

## **Exercise Capacity in Heart Failure: A Systematic Review and Meta-Analysis of HFrEF and HFpEF Disparities in VO<sub>2</sub>peak and 6-Minute Walk Distance**

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### **Citation:**

PROKOPIDIS, Konstantinos, IRLIK, Krzysztof, ISPOGLOU, Theocharis, FERENTINOS, Panagiotis, MITROPOULOS, Alexandros, SCHLÖGL, Mathias, ISANEJAD, Masoud, KEGLER, Kamil, NABRDALIK, Katarzyna and LIP, Gregory YH (2025). Exercise Capacity in Heart Failure: A Systematic Review and Meta-Analysis of HFrEF and HFpEF Disparities in VO<sub>2</sub>peak and 6-Minute Walk Distance. *European Heart Journal Open*: oeaf055. [Article]

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# Exercise capacity in heart failure: a systematic review and meta-analysis of HFrEF and HFpEF disparities in $\text{VO}_{2\text{peak}}$ and 6-minute walking distance

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Received 28 December 2024; revised 20 February 2025; accepted 12 May 2025; online publish-ahead-of-print 14 May 2025

Handling Editor: Giuseppe Vergaro

## Aims

Heart failure (HF) with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) exhibit unique physiological pathways, influencing exercise capacity and functional performance. This systematic review and meta-analysis aimed to compare peak oxygen consumption ( $\text{VO}_{2\text{peak}}$ ), six-minute walk distance (6MWD), cardiac output (CO), and stroke volume (SV), between these phenotypes.

## Methods and results

A systematic literature search of cohort studies via databases (PubMed, Web of Science, Scopus, and Cochrane Library) was conducted from inception until October 2024. A meta-analysis using a random-effects model to calculate the pooled effects was employed. Forty-six studies were included. HFrEF patients demonstrated significantly greater 6MWD compared to HFpEF ( $k = 20$ ; mean difference (MD): 18.09 m, 95% confidence interval (CI) 1.59–34.59,  $I^2 = 86\%$ ,  $P = 0.03$ ), though this difference became insignificant after adjusting for comorbidities. Conversely, HFpEF patients exhibited higher  $\text{VO}_{2\text{peak}}$  ( $k = 20$ ; MD:  $-0.78 \text{ mL/kg/min}$ , 95% CI  $-1.45$ – $-0.11$ ,  $I^2 = 89\%$ ,  $P = 0.02$ ), CO ( $k = 12$ ; MD:  $-1.15 \text{ L/min}$ , 95% CI  $-2.11$ – $-0.19$ ,  $I^2 = 97\%$ ,  $P = 0.02$ ), and SV ( $k = 14$ ; SMD:  $-1.00$ , 95% CI  $-1.60$ – $-0.39$ ,  $I^2 = 95\%$ ,  $P < 0.01$ ). Age was identified as a significant moderator of  $\text{VO}_{2\text{peak}}$ .

## Conclusion

HFpEF patients demonstrated superior  $\text{VO}_{2\text{peak}}$ , CO, and SV compared to HFrEF patients, while the observed 6MWD advantage in HFrEF was likely influenced by comorbidities. Our findings emphasize the importance of tailoring rehabilitation strategies to HF phenotype-specific physiological profiles, particularly focusing on improving  $\text{VO}_{2\text{peak}}$  and cardiac efficiency in HFpEF.

## Keywords

Heart failure •  $\text{VO}_{2\text{peak}}$  • Physical function • HFrEF • HFpEF

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## Introduction

Heart failure (HF) is major clinical and public health problem designated as an emerging epidemic since 1997.<sup>1</sup> This condition consists of two distinct phenotypes identified based on ejection fraction (EF).<sup>2</sup> These phenotypes are HF with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF) sharing common pathophysiological pathways,<sup>3,4</sup> but exhibiting distinct physiological profiles that impact exercise capacity and functional performance beyond EF alone. Heart failure is categorized into four stages based on the relationship between symptoms of dyspnoea and physical activity using The New York Heart Association (NYHA) classification.

In patients with mild HF (NYHA II), cardiac output (CO) may appear normal at rest but fails to increase with physical activity.<sup>5</sup> The relationship between maximal oxygen consumption ( $\text{VO}_{2\text{peak}}$ ), peak CO, and muscle perfusion suggests that inadequate CO increase may trigger anaerobic metabolism at lower workloads, contributing to muscle fatigue. Consequently, patients with HF often reach a symptom-limited  $\text{VO}_2$ , commonly referred to as ' $\text{VO}_{2\text{peak}}$ ', instead of a true  $\text{VO}_{2\text{peak}}$ , further highlighting the need for careful interpretation of these values in clinical practice.

Assessment of patient's exertional capacity may support exercise prescription and provide insights into HF severity<sup>6</sup> and this can be performed with the measurement of  $\text{VO}_{2\text{peak}}$ , reflecting the cardiopulmonary system's capacity during exercise.<sup>7</sup> Previous research indicates that lower  $\text{VO}_{2\text{peak}}$  in HFrEF is linked to reduced stroke volume (SV) and CO due to impaired systolic function.<sup>8</sup>  $\text{VO}_{2\text{peak}}$ , often measured via symptom limited cardiopulmonary exercise (CPET) is a valuable prognostic tool for both HFrEF and HFpEF.<sup>9,10</sup>

CPET, involving gas analysis during progressive exercise, assesses minute ventilation ( $\text{Ve}$ ), oxygen uptake ( $\text{O}_2$ ), and carbon dioxide ( $\text{CO}_2$ ),<sup>10</sup> helps to identify maladaptive physiological responses to exercise and combined with other metrics such as heart rate, blood pressure, and electrocardiogram, enables personalized exercise prescriptions, enhancing clinical insights into exercise intolerance.<sup>11</sup>

Although a symptom limited CPET is an objective measure of functional capacity, the six-minute walk distance test (6MWD) offers a simpler measure to assess functional capacity and endurance in this population,<sup>12</sup> particularly for those with advanced diseases and multiple comorbidities<sup>13</sup> (Giannitsi et al. 2019). Including 6MWD data alongside  $\text{VO}_{2\text{peak}}$  and CPET measures may provide a more comprehensive understanding of patient exercise tolerance, supporting the development of more effective exercise interventions.

Considering that exercise can positively affect  $\text{VO}_{2\text{peak}}$  in both HF phenotypes,<sup>14</sup> understanding potential differences in  $\text{VO}_{2\text{peak}}$ , 6MWD, SV, and CO may be pivotal for optimizing exercise prescriptions and rehabilitation strategies appropriate to each phenotype.

The primary aim of this systematic review and meta-analysis was to systematically compare  $\text{VO}_{2\text{peak}}$ , 6MWD, and related parameters in HFrEF and HFpEF, addressing current knowledge gaps and providing evidence to guide more effective interventions for each phenotype. These may clarify how various end criteria in  $\text{VO}_2$  testing, such as those discussed in Edvardsen et al. (2014), may impact  $\text{VO}_2$  measurements, helping to inform adjustments in exercise protocols based on patient characteristics such as age and sex.<sup>15</sup>

## Methods

The revised 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria were followed,<sup>16</sup> with a protocol registered in the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42024495582).

## Inclusion and exclusion criteria

### Inclusion

- Data pertaining to HFrEF (mean LVEF  $\leq 40\%$ ) and HFpEF (mean LVEF  $\geq 50\%$ ) with mean age 18 years of age or above.
- Data collection will only be eligible from studies that include information for both HF phenotypes.
- Studies may be interventional or observational.

### Exclusion

- Data collection from HFrEF (mean LVEF  $> 40$  and  $\leq 50\%$ ) and HFpEF (mean LVEF 40–49%).
- Not published in English.

## Search strategy

From inception to October 2024, four databases (PubMed, Cochrane Library, Scopus, and Web of Science) were independently searched by two investigators. A detailed description of the keyword search strategy is displayed in [Supplementary material online, Table S1](#).

## Outcomes of interest

We gathered data related to  $\text{VO}_{2\text{peak}}$ , 6MWD, SV, and CO from both HFrEF and HFpEF based on  $\text{VO}_{2\text{peak}}$  was measured in mL/kg/min, CO in L/min, SV in mL, and 6MWD in meters (m).

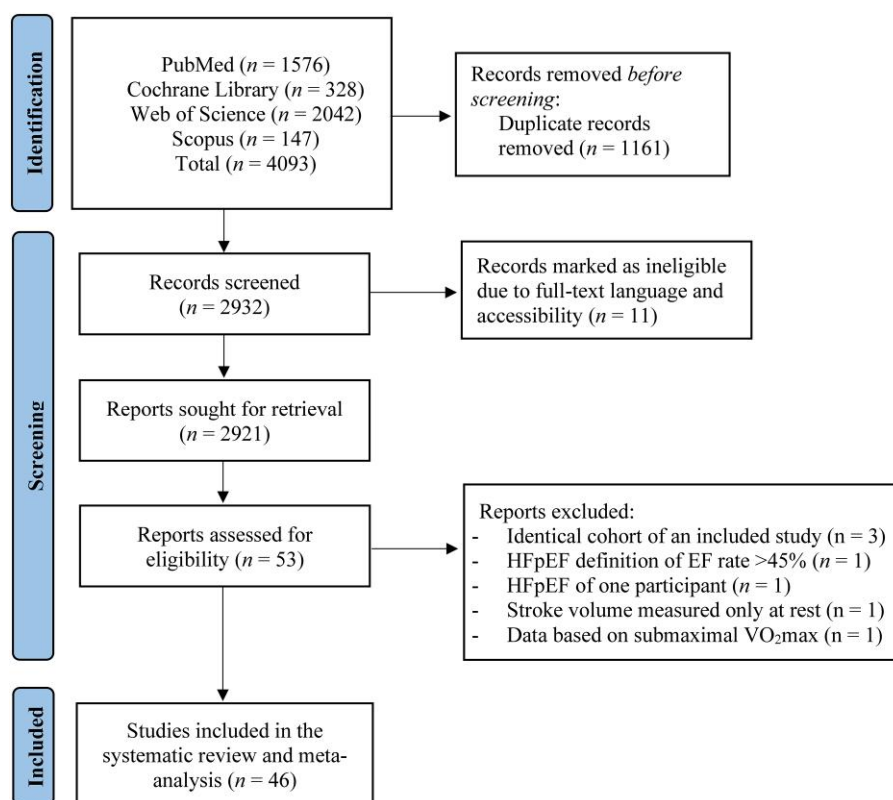
## Data extraction and risk of bias

Two investigators extracted data independently, including details such as the name of the first author, country of origin, participant age, sex, and body mass index (BMI), study design, LVEF rate, phenotype of HF, definition of HF phenotype,  $\text{VO}_{2\text{peak}}$  method of assessment, brain natriuretic peptide levels, reported comorbidities, and outcomes of interest. Any disagreements were resolved by a third investigator. The Newcastle–Ottawa scale (NOS) was utilized to assess study quality/risk of bias (RoB) for cohort studies. NOS assigns a maximum of nine points across three quality parameters: Selection, comparability, and outcome. The evaluation was made by two investigators, and it was classified as high ( $\leq 5$  points), moderate (6–7 points), or low (8–9 points). For cross-sectional studies, it was classified as high ( $\leq 3$  points), moderate (4–5 points), or low (6–7 points).<sup>17</sup> For randomized controlled trials (RCTs), the quality of the studies was evaluated using the risk-of-bias 2 (RoB2) tool.<sup>18</sup> RoB2 assesses bias according to five domains: (i) randomization process; (ii) deviations from intended interventions; (iii) missing outcome data; (iv) measurement of the outcome; and (v) selection of the reported result. Based on its scoring system, bias was defined as 'high', 'some concerns', or 'low'.

## Statistical analysis

Quantitative data were considered as continuous measurements, and differences in outcomes between those with HFrEF vs. HFpEF were compared to determine MDs or standardized MDs (SMDs) in case units of assessment were not uniform. Statistical heterogeneity of outcome measurements across studies was measured using the overlap of their confidence intervals (CI 95%) and expressed as Cochran's Q ( $\chi^2$  test) and  $I^2$  measurements.<sup>19</sup>

The random-effects model and the inverse-variance approach were used to determine statistical significance set at  $P < 0.05$ . The meta-analysis was synthesized using Review Manager (RevMan 5.4.1) software. Furthermore, low heterogeneity was defined as  $I^2$  between 30% and 49%, moderate heterogeneity between 50% and 74%, and high heterogeneity at 75% and above.<sup>20</sup> Sensitivity analysis was performed to assess the robustness of reported statistical results by controlling for studies with increased risk of bias. In the case of substantial heterogeneity, a random-effects meta-regression was carried out to investigate potential sources of variability that could alter estimate rates across studies.<sup>21</sup> Particularly, meta-regressions included factors such as age and BMI. Potential publication bias was evaluated using funnel plots and Egger's weighted regression test to quantitatively assess asymmetry in study results.<sup>22</sup>



**Figure 1** Literature search for the included studies.

## Results

The initial literature search provided 4093 publications. Following the exclusion of duplicates, abstracts, studies that full text could not be obtained and in a different language, 53 full texts were identified as potentially eligible for inclusion in the systematic review and meta-analysis. Of these 53 articles, three could not be included considering a more recent eligible cohort for inclusion in our study, one study defined HFpEF as EF rate above 45%, one study included only one HFpEF participant that could not be converted in our model, one study measured SV only at rest, while another study did not measure  $\text{VO}_2$  on maximal capacity. Overall, 46 studies were included in the systematic review and meta-analysis (Flowchart—[Figure 1](#)), for which, detailed characteristics are presented in [Table 1](#).

As detailed in [Supplementary material online, Table S2](#),  $\text{VO}_{2\text{peak}}$  was assessed via treadmill protocols in two studies and cycle ergometry in the remaining 44 studies. Left ventricular EF was predominantly measured by echocardiography with some studies using cardiac magnetic resonance imaging (cMRI), ventriculography, or employing mixed methods. The age of participants ranged from 50.7 to 80.4 years, with BMI values ranging from 21 to 36.1  $\text{kg/m}^2$ . On average, participants with HFpEF were older and had higher BMI compared to those with HFrEF.

### Heart failure with reduced ejection fraction vs. heart failure with preserved ejection fraction: six-minute walk distance

Our main analysis showed significantly greater 6MWD in HFrEF vs. HFpEF ( $k = 20$ ; MD: 18.09 m, 95% CI 1.59–34.59,  $I^2 = 86\%$ ,  $P = 0.03$ )

([Figure 2](#)). When studies, where a phenotype had higher reported comorbidities over the other, were excluded the findings became statistically insignificant ( $k = 13$ ; MD: 10.97 m, 95% CI –10.87–32.32,  $I^2 = 87\%$ ,  $P = 0.32$ ) (see [Supplementary material online, Figure S1](#)). Exclusion of a study with high risk of bias did not alter the findings of the main analysis ( $k = 19$ ; MD: 19.86 m, 95% CI 3.09–36.63,  $I^2 = 87\%$ ,  $P = 0.02$ ) (see [Supplementary material online, Figure S2](#)).

### Heart failure with reduced ejection fraction vs. heart failure with preserved ejection fraction: $\text{VO}_{2\text{peak}}$ , cardiac output, and stroke volume

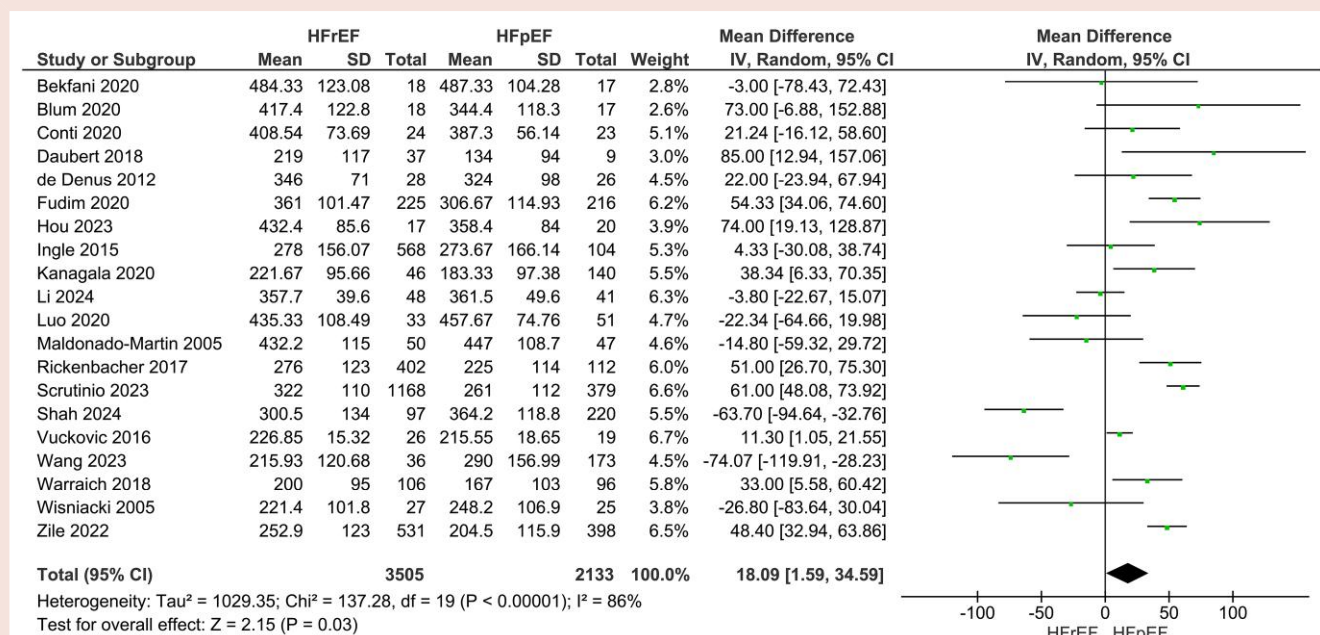
Our main analysis showed significantly lower  $\text{VO}_{2\text{peak}}$  in HFrEF vs. HFpEF ( $k = 20$ ; MD: –0.78 mL/kg/min, 95% CI –1.45–0.11,  $I^2 = 89\%$ ,  $P = 0.02$ ) ([Figure 3](#)). However, sensitivity analysis excluding studies where one phenotype had higher reported comorbidities over the other rendered the results statistically insignificant ( $k = 15$ ; MD: –0.70 mL/kg/min, 95% CI –1.60–0.19,  $I^2 = 91\%$ ,  $P = 0.12$ ) (see [Supplementary material online, Figure S3](#)). Sensitivity analyses excluding studies with high risk of bias also revealed insignificant findings ( $k = 16$ ; –0.77 mL/kg/min, 95% CI –1.56–0.02,  $I^2 = 91\%$ ,  $P = 0.06$ ) (see [Supplementary material online, Figure S4](#)). In addition, these results were accompanied by statistically significant decreases in CO ( $k = 12$ ; MD: –1.15 L/min, 95% CI –2.11–0.19,  $I^2 = 97\%$ ,  $P = 0.02$ ) ([Figure 4](#)) and SV ( $k = 14$ ; SMD: –1.00, 95% CI –1.60–0.39,  $I^2 = 95\%$ ,  $P < 0.01$ ) ([Figure 5](#)). To measure the MD of SV differences between phenotypes, a sensitivity analysis was conducted to remove a study that used SV index. This analysis confirmed that HFrEF had significantly lower SV

**Table 1 Study and participant characteristics of the included studies**

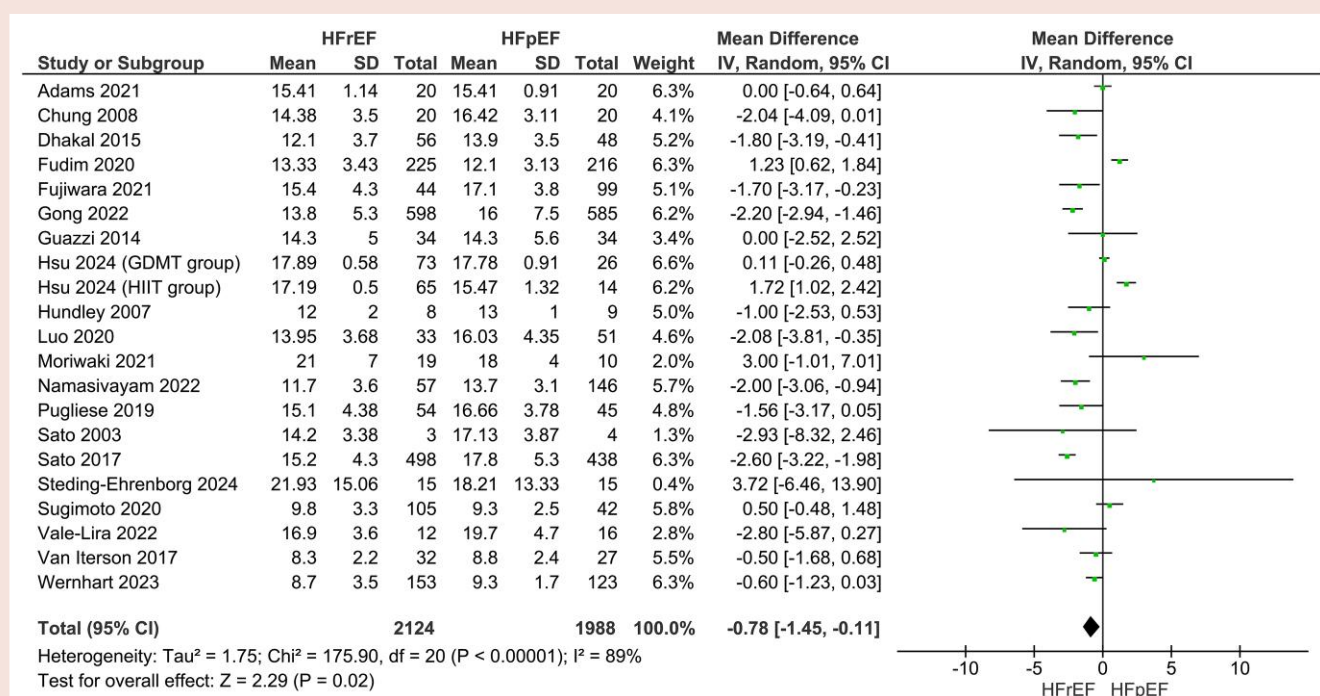
Study	Total n (M/F)	HFrEF			HFpEF		
		n (M/F)	Age	BMI	n (M/F)	Age	BMI
Abe et al. <sup>23</sup>	23 (1/12)	13 (1/12)	75 ± 7.0	—	10 (7/3)	65 ± 12.0	—
Adams et al. <sup>24</sup>	40 (15/5)	20 (15/5)	60.1 ± 1.7	30.4 ± 1.4	20 (5/15)	69.7 ± 1.6	33 ± 1.4
Arvidsson et al. <sup>25</sup>	32 (—/—)	16 (—/—)	65.7 ± 8.1	—	16 (—/—)	70.3 ± 13.8	—
Bekfani et al. <sup>26</sup>	35 (15/3)	18 (15/3)	68 ± 9.0	—	17 (8/9)	71 ± 6.0	28.7 ± 4.6
Blum et al. <sup>27</sup>	35 (15/3)	18 (15/3)	65.4 ± 10.5	28.1 ± 3.8	17 (9/8)	77.9 ± 8.0	27.6 ± 3.8
Charman et al. <sup>28</sup>	38 (—/—)	21 (—/—)	—	—	17 (—/—)	—	—
Chung et al. <sup>29</sup>	40 (17/3)	20 (17/3)	64 ± 10.0	28.3 ± 5.8	20 (14/6)	64 ± 8.0	30.2 ± 5.5
Conti et al. <sup>30</sup>	47 (16/8)	24 (16/8)	63.5 ± 9.6	28.1 ± 4.73	23 (13/10)	63.9 ± 10.3	27.9 ± 2.8
Daubert et al. (OMT alone) <sup>31</sup>	37 (—/—)	28 (—/—)	62.6 ± 12.7	—	9 (—/—)	68.2 ± 12.7	—
de Denus et al. <sup>32</sup>	54 (—/—)	28 (—/—)	63 ± 12.6	—	26 (—/—)	75.6 ± 11.9	—
Dhakal et al. <sup>33</sup>	104 (45/11)	56 (45/11)	59 ± 12.0	27.8 ± 6.0	48 (20/28)	63 ± 12.0	33.7 ± 7.6
Edlund et al. <sup>34</sup>	30 (12/3)	15 (12/3)	66 ± 8.2	—	15 (11/4)	71 ± 18.0	—
Fudim et al. <sup>35</sup>	441 (145/80)	225 (145/80)	62.7 ± 11.2	29.6 ± 6.0	216 (112/104)	69.3 ± 11.2	33.4 ± 8.0
Fujiwara et al. <sup>36</sup>	143 (38/6)	44 (38/6)	58 ± 14.0	23.4 ± 4.4	99 (81/18)	67 ± 12.0	24.2 ± 2.9
Gong et al. <sup>37</sup>	1183 (430/168)	598 (430/168)	58.3 ± 13.1	28.2 ± 5.4	585 (287/298)	58.1 ± 16.0	29.9 ± 7.1
Guazzi et al. <sup>38</sup>	68 (26/8)	34 (26/8)	63 ± 9.0	—	34 (26/8)	62.7 ± 9.3	—
Hou et al. <sup>39</sup>	37 (14/3)	17 (14/3)	—	—	20 (11/9)	—	—
Hsu et al. (GDMT group) <sup>40</sup>	99 (57/16)	73 (57/16)	57.8 ± 3.6	25.5 ± 1.3	26 (16/10)	65.3 ± 5.3	26.4 ± 2.6
Hsu et al. (HIT group) <sup>40</sup>	79 (51/14)	65 (51/14)	59.7 ± 4.9	25.5 ± 1.7	14 (8/6)	66.2 ± 10.7	26.3 ± 2.88
Hundley et al. <sup>41</sup>	17 (4/4)	8 (4/4)	73 ± 7.0	27 ± 5.0	9 (3/6)	74 ± 7.0	30 ± 10.0
Ingle et al. <sup>42</sup>	672 (430/138)	568 (430/138)	74.3 ± 8.2	26.8 ± 4.5	104 (57/47)	75.3 ± 9.8	30.4 ± 5.3
Kanagala et al. <sup>43</sup>	186 (23/23)	46 (23/23)	72 ± 8.0	28 ± 6.0	140 (68/72)	73 ± 9.0	34 ± 7.0
Li et al. <sup>44</sup>	89 (19/29)	48 (19/29)	71.6 ± 4.5	28.4 ± 2.3	41 (26/15)	65.1 ± 4.3	28.6 ± 2.3
Luo et al. <sup>45</sup>	84 (31/2)	33 (31/2)	56.5 ± 15.3	25.6 ± 5.5	51 (42/9)	62.3 ± 6.0	25.4 ± 2.8
Maldonado-Martin et al. <sup>46</sup>	97 (33/17)	50 (33/17)	69.4 ± 5.2	26.7 ± 4.3	47 (6/41)	68.8 ± 6.1	30.5 ± 6.0
Moriwaki et al. <sup>47</sup>	20 (7/3)	10 (7/3)	53 ± 11.0	25 ± 4.0	10 (2/8)	68 ± 18.0	24 ± 6.0
Namasivayam et al. <sup>48</sup>	203 (34/13)	57 (34/13)	60 ± 13.0	27.4 ± 4.4	146 (74/72)	63 ± 13.0	32.9 ± 7.5
Obokata et al. <sup>49</sup>	80 (28/15)	43 (28/15)	67 ± 13.0	21 ± 2.8	37 (22/15)	70 ± 11.0	22.2 ± 3.3
Paolisso et al. <sup>50</sup>	56 (24/11)	35 (24/11)	67 ± 13.0	27 ± 5.0	21 (5/16)	75 ± 9.0	30 ± 7.0
Pugliese et al. <sup>51</sup>	99 (42/12)	54 (42/12)	63.9 ± 11.3	25.7 ± 3.4	45 (32/13)	64.3 ± 12.1	26.9 ± 4.7
Rickenbacher et al. <sup>52</sup>	514 (271/131)	402 (271/131)	75.5 ± 7.5	25.3 ± 4.1	112 (40/72)	80.2 ± 7.1	27 ± 5.4
Sato et al. <sup>53</sup>	6 (—/—)	3 (—/—)	50.7 ± 20.5	—	3 (—/—)	60.3 ± 10.0	—
Sato et al. <sup>54</sup>	936 (419/79)	498 (419/79)	59.1 ± 14.4	22.9 ± 4.1	438 (339/99)	61.8 ± 14.3	23.8 ± 4.1
Schwartzberg et al. <sup>55</sup>	257 (149/25)	174 (149/25)	56 ± 12.0	29.5 ± 5.8	83 (12/71)	69 ± 9.0	33.2 ± 8.3
Scrutinio et al. <sup>56</sup>	1547 (951/217)	1168 (951/217)	65.3 ± 12.3	—	379 (176/203)	73.6 ± 11.9	—
Shah et al. <sup>57</sup>	317 (86/11)	97 (86/11)	74.5 ± 7.3	—	220 (197/23)	74.7 ± 7.1	—
Steding-Ehrenborg et al. <sup>58</sup>	21 (6/4)	10 (6/4)	66 ± 14.6	27 ± 4.8	11 (4/7)	72 ± 15.3	28.8 ± 3.2
Steding-Ehrenborg et al. <sup>59</sup>	30 (12/3)	15 (12/3)	63.3 ± 18.8	29.4 ± 14.1	15 (8/7)	70.7 ± 21.3	29.3 ± 14.1
Sugimoto et al. <sup>60</sup>	147 (79/26)	105 (79/26)	65.5 ± 12.3	26.3 ± 3.9	42 (19/23)	70.8 ± 10.2	28.4 ± 5.0
Vale-Lira et al. <sup>61</sup>	28 (11/1)	12 (11/1)	54.4 ± 7.3	28.3 ± 5.1	16 (8/8)	55.6 ± 11.5	30 ± 4.0
Van Iterson et al. <sup>62</sup>	59 (30/2)	32 (30/2)	55 ± 10.0	28 ± 4.0	27 (16/11)	71 ± 11.0	33 ± 6.0
Vuckovic et al. <sup>63</sup>	45 (14/12)	26 (14/12)	64.3 ± 1.6	33.9 ± 1.6	19 (7/12)	65.7 ± 2.4	33.7 ± 1.8
Wang et al. <sup>64</sup>	209 (25/11)	36 (25/11)	68.3 ± 12.6	24.1 ± 4.8	173 (80/93)	71.8 ± 11.8	24.6 ± 3.8
Warraich et al. <sup>65</sup>	202 (56/50)	106 (56/50)	72.3 ± 7.7	30.6 ± 7.5	96 (37/59)	71.7 ± 7.4	36.1 ± 9.3
Wernhart et al. <sup>66</sup>	276 (130/23)	153 (130/23)	52.8 ± 10.3	28.2 ± 4.6	123 (72/51)	60 ± 12.3	27.2 ± 5.2
Wisniacki et al. <sup>67</sup>	52 (16/11)	27 (16/11)	79.8 ± 5.2	23.2 ± 2.7	25 (12/13)	80.4 ± 4.5	25.5 ± 3.6
Zile et al. <sup>68</sup>	929 (376/155)	531 (376/155)	67.2 ± 11.4	31.4 ± 7.4	398 (200/198)	71.6 ± 9.7	36.3 ± 9.0

Data are expressed as mean ± standard deviation.





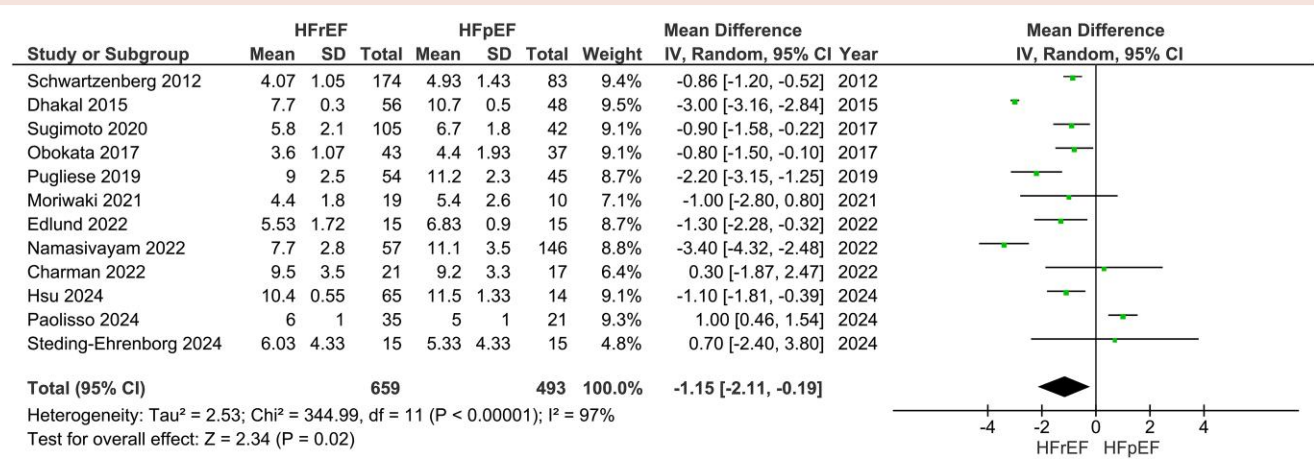
**Figure 2** Differences in six-minute walking distance between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).



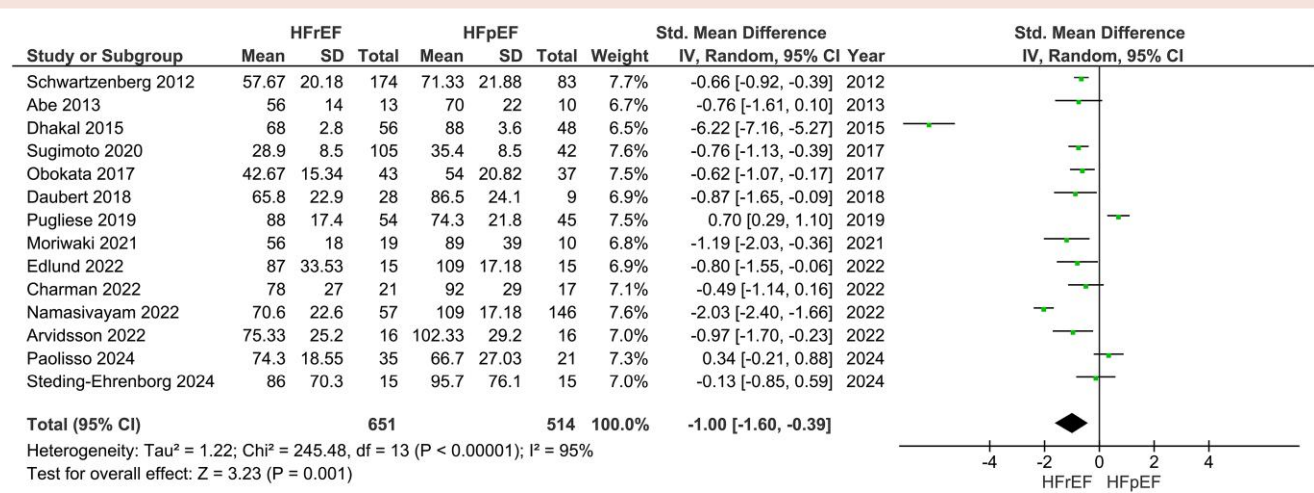
**Figure 3** Differences in VO<sub>2peak</sub> between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

(in mL) compared to HFpEF ( $k = 13$ ; MD:  $-15.05$  mL, 95% CI  $-22.92$ – $-7.18$ ,  $I^2 = 91\%$ ,  $P < 0.01$ ) (see [Supplementary material online, Figure S5](#)). Sensitivity analyses excluding studies with additional reported comorbidities did not alter the results of the main analysis for

either CO ( $k = 9$ ; MD:  $-1.23$  L/min, 95% CI  $-2.19$ – $0.28$ ,  $I^2 = 93\%$ ,  $P = 0.01$ ) (see [Supplementary material online, Figure S6](#)) or SV ( $k = 9$ ;  $-14.99$  mL, 95% CI  $-25.98$ – $-4.00$ ,  $I^2 = 89\%$ ,  $P < 0.01$ ) (see [Supplementary material online, Figure S7](#)).



**Figure 4** Differences in cardiac output between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).



**Figure 5** Differences in stroke volume between heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF).

Publication bias and meta-regression

Potential publication bias based on CO was found ( $P = 0.0314$ ), indicating statistically significant funnel plot asymmetry (see [Supplementary material online, Table S3](#); [Supplementary material online, Supplementary file](#); CO—Publication bias). No publication bias was detected for  $VO_{2peak}$ , SV, and 6MWD (see [Supplementary material online, Table S3](#)). Meta-regression analysis demonstrated that age was a significant moderator of  $VO_{2peak}$  ( $z = 2.19$ ,  $P = 0.03$ , 95% CI 0.02–0.28). In contrast, the proportion of females and BMI were not significant moderators of  $VO_{2peak}$  in this meta-analysis ( $P > 0.05$ ; [Supplementary material online, Table S4](#)).

Risk of bias assessment

No studies with high risk of bias were found regarding the included RCTs. One study had some concerns, particularly in relation to some

missing data, for which, methods to handle them were not fully described, lack of clarity in the blinding of some outcomes, and no specific method of sequence generation described (see [Supplementary material online, Table S5](#)). Furthermore, risk of bias assessment of the included cohort studies showed no studies with increased risk (see [Supplementary material online, Table S6](#)), however, six cross-sectional studies were evaluated as having an increased bias risk (see [Supplementary material online, Table S7](#)).

Discussion

This systematic review and meta-analysis revealed that patients with HFrEF exhibited greater 6MWD compared to HFpEF, however, those with HFpEF demonstrated a greater  $VO_{2peak}$ , SV, and CO. These disparities highlight the distinct pathophysiological profiles of these

phenotypes and reflect differences in age, comorbidities, and cardiovascular function that influence exercise capacity.

## Walking tests and cardiac economy

Our findings on 6MWD disparities between HFrEF and HFpEF complement existing research on walking tests as functional metrics in cardiac populations. However, the clinical significance of 6MWD differences may be limited without incorporating measures of cardiac efficiency. For example, the Heart Rate Walking Speed Index (HRWSI), which evaluates heart rate in relation to walking speed, provides additional insights into cardiac economy and exercise-induced adaptations.<sup>69</sup> This metric could complement traditional walking tests, helping to distinguish between true physiological improvements and variability caused by external factors.

Pertinent to 6MWD, exclusion of studies where one phenotype had an increasing number of reported comorbidities over the other led to a 10.97 m difference favouring HFrEF. This modest difference, although statistically significant in the main analysis, raises questions about its clinical relevance. The 6MWD test is subject to a learning effect, as demonstrated by previous research in patients with asthma and patients with chronic HF, where test-retest reliability testing resulted to improvements of up to 35 m.<sup>70</sup> Our findings align with these observations, suggesting that the small differences in 6MWD between phenotypes may reflect test variability rather than meaningful functional disparities. Despite this, 6MWD remains a valuable metric for functional capacity, particularly in settings where CPET is not feasible.

In patients with asthma, there was a mean increase of 18 m (95% CI 11 to 24 m) in 6MWD (73% of the sample showed improvement),<sup>70</sup> demonstrating a learning effect that could explain such differences. This number is identical to our findings of 18.09 m (95% CI 1.59–34.59 m). In addition, in patients with chronic HF, learning effect was even greater (31 m (95% CI 27–35 m) during a second attempt,<sup>71</sup> therefore, given that the included studies did not report whether another attempt was made and the between-test differences, 6MWD changes between phenotypes may have negligible clinical value.

## Oxygen capacity and $\text{VO}_{2\text{peak}}$

Peak  $\text{VO}_2$  is a validated prognostic marker in HF, though its role in evaluating functional capacity changes post-intervention remains debated.<sup>72,73</sup> Although the main analysis showed statistically significant differences in  $\text{VO}_{2\text{peak}}$  favouring HFpEF, sensitivity analyses accounting for comorbidities and study quality rendered these findings non-significant.  $\text{VO}_{2\text{peak}}$  differences of  $-0.78$  mL/kg/min (95% CI  $-1.45$ – $-0.11$  mL/kg/min) (main analysis) or  $-0.70$  mL/kg/min (95% CI  $-1.60$ – $-0.19$  mL/kg/min) (comorbidities-adjusted analysis) align with prior research suggesting that even small changes in  $\text{VO}_{2\text{peak}}$  (i.e. 6% change or 1 mL/kg/min) can have prognostic value,<sup>74</sup> however, such outcome was based on repeat test variability rather than clinical significance. Nevertheless, in patients with chronic HF, every 6% increase in  $\text{VO}_{2\text{peak}}$  is linked to an 8% lower risk of all-cause mortality and a 7% lower risk of cardiovascular mortality or HF hospitalization.<sup>72</sup>

Interestingly, our meta-regression identified age as a significant moderator of  $\text{VO}_{2\text{peak}}$ , reiterating the importance of specifically designing interventions to address age-related declines in oxygen capacity. Despite these nuances,  $\text{VO}_{2\text{peak}}$  appears to offer greater prognostic value in HFpEF compared to HFrEF. Prior research supports this, with  $\text{VO}_{2\text{peak}}$  strongly linked to clinical outcomes in HFpEF.<sup>75</sup> Accordingly, exercise interventions that target oxygen capacity, such as 3–12 months of structured exercise training, could confer meaningful benefits in terms of  $\text{VO}_{2\text{peak}}$ , exercise duration, and quality of life,<sup>76</sup> while reducing and HF-related hospitalizations.<sup>77</sup> These findings align with the observed associations between  $\text{VO}_{2\text{peak}}$ , SV, and CO, which were significantly higher in HFpEF compared to HFrEF.

## Fidelity of exercise programs

Another important consideration in understanding exercise outcomes is the fidelity of exercise delivery. As demonstrated in cardiac rehabilitation studies, adherence to prescribed exercise intensities and durations (e.g.  $>50\%$  HRR for  $\geq 20$  min) significantly influences improvements in cardiorespiratory fitness.<sup>69</sup> Inconsistent fidelity across exercise training studies may partially explain the variability observed in  $\text{VO}_{2\text{peak}}$  and 6MWD outcomes observed in this review. While our study identified differences between HFrEF and HFpEF, these findings are potentially impacted by inconsistencies in intervention intensity and monitoring across studies. Ensuring rigorous fidelity monitoring in future research could improve the reliability and replicability of findings from exercise interventions.

## Physiological mechanisms and phenotype-specific differences

These observed differences in exercise capacity and oxygen dynamics may be explained by distinct physiological perturbations underpinning each phenotype. For example, patients with HFrEF experience more severe reductions in pulmonary oxygen uptake kinetics during exercise, deoxy-haemoglobin kinetics, and microvascular oxygen delivery compared with HFpEF.<sup>78</sup> In addition, a recent meta-analysis identified low left ventricular global longitudinal strain as a stronger determinant of decreased  $\text{VO}_{2\text{peak}}$ , a parameter more prevalent in HFrEF.<sup>79</sup> Mitochondrial dysfunction is another critical factor with HFrEF associated with reduced energy supply due to lower levels of complex I, malate dehydrogenase, and creatine kinase activity.<sup>24,80</sup> These differences provide a mechanistic basis for poorer exercise capacity and cardiac function in HFrEF.

## Strengths and limitations

In this study, consistent rates of LVEF were employed to categorize HFrEF and HFpEF ensuring robust comparisons between phenotypes. Sources of heterogeneity, including age and BMI, were explored through meta-regression, offering insights into moderating factors. However, these results are based on cross-sectional data, which do not imply causative implications between the two HF phenotypes. Although almost every study utilized cycle ergometry for  $\text{VO}_{2\text{peak}}$  assessment instead of treadmill, variability in exercise protocols (e.g. ramp vs. stepwise increments) may introduce heterogeneity in  $\text{VO}_{2\text{peak}}$  measurements. Additionally, left ventricular EF assessment predominantly relied on echocardiography, though some studies used alternative methods (cMRI, ventriculography, or mixed modalities), and cross-validation between methods was rarely reported. Additionally, publication bias was observed for CO, suggesting caution in interpreting these findings. Lastly, comorbidities and medication count among studies may have been over- or underreported due to potential inaccuracies arising from errors in drug prescription coding or incorrect electronic tabulations.

## Conclusion

This systematic review and meta-analysis highlights distinct differences between HFrEF and HFpEF in terms of exercise capacity and oxygen dynamics. While HFrEF patients demonstrated superior 6MWD, HFpEF patients exhibited higher  $\text{VO}_{2\text{peak}}$ , SV, and CO. These findings highlight the nuanced nature of exercise capacity disparities between phenotypes, influenced by factors such as age and comorbidities. Further research should focus on longitudinal studies to track changes in  $\text{VO}_{2\text{peak}}$ , 6MWD, and HRWSI over time and explore phenotype-specific rehabilitation strategies. Optimizing exercise interventions that target oxygen capacity and cardiac efficiency holds significant



promise for improving clinical outcomes in both HFrEF and HFpEF populations.

## Data availability

Data is available upon request.

## Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

## Author contributions

K.P., P.F., and A.M. conceptualized the study. K.P. wrote the manuscript and conducted the analyses. K.P. and K.I. performed the screening and data extraction of the studies. K.I., P.F., A.M., and K.K. assessed the risk of bias. T.I., M.S., and M.I. revised the manuscript. K.N. and G.Y.H.L. edited, revised the manuscript, and gave relevant intellectual senior contribution.

## Acknowledgements

This study was supported by Dunhill Medical Trust.

## Funding

None.

**Conflict of interest:** None declared.

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