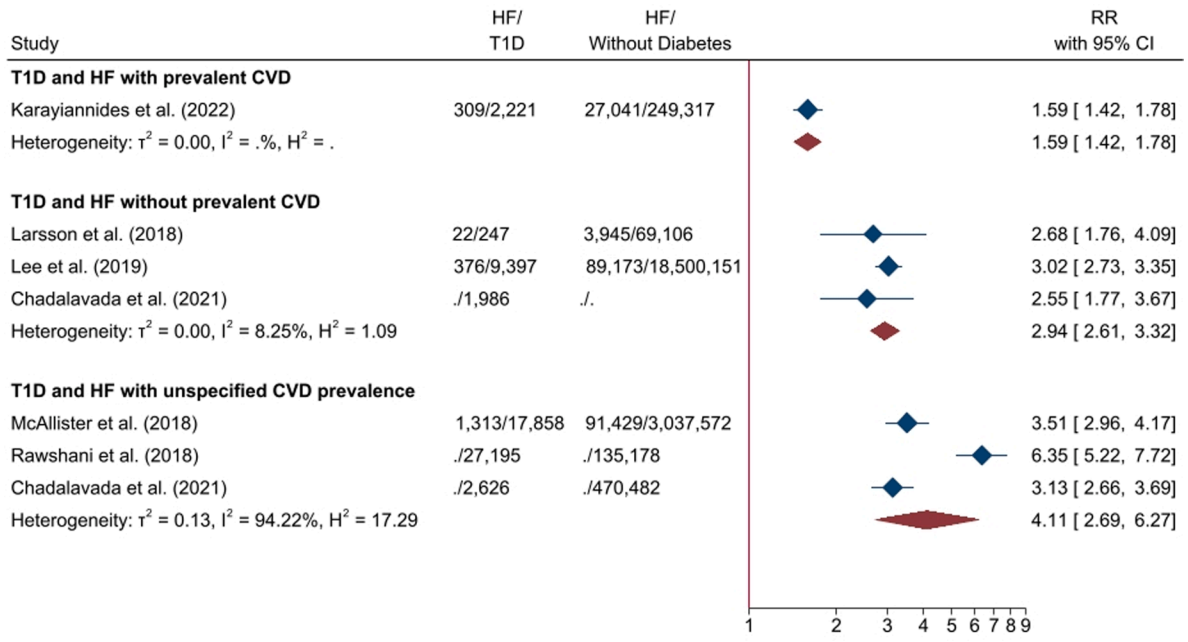

Fig. 3. Forest plot of the association between type 1 diabetes (T1D) and heart failure (HF) in populations with different cardiovascular disease (CVD) prevalence.

T2D have an increased risk of HF, relative to without diabetes, irrespective of CVD prevalence.

4.1. Comparisons with existing literautre

In populations with unspecified CVD prevalence, our findings are consistent with previous meta-analysis as we report similar RR of HF and overlapping 95 % CI to Aune et al's 2018 meta-analysis (RR: 2.06, 95 % CI: 1.73 to 2.46) [14] and Kodama et al's 2020 meta-analysis study (RR: 2.14, 95 % CI: 1.96 to 2.34) [15]. Compared to these studies, our investigation accounted for table 2 fallacy, a notion proposed by Westreich and Greenland [52], by which we only included studies were diabetes was the main exposure of interest and not a secondary variable (i.e., confounder) to minimize biased estimates and misleading interpretations [52]. Moreover, compared to Kodama et al, we excluded studies that did not at minimum account for age and sex as confounding variables, whilst they included 11 studies which did not adjust for any confounders, possibly leading to biased estimates [15]. Moreover, the current study includes 15 more recent articles compared to Kodama et al., allowing for more up-to-date estimates [15].

Our findings are also consistent with Chen et al's 2019 study, reporting that without heart disease, people with T2D have an increased risk of HF, compared to those without diabetes (RR: 1.56, 95 % CI: 1.46 to 1.66) [53]. However, they adjusted for heart disease, compared to excluding at study entry, which the current study addresses to minimise residual confounding. In addition, Chen et al's study only included people of Chinese ethnicity, whereas our study includes people from different continents, improving generalisability [53]. The notable lower RR compared to the current study could be due to various lifestyle and environmental differences [54], such as higher vegetable and green tea consumption in Chinese vs. Western countries [53,54]. This could also be since the author's used inpatient claims data to ascertain HF cases, possibly underestimating the estimates, though unclear [26].

Contradictory to Ohkuma et al's 2019 meta-analysis study [55] we found women with T2D have similar RR of HF, relative to men with unspecified CVD prevalence. An explanation for this difference could be since we applied a more stringent inclusion criterion, for example compared to Ohkuma et al's study, we excluded Pollicardo et al. [56] as people with HF three years prior to study entry were excluded and Ahmad et al. [57] due to irrelevant control group (people with diabetes vs. people without diabetes, obesity and hypertension), minimising biased estimates. Another explanation could be due to heterogeneity in study sample size, definition of heart failure, study design or adjustment of confounders, though unclear.

4.2. Pathological mechanisms

The increased RR of HF in persons with diabetes is likely due to the presence of hyperglycaemia [58,59], known to activate the renin-angiotensin system (RAS) [60] and promote production of reactive oxygen species (ROS) [61,62], leading to increased inflammation, coagulation, and endothelial cell dysfunction, risk factors of HF [58,59]. Alternatively, different underlying mechanisms could be at play by CVD prevalence [63,64], as Verkleji et al. found that T2D persons with prevalent CVD, compared to without CVD, could have greater thrombin generation, increasing their risk of atherosclerosis and subsequently that of HF in T2D individuals with CVD, though unclear [63,65]. Peng et al. reported that T2D individuals with CVD, compared to without CVD, could be presenting with higher von Willebrand factor plasma levels, enhancing platelet aggregation and endothelial dysfunction, leading to the development of HF, though unclear due to limited evidence. Further research is warranted to better understand the underlying mechanisms underpinning this association in detail, particularly comparing people with vs. without diabetes by CVD prevalence [64].

4.3. Strengths and limitations

A strength of our study is the large sample size, including a high number of studies and participants, HF events and duration of follow-up, ranging from 6 months to 22.5 years. Secondly, we excluded studies where 'diabetes' was not the main exposure of interest to reduce the risk of table 2 fallacy and biased estimates [52]. In addition, we only included studies with minimum adjustment for at least age and sex, further reducing the risk of biased estimates, compared to previous meta-analysis [15]. When handling duplicate cohorts, we included the study with the latest available data to provide contemporary results; this included 15 more recent studies since the last published search from 2019 on the topic [15]. An additional strength is our thorough sensitivity analyses, including assessing the robustness of our estimates to the definition of T2D and HF exclusion at baseline.

Some limitations include the high degree of heterogeneity between studies and the potential publication bias, indicating that the results should be interpreted with caution. Second, the lack of studies found for individuals with T1D, particularly with prevalent CVD, could hinder the reliability of our results and further limits the possibility to explore the sources of heterogeneity. Thirdly, the meta-regression results should be considered in relation to the possibility of ecological fallacy [66]. In addition, our meta-regression analysis and subgroup analysis by CVD prevalence was restricted due to limited reporting of baseline characteristics and/or stratification of HF RR (95 % CI) by risk factors: for example, information on study setting (hospital vs. community), diabetes duration, fasting glucose concentrations and HF phenotype (with and without ejection fraction) was scattered.

4.4. Key findings and implications

Our results indicate that, irrespective of CVD prevalence, people with T2D have an increased risk of incident HF, compared to those without diabetes. This highlights a need to target effective HF prevention and management strategies to people with T2D regardless of a previous CVD event. Future research should validate these findings using individual-level data from both trials andlarge observational populations to provide more accurate estimates [16 67]. Furthermore, there were limited studies investigating the association between T1D and HF, compared to people without diabetes, by CVD prevalence, particularly in individuals with prevalent CVD. Lastly, we identified potential publication bias in cohorts with prevalent CVD and high heterogeneity in all populations, with meta-regression analysis suggesting 'diabetes ascertainment' and 'continent' as potential sources of heterogeneity in T2D populations with and without CVD, respectively. The substantial heterogeneity could also be due to other risk factors (i.e., medications, fasting glucose concentrations, percentage ejection fraction, duration of diabetes, body mass index, ethnicity), though unclear due to limited data. Future research with more granular individual-level data should account for such risk factors at the study design stage and prioritize reporting detailed cohort baseline characteristics in people with vs. without diabetes to examine potential sources of heterogeneity between studies.

4.5. Conclusion

Individuals with T2D have an increased risk of developing HF, whose magnitude is unrelated to the presence of prevalent CVD. Effective strategies proven to lower HF risk should be considered in subjects with T2D irrespective of CVD history to most optimally lower HF risk.

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CRediT authorship contribution statement

Francesco Zaccardi: conceptualization, data collection, data analysis, validation, interpretation of results, investigation, methodology, project administration, supervision, writing - revising and editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf. Miss Kajal Panchal declares this research was supported by the National Institute for Health Research (NIHR) Applied Research Collaboration East Midlands (ARC EM).

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Appendix A. Supplementary data

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