# Exercise tolerance can explain the obesity paradox in patients with systolic heart failure: data from the MECKI Score Research Group

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| **Aims** | Obesity has been found to be protective in heart failure (HF), a finding leading to the concept of an obesity paradox. We hypothesized that a preserved cardiorespiratory fitness in obese HF patients may affect the relationship between survival and body mass index (BMI) and explain the obesity paradox in HF. |
| **Methods and results** | A total of 4623 systolic HF patients (LVEF $31.5 \pm 9.5\%$, BMI $26.2 \pm 3.6 \, kg/m^2$) were recruited and prospectively followed in 24 Italian HF centres belonging to the MECKI Score Research Group. Besides full clinical examination, patients underwent maximal cardiopulmonary exercise test at study enrolment. Median follow-up was 1113 (553–1803) days. The study population was divided according to BMI ($<25$, $25–30$, $>30$ to $\le 35 \, kg/m^2$) and predicted peak oxygen consumption (peak $VO_2$, $<50\%$, $50–80\%$, $>80\%$). Study endpoints were all-cause and cardiovascular deaths including urgent cardiac transplant. All-cause and cardiovascular deaths occurred in 951 (28.6%, 57.4 per person-years) and 802 cases (17.4%, 48.4 per 1000 person-years), respectively. In the high BMI groups, several |

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prognostic parameters presented better values [LVEF, peak VO$_2$, ventilation/carbon dioxide slope, renal function, and haemoglobin ($P < 0.01$)] compared with the lower BMI groups. Both BMI and peak VO$_2$ were significant positive predictors of longer survival: both higher BMI and peak VO$_2$ groups showed lower mortality ($P < 0.001$). At multivariable analysis and using a matching procedure (age, gender, LVEF, and peak VO$_2$), the protective role of BMI disappeared.

**Conclusion**     Exercise tolerance affects the relationship between BMI and survival. Cardiorespiratory fitness mitigates the obesity paradox observed in HF patients.

**Keywords**     Exercise tolerance ● Cardiopulmonary exercise testing ● Heart failure ● Prognosis ● Matching analysis ● MECKI score

# Introduction

Obesity, commonly defined by increased body mass index (BMI), has been found to be protective in heart failure (HF), a finding leading to the accepted concept of an obesity paradox.[1−3] This somewhat surprising evidence has been analysed and studied under different perspectives in a broad set of HF patients, and it remains substantially unexplained, with competing and complementary views being proposed.[1−3] It has been suggested that increased levels of serum lipoproteins play a role by counteracting bacterial cytokines and endotoxins,[4] while low levels of adiponectin[5] and a decreased response to sympathetic activation[6] have been associated with a protective background. Independently of the protective neuro-hormonal and inflammatory role that an increased BMI may bear, the multiple interactions between obesity and major clinical determinants of the natural history of the disease are still under scrutiny.

Some investigators have suggested that the obesity paradox may be partly explained by confounding factors.[7,8] Cardiorespiratory fitness is strongly related to prognosis in healthy individuals and in cohorts with cardiovascular (CV) diseases.[9] A number of studies have reported the importance of exercise capacity and other cardiopulmonary exercise test (CPET) variables in predicting prognosis in HF. Indeed, the classic cut-off point for peak oxygen consumption (peak VO$_2$) of 14 mL O$_2$/kg/min proposed by Mancini et al.[10] is still frequently used to classify patients with HF into low-risk and high-risk groups. A strong obesity paradox has also been found in cohorts of patients with coronary heart disease,[11] but it was not present in those with high levels of exercise tolerance.[12] Similar findings have been more recently reported in systolic HF patients.[13]

We aimed at further investigating the impact of exercise tolerance and cardiorespiratory capacity on the obesity paradox in a larger cohort of systolic HF patients, using a multicentre database based on CPET.[13]

# Methods

## Population and study procedures

We performed a cohort study on 4843 patients with a history of HF with reduced LVEF, enrolled and prospectively followed in 24 Italian HF centres. All patients were derived from the MECKI score database, a database of chronic HF patients that is continuously updated and that allowed us to validate a new prognostic HF risk model, the Metabolic Exercise test data combined with Cardiac and Kidney Indexes (MECKI) score.[14] For the present analysis, 220 patients with severe pathological obesity, as arbitrarily defined by BMI >35, were excluded, reducing the study cohort to 4623 cases.

At enrolment, inclusion and exclusion criteria were evaluated as previously reported,[14] and clinical history was recorded. Then, physical examination, laboratory analyses, ECG, and transthoracic echocardiography were performed, as previously described.[14] CPET was performed, depending on the enrolling centre's equipment, using a ramp protocol on an electronically braked cycle-ergometer or a Bruce modified protocol on a treadmill. Peak VO$_2$ data measured at treadmill exercise were reduced by 10% to allow an appropriate comparison between the two different procedures; the CPET protocol was set to reach peak exercise in 8−12 min, but tests were stopped as patients reported maximal effort, and exercise parameters were calculated as previously described.[14] Peak VO$_2$ % of predicted was calculated according to Hansen et al.[15]

## Follow-up and study endpoints

Follow-up was carried out according to the local HF programme, and it ended with the last clinical evaluation or with the patients' death or heart transplantation. If a patient died outside the hospital where they were being followed up, medical records of the event and a report of the cause of death were considered. The primary study endpoint was all-cause death (total mortality) and CV deaths. Urgent cardiac transplant was considered as death both for total and CV mortality. Procedures of data management were performed as previously described.[14]

## Data analysis

Data analysis was performed in two steps. The first part of the analysis considered the entire population (4623 patients), which was divided into four groups according to BMI: <25, 25−30, >30 to ≤35, and >35 kg/m$^2$. Subsequently, to assess the role of cardiopulmonary capacity on survival, the study population was also divided into three subgroups according to predicted peak VO$_2$ (<50, 50−80, and >80%). Demographic, laboratory, echocardiographic, CPET, and follow-up data were compared between groups, and Cox univariable and multivariable regression analysis and Kaplan−Meier survival analysis were performed for the previously described study endpoints (CV mortality and total mortality). Kaplan−Meier analysis was arbitrarily truncated at 3 years.

In the second step, as a confirmation of the first analysis, we performed a 1:1:1 statistical matching between the three BMI classes. A total of 628 patients per group matched for the following arbitrarily selected variables: age $\pm 5$ years, gender, LVEF $\pm 5$, and peak $VO_2 \pm 150$ (mL/min). Kaplan−Meier survival analysis was then repeated as previously described.

A further analysis of the BMI <25 group, differentiating BMI <18.5 and 18.5−25 groups, was also performed; however, since the percentage of patients with BMI <18.5 was very limited (<2%), and thus not comparable with the other groups, no further statistical evaluation was performed (the analysis is presented as Supplementary material online, *Tables* and *Figure S1*).

## Statistical analysis

Numerical variables were summarized as mean $\pm$ standard deviation. Analysis of variance (ANOVA) was used when appropriate for between-group comparison. Skewed data are reported as median and interquartile range and compared by Kruskall−Wallis test. Categorical variables, expressed as percentage or frequency, were compared by $\chi^2$ test. Bonferroni correction was employed to account for multiple comparisons.

Two multivariable Cox proportional hazard models were used for assessing the independent prognostic value of BMI: the first one adjusted for class of $VO_2$ % of predicted, and the second one for peak $VO_2$ (absolute value), age, gender, and LVEF.

Moreover, in order to reduce the presence of confounding factors that could have affected the comparison, BMI groups were matched according to gender, age, LVEF, and peak $VO_2$. Survival was estimated by Kaplan−Meier analysis and compared by log-rank test. Unadjusted hazard ratios and 95% confidence intervals were calculated. A *P*-value <0.05 was used to define statistical significance. All analyses were performed using the SAS 9.2 statistical package.

## Results

Mean age of the study population was $61.6 \pm 12.6$ years, 17.2% were female, average BMI was $26.2 \pm 3.6$ kg/m$^2$, LVEF $32.8 \pm 7.7$%, and peak $VO_2$ $1129 \pm 416$ mL/min. Regarding therapy, 93.7% were on ACE inhibitors or ARBs, 80.8% on beta-blockers, while 51.0% were on a mineralocorticoid antagonist. Median follow-up was 1113 (553−1803) days; 6.8% of patients were tested with a treadmill and 93.2% with cycle-ergometer. Exercise effort was, on average, maximal or nearly maximal in all groups from a metabolic point of view, as shown by the peak exercise respiratory exchange ratio (RER; *Table 1*). Total and CV mortality occurred in 28.6% and 17.4%, respectively, of the entire study population, including, in both cases, urgent cardiac transplant, which occurred in 110 cases.

### Body mass index groups

Grouping patients according to BMI <25, between 25 and 30, and between 30 and 35 showed that patients presented different clinical characteristics (*Table 1a*). The highest BMI group patients were younger, with more favourable LVEF, peak $VO_2$, ventilation vs. carbon dioxide production slope, renal function, and haemoglobin level. They had a larger use of beta-blockers (*Table 1a*).
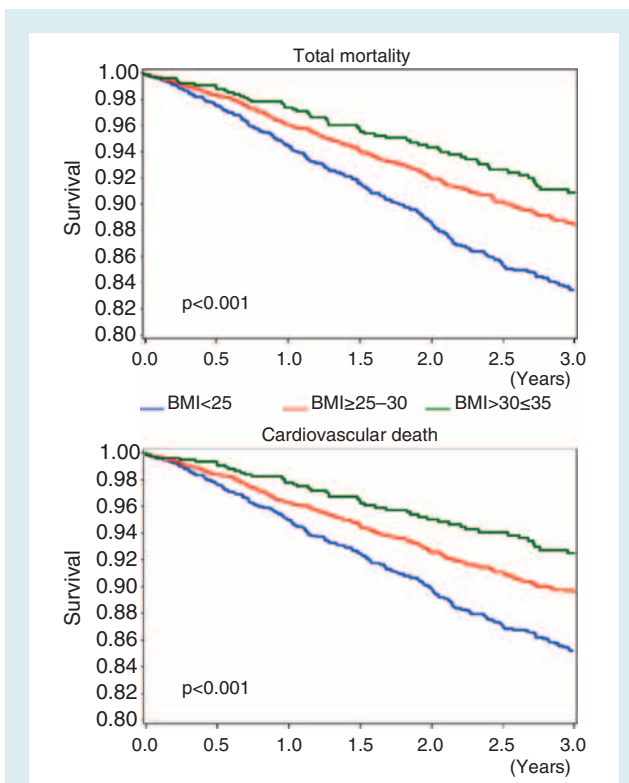


**Figure 1** Survival analysis in the entire study population ($n = 4623$) grouped according to body mass index (BMI). The Kaplan−Meier curves were truncated at 3 years. Upper panel: total mortality + urgent cardiac transplant. Lower panel: cardiovascular death + urgent cardiac transplant. $P < 0.001$ in both cases.

Body mass index was a significant predictor of both total and CV death, and the highest mortality rate occurred in the lowest BMI group (<25) ($P < 0.001$) (*Figure 1*; *Table 1b*). Even separately analysing underweight patients (BMI <18.5) in the <25 BMI group, the results did not differ, i.e. the detrimental effects of the leaner condition were confirmed.

Interestingly, the very severely obese subjects (BMI >35), although they had more favourable clinical characteristics than the less obese (younger age, higher peak $VO_2$, see *Table 1a*), presented an intermediate mortality between BMI 25−30 and BMI >30 to $\leq$35 groups (*Table 1b*).

## Predicted peak oxygen consumption groups

Peak $VO_2$ was a significant predictor of mortality: patients with predicted peak $VO_2 < 50$% ($n = 1908$) presented a worse survival than those with predicted peak $VO_2$ ranging from 50% to 80% ($n = 2363$) and those with predicted peak $VO_2 > 80$% ($n = 352$), for both total and CV deaths (*Table 2*).

As patients were grouped for peak $VO_2$, BMI did not affect survival (*Table 3*).

**Table 1 Population data according to body mass index**

**a**

| | Low BMI <25 (n = 1765) | Medium BMI 25–30 (n = 2087) | High BMI >30 to ≤35 (n = 771) | Very high BMI >35 (n = 220) | P-value | Post-hoc by Bonferroni | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Low vs. medium | Low vs. high | Medium vs. high | Low vs. very high | Medium vs. very high | High vs. very high |
| Age (years) | 62.0 ± 13.5 | 61.9 ± 12.1 | 59.7 ± 11.6 | 55.1 ± 11.7 | <0.001 | NS | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Gender | | | | | | | | | | | |
| Males, n (%) | 1339 (76%) | 1818 (87%) | 670 (87%) | 172 (78%) | <0.001 | <0.001 | <0.001 | NS | <0.001 | 0.005 | 0.014 |
| Females, n (%) | 426 (24%) | 269 (13%) | 101 (13%) | 48 (22%) | 0.01 | 0.016 | NS | NS | NS | NS | NS |
| Height (cm) | 169 ± 8 | 170 ± 8 | 169 ± 8 | 170 ± 10 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| Weight (kg) | 65.1 ± 8.6 | 79.0 ± 8.3 | 91.3 ± 9.5 | 110.6 ± 14.8 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| BMI (kg/m²) | 22.6 ± 1.9 | 27.2 ± 1.4 | 31.8 ± 1.4 | 38.2 ± 2.8 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| LVEF (%) | 31.9 ± 11.3 | 33.4 ± 10.7 | 33.2 ± 9.9 | 33.4 ± 10.5 | <0.001 | <0.001 | 0.021 | NS | NS | NS | NS |
| VO₂ peak (mL/min) | 985 ± 382 | 1189 ± 408 | 1295 ± 413 | 1438 ± 465 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| VO₂ peak/kg (mL/min/kg) | 15.1 ± 5.1 | 15.0 ± 4.6 | 14.1 ± 4.1 | 13.0 ± 3.8 | <0.001 | NS | <0.001 | <0.001 | <0.001 | <0.001 | 0.009 |
| VO₂ (% predicted) | 49.7 ± 15.9 | 57.1 ± 16.0 | 61.8 ± 16.9 | 67.3 ± 17.8 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |
| VE/VCO₂ slope | 34.1 ± 8.6 | 32.2 ± 7.1 | 31.5 ± 6.4 | 30.3 ± 6.4 | <0.001 | <0.001 | <0.001 | NS | <0.001 | 0.0027 | NS |
| Peak RER | 1.12 ± 0.12 | 1.11 ± 0.12 | 1.09 ± 0.12 | 1.08 ± 0.11 | 0.016 | <0.001 | <0.001 | <0.011 | <0.001 | <0.001 | NS |
| MDRD (mL/min) | 70.4 ± 24.2 | 70.4 ± 22.7 | 73.3 ± 23.8 | 72.6 ± 23.2 | <0.001 | NS | 0.031 | 0.025 | NS | NS | NS |
| Hb (g/dL) | 13.2 ± 1.6 | 13.5 ± 1.6 | 13.8 ± 1.6 | 13.8 ± 1.6 | <0.001 | <0.001 | <0.001 | 0.001 | <0.001 | NS (0.077) | NS |
| Follow-up (days) | 1102 (518–1824) | 1119 (564–1838) | 1119 (614–1724) | 1064 (480–1672) | NS | | | | | | |
| Idiopathic aetiology | 740 (46.7%) | 802 (42.1%) | 322 (44.9%) | 117 (53.9%) | 0.003 | NS | NS | NS | 0.001 | 0.001 | NS |
| Ischaemic aetiology | 764 (48.2%) | 1020 (53.5%) | 373 (52.0%) | 82 (37.8%) | NS | | | | | | |
| Valvular aetiology | 81 (5.1%) | 83 (4.4%) | 22 (3.1%) | 7 (3.2%) | NS | | | | | | |
| Atrial fibrillation | 270 (15.3%) | 334 (16.0%) | 129 (16.7%) | 34 (15.4%) | NS | | | | | | |
| ACE inhibitors | 1355 (77.0%) | 1592 (76.4%) | 593 (76.9%) | 163 (74.1%) | NS | | | | | | |
| ARBs | 276 (15.7%) | 378 (18.2%) | 140 (18.2%) | 58 (26.4%) | <0.001 | | | | | | |
| Beta-blockers | 1454 (82.6%) | 1741 (83.5%) | 671 (87.0%) | 198 (90%) | 0.003 | NS | 0.032 | NS | 0.029 | Ns (0.07) | NS |
| Diuretics | 1416 (80.3%) | 1676 (80.6%) | 635 (82.5%) | 197 (89.6%) | 0.006 | NS | NS | NS | 0.006 | 0.007 | NS |
| Statin | 632 (43.4%) | 945 (52.2%) | 355 (53.5%) | 100 (49.0%) | <0.001 | <0.001 | <0.001 | NS | NS | NS | NS |
| Allopurinol | 378 (26.0%) | 523 (28.9%) | 214 (32.2%) | 84 (41.2%) | <0.001 | NS | 0.021 | NS | <0.001 | 0.0014 | NS |
| Aldosterone antagonists | 907 (51.5%) | 1048 (50.2%) | 403 (52.3%) | 124 (56.6%) | NS | | | | | | |
| Antiplatelets | 890 (50.2%) | 1128 (54.1%) | 445 (57.8%) | 103 (47.0%) | <0.001 | NS | 0.002 | NS | NS | NS | 0.03 |
| Anticoagulants | 529 (30.1%) | 630 (30.2%) | 209 (27.1%) | 69 (31.5%) | NS | | | | | | |
| Digitalis | 465 (26.4%) | 436 (20.9%) | 163 (21.1%) | 50 (22.8%) | <0.001 | <0.001 | 0.023 | NS | NS | NS | NS |
| Amiodarone | 411 (23.3%) | 500 (24.0%) | 191 (24.9%) | 44 (20.1%) | NS | | | | | | |

**b**

| | Low BMI <25 (n = 1765) | | Medium BMI 25–30 (n = 2087) | | High BMI >30 to ≤35 (n = 771) | | Very high BMI >35 (n = 220) | | P-value | Post-hoc by Bonferroni | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % | | Low vs. medium | Low vs. high | Medium vs. high | Low vs. very high | Medium vs. very high | High vs. very high |
| Total mortality (absolute) | 436 | 24.7 | 393 | 18.9 | 122 | 15.8 | 41 | 18.6 | **<0.001** | <0.001 | <0.001 | NS | NS | NS | NS |
| Total mortality (1000 person-years) | 69.3 | | 51.9 | | 45.3 | | 55.1 | | **<0.001*** | <0.001 | <0.001 | NS | NS | NS | NS |
| Cardiovascular mortality (absolute) | 374 | 21.3 | 332 | 16.0 | 96 | 12.5 | 34 | 15.4 | **<0.001** | <0.001 | <0.001 | NS | NS | NS | NS |
| Cardiovascular mortality (1000 person-years) | 59.4 | | 43.9 | | 35.6 | | 45.7 | | **<0.001*** | <0.001 | <0.001 | NS | NS | NS | NS |

P calculated by analysis of variance (ANOVA).
Data are median ± SD except for follow-up, which is median and interquartile range.
BMI, body mass index; Hb, haemoglobin; MDRD, Modification of Diet in Renal Disease; VO₂, oxygen uptake; VE/VCO₂, ventilatory efficiency.
* P calculated by χ² except for incidence of mortality calculated by log rank test.

**Table 2** Mortality in the heart failure population grouped according to peak oxygen consumption

| | VO$_2$ < 50% (n = 1908) | | VO$_2$ 50−80% (n = 2363) | | VO$_2$ > 80% (n = 352) | | P-value | Post-hoc by Bonferroni | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | | | | | VO$_2$ < 50% vs. VO$_2$ 50−80% | VO$_2$ < 50% vs. VO$_2$ > 80% | VO$_2$ 50−80% vs. VO$_2$ > 80% |
| | n | % | n | % | n | % | | | | |
| Total mortality (absolute) | 596 | 31.3 | 341 | 14.4 | 14 | 4.0 | <0.001 | <0.001 | <0.001 | <0.001 |
| Total mortality (1000 person-years) | 89.8 | | 39.0 | | 11.8 | | <0.001* | <0.001 | <0.001 | <0.001 |
| Cardiovascular mortality (absolute) | 518 | 27.2 | 274 | 11.7 | 10 | 2.8 | <0.001 | <0.001 | <0.001 | <0.001 |
| Cardiovascular mortality (1000 person-years) | 78.1 | | 31.4 | | 8.5 | | <0.001* | <0.001 | <0.001 | <0.001 |

VO$_2$, oxygen consumption.
*P calculated by $\chi^2$ except for incidence of mortality calculated by log rank test.

**Table 3** Mortality in the three peak oxygen consumption groups according to body mass index

| | | n | No. of events total mortality | % | 1000 person-years | No. of events cardiovascular mortality | % | 1000 person-years |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| VO$_2$ < 50% (n = 1944) | Low BMI <25 | 980 | 336 | 34.3 | 94.5 | 296 | 30.3 | 83.3 |
| | Medium BMI 25−30 | 735 | 209 | 28.4* | 86.0 | 179 | 24.4* | 73.7 |
| | High BMI >30 to ≤35 | 193 | 51 | 26.4 | 78.4 | 43 | 22.3 | 66.1 |
| | Very high BMI >35 | 36 | 16 | 44.4 | 137.2 | 13 | 36.1 | 111.5 |
| | Global | | 596 | 31.3 | 89.8 | 518 | 27.2 | 78.1 |
| | P-value | | | 0.007 | NS | | 0.008 | NS |
| VO$_2$ 50−80% (n = 2496) | Low BMI <25 | 717 | 97 | 13.6 | 38.7 | 75 | 10.5 | 29.9 |
| | Medium BMI 25−30 | 1176 | 178 | 15.2 | 39.1 | 148 | 12.6 | 32.5 |
| | High BMI >30 to ≤35 | 470 | 66 | 14.0 | 39.3 | 51 | 10.9 | 30.4 |
| | Very high BMI >35 | 133 | 24 | 18.0 | 51.2 | 20 | 15.2 | 42.7 |
| | Global | | 341 | 14.4 | 39.0 | 274 | 11.7 | 31.4 |
| | P-value | | | NS | NS | | NS | NS |
| VO$_2$ > 80% (n = 403) | Low BMI <25 | 68 | 3 | 4.4 | 12.9 | 3 | 4.4 | 12.9 |
| | Medium BMI 25−30 | 176 | 6 | 3.4 | 10.2 | 5 | 2.8 | 8.5 |
| | High BMI >30 to ≤35 | 108 | 5 | 4.6 | 13.9 | 2 | 1.9 | 5.6 |
| | Very high BMI >35 | 51 | 1 | 2 | 6.3 | 1 | 2 | 6.3 |
| | Global | | 14 | 4.0 | 11.8 | 10 | 2.8 | 8.5 |
| | P-value | | | NS | NS | | NS | NS |
| | Total | 4843 | 951 | 19.7 | 57.4 | 802 | 16.6 | 48.4 |

*P <0.05 vs. BMI <25 at Bonferroni post-hoc test.
BMI, body mass index; VO$_2$, oxygen consumption.

At univariable analysis, both BMI and peak VO$_2$, as absolute values and predicted values, were associated with prognosis. Cox analysis showed that BMI class adjusted for peak VO$_2$ % of the predicted value (class) or by age, gender, LVEF, and peak VO$_2$ (absolute value) lost its prognostic capacity considering either total or CV death (*Table 4*).

When patients of the three BMI groups were matched according to age, gender, LVEF, and peak VO$_2$ absolute value, 628 triplets of matched subjects were obtained (*Table 5*). No significantly different prognosis was observed for both total and CV death, regardless of the BMI group (*Figure 2*). It is of note that patients with BMI >35 were not included in the matching analysis due to the low sample size (n = 220).

# Discussion

This study aimed at investigating the role of cardiorespiratory fitness in the prognosis of obese HF patients in a large cohort of stable patients undergoing CPET. Some important observations can be made. First, the obesity paradox in patients with systolic HF was also confirmed in the present group of patients referred for CPET. Secondly, the important role of cardiopulmonary exercise capacity in the prognosis of patients with systolic HF receives further confirmation. Thirdly, and most importantly, the prognostic contribution of peak VO$_2$ overwhelms the prognostic capacity of BMI. Furthermore, the prognostic role of BMI disappears if more variables are considered, such as age, gender, LVEF, and peak VO$_2$. Consequently, high BMI patients have a better prognosis compared

**Table 4 Mortality according to body mass index and peak oxygen consumption**

|  | P-value | Hazard ratio | 95% CI | |
|---|---|---|---|---|
| CV mortality | | | | |
| BMI class unadjusted | <0.001 | 0.771 | 0.696–0.855 | |
| VO$_2$ % class unadjusted | <0.001 | 0.388 | 0.34–0.444 | |
| VO$_2$ peak unadjusted (mL/min) | <0.001 | 0.998 | 0.998–0.999 | |
| BMI class adjusted by VO$_2$ % class | 0.3119 | 0.947 | 0.853–1.052 | |
| BMI class adjusted by VO$_2$ peak, age, gender, LVEF | 0.1983 | 1.067 | 0.967–1.177 | |
| Total mortality | | | | |
| BMI class unadjusted | <0.001 | 0.804 | 0.732 | 0.884 |
| VO$_2$ % class unadjusted | <0.001 | 0.42 | 0.372 | 0.475 |
| VO$_2$ peak unadjusted (mL/min) | <0.001 | 0.999 | 0.998 | 0.999 |
| BMI class adjusted by VO$_2$ % class | 0.5701 | 0.973 | 0.884 | 1.07 |
| BMI class adjusted by VO$_2$ peak, age, gender, LVEF | 0.1983 | 1.067 | 0.967 | 1.177 |

BMI, body mass index; CV, cardiovascular; VO$_2$, oxygen consumption.

**Table 5 Age, gender, left ventricular ejection fraction, and peak oxygen consumption in heart failure patients used for matching analysis**

|  | BMI <25 (n = 628) | BMI ≥25–30 (n = 628) | BMI >30 to ≤35 (n = 628) |
|---|---|---|---|
| Age (years) | 59.1 ± 12.8 | 59.9 ± 11.8 | 59.8 ± 11.7 |
| Gender (M/F) | (556/72) | 556/72 | 556/72 |
| LVEF (%) | 32.8 ± 9.1 | 32.7 ± 9.4 | 32.7 ± 9.2 |
| Peak VO$_2$ (mL/min) | 1227 ± 401 | 1240 ± 395 | 1242 ± 394 |

BMI, body mass index; F, females; M, males; VO$_2$, oxygen consumption.

with slimmer patients. However, obese groups presented a less advanced HF condition, as indicated by the presence of several more favourable prognostic indicators; they were better treated, and they presented a more preserved exercise tolerance.

Obese subjects are significantly represented in both the general and HF population. In the present cohort of HF patients able to perform a CPET, 16.3% of patients had a BMI ranging between 30 and 35. Notably, we excluded from the present analysis 220 patients with extreme obesity (BMI >35), which account for 4.5% of the overall cohort of HF patients in the MECKI score database, because extreme obesity is a pathological status associated with several possible conditions, besides HF, which affect exercise capacity, including orthopaedic reasons—the work of lifting up the increased body weight, particularly on a treadmill—and mechanical difficulties in performing exercise.

However, a number of studies have now found that overweight and obese patients with HF have a better prognosis than normal weight or underweight HF patients.[1–4] Also in our cohort of HF patients, high BMI patients have a better prognosis (Figure 1). Many investigators have suggested that the obesity paradox may at least partly be explained by confounding factors.[6] In cohorts with CAD, patients with high levels of exercise capacity did not seem to have an obesity paradox.[7,8] On the other hand, in higher risk patients with CAD and low levels of exercise tolerance, a strong obesity paradox was present, with overweight and obese individuals having a better prognosis than their lean counterparts with low exercise tolerance.[7–9]

In HF, there is not only an 'obesity paradox': higher levels of blood pressure and cholesterol are also associated with a better prognosis.[16]

In the present study, we evaluated a large database of HF patients with—on average—mild LV systolic dysfunction, all of which underwent an exercise test, aiming at further investigating the role of obesity in this population. We specifically investigated the role of exercise capacity vs. BMI. First of all, on average, the exercise effort performed by the patients was relevant, nearly maximal, as documented by the high RER reached at peak exercise in all BMI groups (Table 1a).[17] If anything, a lower RER value was observed in the 30–35 BMI group that had the highest exercise performance. Secondly, we observed that peak VO$_2$ maintains its prognostic value in all BMI groups, confirming the pivotal role of exercise evaluation in HF patients regardless of BMI. Thirdly, when peak VO$_2$ is considered as a covariate in the survival analysis, the so-called 'obesity paradox' is lost. Regardless of whether the different BMI populations were normalized for peak VO$_2$, either expressed as absolute value or as a percentage of the predicted value, prognostic differences between the BMI classes were lost. Indeed, we observed that BMI distinguished, in the HF population, patients with different clinical characteristics and different prognosis. Specifically, those with a higher BMI all presented better prognostic parameters, were better treated, and
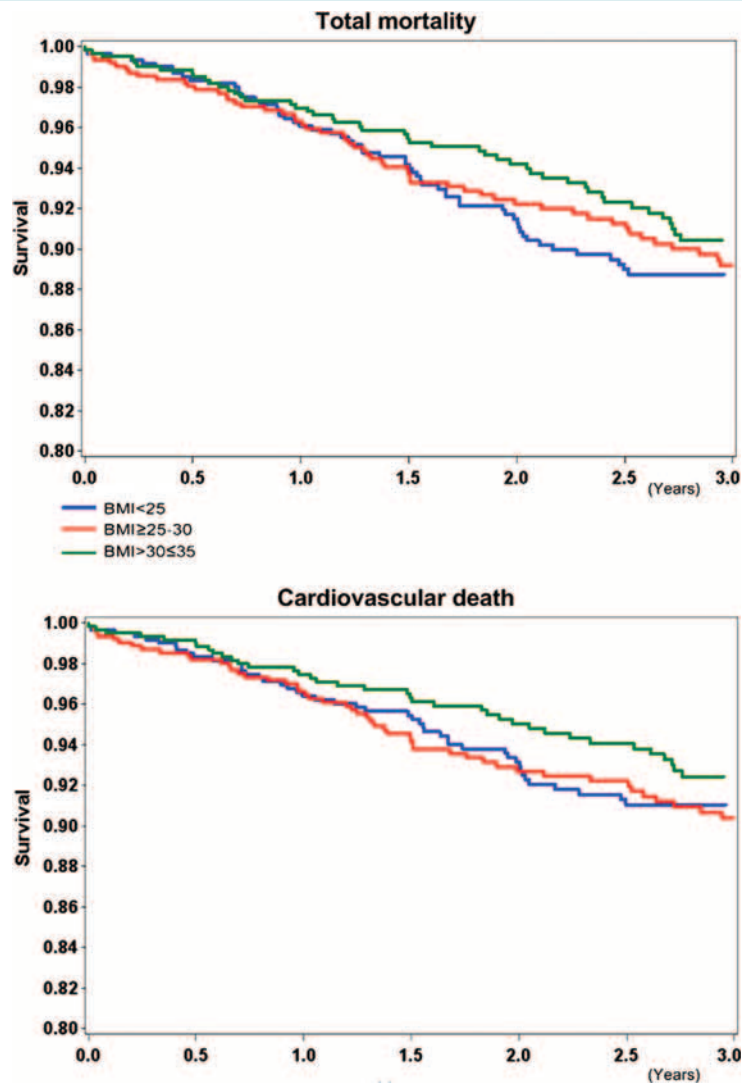
**Figure 2** Survival analysis according to body mass index (BMI) in the 628 patients matched for age, gender, peak oxygen consumption, and LVEF. Upper panel: total mortality + urgent cardiac transplant. Lower panel: cardiovascular death + urgent cardiac transplant. Differences were not significant.

showed a longer survival. It is unclear why patients with high BMI and low peak $VO_2$ were not enrolled in this database derived from the MECKI Score Research Group. It is of note that this is probably the largest HF population analysed with CPET. However, because all patients who met the MECKI score criteria were analysed, it is possible that referring physicians were reluctant to request and/or perform an exercise evaluation in obese subjects with severe HF.

To confirm the Cox analysis, we also performed a matching procedure considering, on top of peak $VO_2$ (absolute value), age, gender, and LVEF. We were able to identify a relevant number of triplets of cases ($n = 628$) to be considered for the three BMI classes. Obese HF subjects matched for peak $VO_2$, age, gender, and LVEF have a similar prognosis to that of HF patients with BMI <25

or between 25 and 30. This confirms that the 'obesity paradox' in HF is due to a patient selection bias.

The results presented here are consistent with recent studies performed in smaller populations of advanced systolic HF patients, showing that the obesity paradox was only observed in patients with lower cardiorespiratory fitness.[13,18] Consequently, this finding supports the superior prognostic power of improved functional capacity and the importance of physical conditioning that attenuates the obesity paradox.

Progressive declines in physical activity over five decades have occurred and have primarily caused the obesity epidemic. In light of the obesity paradox, the potential value of purposeful weight loss and increased physical activity to affect levels of fitness should be underlined.[19]

Exercise training is not the single intervention that increases peak $VO_2$ and survival, but there is evidence that cornerstone therapies such as ACE inhibitors and ARBs improve not only LV systolic function, and prognosis, but also exercise capacity (peak $VO_2$).[20,21] Also long-term beta-blocker therapy increases exercise time and improves ventilator response to exercise, and therefore patients are less symptomatic for a given ventilation during exercise following beta-blocker treatment.[22,23]

## Study limitations

Some limitations of the MECKI score database have already been discussed.[14,24] The patients were relatively young; mean age was 62 years, probably reflecting the inclusion of patients referred for CPET. Only 15% of the patients were females; pathophysiological and clinical gender-related differences have been found in HF. Only HF patients with reduced LVEF were included; thus, the results cannot be extrapolated to patients with preserved EF. Moreover, we evaluated patients able to perform a CPET, so that patients with very severe HF were excluded. Therefore, our findings should not be considered when evaluating patients with the above-reported characteristics. We focused on peak $VO_2$ instead of other CPET-derived prognostic variables, because peak $VO_2$ is the most widely used measure of exercise capacity in HF. Further studies addressing the influence of BMI on $VE/VCO_2$ would be of interest. Finally, the obese subjects presented a RER without a statistically significant difference with respect to the other BMI groups ($1.08 \pm 0.12$ vs. $1.11 \pm 0.12$ high vs. medium BMI). Accordingly exercise intensity differences, due to patients effort, are unlikely to have any clinical relevance.

## Conclusion

In practical terms, these results suggest that exercise tolerance affects the relationship between BMI and survival. Thus, the obesity paradox in systolic HF is due to a patient selection bias and, at least in the present population, it does not exist. Consequently, assessing obese subjects without considering their exercise capacity, as assessed by CPET, may be misleading.

## Acknowledgements

## Supplementary Information

Additional Supporting Information may be found in the online version of this article:
**Table 1a and b.** Initial study population ($n = 4843$) data according to BMI.
**Table 3.** Mortality in the 3 peakVO2 groups according to BMI.
**Figure 1.** Survival according to BMI. Survival analysis in the initial entire study population ($n = 4843$) grouped according to BMI ($<18.5$ blue line, $n = 67$, $18.5-25$, green line, $n = 1698$, $25-30$, black line, $n = 2087$ and $30-35$, grey line, $n = 771$, $>35$, red line, $n = 220$). The! Kaplan Meier curves were truncated at 3 years. Total mortality + urgent cardiac transplant..

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## References

1. Oreopoulos A, Padwal R, Kalantar-Zadeh K, Fonarow GC, Norris CM, McAlister FA. Body mass index and mortality in heart failure: a meta-analysis. *Am Heart J* 2008;**156**:13–22.
2. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Woo MA, Tillisch JH. The relationship between obesity and mortality in patients with heart failure. *J Am Coll Cardiol* 2001;**38**:789–795.

3. Clark AL, Fonarow GC, Horwich TB. Waist circumference, body mass index, and survival in systolic heart failure: the obesity paradox revisited. *J Card Fail* 2011;**17**:374−380.

4. Rauchhaus M, Clark AL, Doehner W, Davos C, Bolger A, Sharma R, Coats AJ, Anker SD. The relationship between cholesterol and survival in patients with chronic heart failure. *J Am Coll Cardiol* 2003;**42**:1933−1940.

5. Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, Hildebrandt P. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. *Circulation* 2005;**112**:1756−1762.

6. Weber MA, Neutel JM, Smith DH. Contrasting clinical properties and exercise responses in obese and lean hypertensive patients. *J Am Coll Cardiol* 2001;**37**:169−174.

7. Ades PA, Savage PD. The obesity paradox: perception vs knowledge. *Mayo Clin Proc* 2010;**85**:112−114.

8. Das SR, Alexander KP, Chen AY, Powell-Wiley TM, Diercks DB, Peterson ED, Roe MT, de Lemos JA. Impact of body weight and extreme obesity on the presentation, treatment, and in-hospital outcomes of 50,149 patients with ST-segment elevation myocardial infarction results from the NCDR (National Cardiovascular Data Registry). *J Am Coll Cardiol* 2011;**58**:2642−2650.

9. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, Sugawara A, Totsuka K, Shimano H, Ohashi Y, Yamada N, Sone H. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA.* 2009;**301**:2024−2035.

10. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH Jr, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. *Circulation* 1991;**83**:778−786.

11. Romero-Corral A, Montori VM, Somers VK, Korinek J, Thomas RJ, Allison TG, Mookadam F, Lopez-Jimenez F. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;**368**:666−678.

12. Goel K, Thomas RJ, Squires RW, Coutinho T, Trejo-Gutierrez JF, Somers VK, Miles JM, Lopez-Jimenez F. Combined effect of cardiorespiratory fitness and adiposity on mortality in patients with coronary artery disease. *Am Heart J* 2011;**161**:590−597.

13. Lavie CJ, Cahalin LP, Chase P, Myers J, Bensimhon D, Peberdy MA, Ashley E, West E, Forman DE, Guazzi M, Arena R. Impact of cardiorespiratory fitness on the obesity paradox in patients with heart failure. *Mayo Clin Proc* 2013;**88**:251−258.

14. Agostoni P, Corra U, Cattadori G, Veglia F, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magri D, Fiorentini C, Mezzani A, Salvioni E, Scrutinio D, Ricci R, Bettari L, Di Lenarda A, Pastormerlo LE, Pacileo G, Vaninetti R, Apostolo A, Iorio A, Paolillo S, Palermo P, Contini M, Confalonieri M, Giannuzzi P, Passantino A, Cas LD, Piepoli MF, Passino C. Metabolic exercise test data combined with cardiac and kidney indexes, the MECKI score: a multiparametric approach to heart failure prognosis. *Int J Cardiol* 2013;**167**:2710−2718.

15. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. *Am Rev Respir Dis* 1984;**129**:S49−S55.

16. Lavie CJ, Mehra MR, Milani RV. Obesity and heart failure prognosis: paradox or reverse epidemiology? *Eur Heart J* 2005;**26**:5−7

17. Corra U, Piepoli MF, Adamopoulos S, Agostoni P, Coats AJ, Conraads V, Lambrinou E, Pieske B, Piotrowicz E, Schmid JP, Seferovic PM, Anker SD, Filippatos G, Ponikowski PP. Cardiopulmonary exercise testing in systolic heart failure in 2014: the evolving prognostic role: a position paper from the Committee on Exercise Physiology and Training of the Heart Failure Association of the ESC. *Eur J Heart Fail* 2014;**16**:929−941.

18. Clark AL, Fonarow GC, Horwich TB. Impact of cardiorespiratory fitness on the obesity paradox in patients with systolic heart failure. *Am J Cardiol* 2015;**115**:209−213.

19. Lavie CJ, McAuley PA, Church TS, Milani RV, Blair SN. Obesity and cardiovascular diseases: implications regarding fitness, fatness, and severity in the obesity paradox. *J Am Coll Cardiol* 2014;**63**:1345−1354.

20. Guazzi M, Palermo P, Pontone G, Susini F, Agostoni P. Synergistic efficacy of enalapril and losartan on exercise performance and oxygen consumption at peak exercise in congestive heart failure. *Am J Cardiol* 1999;**84**:1038−1043.

21. de Vries RJ, Quere M, Lok DJ, Sijbring P, Bucx JJ, van Veldhuisen DJ, Dunselman PH. Comparison of effects on peak oxygen consumption, quality of life, and neurohormones of felodipine and enalapril in patients with congestive heart failure. *Am J Cardiol* 1995;**76**:1253−1258.

22. Witte KK, Thackray S, Nikitin NP, Cleland JG, Clark AL. The effects of long-term beta-blockade on the ventilatory responses to exercise in chronic heart failure. *Eur J Heart Fail* 2005;**7**:612−617.

23. Kataoka M, Satoh T, Yoshikawa T, Nakamura I, Kohno T, Yoshizawa A, Anzai T, Ogawa S. Comparison of the effects of carvedilol and metoprolol on exercise ventilatory efficiency in patients with congestive heart failure. *Circ J* 2008;**72**:358−363.

24. Agostoni P, Corra U, Cattadori G, Veglia F, Battaia E, La Gioia R, Scardovi AB, Emdin M, Metra M, Sinagra G, Limongelli G, Raimondo R, Re F, Guazzi M, Belardinelli R, Parati G, Magri D, Fiorentini C, Cicoira M, Salvioni E, Giovannardi M, Mezzani A, Scrutinio D, Di Lenarda A, Mantegazza V, Ricci R, Apostolo A, Iorio A, Paolillo S, Palermo P, Contini M, Vassanelli C, Passino C, Piepoli MF. Prognostic value of indeterminable anaerobic threshold in heart failure. *Circ Heart Fail* 2013;**6**:977−987.