

The Burden of Heart Failure with Preserved Ejection Fraction in American Women is Growing: An Epidemiological Review

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ABSTRACT

Heart failure (HF) is one of the leading causes of death in the United States. Heart failure with preserved ejection fraction (HFpEF), one of two common heart failure divisions, currently has no clinically effective treatment and disproportionately affects women. We performed a reproducible review of epidemiological literature within the United States National Library of Medicine's PubMed database to describe the incidence and prevalence of HFpEF in American women. Both the incidence and prevalence of HFpEF in American women have risen in recent decades ($p < 0.05$ and $p < 0.001$, respectively) and are projected to continue rising. In addition, HFpEF has recently become the most common form of HF, accounting for 56% of all HF cases (Paulus, 2020). The upward trend in incidence and prevalence of HFpEF in women within the United States increases the importance of developing effective treatment options.

KEYWORDS: HFpEF, Epidemiology, Cardiovascular Disease, Diastolic Heart Failure, Heart Failure, Heart Failure with Preserved Ejection Fraction.

INTRODUCTION

Defining and Classifying HFpEF

Cardiovascular disease (CVD) is the most common cause of death in the United States (Heron, 2019). Heart failure (HF) is a chronic progressive form of CVD defined by the inability of the heart to pump enough blood to maintain sufficient corporeal perfusion (Natterson-Horowitz et al., 2021). HF is commonly divided into two types depending on whether the left ventricular ejection fraction (LVEF) is compromised or preserved, resulting in HFrEF or HFpEF, respectively (Federmann & Hess, 1994). The LVEF is the fraction of left ventricular blood volume ejected during systole compared to the left ventricular blood volume at the end of diastole (Kosaraju et al., 2020). Heart failure with reduced ejection fraction (HFrEF), commonly referred to as systolic heart failure, occurs when the left ventricular wall's ability to contract forcefully during systole is impaired, reducing the left ventricular blood volume circulated to the rest of the body. Heart failure with preserved ejection fraction (HFpEF), commonly referred to as diastolic heart failure, occurs when the left ventricle stiffens, impairing the ability of the ventricle to accommodate blood filling during relaxation.

Treating HFpEF

Despite success in development and implementation of drug-based therapies for HFrEF, no analogous treatment of HFpEF has been shown to effectively reduce its morbidity or mortality (Ilieșiu & Hodorozea, 2018). This lack of effective HFpEF treatment is particularly alarming as HFpEF currently accounts for 56% of all cases of heart failure, a number which has risen significantly in the past decade (Paulus, 2020). In addition to its symptomatic burden on the patient, HF presents a substantial financial burden to the American healthcare system, responsible for nearly \$40 billion in expenditures, a figure projected to increase in coming years (Bui, Horwich, & Fonarow, 2011; Heidenreich et al., 2013).

Compared to men, women exhibit increased susceptibility to both HF and HFpEF, with the latter seen at a prevalence nearly two-fold higher in women than in men (Chang et al., 2014; Goyal et al., 2016; Goyal et al., 2017; Tadic et al., 2019). Understanding sex differences in exposure and response to cardiovascular events may illuminate advances in HFpEF prevention and treatment. The purpose of this review is to chronicle the epidemiology of HFpEF in American women through a review of the United States National Library of Medicine's PubMed database. HFpEF's rising prevalence, combined with a lack of effective drug or device-based treatment, presents a growing need to synthesize and advance our understanding of this chronic progressive condition.

MATERIALS AND METHODS

To perform a review examining HFpEF in American women, we used the Sciome Workbench for Interactive computer-Facilitated Text-mining (SWIFT)-Review, which uses statistical text mining to sort search results for high-efficiency manual screening (Howard et al., 2016; Baccouche & Shivkumar, 2020). The complete results of 38 unique search terms processed by the United States National Library of Medicine's PubMed database were screened using our predefined inclusion criteria (Table 1) and a reproducible PRISMA-compatible strategy (Figure 1).

Inclusion Criteria

- Consists of primary research
 - Includes the outcome HFpEF in American women
 - Epidemiological study design/goals
 - Conducted on human subjects
 - English language
 - Full-text freely available to University of Cambridge
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Table 1. Study inclusion criteria.

Search terms were chosen to cast a broad net, thereby reducing the risk of missing key studies with narrowly defined terms. The search terms and associated Boolean operators are as follows:

[HFpEF AND (women OR American women OR USA women OR female OR American female OR USA female OR epidemiology OR (epidemiology AND women) OR (epidemiology AND American women) OR (epidemiology AND USA women) OR (epidemiology AND female) OR (epidemiology AND American female) OR (epidemiology AND USA female)]

OR

[Diastolic heart failure AND (women OR American women OR USA women OR female OR American female OR USA female OR epidemiology OR (epidemiology AND women) OR (epidemiology AND American women) OR (epidemiology AND USA women) OR (epidemiology AND female) OR (epidemiology AND American female) OR (epidemiology AND USA female)]

OR

[Diastolic dysfunction AND (women OR American women OR USA women OR female OR American female OR USA female OR epidemiology OR (epidemiology AND women) OR (epidemiology AND American women) OR (epidemiology AND USA women) OR (epidemiology AND female) OR (epidemiology AND American female) OR (epidemiology AND USA female)].

RESULTS

From the review, six studies were identified which fit our search criteria. This paper presents epidemiological data on HFpEF in women within the United States over time and stratified by age, where data were available. Much of the data represented by these studies are taken directly from precise records of a predefined population, and thus the use of confidence intervals is not appropriate (as the parameter of interest is known). For this reason, some figures in this paper do not include confidence intervals, but p-values for trend are included in figure captions where available. Table 2 summarizes the study design, population source, and sample sizes of each of this review's included studies and provides study-specific commentary. All study populations were located within the United States.

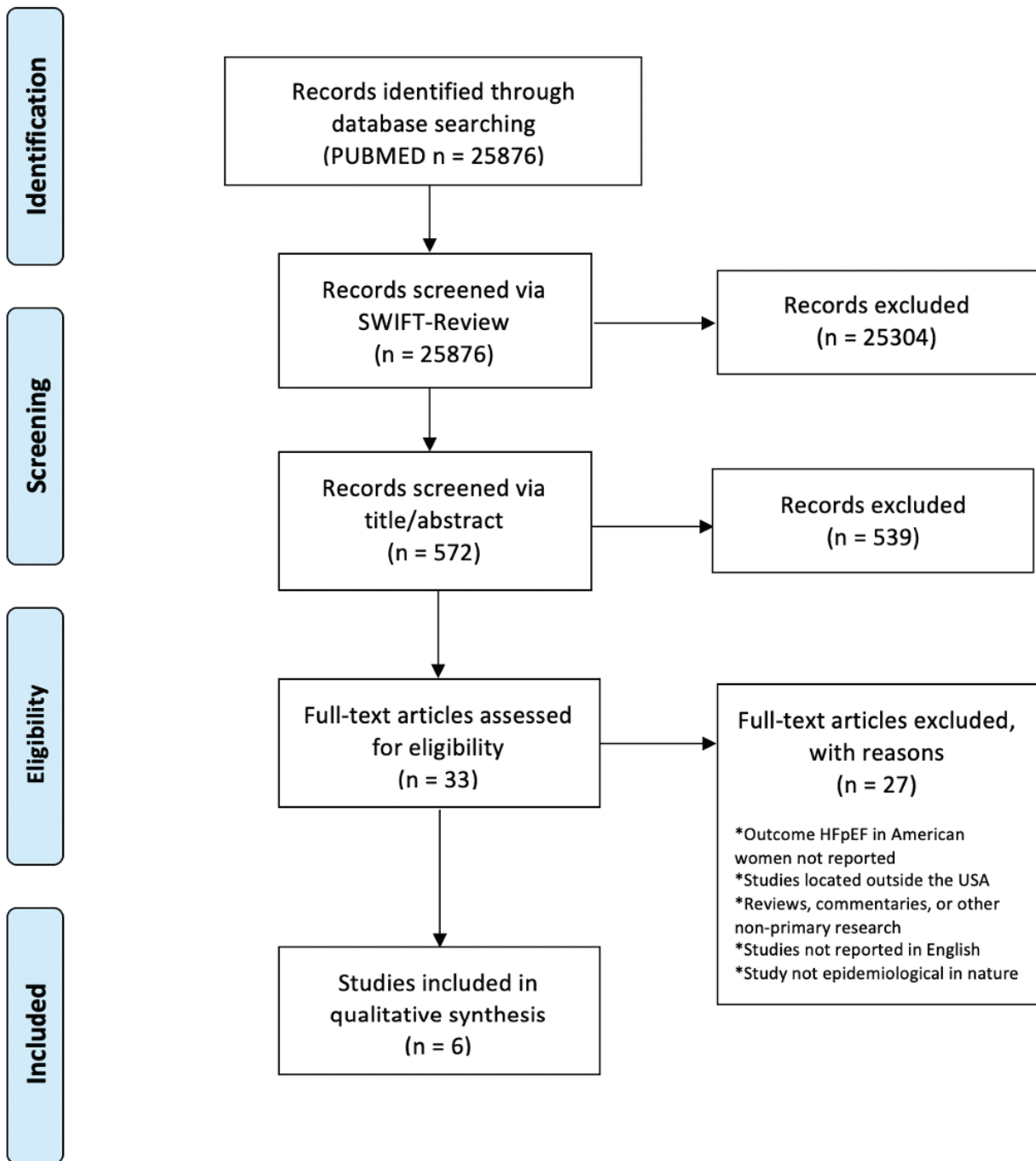


Figure 1. Reproducible, PRISMA-compatible review workflow.

Study Authors & Date	Study Design	Population Source(s)	Sample Size	Comments & Limitations
Chang et al., 2014	Prospective Cohort	Community-based	6,399	Much of the study's descriptive and analytical statistics fail to stratify the HF category into subcategories, limiting its usefulness for this review.
Gerber et al., 2015	Prospective Cohort	Community-based	2,762	Comparably low sample size reduces the power of this study.
Goyal et al., 2016	Prospective Cohort	Community-based	5,046,879	Large sample size mitigates probability of error/misrepresentation. HFpEF data available by sex and over time, permitting detailed categorical descriptive analysis. Echocardiographic data not available to confirm diagnosis of HFpEF; HFpEF instead defined based on ICD-9-CM codes for diastolic HF in the absence of systolic HF, since LVEF data was unavailable. Much of the region- and time-specific data is not stratified by sex, a seemingly major oversight given the well-documented sex-based disparity in HFpEF susceptibility.
Goyal et al., 2017	Prospective Cohort	Community-based	1,889,608	Large sample size mitigates probability of error/misrepresentation. Echocardiographic data not available to confirm diagnosis of HFpEF.
Ramachandran et al., 2018	Prospective Cohort	Community-based	12,857	Much of the region- and time-specific data is not stratified by sex, a seemingly major oversight given the well-documented sex-based disparity in HFpEF susceptibility.
Tsao et al., 2018	Prospective Cohort	Community-based	15,217	Incidence of HFpEF over time by race is not stratified by sex, limiting the ability to perform a descriptive analysis of HFpEF incidence in women over time by race.

Table 2. Overview of review results.

Incidence and Prevalence

Data from Tsao et al. suggest that the age-standardized incidence of HFpEF in US women over time has increased significantly in recent decades (Figure 2).

To corroborate Tsao et al.'s findings, Vasan et al. observed that the prevalence of HFpEF increased significantly ($p < 0.001$) over the 3-decade period from 1984 to 2014 (Vasan et al., 2018). Gerber et al. collected and age-standardized data on the incidence of HFpEF in women

Incidence of HFpEF in US Women Over Time

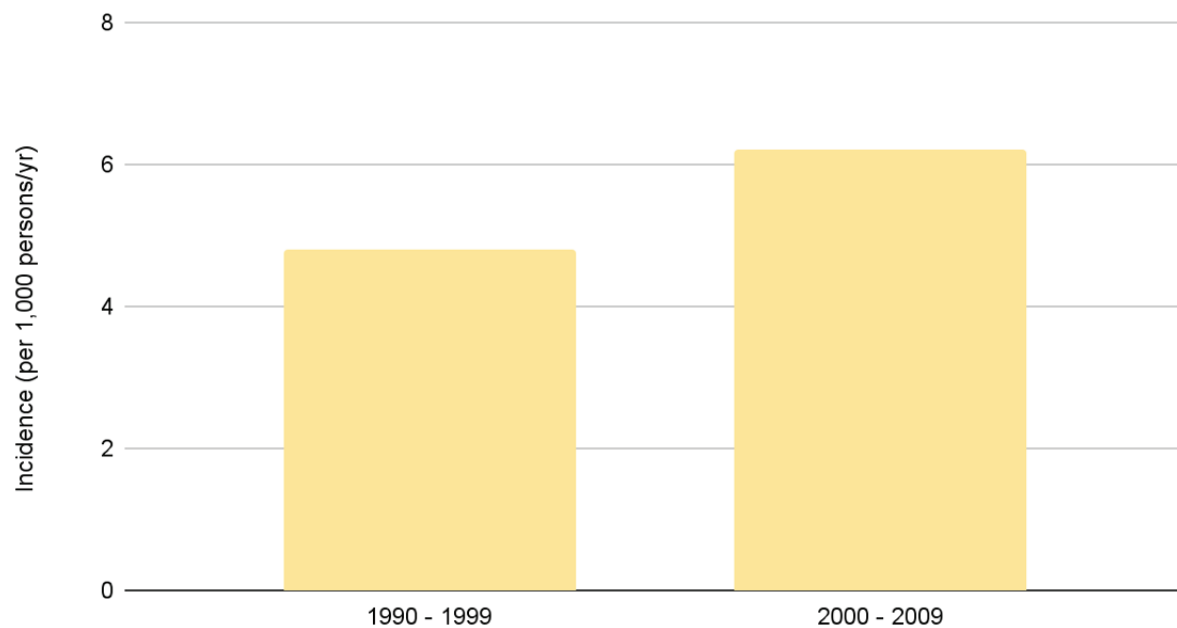


Figure 2. Age-standardized incidence per 1,000 persons/year of HFpEF in female FHS and CHS participants over two decades ($n = 9082$). Patients in the study aged 60-95. Data retrieved from Tsao et al., 2018. P for trend < 0.05 .

Incidence of HFpEF in US Women Over Time

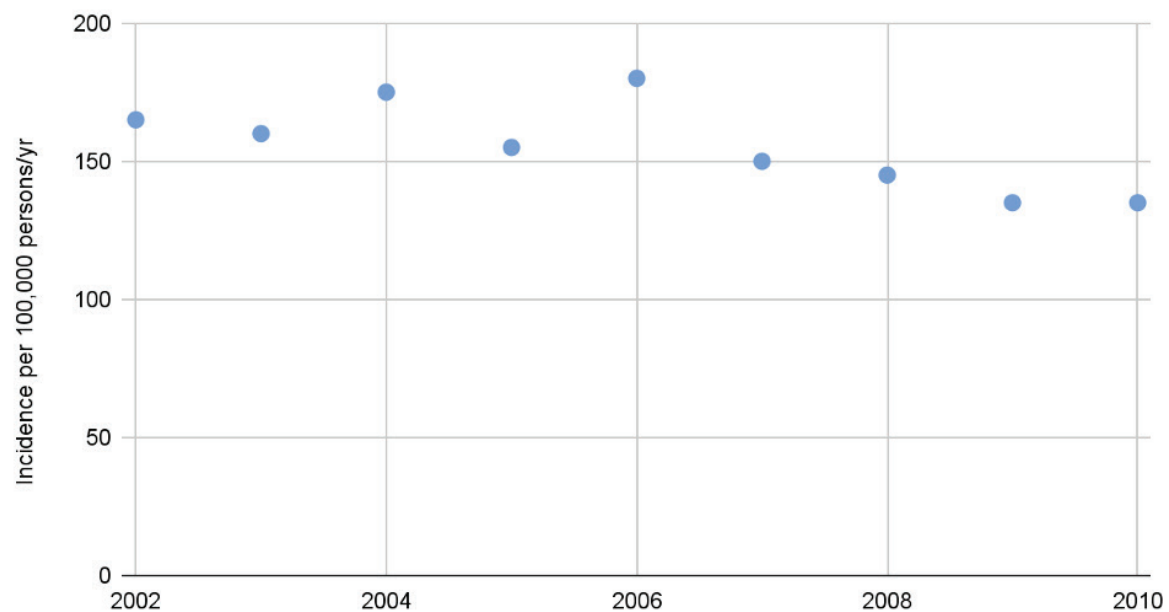


Figure 3. Age-standardized incidence of HFpEF in women in Olmsted County, Minnesota, USA, from 2002 to 2010. Data retrieved from Gerber et al., 2015. P for trend unpublished.

in Olmsted County, Minnesota, from 2002 to 2010, shown in Figure 3 (p-values for trend not published).

Chang et al. report that between 2005 and 2009, the age-adjusted incidence of HFpEF in white women was 9.9 per 1,000 persons/year, and in black women was 13.3 per 1,000 persons/year (Chang et al., 2014).

Age and Sex Distributions

Another key study by Goyal et al. used hospitalization data from the Nationwide Inpatient Sample to provide information on the distribution of sex within HFpEF patients over time, shown in Figure 4 (Goyal et al., 2016).

In 2017, Goyal et al. observed that among 1,208,763 hospitalizations of women for HFpEF from 2008 to 2012, the majority (>60%) occurred in persons 74 or older, shown in Figure 5.

Distribution of HFpEF by sex from 2003 to 2012

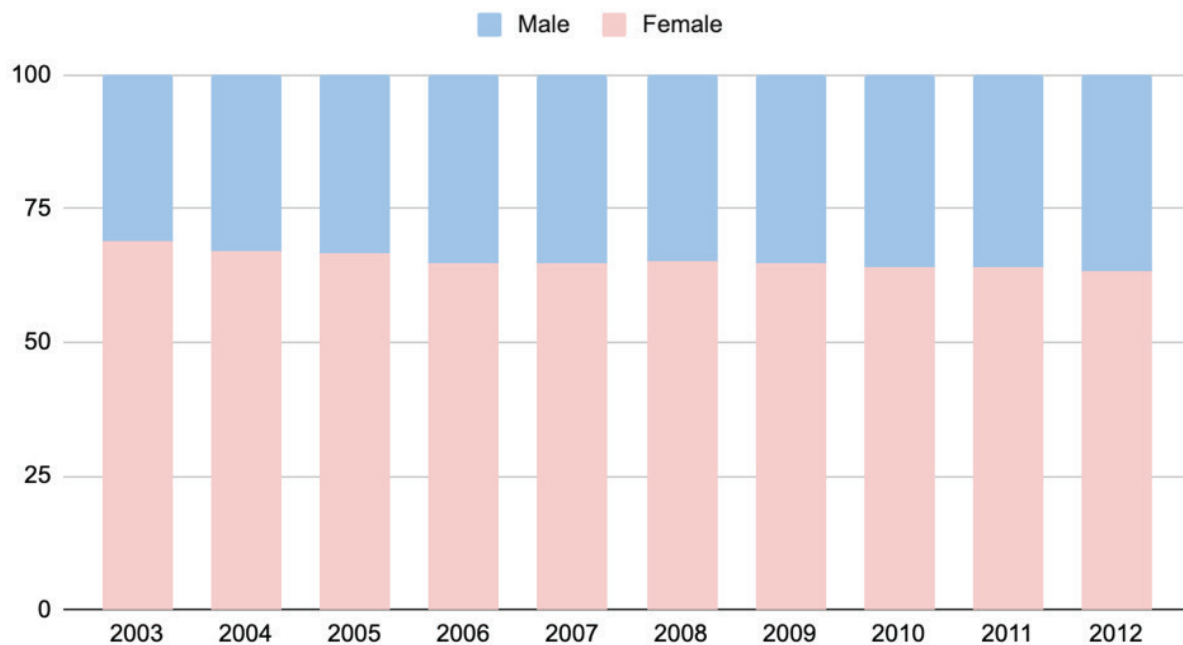


Figure 4. Distribution of HFpEF by sex from 2003 to 2012. Data retrieved from Goyal et al., 2016. P for trend < 0.001.

DISCUSSION

Key Findings

The results of our review suggest that both the incidence and prevalence of HFpEF in American women have increased significantly in recent decades. The juxtaposition of continuous advances in the treatment of other high-impact causes of mortality (like cancer, HFrEF, and diabetes, to name a few) against the lack of progress in treating HFpEF will likely exacerbate this increase in the decades to come.

Age-Stratification of Female HFpEF Hospitalizations from 2008 to 2012

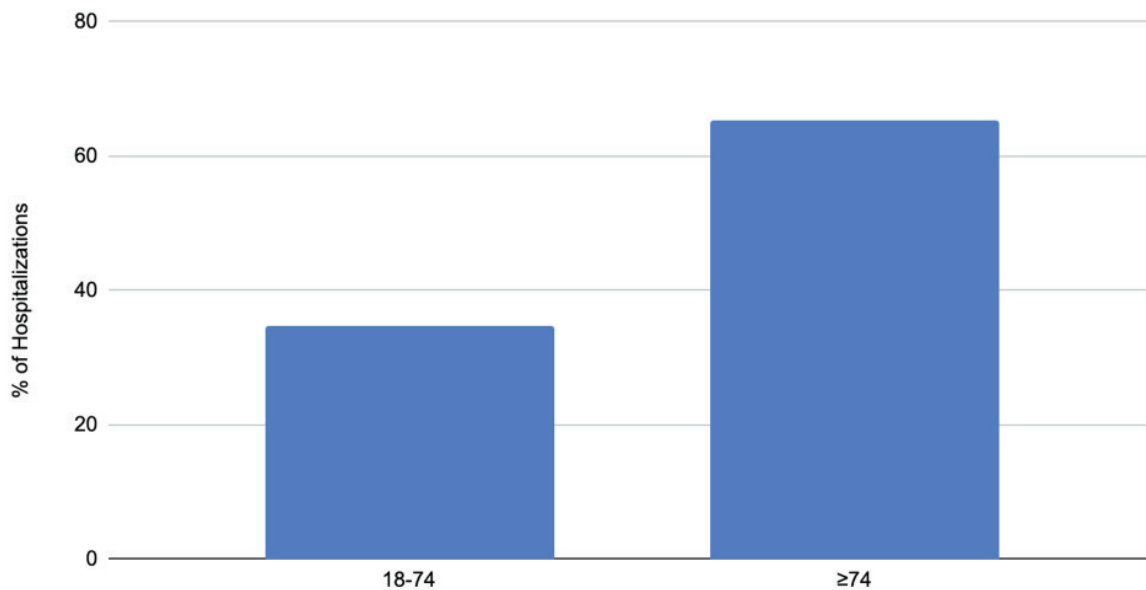


Figure 5. Age-stratification of hospitalizations of women for HFpEF from 2008 to 2012 in the US (n = 1,208,763). Data retrieved from Goyal et al., 2017.

Strengths and Limitations

Table 2 displays an overview of the studies included in the final review. Many of the studies had large sample sizes, lending credibility to their findings and our descriptive analysis. In addition, despite a frequent lack of echocardiographic data or left ventricular ejection fraction (LVEF) data to confirm the diagnosis of HFpEF, most sampled data used validated ICD-9-CM codes to diagnose HFpEF. Even if possible, it would be economically and laboriously impractical to individually validate HFpEF diagnosis via the collection and evaluation of echocardiographic/LVEF data.

The findings of Gerber et al. in 2015 (Figure 3) should be interpreted with caution, as p-values for trend were not published. Other trends (Figures 2 and 4) included p-values for trend from the original studies and should be weighted more when qualitatively assessing the findings of this review.

Given that there is a significant disparity-by-sex in the development of HFpEF, a non-trivial limitation in Chang et al., 2014, Goyal et al., 2016, and Ramachandran et al., 2018 is that analysis of HFpEF is not sex-stratified by each demographic factor, limiting the ability of this paper to analyze and compare findings. This appears to be an oversight in an epidemiological analysis of HFpEF, as sex will likely confound findings. For this reason, many potential risk factors (such as location) were not analyzed within this paper since sex-stratified data were not presented. It is suggested that future data collection and epidemiological analysis of HFpEF by demographic (race, geographic location, socioeconomic status, age, etc) be stratified by sex to avoid this preventable confounding effect.

In preparing search terms for the review, we were cognizant of several different terms used synonymously with HFpEF within the field of cardiology, including but not limited to diastolic

heart failure and diastolic dysfunction. In order to avoid missing relevant studies, we cast a wide Boolean search net with the intention of using SWIFT-Review to reproducibly and efficiently narrow the large number of results.

Although there is often slight variance in the LVEF cutoffs in the diagnosis of HFpEF, this variance (typically choosing between 50% or 55% as the threshold for preserved ejection fraction) is minor enough that between-study variance is unlikely to significantly affect conclusions. LVEF cutoffs were not defined across all studies.

Further Steps

Future epidemiological studies on the association between risk factors and HFpEF incidence are strongly encouraged to present results explicitly stratified by sex to account for the growing sex disparity in susceptibility to HFpEF. The robustly documented rise of both HFpEF incidence and prevalence in American women over the past several decades, coupled with the shortcomings of modern medicine in meaningfully attenuating/reversing HFpEF progression, call for accelerated action in the research, development, and implementation of new HFpEF solutions.

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