POST-PRINT

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

Brief: Exercise capacity in elderly cardiac patients

Thimo Marcin[a], Prisca Eser[a], Eva Prescott[b], Nicolai Mikkelsen[b] Leonie F. Prins[c], Evelien Kolkman[c], Óscar Lado-Baleato[d], Carmen Cardaso-Suaréz [d], Wendy Bruins[e], Astrid E van der Velde[e], Carlos Peña Gil[f], Marie-Christine Iliou[g], Diego Ardissino[h], Uwe Zeymer[i], Esther P Meindersma[e,j], Arnoud.W.J. Van't Hof[e,k,l], Ed P. de Kluiver[e], Matthias Wilhelm[a]

a. Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Switzerland
b. Department of Cardiology, Bispebjerg Frederiksberg University Hospital, Copenhagen, Denmark
c. Diagram B.V., The Netherlands
d. Department of Statistics, Mathematical Analysis, and Optimization, Universidade de Santiago de Compostela, Santiago de Compostela, Spain
e. Isala Heart Centre, The Netherlands
f. Department of Cardiology, Hospital Clínico Universitario de Santiago. SERGAS. FIDIS. CIBER CV. University of Santiago de Compostela, Spain
g. Department of Cardiac Rehabilitation, Assistance Publique Hopitaux de Paris, France
h. Department of Cardiology, Parma University Hospital, Italy
i. Klinikum Ludwigshafen and Institut für Herzinfarktforschung Ludwigshafen, Ludwigshafen, Germany
j. Department of Cardiology, Radboud University, Nijmegen, The Netherlands
k. Department of Cardiology, Maastricht University Medical Center, Maastricht, the Netherlands
l. Department of Cardiology, Zuyderland Medical Center, Heerlen, the Netherlands

T.M, P.E and M.W reports grants from State Secretariat for Education, Research and Innovation SERI, Swiss National Funding Agency, A.W.J.W.H reports grants from Medtronic, grants and personal fees from Astra Zeneca, outside the submitted work, M-C-I, W.B, L.F.P, E.K, E.P.d.K, reports grants from European Union, U.Z reports grants and personal fees from Astra Zeneca, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, grants and personal fees from BMS, personal fees from Daiichi Sankyo, personal fees from Eli Lilly, grants and personal fees from Novartis, grants and personal fees from MSD, personal fees from Trommsdorf, personal fees from Amgen, outside the submitted work. All other authors have no conflicts of interest to disclose.

Adress for correspondence:
Matthias Wilhelm, MD, Preventive Cardiology & Sports Medicine, Department of Cardiology
Inselspital, Bern University Hospital, University of Bern
CH-3010 Bern, Switzerland
Tel/Fax: +41 31 632 9871/+41 31 632 8977
Matthias.wilhelm@insel.ch

Total word count: 5712

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 VO2; 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 VO2 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 VO2 per body mass but not per lean mass. Haemoglobin was significantly linked to peak VO2 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 VO2 per lean mass rather than body mass allows a more appropriate comparison between sexes. Haemoglobin is strongly related to peak VO2 and should be considered in studies assessing exercise capacity, especially in studies on patients after cardiac surgery.

Abstract word count: 263

Key words: cardiac rehabilitation, cardiopulmonary exercise testing, exercise capacity, peak VO2

Netherlands Trial Register, Trial NL5166: https://www.trialregister.nl/trial/5166

Abbreviation list

CVD	cardiovascular disease
CAD	coronary artery disease
CR	cardiac rehabilitation
VHD	valvular heart disease
peak VO2	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 MALTAB 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*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 extend 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

Acknowledgements

We greatly appreciated the support by all not personally named people involved in the EU-CaRE study

Declaration of Conflicting Interests:

TM, PE and MW reports grants from State Secretariat for Education, Research and Innovation SERI, Swiss National Funding Agency, AWJWH reports grants from Medtronic, grants and personal fees from Astra Zeneca, outside the submitted work, MCI, WB, LFP, EK, EPdK, reports grants from European Union, UZ reports grants and personal fees from Astra Zeneca, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim, grants and personal fees from BMS, personal fees from Daiichi Sankyo, personal fees from Eli Lilly, grants and personal fees from Novartis, grants and personal fees from MSD, personal fees from Trommsdorf, personal fees from Amgen, outside the submitted work

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by the European Union's Horizon 2020 research and innovation programme under grant agreement No 634439. For the Swiss consortium partner, funding was received by the Swiss State Secretariat for Education, Research and Innovation under contract number 15.0139.

References

1. Stensvold D, Bucher Sandbakk S, Viken H, Zisko N, Reitlo LS, Nauman J, et al. Cardiorespiratory Reference Data in Older Adults: The Generation 100 Study. Medicine and science in sports and exercise. 2017;49(11):2206-15.
2. Vanhoutte PM, Shimokawa H, Feletou M, Tang EH. Endothelial dysfunction and vascular disease - a 30th anniversary update. Acta physiologica. 2017;219(1):22-96.
3. Kendir C, van den Akker M, Vos R, Metsemakers J. Cardiovascular disease patients have increased risk for comorbidity: A cross-sectional study in the Netherlands. The European journal of general practice. 2018;24(1):45-50.
4. Sachdev M, Sun JL, Tsiatis AA, Nelson CL, Mark DB, Jollis JG. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. Journal of the American College of Cardiology. 2004;43(4):576-82.
5. 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.
6. Hung RK, Al-Mallah MH, McEvoy JW, Whelton SP, Blumenthal RS, Nasir K, et al. Prognostic value of exercise capacity in patients with coronary artery disease: the FIT (Henry Ford ExercIse Testing) project. Mayo Clinic proceedings. 2014;89(12):1644-54.
7. Vanhees L, Fagard R, Thijs L, Staessen J, Amery A. Prognostic significance of peak exercise capacity in patients with coronary artery disease. Journal of the American College of Cardiology. 1994;23(2):358-63.
8. Doimo S, Fabris E, Piepoli M, Barbati G, Antonini-Canterin F, Bernardi G, et al. Impact of ambulatory cardiac rehabilitation on cardiovascular outcomes: a long-term follow-up study. Eur Heart J. 2018.
9. Anderson L, Thompson DR, Oldridge N, Zwisler AD, Rees K, Martin N, et al. Exercise-based cardiac rehabilitation for coronary heart disease. The Cochrane database of systematic reviews. 2016(1):CD001800.
10. Forman DE, Arena R, Boxer R, Dolansky MA, Eng JJ, Fleg JL, et al. Prioritizing Functional Capacity as a Principal End Point for Therapies Oriented to Older Adults With Cardiovascular Disease: A Scientific Statement for Healthcare Professionals From the American Heart Association. Circulation. 2017;135(16):e894-e918.
11. Prescott E, Meindersma EP, van der Velde AE, Gonzalez-Juanatey JR, Iliou MC, Ardissino D, et al. A EUropean study on effectiveness and sustainability of current Cardiac Rehabilitation programmes in the Elderly: Design of the EU-CaRE randomised controlled trial. European journal of preventive cardiology. 2016;23(2 suppl):27-40.
12. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16 to 72 years. The British journal of nutrition. 1974;32(1):77-97.
13. Kokkinos P, Kaminsky LA, Arena R, Zhang J, Myers J. A new generalized cycle ergometry equation for predicting maximal oxygen uptake: The Fitness Registry and the Importance of Exercise National Database (FRIEND). European journal of preventive cardiology. 2018;25(10):1077-82.
14. Ades PA, Savage PD, Brawner CA, Lyon CE, Ehrman JK, Bunn JY, et al. Aerobic capacity in patients entering cardiac rehabilitation. Circulation. 2006;113(23):2706-12.

15. Van de Veire NR, De Winter O, Gir M, De Buyzere M, Van de Wiele C, De Sutter J. Fasting blood glucose levels are related to exercise capacity in patients with coronary artery disease. American heart journal. 2006;152(3):486-92.
16. Digenio AG, Noakes TD, Cantor A, Groeneveld H, Daly L, Mavunda D, et al. Predictors of exercise capacity and adaptability to training in patients with coronary artery disease. Journal of cardiopulmonary rehabilitation. 1997;17(2):110-20.
17. Krachler B, Savonen K, Komulainen P, Hassinen M, Lakka TA, Rauramaa R. Cardiopulmonary fitness is a function of lean mass, not total body weight: The DR's EXTRA study. European journal of preventive cardiology. 2015;22(9):1171-9.
18. Hollenberg M, Yang J, Haight TJ, Tager IB. Longitudinal changes in aerobic capacity: implications for concepts of aging. The journals of gerontology Series A, Biological sciences and medical sciences. 2006;61(8):851-8.
19. Weiss EP, Spina RJ, Holloszy JO, Ehsani AA. Gender differences in the decline in aerobic capacity and its physiological determinants during the later decades of life. Journal of applied physiology. 2006;101(3):938-44.
20. Batalli A, Ibrahimi P, Bytyci I, Ahmeti A, Haliti E, Elezi S, et al. Different determinants of exercise capacity in HFpEF compared to HFrEF. Cardiovascular ultrasound. 2017;15(1):12.
21. Ellingsen O, Halle M, Conraads V, Stoylen A, Dalen H, Delagardelle C, et al. High-Intensity Interval Training in Patients With Heart Failure With Reduced Ejection Fraction. Circulation. 2017;135(9):839-49.
22. Hassel E, Stensvold D, Halvorsen T, Wisloff U, Langhammer A, Steinshamn S. Lung function parameters improve prediction of VO2peak in an elderly population: The Generation 100 study. PloS one. 2017;12(3):e0174058.
23. Calbet JA, Lundby C, Koskolou M, Boushel R. Importance of hemoglobin concentration to exercise: acute manipulations. Respiratory physiology & neurobiology. 2006;151(2-3):132-40.
24. Shah AD, Nicholas O, Timmis AD, Feder G, Abrams KR, Chen R, et al. Threshold haemoglobin levels and the prognosis of stable coronary disease: two new cohorts and a systematic review and meta-analysis. PLoS medicine. 2011;8(5):e1000439.
25. Zakai NA, French B, Arnold AM, Newman AB, Fried LF, Robbins J, et al. Hemoglobin decline, function, and mortality in the elderly: the cardiovascular health study. American journal of hematology. 2013;88(1):5-9.
26. Weiss G, Goodnough LT. Anemia of chronic disease. The New England journal of medicine. 2005;352(10):1011-23.
27. Foley KO, Brubaker PH, Matrazzo B, Berry MJ, Pribanich S, Miller HS. Effects of cardioselective beta blockers on ventilation and gas exchange in patients with heart disease during ramp treadmill testing. The American journal of cardiology. 1997;80(9):1215-6.
28. Montero D, Flammer AJ. Effect of Beta-blocker Treatment on V O2peak in Patients with Heart Failure. Medicine and science in sports and exercise. 2018;50(5):889-96.
29. Hassel E, Stensvold D, Halvorsen T, Wisloff U, Langhammer A, Steinshamn S. Association between pulmonary function and peak oxygen uptake in elderly: the Generation 100 study. Respiratory research. 2015;16:156.
30. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. Jama. 2009;301(19):2024-35.
31. Ahmeti A, Henein MY, Ibrahimi P, Elezi S, Haliti E, Poniku A, et al. Quality of life questionnaire predicts poor exercise capacity only in HFpEF and not in HFrEF. BMC cardiovascular disorders. 2017;17(1):268.

32. Daullxhiu I, Haliti E, Poniku A, Ahmeti A, Hyseni V, Olloni R, et al. Predictors of exercise capacity in patients with chronic heart failure. Journal of cardiovascular medicine. 2011;12(3):223-5.
33. Edvardsen E, Hansen BH, Holme IM, Dyrstad SM, Anderssen SA. Reference values for cardiorespiratory response and fitness on the treadmill in a 20- to 85-year-old population. Chest. 2013;144(1):241-8.
34. Rapp D, Scharhag J, Wagenpfeil S, Scholl J. Reference values for peak oxygen uptake: cross-sectional analysis of cycle ergometry-based cardiopulmonary exercise tests of 10 090 adult German volunteers from the Prevention First Registry. BMJ open. 2018;8(3):e018697.
35. Kaminsky LA, Imboden MT, Arena R, Myers J. Reference Standards for Cardiorespiratory Fitness Measured With Cardiopulmonary Exercise Testing Using Cycle Ergometry: Data From the Fitness Registry and the Importance of Exercise National Database (FRIEND) Registry. Mayo Clinic proceedings. 2017;92(2):228-33.
36. Ross RM, Murthy JN, Wollak ID, Jackson AS. The six minute walk test accurately estimates mean peak oxygen uptake. BMC pulmonary medicine. 2010;10:31.

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 × age [years] for females and 30.51 – 0.19 × 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

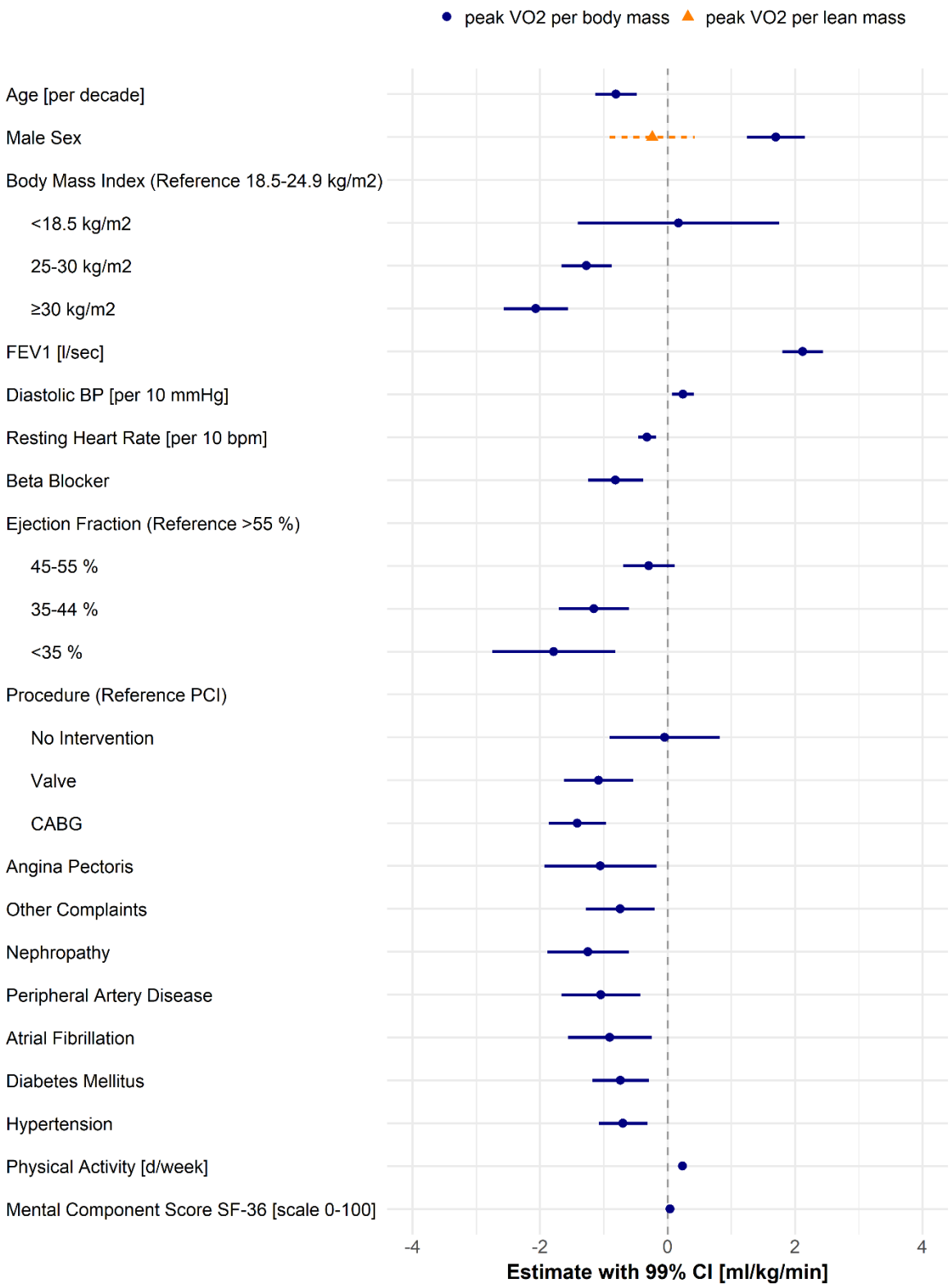

peak VO2 per body mass
peak VO2 per lean mass
Age [per decade]
Male Sex
Body Mass Index (Reference 18.5-24.9 kg/m2)
<18.5 kg/m2
25-30 kg/m2
≥30 kg/m2
FEV1 [l/sec]
Diastolic BP [per 10 mmHg]
Resting Heart Rate [per 10 bpm]
Beta Blocker
Ejection Fraction (Reference >55 %)
45-55 %
35-44 %
<35 %
Procedure (Reference PCI)
No Intervention
Valve
CABG
Angina Pectoris
Other Complaints
Nephropathy
Peripheral Artery Disease
Atrial Fibrillation
Diabetes Mellitus
Hypertension
Physical Activity [d/week]
Mental Component Score SF-36 [scale 0-100]
-4
-2
0
2
4
Estimate with 99% CI [ml/kg/min]

Figure 2

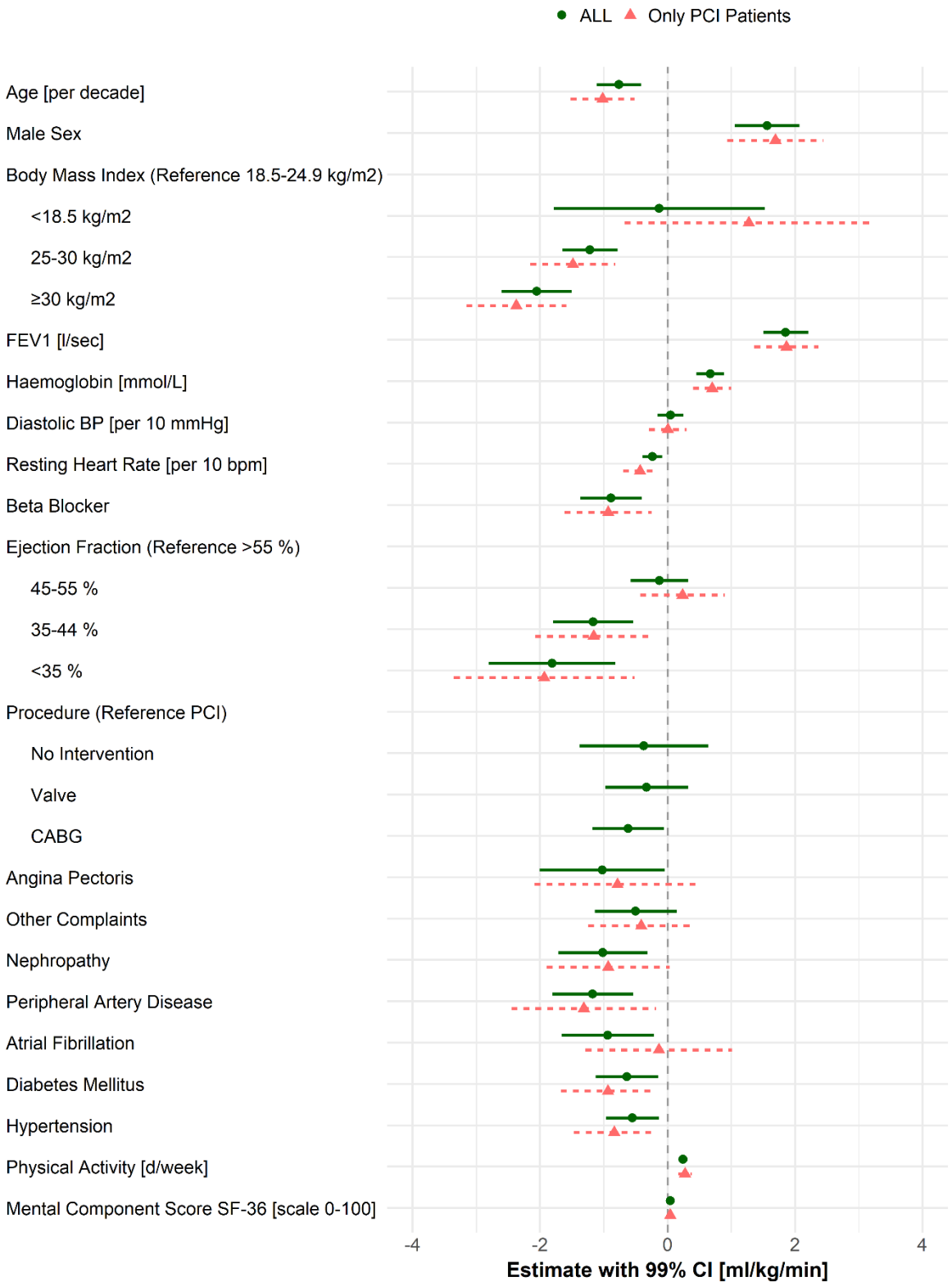

ALL
Only PCI Patients
Age [per decade]
Male Sex
Body Mass Index (Reference 18.5-24.9 kg/m2)
<18.5 kg/m2
25-30 kg/m2
≥30 kg/m2
FEV1 [l/sec]
Haemoglobin [mmol/L]
Diastolic BP [per 10 mmHg]
Resting Heart Rate [per 10 bpm]
Beta Blocker
Ejection Fraction (Reference >55 %)
45-55 %
35-44 %
<35 %
Procedure (Reference PCI)
No Intervention
Valve
CABG
Angina Pectoris
Other Complaints
Nephropathy
Peripheral Artery Disease
Atrial Fibrillation
Diabetes Mellitus
Hypertension
Physical Activity [d/week]
Mental Component Score SF-36 [scale 0-100]
-4
-2
0
2
4
Estimate with 99% CI [ml/kg/min]

Figure 3

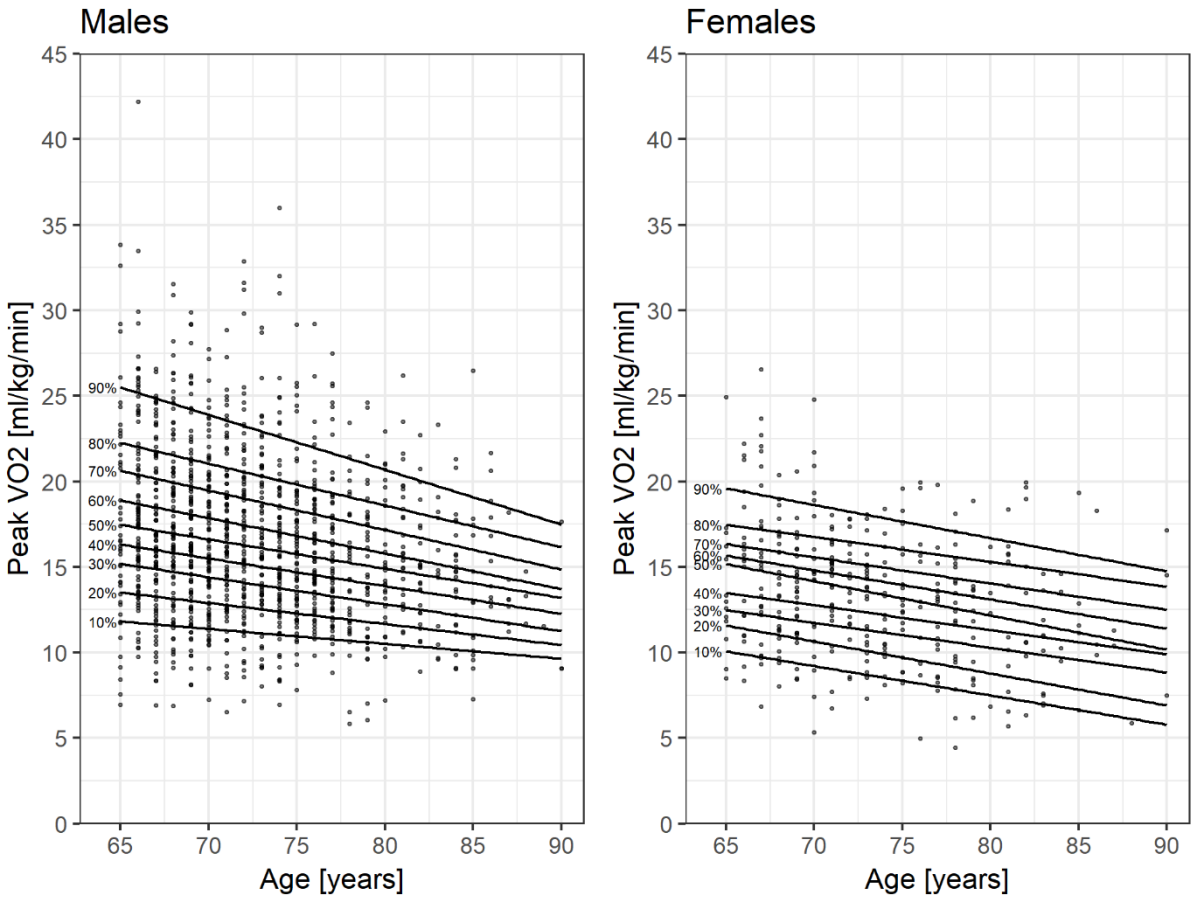

Males
Females
Peak VO2 [ml/kg/min]
Age [years]
90%
80%
70%
60%
50%
40%
30%
20%
10%
0
5
10
15
20
25
30
35
40
45
65
70
75
80
85
90

Figure 4

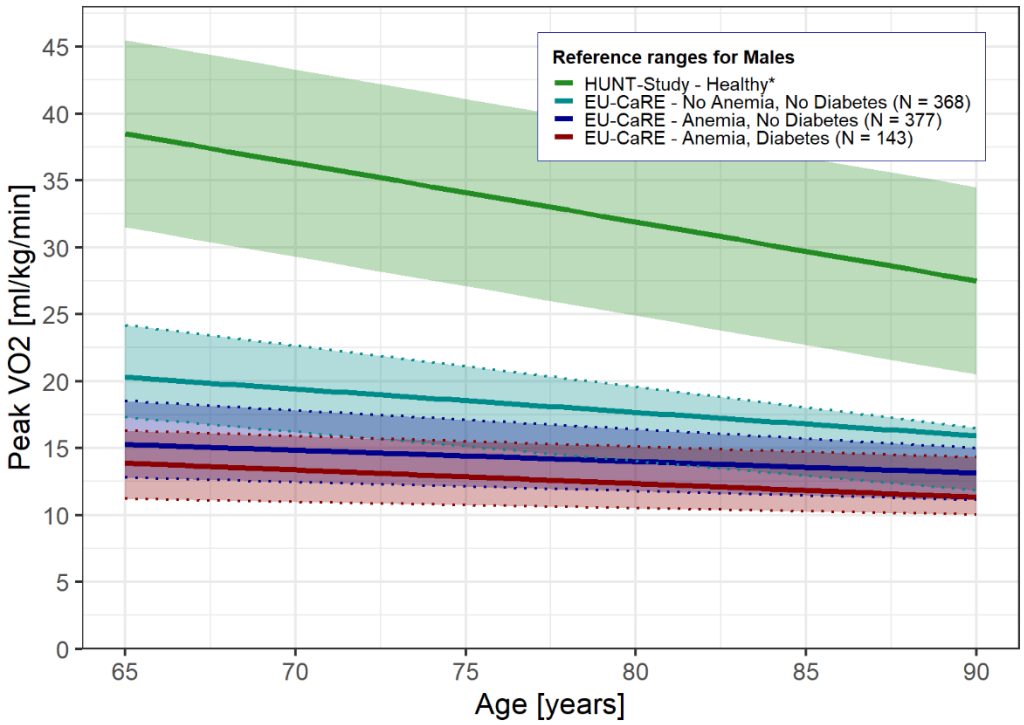

Reference ranges for Males
HUNT-Study - Healthy*
EU-CaRE - No Anemia, No Diabetes (N = 368)
EU-CaRE - Anemia, No Diabetes (N = 377)
EU-CaRE - Anemia, Diabetes (N = 143)
Peak VO2 [ml/kg/min]
0
5
10
15
20
25
30
35
40
45
65
70
75
80
85
90
Age [years]

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)	
Comorbidities:				
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)	*
Cardiovascular Risk Factors:				
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:*

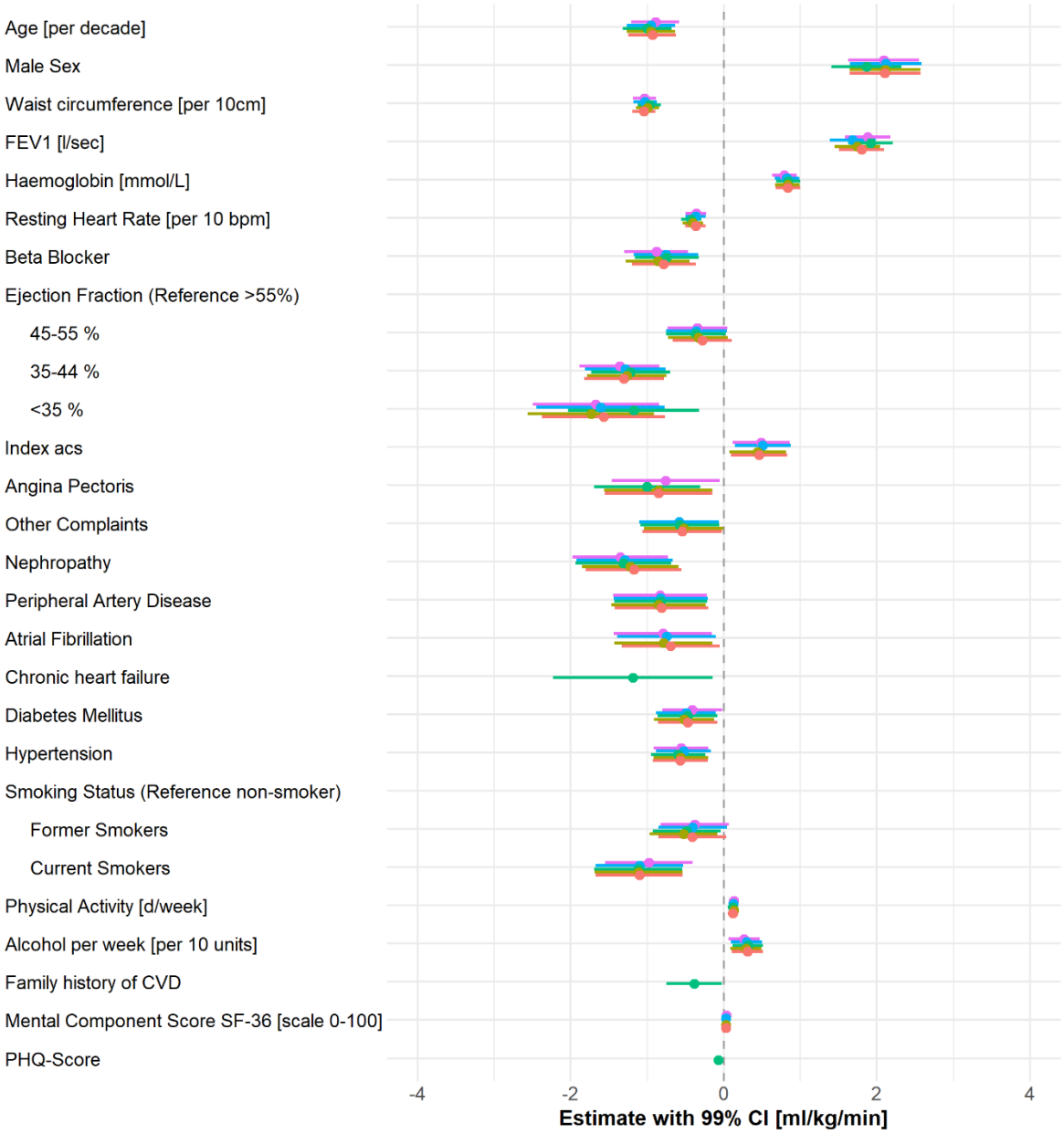
Peak VO2, patient anthropometric data (age, height, BMI, waist circumference, sex, blood pressure), socio-behavioural factors (education, volunteer work, form of living), index procedure (CABG, PCI, valve, stable CAD without revascularization), cardiovascular risk factors (diabetes mellitus, smoking, hypertension, hypocholesteraemia, 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 R^2 = 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/m2)		
<18.5 kg/m2	0.17	[-2.14; 2.49]
25-30 kg/m2	-1.27	[-1.81; -0.73] *
≥30 kg/m2	-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 pbm]	-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 R^2 = 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/m2)		
<18.5 kg/m2	-5.24	[-285.78; 275.31]
25-30 kg/m2	-1.02	[-1.71; -0.33] *
≥30 kg/m2	-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 pbm]	-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 R^2 = 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/m2)		
<18.5 kg/m2	-0.56	[-3.26; 2.14]
25-30 kg/m2	-1.63	[-2.77; -0.49]
≥30 kg/m2	-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 pbm]	-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.

*$p < 0.01$