

POST-PRINT

Predictors of pre-rehabilitation exercise capacity in elderly European cardiac patients – The EU-CaRE study

Brief: Exercise capacity in elderly cardiac patients

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Abstract

Aims: Functional capacity is an important endpoint for therapies oriented to older adults with cardiovascular diseases. The literature on predictors of exercise capacity is sparse in the elderly population. In a longitudinal European study on effectiveness of cardiac rehabilitation (CR) of seven European countries in elderly (>65 years) coronary artery disease (CAD) or valvular heart disease (VDH) patients, predictors for baseline exercise capacity were determined, and reference ranges for elderly cardiac patients provided.

Methods: Mixed models were performed in 1282 patients (mean age 72.9 ± 5.4 years, 79% male) for peak oxygen consumption relative to weight (peak VO_2 ; ml/kg/min) with centre as random factor and patient anthropometric, demographic, social, psychological, and nutritional parameters, as well as disease aetiology, procedure, comorbidities and cardiovascular risk factors (CVRF) as fixed factors.

Results: The most important predictors for low peak VO_2 were coronary artery bypass grafting or valve surgery, low resting forced expiratory volume, reduced left ventricular ejection fraction, nephropathy and peripheral arterial disease. Each cumulative comorbidity or CVRF reduced exercise capacity by 1.7 ml/kg/min and 1.1 ml/kg/min, respectively. Males had a higher peak VO_2 per body mass but not per lean mass. Haemoglobin was significantly linked to peak VO_2 in both surgery and non-surgery patients.

Conclusions: Surgical procedures, cumulative comorbidities and CVRFs were the factors with the strongest relation to reduced exercise capacity in the elderly. Expression of peak VO_2 per lean mass rather than body mass allows a more appropriate comparison between sexes. Haemoglobin is strongly related to peak VO_2 and should be considered in studies assessing exercise capacity, especially in studies on patients after cardiac surgery.

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Key words: cardiac rehabilitation, cardiopulmonary exercise testing, exercise capacity, peak VO_2

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Abbreviation list

CVD	cardiovascular disease
CAD	coronary artery disease
CR	cardiac rehabilitation
VHD	valvular heart disease
peak VO ₂	peak oxygen consumption
CVRF	cardiovascular risk factors
PCI	percutaneous intervention
CABG	coronary artery bypass grafting
BMI	body mass index
LVEF	Left ventricular ejection fraction
MET	Metabolic equivalent
CPET	cardiopulmonary exercise testing

Introduction

Exercise capacity has been found to be reduced in patients with cardiovascular disease (CVD) compared to healthy people of the same age.(1) The reason for this may be linked to the coronary artery disease (CAD) itself, a reduced left ventricular function caused by CAD, the often associated endothelial dysfunction,(2) or secondary to comorbidities commonly associated with CAD, such as diabetes,(3) nephropathy, and/or peripheral vascular disease(4), or cardiovascular risk factors.(5)

In CAD patients, heart failure patients, diabetic and nephropathy patients, as well as in the generally healthy population, those with higher exercise capacity have better prognosis.(6, 7) This is why in many studies exercise capacity has served as a surrogate measure for hard outcomes, which require longer follow-up times. Further, cardiac rehabilitation (CR) has been shown to increase exercise capacity and result in improved prognosis (8, 9). The American Heart Association has recently recommended prioritizing functional capacity as a principal endpoint for therapies oriented to older adults with cardiovascular disease.(10) However, the literature on predictors of exercise capacity is sparse in elderly CAD patients.

The present study aims firstly, to identify predictors for peak oxygen consumption (peak VO₂) at the start of CR. Knowledge on independently influencing factors for exercise capacity is an important prerequisite for improving future study designs by providing information on the important confounding variables which, firstly, will need to be measured, and, secondly, included in the analyses. Secondly, we aimed to quantify the effects of single and cumulative comorbidities and cardiovascular risk factors (CVRF) on exercise capacity. Thirdly, we aimed at composing reference ranges for elderly male and female patients with CAD and valvular heart disease (VHD).

Methods

The EU-CaRE study is a prospective multi centre- and country cohort study with eight participating CR units in seven countries (Denmark, France, Germany, the Netherlands, Italy, Spain and Switzerland) aiming to assess the effectiveness and sustainability of current CR in Europe in elderly patients.(11) The study was approved by all relevant medical ethics committees and registered at register.nl (NL5166). All participants gave written informed consent before they were included in the study.

Study population

Patients commencing CR after a recent acute coronary syndrome (ACS), coronary revascularization (percutaneous intervention=PCI, or coronary artery bypass grafting=CABG), surgical or percutaneous treatment for valvular disease, or documented CAD defined by standard non-invasive or invasive methods were included. Patients were assessed at baseline before commencing CR, after completing the CR program and at 1-year follow-up. For the present study, only baseline data is used. Changes on peak VO₂ will be analysed elsewhere.

Statistical analysis

All statistics were performed with R (Version 3.5.1, R Core Team, 2017). A list of potential predictors included in the model is provided in the online appendix. A mixed linear model was performed for peak VO₂ [ml/min/kg] with centre as random variable and all potential predictors as independent variables (lme function from nlme package). Collinearities were assessed by generalized variance inflation factors (GVIF from car package). Non-significant variables were eliminated from the model manually by individually removing the variable with the largest p-value until any insignificant ($p > 0.01$) parameters were removed from the model. Due to multiple testing, alpha was set at 0.01 for all analyses. For the resulting model, diagnostics were performed for

checking fulfilment of model assumptions. In case of presence of assumption violations, a more flexible GAMLSS model (Generalized Additive Models for Location, Scale and Shape) was performed using the `gamlss` package. In order to reduce potential sex differences, the same model was performed for the dependent variable peak VO₂ per lean body mass.

Sub-analyses were performed entering haemoglobin as an independent variable for the subpopulation of patients with available haemoglobin data. Further, the same models as described above were performed for the more homogeneous subpopulation of PCI patients.

To assess the effect of single CVRFs on weight adjusted peak VO₂, we performed mixed linear models adjusting only for age and sex (fixed factors) and centre (random factor) in order to avoid adjusting for spurious collinearities between CVRFs and comorbidities and to have a direct comparison between the different comorbidities and CVRFs.

Data collection

The following data were registered at baseline: indication for CR (index event) and time from index event to CR entry testing. Further baseline data included demographic and socioeconomic factors, cardiac symptoms assessed by the Canadian Cardiac Society grading of angina (CCS), cardiovascular risk factors (CVRF) as well as comorbidities, gathered through hospital records, interviewing, questionnaires and clinical assessment.

The clinical assessment of patients included cardiopulmonary exercise testing (CPET) or alternatively six-minute walk test in patients not able to perform a CPET, blood pressure, body mass index (BMI), waist-to-hip ratio, lean body mass assessed by skin fold measurement,(12) spirometry and electrocardiogram. Left ventricular ejection fraction (LVEF) was from hospital

records. Haemoglobin was determined from a blood sample taken between index procedure and baseline visit.

To assess physical activity before index event, patients were asked on how many days per week they were doing more more than 30 min of moderate exercise. Questionnaires were used to assess quality of diet (MEDAS), quality of life (SF-36v2), degree of anxiety (GAD-7) and depression (PHQ-9).

CPETs were performed on a cycle ergometer with an individualized ramp protocol aiming to achieve voluntary exhaustion within 8 to 12 min of ramp duration. Peak VO₂ of all CPETs were determined at the core lab (Uni Bern) by an automated procedure on raw data files using MATLAB software from MathWorks®. The highest 30s moving average was considered as peak VO₂. Visual quality control was performed by one experienced operator (TM) and in case of doubtful quality by a second operator (MW). Gas measurements were excluded from the analysis in case of suspected mask leakage or equipment failure, as well as if the ramp duration was less than 3 min (unreliable due to the delayed response in oxygen uptake with increasing workload). In these cases, peak VO₂ was estimated from the maximum workload [Watt] using a recently proposed formula.⁽¹³⁾ Likewise, peak VO₂ was estimated by the ASCM formula for the six-minute walk test ($4.948+0.02*\text{distance}$). Peak VO₂ was also expressed as metabolic equivalent (MET, =3.5 ml/kg/min VO₂).

Results

The final model included 1282 of 1633 patients (number of cases reduced due to missing data in any of the included variables). Peak VO₂ was measured from 1175 CPETs and calculated from 83 ergometries and 24 six-minute walk test. A summary of the main characteristics of the study population is given in Table 1.

Collinearities were weak and GVIFs below 2, except for BMI and waist circumference with a GVIF of 3.87 and 3.89, respectively. Consequently, we omitted waist circumference (because of more missing data) from the model to prevent the mutual weakening of these two variables within the model. Twenty-two predictors remained in the model with centre as random factor. This resulting model explained 52% of the total variance in peak VO₂. Because the mixed linear model violated the assumptions of kurtosis and homoscedasticity, we also performed a GAMLSS model. Mean effects of this model are presented in Figure 1. The following variables were significant: Age, male sex, BMI, FEV₁, LVEF, diastolic BP, resting heart rate, beta blocker, index procedure, angina pectoris, other complaints (pain or palpitations that interfere with exercise), nephropathy and peripheral arterial disease. Atrial fibrillation, diabetes mellitus, hypertension, physical activity, and mental component score (Figure 1). The interaction between index procedure and lag time from index event to exercise testing as well as the interaction between age and sex were entered into the model, but were not significant. The output of the model is also presented numerically in Supplement Table 1 for pooled sexes and in Supplement Table 2 and 3 for both sexes individually.

In the model for the subpopulation with available haemoglobin data (model including 1033 patients), haemoglobin was significant (Figure 2). Haemoglobin levels explained some of the differences between the groups with different index procedures (CABG and valve surgery being lower than PCI and no procedure). However, haemoglobin was also a significant predictor for peak VO₂ in the subgroup analysis of the PCI patients only (model including 541 patients, Figure 2). Effects of comorbidities and CV risk factors adjusted for age, sex, and centre only are shown in Table 2. Each additional comorbidity reduced peak VO₂ by 1.7 ml/kg/min or half a MET and each additional CVRF by 1.1 ml/kg/min. In the 1333 patients with available haemoglobin data, anaemia reduced exercise capacity by 3.23 ml/kg/min (almost 1 MET) (Table 2).

Reference ranges for our 1230 male and 352 female patients with CAD or VHD between age 65 and 90 are shown in Figure 3.

Discussion

This is the first study to identify predictors for exercise capacity in a large cohort of elderly CAD and/or VHD patients. The most important predictors were age, CABG, valve surgery, reduced LVEF, nephropathy and PAD. Each additional comorbidity or CVRF reduced exercise capacity by 1.7 and 1.1 ml/kg/min, respectively. Female sex was also associated with lower peak VO₂, however, this difference disappeared when peak VO₂ was expressed per lean mass rather than body weight. Resting forced expiratory volume in the first second and haemoglobin were strongly associated with peak VO₂. Finally, our data set provides reference ranges from 1582 CAD and VHD elderly patients commencing CR.

Predictors for peak VO₂

In line with our results, the largest existing study that has assessed predictors of exercise capacity in 2869 patients (mean age 62 years) commencing CR has found CABG, angina at stress testing and hypertension associated with peak VO₂(14) and another large study in nearly 1000 younger CAD patients (mean age 63 years) found sex, age, BMI, NYHA class, resting and peak heart rate, beta blocker and fasting blood glucose as significant predictors, (15) . Likewise, in 171 CAD patients from South Africa age, sex, ejection fraction, and forced vital capacity were found to be predictors of exercise capacity.(16)

In our study, females had an 11% lower peak VO₂ relative to body weight compared to males despite multivariate adjustment. This sex difference disappeared completely when peak VO₂ was

expressed relative to lean mass. Effects of other factors remained very similar in the model for peak VO₂ per lean mass. Relating VO₂ to lean rather than body mass has previously been found to be superior (17) and to reduce sex differences.(18) Sex differences in absolute peak VO₂ (ml/min) have been found to diminish with increasing age in elderly sedentary people, due to the fact that men have a steeper age-related decrease in VO₂ peak.(19) However, we found only a modest age decline in peak VO₂ with 0.95 ml/kg/min per decade and no significant difference between males and females. This is in contrast to a previous study on patients entering CR, which showed a decline of 2.4 ml/kg/min per decade in males and 1.16 in females.(5) The same study found that peak VO₂ was significantly influenced by the index-procedure with CABG patients having the lowest exercise capacity. We found that haemoglobin largely accounted for the difference in peak VO₂ between index procedures with open surgery (CABG and VHD patients, of whom 87% were anaemic) and minimally invasive or non-surgical procedures (of whom 25% were anaemic). Only few prior studies have reported exercise capacity and haemoglobin values in CAD patients (16, 20), in contrast to some large studies on predictors of peak VO₂ (14, 15) and large exercise trials (21) who did not report haemoglobin. This is despite the fact that haemoglobin has been found to be an important contributor to oxygen uptake and exercise capacity as it is responsible for the blood's capacity to transport oxygen from the lung to the muscle cells.(22, 23) Outcome in CAD patients has also been found to be related to haemoglobin levels,(24, 25) possibly because haemoglobin may be a marker of other chronic diseases.(26) However, low haemoglobin levels caused by blood loss during surgery are likely to be restored with time and will be accompanied by some spontaneous recovery of exercise capacity, which should not mistakenly be ascribed to the exercise-training effect of CR.

Beta blockers were associated with lower exercise capacity, most likely mediated via a decreased maximal heart rate. Acute experiments with beta blockers in heart patients have led to a decrease in maximal heart rate of over 20 bpm and to a lesser extent in peak VO₂.⁽²⁷⁾ Conversely, in heart failure patients, the decrease in maximal heart rate by beta blockers has not been found to decrease exercise capacity⁽²⁸⁾. In our study, the association between beta blocker use and lower peak VO₂ may either be due to a reduction in maximal heart rate with beta blocker or by patient selection with more severe CAD to beta blocker prescription.

FEV₁ and FVC are measured during resting spirometry, and are obtainable with minimal requirements for time, equipment and patient collaboration. FVC has previously been shown to correlate with peak exercise capacity in CAD patients.⁽¹⁶⁾ FEV₁, closely linked to FVC has been found to be an important predictor of peak VO₂. Contrary to the generation 100 study,⁽²⁹⁾ in our study in both males and females there was a linear relationship with FEV₁ across the full range of peak VO₂ values ($r=0.54$). While physical training would concomitantly increase skeletal and respiratory muscle function, this finding lends room to speculations on effectiveness of respiratory training for increasing exercise capacity, especially in patients unable to exercise.

Most comorbidities and CVRF recorded in the present study were associated with lower VO₂ peak when adjusted for age and sex as fixed effect and centre as random effect only (Table 2). The largest effects were found for nephropathy, peripheral arterial disease, atrial fibrillation, diabetes mellitus, obesity and inactivity. The addition of each comorbidity or CVRF was associated with a decrease of 1.7 and 1.1 ml/kg/min, respectively. This may be put in perspective with the finding that the loss of each MET is associated with a 13% increase in all-cause mortality rate and a 15% increase in CAD events.⁽³⁰⁾ Previous studies assessing the associations between CVRF and

comorbidities with peak VO₂ were performed in much smaller populations and, possibly as a consequence, only found some of these factors to be significant.(31, 32)

Reference ranges

There is a paucity of data on peak VO₂ in the elderly, and particularly in elderly with CAD or VHD. Existing reference populations have included relatively few subjects older than 65 years.(33-35) The HUNT Fitness study included 1046 healthy elderly dwellers older than 60 years, but only 269 of them were older than 70 years (mean peak VO₂ of 26.5 ± 4.7 (SD) for females and 34.1 ± 7 ml/kg/min for males)(5). The Generation 100 study also provided reference ranges for 297 older volunteers (mean age 73 years) with a history of cardiovascular disease.(1) This diseased population with a mean age of 72.9 years had a mean peak VO₂ on the treadmill of 29.3 ± 6.9 ml/kg/min, which was considerably higher than the median of approximately 18 ml/kg/min of our reference range in males for age 73. Our reference ranges are comparable to a previous American study on 2896 patients (mean age 61 years, 724 patients ≥ 70 years) entering CR after a recent acute cardiac event and confirm the low exercise capacity in elderly patients commencing CR. The reference ranges shown in Figure 3 provide useful data for clinicians caring for elderly patients acutely after CAD or VHD and researchers planning clinical studies in these populations. Figure 4 illustrates the importance of the most common CVRF and comorbidities in reducing exercise capacity, by showing peak VO₂ of our population with and without anemia and diabetes compared to the healthy volunteers of the HUNT study.

Strengths

The strengths of the current study are the large sample size and comprehensiveness of data on patient and disease characteristics, physical function, CVRF and comorbidities, which allowed the direct comparison between effect sizes of different predictors for exercise capacity. Automatic

processing of CPETs by one core lab improved comparison of peak VO₂ data from different centres. Further, the assessment of skinfold thickness and calculation of peak VO₂ per lean body mass allowed a more appropriate comparison of males and females. The inclusion of haemoglobin partly explained the lower exercise capacity of surgery patients and allowed the quantification of an increase in VO₂ peak of 0.73 ml/min/kg per increase in 1 mmol/l haemoglobin.

Limitations

Our model explained 52% of the total variance in peak VO₂, leaving a considerable part of variance unexplained. Five percent of the variance could uniquely be explained by centre differences, probably due to patient characteristics not directly assessed in the present study. Given the explorative identification of influencing factors on peak VO₂, statistical significance has to be interpreted with caution. However, the identified predictive variables were mostly highly significant ($p < 0.0001$) and robust to changes in the model specification. Reproducibility and accuracy of peak VO₂ measurements, resting heart rate, BP, skinfold thickness, FVC and FEV₁ have known limitations. The model identifying predictors for peak VO₂ was based on 1282 cases out of a total data set of 1582 VO₂ peak data. Nevertheless, we compared the complete peak VO₂ data to the peak VO₂ data included in the model within each centre and found excellent agreement (differences < 3%). Additionally, we imputed the dataset by multiple imputation and computed an automatic stepwise backward modelling, which resulted in a model comparable to that shown in Figure 2. Methods and resulting models of these additional analyses are provided in Supplement Figure 1. The model included data from 107 patients with calculated rather than measured peak VO₂ values. This approximation has previously been found to be valid.(13, 36).

Conclusions

Parameters associated with disease severity and surgical procedures were the strongest predictors for exercise capacity in elderly CAD patients. For each cumulative comorbidity or CVRF peak VO₂ decreased by 0.5 and 0.3 MET respectively, while the age-associated decline in VO₂ peak was small in this population of elderly CAD patients. It is more appropriate to express exercise capacity relative to lean body mass rather than to body mass when males are compared to females. Due to the considerable large proportion of elderly patients with anemia and the direct physiologic link with peak VO₂, routine measurement of haemoglobin in elderly patients is recommended and should always be included in studies on exercise capacity. FEV₁ may serve as an easily obtainable surrogate measure of exercise capacity in the elderly population with CVD.

Author contribution

TM, PE, EP, WB, AVdV, MCI, DA, UZ, AWJWH, EK and MW contributed to the conception or design of the work. All authors contributed to the acquisition, analysis, or interpretation of data for the work. PE and TM drafted the manuscript. All authors critically revised the manuscript, gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy

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Figure legends

Figure 1: Mean effects of the GAMLSS model for peak VO₂ per body weight including data of 1282 patients. Filled circles display mean effects with 99% confidence intervals. The orange triangle shows the sex effect of the corresponding model for peak VO₂ per lean body weight as dependent variable, calculated by formula based on body weight and skinfold thickness. Please note that the other effects of the model for peak VO₂ per lean body weight were comparable to the effects in the model for peak VO₂ per body weight and are not shown. The model included continuous, binary and categorical independent variables. For categorical variables reference category is indicated.

BP, blood pressure; CABG, coronary artery bypass graft; FEV₁, forced expiratory volume in the first second; PCI, percutaneous intervention; SF-36, Short Form Survey

Figure 2: Mean effects of the GAMLSS model for peak VO₂ per body weight for the subpopulation of 1033 patients with available haemoglobin data. Filled circles depict mean effects with 99% confidence intervals of patients with different index procedures. The orange triangles with 99% dashed index intervals depict mean effects of the same model for the 541 patients with PCI only. The model included continuous, binary and categorical independent variables. For categorical variables reference category is indicated.

BP, blood pressure; CABG, coronary artery bypass graft; FEV₁, forced expiratory volume in the first second; PCI, percutaneous intervention; SF-36, Short Form Survey

Figure 3: Reference ranges of peak VO₂ values of 1230 male and 352 female CAD or VHD patients. Lines indicate percentiles. Mean peak VO₂ by age is estimated by $26.03 - 0.17 \times \text{age}$ [years] for females and $30.51 - 0.19 \times \text{age}$ [years] for males.

Figure 4: Medians and interquartile range of peak oxygen consumption according to age are shown for three male subgroups of the EU-CaRE study compared with an illustration of a healthy male population from the HUNT study (mean and standard deviation).

* Aspenes ST, Nilsen TI, Skaug EA, Bertheussen GF, Ellingsen O, Vatten L, et al. Peak oxygen uptake and cardiovascular risk factors in 4631 healthy women and men. *Medicine and science in sports and exercise*. 2011;43(8):1465-73. This study has determined peak VO₂ on a treadmill, which results in slightly higher VO₂ values compared to cycle ergometry.

Figure 1

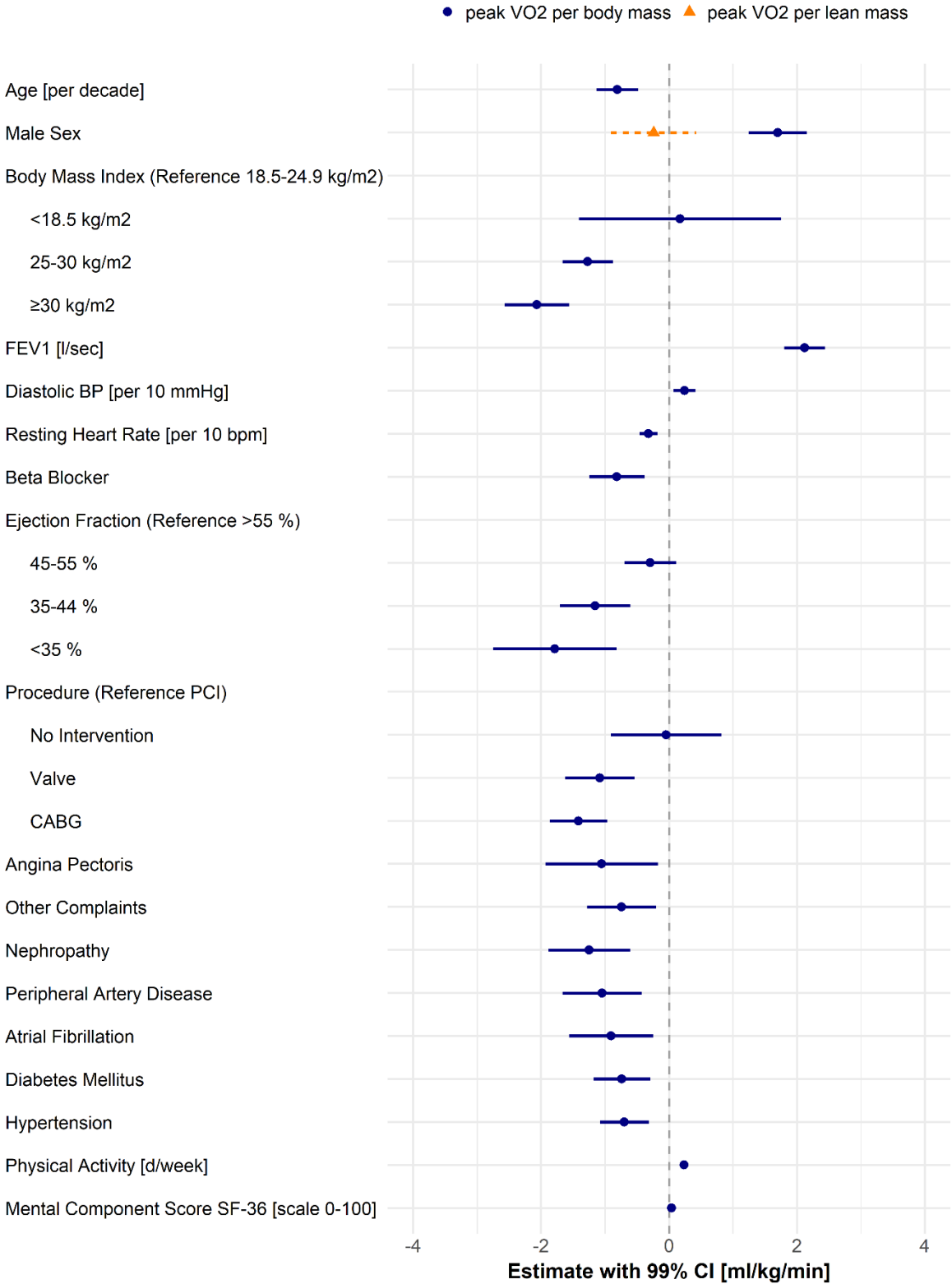


Figure 2

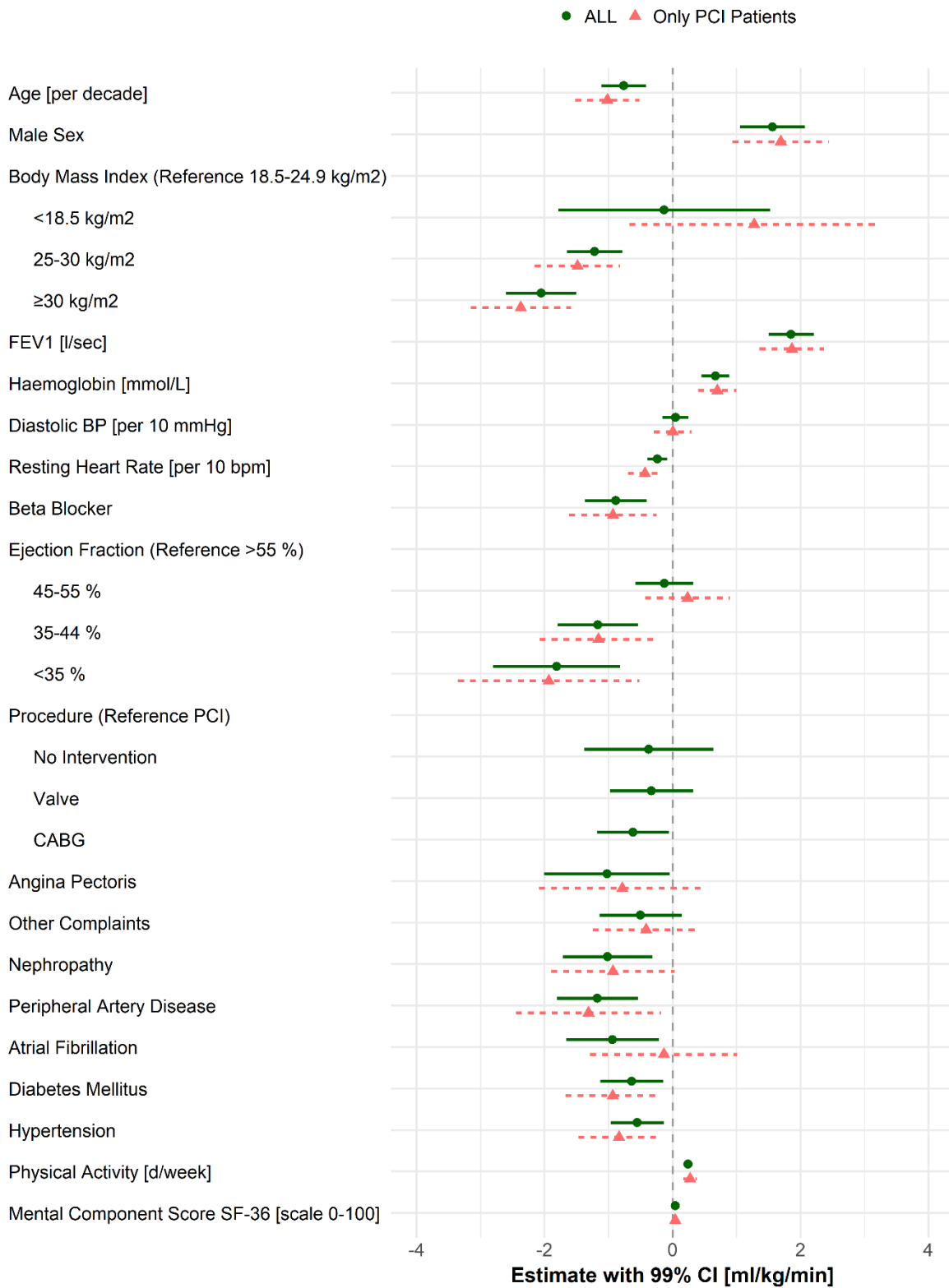


Figure 3

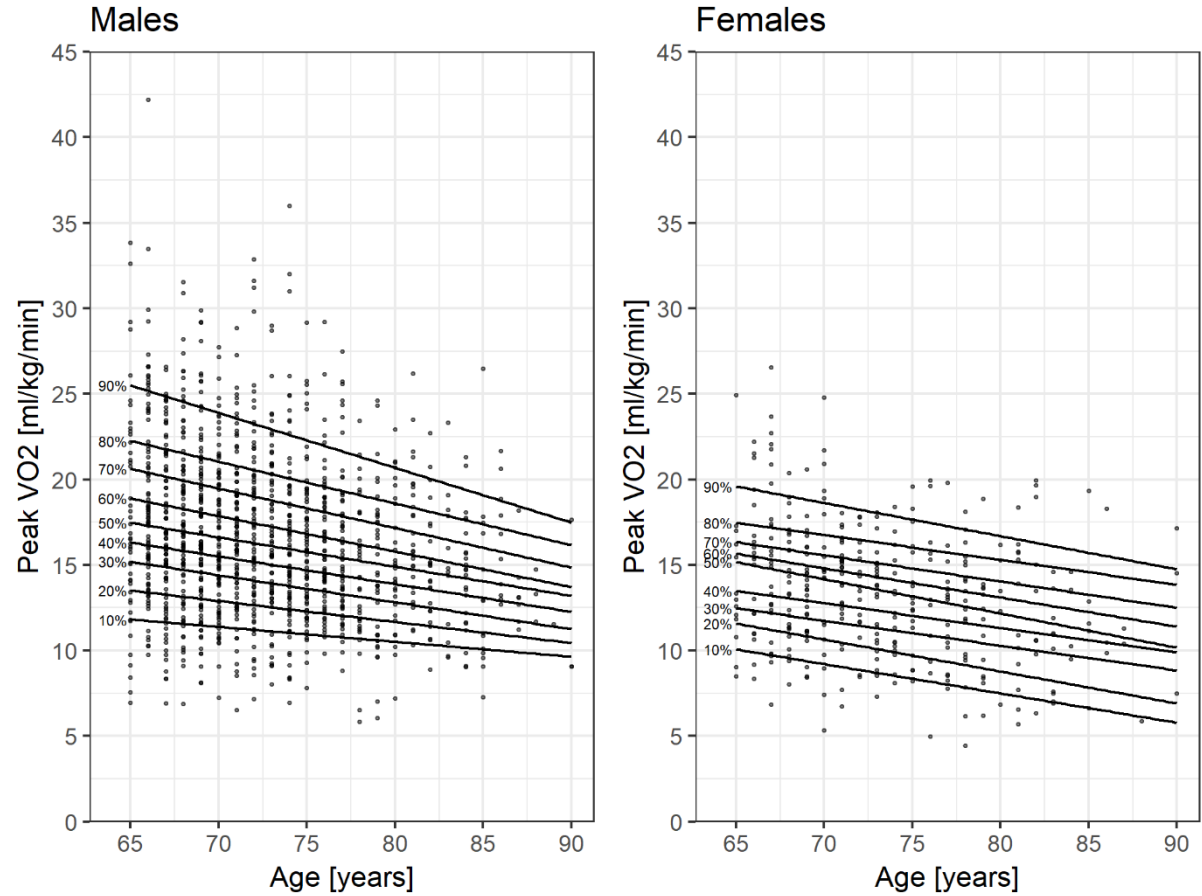


Figure 4

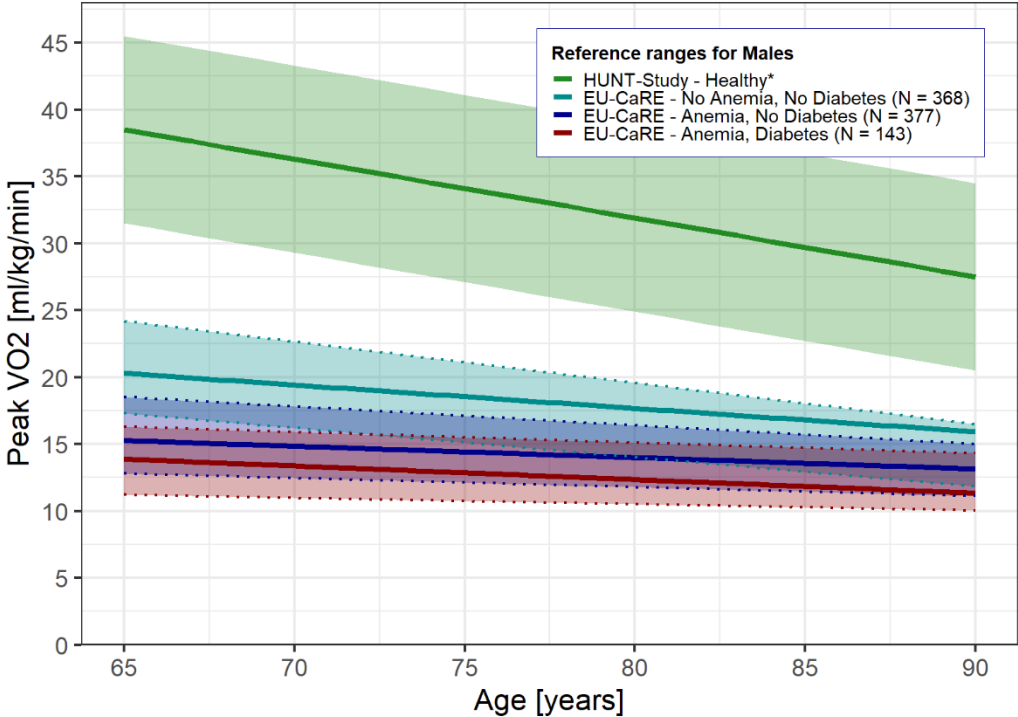


Table 1: Characteristics of the 1282 patients included in the final multivariate model.

Variable	N (%)	Mean (SD)
Age [y]		72.9 (5.4)
Male Sex	1011 (79%)	
Caucasian Ethnicity	1262 (98%)	
Peak VO2 [ml/kg/min]		16.1 (4.8)
Body mass index [kg/m2]		27.3 (4.0)
Ejection Fraction [%]		
>55	753 (59%)	
45-55	327 (26%)	
35-44	154 (12%)	
<35	48 (4%)	
Acute Coronary Syndrome	702 (55%)	
Procedure		
PCI	706 (55%)	
None	74 (6%)	
Valve	135 (10%)	
CABG	367 (29%)	
Center		
Zwolle	202 (16%)	
Copenhagen	179 (14%)	
Paris	128 (10%)	
Bern	147 (11%)	
Santiago	194 (15%)	
Ludwigshafen	214 (17%)	
Parma	193 (15%)	
Nijmegen	25 (2%)	

CABG, coronary artery bypass grafting; PCI, percutaneous intervention; SD, standard deviation; Valve, valve replacement; VO2, oxygen consumption

Table 2: Effects (estimates) for comorbidities and cardiovascular risk factors of mixed linear models for peak VO₂ (ml/min/kg) adjusted for age and sex as fixed factors and center as random factor including 1498 cases. Estimates depict the mean difference between patients with versus those without each factor, for cumulative comorbidities/cardiovascular risk factors it is the increment per additional comorbidity/risk factor. Percentages indicate the population with the comorbidity/CV risk factor.

Variable	Proportion with the risk factor	Coefficient	(99% CI)	
<i>Comorbidities:</i>				
Nephropathy	7.6%	-2.94	(-4.00; -1.89)	*
Peripheral artery disease	7.4%	-2.17	(-3.24; -1.10)	*
Atrial Fibrillation	6.8%	-2.06	(-3.18; -0.95)	*
Diabetes Mellitus	23.5%	-2.10	(-2.75; -1.45)	*
COPD	6.4%	-1.69	(-2.83; -0.55)	*
Obstructive sleep apnoea	2.4%	-1.52	(-3.33; 0.30)	*
Depression	2.7%	-1.32	(-3.05; 0.40)	
TIA/ CVA diagnosed by neurologist	6.3%	-1.08	(-2.24; 0.08)	
Rheumatoid Arthritis	1.9%	-0.99	(-3.06; 1.08)	
Cumulative Comorbidities §		-1.71	(-2.06; -1.36)	*
Anemia#	50.7%	-3.23	(-3.85; -2.61)	*
<i>Cardiovascular Risk Factors:</i>				
Obesity	22.7%	-2.16	(-2.84; -1.49)	*
Hypertension	66.9%	-1.69	(-2.29; -1.10)	*
Inactivity †				
No activity	22.1%	-2.02	(-2.78; -1.24)	*
<5 days	32.5%	-0.64	(-1.32; 0.03)	
Smoking ‡				
Current smoking	9.1%	-1.08	(-2.09; -0.07)	*
Former smoking	16.0%	-0.96	(-1.74; -0.18)	*
Dyslipidemia	67.6%	-0.56	(-1.18; 0.06)	
Family CV history	30.9%	-0.36	(-1.01; 0.28)	
Alcohol intake ≥ 14 units per week	14.6%	0.07	(-0.75; 0.89)	
Cumulative of CV risk factors [?]		-1.11	(-1.36; -0.86)	*

CI, confidence interval; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; TIA, transient ischemic attack

* p < 0.01

† Compared to patients with at least 5 to 7 days per week with 30 min of moderate physical activity.

‡ Compared to non-smokers.

§ Cumulative comorbidities including only significant comorbidities.

? Cumulative CV risk factors including only significant CV risk factors

Only available in 1305 patients and therefore not included in cumulative comorbidities.

Supplement Figure 1 Methods

1. Step: Imputation

The following variables were imputed with multiple imputation (5 imputations, 10 iterations) with predictive mean matching for all variables using the function *mice* from *mice package, R*:

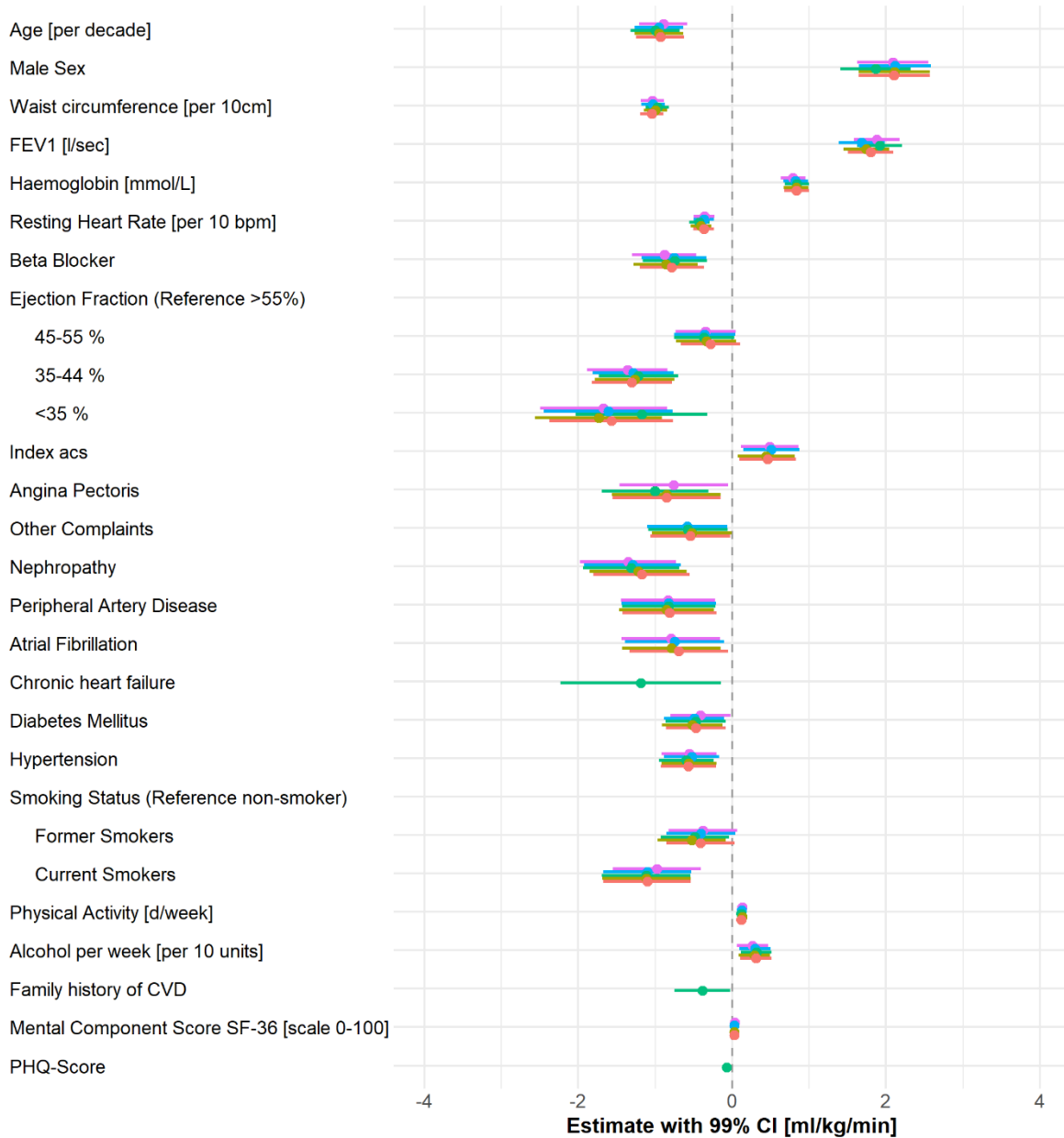
Peak VO₂, patient anthropometric data (age, height, BMI, waist circumference, sex, blood pressure), socio-behavioural factors (education, volunteer work, form of living), index procedure (CABG, PCI, valve, stable CAD without revascularization), cardiovascular risk factors (diabetes mellitus, smoking, hypertension, hypocholesteremia, family history of CVD, alcohol consumption, physical inactivity), exercise limiting medication (beta blocker), comorbidities (nephropathy, rheumatic disease, chronic obstructive pulmonary disease, peripheral arterial disease, depression, obstructive sleep apnea, cerebrovascular accident), cardiac complaints (angina pectoris, chronic heart failure, arterial fibrillations, rhythm other than sinus, other complaints), cardiac disease history (previous CABG, PCI or ACS), resting heart and lung function (heart rate, forced vital capacity, forced expiratory volume in first second), haemoglobin and questionnaire scores (GAD sum score, PHQ9 sum score, Mediterranean diet score, mental component score of SF36).

2. Step: Stepwise linear mixed model

A stepwise backward variable selection was performed on each of the 5 imputed datasets with peak VO₂ as response variable, center as random factor and all other variables mentioned in the list above as explanatory variables using *step* function from *lmerTest* package. The output of the resulting models for each imputed dataset is presented in the Figure below.

Results and discussion

The automatic stepwise backward variable selection and modeling on the imputed datasets resulted in 5 models comparable to the model presented in Figure 2 of the main article (Supplement Figure 1). Index intervention was removed from the models with the imputed data sets since this variable was no longer significant, most likely because haemoglobin remained in the models, which explained much of the difference between the different index interventions. Additionally, waist circumference was included instead of BMI, suggesting a stronger relationship of waist circumference with exercise capacity than BMI with exercise capacity. In the model presented in Figure 2 of the main article, waist circumference was omitted in favour of BMI because it was missing in 120 cases.



Supplement Figure 1: Mean effects of the mixed linear model for peak VO2 per body weight for the population with imputed data of 1633 patients. Shown are mean effects with 99% confidence intervals of the five imputed datasets. The model included continuous, binary and categorical independent variables. For categorical variables the according reference category is indicated.

FEV1, forced expiratory volume in the first second; acs, acute coronary syndrome; CVD, cardiovascular disease; SF-36, Short Form Survey; PHQ, patient health questionnaire

Supplement Table 1: Generalised additive model for location, scale and shape for peak VO₂ per body weight including data of 1282 patients (Nagelkerke R² = 0.52, Generalized AIC = 6721.48).

Variable	Estimate	[99% CI]
Intercept	16.85	[11.86; 21.84] *
Age [per decade]	-0.08	[-0.13; -0.03] *
Male Sex	1.70	[1.08; 2.32] *
Procedure (Reference PCI)		
No Intervention	-0.04	[-1.13; 1.04]
Valve	-1.08	[-1.85; -0.31] *
CABG	-1.42	[-2.00; -0.84] *
FEV1 [l/sec]	2.12	[1.68; 2.56] *
Other Complaints	-0.74	[-1.46; -0.02] *
Ejection Fraction (Reference >55 %)		
45-55 %	-0.29	[-0.83; 0.25]
35-44 %	-1.15	[-1.87; -0.43] *
<35 %	-1.78	[-2.92; -0.65] *
Angina Pectoris	-1.06	[-2.09; -0.02] *
Beta Blocker	-0.82	[-1.40; -0.23] *
Body Mass Index (Reference 18.5-24.9 kg/m ²)		
<18.5 kg/m ²	0.17	[-2.14; 2.49]
25-30 kg/m ²	-1.27	[-1.81; -0.73] *
≥30 kg/m ²	-2.07	[-2.72; -1.42] *
Diabetes Mellitus	-0.74	[-1.27; -0.20] *
Hypertension	-0.70	[-1.20; -0.19] *
Arterial Fibrillation	-0.90	[-1.75; -0.06] *
Nephropathy	-1.25	[-2.11; -0.39] *
Peripheral Artery Disease	-1.05	[-1.88; -0.21] *
Physical Activity [d/week]	0.24	[0.15; 0.32] *
Mental Component Score SF-36	0.04	[0.02; 0.06] *
Resting Heart Rate [per 10 bpm]	-0.03	[-0.05; -0.01] *
Diastolic BP [per 10 mmHg]	0.02	[0.00; 0.05] *

CI, confidence interval; FEV1, forced expiratory volume in the first second; BP, blood pressure; PCI, percutaneous intervention; CABG, coronary artery bypass graft; NYHA, New York heart association; CVD, cardiovascular disease; SF-36, Short Form Survey.

*p < 0.01

Supplement Table 2: Generalised additive model for location, scale and shape for peak VO2 per body weight including data of 1011 male patients (Nagelkerke R² = 0.50, Generalized AIC = 5358.41).

Variable	Estimate	[99% CI]
Intercept	19.44	[13.76; 25.12] *
Age [per decade]	-0.09	[-0.15; -0.04] *
Procedure (Reference PCI)		
No Intervention	0.28	[-1.25; 1.81]
Valve	-1.16	[-2.20; -0.12] *
CABG	-1.55	[-2.19; -0.90] *
FEV1 [l/sec]	2.27	[1.78; 2.76] *
Other Complaints	-0.87	[-1.72; -0.02] *
Ejection Fraction (Reference >55 %)		
45-55 %	-0.19	[-0.84; 0.47]
35-44 %	-1.19	[-2.05; -0.32] *
<35 %	-1.72	[-3.09; -0.34] *
Angina Pectoris	-1.14	[-2.44; 0.15]
Beta Blocker	-0.93	[-1.71; -0.14] *
Body Mass Index (Reference 18.5-24.9 kg/m ²)		
<18.5 kg/m ²	-5.24	[-285.78; 275.31]
25-30 kg/m ²	-1.02	[-1.71; -0.33] *
≥30 kg/m ²	-1.98	[-2.88; -1.07] *
Diabetes Mellitus	-0.75	[-1.36; -0.14] *
Hypertension	-0.74	[-1.32; -0.15] *
Arterial Fibrillation	-0.99	[-2.00; 0.01]
Nephropathy	-1.23	[-2.34; -0.12] *
Peripheral Artery Disease	-1.34	[-2.27; -0.41] *
Physical Activity [d/week]	0.26	[0.16; 0.36] *
Mental Component Score SF-36	0.04	[0.01; 0.07] *
Resting Heart Rate [per 10 bpm]	-0.04	[-0.06; -0.02] *
Diastolic BP [per 10 mmHg]	0.02	[-0.01; 0.05]

CI, confidence interval; FEV1, forced expiratory volume in the first second; BP, blood pressure; PCI, percutaneous intervention; CABG, coronary artery bypass graft; CVD, cardiovascular disease; SF-36, Short Form Survey.

*p < 0.01

Supplement Table 3: Generalised additive model for location, scale and shape for peak VO2 per body weight including data of 271 female patients (Nagelkerke R² = 0.44, Generalized AIC = 1389.38).

Variable	Estimate	[99% CI]
Intercept	14.22	[4.76; 23.68]
Age [per decade]	-0.06	[-0.15; 0.04]
Procedure (Reference PCI)		
No Intervention	-0.55	[-2.43; 1.33]
Valve	-1.17	[-2.62; 0.28]*
CABG	-0.99	[-2.38; 0.40]
FEV1 [l/sec]	2.42	[1.31; 3.53]
Other Complaints	-0.55	[-1.97; 0.88]
Ejection Fraction (Reference >55 %)		
45-55 %	-0.42	[-1.53; 0.69]
35-44 %	-0.68	[-2.33; 0.98]*
<35 %	-1.46	[-4.04; 1.12]
Angina Pectoris	-1.11	[-2.98; 0.76]
Beta Blocker	-0.65	[-1.81; 0.51]
Body Mass Index (Reference 18.5-24.9 kg/m ²)		
<18.5 kg/m ²	-0.56	[-3.26; 2.14]
25-30 kg/m ²	-1.63	[-2.77; -0.49]
≥30 kg/m ²	-2.24	[-3.41; -1.07]
Diabetes Mellitus	-0.82	[-2.03; 0.40]
Hypertension	-0.50	[-1.55; 0.55]*
Arterial Fibrillation	-1.37	[-3.11; 0.36]*
Nephropathy	-0.91	[-3.11; 1.29]
Peripheral Artery Disease	-0.02	[-2.13; 2.09]
Physical Activity [d/week]	0.17	[-0.01; 0.34]
Mental Component Score SF-36	0.03	[-0.01; 0.07]
Resting Heart Rate [per 10 bpm]	-0.02	[-0.07; 0.02]
Diastolic BP [per 10 mmHg]	0.03	[-0.01; 0.07]

CI, confidence interval; FEV1, forced expiratory volume in the first second; BP, blood pressure; PCI, percutaneous intervention; CABG, coronary artery bypass graft; CVD, cardiovascular disease; SF-36, Short Form Survey.

*p < 0.01

