Title Page

Full Title:
Global Prevalence of Myocardial Fibrosis among Individuals with Cardiometabolic Conditions: A Systematic Review and Meta-Analysis

Short Running Title:
Prevalence of Myocardial Fibrosis

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Abstract

Background: Cardiometabolic conditions including hypertension, diabetes, hyperlipidaemia and obesity are significant risk factors for cardiovascular diseases. Myocardial fibrosis (MF) is a complication and final common pathway of these conditions, potentially leading to heart failure, arrhythmias and sudden death. Existing reviews explored pathophysiological changes and treatment of MF, but the global prevalence of MF among individuals with cardiometabolic conditions remain limited.

Objectives: To evaluate the global prevalence of MF in individuals with cardiometabolic conditions and explore factors influencing its rate.

Methods: CINAHL, Cochrane Library, Embase, PubMed, ProQuest Theses and Dissertations, Scopus, and Web of Science were systematically reviewed until January 2024. Studies included individuals with hypertension, type 2 diabetes mellitus, hyperlipidaemia, and obesity, with MF prevalence assessed via biopsy or Late Gadolinium Enhancement-Cardiac Magnetic Resonance (LGE-CMR). Meta-analysis was conducted using jamovi and factors associated with MF were synthesised narratively. This review is registered on PROSPERO, CRD42024544632.

Results: The meta-analysis included 52 articles involving 5,921 individuals. 32.7% of individuals with cardiometabolic conditions developed MF, with hypertension demonstrating the highest prevalence [35.2%(95%CI:25.5-45.0)]. Biopsy-based studies reported a higher prevalence

[75.6%(95%CI:53.6-97.6)] compared to LGE-CMR studies [26.8%(95%CI:20.6-33.0)]. Key factors associated with MF included increased LV mass/ LV hypertrophy, reduced LV function, and myocardial stiffness.

Conclusions: This first global review estimates that one-third of individuals with cardiometabolic conditions develop MF, with the rate expected to rise. Standardized CMR measures cut-offs are needed to address prevalence inconsistencies. Future research should explore MF prevalence using diverse samples, combined CMR measures, considering socio-demographic and clinical factors for more accurate estimates.

Lay Summary:

About one in three people with high blood pressure, diabetes, high cholesterol, and obesity develop myocardial fibrosis (MF)—a type of heart tissue scarring which disrupt normal heart function, increasing the risk of heart failure, life-threatening heart rhythms, and even death.

- Different methods to assess MF (such as biopsies versus heart imaging) led to variations in reported rates, largely due to limitations in heart imaging for detecting certain types of MF.
- Future research should explore how common MF is across different populations. Using a combination of advanced heart imaging techniques and considering patient characteristics such as medical history and clinical details could help provide more accurate insights into this condition and how to manage it.

Keywords:

Cardiometabolic risk factors, myocardial fibrosis, cardiac magnetic resonance, late gadolinium enhancement, endomyocardial biopsy, prevalence

Abbreviations:
BMI: Body mass index
CAD: Coronary artery disease
CMR: Cardiac magnetic resonance
CVD: Cardiovascular disease
ECM: Extracellular matrix
ECV: Extracellular volume
LV: Left ventricle
MI: Myocardial infarction
PRISMA: Preferred reporting items for systematic reviews and meta-analyses
T2DM: Type 2 diabetes mellitus

Introduction

Cardiometabolic conditions represent a constellation of diseases including hypertension, diabetes, hyperlipidaemia and obesity that are risk factors for cardiovascular diseases (CVD) [1]. The rising prevalence of cardiometabolic conditions have emerged as a leading global health concern due to worrying trends of morbidity and mortality worldwide [2]. Cardiometabolic conditions are closely interrelated and often occur in tandem, suggesting a co-pathogenesis of metabolic abnormalities [3] that lead to adverse health outcomes. Among various complications associated with cardiometabolic conditions, myocardial fibrosis stands out as a critical pathological process with significant clinical implications [4-6].

Myocardial fibrosis is characterised by the expansion of the myocardial interstitium due to the excessive accumulation of extracellular matrix (ECM) [7]. This results in increased matrix stiffness leading to abnormalities in cardiac function [8]. From a histological perspective, myocardial fibrosis can be classified into two subtypes: 1) replacement fibrosis, where

macroscopic collagen-based scar form in response to cardiomyocyte death, and 2) interstitial myocardial fibrosis characterised by microscopic deposition of ECM proteins in interstitial areas without directly association with cardiomyocyte death [9]. Replacement and interstitial fibrosis often co-exist and are constant features of pathologic cardiac remodelling, a common complication of cardiometabolic conditions [10]. Therefore, myocardial fibrosis is considered an integral component of various CVD and significant independent predictor of adverse cardiac outcomes including heart failure, arrhythmias and sudden death [9].

Traditionally, myocardial fibrosis is evaluated by histopathological analysis of endomyocardial biopsy or autopsy specimens, which remains the gold standard for its identification and quantification [9]. The extent is quantified by measuring collagen volume fraction. Currently, cardiac magnetic resonance (CMR) has emerged as the new gold-standard for non-invasive imaging to evaluate the extent and characteristics of myocardial fibrosis [11]. Late gadolinium enhancement (LGE) imaging is utilised to detect replacement fibrosis while interstitial fibrosis can be assessed through validated T1 mapping approaches including native T1, myocardial extracellular volume (ECV) fraction and indexed ECV/indexed interstitial volume [12,13].

Despite its clinical importance and prognostic value, the global prevalence of myocardial fibrosis in individuals with cardiometabolic conditions has not been quantified. Existing and ongoing prevalence reviews have primarily focused on other populations such as intensive endurance athletes [14], patients with aortic stenosis [15] and individuals with human immunodeficiency viruses [16]. The reviews involving cardiometabolic conditions specifically examined the association between myocardial fibrosis and diabetes [17,18]. Understanding the prevalence of

myocardial fibrosis in individuals with cardiometabolic conditions is crucial for early detection, risk stratification and treatment which are essential to delay the progression of CVD and reduce mortality.

To address these gaps in the literature, this review aims to (1) evaluate the global prevalence of myocardial fibrosis in individuals with cardiometabolic conditions and (2) explore factors influencing its prevalence. By contributing to the current literature, this review seeks to inform the international community and support the development of better management strategies for cardiometabolic conditions and improved patient outcomes.

Methods

This review was reported according to to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [19]. The PRISMA 2020 checklist was used to improve transparency in systematic reviews (Supplemental Table 1). The study protocol was registered in the PROSPERO database under registration number CRD42024544632. We incorporated a narrative synthesis to explore additional factors associated with myocardial fibrosis, that was not specified in the registered protocol for a more comprehensive analysis.

Eligibility Criteria

The eligibility criteria developed based on the mnemonic CoCoPop (Condition, Context, Population) [20] is presented in Supplemental Table 2. We included studies that (1) measured myocardial fibrosis prevalence as an outcome (for observational studies) or baseline myocardial

fibrosis (for experimental studies), (2) identified myocardial fibrosis by either biopsy or LGE-CMR techniques, and (3) recruited a population of individuals with any cardiometabolic conditions (hypertension, type 2 diabetes mellitus (T2DM), hyperlipidaemia, and obesity) from any setting, including those with existing CVD. This review included both published and unpublished experimental and observational studies (cross-sectional, case-control and cohort studies) in the English language. Qualitative studies, case reports/series and reviews were excluded.

Study Design and Search Strategy

Three databases were searched for similar and ongoing systematic reviews to prevent duplication: (1) JBI Database of Systematic Reviews and Implementation Reports, (2) Cochrane Database of Systematic Reviews, (3) PROSPERO. A three-step comprehensive search strategy was employed following the preliminary search. First, we conducted an extensive search in seven databases, including Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, Excerpta Medica DataBASE (Embase), PubMed, ProQuest Theses and Dissertations, Scopus, and Web of Science without publication time frame limitation, from inception to January 2024. Second, we searched on ClinicalTrials.gov for ongoing clinical trials and Google Scholar for relevant studies. Third, we performed a hand search on reference list of included studies and similar reviews to maximise the number of potential studies.

Utilising The Peer Review of Electronic Search Strategies (PRESS) checklist [21], the search strategy was created by the research team then peer-reviewed by the university librarian (Supplemental Table 3). Both free-text and controlled (e.g. MeSH or Emtree) search terms were adapted according to the syntax rules of each database and combined with Boolean operators.

Study Selection

Duplicate records were electronically and manually removed using EndNote X21 reference management tool [22]. The title and abstract of studies were screened independently for relevance by two reviewers (YTM, AS). The records were then exported into Rayyan web [23] for further screening. Kappa statistics was calculated to determine the interrater agreement between the reviewers, where a score of greater than 0.4 is acceptable [24]. Discrepancies were resolved through discussion with a third reviewer (WW).

Data Extraction

Details about the study details, study characteristics (geographical location, study design, study population, participants' mean/median age, sample size, number of male/female), measurement used to identify myocardial fibrosis, type of fibrosis, prevalence of myocardial fibrosis, and factors associated with myocardial fibrosis were extracted independently by two reviewers (YTM, AS). Discrepancies was resolved through discussion with a third reviewer (WW) and authors was contacted via email for clarifications and additional information.

Individual Quality Assessment

The methodological quality of each included study was appraised independently by two reviewers (YTM, AS) using the adapted risk of bias assessment tool developed by Hoy et al. [25]. The instrument consists of ten dichotomised items (low versus high risk of bias), with four items evaluation external validity and six items evaluating internal validity, with a range of scores from 0 to 10 (Supplemental Table 4). The item on the length of the shortest prevalence period was not assessed in our study as it was not applicable. Our team assigned a score either as 0 (low risk) or

1 (high risk) to each item. Studies are rated low risk (score 0-3), moderate (score of 4-6), and high risk (score 7-9), based on a previous study [26]. A third reviewer (WW) was consulted in cases of disagreements.

Publication bias

We examined publication bias in meta-analyses with ten or more trials [27] using the jamovi software package [28]. To detect publication bias, we analysed the asymmetry of funnel plot [29] and conducted Egger's regression asymmetry ($p<0.10$) [30].

Statistical Analysis

The meta-analysis was conducted using the jamovi software package [28]. Prevalence was calculated using the following formula:

$$Prevalence\ (p) = \frac{Number\ of\ individuals\ with\ myocardial\ fibrosis\ (n)}{Total\ number\ of\ individuals\ sample\ (N)}$$

With high heterogeneity between studies [31], we chose the Maximum Likelihood estimation of random-effects model [32] to pool study-specific estimates and derive prevalence estimates of myocardial fibrosis, which were presented using forest plots. Raw proportion was chosen as the effect size model measure. The pooling of data was accompanied with 95% CI, and the overall prevalence estimates were determined using Z-statistics at the 0.05 level of significance [33]. The Tau^2, I^2 and Cochran Q tests were performed to analyse the statistical heterogeneity of prevalence estimates [34]. The I^2 values were interpreted as follows: ≤40% indicating unimportant heterogeneity, 30-60% indicating moderate heterogeneity, 50-90% indicating substantial heterogeneity, and ≥75% indicating considerable heterogeneity [35].

Subgroup Analysis

Given the significant statistical heterogeneity observed across the included studies, we conducted subgroup analyses to identify the variables explaining this heterogeneity and influencing prevalence. The following pre-specified study-level characteristics: geographical location (Europe versus (vs) Asia vs North America/Oceania), country income (middle vs high income, based on the World Bank classification), population (hypertension vs T2DM vs obesity/hyperlipidaemia/mixed population), measure (biopsy vs LGE-CMR), mean/median age (under 50 vs at least 50 years old) and risk of bias (low vs moderate) were included in the subgroup analysis. Age-dependent changes lead to interstitial extracellular matrix deposition, causing myocardial fibrosis [7]. Since middle age is generally defined as 40 to 60 years [36], 50 was chosen as the cutoff. The Q difference between subgroup differences was calculated by weighting effect sizes to test for group differences in prevalence estimates while accounting for both within and between-subgroup variances [35]. A p-value <0.05 indicated a significant subgroup difference.

Results

A total of 53,115 records were retrieved from seven databases. After removing 26,245 duplicates electronically and manually, 26,870 records underwent title and abstract screening. Subsequently 172 full-text reports were shortlisted for full-text retrieval, of these 124 records were excluded for various reasons (Supplemental Table 5). Four eligible studies were identified via other methods. Finally, a total of 52 studies were included in this meta-analysis as presented in Figure 1. Reviewer agreement on study selection was substantial (κ=0.61).

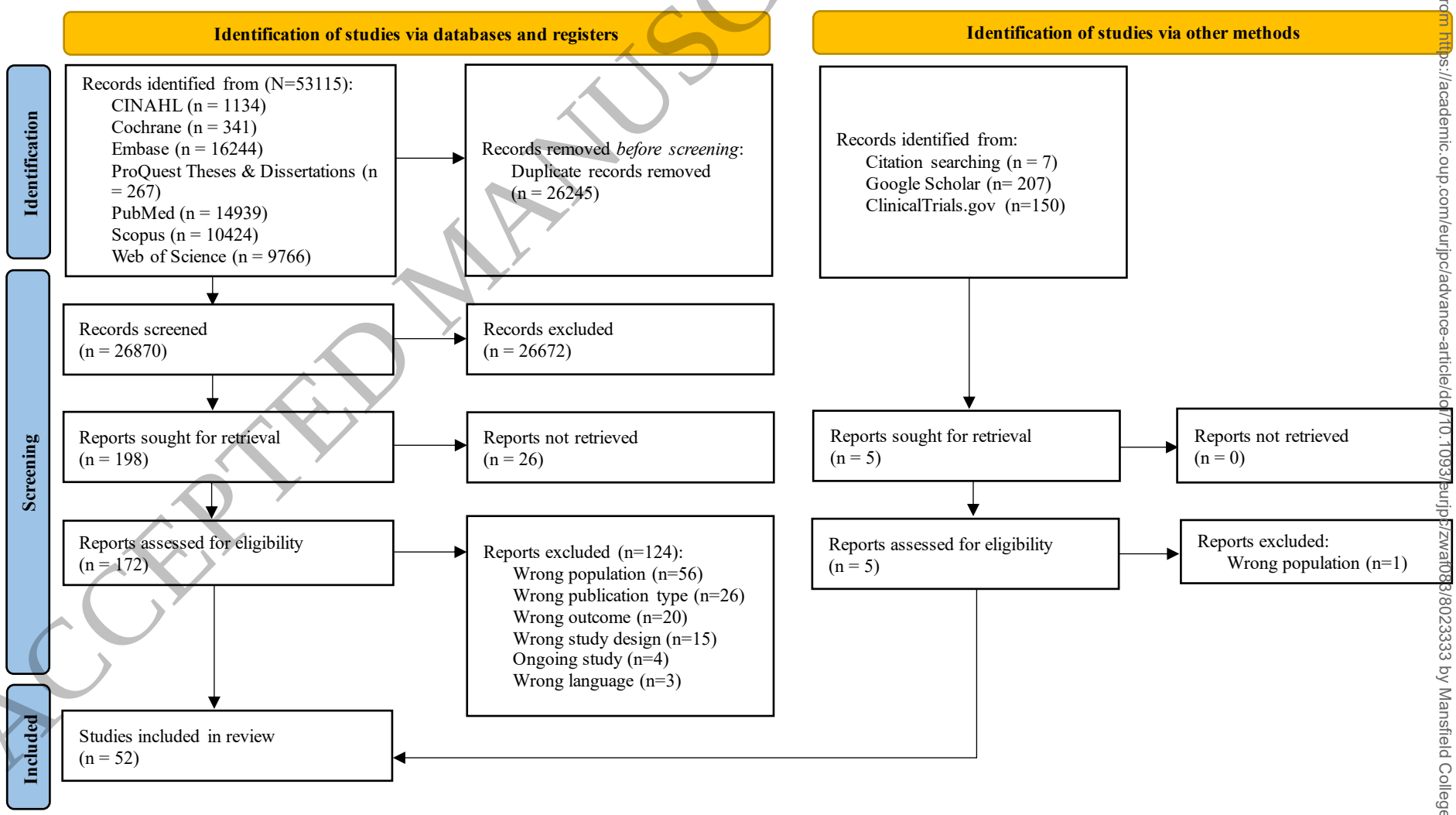

Figure 1. PRISMA 2020 Flow Diagram of Included Studies in the Meta-Analysis of Myocardial Fibrosis among Individuals with Cardiometabolic Conditions.

Characteristics of Included Studies

The review included 52 studies involving 5,921 individuals with cardiometabolic conditions across 16 countries (Table 1). Most included studies were conducted in Europe (number of studies, k=26), followed by Asia (k=20), North America (k=5) and Oceania (k=1). Participants were mainly recruited from hospitals (k=24), outpatient clinics (k=11), communities (k=1), or a combination (k=2), while 14 studies did not report recruitment settings. The studies were primarily cross sectional (k=34), with others being case control (k=8), and cohort (k=10). The study population had cardiometabolic conditions such as hypertension (k=28), T2DM (k=20), obesity (k=4), hyperlipidaemia (k=1), or combination of these (k=1). Interestingly, majority of the studies (k=32) also reported the presence of additional cardiometabolic conditions in some participants alongside their primary target population. Participants' mean body mass index (BMI) ranged from 23.6 to 35.6m^2/kg, with one-fifth of the studies reporting a BMI greater than 30m^2/kg, indicative of obesity. Two studies provided prevalence data for two different populations. Sample sizes ranged from 9 to 1644, with mean ages between 30.9 and 74.3 years. Myocardial fibrosis, mainly focal and interstitial fibrosis was measured using the LGE-CMR technique (k=45) and endomyocardial biopsy (k=7) respectively.

Risk of Bias Assessment

The individual risk of bias assessment is presented in Supplemental Table 6. Scores ranged from 1 to 4, with a median score of 3. Only five studies had an overall moderate risk of bias, each scoring 4. The remaining 47 studies had an overall low risk of bias with scores ranging from 1 to 3. None of the studies received a score of 0. All but one study [37] was rated as high risk for the domain

on selection for the domains. Only one study was rated high risk for non-response bias [38]. All studies were rated low for measurement bias. Five studies were rated as high risk for data analysis bias.

Table 1. Summary of Characteristics of Included Studies in the Meta-Analysis of the Prevalence of Myocardial Fibrosis among Individuals with cardiometabolic conditions.

Author (Year)	Country/ Setting	Study Design	Study Population/ Duration of CC [Mean (SD)/ Median (Range)]	Age [Mean (SD)/ Median (Range)]	Proportion of Male/ Female (%)	Presence of other CC	BMI [Mean (SD)/ Median (Range)]	MF Measure	Type of MF	n/N	Risk of bias
Ahmed et al. (1997)	United States/ Hospital	Cross sectional	Obese/ NR	48(17)	70/30	Yes (HTN)	NR	Biopsy (Autopsy)	NR	10/10	Low
Al-Badri et al. (2018)	United States/ Outpatient Clinic	Cross sectional	T2DM/ NR	[HbA1C] <6.5: 66(61–72); 6.5-7.5:67(62–71); >7.5: 64(59–69)	89/11	Yes (HTN)	[HbA1C] <6.5: 29.1 (24.2-34); 6.5: 33.2(28.9-37.4); >7.5: 32.7(27.8-37.5)	LGE	Focal	4/47	Low
Anderson et al. (2009)	Germany/ NR	Cross sectional	HTN/ > 1 year	62.65(12.6)	35/65	NR	NR	LGE	Focal	9/20	Low
Arcari et al. (2020)	Germany/ Hospital	Cross sectional	HTN/ NR	54(16)	56/44	Yes (T2DM, HLD)	28(2)	LGE	Focal	34/163	Low

Bhaskar et al. (2023a)	India/ Hospital	Cross sectional	T2DM/ NR	55.5(11.8)	31/69	NR	NR	LGE	NA	0/155	Low
Bhaskar et al. (2023b)	India/ Hospital	Cross sectional	T2DM with MI/ NR	61.5(9.1)	61/39	NR	NR	LGE	Focal	27/45	Low
Bratis et al. (2014)	United Kingdom/ Hospital	Cross sectional	T2DM with LV systolic dysfunction/ > 10 years	67(8.4)	64/36	Yes (HLD)	NR	LGE	NA	0/11	Low
Brilla et al. (2003)	Germany/ NR	Cross sectional	HTN/ ≥ 5 years	60(9)	69/31	NR	NR	Biopsy (Endo-myocardial)	Diffuse interstitial	97/97	Low
Chen et al. (2023)	Germany/ NR	Cross sectional	HTN (Resistant) with dyspnoea or angina/ NR	63(12)	64/36	Yes (T2DM, HLD)	31(5)	LGE	Focal	21/50	Low
Dattani et al. (2023)	United Kingdom/ Hospital	Cross sectional (Secondary analysis)	T2DM with aortic stenosis/ NR	70(63–75)	79/21	Yes (HTN, HLD)	30.1(5.2)	LGE	Focal	32/56	Low
Dennis et al. (2022)	Australia/ Outpatient clinic	Case-control	T2DM/ 11.2(6.7-20.1)	61(56–63)	61/39	Yes (HTN)	28 (26–32)	LGE	Focal	11/49	Moderate
Duce et al. (2015a)	United Kingdom/ Outpatient clinic, Community	Cross sectional	T2DM/ 9(6.2)	63(8)	56/44	Yes (HTN)	30(6)	LGE	Focal	3/55	Low
Duce et al. (2015b)	United Kingdom/ Outpat	Cross sectional	T2DM with CVD/	65(7)	76/24	Yes (HTN)	31(4)	LGE	Focal	9/34	Low

	ient clinic, Community		10.4(4.7)								
Edwards et al. (2015)	United Kingdom/ Outpatient clinic	Case-control	HTN/ NR	57(10)	56/44	NR	28(5)	LGE	Focal	1/43	Low
Elliott et al. (2019)	United States/ Outpatient clinic	Cohort	T2DM/ NR	60(8)	51/49	Yes (HTN, HLD)	31(6)	LGE	Focal	9/70	Moderate
Ferreira et al. (2016)	United Kingdom/ Hospital	Case-control	HTN/ NR	55(7)	64/36	No	27.1	LGE	Focal	2/14	Low
Frustaci et al. (2013)	Italy/ Outpatient clinic	Cohort	HTN with LV dysfunction/ > 1 year	52(11)	76/34	NR	NR	Biopsy (Endo-myocardial)	NR	17/45	Low
Gallo et al. (2021)	France/ Hospital	Case-control	HLD/ 30.9(11.2)	48.9(5.0)	58/42	Yes (HTN)	25.4(4.3)	LGE	Focal	5/72	Low
Gao et al. (2021a)	China/ Hospital	Case-control	T2DM/ NR	55.5(11.8)	31/69	Yes (HLD)	23.7(3.1)	LGE	Focal	0/156	Low
Gao et al. (2021b)	China/ Hospital	Case-control	T2DM with MI/ NR	61.5(9.1)	61/39	Yes (HLD)	25.3(3.4)	LGE	Focal	28/46	Low
He et al. (2023a)	China/ Hospital	Cohort	Obese/ NR	45(11)	74/26	Yes (HTN, DM, HLD)	31(3)	LGE	Focal	3/24	Low
He et al. (2023b)	China/ Hospital	Cohort	Obese with heart failure/ NR	46(14)	75/25	Yes (HTN, DM, HLD)	31(2)	LGE	Focal	29/82	Low
Hinojar et al. (2015)	United Kingdom, Germany, Australia/ NR	Cross sectional	HTN with LVH/ NR	54(13)	65/35	NR	NR	LGE	Focal	16/69	Low

Hostiuc et al. (2013)	Romania/ NR	Case-control	T2DM/ NR	NR(56-73)	60/40	NR	NR	Biopsy (Autopsy)	Diffuse interstitial	10/10	Low
Iyer at al. (2022)	Singapore/ Hospital	Cohort	HTN/ 10(9)	58(11)	61/39	Yes (DM, HLD)	26.4(4.5)	LGE	Focal	145/786	Low
Jiang et al. (2018)	China/ NR	Cross sectional	HTN with LVH/ NR	54.4(15.3)	75/25	Yes (DM, HLD)	NR	LGE	Focal	15/44	Low
Jiang et al. (2020)	China/ Hospital	Case-control	T2DM/ 8.0(3.0-12.0)	56.2(12.0)	37/63	Yes (HTN)	23.6(2.7)	LGE	Focal	7/135	Low
Khan et al. (2014a)	United Kingdom/ Outpatient clinic, Hospital	Case-control	T2DM/ 4.7(4.0)	31.8(6.6)	45/55	NR	33.9(5.8)	LGE	Focal	6/20	Low
Khan et al. (2014b)	United Kingdom/ Outpatient clinic, Hospital	Case-control	Obese/ NR	30.9(5.6)	60/40	NR	33.4(2.4)	LGE	Focal	1/10	Low
Khan et al. (2020)	United States/ Hospital	Cohort	T2DM/ NR	61.5(56-67)	47/53	Yes (HTN, HLD)	29.7(25.9-37.5)	LGE	Focal	24/70	Low
Krittayaphong et al. (2010)	Thailand/ Hospital	Cohort	HTN with known or suspected CAD/ NR	65(11)	48/52	Yes (DM, HLD)	25(4)	LGE	Focal	453/1644	Low
Kuruvilla et al. (2015)	United States/ NR	Cross sectional	HTN/ NR	61(12)	43/57	NR	NR	LGE	Focal	2/23	Low
Levelt et al. (2016)	United Kingdom/ Outpat	Cross sectional	T2DM/ 7(1-8)	55(9)	52/48	NR	29.6(5.7)	LGE	NA	0/46	Low

	ient clinic										
Li et al. (2024)	China/ Hospital	Cohort	T2DM with LV dysfunction & dilated LV end-diastolic diameter / NR	55(12)	74/26	Yes (HTN)	24.5(3.9)	LGE	Focal	86/155	Low
Liang et al. (2022)	China/ Hospital	Cross sectional	HTN with LVH/ NR	48.5(16.3)	89/11	Yes (DM)	NR	LGE	Focal	9/35	Low
Luneva et al. (2022a)	Russia/ Outpatient clinic	Cross sectional	T2DM/ 9.0(5.0–12.0)	57.5(8.4)	46/54	Yes (HTN, HLD)	32.9(6.5)	LGE	Focal	22/37	Low
Luneva et al. (2022b)	Russia/ Outpatient clinic	Cross sectional	Combination of any 2: Obese/ HTN/ T2DM/ T2DM> 1 year, Obese/HTN: NR	54.0(8.9)	44/56	NA	35.6(2.7)	LGE	Focal	4/27	Low
Mather et al. (2010)	United Kingdom/ NR	Cohort	T2DM/ NR	61(10.8)	91/9	Yes (HTN)	NR	LGE	Focal	21/22	Low
Puntmann et al. (2010)	Germany/ Hospital	Case-control	HTN/ NR	55(8)	67/33	NR	26(4)	LGE	NA	0/39	Low
Querejeta et al. (2000)	Spain/ Outpatient clinic	Cross sectional	HTN/ Non-severe MF: 5.30(1.40) Severe MF: 9.54(2.73)	56(39-70)	73/27	NR	NR	Biopsy (Endo-myocardial)	Diffuse interstitial	26/26	Low
Redheuil et al. (2020)	France / Hospital	Cross sectional	HTN/ NR	46(13)	45/55	NR	25(3.6)	LGE	Focal	1/20	Low

Rodrigues et al. (2016)	United Kingdom/ Outpatient clinic	Cross sectional	HTN with LVH subset/ NR	51(15)	50/50	Yes (DM)	31(6)	LGE	Focal	27/129	Low
Shang et al. (2017)	China/ Hospital	Cross sectional	T2DM with LV diastolic dysfunction/ 7.0 (2.8–11.0)	54.6(8.6)	53/47	NR	24.3(2.7)	LGE	NA	0/38	Low
Shen et al. (2023)	China/ Hospital	Cross sectional	HTN with LV systolic dysfunction & dilated LV end-diastolic diameter / 6.0 (2.0-10.0)	52.0(12.7)	76/24	NR	25.0(6.3)	LGE	Focal	72/91	Low
Sørensen et al. (2020)	Denmark/ Hospital	Cross sectional	T2DM/ 13(8)	59(11)	71/29	Yes (HTN, HLD)	31.1(4.6)	LGE	Focal	17/193	Low
Sugihara et al. (1988)	Japan/ NR	Cross sectional	HTN with cardiac complaints/ NR	49(8)	68/32	NR	NR	Biopsy (Endo-myocardial)	Interstitial	5/25	Moderate
Swoboda et al. (2017)	United Kingdom/ Outpatient clinic	Cohort	T2DM with microalbuminuria subset/ Positive: 5.3(4.4) Negative: 4.6(4.4)	[Microalbuminuria] Positive: 60.2(12.7) Negative: 61.1(9.1)	82/18	NR	[Microalbuminuria] Positive: 29.1(4.6) Negative: 28.6(4.0)	LGE	Focal	17/100	Low
Taghavi et al. (2018)	Iran/ NR	Cross sectional	HTN with heart failure/ NR	50(NR)	80/20	NR	NR	LGE	Focal	5/20	Moderate

Treibel et al. (2015)	United Kingdom/ Outpatient clinic	Cross sectional	HTN with LVH subset/ NR	58.5(49.0-65.5)	52/48	NR	29.8(4.5)	LGE	Focal	11/40	Low
Von Knobelsdorff-Brenkenhoff et al. (2016)	Germany/ NR	Cross sectional	HTN with LVH/ NR	56(12)	89/11	NR	NR	LGE	Focal	3/9	Low
Wang et al. (2017)	China/ Hospital	Cross sectional	HTN/ NR	53.5(13.8)	93/7	Yes (DM, HLD)	26.5(4.3)	LGE	Focal	40/134	Low
Wang et al. (2024)	China/ NR	Cross sectional	HTN with LVH/ NR	45(17)	68/32	Yes (DM, HLD)	NR	LGE	Focal	33/59	Low
Westaby et al. (2022)	United Kingdom/ NR	Cross sectional	HTN with LVH (sudden death)/ NR	54(16)	56/44	Yes (DM, Obesity)	31(9)	Biopsy (Autopsy)	NR	59/75	Low
Wu et al. (2017)	China/ NR	Cross sectional	HTN with LVH/ NR	55(6)*	80/20*	NR	NR	LGE	Focal	2/20	Low
Yang et al. (2023a)	China/ Hospital	Cross sectional	HTN/ NR	48(13)	65/35	NR	25.4(3.8)	LGE	Focal	26/79	Moderate
Yang et al. (2023b)	China/ Hospital	Cross sectional	HTN with arrhythmias/ NR	52(10)	61/39	NR	25.7(2.7)	LGE	Focal	29/54	Low
Yokota et al. (2013)	Japan/ Hospital	Cross sectional	HTN with LVH/ NR	[Nocturnal blood pressure] Dipper: 71.5(10.7) Non-Dipper: 74.3(10.1)	[Nocturnal blood pressure] Dipper: 74/26 Non-Dipper: 50/50	Yes (DM, HLD)	[Nocturnal blood pressure] Dipper: 24.4(3.3) Non-Dipper:	LGE	Focal	22/47	Low

							25.1(3.2)				
Zhang et al. (2023)	China/ Hospital	Cohort	T2DM with LV dysfunction & dilated LV end-diastolic diameter or stenosis present in ≥ 1 coronary artery or MI or revascularisation / NR	55.9(14.0)	78/22	Yes (HTN, HLD)	25.8(4.2)	LGE	Focal	114/158	Low
Zhao et al. (2023)	China/ Community	Cross sectional	Obese with metabolic syndrome component subset/ NR	38(11)	50/50	Yes (HTN, HLD)	34(6)	LGE	Focal	9/88	Low

BMI = Body Mass Index; CAD = Coronary Artery Disease; CC = Cardiometabolic Conditions; CVD = Cardiovascular Disease; HLD = Hyperlipidaemia; HTN = Hypertension; LGE = Late Gadolinium Enhancement; LV= Left ventricle; LVH= left ventricle hypertrophy; MI = Myocardial Infarction; NA = Not applicable; NR = Not Reported; T2DM=Type 2 Diabetes Mellitus; *values for entire population with HTN with LVH

Studies labelled with 'a' and 'b' originate from the same study but report data separately for different population groups.

Global Prevalence of Myocardial Fibrosis among Individuals with Cardiometabolic Conditions

The global prevalence of myocardial fibrosis among individuals with cardiometabolic conditions was 32.7 (25.4-40.1) using a random-effects as illustrated the forest plot (Figure 2). The analysis indicated considerable heterogeneity with I^2 of 99.5% and τ^2 of 0.08. To address the significant heterogeneity, subgroup analyses were performed to explore the sources of heterogeneity in the prevalence estimates across studies (Table 2).

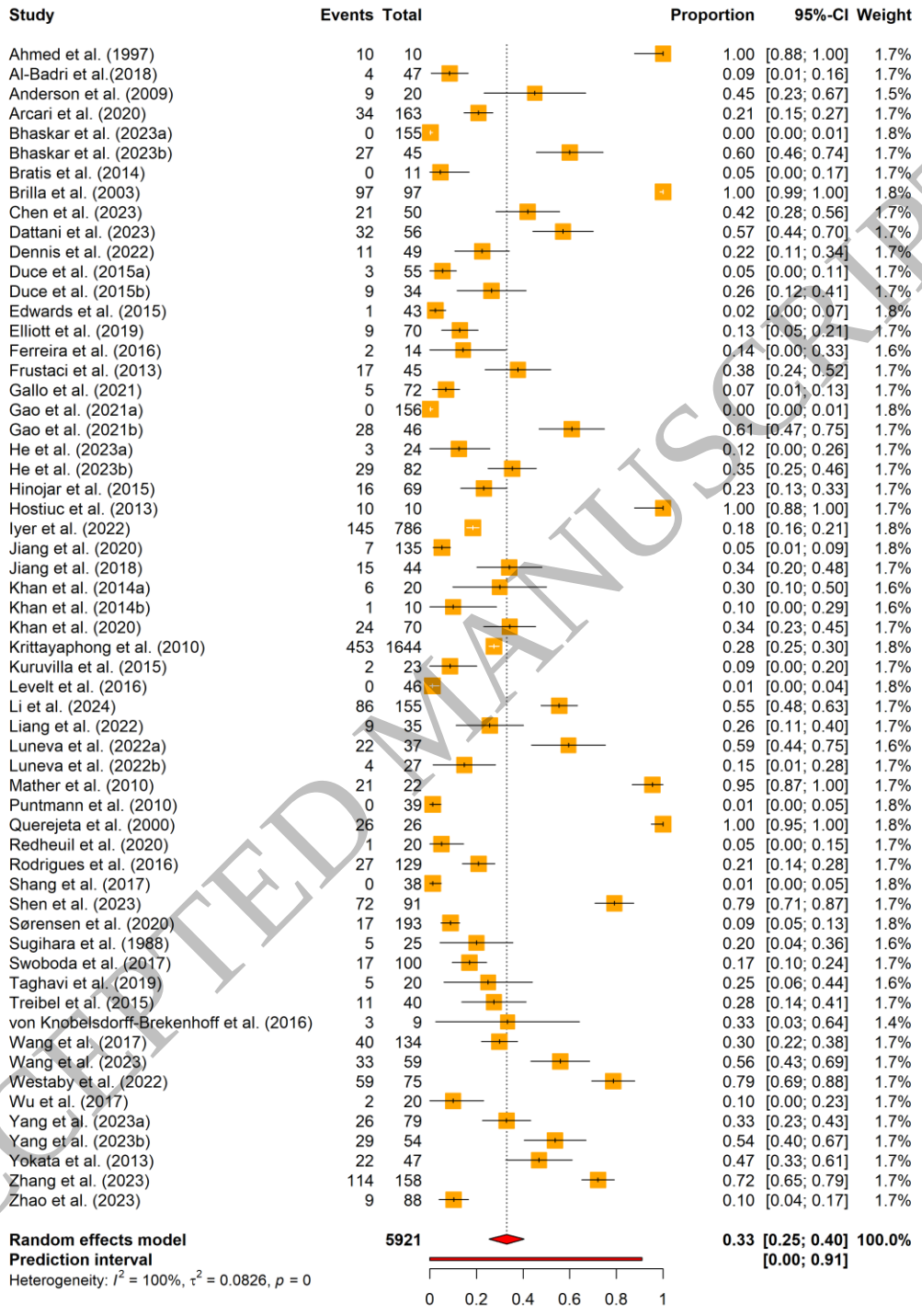

Figure 2. Forest Plot for the Global Prevalence of Myocardial Fibrosis among Individuals with Cardiometabolic Conditions.

Table 2. Global and Subgroup Analysis for Prevalence of Myocardial Fibrosis among Individuals with Cardiometabolic Conditions.

Variables	No. of studies (N)	Prevalence (95%CI)[a]	I^2	p-value	τ^2	$p_{subgroup}$
Global Analysis	52 (5921)	32.7 (25.4-40.1)	99.50	<0.001	0.083	-
Subgroup Analysis						
Geographical Location						
Europe	26 (1532)	33.9 (22.2-45.5)	99.09	<0.001	0.099	0.991
Asia	20 (4120)	31.9 (22.6-41.3)	99.47	<0.001	0.052	
North America and Oceania	6 (269)	30.2 (6.0-54.4)	97.13	<0.001	0.087	
Country Income						
Middle Income	22 (3540)	35.6 (25.5-45.8)	99.63	<0.001	0.070	0.468
High Income	30 (2381)	30.3 (19.9-40.6)	98.63	<0.001	0.085	
Population[b]						
Hypertension	28 (3900)	35.2 (25.5-45.0)	98.86	<0.001	0.085	0.444
Biopsy	5(268)	67.6 (39.5-95.7)	99.06	<0.001	0.100	
LGE-CMR	23(3632)	28.0(20.5-35.61)	96.56	<0.001	0.032	
Type 2 Diabetes Mellitus	20 (1708)	31.6 (19.2-44.0)	99.68	<0.001	0.090	
Biopsy	1(10)	-	-	-	-	
LGE-CMR	19(1698)	28.7(17.0-40.3)	99.63	<0.001	0.075	
Obesity, Hyperlipidaemia, Mixed	6 (313)	26.5 (4.6-48.3)	97.16	<0.001	0.083	
Biopsy	1(10)	-	-	-	-	
LGE-CMR	5(303)	14.9(6.8-22.9)	75.17	0.004	0.007	
Measure						
Biopsy[c]	7 (288)	75.6 (53.6-97.6)	98.64	<0.001	0.085	**<0.001**
LGE-CMR	45 (5633)	26.8(20.6-33.0)	99.07	<0.001	0.049	
Mean/Median Age[d]						
≥50 years old	42 (5387)	32.5(24.3-40.7)	99.55	<0.001	0.078	0.639
<50 years old	10 (524)	28.3(14.2-42.4)	95.28	<0.001	0.058	
Risk of Bias						
Low risk	47 (5624)	33.3(25.3-41.3)	99.54	<0.001	0.086	0.658
Moderate risk	5 (297)	27.6(16.8-38.3)	78.73	<0.001	0.014	

No. = Number; 95% CI = 95% Confidence Interval; I^2 = Heterogeneity; CMR = Cardiac Magnetic Resonance; LGE = Late Gadolinium Enhancement

[a]Model Estimator: Maximum Likelihood; [b]Population: Two studies with different populations; [c]Biopsy: Endomyocardial biopsy and autopsy; [d]Mean/Median Age: One study with different age groups, Hostiuc et al. (2013) excluded as age was not reported

Prevalence of Myocardial Fibrosis by Geographical Location

The highest prevalence of myocardial fibrosis was observed in studies conducted in Europe, with a rate of 33.9% (95CI%: 22.2-45.5; I^2=99.1%; 26 studies, N=1532). This was followed by Asia 31.9% (95%CI: 22.6-41.3; I^2=99.5%; 20 studies, N=4120) and North America/Oceania 30.2% (95%CI: 6.9-54.4; I^2=97.13%; 6 studies, N=269). Subgroup differences across the regions were found to be statistically insignificant (p=0.991).

Prevalence of Myocardial Fibrosis by Country Income

The prevalence of myocardial fibrosis was higher in middle-income countries at 35.6% (95%CI: 25.5-45.8; I^2=99.6%; 22 studies, N=3540) compared to high-income countries at 30.3% (95%CI: 19.9-40.6; I^2=98.6%; 30 studies, N=2381). No studies were conducted in low-income countries. The subgroup differences were statistically insignificant (p=0.468).

Prevalence of Myocardial Fibrosis by Population

The prevalence of myocardial fibrosis was found to be the highest in individuals with hypertension at 35.2% (95%CI: 25.5-45.0; I^2=98.9%; 28 studies, N=3900), followed by T2DM at 31.6% (95%CI: 19.2-44.0; I^2=99.7%; 20 studies, N=1708) and obesity/hyperlipidaemia/mixed population at 26.5% (95%CI: 4.6-48.3; I^2=97.2%; 6 studies, N=313). Subgroup differences across the populations were statistically insignificant (p=0.444).

Among hypertensive individuals, myocardial fibrosis prevalence in hypertensive individuals was 67.6% (95%CI:39.5-95.7; I^2=99.1%, 5 studies; N=268) using biopsy and 28.0% (95%CI:20.5-35.61; I^2=96.6%, 23 studies; N=3632) using LGE-CMR. In T2DM, myocardial fibrosis prevalence

using LGE-CMR was 28.7% (95%CI:17.0-40.3; I^2=99.6%, 19 studies; N=1698), and for obesity/ hyperlipidaemia/ mixed population, it was 14.9%(95%CI:6.8-22.9; I^2=75.2%, 5 studies; N=303). A pooled estimate for biopsy in T2DM and obesity/hyperlipidaemia/mixed population could not be obtained due to limited data.

Prevalence of Myocardial Fibrosis by Outcome Measure

The prevalence of myocardial fibrosis was found to be higher in studies utilising biopsy at 75.6% (95%CI: 53.6-97.6; I^2=98.6%; 7 studies, N=288), compared to those employing LGE-CMR technique at 26.8% (95%CI: 20.6-33.0; I^2=99.1%; 45 studies, N=56633). The subgroup differences were statistically significant (p<0.001).

Prevalence of Myocardial Fibrosis by Mean/Median Age

The prevalence of myocardial fibrosis was higher in studies where the mean or median age was at least 50 years at 32.5% (95%CI: 24.3-40.7; I^2=99.6%; 42 studies, N=5387), compared to those where the mean or median age was less than 50 years, with a rate of 28.3% (95%CI: 14.2-42.4; I^2=95.3%; 10 studies, N=524). The subgroup differences were statistically insignificant (p=0.639). The study conducted by Hostiuc et al. [39] excluded from this subgroup analysis as mean/median age was not reported.

Prevalence of Myocardial Fibrosis by Study Quality

The prevalence of myocardial fibrosis was higher in studies appraised as low risk at 33.3% (95%CI: 25.3-41.3; I^2=99.5%; 47 studies, N=5624), compared to those appraised as moderate risk at 27.6% (95%CI: 16.8-38.3; I^2=78.7%; 5 studies, N=297). The subgroup differences were statistically insignificant (p=0.658).

Factors associated with Myocardial Fibrosis

Cardiovascular risk factors like hypertension [40], T2DM [38] and obesity [41] were associated with elevated native T1 or ECV, indicative of diffuse myocardial fibrosis (Table 3). However, hyperlipidaemia was not associated with markers of diffuse myocardial fibrosis.

In these three cardiometabolic conditions, increased LV mass including LV hypertrophy [41-44], reduced LV function [41, 45-52], myocardial stiffness [41, 50, 52] were associated with CMR markers of diffuse and replacement myocardial fibrosis . In hypertension, female gender [44], Afro-Caribbean/Black ethnicity [44], cardiac stress and injury markers [43], epicardial adipose tissue thickness [53], and a non-dipper blood pressure pattern [54] were associated with presence of LGE, increased ECV, native T1. In T2DM , male gender [38], metformin treatment [42], poor glycaemic control [55], higher glycated haemoglobin [42], longer diabetes duration [38, 45], and, reduced peak maximal oxygen consumption [38], lower stress-related myocardial blood flow [56], were associated with presence of LGE or increased ECV.

Publication Bias

Visual inspection of the funnel plot generated suggested relative asymmetry (Supplemental Figure 1). However, the regression-based Egger's test had a p-value of 0.18, indicating the absence of a small-studies effect.

Table 3. Factors associated with Myocardial Fibrosis among Individuals with Cardiometabolic Conditions

Author (Year)	Study Population	Factor(s) Associated with Myocardial Fibrosis
Al-Badri et al. (2018)	T2DM	Poorer glycaemic control is associated with increased in indexed ECV (p=0.006).
Anderson et al. (2009)	HTN	Higher LV end diastolic pressure was associated with the presence of LGE (p<0.05).
Brilla et al. (2003)	HTN	Greater myocardial stiffness was associated with increased collagen volume fraction (p<<0.02).
Chen et al. (2023)	HTN (Resistant) with dyspnoea or angina	Reduced LV global radial strain was associated with higher incidence of LGE.
Dennis et al. (2022)	T2DM	Male gender (p=0.04), duration of T2DM diagnosis (p=0.02), reduced peak maximal oxygen consumption (p=0.01) and metabolites (Choline, Cysteamine) were positively associated with increased ECV, while metabolite, Isoleucine was associated with the presence of LGE (p=0.04)
Iyer at al. (2022)	HTN	Greater LV mass, reduced LV global longitudinal strain and elevated circulating markers of cardiac wall stress and myocardial injury were associated with the presence of non-ischemic LGE (p<0.001).
Jiang et al. (2018)	HTN with LVH	Lower LV ejection fraction was associated with increased ECV in the presence of LGE (p=0.002).
Jiang et al. (2020)	T2DM	Lower longitudinal diastolic peak diastolic strain rate is associated with increased ECV (p=0.026).
Kuruvilla et al. (2015)	HTN	Lower peak systolic circumferential strain and early diastolic circumferential strain rate was associated with increased ECV.
Luneva et al. (2022)	T2DM	Treatment with Metformin, higher glycated haemoglobin, LV hypertrophy, higher tissue inhibitor of metalloproteinase 1 levels were associated with the presence of LGE (<0.05).
Shang et al. (2017)	T2DM with LV diastolic dysfunction	Duration of T2DM diagnosis (p=0.0005) and lower LV diastolic dysfunction (p=0.012) was associated with increased ECV.
Sørensen et al. (2020)	T2DM	Lower stress-related myocardial blood flow was associated with increased ECV (p<0.001).
Treibel et al. (2015)	HTN with LVH subset	Presence of LV hypertrophy (<0.0001) and its measures (higher maximal wall thickness, LV mass index (p<0.001), as well as higher ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity in the lateral wall (p < 0.01), higher central aortic pressure (p < 0.01) and higher electrocardiogram voltage sum by Comell p = 0.01) were associated with increased native T1. Female gender (p<0.05), Afro-Caribbean/blacks (p<0.00001), LV hypertrophy was associated with higher ECV.

Wang et al. (2017)	HTN	Lower LV global function and LV hypertrophy were associated with increased ECV (p<0.001).
Wu et al. (2017)	HTN with LVH	Lower peak systolic and early diastolic circumferential strain rates were associated with increased native T1 and ECV (p<0.005).
Yang et al. (2023)	HTN with arrhythmias subset	Increased epicardial adipose tissue thickness metrics were associated with increased native T1 (p<0.05).
Yokota et al. (2013)	HTN with LVH	Non-dipper pattern (mean nocturnal systolic BP decline less than 10% and riser relative to mean daytime systolic BP) was associated with presence of LGE (p=0.044).
Zhang et al. (2023)	T2DM with LV dysfunction & dilated LV end-diastolic diameter or stenosis present in ≥ 1 coronary artery or MI or revascularisation/	Lower LV global peak longitudinal systolic strain rate was associated with the presence of LGE (p=0.033).
Zhao et al. (2023)	Obese with metabolic syndrome component subset	Higher LV mass, LV end diastolic volume, LV end systolic volume as well as decreased global longitudinal strain and early diastolic strain rate were associated with increased ECV (p<0.001).

ECV = Extracellular Volume; HTN= Hypertension; LGE= Late Gadolinium Enhancement; LV= Left Ventricle; LVH= Left Ventricle Hypertrophy; T2DM= Type 2 Diabetes Mellitus

Discussion

Based on literature review, our review is the first to provide a comprehensive global-level analysis of myocardial fibrosis prevalence in individuals with cardiometabolic conditions. The review included 52 studies involving 5,921 individuals across 16 countries. Approximately 1 in 3 individuals with cardiometabolic conditions developed myocardial fibrosis during their lifetime, with individuals with hypertension demonstrating the highest prevalence. Our review also highlighted that the prevalence of myocardial fibrosis was significantly higher in studies that utilised the biopsy compared to those that employed the LGE-CMR technique. Key factors associated with myocardial fibrosis across the cardiometabolic conditions included increased LV mass/ LV hypertrophy, reduced LV function, and myocardial stiffness.

Prevalence of Myocardial Fibrosis by Outcome Measure

Our review observed significantly higher prevalence of myocardial fibrosis when measured using endomyocardial biopsies or autopsy compared to LGE-CMR. Endomyocardial biopsies/ autopsies are the gold standard for identifying and characterising of both replacement and diffuse interstitial myocardial fibrosis through visualisation and measurement of collagen volume fraction to determine the extent of fibrosis [12]. However, these invasive methods have low representativeness and are prone to sampling error, making it less suitable for routine clinical practice [9], prompting the development of non-invasive methods. LGE-CMR is the gold standard for non-invasive imaging of replacement fibrosis due to its strong detection capabilities but has limitations for diffuse interstitial fibrosis, which requires regions of presumed normal myocardium for contrast [57]. This highlights the need for standardised cut-off values for diffuse myocardial fibrosis in advanced CMR measures such as T1 mapping with elevated T1 values, ECV and indexed interstitial volume to improve consistency in prevalence estimates across outcome measures. These techniques, including the novel indexed interstitial volume, has demonstrated strong correlation with histology [12, 13]. Combining CMR measures of focal and diffuse fibrosis will better identify different myocardial fibrosis types which often coexist and improve the prevalence estimates.

Prevalence of Myocardial Fibrosis by Population/ Age

Although statistically insignificant, the prevalence of myocardial fibrosis varied across the different populations, being highest in individuals with hypertension, followed by those with diabetes and then obesity/hyperlipidaemia/mixed population. This non-significance may be attributed to the presence of cardiometabolic multimorbidity, defined as the co-existence of at least two cardiometabolic conditions [58], which is increasingly prevalent globally [59]. Multi-

morbidity was commonly observed among the participants, highlighting the interplay between cardiometabolic conditions. For example, individuals with obesity were more likely to develop T2DM and hypertension, and were also associated with hyperlipidaemia [60]. In the co-morbidity-inflammation paradigm, metabolic comorbidities are presumed to drive the development and severity of CVD like heart failure through processes ranging from systematic inflammation to myocardial fibrosis [61]. The Framingham Heart Study supports this, demonstrating that hypertension, diabetes and obesity interact synergistically to influence cardiac remodelling, leading to LV hypertrophy [62] and eventually myocardial fibrosis. Additionally, Pua et al. [63] found that myocardial fibrosis was significantly higher in individuals with both hypertension and diabetes compared those with hypertension alone, suggesting acceleration of adverse cardiac remodelling, beyond the hemodynamic consequences of elevated blood pressure. Our review also highlighted other sociodemographic and clinical factors such as gender, duration of condition, comorbidities, treatments that are associated with myocardial fibrosis and may influence its prevalence.

Moreover, the non-significance may stem from differences in outcome measurements used across populations, as suggested by our subgroup analysis. A notable discrepancy in prevalence was observed among hypertensive individuals depending on the measurement method: biopsy (67.6%) versus LGE-CMR (28.0%). Since diffuse myocardial fibrosis is characteristic of hypertensive heart disease [64] many studies included could not detect it using LGE-CMR, explaining this discrepancy. Unfortunately, we could not draw similar conclusions for T2DM and obesity/hyperlipidaemia/mixed populations due to a limited number of studies. However, discrepancies are expected in these populations, as they are associated with diffuse myocardial fibrosis, suggesting a need for further research in these conditions.

In addition to the ageing heart, which is often associated with LV hypertrophy and myocardial fibrosis [65], cardiometabolic comorbidity may also contribute to its higher prevalence in studies with individual with mean/median age 50 and above, though statistically insignificant. This is due to the increasing prevalence of cardiometabolic comorbidity with age [66]. Zhang et al. [59] reported that the prevalence of cardiometabolic multimorbidity rose from 5.2% in individuals aged 40 and above to 11.6% in those aged 60 and above. Therefore, the prevalence of myocardial fibrosis is expected to rise with the growing prevalence of cardiometabolic multimorbidity and aging population.

Prevalence of Myocardial Fibrosis by Geographical Location/ Country Income

The insignificant differences in myocardial fibrosis prevalence across regions may be due to the varying prevalence of cardiometabolic conditions in these regions. For instance, hypertension is the most prevalent in Africa [67], obesity in the regions of America [68], diabetes in North America and Middle East [69], and hyperlipidaemia in Europe [70]. As these cardiometabolic conditions patterns likely influence the prevalence of myocardial fibrosis, cardiometabolic condition epidemiology should be considered when interpreting regional data. Additional factors such as healthcare access, lifestyle differences and income disparities within these regions may also contribute to lack of significant difference.

Although not statistically significant, the prevalence of myocardial fibrosis is higher in middle-income countries compared to high-income countries. (HIC) This is reflected in cardiovascular mortality rates, where the decline has been greater in HICs (43.4%) than in upper-middle-income

(27.7%), lower-middle-income (18.9%), and low-income countries (15.4%) [71]. Notably, LMIC account for 80% of all cardiovascular deaths worldwide [72], significantly influenced by high rates of cardiometabolic conditions – hypertension (66%) [67], diabetes (80%) [73], obesity (70%) [74] found in these regions. This disparity may be driven by differences in the management of cardiometabolic conditions, health system infrastructure, and inequitable access to healthy eating, active living, and unpolluted environments [75]. Barriers such as poor health literacy, limited access to healthcare, shortages of trained providers, and weak healthcare systems hinder prevention, early diagnosis, and timely management of cardiometabolic conditions complications like myocardial fibrosis [76]. These factors perpetuate major disparities in outcomes cardiovascular outcomes between LMICs and high-income countries. This underscores the need for improved primary and secondary prevention strategies globally, especially in LMIC. Contextualizing preventive and curative interventions can help bridge the gap between scientific knowledge and practice [76], potentially mitigating myocardial fibrosis prevalence and reducing cardiovascular mortality.

Strengths and Limitations of this review

Our review has several strengths. This meta-analysis employed subgroup analyses to explore the sources of heterogeneity and investigated the prevalence of myocardial fibrosis across different factors, including geographical location, country income, population, measurement technique, age and risk of bias. We strictly adhered to the PRISMA guidelines and devised a comprehensive search strategy.

However, several limitations should be acknowledged. First, we could not account for the prevalence of interstitial myocardial fibrosis measured by CMR measures like T1 mapping, due to the lack of a standardized cut-off value for diagnosis, leading to large discrepancies in prevalence between outcome measures. Second, most studies did not differentiate between ischemic and non-ischemic LGE. Third, the included studies had small sample sizes, limited study sites and countries, which may not be a global representation. Fourth, only studies in English were included, limiting the generalizability of the findings. Fifth, the pooled prevalence should be interpreted with caution due to substantial differences in effect estimates and high heterogeneity, likely explained by variations in study populations and designs. Lastly, subgroup analyses by comorbidities, cardiometabolic condition duration, treatments, or gender could not be conducted, as these variables were not consistently stratified or reported across all included studies.

Implications for Future Practice, Policy and Research

Our study highlights the need for policy makers to strengthen national efforts in promoting routine screening for cardiometabolic conditions and implement contextualised prevention strategies targeting cardiometabolic multimorbidity. These strategies should emphasize lifestyle modifications and early diagnosis to prevent myocardial fibrosis and its progression to reduce adverse cardiac outcomes. This is especially crucial in LMIC, where access to healthy living habits and healthcare is inequitable. Healthcare providers should develop personalised treatment plans tailored to patient-specific factors such as age, comorbidities can further enhance the effectiveness of the management and reduce the prevalence and progression of myocardial fibrosis.

Future research should focus on the prevalence of myocardial fibrosis using larger sample sizes and national registries across different geographical regions to enhance global representativeness. Studies should employ combined CMR measures to assess myocardial fibrosis in individuals with obesity, hyperlipidaemia, and mixed cardiometabolic conditions, considering the rapid increase, the interconnected nature of these conditions and co-existence of different myocardial fibrosis types. Additionally, research in low-income countries is crucial as they bear the highest CVD burden. Increased data from these regions would raise awareness and inform global, regional, and national policies. Given the prevalence of myocardial fibrosis in individuals with cardiometabolic conditions, studies should explore the prognostic value of the different CMR measures with standardised cut-offs in predicting adverse cardiac events. Future studies should also report or stratify myocardial fibrosis prevalence based on socio-demographic and clinic factors such as duration of cardiometabolic exposure, comorbidities and treatment history that may impact myocardial fibrosis prevalence.

Conclusions

This is the first review to evaluate the global prevalence of myocardial fibrosis in individuals with cardiometabolic conditions. About one-third of these individuals develop myocardial fibrosis and this rate is expected to rise due to increasing prevalence of cardiometabolic conditions, worsening cardiometabolic comorbidity and aging populations globally. Variations in myocardial fibrosis prevalence by outcome measures highlight the need for standardized CMR measures cut-off, such as T1 mapping to improve consistency. Our study discusses the potential impact of cardiometabolic multimorbidity and geographic factors on myocardial fibrosis prevalence and emphasizes the importance for contextualised primary and secondary prevention approaches for

cardiometabolic conditions, especially in LMIC countries. Future research should explore myocardial fibrosis prevalence using diverse population samples, utilise combined CMR measures, and consider key socio-demographic and clinical factors for more accurate global estimates, guiding effective policy and resource allocation.

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Declaration of Interest:

The authors declare no conflicts of interest.

Data Availability Statements:

The data underlying this article are available in the article and in its online supplementary material.

Authorship:

YTM, WW and CWLC conceptualized the manuscript. YTM performed the statistical analyses, interpreted the data and drafted the manuscript. YTM and CWAS contributed to the screening and data extraction. WW, CWLC and LJC contributed to the statistical analyses and intepretations. WW, CWLC, LW, RF, MD provided critical revision to the manuscript. All authors reviewed and approved the final version of the manuscript.

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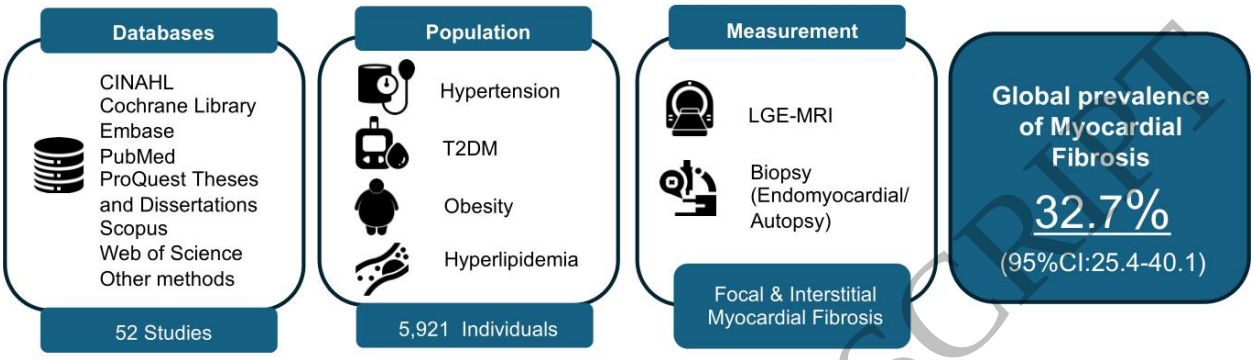

Graphical Abstract
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