

Towards better recovery

*Optimizing rehabilitation care in cardiac surgery:
the relevance of handgrip strength, physical activity, and quality of life.*

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General Introduction

The focus of this thesis is on the relationship between handgrip strength, physical activity, and quality of life in patients awaiting cardiac surgery. It also explores the potential role of preoperative interventions, such as prehabilitation, in optimising patient health before and after surgery. This includes the Heart-ROCQ programme, which offers a combined pre- and postoperative rehabilitation pathway.

Cardiac surgery patients

Cardiovascular disease is one of the leading causes of morbidity globally.¹ Cardiac surgery is one of the treatment options for cardiovascular disease. The goal of cardiac surgery is to restore blood supply and/or cardiac functioning, thereby relieve symptoms, prolong survival, and minimize the risk of complications.²⁻⁴ When coronary arteries are severely diseased and medical or interventional treatments are no longer an option, patients may undergo coronary artery bypass graft (CABG) surgery.^{2,5} During this CABG surgery other blood vessels are used to bypass blocked arteries, thereby restoring blood flow in the coronary arteries and adjoining tissue areas, thus relieving symptoms like chest pain and shortness of breath.² Another type of cardiac surgery involves surgery to repair or replace a heart valve. Heart valve surgery is performed on patients with severe malfunctioning of one or more heart valves (i.e., regurgitation and stenosis) which can impede blood flow through the heart, thereby weakening the overall pump function.^{3,6} Lastly, aortic surgery may be required in patients with severe dilatation of the aortic artery, which can impair blood pressure regulation and blood supply to the body.^{4,7} During this surgery, affected parts of the aorta are replaced with a graft.^{4,7} Untreated severe dilatation of the aorta can lead to dissections and tears, thereby increasing the risk of severe complications such as acute aortic regurgitation, myocardial ischemia, cardiac tamponade, acute stroke or malperfusion syndromes.^{4,7}

One of the challenges of research in this patient group, is its considerable heterogeneity. Patients undergoing cardiac surgery often have multiple risk factors that triggered the cardiac condition.²⁻⁵ Age is one of the main factors, as heart disease is more common in elderly.⁷ In addition, lifestyle factors such as obesity, smoking, hypertension, physical inactivity and sedentary behaviour are important risk factors as well.^{2,7,8} It is not uncommon for patients

with heart problems to also suffer from other comorbidities, such as diabetes or lung disease, further burdening overall health.^{2,4,5} Over the past decades, there has been a trend towards operating on increasingly complex patients often with multiple comorbidities, especially in CABG surgery.^{7,9,10} Thus, there are different types of surgery, different causes for the conditions and often comorbidities are present, so the approach to treatment will differ from patient to patient.

Taking into account the diagnosis, the mechanisms, and consequences of the disease, the decision to operate is recommended to be done based on the advice of a multidisciplinary Heart Team and shared-decision making with the patient.^{2-4,6,7} While some patients with cardiovascular disease require cardiac surgery, others are treated using less invasive approaches. Over the past decades, surgical and interventional techniques have developed.^{2,3} Minimally invasive surgical techniques, such as using an incision between the ribs in mitral valve surgery (the HeartPort technique) and using a smaller incision through the sternum with aortic valve surgery (mini-AVR), have reduced the impact compared to full sternotomy.³ In parallel, less invasive interventions, including the transcatheter aortic valve implantation (TAVI) and the use of percutaneous coronary intervention (PCI), have become increasingly common.^{2,3} These new interventional techniques may have contributed to a decline in the number of cardiac surgeries performed annually in the Netherlands from around 15,000 in 2013 to approximately 13,500 surgeries in 2023.¹¹ Although care of patients improved, cardiac surgery patients remain vulnerable to postoperative complications, such as arrhythmias, pulmonary dysfunction, and delirium.¹²⁻¹⁴ Therefore, to improve the outcome and reduce the societal burden of these surgeries, there is a need for understanding the multifactorial risk profile, including above mentioned complications, within the broader context of patients' physical and mental functioning and health both before and after cardiac surgery. The roles of handgrip strength, physical activity, and quality of life will be central concepts studied in this cardiac patient group.

Physical fitness

As a consequence of disease mechanisms, age, and lifestyle, many cardiac surgery patients are in poor physical (and mental) condition before surgery, which can negatively impact recovery and postoperative outcomes.¹⁵⁻¹⁸ This is especially true for patients with arteriosclerosis, who often have a higher inflammatory state prior to surgery, which may

contribute to an increased risk of postoperative cognitive dysfunction and impaired exercise capacity after surgery.^{19–22}

In this context, physical fitness has emerged as a key determinant of surgical resilience. Physical fitness is defined as “a set of attributes that are either health or skill-related. The degree of which people have these attributes can be measured with specific tests.”²³ “The health-related components of physical fitness are (a) cardiorespiratory endurance, (b) muscular endurance, (c) muscular strength, (d) body composition, and (e) flexibility.”²³ The skill-related attributes consist of agility, balance, coordination, speed, power, and reaction time.²³

A substantial proportion of cardiac surgery patients suffer from sarcopenia (~28%), a multifactorial geriatric syndrome characterised by progressive and generalised decline of muscle strength, muscle mass and physical performance.^{24,25} Sarcopenia has been associated with adverse postoperative outcomes, including longer hospital stays, a higher risk of serious cardiac events, and reduced long-term survival.^{26,27}

Closely related to sarcopenia is frailty, an age-related state of increased vulnerability decreasing the ability to maintain homeostasis, particularly in response to stressors such as major surgery.²⁸ Frailty has been linked to higher rates of morbidity and mortality in cardiac surgery patients and is becoming an important outcome for preoperative patient selection.^{3,6,7,28–30} Given that reduced muscle strength is central to both frailty and sarcopenia, it is emerging as a critical marker of physical fitness in this patient population. Consequently, evaluating and improving physical fitness prior to cardiac surgery may reduce sarcopenia and frailty and potentially contribute to improved surgical tolerance and faster recovery.

Handgrip strength

As a key component of physical fitness, muscle strength is often assessed using handgrip strength tests, which are widely used due to their simplicity and reliability.³¹ Handgrip strength is associated with all-cause death, cardiovascular disease and postoperative complications.^{32,33} Muscle strength is important for activities of daily living and therefore in individual independence and their reliance on care.³⁴ This is particularly relevant for vulnerable populations, such as the elderly and cardiac patients.

Recent updates to the World Health Organization (WHO) physical activity guidelines emphasize the importance of muscle strengthening activities, further underlining the clinical relevance of assessing muscle strength.³⁵ Handgrip strength is a commonly used measure in both older and clinical populations and has consistently been linked to health-related quality of life (HR-QoL) in older adults.²⁴

In cardiac surgery patients, handgrip strength is expected to decline during hospitalisation following surgery.^{33,36} While previous studies have examined preoperative handgrip strength as a predictor of outcomes, little is known about how handgrip strength changes over time and how these trajectories are associated with postoperative recovery and HR-QoL in this patient group. In addition, exploring the relationship between preoperative handgrip strength and cognitive functioning may offer further insights into patient vulnerability prior to cardiac surgery.

Physical activity

Physical activity, defined as any bodily movement produced by skeletal muscles that results in energy expenditure,²³ may improve physical fitness before cardiac surgery. Physical activity contributes to physical and mental wellbeing, prevention of non-communicable diseases, and overall quality of health, which is reflected in the World Health Organization's guidelines that recommend regular physical activity (consisting of the following dose-characteristics: context, form, frequency, duration and intensity) and a reduction in sedentary time for all individuals, regardless of health status.³⁵ Public health benefits from promoting physical activity, as it contributes to reducing the burden of the disease and lowering health care costs.³⁵ However, among specific patient populations, more research is needed on physical activity to develop appropriate guidelines.³⁷

Since physical inactivity is deemed a risk factor of cardiovascular disease, it is expected that cardiac surgery patients are less physically active than the healthy population.⁸ Chronic low-grade systemic inflammation is prevalent among cardiovascular patients, especially undergoing CABG surgery.²⁰ Physical inactivity is associated with this systemic inflammatory state, which has been linked to an exaggerated inflammatory response to surgical insults, thereby increasing the risk of postoperative cognitive, cardiovascular, and pulmonary dysfunction.^{20,21,38} Thus higher levels of physical activity may enhance a better

preoperative health status and modulate the inflammatory state, potentially improving postoperative outcomes and recovery.^{20,21,39–41} However, there is still a lack of understanding the role of physical activity and its dose-characteristics in health and quality of life in patients awaiting cardiac surgery; and on another note, no specific physical activity guidelines exist for this population.³⁵ Therefore, gaining insight into their physical activity levels is essential to inform tailored interventions and improve preoperative care.

Physical activity can be assessed through various methods, including questionnaires and portable activity monitors.^{42,43} Questionnaires are commonly used in larger populations, as they are easy and inexpensive to use.^{42,43} These questionnaires rely on self-reported perception of their physical activity levels, providing a subjective assessment.^{42,43} In contrast, more expensive and complex accelerometers, which are widely used as portable activity monitors, offer an objective measurement of physical activity by capturing body movements to estimate energy expenditure.^{42,43} Higher levels of preoperative physical activity and reducing sedentary time has been linked to better health outcomes, including mental well-being, the risk of cardiac surgery, postoperative complications, and hospitalization.^{44–47} It is therefore essential to investigate how both physical activity and exercise can be safely and effectively integrated into rehabilitation of patients awaiting cardiac surgery.

Postoperative rehabilitation as usual care

According to the WHO in 1948, health is not just the absence of disease or infirmity, but a state of complete physical, mental, and social well-being. This definition forms the basis of The International Classification of Functioning, Disability and Health (ICF) model, which provides a framework of health in multiple domains: body functions and structures, activities, and participation, with influence of personal and environmental factors.⁴⁸ Rehabilitation in this context should not only focus on treating symptoms, but also on reducing the impact of health conditions on daily life and supporting individuals in regaining participation. Furthermore, rehabilitation should be multidisciplinary in nature and aim to optimise physical, mental, and social well-being. Indeed, Dutch guidelines for exercise-based cardiac rehabilitation incorporated these goals.⁴⁹

Rehabilitation for cardiac surgery patients as part of usual care in the Netherlands consists of postoperative outpatient rehabilitation including exercise training and has been shown to

improve survival rates.⁵⁰ The definition of exercise is a structured part of the physical activity domain, it differs in the fact that exercise is planned, structured, repetitive and purposive to improve one or more components of physical fitness.²³ Postoperative rehabilitation is well-studied and clearly defined in the guidelines, and has been shown to reduce morbidity and mortality in cardiac patients.^{49,50} Usually, rehabilitation starts 3-6 weeks after discharge from the hospital with a duration of 6 weeks. This period of 3-6 weeks directly after hospitalization could be used for interventions. Indeed, postoperatively, early (inpatient) rehabilitation has been shown to be safe, and to improve exercise capacity and quality of life.^{51,52} However, the current guidelines in the Netherlands are still limited for early postoperative inpatient rehabilitation and are mainly focused on outpatient rehabilitation.⁴⁹ The Heart-ROCQ programme, which is being investigated in a currently ongoing RCT study, consists of both postoperative early inpatient and outpatient rehabilitation combined with preoperative rehabilitation.

Prehabilitation

Emergency cardiac surgery patients have little time for preoperative interventions, however, a substantial proportion of patients are on a waiting list and could potentially benefit from targeted preoperative rehabilitation (prehabilitation) during this waiting period before cardiac surgery. During the waiting period patients may experience further declines in physical, social, and psychological functioning, which also has been associated with mortality and morbidity.⁵³⁻⁵⁵ It is therefore important to investigate whether exercise capacity and muscle strength can be improved by providing prehabilitation to cardiac surgery patients.

Prehabilitation, including total body exercises, has gained increasing interest and has shown promising effects, especially in other populations such as patients undergoing orthopaedic and abdominal surgery.⁵⁶ Only small studies have been conducted in cardiac surgery patients, and pooled studies showed that prehabilitation improves exercise capacity, reduces length of hospital stay and lowers the risk of postoperative complications.^{40,41,57} Which elements and mechanisms that are responsible for the efficacy of these prehabilitation programmes is yet unknown. In addition, practical aspects such as compliance, form and actual exercise load has a great impact on the efficacy of such programmes and should be evaluated as well.⁵⁸ The additional value of preoperative rehabilitation should be compared to current standard care by evaluating in terms of physical fitness and cardiac complications, as well as mental wellbeing

and quality of life. In the context of rising healthcare demands and limited human and financial resources, preventive strategies such as prehabilitation may contribute to not only improved individual outcomes, but also to reduced pressure on the health care system and a more efficient use of available resources.

Quality of life and mental wellbeing

Quality of life (QoL) is becoming a more important variable to take into consideration for the decision to operate in cardiac patients.^{2-4,6} In clinical research, QoL is often assessed as health-related quality of life (HR-QoL), which reflects the patient's perceptions of the impact of the disease and treatment on their physical, social, and mental wellbeing.⁵⁹ Mental wellbeing significantly influences prognosis of cardiovascular disease, as depression, anxiety and stress have all been identified as risk factors for increased morbidity and mortality.² Among patients awaiting CABG surgery, symptoms of depression and anxiety are common (14-43%) and has been associated with longer hospital stay and higher mortality and morbidity rates.^{2,60}

While HR-QoL after aortic surgery may initially decline and gradually return to baseline, CABG surgery has been shown to improve HR-QoL.^{4,61} As previously discussed, higher levels of handgrip strength, physical activity, and participation in rehabilitation might be associated with improved HR-QoL. However, a more detailed understanding of these associations is still lacking in patients awaiting cardiac surgery. It is therefore important to assess preoperative levels of physical activity and handgrip strength, explore their association, and to determine to what extent they contribute to better postoperative outcomes and QoL. Targeting improvements in HR-QoL, preoperative health and postoperative recovery, the Heart-ROCQ programme offers pre- and postoperative rehabilitation to patients undergoing cardiac surgery.

Thesis aims

Cardiac surgery plays an important role in improving quality of life in patients with cardiovascular disease. With an aging population, rising health care demands, a significant number of cardiac surgeries performed, and a heterogeneous patient group, optimizing preoperative care has become increasingly important. Improvements of handgrip strength and

physical activity prior to surgery are assumed to reduce postoperative complications and accelerate recovery. However, evidence on the impact of these factors specifically in the vulnerable group of cardiac surgery patients remains limited. Given their vulnerability, careful assessment and monitoring are essential to ensure safety when implementing preoperative interventions. This thesis investigates the roles of handgrip strength and physical activity in the recovery of patients awaiting cardiac surgery, their association, and how these factors relate to health and quality of life. Furthermore, it explores the potential of prehabilitation programmes, including the feasibility of the Heart-ROCQ programme, which offers pre- and postoperative rehabilitation to this patient group. The findings from this thesis may help in the development of clinical guidelines and contribute to tailored prehabilitation programmes.

Outline of the thesis

Chapter 2 focuses on handgrip strength in relation to health-related quality of life of patients undergoing CABG surgery. It includes an analysis of trajectories of handgrip strength over time in this patient sample. In this prospective cohort study, preoperative risk factors, distinct trajectories of and change scores of handgrip strength and their relation to postoperative health-related quality of life are presented.

Chapter 3 describes the levels of subjective physical activity of CABG patients. Furthermore, this prospective pilot study evaluates the effects of preoperative subjective physical activity on handgrip strength and postoperative outcomes including quality of life and cognitive functioning.

Chapter 4 focuses on the evaluation of preoperative physical activity levels and dose-characteristics. This study involves a cross-sectional subanalysis of Chapter 3 using both a subjective and objective method for assessing physical activity.

Chapter 5 contains a feasibility study of pre- and postoperative physical rehabilitation for cardiac surgery patients. It examined safety, compliance to the physical component of the programme, and the training load and exercise capacity during training sessions.

Chapter 6 describes the protocol of the randomised controlled trial of pre-and postoperative rehabilitation compared to usual care. It describes the primary combined weighted endpoint of health-related quality of life and cardiac events. Moreover, secondary outcomes focusing on physical, social, and mental well-being are discussed.

Chapter 7 includes an analysis of subjectively and objectively measured physical activity and its association with handgrip strength in patients awaiting cardiac surgery. This study used baseline data of a cohort of Chapter 6.

Chapter 8 includes a summary and discussion of findings and insights from the studies included in this thesis and the study outcomes in a broader context.

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TITLE

Muscle strength trajectories and their association with postoperative health-related quality of life in patients undergoing coronary artery bypass grafting surgery – a prospective cohort study

AUTHORS

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ABSTRACT

Background: Patients with sarcopenia have a higher risk of poor recovery after coronary artery bypass grafting (CABG). Little is known about the impact of changes in muscle strength (the primary indicator for sarcopenia) on health-related quality of life (HR-QoL). This study aimed to (1) identify subgroups with different muscle strength trajectories, (2) identify differences in preoperative risk factors among trajectory group membership, and (3) explore their prognostic value on postoperative HR-QoL in patients undergoing CABG.

Methods: In this prospective observational study 131 patients undergoing elective CABG completed grip strength tests and HR-QoL questionnaires. Latent Class Growth Mixture Modelling (LCGMM) was used to identify clinically relevant trajectories (> 5% of study population) for weight-normalised grip strength, measured at admission, 3 days, and 6 months after surgery. Differences between trajectory group membership at baseline were evaluated. The impact of trajectory group membership on postoperative HR-QoL was evaluated with multiple linear regression models.

Results: Due to low numbers (n = 15), female patients were excluded from LCGMM and subsequent statistical analyses. In males (n = 116), we identified two main weight-normalised grip strength trajectories: a “stable average” trajectory with a slight decline immediately post-surgery and recovery to preoperative levels (n = 85) and a “high” trajectory with a considerable immediate decline after surgery but followed towards a

47 higher level of recovery compared to preoperative level (n = 27). The “stable average”
48 patients were older (68 vs. 57 years; P = 0.003), had more diabetes (27% vs. 4%; P = 0.01)
49 and had a higher BMI (27.8 vs. 24.8; P = 0.005) compared to the “high” group. After
50 correction for age, diabetes, and baseline HR-QoL, group trajectory membership was not
51 associated with postoperative HR-QoL, yet an increase in individual change scores of
52 weight-normalised grip strength was associated with a better postoperative HR-QoL. We
53 also identified one small trajectory group (n = 4, ≤5%).

54 **Conclusions:** This study showed two relevant weight-normalised grip strength trajectories
55 in male patients undergoing CABG, varying in important preoperative risk factors. While
56 change scores of grip strength per weight did predict postoperative HR-QoL, the trajectory
57 subgroups could not predict postoperative HR-QoL. Future research should focus on female
58 patients, reacting potentially different on CABG and/or rehabilitation treatment.

59

60 **Trial registration:** NCT03774342, 12-12-2018.

61

62 **KEYWORDS**

63 Cardiac surgical procedures, Health status, Quality of life, Sarcopenia, Muscular atrophy,
64 Muscle strength, Muscle weakness, Therapeutics, Sex

65

66

67 BACKGROUND

68 Approximately 28% of patients undergoing coronary artery bypass grafting (CABG) have
69 sarcopenia [1]. This multifactorial geriatric syndrome is considered a muscle disease with
70 progressive and generalised loss of skeletal muscle strength as a principal determinant [2].
71 Additional components of sarcopenia are declines in muscle mass, muscle quality and
72 physical performance [2]. Cardiac surgical patients with sarcopenia have longer hospital
73 stays, a higher risk of major adverse cardiac events, and decreased long-term survival after
74 cardiac surgery [3, 4]. Since sarcopenia is associated with ageing and more elderly patients
75 are listed for major cardiac surgery, the role of sarcopenia will further increase in cardiac
76 surgical treatment and rehabilitation care. This requires health-care professionals to search
77 for optimal interventions to prevent adverse outcomes and improve patient-reported
78 outcome measures, such as health-related quality of life (HR-QoL) [5].

79 As in many other research areas, HR-QoL is, nowadays, seen as an important
80 outcome in cardiac surgery [6]. It reflects patients' experience of the impact of the disease
81 or treatment on their individual health on physical, social, and mental dimensions [7]. HR-
82 QoL is, given the decrease in postoperative mortality, a useful complement to traditional
83 clinical outcomes and is widely used, for example, when deciding whether or not to operate
84 or when evaluating rehabilitation programmes [6, 8, 9]. Monitoring sarcopenia and
85 understanding of the impact of sarcopenic parameters in CABG and how it affects post-
86 operative HR-QoL, are needed to enhance the development of effective interventions in
87 patients undergoing CABG [7].

88 The principal physical outcome of sarcopenia, muscle strength, is determined by
89 muscle mass, quality, volume, length and activation level, and as such among others
90 associated with aging and/or physical inactivity [1, 10]. (Weight-normalised) grip strength
91 is a widely used indicator of muscle strength in elderly or clinical populations and can be
92 easily and reliably determined with an inexpensive hand-held dynamometer [11, 12]. A

person's grip strength has prognostic value for all-cause death, cardiovascular disease, and postoperative complications after cardiac surgery [13, 14].

Despite a clear positive association between grip strength and HR-QoL is acknowledged in elderly [1], this association is not yet confirmed in CABG patients. Although, several studies have found associations between other physical outcomes, such as left ventricular function or unstable angina, and HR-QoL in CABG patients [6], a recent study found no association between preoperative or acute postoperative grip strength with immediate postoperative HR-QoL in this patient group [15]. This study, however, did not study associations between changes in preoperative and postoperative grip strength and HR-QoL. Interestingly, changes in preoperative and postoperative grip strength, or grip strength recovery, have been more predictive of postoperative complications after cardiac surgery than using only measures of preoperative grip strength [16]. Monitoring changes in grip strength over time thus provides a more important measure of surgical outcome, than just a single cross-sectional grip strength measurement.

Such changes in pre- and postoperative scores are often compared with each other on group level (mean $\pm$ SD), thus evaluating a single trajectory of the whole group. Since most groups consists of patients with various characteristics such as gender, preoperative risk factors, surgery parameters and so on, this approach may mask important diversity in recovery among patients. This heterogeneity of 'increasers' and 'decreasers' may be missed by evaluating only group means. In contrast, latent class growth mixture modelling (LCGMM) is a good alternative to determine subgroups within a given population with similar time courses or trajectories [17]. LCGMM may also provide more insight into how grip strength develops over time within potential subgroups, and how these are associated to postoperative recovery, functioning and HR-QoL. The present study aimed to (1) identify distinct trajectories of the development of grip strength over time (i.e., preoperative until 6 months after CABG); (2) identify differences in preoperative risk factors and preoperative

119 sarcopenia parameters between trajectory groups; and (3) explore the prognostic value of
120 these distinct subgroups on postoperative HR-QoL.

121

122 METHODS

123 *DESIGN OVERVIEW*

124 This prospective single-centre cohort study was conducted in the University Medical Center
125 Groningen (UMCG). Patients were identified and informed by the attending doctor or nurse
126 practitioner on the date of admission, usually the day before surgery. After informed
127 consent, patients were included and preoperative measurements were obtained.
128 Postoperative assessment of muscle strength was performed in the hospital three days after
129 surgery (short-term) and 6 months after surgery (long-term) at the patients' homes. On
130 these time points we also performed bioelectrical impedance analysis (BIA) as a potential
131 indicator of muscle mass and quality. HR-QoL was measured at baseline and 6 months after
132 surgery. All methods were performed in accordance with the Guidelines for Reporting on
133 Latent Trajectory Studies (GRoLTS-checklist) and the STROBE-guidelines [18].

134

135 *ELIGIBILITY CRITERIA*

136 Adult patients admitted for elective, on-pump CABG in the University Medical Center
137 Groningen, the Netherlands were considered for the study. Exclusion criteria were previous
138 cardiac surgery and combined surgery, pre-existing neurological condition (i.e., dementia,
139 stroke, epilepsy), psychiatric illness, pre-existing muscular diseases, or missing extremities
140 (not possible to measure muscle mass of the extremities) and presence of an ICD or hip
141 replacements because of interference with BIA equipment. When patients were likely to
142 have difficulty understanding the Dutch language, they were also excluded from the study.

143

144 *OUTCOME MEASURES*

145 Grip strength as measure of muscle strength was tested with a Jamar Hydraulic hand-held
146 dynamometer (Model 5030J1), which has good to excellent ($r > 0.80$) test-retest reliability
147 [12]. To become familiar with the grip strength test, patients were asked to perform one
148 practice-trial followed by three consecutive tests for each hand. The highest score of
149 patients' dominant hand of the handgrip test, which was normalized for preoperative
150 weight, was used for analyses. Reference values were used to interpret the magnitude of grip
151 strength [19].

152 HR-QoL was measured using the valid and reliable RAND-36 version-2
153 questionnaire [20]. This questionnaire is a widely used and validated instrument containing
154 eight health domains: physical functioning (PF, ten items), social functioning (SF, two
155 items), role limitations due to physical health problems (RP, four items), role limitations
156 due to emotional problems (RE, three items), mental health (MH, five items), vitality (V,
157 two items), bodily pain (BP, two items), and general health perception (GH, five items).
158 Each domain is transformed to a scale between 0 and 100, a higher score is equals better
159 health. Two summarized scores were calculated: a physical component score (PCS, which
160 included PF, RP, BP, and GH) and a mental component score (MCS, which included MH,
161 RE, SF, and V) [20, 21].

162

163 *PREOPERATIVE RISK FACTORS AND PREOPERATIVE SARCOPENIC PARAMETERS*

164 Preoperative risk factors, including age, sex, body mass index, European System for Cardiac
165 Operative Risk Evaluation II (EuroSCORE II), and the presence of comorbidities such as
166 diabetes, pulmonary disease, arterial vascular disease, renal disease, and impaired

167 ventricular function, were retrieved from the electronic patient medical records [21–23].
168 Definitions of these risk factors are included in Additional file 1: Table S1.

169 In addition to muscle strength, preoperative sarcopenic parameters included the
170 secondary parameters of sarcopenia: muscle quantity and quality. Bioelectrical Impedance
171 analysis at 50 kHz (BIA 101 Anniversary edition, AKERN, Florence, Italy) was used to
172 determine the so-called appendicular skeletal muscle mass (ASMM) as an estimate of
173 muscle quantity and BIA-derived phase angle (PA) as an estimate of muscle quality.
174 Electrodes were placed on the hand and foot at the side while lying supine. The equation
175 used are supplied in Additional file 1.

176

177 *PERIOPERATIVE AND POSTOPERATIVE CHARACTERISTICS*

178 Perioperative data included duration of surgery, time on cardiopulmonary bypass (CPB),
179 cross clamp time, and the number of (arterial) grafts. The following postoperative
180 complications were collected: delirium, atrial fibrillation, myocardial infarction, surgical re-
181 exploration, deep sternal wound infection, and renal failure all within 30 days after surgery
182 and stroke/transient ischemic attack within 72h after surgery [9, 21, 24–26]. Additional
183 postoperative variables were duration of stay at the Intensive Care Unit and discharge
184 destination. The definitions are included in the Additional file 1: Table S2.

185

186 *STATISTICAL ANALYSES*

187 Descriptive statistics were used to present pre-, peri-, and postoperative characteristics. To
188 identify subgroups of distinct trajectories of grip strength development over time LCGMM
189 was performed using the ‘lcm’ package in R (V. 4.1.2) [27]. The default mode of the
190 argument ‘idiag’ of the ‘lcm’ package was used, indicating unstructured variance-

191 covariance matrix for the random effects [27]. An exploratory approach was chosen,
192 meaning that as many classes as possible that yielded clinical relevant solutions were
193 estimated [28]. First, quadratic trajectories were tested, which was expected to be the best
194 representing pattern to the data [28]. Then, linear trajectories were tested for further
195 exploration. Also, Latent Class Growth Modelling (LCGM, i.e., no allowance of within-class
196 variances) were evaluated, however these models showed poorer fit with the data compared
197 to LCGMM models (data not shown). Therefore, LCGMM models were chosen in favour of
198 LCGM models. Time was coded '0 for preoperative', '1 for three days', and '2 for 6 months'.
199 The 'grid search' function was used, in which the number of random start values was set on
200 100 with 30 final iterations. The model was selected based on model fit indices and clinical
201 interpretability. The model fit indices included (1) a lower Bayesian Information Criteria
202 (BIC), in which a difference of 10 points was considered as sufficient improvement [29], and
203 (2) a higher average posterior probability of trajectory group membership (i.e. the
204 probability to belong to a class), which should be greater than or equal to 0.7 for each
205 subgroup [17]. Models with clinically interpretable solutions and larger groups were
206 selected in favour of uninterpretable solutions and smaller groups [30]. Small trajectory-
207 groups ($\leq 5\%$) were not included in subsequent statistical analyses.

208 After model selection, differences in preoperative risk factors, sarcopenia
209 parameters, and HR-QoL were first analysed between the identified subgroups using
210 Pearson's chi-squared test (binary or categorical variables) or (multiple or repeated)
211 ANOVA using post-hoc tests with Bonferroni correction (continuous variables). Degrees of
212 freedom were adjusted according to Greenhouse-Geisser when sphericity was violated. For
213 binary or categorical variables, the Fisher's exact test was used, when $> 20\%$ of the cells had
214 an expected count less than 5. For continuous variables, the Kruskal-Wallis test with
215 Dunn's multiple-comparison post-hoc test (using a Bonferroni correction) was used when
216 normality could not be assumed.

217 Second, the impact of trajectory group membership on postoperative HR-QoL at 6
218 months was evaluated by three (multiple) linear regression models. In the first model,
219 univariable analyses were conducted in which trajectory group membership of grip strength
220 (independent) was related to postoperative HR-QoL (dependent). The association was
221 adjusted for age in model 2 and adjusted for the risk factors diabetes and baseline HR-QoL
222 in model 3.

223 Additional analyses were performed to determine whether more ‘traditional’
224 statistical approaches of change scores would provide a stronger or weaker predication of
225 postoperative HR-QoL by grip strength per weight. Individual change scores for weight-
226 normalised grip strength were calculated as the value after 6 months divided by the
227 preoperative value. Subsequently, the same regression analyses were performed with the
228 change score as independent variable.

229 All analyses were performed separately for males and females, because of the
230 different relationship between sarcopenic parameters and HR-QoL by sex [6, 31]. All
231 analyses were tested 2-sided and p-values of < 0.05 were considered statistically significant.
232 All data were analysed using Stata SE/17.0 (StataCorp LLC, revision April 2021, Lakeway,
233 TX, USA) and SPSS version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for
234 Windows, Armonk NY).

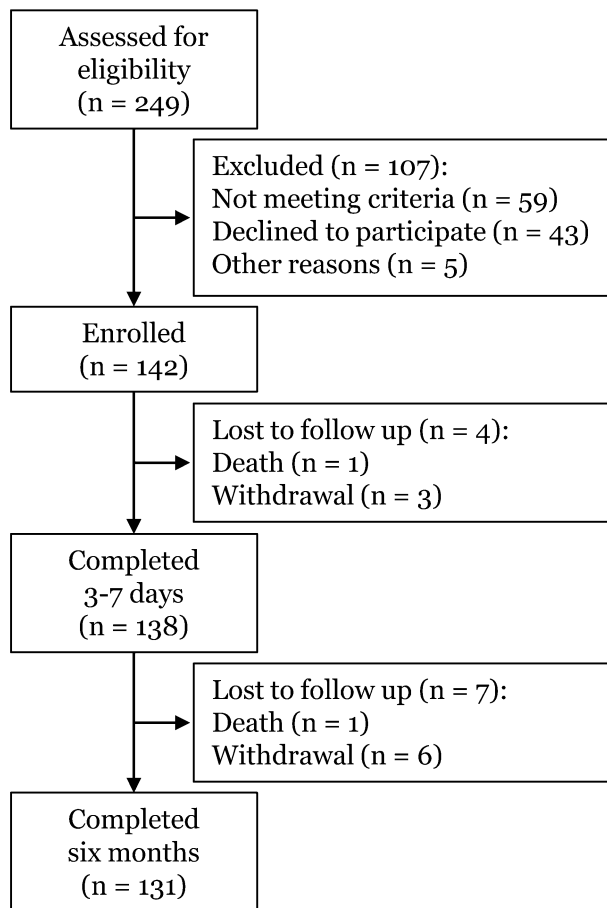


Fig. 1 Flow chart of the present study.

RESULTS

A total of 142 patients undergoing elective CABG enrolled in this prospective study between October 2018 and July 2019 (Fig. 1). Eleven patients were excluded from analysis, because two patients died and nine patients were lost to follow up (Additional file 1: Table S3). Table 1 and 2 present the baseline, peri-operative, and postoperative characteristics. One male did not dare to perform the grip strength test on day three after surgery. In addition, due to logistical reasons, this measurement could not be performed on one female, as she was transferred to another hospital as part of routinely standard care before measurements could be performed. Another three patients did not perform the grip strength test with the dominant hand at baseline, therefore the measurements of the non-dominant hand of these

248 patients were used. In 33 patients (25%), the radial artery of the non-dominant hand was
249 used for grafting. As a result, only one male performed the grip strength test with the hand
250 whose arterial graft had been used. This patient did not show outlying grip strength values.
251 Unfortunately, we were unable to obtain useful subsequent BIA measurements due to
252 technical and methodological reasons. Direct post-operative measurements showed very
253 high variation and were not reproducible and device malfunction made a number of
254 measurements at 6 months. Due to low numbers of female patients ($n = 15$), LCGMM and
255 the subsequent statistics (between-groups differences and linear regression) could not be
256 performed in females. Additional file 2: Fig. S4 shows the individual changes of grip
257 strength per weight and HR-QoL for females.

258

259

260 **Table 1** Baseline characteristics of patients undergoing coronary artery bypass graft

Baseline characteristics	Female n = 15	Male n = 116	Total group n = 131
Age (years)	65 (58, 68)	67 (56, 72)	66 (56, 72)
BMI (kg/m ²)	30.5 (28.0, 35.1)*	26.8 (24.5, 30.0)	27.1 (24.8, 30.8)
EuroSCORE II	1.7 (1.3, 2.4)	1.5 (1.1, 2.2)	1.5 (1.1, 2.2)
Diabetes mellitus	4 (27%)	26 (22%)	30 (23%)
Pulmonary disease	3 (20%)	11 (10%)	14 (11%)
Arterial vascular disease	0 (0%)	7 (6%)	7 (5%)
Renal disease	1 (7%)	12 (10%)	13 (10%)
LVEF			
> 50%	0 (0%)	1 (1%)	1 (1%)
30-50%	4 (27%)	35 (30%)	39 (30%)
< 30%	11 (73%)	80 (69%)	91 (70%)
Preoperative sarcopenia parameters			
Grip strength (N/kg)	2.4 ± 0.6*	4.9 ± 1.1	4.6 ± 1.3
ASMM (kg)	22.2 (20.2, 22.8)*	26.0 (23.8, 28.2) ¹	25.6 (22.9, 28.0)
ASMM (kg/m ²)	7.5 (7.2, 7.9)*	8.1 (7.4, 8.7) ¹	7.9 (7.4, 8.6)
Phase angle	6.2 ± 1.1	6.6 ± 0.9 ¹	6.6 ± 0.9
Resistance	470.3 ± 35.0*	430.2 ± 63.5 ¹	434.9 ± 62.1
Reactance	50.7 ± 9.5	49.6 ± 7.5 ¹	49.7 ± 7.7
Preoperative Health-related quality of life			
PCS baseline ^{2,3}	51.1 (37.9, 61.8)*	65.6 (52.8, 81.2)	63.7 (50.1, 78.1)
MCS baseline ^{2,4}	61.9 (51.6, 71.8)*	76.8 (61.3, 90.1)	73.8 (60.1, 87.8)
PCS 6 months	68.1 (59.4, 92.5)	75.0 (60.9, 87.5)	74.9 (60.3, 88.4)
MCS 6 months	73.4 (50.2, 88.1)	80.3 (64.6, 88.9)	79.4 (64.5, 88.4)

261 Values are presented as n (% yes), mean±SD or median (IQR).
262 ASMM appendicular skeletal muscle mass, BMI body mass index, IQR interquartile range,
263 LVEF left ventricular ejection fraction, MCS mental component score, PCS physical component
264 score.
265 ¹ Value for three patients unknown.
266 ² Score range: 0-100; a higher score is equivalent to better health-related quality of life.
267 ³ Physical component score for two patients unknown.
268 ⁴ Mental component score for one patient unknown.
269 * Significantly different compared to male patients (P < 0.05).

270
271

272 **Table 2** Peri-operative and postoperative characteristics of patients undergoing coronary
273 artery bypass graft

Peri-operative characteristics	Female n = 15	Male n = 116	Total group n = 131
Number of grafts			
One graft	0 (0%)	1 (1%)	1 (1%)
Two grafts	15 (100%)	113 (97%)	128 (98%)
Three grafts	0 (0%)	2 (2%)	2 (2%)
Number of arterial grafts			
No arterial graft	0 (0%)	3 (3%)	3 (2%)
Use of 1 arterial graft	11 (73%)	81 (70%)	92 (70%)
Use of 2 or more arterial grafts	4 (27%)	32 (27%)	36 (28%)
Surgical time (min)	244 (215, 279)	255 (229, 279)	253 (227, 279)
CPB-time ¹ (min)	107 (90, 121)	104 (85, 125)	106 (86, 123)
Cross clamp time ² (min)	60 (52, 78)	61 (47, 77)	61 (48, 78)
Postoperative characteristics			
Delirium	1 (7%)	5 (4%)	6 (4.6%)
Atrial fibrillation	0 (0%)	14 (12%)	14 (10.7%)
Myocardial infarction	0 (0%)	1 (19%)	1 (0.8%)
Surgical re-exploration	0 (0%)	2 (2%)	2 (1.5%)
Deep sternal wound infection	0 (0%)	2 (2%)	2 (1.5%)
Stroke/TIA	0 (0)	0 (0)	0 (0)
Renal failure	0 (0)	0 (0)	0 (0)
Prolonged ICU stay	4 (27%)	30 (26%)	34 (26%) ³
Discharge destination			
Home	6 (40%)*	88 (76%)	94 (71.8%)
Other hospital	8 (53%)	10 (9%)	18 (13.7%)
Rehabilitation Centre	1 (7%)	18 (16%)	19 (14.5%)

274 Values are presented as n (% yes) or median (IQR).

275 CPB cardiopulmonary bypass, ICU intensive care unit, IQR interquartile range, TIA transient
276 ischemic attack.

277 ¹ CPB-time for one patient unknown.

278 ² n = 124, 7 patients no use of CPB, but surgery was performed on beating heart.

279 ³ median (IQR): 21 (18, 24).

280 * Significantly different compared to male patients (P < 0.001).

281

282 MALE GRIP STRENGTH PER WEIGHT TRAJECTORIES

283 For males, the model fit indices for quadratic and linear LCGMM models with one to five
284 trajectories are presented in Additional file 2: Table S4. Figures of the distinct trajectories of
285 these models are shown in Additional file 2: Figs. S1 and S2. As expected, the models with

286 quadratic trajectories showed better statistical fit compared to models with linear
287 trajectories.

288 Based on the BIC, a two-class quadratic solution could be considered as best fit
289 model, but class 1 consisted only of 3%, which was too small to be considered as clinically
290 relevant (Additional file 2: Table S4, Figs. S1 and S2). Therefore, a three-class model was
291 selected, which identified the two main trajectories: “stable average” grip strength (n = 85,
292 73%), “high” grip strength (n = 27, 23%), and one small trajectory: “high-low” grip strength
293 (n = 4, 3%). The three trajectory groups are visualized in Fig. 2 and Additional file 2: Fig.
294 S3. The small “high-low” group was not statistically explored ($\leq 5\%$). In the “stable average”
295 group, grip strength per weight showed a slight but significant decrease (from 4.5 to 4.2
296 N/kg, P-value < 0.001, $F(1.8,153.0) = 23.3$, Fig. 2) and increased to the same preoperative
297 level at 6 months after surgery (from 4.5 to 4.5 N/kg, P-value = 1.000, $F(1.8,153.0) = 23.3$).
298 The “high” grip strength group had the highest preoperative values but showed a
299 considerable and significant decrease of 13% after surgery (from 6.1 to 5.3 N/kg, P-value <
300 0.001, $F(1.6,19.0) = 98.2$). Subsequently, the values rose to a significantly higher level
301 compared to preoperatively (from 6.1 to 6.8 N/kg, P-value < 0.001, $F(1.6,19.0) = 98.2$).
302 Table 3 shows the preoperative risk factors and preoperative sarcopenia parameters for the
303 2 main trajectories. The “stable average” patients were significantly older (68 vs. 57 years; P
304 = 0.003), had more diabetes (27% vs. 4%; P = 0.01) and had a higher BMI (27.8 vs. 24.8; P
305 = 0.005) compared to the “high” grip strength group. In contrast, the left ventricular
306 ejection fraction was higher in the “stable average” group compared to the “high” grip
307 strength group. Also, ASMM seemed higher in the “stable average” group compared to the
308 “high” grip strength group, but this difference was not significant (8.2 vs. 7.7; P = 0.069).
309 The preoperative sarcopenic parameters, grip strength, phase angle, and reactance were
310 significantly lower in the “stable average” group compared to the “high” grip strength group
311 (P < 0.05, Table 3).

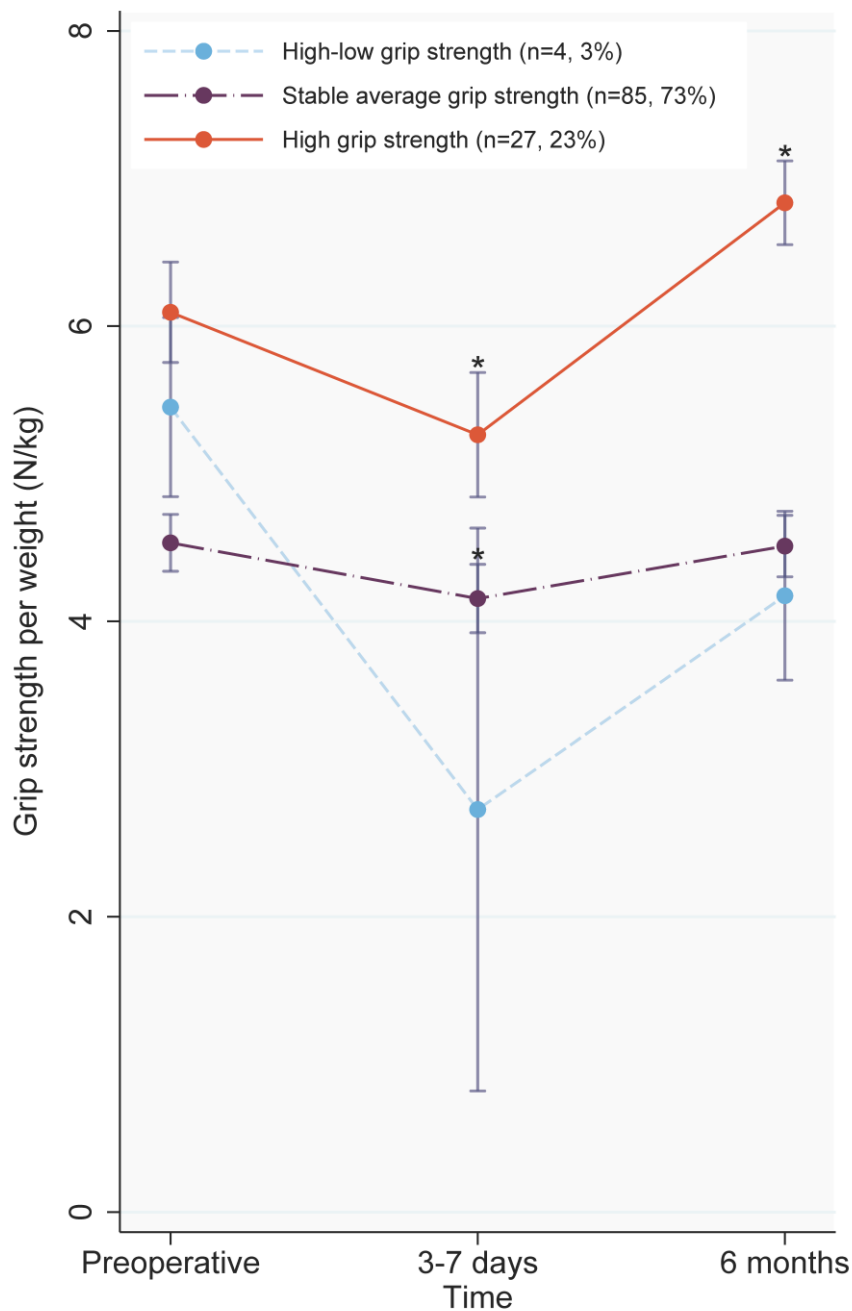


Fig. 2 Three identified (weight-normalised) grip strength trajectories in men undergoing coronary artery bypass graft. Mean $\pm$ 95% Confidence Interval are presented; * Significantly different compared to preoperative (P-value < 0.001) Preoperative: 2 (IQR: 1-3) days before surgery; 3-7 days: 3 (IQR: 3-3) days after surgery; 6 months: 193 (IQR: 188-201) days after surgery. IQR: interquartile range.

Table 3 Differences in preoperative risk factors and preoperative sarcopenia parameters among trajectory group membership

	High-low grip strength n = 4 (3%)	Stable average grip strength n = 85 (73%)	High grip strength n = 27 (23%)	P-value ¹
Preoperative risk factors				
Age (years)	63.0 (57.5, 71.5)	68.0 (58.0, 74.0)	57.0 (51.0, 68.0)	0.003 ²
BMI (kg/m ²)	27.5 (26.3, 29.1)	27.8 (25.6, 30.9)	24.8 (21.7, 26.1)	0.005 ²
Diabetes mellitus	2 (50%)	23 (27%)	1 (4%)	0.010 ³
Pulmonary disease	0 (0%)	9 (11%)	2 (7%)	1.000 ⁴
Arterial vascular disease	0 (0%)	7 (8%)	0 (0%)	0.190 ⁴
Renal disease	0 (0%)	11 (13%)	1 (4%)	0.290 ⁴
LVEF = < 50%	0 (0%)	22 (26%)	14 (52%)	0.012 ³
EuroSCORE II	1.7 (1.4, 2.3)	1.5 (1.1, 2.3)	1.3 (1.1, 1.9)	0.093 ²
Preoperative sarcopenia parameters				
Grip strength (N/kg)	5.5 ± 0.4	4.5 ± 0.9	6.1 ± 0.9	<0.001 ⁵
ASMM (kg)	26.0 (23.0, 27.1)	26.1 (24.4, 28.8)	24.7 (22.9, 27.4)	0.110 ²
ASMM (kg/m ²)	7.8 (7.2, 8.8)	8.2 (7.6, 8.8)	7.7 (7.3, 8.4)	0.069 ²
Phase angle (PA)	6.8 ± 0.7	6.5 ± 0.9	7.0 ± 0.9	0.030 ⁵
Resistance (Rz)	456.1 ± 77.3	427.7 ± 65.7	434.4 ± 54.8	0.640 ⁵
Reactance (Xc)	54.6 ± 8.2	48.4 ± 7.1	52.7 ± 7.6	0.010 ⁵
Preoperative Health-Related quality of life				
PCS baseline ⁶	62.6 (45.6, 75.6)	63.7 (53.8, 78.5)	70.3 (57.5, 83.4)	0.280 ²
MCS baseline ⁶	78.6 (46.4, 95.5)	76.9 (62.3, 90.1)	73.3 (59.8, 83.4)	0.510 ²
PCS 6 months ⁶	57.2 (50.6, 74.7)	73.6 (60.6, 88.6)	77.2 (65.9, 86.9)	0.630 ²
MCS 6 months ⁶	63.6 (35.5, 82.5)	80.9 (69.2, 89.7)	75.8 (57.8, 85.6)	0.200 ²

Values are presented as n (% yes), median (IQR), or mean ± SD.

ASMM appendicular skeletal muscle mass, BMI body mass index, IQR interquartile range, LVEF left ventricular ejection fraction, MCS mental component score, PCS physical component score.

¹ Difference between “stable average” and “high” grip strength trajectory.

² Wilcoxon rank-sum.

³ Pearson’s chi squared test.

⁴ Fisher’s exact test.

⁵ Two sample t test.

⁶ Score range: 0-100; a higher score is equivalent to better health-related quality of life.

IMPACT OF TRAJECTORY GROUP MEMBERSHIP ON POSTOPERATIVE HR-QoL

The group comparison in Table 3 showed no statistical differences for postoperative HR-QoL. Results of the (multiple) regression analysis of the association between trajectory group membership and postoperative HR-QoL (Table 4) stressed the absence of an

association between trajectory group membership and HR-QoL, also after (significant) correction for age, diabetes, and baseline HR-QoL.

Table 4 Linear regression parameters for associations of ‘grip strength per weight’-trajectory membership with postoperative health-related quality of life after coronary artery bypass grafting

	Grip strength per weight (N/kg)	Trajectory		
		Physical component score		
		Beta	95% CI	P-value
Model 1: Univariable	Stable vs high grip strength	-0.065	-0.254 to 0.124	0.496
Model 2: Age	Stable vs high grip strength	-0.058	-0.256 to 0.139	0.584
	Age	-0.025	-0.222 to 0.172	0.803
Model 3: Age, HR-QoL, and DB	Stable vs high grip strength	0.074	-0.099 to 0.248	0.398
	Age	-0.163	-0.328 to 0.008	0.061
	Diabetes	-0.340	-1.216 to -0.410	<0.001
	Baseline PCS or MCS	0.428	0.261 to 0.585	<0.001
		Mental component score		
		Beta	95% CI	P-value
		Beta	95% CI	P-value
Model 1: Univariable	Stable vs high grip strength	0.099	-0.089 to 0.287	0.300
Model 2: Age	Stable vs high grip strength	0.054	-0.140 to 0.248	0.583
	Age	0.161	-0.033 to 0.355	0.103
Model 3: Age, HR-QoL, and DB	Stable vs high grip strength	0.099	-0.059 to 0.256	0.218
	Age	-0.009	-0.164 to 0.146	0.912
	Diabetes	-0.259	-0.405 to -0.103	0.001
	Baseline PCS or MCS	0.569	0.412 to 0.708	<0.001

CI Confidence Interval, HR-QoL Health-Related Quality of Life, DB Diabetes, MCS mental component score, PCS physical component score.

ADDITIONAL ANALYSES

In contrast to trajectory membership, the individual relative change score for weight-normalized grip strength (i.e., values of 6 months divided by baseline) was positively associated with the PCS of postoperative HR-QoL but was not associated with the MCS of postoperative HR-QoL (Table 5). These associations were also shown after correction for age, diabetes, and baseline scores of the PCS and MCS.

Table 5 Linear regression parameters for associations of ‘grip strength per weight’-change scores (N/kg) with postoperative health-related quality of life after coronary artery bypass grafting

	Grip strength per weight (N/kg)	Physical component score		
		Beta	95% CI	P-value
Model 1: Univariable	Relative change scores ¹	0.263	0.079 to 0.444	0.005
Model 2: Age	Relative change scores ¹	0.262	0.076 to 0.446	0.010
	Age	-0.008	-0.192 to 0.177	0.935
Model 3: Age, HR-QoL, and DB	Relative change scores ¹	0.216	0.058 to 0.369	0.007
	Age	-0.107	-0.260 to 0.051	0.185
	Diabetes	-0.298	-1.090 to -0.334	<0.001
	Baseline PCS or MCS	0.408	0.246 to 0.559	<0.001
		Mental component score		
		Beta	95% CI	P-value
Model 1: Univariable	Relative change scores ¹	0.040	-0.149 to 0.229	0.677
Model 2: Age	Relative change scores ¹	0.063	-0.125 to 0.251	0.509
	Age	0.184	-0.004 to 0.372	0.055
Model 3: Age, HR-QoL, and DB	Relative change scores ¹	0.047	-0.101 to 0.192	0.535
	Age	0.029	-0.122 to 0.178	0.711
	Diabetes	-0.226	-0.368 to -0.075	0.003
	Baseline PCS or MCS	0.571	0.413 to 0.710	<0.001

CI Confidence Interval, *HR-QoL* Health-Related Quality of Life, *DB* Diabetes.

¹ Value 6 months divided by preoperative value

DISCUSSION

The aim of this study was to identify different trajectories of weight-normalised muscle strength in patients undergoing CABG. Subsequently, the characteristics of these trajectories and their prognostic value on postoperative HR-QoL were examined, although this was not possible in the small group of females (n = 15). In males (n = 116), we identified two main trajectories. In 85 patients (73%) we observed a “stable average” pathway with a slight decrease followed by recovery to preoperative levels. In 27 patients (23%) we saw a “high” trajectory with a significant decrease of 13% immediately after surgery but a stronger recovery compared to preoperative levels. Preoperative risk factors (i.e., sarcopenic parameters, age, diabetes, and obesity), were more prevalent in the “stable average” trajectory group than in the “high” grip strength group. Trajectory group membership was,

369 however, not a significant predictor of postoperative HR-QoL, nor for physical or mental
370 component scores. Individual change scores in weight-normalized grip strength were
371 however significantly associated with HR-QoL, also after correction for age, diabetes, and
372 baseline HR-QoL.

373 Two main and a small subgroup were defined with distinct quadratic time courses.
374 The slight decrease in grip strength in largest trajectory group (73%) is comparable with the
375 observations by Fu and colleagues [16] in which grip strength of cardiac surgical patients
376 was almost fully recovered at the third postoperative day. Similarly, Teng and colleagues [3]
377 showed a stable trajectory of grip strength up to one year after cardiac surgery. In contrast,
378 Da Silva and colleagues [14] showed a significantly reduced grip strength at hospital
379 discharge in cardiac surgical patients. Such decline was also seen in the second subgroup;
380 the “high” grip strength group (23%). This group had preoperatively a higher score
381 compared to healthy age-matched references [19], suggesting a positive patient selection. A
382 relatively large decline in muscle strength was seen in this group. However, this group
383 showed a high capacity to recover as the values at 6 months were higher compared to the
384 preoperative values. The small “high-low” group ($n = 4$) seemed - despite having a high
385 preoperative grip strength - to follow a less favourable trajectory, as the grip strength
386 decreased severely immediately after surgery, and it seemed that they did not reach
387 preoperative level. Although all four patients experienced at least one postoperative
388 complication, we could not find one unique reason for being in this subgroup. Moreover,
389 the sample size of this group was too small to elaborate further analyses.

390 To our knowledge, this is the first study to investigate the effects of distinct
391 trajectories of muscle strength on postoperative HR-QoL in patients undergoing CABG.
392 LCGMM has proven to be an adequate and advanced statistical technique to identify
393 meaningful groups or classes of individuals over time [32]. This can be meaningful when
394 tailoring the treatment. Also in the present study, the main trajectory subgroups differed on

395 important preoperative risk factors (e.g., sarcopenic parameters, age, diabetes and obesity),
396 known to affect surgical outcomes and postoperative HR-QoL [6, 8, 15]. Unexpectedly, grip
397 strength trajectory group membership and postoperative HR-QoL were not associated in
398 our results. Despite significant group differences in grip strength at each time point, the
399 trajectories are possibly less distinctive. First, the BIC-values of the models for 1 trajectory
400 and 3 trajectories differed by less than 10 points (which was considered as sufficient
401 improvement). Second, LCGMM allows some variation within subgroups, which is shown in
402 Additional file 2: Fig. S3A, B. LCGMM was, however, chosen in favour of Latent Class
403 Growth Modelling (LCGM, i.e., no allowance of within-class variances), due to higher BIC-
404 values that indicate a better fit with the data. Secondly, a positive selection of patients was
405 possibly included, which potentially impacted our results. Our study group showed higher
406 levels of grip strength as well as HR-QoL at baseline and at 6 months compared to literature
407 [6, 8, 19, 32]. In addition, there was a tendency of lower preoperative grip strength values
408 and HR-QoL in dropouts compared to included patients (P-value range: 0.095-0.170 with
409 low sample size, $n = 11$, Additional file 1: Table S3). A wider spread and lower values would
410 increase the variance and could lead to more distinct trajectory groups. On the other hand,
411 older age, high BMI, and male sex are typical characteristics for patients undergoing CABG,
412 indicating a representative population in our study[4, 14–16].

413 The present study was limited by low numbers of females ($n = 15$), allowing no
414 separate trajectory analyses. Although there is a clear role for sex in the measurement of
415 muscle strength measures, the effects of CABG on muscle strength and HR-QoL in female
416 patients have been understudied, as fewer female patients undergo CABG [19]. In
417 agreement with previous studies [6, 31], our study indicates that females have lower muscle
418 strength and HR-QoL (Table 1, Additional file 2: Fig. S4). With growing evidence that
419 gender differences must be taken into account at all stages of cardio- and/ or rehabilitation-

therapeutic strategies [33], future research should stratify analyses by sex. In addition, multi-centre studies are needed to ensure enough female patients.

A limitation of this study was, that we were not able to present the presence of sarcopenia in more detail. Regrettably, BIA measurements produced implausible results post-surgery and were hampered by practical problems for a number of follow-up measurements. Furthermore, ASMM at baseline showed a non-significant but opposite relation with grip strength at baseline. Also, based on the revised European Working Groups on Sarcopenia in Older People (EWGSOP) 2018 guidelines [2], the prevalence of low muscle mass in our study was only 3% (contrary to 50% according to the original EWGSOP 2010 guidelines [34]). This small subgroup was not suitable for further analyses. Meaningful cut-off levels to identify sarcopenia remain to be established for this study population. While the original EWGSOP guidelines proposed low muscle mass as the primary parameter for diagnosing sarcopenia, which was determined using the BIA-based equations and cut-off values of Janssen et al. (2000 [35], 2004 [36]), the current EWGSOP advises muscle strength as the primary parameter, while muscle mass is determined by different equations and cut-off values (i.e., Sergi et al. [37] and Gould et al. [38], respectively). A recent systematic review confirmed lower levels of sarcopenia among older adults when using revised EWGSOP guidelines [39]. Moreover, sarcopenia according to the revised EWGSOP 2018 guidelines seemed to be worse at predicting adverse outcomes, such as risk of hospitalisation and mortality. Possibly, BIA may be less suitable for use in surgical populations with major fluid shifts and/or obesity, as both factors are known to considerably affect the parameters generated by this device [40].

An important clinical finding was that patients with high preoperative grip strength experience a considerable decline in grip strength a few days after surgery. Because changes in grip strength per weight are associated with HR-QoL and most improvements in HR-QoL are shown during the first 2 months after CABG [32], future research should examine the

446 recovery of grip strength and its impact on HR-QoL at shorter time intervals and earlier
447 than 6 months after surgery. Because the immediate decrease in grip strength after CABG
448 may impact HR-QoL at an earlier moment, possible different treatment strategies i.e.,
449 preoperative or early rehabilitation may be suitable for subgroups of patients.

450 Besides grip strength, future research should focus on a broader context of
451 rehabilitation outcomes. For example, evaluation of strength of the lower extremities could
452 be of added value, as hospital immobility can affect the lower extremities more severely [41,
453 42].

454 CONCLUSIONS

455 This prospective study showed two relevant weight-normalised grip strength trajectories in
456 male patients undergoing CABG, varying in important preoperative risk factors. While
457 change scores of grip strength per weight did predict postoperative HR-QoL, the trajectory
458 subgroups could not predict postoperative HR-QoL. Changes in easy-to-measure hand grip
459 muscle strength are thus clinically relevant for postoperative HR-QoL. Pre- and
460 postoperative rehabilitation could further enhance level and stability of muscle strength
461 over time, potentially improving surgical outcome and HR-QoL. Future research should
462 focus on female patients, reacting potentially different on CABG and/or rehabilitation
463 treatment and on the development of easy clinical ways to identify sarcopenia that are
464 reliable for surgical populations.

465

466 ABBREVIATIONS

467	ASMM	Appendicular skeletal muscle mass
468	BIA	Bioelectrical impedance analysis
469	BIC	Bayesian information criteria
470	BMI	Body mass index

471	CABG	Coronary artery bypass grafting
472	CPB	Cardiopulmonary bypass
473	EWGSOP	European Working Group on Sarcopenia in Older People
474	HR-QoL	Health-related quality of life
475	LCGMM	Latent class growth mixture modelling
476	MCS	Mental component score
477	PA	Phase angle
478	PCS	Physical component score
479	RI	Resistive index
480	Rz	Resistance
481	UMCG	University Medical Center Groningen
482	Xc	Reactance

483

484 SUPPLEMENTARY INFORMATION

485 The online version contains supplementary material available at

486 <https://doi.org/10.1186/s12872-023-03056-7>.

487 Additional file 1. Definitions and equations of preoperative risk factors and postoperative
488 complications. Characteristics of patients who dropped out and who completed the study.

489 Additional file 2. Results of Latent Class Growth Mixture Models (LCGMM) for grip
490 strength per weight in males and figures of individual trajectories before and after coronary
491 artery bypass grafting for grip strength per weight and Health-Related Quality of life (HR-
492 QoL) in females.

493

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497

498 *AUTHOR CONTRIBUTIONS*

499 Conception and study design: FB, WD and MAM; Methodology and analyses: JH, TH;
500 Investigation and project administration: FB; Data curation: FB, JH; Writing – Original
501 draft: JH; Visualisation: JH; Reviewing and Editing: JH, SD, FB, TH, JF, LHVvdW, MN,
502 WD; Supervision: JF, LHVvdW, MN, PvdH, MAM, WD; All authors approved the final
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508

509 *AVAILABILITY OF DATA AND MATERIALS*

510 The datasets used and/or analysed during the present study are available from the
511 corresponding author on reasonable request.

512

513 *DECLARATIONS*

514 *ETHICS APPROVAL AND CONSENT TO PARTICIPATE*

515 Participants were included after giving written informed consent. This study was conducted
516 in agreement with the principles of the Helsinki declaration [43] and approved by the
517 Medical Ethical Committee of the UMCG (Reference Number 2018/226).

518

519 *CONSENT FOR PUBLICATION*

520 Not applicable.

521

522 *COMPETING INTERESTS*

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527

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Title

A prospective pilot study assessing levels of preoperative physical activity and postoperative neurocognitive disorder among patients undergoing elective coronary artery bypass graft surgery

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Abstract

Physical inactivity and a sedentary lifestyle are associated with a chronic low-level inflammatory state which has been implicated in the pathogenesis of cardiovascular disease. There is growing interest in exercise programs as part of surgical 'prehabilitation'. We therefore studied preoperative physical activity levels of patients undergoing elective Coronary Artery Bypass Graft (CABG) surgery, and performed an exploratory analysis of the influence of physical activity on postoperative outcome. The Short Questionnaire to Assess Health (SQUASH) was used to assess physical activity among 100 patients, of mean (SD) age 65.4 (7.6) years. Additionally, handgrip strength was measured, and the get-up-and-go test was conducted. Anxiety, depression, and quality of life were assessed, and a computerised cognitive test battery was used to assess cognitive performance preoperatively, and three months after surgery. Preoperatively, 76% of patients met the recommended national guidelines for physical activity. The incidence of pre-existing medical conditions, and other pre-operative patient features were similar in active and inactive patients. Preoperative physical activity was significantly inversely related to the logistic EuroSCORE. The level of physical activity was also significantly inversely related with preoperative C-reactive protein (CRP) and peak postoperative CRP, but physical activity did not appear to be associated with any adverse postoperative outcomes or extended length of hospital stay. The incidence of postoperative neurocognitive disorder (PNCD) at 3 months postoperatively was 26%. Cognitive performance was not related with physical activity levels. In summary, this was the first study to assess activity levels of cardiac surgical patients with the SQUASH questionnaire. The majority of patients were physically active. Although physical activity was associated with lower levels of inflammation in this pilot study, it was not associated with an improved clinical or cognitive postoperative outcome.

Introduction

In recent years, there has been considerable interest in the relationship between physical activity, fitness, and health. For patients undergoing surgery, not only does pre-operative physical activity have the potential to improve their general health, it also might influence the outcome of the operation itself [1-4]. For cardiac surgery however, physical activity is a double-edged sword. Although a sedentary lifestyle (i.e. physical inactivity) is a known risk factor for cardiovascular disease [5], patients may be unwilling, or even unable to comply with exercise programs because of fear, or because their exercise tolerance is limited by angina or dyspnoea.

The disadvantages of a sedentary lifestyle are well-known, and the underlying mechanisms have also been determined [6]. Physical inactivity has been shown to be associated with a chronic-low level inflammatory state [6-8]. This systemic inflammatory state plays a key factor in the pathogenesis of diseases such as atherosclerosis and insulin resistance [9, 10]. Indeed, an inactivity-associated inflammatory state has consistently been associated with a decreased health related quality of life (HRQL), and an increased incidence of non-communicable diseases, such as coronary heart disease (CHD) and type II diabetes mellitus [8, 11-13]. It has also been associated with colon- and breast cancer [8, 11].

There is growing evidence that physical activity is likely associated with improved cognitive function, probably mediated by an attenuation of brain inflammation [6, 14-17]. A recent study comparing physically active and inactive persons showed indeed evidence of this relationship: that inadequate levels of physical activity were associated with higher levels of pro-inflammatory marker IL-12p40, smaller lateral prefrontal cortical and hippocampal volumes, and worse cognitive function over a 6 year period [18]. These findings were consistent with those of previous studies showing that higher levels of pro-inflammatory markers such IL-6 are associated with reduced overall grey matter and hippocampal volume, and worse cognitive performance [19-22].

Frailty is an age-related decline in multiple physiological systems which renders affected individuals susceptible to sudden health deterioration in response to stressors [23]. Among cardiac surgical patients, frailty has been associated with increased length of hospital stay, mortality, major adverse cardiovascular and cerebral events, and a reduced functional status [24-26]. It is also associated with neurocognitive complications such as delirium and postoperative neurocognitive disorder (PNCD) [27, 28]. Given the above-mentioned associations and the widely held perception that patients with ischemic heart disease mostly have sedentary lifestyles, the interest in preoperative rehabilitation (prehabilitation) has also been focused on patients undergoing cardiac surgery. However, a prehabilitation program, often consisting of preoperative physical and/or cognitive therapy, would probably be more beneficial for physically inactive patients awaiting cardiac surgery.

The main aim of the current study was thus to generate an inventory of preoperative levels of physical activity, and compare these to the recommendations of the Dutch National Institute for Public Health and Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM), among patients undergoing coronary artery bypass graft surgery (with or without the use of cardiopulmonary bypass) in our hospital. The secondary goals were to assess the feasibility and performance on tests indicating sarcopenia and frailty (grip strength, and the 'get-up-and-go' test), quality of life questionnaires in cardiac patients undergoing surgery. Given the purportedly high incidence of cognitive decline among elderly patients after cardiac surgery [29-31], and the potential associations among physical activity, inflammation, and cognitive function (and the possible role of inflammation in PNCD [26, 32]) we also assessed cognitive function before and after surgery.

Materials and methods

After approval of the study by the Groningen Medical Ethics Committee (approval reference number: NL49262.042.14 [METc 2014/219 Sarcopenie]), 100 patients undergoing elective coronary artery surgery were enrolled in this prospective longitudinal observational study performed at the University Medical Centre Groningen (UMCG), the Netherlands, between January 2015 and March 2017. All subjects completed and signed an informed consent form prior to their enrolment in the study.

Inclusion criteria were age > 18 years old and suitability for undergoing coronary artery surgery with or without cardiopulmonary bypass (CPB). Patients operated for coronary artery disease combined with a valve procedure and reoperations will not be eligible for inclusion. Patients were further required to be able to stand and walk independently, and to be prepared to allow a researcher to repeat the assessments three months after surgery, at their own home or at the hospital. Patients are required to participate in online screening modules for cognitive function (ie they should be able to operate a computer touch pad or mouse, and to read large text on a computer screen). Furthermore, patients need to be able to perform the handgrip strength test on both sides.

Patients were also excluded from participation if they were unable to understand or read Dutch instructions. Patients expected to have an extended postoperative intensive care stay, or those with a diagnosed history of a recent depression, anxiety, dementia, stroke or other neurological disorders or severe cerebrovascular insults were also excluded from participation. Finally, patients not able to perform the get-up-and-go test or any of the other tests were also considered ineligible for this study.

Primary outcome measurements

Data collection was conducted at four time points; at the preoperative anaesthetic screening visit (4 – 6 weeks before surgery), 1 day before surgery, 4 days after surgery and finally 3 months after surgery

(Fig 1). All questionnaires, assessments, and neuropsychological tests were administered by trained research assistants. The surgery and anesthesia for all patients were performed in a conventional manner with routine pre and postoperative care.

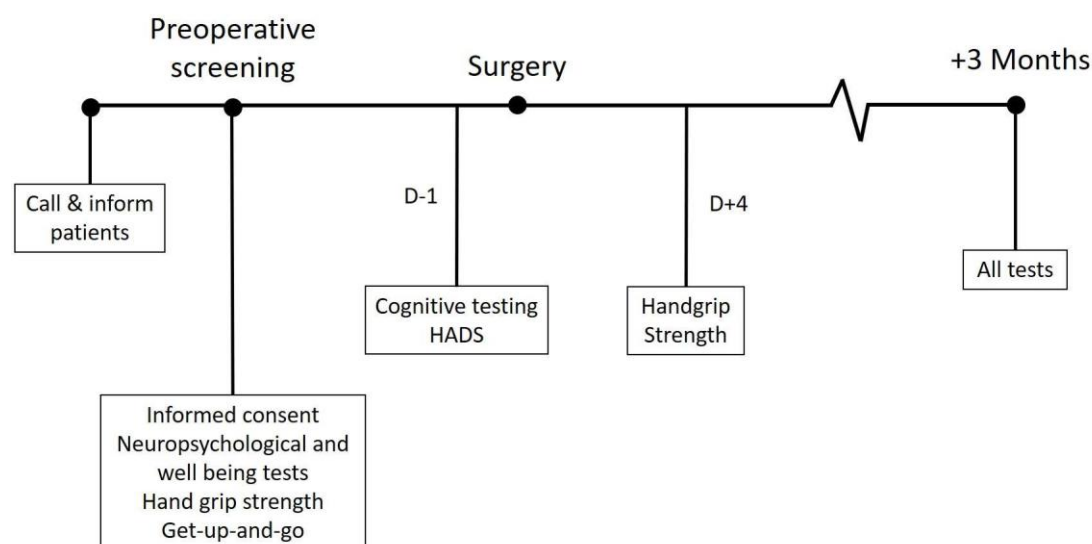


Fig 1. Data collection timeline. A timeline of data collection per patient. D-1 = one day before surgery; D+4 = four days after surgery; HADS = Hospital Anxiety and Depression Scale.

Physical activity

The primary outcome of this study was perioperative levels of physical activity, assessed using the Short Questionnaire to Assess Health (SQUASH) (24), at the preoperative screening visit and 3 months after surgery. The SQUASH questionnaire was developed in the Netherlands, and has been validated using an activity monitor in both the healthy adult population and in patients who have undergone total hip arthroplasty [33, 34]. It has been adopted by various Dutch governmental health-institutions to assess fitness and health activity in the general population. The 2011 SQUASH questionnaire modified by the Dutch Centre for Big Data and Statistics (CBS) was selected for this study. The questionnaire uses a combination of open and closed questions to determine the amount of time and effort spent on various activities (S1 Table). Using the Ainsworth compendium of physical activities, each activity is assigned a Metabolic Equivalent of Task (MET) value (S2 Table) [35, 36].

The amount and intensity of these activities can then be allocated to one of three categories defined by the RIVM at the time of the study; Dutch Norm of Healthy Activity (Nederlandse Norm Gezond Bewegen - NNGB), Fitnorm and Combinorm (Table 1) [37-39].

Table 1 Dutch National Institute for Public Health and Environment (RIVM) recommendations for duration and intensity of physical activity

	Time	Intensity			
		Adults (18-54 yrs)		Elderly (55+ yrs)	
NNGB	At least: • 30 minutes a day, 5 days a week	Moderate activities at 4 – 6.5 MET	intensive activities at 4 – 6.5 MET	Moderate activities at 3-5 MET	intensive activities at 3-5 MET
Fitnorm	At least: • 20 minutes a day, 3 days a week	Vigorous activities at ≥6.5 MET	intensity activities at ≥6.5 MET	Vigorous activities at ≥5 MET	intensity activities at ≥5 MET
Combinorm	Activity levels sufficient if at least one of the NNGB and Fitnorm criteria are met.				

NNGB, Nederlandse Norm Gezond Bewegen; MET, Metabolic Equivalent of Task.

For the purposes of the current study, we defined a patient as being physically inactive if they fulfilled the Combinorm criteria of inactivity: less than 30 minutes of moderate activity per day for 5 days a week *or* less than 20 minutes of intense activity for 3 days a week. Postoperative statistical analyses were also performed using ‘*Activity scores per week*’ from the SQUASH [34]. In order to calculate the *activity score*, first an *intensity score* is assigned to an activity based on the MET-value for that activity and the degree of effort the patient’s report doing these activities (Table 2). The *activity score* is calculated by multiplying the total amount of minutes spent on an activity by its *intensity score*. Activity scores are then calculated for light, moderate and vigorous activities. The *total activity score* per week is then calculated taking the sum of all the activity scores for light, moderate and vigorous activities.

Table 2 Intensity scores assigned to various levels of activity and self-reported effort.

Ainsworth and Dutch norms for the intensity of an activity	Self-reported intensity/effort level		
	Light	Moderate	Vigorous
Light	1	2	3
Moderate	4	5	6
Vigorous	7	8	9

After the study started, the ethical committee approved an amendment to allow an objective measurement of movement and energy expenditure, using the portable Sensewear apparatus (Body Media, Pittsburgh, PA, USA). These data will be reported separately (manuscript by Dijkstra et al. is yet to be submitted).

Secondary outcome measurements

Handgrip strength and ‘get-up-and-go’ test

Further measurements were used to assess muscle strength and mobility: handgrip strength and the get-up-and-go test respectively. Handgrip strength was tested bimanually using a JAMAR™ hydraulic hand dynamometer (Sammons Preston Ltd, Bolingbrook, IL., USA). The subjects performed the test three times per hand with the elbow at the side of their body at 90 degrees flexion and the wrist rotated in neutral position with thumbs towards the ceiling, for maximum isometric force according to the instrumental protocol. Handgrip strength was expressed in kilograms. The mean of these measurements was calculated per hand. This mean value was then expressed as a percentage value of age and gender matched control data [40]. Impairment of handgrip strength was indicated when the strength of the dominant hand was below <85% [41].

The Get-up-and-Go test entails the time taken for a patient to get up from a seated position (a chair without side-supports), walk 3 meters, and return to their seat at their normal pace. This test was

performed twice, and the mean time was selected for further analysis. Frailty is indicated in patients who take longer than 12 seconds to complete the task [42].

Cognitive function testing

Cognitive function was assessed by administering the CogState brief computerised cognitive test battery (Cogstate Ltd, Melbourne, Vic., Australia). The test-battery was conducted twice before surgery, the first as a practice test and the second as a baseline measurement [43]. The tests were repeated 3 months after surgery. The test battery consists of four tests; a detection task, an identification task, a one card learning task, and the one back task. These tests assess four neurocognitive domains; psychomotor speed, selective attention, long-term memory and working memory, respectively [44]. Impairment within these domains is typical for postoperative neurocognitive disorder [45]. Each round of testing took approximately 15-20 minutes. Standardised written instructions on how to perform the tasks were included in the test battery in order to minimise inter-observer variability. These test scores were analysed to determine the incidence of PNCD at 3 months after surgery. PNCD was defined as a decline in cognitive performance beyond natural variation. Our approach to analysing the cognitive tests was similar to that outlined by Rasmussen et al. [46]. A standardised change Z-score was calculated for each cognitive test, equivalent to the Reliable Change Index, taking into account the test-retest variability among an age-matched normal control population [46]. These scores were then also summed to generate a composite-Z score. We defined PNCD as present in an individual when their standardised change-Z score was less than the -2 in two or more cognitive domains and/or when their composite-Z score was ≤ -2 [46, 47].

Neuropsychological and wellbeing assessments

Patients diagnosed with an anxiety or depression disorder were excluded from participation in the study. However, as anxiety and depression are associated with impaired cognitive function [46], we thus screened enrolled patients for pre- and postoperative depression and anxiety using the

Hospital Anxiety and Depression Scale (HADS) [48]. Patients completed the questionnaire at the time of preoperative screening, after admission just prior to the start of the first cognitive test session and at 3 months after surgery. A cut-off HADS score of ≥ 8 was used to identify patients with (undiagnosed) depression and/or anxiety [48, 49]. All neuropsychological tests were administered by trained research assistants.

Questionnaires were used to assess health status, quality of life and health limitations. General health status was assessed using the EuroQol-5D (EQ-5D) survey [50], health-related quality of life perception was assessed using the Research and Development-36 (RAND-36) questionnaire [51], and after another amendment the ethical review board approved the inclusion of an assessment for health limitations (disabilities) in various domains of functioning using the World Health Organisation, Disability Assessment Schedule (WHODAS-2.0) questionnaire [52]. These assessments were also made at the time of preoperative screening, and 3 months after surgery.

Other secondary outcomes

Other secondary outcomes include the routinely collected laboratory values (e.g. C-reactive protein (CRP), leukocytes, and thrombocytes), information regarding medical history, logistic EuroSCORE (a measure of cardiac risk [53]) and the incidence of routinely collected outcome parameters. The latter includes process variables (such as duration post-operative ventilation, ICU stay, hospital stay) and complications (wound infection or breakdown, re-operation, delirium, atrial fibrillation, renal failure).

Sample size analysis.

In a previous study on fitness in healthy male and female septuagenarians, 23% were found to be unfit and 76% were physically active or to have exercised frequently [54]. Although elective CABG patients are expected to be younger, they are also expected to have lower levels of physical activity. It was thus estimated that 50% of the patients who would be included in the study would have an inactive lifestyle. The sample size of 100 was chosen for practical and pragmatic reasons. If, with a

sample size of 100, the proportion of physically active patients turned out to be 50%, then the 95% confidence interval (CI) for the true population value of this proportion would be 40.4 – 59.6%. As such, this study is a baseline measurement or a pilot study, with the sample size pragmatically chosen, and its goal was to inform future studies.

Statistical analysis

Analyses were performed using SPSS statistics software version 23 (IBM, New York, NY, USA). The normality of distribution of the data was tested by assessing histograms and when appropriate with the Kolmogorov-Smirnov test. Non-parametric data are presented with medians and interquartile range (IQR), whereas, parametrically distributed data are presented with their mean and standard deviation (SD) and binary variables are presented with the incidence and percentage of sample size. Analyses of normally distributed continuous data were conducted using the Student t-test. For non-parametric continuous data, the Mann-Whitney-U test was conducted. For nominal variables, such as gender and the incidence of anxiety or depression, a chi-square test was performed when appropriate. A theory driven approach was used for the selection of variables to be included into correlation and regression analyses. Correlations between variables were analysed using the Pearson or Spearman rank-order correlation coefficient. In the event of a significant correlation, (multiple) linear regression would be used to assess this relationship. To evaluate the potential independent prognostic effect of physical activity on inflammation, a multivariable linear regression analyses was used to control for age and BMI, which are variables known to be associated with inflammation [6, 9, 10]. Univariate and Multivariate logistical regression was used to assess the possible risk factors for physical inactivity and PNCD. If determinants were found significant ($p < 0.2$) in univariate analyses, multivariate regression was performed. Odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs) were calculated and reported. A two-sided probability value of < 0.05 was considered statistically significant.

Pre- and post- rehabilitation

After the start of the present study, the department of cardiothoracic surgery introduced a pre-and postoperative rehabilitation program to their standard care package. A number of patients who had already been included into current study were offered the chance to participate in this program, and eventually 31 patients participated in the prehabilitation program **after** they had completed the SQUASH questionnaire. In addition, 3 patients participated in an alternative in- and outpatient postoperative rehabilitation program.

The prehabilitation program included multiple physical therapy sessions consisting of inspiratory muscle training, aerobic cycling, resistance training and body awareness therapy. Furthermore, multiple sessions of group education, work and psychological guidance, dietary advice and additional counselling in order to quit smoking was also administered. Patients participated in these activities from at least three weeks prior to the surgery. In addition to the group education, psychological guidance and counselling sessions, the alternative postoperative rehabilitation program also consisted of aerobic cycling, resistance training, swimming, and sport and games.

Since participation in these programs could have influenced the secondary outcomes, only the postoperative data of patients who **did not** attend the prehabilitation program will be included in the statistical analyses, using the total activity scores as an indicator for physical activity instead of the dichotomized Combinorm as independent variable. When assessing cognitive function 3 months after surgery, both the patients who attended the prehabilitation program and the alternative postoperative rehabilitation program were excluded from analyses.

Results

A total of 100 patients undergoing elective CABG were enrolled in the study (see CONSORT diagram, Fig 2). The baseline demographic, clinical and surgical characteristics, of the patients are presented in Table 3. The mean (SD) age of the patients was 65.4 (7.6) years old, and 89% of the patients were men. The median waiting time between preoperative anaesthetic screening and surgery was 29 days. The shortest waiting time was 6 days and longest 110 days.

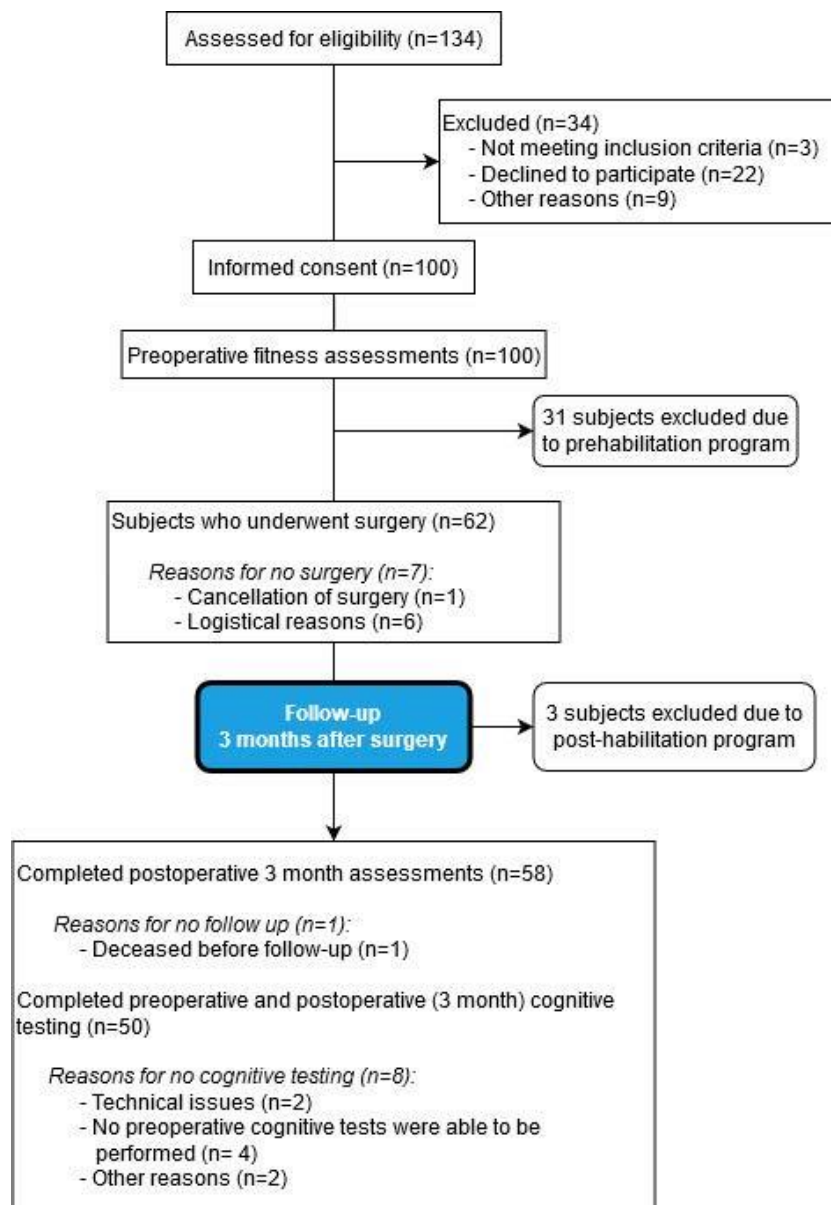


Fig 2. CONSORT flow diagram. A consort flow diagram of all the patients included into the study.

Table 3 Demographic and clinical characteristics of all patients included into the study.

	All patients (n = 100)	Preoperatively active (n = 76)	Preoperatively inactive (n = 24)	p value
Demographics				
Male Sex	89(89%)	68 (89.5%)	21 (87.5%)	0.788
Age, mean (SD), years	65.4(7.6)	65.9(7.5)	63.8(7.9)	0.238
BMI, mean (SD)	28.1(4.7)	27.1 (4.7)	28.6(4.6)	0.359
Level of education, median (IQR) †	5 (4-6)	5 (4-6)	5 (4-6)	0.538
Logistic EuroSCORE, median (IQR)	2.5(1.4-4.0)	2.4 (1.4-4.0)	2.5(1.3-4.4)	0.681
Pre-existing medical conditions				
Diabetes	31(31%)	22(29%)	9(38%)	0.430
Hypertension	54(54%)	43(57%)	11(46%)	0.357
COPD	11(11%)	9(12%)	2(8%)	0.632
Respiratory	12(12%)	9(12%)	3(13%)	0.931
Other	64(64%)	47(61.8%)	17(71%)	0.424
Preoperative lab test results				
CRP, median (IQR), mg.l ⁻¹	5(1-4)	1.8(0.7-3.3)	3.6(1.5-12)	0.006
Leukocytes, median (IQR), × 10 ⁹ .l ⁻¹	7.7(6.6-8.7)	7.3(6.7-8.7)	7.2(6.5-8.9)	0.831
Thrombocytes, median (IQR), × 10 ⁹ .l ⁻¹	243(203-277)	238(203-287)	242(218-273)	0.687

*Data are presented as number (%), unless otherwise indicated.

† Level of education according to Verhage Classification of Dutch Education Levels, ranging from less than elementary school (1) to university degree (7). BMI = body mass index; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; HADS = hospital anxiety and depression score; IQR = interquartile range; SD = standard deviation

Pre-operative physical activity

SQUASH questionnaires were completed by all patients. Of the 100 patients, a total of 76 patients fulfilled the Combinorm criteria for a healthy level of physical activity. Fig 3 illustrates the total activity scores for physically active and inactive patients. There were no significant differences in any demographic or clinical characteristics, or incidences of pre-existing medical conditions between the two groups. Using univariate and multivariate logistic regression no significant risk factors for physical inactivity were identified (S3 Table). Furthermore, neither age or BMI were significantly correlated with total activity score. There was a statistically significant negative relationship between total activity score and logistic EuroSCORE (Spearman's rho = -.254, p = 0.047).

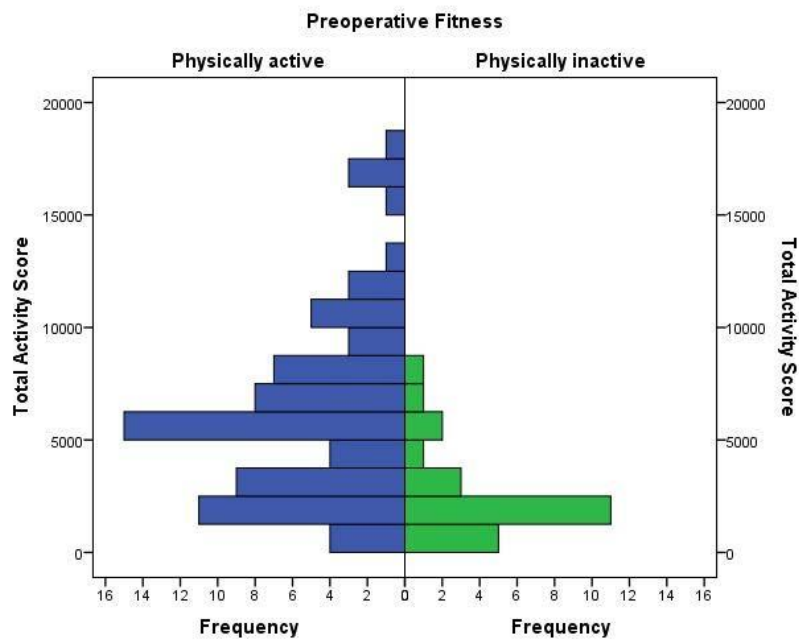


Fig 3. Physical activity and total activity scores. A mirrored bar chart of the various total activity scores for physically active (blue) and inactive (green) patients (n=100).

Strength and mobility assessments

Preoperative handgrip strength tests were performed in 97 of the 100 patients and again, 4 days after surgery, in 57 (91%) of 62 patients who underwent surgery. Grip strength was similar between physically active and inactive patients (S4 Table). Fifteen patients were identified with an impaired handgrip strength (<85%) preoperatively, of whom 10 (13.2%) were physically active, and 5 (20.8%) were inactive ($p = 0.359$). Timed get-up-and-go tests were performed in 96 patients. Of them, five (5.2%) patients took longer than 12 seconds to complete the test. Of these five patients, three (4.1%) were classified as physically active and two (8.7%) as physically inactive according to the Combinorm criterion.

Cognitive function tests

There were 50 patients who performed all the cognitive function tests and did not participate in the prehabilitation program, and their data were subjected to PNCD analysis. Among these patients, postoperative neurocognitive disorder was identified in 13 (26%) patients at 3 months. All of the patients that fulfilled the criteria for PNCD did so on the basis of a composite-Z score ≤ -2 . Three patients fulfilled the criteria of a standardised change-Z score < -2 in ≥ 2 cognitive domains. There was no correlation between the total activity score and the composite Z-score 3 months of surgery (Pearson's $\rho = -.089$, $p = 0.550$, Fig 4). No other variables were significantly related to composite Z-score. In addition, the composite-Z scores were not associated with preoperative handgrip strength (Dominant hand: Pearson's $\rho = 0.156$, $p = 0.279$). Through simple linear regression and multiple linear regression no significant predictors were found for composite Z-score. Through logistic regression no significant risk factors (physical activity, impaired handgrip strength, education level, age, the use of CPB, postoperative complications, postoperative anxiety or depression) could be identified for PNCD (S5 Table).

When comparing the baseline cognitive scores for active and inactive patients, no statistically significant differences were identified. The baseline standardised scores for each cognitive domain, for both active and inactive patients, are presented in S6 Table.

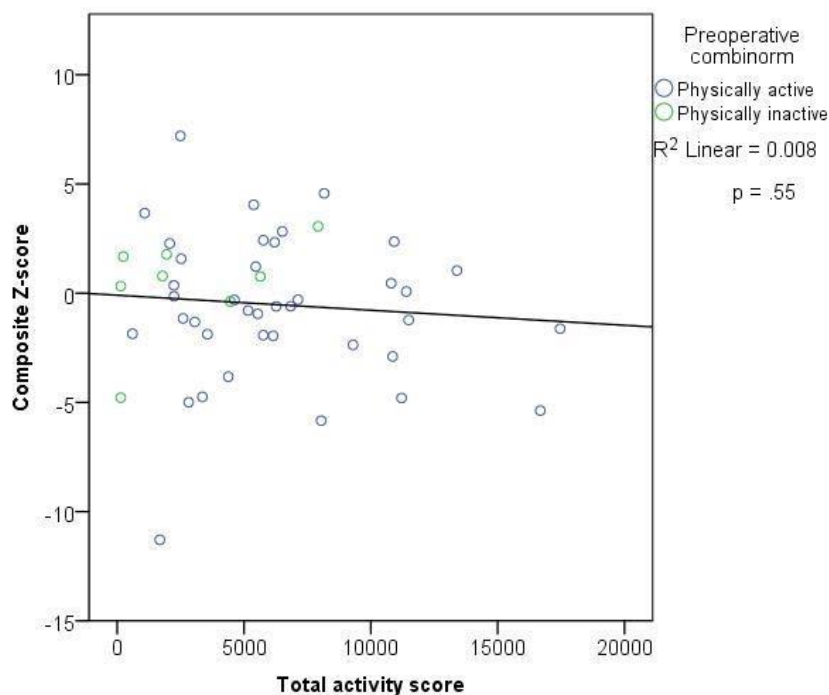


Fig 4. Total activity scores and composite Z-score. A linear regression model for total activity score and composite Z-score. There was no significant relationship $p = .55$. Active (blue) and inactive (green) patients have also been distinguished ($n = 47$).

Neuropsychological and wellbeing assessments

The results of these assessments are summarised in S7 Table. During preoperative screening, 14 (18.9%) physically active and 7 (28%) inactive patients had HADS score ≥ 8 for either anxiety or depression. Anxiety and depression scores were not correlated with the total activity score (Spearman's $\rho = .053$, $p = 0.607$ and Spearman's $\rho = -.179$, $p = 0.081$ respectively). Preoperatively physically inactive patients scored significantly lower in 5 domains of the RAND-36; physical function ($p = 0.011$), social function ($p = 0.015$), physical role limitations ($p = 0.007$), emotional role limitations ($p < 0.001$), and vitality ($p = 0.014$). Nevertheless, no differences between active and inactive patients were measured with the EQ5D and WHODAS. After 3 months, no differences were seen in any of the neuropsychological assessments between the active and inactive patients.

Other outcomes

Median (IQR) length of stay in the ICU was 1 (1-1) day for both physically active and inactive patients. The median (IQR) length of stay in the hospital after surgery was 7 (6-8) days for the active group and 6 (5-10) days for the inactive group. There were no significant differences in total activity scores between patients with and without postoperative complications.

Preoperative laboratory values for leukocytes and thrombocytes were similar between active and inactive patients. Preoperative median (IQR) CRP levels were 1.8 (0.7-3.3) and 3.6 (1.5-12) for active and inactive patients, respectively. This difference is statistically significant ($p = 0.006$), but not clinically relevant. The total activity score was also significantly negatively related to preoperative CRP (Spearman's $\rho = -0.259$, $p = 0.010$, $n = 100$).

Peak postoperative CRP was also correlated with the total activity scores (Pearson's $\rho = -0.346$, $p = 0.007$, $n = 59$). A simple linear regression was used to predict peak CRP based on preoperative total activity scores (Fig 5). A significant regression equation was found ($F(1, 57) = 7.747$, $p = 0.007$), with an R^2 of .120. Patients predicted CRP is equal to -0.006 [total activity score] + 197.4. The model for CRP appears to be more accurate for people with lower activity scores. A multiple linear regression was calculated to predict peak postoperative CRP based total activity scores, corrected for age, and BMI (Table 4). A significant regression equation was found ($F(3,55) = 4.566$, $p = 0.006$), with an R^2 of 0.199. CRP remained a significant predictor when correcting for age and BMI.

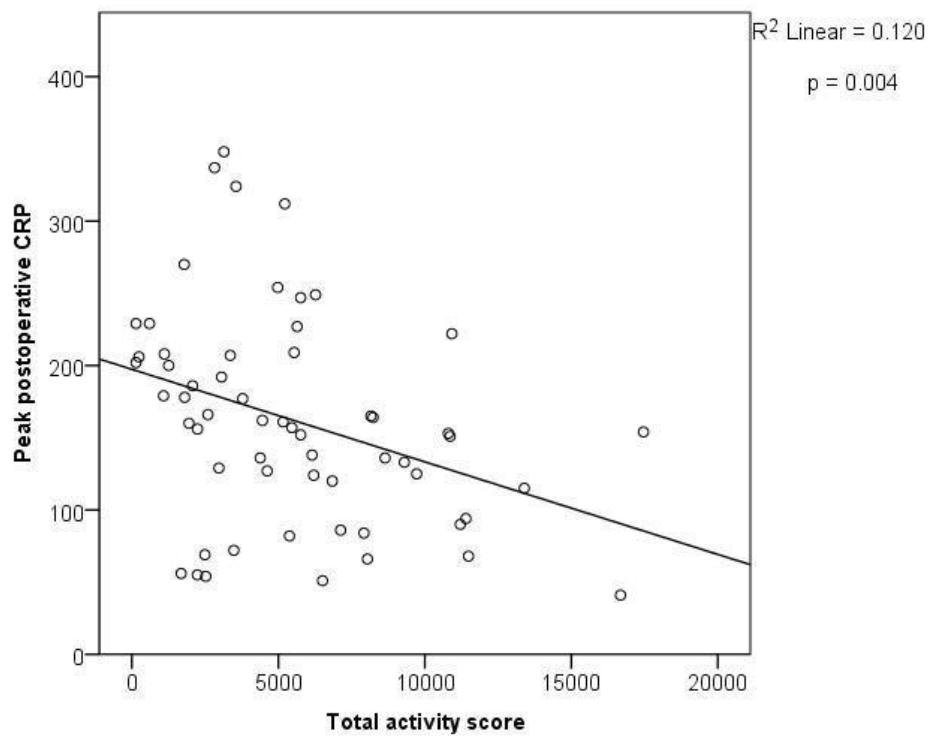


Fig 5. Total activity score and peak postoperative CRP. A significant linear regression model between total activity score and peak postoperative C-reactive protein (CRP) ($n = 59$). Total activity was inversely related to peak CRP ($p = .007$).

364 **Table 4.** Simple and multiple linear regression models for peak postoperative C-reactive
 365 protein (n = 59).

	B	beta	p value
Step 1			
Total activity score	-0.006	-0.346	0.007
Step 2			
Total activity score	-0.006	-0.315	0.012
Age	2.5	0.243	0.0503
BMI	2.7	0.160	0.191

R² at step 1 = .120, R² at step 2 = .199, $\Delta R^2 = 0.08$

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Discussion

When this study was conducted, the Dutch National Institute for Public Health (RIVM) recommended that people perform ≥ 30 minutes of moderate exercise 5 days per week (the so-called NNGB criteria) **OR** ≥ 20 minutes of vigorous exercise 3 days per week (the so-called Fitnorm). We have shown that during the conduct of our study, 76% of the included patients met at least one of the two criteria (the so-called Combinorm). Preoperatively, patients with lower activity scores were more likely to have higher Logistic EuroSCOREs, suggesting that cardiac morbidity may have a significant adverse effect on physical function (or possibly the converse). Preoperatively, physically inactive patients also reported lower quality of life scores, however this was limited to only some items of the RAND36 and not reflected in the EQ5D or WHODAS.

No potential risk factors for physical inactivity were found. Nevertheless, it is important to recognise that the level of physical activity a person is able to do is multifactorial, determined by existing comorbidities and environmental factors, related to work and even seasons. Interestingly, after surgery, patients with lower activity scores appeared to have significantly higher peak levels of CRP, which may be a demonstration of the known anti-inflammatory benefits of exercise [6]. This increased inflammatory response to surgery was not, however, accompanied by postoperative complications or cognitive decline. Furthermore, there were no other differences in postoperative outcomes between inactive and active patients.

The proportion of patients classified as physically active in the current study was higher than anticipated. In fact, the levels of physical activity reported by our patients were similar to those found among the general population level of people 55 years and older in the Netherlands [55]. Previous literature from the Netherlands has indicated that the percentage of physically active patients undergoing cardiac surgery is between 56-57% [56-58]. Interestingly, the criteria used in those studies to determine preoperative levels of physical activity (the Corpus Christi Heart Project classification) was less demanding than the Dutch national recommendations, as it requires only 15 min/day of 'fairly light' intensity activities for a person to be considered physically active [59]. Furthermore, these

studies were able to identify significant pre- and postoperative differences in outcome between active and inactive patients. For instance, Noyez et al. found that inactive patients were significantly more obese, older and had higher logistic Euroscores [57]. The high proportion of fit patients in the current study, may reflect the differences in patient population studied. The patients in the current study had a median (IQR) EuroSCOREs of 2.6 (1.5-4.2), which is associated with a low to medium cardiac risk, whereas the previous studies tended to include both older (mean (SD) age of 68.7 (10.9)) and higher-risk patients (a mean (SD) Logistic Euroscore of 5.06(5.6)) [56-58]. The unexpectedly high proportion of active patients in the present study may also have been the result of a selection bias (see below). Our results on preoperative physical activity, nevertheless indicate that there may be more variation in the larger cardiac surgery patient population than that which was previously assumed.

To the best of our knowledge, this is the first study to have used the SQUASH questionnaire to determine preoperative physical activity among cardiac patients. The questionnaire was developed to assess compliance of the Dutch population with the weekly duration and intensity of physical activity recommended by the RIVM. The SQUASH was found to be a reliable tool to assess physical activity behaviour in both the Dutch general population and Dutch patients who have undergone Total Hip Arthroplasty [33, 34]. In Denmark the SQUASH was found to be poor at measuring physical activity on an individual level but still reliable in distinguishing between individuals [60]. Nonetheless, the SQUASH remains the nationally standardised and recommended tool for assessment of physical activity in the Netherlands, and was selected for our study for this reason.

The SQUASH questionnaire, which asks participants to self-report their levels of physical activity and its intensity, has the same risks of biases suffered by many other questionnaires, as it provides subjective information. Patients were asked to report the intensity of their physical activity. The intensity of an activity experienced by a patient is a subjective construct. An activity that would normally be considered of moderate intensity to a healthy adult, could be considered vigorous by a cardiac patient, because they experience symptoms such as shortness of breath or chest pain during lower intensity activities. A customised questionnaire designed for a specific patient group would be necessary to account for this subjective construct. It is also possible that physically inactive patients

may be somewhat embarrassed or ashamed by their lack of activity, or by guilt that their cardiac condition might have been caused by inactivity and thus self-inflicted. Despite the fact that their answers were treated anonymously, unfit patients may have been inclined to provide more socially acceptable answers, and thereby to have overestimated their overall level of fitness [33, 61, 62]. The SQUASH questionnaire may offer an interesting tool to discriminate levels of physical activity when further compared to objective fitness assessments using activity monitors. Unlike activity monitors, the strength of using the SQUASH questionnaire is that it offers insight on the type and nature of physical activity that patients participate in. Furthermore, the SQUASH is both more feasible and generalizable to the clinical practice because it is brief and not as taxing as requiring patients to equip an activity monitor for multiple days.

Furthermore, many of our patients reported that they cycled frequently. Unfortunately, we did not ask them to report the type of bicycle they used, and electronic bicycles were starting to become more popular during the study. These bicycles offer varying degrees of assistance to the user, which makes it difficult to interpret the physical effort involved without further specification. Alternatively, electronic bicycles increases the duration of physical activity. Another likely source of bias is a degree of selection bias is that patients who are fitter and/or more self-aware of their health and activity may be likely to be more motivated to consent to involvement in a study of physical activity. Finally, although a degree of recall bias is also possible, some studies have demonstrated that retrospective and proxy reports of physical function do not undermine the predictive validity of questionnaires [63, 64]. Often where differences have been identified, they were limited primarily to mental health and disease symptoms rather than physical functioning [65, 66].

There is growing interest in the influence of frailty and sarcopenia on postoperative outcomes. One of the goals of our study was thus to explore the feasibility of assessing two components of frailty, weakness (handgrip strength) and slowness (get-up-and-go test) [41, 42], in the perioperative setting. Our study shows that these measurements are indeed feasible. In both active and inactive patients, handgrip strength was within the standard age and gender related ranges. With the exception of patients who underwent radial artery grafting, we were successful at measuring grip-strength

bimanually four days after surgery. Preoperatively, the number of impaired handgrip strengths or get-up-and-go tests, indicative of frailty, were also similar between the active and inactive patients which suggests that few of our patients were markedly frail before surgery. Unlike the current study, previous literature has found that poorer preoperative grip strengths may be related to higher cardiac risk scores [67]. Handgrip strength also appears to be an effective tool at predicting postoperative complications after cardiac surgery [68]. Our study could have been enhanced by including CT scan measurements of total psoas area (a valid measure of sarcopenia and frailty), or of leg strength as an additional indicator of weakness. Had we included the latter, postoperative measurements would likely have been limited by leg pain related to saphenous vein harvesting. A larger, more adequately powered study would be necessary to confirm or refute the clinical usefulness of these measurements in a cardiac surgical population.

Cognitive Function

For the assessment of PNCD we applied the criterion recommended by the expert working party on post-operative neurocognitive disorders for major neurocognitive disorder – i.e. >2 standardised Z-score in cognitive function test scores [47]. As in previous studies on PNCD, we applied this stricter definition for PNCD and corrected for learning effects and age-related test-retest variability in neuropsychological test performance over time. The overall incidence of PNCD at 3-months after surgery was close to that which we anticipated, 26%, and is also consistent with incidences reported in earlier literature [69, 70]. The study was not powered to investigate this outcome, and so the following findings should be viewed in this light. No significant reduction of cognitive function was identified in patients in our study who were physically inactive compared with those who were active. Activity scores were also unrelated with composite Z-scores. Although previous studies have associated grip strength with cognitive function, particularly of healthy older adults, our study could not confirm this relationship. Pre-existing medical conditions, as well as postoperative complications did not appear to be associated with PNCD or composite Z-score.

The beneficial effects of physical activity on the brain and on cognitive function have been well documented in human and animal studies [6, 14-17]. Adequate levels of preoperative physical activity may improve cognitive function and thus the preoperative cognitive reserve mentioned above, and may thereby help reduce the risk of postoperative cognitive decline. Indeed, Hayashi et al. reported that a lower preoperative exercise capacity, assessed by the 6-minute-walking distance in patients undergoing cardiac surgery was associated with an increased incidence of PNCD [71]. However, their study assessed cognitive function only 14 days after surgery using the mini mental state examination, which is a sub-optimal tool for detecting PNCD due to both floor- and ceiling-effects, and poor sensitivity for detecting mild or medium cognitive impairment [72, 73]. Furthermore, a decline in cognitive performance at 14 days after surgery is not necessarily caused by persistent neurocognitive disorder, as this is also likely to be related to delirium or delayed cognitive recovery caused by pain, residual drug effects, limited mobility, and fatigue [46, 47]. Contrary to Hayashi et al.'s findings, we found no association between preoperative activity scores, muscle strength and mobility, and a reduced cognitive performance or PNCD.

Our study has some limitations, some of which have already been highlighted and addressed. The primary aim of this study was to investigate the level of fitness of patients undergoing cardiac surgery. For this reason, a pragmatic sample size of 100 patients was selected. In an attempt to include a somewhat homogenous population, we included elective CABG surgery patients, and excluded patients undergoing combined CABG and valve replacement procedures. The patients included in our study had a low risk of postoperative complications. The small number of physically inactive patients may have been due to selection and inclusion biases, and the low incidence of postoperative complications might have been influenced by the low-to-medium risk levels of the patients (as suggested by their EuroSCORE). Furthermore, as inflammation was only a secondary parameter in this study, data regarding preoperative medications was not collected. Certain medications are known to effect pre- and postoperative inflammation. Therefore, we recommended that future studies assessing peri- and postoperative inflammation should include medication history within their analyses.

During this study preoperative physical activity was measured once, at the preoperative screening. The waiting time between screening and surgery was >4 weeks for more than half of our patients. During this period some patients may have improved or lowered their activity levels, unknown to us. Although we were able to determine the level of physical activity of patients who need to undergo cardiac surgery, future research on this topic should assess physical function closer to the surgery date in order to gain a more accurate indication of the level physical activity for patients about to enter cardiac surgery.

More recently the WHO has placed more emphasis on strength training. After our study was finished, the RIVM adjusted their recommendations for physical activity to also put emphasis on muscle strengthening activities and reduced sedentary lifestyles [37, 74]. In the Netherlands, this new guideline (the so-called 'Beweerichtlijn') has adjusted the MET values for certain activities and in addition they now recommend that adults also do muscle and skeletal-strengthening activities at least twice a week [37]. As we did not include questions specifically directed towards strength training in our study, we cannot retrospectively assess compliance with these new guidelines. Among the general population it is known that only 45% meet the recommendations of the newer guideline, whereas 75% of the general adult population met the Combinorm criteria that were used in our study [55]. Our expectation is that if we were able to apply the newer RIVM guidelines, we would have found a lower proportion of patients meeting the criteria for healthy levels of physical activity. New research is needed to assess compliance among cardiac (surgery) patients with these newer guidelines.

In summary, we are the first to have used the SQUASH questionnaire to quantify levels of physical activity among cardiac surgical patients. We have found that among 100 low to medium-risk patients undergoing elective coronary artery bypass surgery, 76% fulfilled the then current Dutch guidelines for physical activity. Although a significant association was found between preoperative levels of physical activity and cardiac risk (indicated by logistic EuroSCORE), studies are needed to determine if this relationship is causal. Consistent with previous studies, the degree of physical activity appeared to correlate significantly with the level of inflammatory response to surgery, as measured in peak postoperative CRP. This however, was not associated with postoperative complications or

cognitive performance. This finding requires further verification in studies specifically powered to examine these associations. Finally, the SQUASH, as well as measurements for grip strength were easy to administer and feasible to use in our population of patients.

Supporting information

Supplementary information associated with this article can be found online at <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0240128#sec021>

S1 Table Components of the Short Questionnaire to Assess Health (SQUASH)

S2 Table Different intensity categories for physical activities based on age and Metabolic Equivalent of Task (MET) according to values assigned in the Ainsworth compendium for physical activity.

S3 Table Univariate logistic regression for patients meeting the preoperative physical activity according to the combinorm..

S4 Table Pre-operative physical activity and frailty assessments.

S5 Table Univariate and multivariate logistic regression analyses for postoperative neurocognitive disorder (PNCD)

S6 Table. Standardized scores for each cognitive domain prior to surgery, physically active vs. physically inactive.

S7 Table. Preoperative neuropsychological and wellbeing test results.

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Title

Physical activity and dose-characteristics in free-living conditions among patients awaiting coronary artery bypass graft surgery: a cross-sectional study

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ABSTRACT

Background: Physical activity prior to elective coronary artery bypass grafting (CABG) surgery can potentially improve postoperative outcomes. The aim of the study was to evaluate subjectively and objectively physical activity levels and dose-characteristics in free-living conditions in patients awaiting CABG surgery.

Methods: A single-centered cross-sectional subanalysis of 32 participants awaiting elective CABG surgery. Physical activity during the preoperative period was assessed subjectively with the SQUASH questionnaire and objectively with the Sensewear activity monitor (accelerometer with physiological sensors). The Wilcoxon signed-rank test was used to assess differences and Bland-Altman plots were used to assess the agreement between the measurement methods. Descriptive statistics were used for the dose-characteristics and Cohen's Kappa for the proportion of participants fulfilling the Dutch guideline for healthy physical activity (NNGB).

Results: Duration of vigorous activity was significantly higher when measured subjectively (120 min/week) than objectively (7 min/week, $p = 0.001$). Bland-Altman plots showed that differences between the methods increased with longer durations of moderate and total activity. The dose-characteristics of physical activity measured with the SQUASH varied widely among the participants and it consisted mainly of leisure time activities and light household activities. The percentage of participants complying with the NNGB guideline was 74% when measured subjectively and 90% when measured objectively ($\kappa = 0.259$, $p = 0.089$).

Conclusions: Surprisingly, both measurement methods suggest that the majority of patients awaiting CABG surgery met the recommendations of the NNGB guideline. The agreement between the methods however decreased with higher physical activity levels. Despite its

43 limitations, the study suggests the complementary value of a subjective and objective
44 measurement of physical activity in free-living conditions among CABG patients.

45 **KEYWORDS:** Exercise, Cardiac Surgical Procedures, Accelerometry, Prevention,
46 Preoperative Period, Self Report, Fitness Trackers, Adult, Activities of Daily Living, Healthy
47 Lifestyle

48

49

BACKGROUND

Patients presenting for coronary artery bypass grafting (CABG) surgery are commonly thought to have an unhealthy and inactive lifestyle [1–3]. In addition, and possibly because of lifestyle risks, these patients usually have a pre-existing low-level baseline inflammatory state [4]. This may predispose them to an exaggerated inflammatory response to surgical insults, thereby increasing the risk of postoperative cognitive, cardiovascular, and pulmonary dysfunction [4, 5]. Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that results in energy expenditure [6]. PA before surgery, also as implemented in preoperative rehabilitation programmes (prehabilitation), can indeed help to attenuate the inflammatory state and to optimise the physiological reserves for surgery, and thereby improve postoperative outcomes and recovery [4, 5, 7–9]. Levels of PA and its dose-characteristics are largely unknown in this population [10], yet are deemed important from an exercise physiological and health perspective in the initiation and planning of preoperative rehabilitation or other preventive measures for patient groups as well as at the individual level [11].

Multiple types of assessments for measuring the level of PA are used depending on financial and research resources [12, 13]. Questionnaires are the preferred strategy to assess PA in larger populations and have also been used in studies of PA prior to cardiac surgery [13–18]. The Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) is a reliable and validated tool that is widely used to assess PA in the Netherlands [19]. While self-report measures like the SQUASH are easy to implement, offer a very low burden to participants, and are relatively inexpensive, they are thought to be subject to recall bias [12, 13].

Highly accurate objective methods do exist, including the doubly labelled water (DLW) method which is considered the 'gold standard' for measuring levels of energy

expenditure (EE) of PA during free-living conditions [12, 13]. These objective methods are, however, very expensive and impractical for clinical research.

Alternatively, portable activity monitors offer a more practical method of objective PA assessment [12, 13]. Their advantage is that they provide information about PA in free-living conditions, while remaining less expensive than the highly accurate objective methods and are less vulnerable to responder bias associated with questionnaires. Nonetheless, activity monitors can be more burdensome for subjects because they need to be worn for multiple days. The Sensewear (Bodymedia, Pittsburgh, PA, USA) is a portable activity monitor that has been shown to accurately estimate total energy expenditure for older adults in free-living conditions in comparison to the DLW method [20–22]. Accelerometers like the Sensewear have been used for PA monitoring in a variety of cardiac patient groups, especially for assessing the effect of postoperative cardiac rehabilitation, but little is known about PA levels during regular daily life in patients awaiting cardiac surgery [21, 23–28]. To our knowledge, no study has yet evaluated PA levels in free-living conditions in patients awaiting CABG surgery measured both subjectively via a questionnaire and objectively with an accelerometer.

People with cardiovascular problems, especially those awaiting CABG, are expected to be less physically active than the overall population. The Dutch guideline for healthy PA (‘Nederlandse Norm Gezond Bewegen’ NNGB) is similar to the recommendations from the World Health Organization and other national recommendations, and recommended that adults should be physically active with moderate intensity for at least half an hour on at least five days per week, but preferably every day [29].

Questionnaires and monitors for assessing PA, like the SQUASH and Sensewear, have been designed and validated in the healthy population, but not yet in cardiac surgery patients who are likely to respond to PA differently due to their limited cardiac reserve. The first aim of this cross-sectional study was to evaluate the levels of PA in free-living conditions

subjectively by using the SQUASH questionnaire and objectively by using the portable activity monitor Sensewear among patients awaiting CABG surgery. Secondary objectives of the study were to evaluate the dose-characteristics of PA in this patient group and compare the results of both methods to the Dutch guideline for healthy physical activity (NNGB). The results of this study could offer insight into the expectations of preoperative rehabilitation (prehabilitation) programmes for this patient group [30].

METHODS

Design overview

This study is a cross-sectional subanalysis of data nested within the ‘Sarcopenia study’. The Sarcopenia study was a single-centered longitudinal observational study analysing levels of perioperative PA and postoperative outcomes in CABG patients. Details of the study protocol, including the sample size calculation, are described elsewhere [31]. The study was approved by the medical ethics committee (METC: reference number 2014/219) of the University Medical Centre Groningen (UMCG), the Netherlands, and all included participants gave written informed consent. All participants in the Sarcopenia study were asked to complete the SQUASH questionnaire and to undergo assessments for mental, cognitive, and physical health. There are no guidelines for physical activity in patient awaiting elective CABG surgery in the Dutch hospital environment. Patients awaiting CABG surgery were generally advised to continue their usual activities as much as possible without triggering symptoms. Patient and surgical characteristics, including blood samples, were routinely collected in surgical databases as part of usual care procedure.

After the start of the study, the ethics committee approved an application to amend the protocol to allow use of the Sensewear monitor as well. The current study only involved the

data of the participants who used the Sensewear monitor and received their operations between December 2015 and March 2017. The investigation conforms with the principles outlined in the Declaration of Helsinki.

Participants

Patients scheduled for elective coronary artery bypass grafting surgery at the UMCG were included in this study. Recruitment took place during the preoperative screening after the consultation with the anaesthesiologist. Further inclusion criteria of the Sarcopenia study were that participants must have been above 18 years old, had to be able to stand and walk independently and perform the tests of physical fitness and cognitive functioning.

Exclusion criteria as stated by the Sarcopenia study protocol were a combination of CABG with a valve procedure or reoperations, if postoperative intensive care stay was expected to be extended, or a recent history of depression or severe anxiety, or a history of cognitive impairment (i.e., dementia, other neurological disorders, stroke, or other severe cerebrovascular insults). Patients were excluded if they were unable to understand or read Dutch instructions.

Self-reported physical activity

Participants were asked to fill in the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) after their preoperative anaesthetic screening visit. It is a standardised self-reported recall questionnaire which consists of both open and closed questions to assess the dose-characteristics (i.e., frequency, the duration, and the perceived intensity) of several activities of an average week in recent months [19]. There are four recordable domains of activity in the SQUASH: commuting, activities at work, household

activities, and leisure time. Outcome measures of the SQUASH questionnaire were the durations of PA in the intensity categories (min/ week, light, moderate, and vigorous), dose-characteristics of PA, and the proportion of participants fulfilling the NNGB guideline. Dose-characteristics for each activity domain were evaluated in terms of frequency (times/ week), duration (min/week), intensity score, and activity score.

Data analysis self-reported physical activity

A syntax file for IBM SPSS statistical package (version 22, SPSS, Inc., Chicago, Illinois, U.S.A.) was used to evaluate the outcome measures of the SQUASH questionnaire, as per Wendel-Vos et al., 2003 [19]. We applied the classification used in Ainsworth's compendium of physical activities to assign each activity reported in the SQUASH questionnaire a metabolic equivalent of task (MET) score [32]. With the MET cut-off scores the activity was assigned to an intensity category (Table 1). The time spent on activities in the specified intensity categories and in the specific activity domains were summed. Time spent in total activity was the summation of moderate and vigorous activity.

Furthermore, an intensity score was given to the activity in each domain by a combination of the perceived intensity reported by the participants in the questionnaire and the intensity category based on Ainsworth's compendium [32]. The intensity score was 1-3 MET for light, 4-6 MET for moderate, and 7-9 MET for vigorous level according to the compendium, sequentially from light, moderate to vigorous according to the perceived intensity. In addition, an activity score was computed by multiplying the total minutes of the activity with its intensity score. Finally, we determined whether the PA of individual participants met the NNGB guideline in existence at the time. The NNGB recommended that adults should be physically active with moderate intensity for at least half an hour on at least

five days per week, but preferably every day [29]. This may be considered as 150 min/ week, which is the duration recommended by the current World Health Organization (WHO) guideline [10]. Thus, we considered participants to have met the NNGB guideline if they reported that they had been moderately or vigorously active for at least 150 min/week.

Portable physical activity monitor

After the preoperative anaesthetic screening visit, participants were given the Sensewear Mini Armband Model MF-SW (Bodymedia, Pittsburgh, PA, USA). They were given verbal and written instructions about the use of this device. The device contains multiple sensors of acceleration in three axes, heat flux, skin temperature and galvanic skin response. The Sensewear has been validated for estimating daily energy expenditure compared with indirect calorimetry and DLW method [20–22]. Data was recorded at a standard epoch length of 60s. Participants were instructed to wear the monitor on the back of the left upper arm in free-living conditions for three consecutive days, also during the night, leaving it off one hour per day and removing it to perform water-based activities. Participants received no instructions on which specific days the device should have been worn. The device had no on/off button and turned on and began collecting data within ten minutes of being worn. Participants were asked to fill in an additional daily logbook about their physical activities during the days that the device was worn. The Sensewear was used to determine which participants fulfilled the NNGB guideline, the durations of PA in the intensity categories (min/week, sedentary, moderate, and vigorous) and total energy expenditure (kcal).

Data analysis portable physical activity monitor

The Sensewear software (SenseWear 8.1, Bodymedia, Pittsburgh, PA, USA), which takes account of patient characteristics (i.e., age, gender, weight, height, handedness, and

smoker/non-smoker), determined the amount and intensity of PA during each day (Table 1). Only valid days, defined as days when the Sensewear was worn for more than ten waking hours, were included in the analysis. The durations of PA in the intensity categories during waking hours and total energy expenditure of the entire day were calculated, averaged over the valid days, and extrapolated to a whole week (multiplied by seven) in MATLAB (version R2014a, Mathworks, Natick, Massachusetts, U.S.A.). Subsequently, the data in MATLAB was exported to a Microsoft excel file (version 2010, Redmond, WA, U.S.A) which was imported into the SPSS database. The duration of total activity was the summation of moderate and vigorous activity. The total duration of moderate and vigorous activity per participant was used to determine whether the Sensewear data indicated that the PA levels of the participant met the NNGB recommendations.

Table 1 Validated cut-off scores for determining the levels of physical activity using the SQUASH questionnaire and the Sensewear monitor.

	Light / Sedentary^a		Moderate		Vigorous	
Age	SQUASH	Sensewear	SQUASH	Sensewear	SQUASH	Sensewear
18 - 55 years	< 4 MET	< 4 MET	4 – 6.5 MET	4 – 6 MET	≥ 6.5 MET	≥ 6.0 MET
> 55 years	< 3 MET	< 3 MET	3 – 5 MET	3 – 6 MET	≥ 5 MET	≥ 6.0 MET

Abbreviations MET metabolic equivalent of task.

^a SQUASH only light activities, Sensewear combines light activities and sedentary time.

Statistical Analysis

Descriptive statistics of all relevant variables were calculated and analysed with SPSS software (version 22, SPSS, Inc., Chicago, Illinois, U.S.A.). Paired samples t-tests were carried out to assess differences between the two methods measuring moderate, vigorous, and total physical activity. When the data were not normally distributed, the non-parametric equivalent, the Wilcoxon signed-rank test, was used. Bland-Altman plots were prepared with 95% limits of agreement to illustrate the agreement between the two methods for the PA levels [33]. Cohen's Kappa (κ) was used to assess the agreement between the two methods in determining compliance with the NNGB guideline. Two-sided statistical tests were performed and the results considered significant at an alpha of 5%.

RESULTS

Participants

Characteristics of the participants included in this cross-sectional subanalysis are summarized in Table 2 and the flowchart of the included participants and reasons for exclusion are shown in Fig. 1. In one participant the planned CABG procedure was cancelled. The SQUASH questionnaires were completed 28 ± 13 days before surgery. The Sensewear was worn starting 25 ± 13 days before surgery. Sensewear data were available for 59% of the 32 participants included in this subanalysis. Participants wore the Sensewear for an average of 3.8 ± 0.7 days, 1052 ± 150 min a day, 752 ± 159 min when being awake. The mean number of valid days (> 10 h during waking hours) was 2.8 ± 0.6 days. 55% of the participants wore the device during the weekend, and of these participants, 70% wore the device on both weekend days. Of all days we considered valid days of Sensewear use, 32% were weekend days. As a weekend represents 2/7 (29%) of a week, we consider that weekend and week days are proportionally well represented. One participant was excluded from the analysis because the measurement

239 did not contain any valid days. One participant observed skin irritation after wearing the
 240 Sensewear but was able to complete the assessment.

241

242 **Table 2** Patient characteristics (n = 32)

	CABG patients
Age (years)	65 ± 9
Gender (male)	29 (91)
Height (m)	1.77 ± 0.07
Weight (kg)	84 ± 14
BMI (kg/m ²)	27 ± 3
Handedness (Right-handed)	31 (97)
Hypertension	20 (63)
Diabetes Mellitus	7 (22)
COPD	4 (13)
Smoking	5 (16)
Logistic EuroSCORE (n = 31) ^a	4.86 ± 5.33
Preoperative inflammatory markers	
CRP (mg/l)	4 ± 6
Leukocytes (×10 ⁹ /l)	8 ± 2
Thrombocytes (×10 ⁹ /l)	246 ± 56

243 Data are presented as mean ± SD or as the absolute n (%).

244 *Abbreviations BMI* Body Mass Index, *CABG* coronary artery bypass grafting, *COPD* chronic
 245 obstructive pulmonary disease, *CRP* C-reactive protein

246 ^a one participant eventually did not undergo surgery.

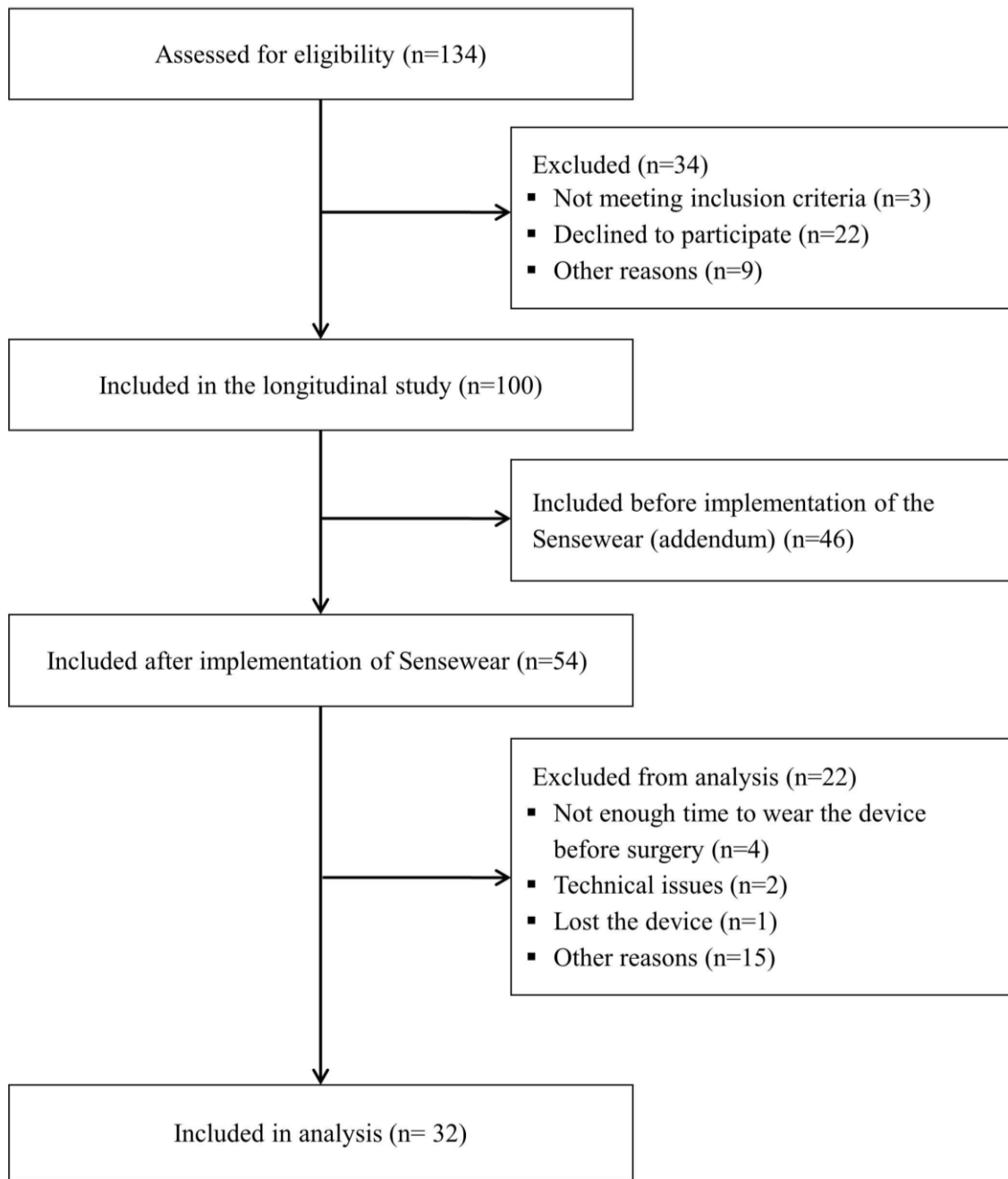


Fig. 1 Flow diagram of participants included in the longitudinal Sarcopenia study [31] and included in the study

Physical activity levels

The durations of PA in the intensity categories as assessed by the two methods are shown in Table 3. The durations of vigorous activities registered by the methods were significantly different. Figure 2 shows that most data points lay between the limits of agreement in the Bland Altman plots, but that differences between the assessments increased with longer durations of activity. Light activities reported via the SQUASH questionnaire had a median [range] duration of 828 [10-3360] min/week. Participants were sedentary according to the Sensewear for a median [range] of 6090 [3885-7203] min/week. The mean $\pm$ SD total daily energy expenditure according to the Sensewear was 2350 ± 532 kcal.

Table 3 Physical activity prior to CABG surgery measured by the SQUASH questionnaire and the Sensewear monitor. (n = 31)

	SQUASH	Sensewear	P value ^a
Moderate (min/week)	180 [0-3150]	483 [7-2884]	0.092
Vigorous (min/week)	120 [0-1035]	7 [0-427]	0.001*
Total (min/week)	480 [0-3150]	490 [7-3031]	0.891

Data are presented as the median [range].

Abbreviations CABG coronary artery bypass grafting

^a non-parametric Wilcoxon signed-rank test.

* significant result $p < 0.05$

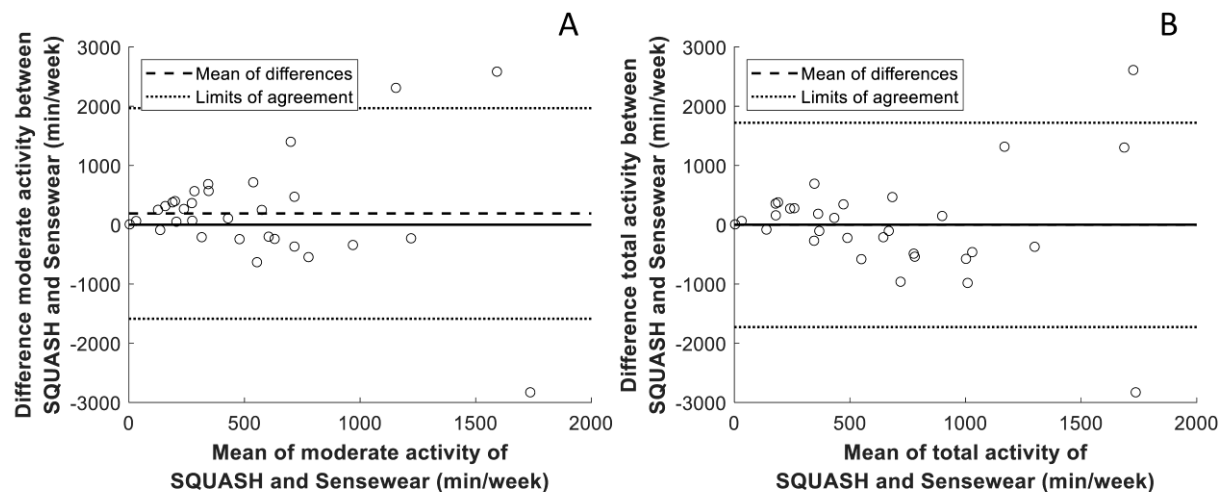


Fig. 2 Bland-Altman plots for moderate (A) and total (B) physical activity (min/week) measured by the self-reported measure, the SQUASH questionnaire, and the arm worn physical activity monitor, the Sensewear, of the patients awaiting coronary artery bypass grafting (n = 31)

Dose-characteristics of physical activity

The evaluation of dose-characteristics determined from the results of the SQUASH questionnaire (Table 4) shows considerable diversity in context and forms of PA as well as in intensity, frequency, and duration among the participants. Moreover, it shows that 10% of participants had walked or cycled to work or school, and mostly only light activities were performed during work (26% of participants). The majority of the participants (84%) reported performing light intensity household activities (median [range] 210 [0-1680] min/week) and 26% of participants performed vigorous household activities (median [range] 0 [0-750] min/week). Leisure time activities mainly consisted of walking (71% of participants, median [range] 105 [0-1050] min/week) and playing sports (65% of participants, median [range] 170 [0-1260] min/week). Among those who engaged in sports, the median [range] estimated MET-value across all reported sports activities was 2.3 [1.3–6.0].

286

287 **Table 4** Physical activity prior to CABG surgery in the four domains of the SQUASH
 288 questionnaire (n = 31)

Domain	Number of participants (n)	Frequency (days/week)	Duration per week (min/week)	Intensity score ^a	Activity score ^b
Commuting	3		0 [0-360]		0 [0-3240]
Walking	0	0	0 [0-0]	0 [0-0]	0 [0-0]
Bicycling	3	0 [0-4]	0 [0-360]	0 [0-9]	0 [0-3240]
Activities at work	9		0 [0-360]		0[0-3240]
Light	8		0 [0-2400]	0 [0-0]	
Intense	1		0 [0-3000]	5 [5-5]	
Household activities	26		240 [0-1800]		0 [0-3750]
Light	26	5 [0-7]	210 [0-1680]	0 [0-0]	0 [0-0]
Intense	8	0 [0-5]	0 [0-750]	5 [5-5]	0 [0-3750]
Leisure time	26		870 [0-1720]		[525-9310]
Walking	22	3 [0-7]	105 [0-1050]	4 [0-6]	600 [0-5250]
Bicycling	11	0 [0-7]	0 [0-630]	0 [0-8]	0 [0-4410]
Gardening	13	0 [0-6]	0 [0-780]	0 [0-8]	0 [0-6240]
Odd jobs	15	0 [0-7]	0 [0-720]	0 [0-6]	0 [0-2880]
Sports	20		170 [0-1260]		0 [0-2400]

289 Data are presented as the median [range] or n.

290 *Abbreviations CABG* coronary artery bypass grafting

291 ^a Intensity based on a combination of perceived intensity and the Ainsworth compendium

following Wendel-Vos et al., 2003.

^b Activity score = minutes/week x intensity score.

Dutch guideline for healthy physical activity (NNGB)

Analysis of the SQUASH questionnaire results revealed that 74% of the participants met the NNGB guideline for healthy physical activity, whereas the results from the Sensewear monitor suggested that 90% of the participants fulfilled the NNGB guideline. The agreement between the measurements had a Cohen's Kappa value of 0.259 ($p = 0.089$).

DISCUSSION

The aim of this cross-sectional study was to evaluate the levels of PA and dose-characteristics in free-living conditions by using a subjective and objective method in patients awaiting CABG surgery. For vigorous levels of PA, the self-reported duration was much higher than the objectively measured duration. In general, the objectively measured duration of vigorous activity was minimal. Differences between the assessments increased with longer durations of moderate and total activity. The dose-characteristics of PA varied widely among the participants and it consisted mainly of leisure time activities and light household activities, and almost no activities during commuting and work. A non-significant, fair agreement was observed between the two methods for determining whether participants met the NNGB guideline.

Little is known about PA levels prior to CABG surgery, especially when assessed with activity monitors in free-living conditions [14, 15]. In this study, the majority of participants met the criteria of the NNGB guideline before surgery. Interestingly, the proportion of the general Dutch population who complied with the NNGB guideline was lower than the

percentage than we found among our patients, regardless of whether it was assessed with the SQUASH questionnaire or the Sensewear [34]. This was contrary to our expectation that CABG patients would have lower levels of PA, since inactivity, among others, is a risk factor for arteriosclerosis.

This finding may be associated with the appreciation and perceptions of patients of their PA in the context of a potentially reduced physical work capacity, fear of exercise-induced chest pain, or breathlessness, and their tendency to higher levels of perceived fatigue, which will be different from those in the healthy population [35]. It is notable that the Sensewear data, which was an objective assessment, also showed high levels of total PA. This might be because the Sensewear also measures heat flux, skin temperature and the galvanic skin response in addition to monitoring movement, and these measurements provide an objective assessment of the influence of the activity on the cardiovascular system, showing higher activity intensities for activities that are less demanding on healthier patients. Thus, cardiac patients could have experienced their exercise as more intense, they actually performed more PA compared to the general Dutch population, or both.

Although total physical activity appears high for this patient group, total energy expenditure was lower than that reported in healthy adults using the DLW method [36]. It is possible that after bouts of moderate or vigorous exercise, participants were more sedentary and/ or resting causing a reduction in their total daily energy expenditure. Total energy expenditure might be a more appropriate measure for the level of PA throughout the day, consistent with the updated WHO guidelines that stated that every bout of PA is relevant, including those lasting less than 10 min [10]. However, it is not possible to capture total energy expenditure using questionnaires, the method preferred for evaluation of the behaviour of larger populations. Participants in our study were sedentary for the majority of the day, which is similar to the findings of other studies of patients undergoing cardiac rehabilitation

[24, 25]. As a sedentary lifestyle increases the risk of postoperative complications and mortality, to limit the amount of time that patients are sedentary might be worthwhile in this patient group [37]. The updated WHO guidelines also shows the importance of the whole spectrum of PA, implying that a decreasing time spent sedentary by spending a longer duration on light activities is also beneficial [38]. Nonetheless, more research on PA among specific patient populations, such patients requiring cardiac surgery, is needed [38].

Although subjective and objective methods showed high levels of PA in our study, the agreement between these two methods was rather low. The results of the Bland-Altman plots show that when PA increases, for both moderate and total physical activity, the agreement between the two methods decreases. These results seem to be consistent with other research which found that self-reported measures tend to overestimate PA levels compared to objective measures [14, 21]. An explanation for the lower levels of agreement may be that the validated methods use different data processing techniques and MET cut-off scores. Furthermore, these underlying algorithms are largely based on studies in healthy individuals [15, 21, 23]. A trend can be observed where the technology of PA devices is improving, but validation studies remain scarce, particularly studies involving patient specific algorithms that could potentially have higher validity than algorithms designed for healthy populations [39]. A study using the Sensewear in healthy adults found that it underestimated higher intensities of PA, but it is unknown if this also applies to patients with cardiovascular problems [22]. Both the perceived and the objective PA construct require validation among specific patient groups, including ours, and should be updated with the most recent available data [39].

Little is known about PA behaviour in patient populations in terms of dose-characteristics (i.e., context, form, duration, intensity, frequency). It is assumed that both the subjective SQUASH and the objective Sensewear methods have their value, largely complementary to one another. This complementary value has been emphasized in a recent

review, which notes that none of the device-based PA tools can fully capture the complete construct of PA, including its dose-characteristics [39]. Indeed, the Sensewear provides an objective intensity and duration indicator of accelerometry-based PA and energy expenditure throughout the day in free-living conditions, while the SQUASH provides us estimates for similar gross measures, but additionally provides information on context and form-dependent indicators of PA in intensity, frequency, and duration.

In addition to the aforementioned challenges in assessing PA in free-living conditions in patients awaiting elective CABG surgery, these patients may be at risk during exercise and seem to experience exercise as more intense than the healthy population. Therefore, it is important that these patients can exercise in a safe environment, for example in a structured exercise programme in a rehabilitation centre. Furthermore, such a prehabilitation programme may improve their physical functioning and recovery from surgery [8, 9, 40].

In the time since our study data were collected, research on preventive measures and prehabilitation has gained increasing attention [8], which may have also shifted patients' perspectives on PA before surgery over recent years. It is possible that patients are currently more physically active than in 2015-2017. Indeed, the percentage of individuals adhering to physical activity guidelines has increased over the last decades, both in the general population in the Netherlands and among patients with cardiovascular disease in the United States, although this increase has been minimal [34, 41]. Given those trends, the impact of attempts to implement prehabilitation programmes (which is still not common) probably did not significantly affect current PA behaviour in daily life. Our results can be interpreted as a baseline understanding of PA behaviour during regular daily life in patients awaiting cardiac surgery.

Baseline dose-characteristics of PA in daily life at the group level help understand the construct of PA in patients, are useful for evaluating individual scores and to determine the

dose-characteristics needed to tailor structured PA in prehabilitation [11]. Currently there are no guidelines for preoperative exercise for patients awaiting cardiac surgery, so it is important to evaluate their exercise performance during the programme both subjectively and objectively in order to evaluate the dose-response characteristics in patients prior to CABG [30]. Activity related monitoring and exercise technology may help the development of home-based rehabilitation care, both pre- and postoperatively [8]. In the context of growing healthcare demand in the face of limited and finite personnel and financial resources, such home-based rehabilitation may be cost-effective, particularly if combined with some form of remote supervision or monitoring. Patient safety and supervision are critical here.

Some additional limitations of the study mentioned. Among these limitations is the small sample size combined with the single-centre design, which limits both statistical power and generalizability. Another is selection bias, as it is possible that the more physically active patients agreed to be included in the study. A form of observation bias is also possible, as wearing of the monitor may have reminded participants of the need for physical activity. In addition, the SQUASH questionnaire was completed prior to the period when the Sensewear was worn, and therefore refers to a different period of time. As is usual practice in our institution, patients only have one preoperative anaesthetic screening visit, and it was therefore during this visit that participants were given instructions on how to fill in the questionnaires and use the Sensewear. This probably led to a limited overlap of the two time windows of measurement in each of the two instruments, which is not uncommon in similar studies [21]. Nonetheless, it would have provided more robust results if the two instruments had been used over exactly the same time period. Also, a longer duration of data collection with the Sensewear monitor (at least 7 days) combined with a logbook documenting specific activities and timestamps, would have provided a better time sample of PA. This approach could have improved our understanding of the average PA for a whole week including both

week and weekend days. Despite these (common) limitations in the measurement time frames of both techniques, comparing the two from different perspectives, under the assumption that they both measure complementary aspects of PA, is still valid and helps bridge our lack of understanding of PA (and their dose-characteristics) in daily life among patients awaiting cardiac surgery.

CONCLUSIONS

In a cohort of patients awaiting CABG surgery, both subjective and objective measures of PA suggested that the majority of CABG patients fulfilled the NNGB guideline. However, the agreement between the subjective and objective methods decreased with higher levels of PA. This study suggests that the two methods used in this patient group complement each other, since the SQUASH provides information on context and form-dependent indicators of PA and the Sensewear provides objective intensity and durations of PA and its energy expenditure. Future research should involve a larger group of cardiac surgery patients to determine preoperative levels and the dose-response relationship of PA in order to further help specify physical activity guidelines in this patient group.

ABBREVIATIONS

CABG	Coronary artery bypass grafting
DLW	Doubly labelled water
EE	Energy expenditure
MET	Metabolic equivalent of task
NNGB	The Dutch guideline for healthy physical activity
PA	Physical activity

440 SQUASH Short QUestionnaire to ASsess Health-enhancing physical activity

441 UMCG University Medical Centre Groningen

442 WHO World Health Organization

443

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446

447 Authors' contributions

448 Conceptualization: SD, SRT, LHVvdW, RH, ARA; Formal Analysis, and Methodology: SD,

449 LHVvdW; Investigation and project administration: SD; Data curation: SD; Writing –

450 Original draft: SD; Visualization: SD; Writing -Review and Editing: SRT, IT, SDA, RH,

451 LHVvdW, MAM, ARA; Supervision: LHVvdW, MAM, ARA; Funding Acquisition: SD,

452 MAM, ARA; All authors read and approved the final manuscript.

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458 unrestricted research funding and/or reimbursement for consultancy for Ever Pharma,

459 Terumo, PAION and Philips (all for work unrelated to this study; all payments to institution).

460

461 Data availability

462 All data generated or analysed during this study are included in this published article [and its

463 supplementary information files].

464

465 DECLARATIONS

466 Ethics approval and consent to participate

467 The Sarcopenia study was approved by the ethics committee of the University Medical Centre
468 Groningen (UMCG), the Netherlands, and all included patients gave written informed consent
469 (METC: 2014/219).

470

471 Consent for publication

472 Not applicable.

473

474 Competing interests

475 SD and MAM report grants from “Stichting Beatrixoord Noord-Nederland”, Edwards
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481

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Title

Feasibility of preoperative and postoperative physical rehabilitation for cardiac surgery patients – a longitudinal cohort study

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23 Abstract

24 **Background** This study aimed to determine the feasibility of a preoperative and postoperative (in-
25 and outpatient) physical rehabilitation program, the Heart-ROCQ-pilot program.

26 **Methods** This cohort study included patients undergoing cardiac surgery (including coronary artery
27 bypass graft surgery, valve surgery, aortic surgery, or combinations of these surgeries) and
28 participated in the Heart-ROCQ-pilot program. Feasibility involved compliance and characteristics
29 of bicycle and strength training sessions in the three rehabilitation phases.

30 **Results** Of the eligible patients, 56% (n = 74) participated in the program (41% of exclusions were
31 due to various health reasons). On average across the rehabilitation phases, the compliance rates of
32 bicycle and strength training were 88% and 83%, respectively. Workload to heart rate (W/HR) ratio
33 and total absolute volume load for bicycle and strength training, respectively, improved in each
34 rehabilitation phase ($P < 0.05$). The W/HR-ratio was higher during the last postoperative session
35 compared to the first preoperative session (0.48 to 0.63 W/beat, $P < 0.001$) and similar to the last
36 preoperative session (0.65 to 0.64 W/beat, $P < 0.497$). During less than 1% of the bicycle sessions,
37 patients reported discomfort scores of 5 to 6 (scale 0-10, with higher scores indicating a higher
38 level).

39 **Conclusions** The Heart-ROCQ-pilot program was feasible for patients awaiting cardiac surgery.
40 Patients were very compliant and were able to safely increase the training load before surgery and
41 regained this improvement within eight weeks after surgery.

42

43 **Keywords** Cardiac surgical procedures, Preoperative Exercise, Therapeutics, Observational study,
44 Ergometry, Endurance training, Coronary artery disease

45

46 **Background**

47 Many cardiac surgery patients are in poor physical condition before surgery, and this may affect
48 postoperative surgical outcomes [1–3]. Unfortunately, elective patients experience further declines in
49 physical, social, and psychological functioning during the waiting period for cardiac surgery [4, 5]. A
50 longer waiting period has therefore been assumed to increase the risk of postoperative adverse events
51 and mortality [4, 6]. In addition to the (high) impact of the surgery, patients experience further
52 declines in physical functioning due to inactivity as well as bed rest during hospitalization after
53 surgery [7, 8].

54 Preoperative rehabilitation (prehabilitation) with total body exercises has shown promising
55 effects for the recovery after surgery in both cardiac and non-cardiac patient groups (e.g. improved
56 physical capacity and shorter hospital stay) [9]. However, in cardiac surgery there have only been a
57 limited number of prehabilitation studies, mainly focusing on inspiratory muscle training [10]. Little
58 is known about the feasibility of prehabilitation in this patient group including total body exercises
59 such as bicycle or strength training. As such, there are currently no practice guidelines for exercise
60 training in the preoperative phase [11, 12].

61 Postoperatively, early (inpatient) rehabilitation has been shown to be safe, and to improve
62 exercise capacity and quality of life [13–16]. However, the current guidelines are also limited for
63 early postoperative inpatient rehabilitation. In contrast, postoperative outpatient rehabilitation is well
64 studied and clearly defined in the guidelines, and therefore part of usual care in the Netherlands.
65 Although clear evidence is available for the efficacy of postoperative outpatient rehabilitation (e.g.,
66 reduction in morbidity and mortality), many cardiac surgery patients are not enrolled (40%) in this
67 type of rehabilitation [11, 17]. It is likely that enrolment in postoperative outpatient rehabilitation
68 will increase when prehabilitation is offered [5].

69 Moreover, the combination of preoperative, early postoperative inpatient, and postoperative
70 outpatient cardiac rehabilitation may speed up recovery from surgery, prevent adverse events, and

71 prevent further progression of cardiovascular disease. The Heart-ROCQ-pilot program is one of the
72 first programs with this combination of cardiac rehabilitation. Unlike previous prehabilitation [5, 18–
73 20] or early postoperative (inpatient) programs [13–15] for cardiac surgery patients, the program
74 combines both bicycle and strength training during pre- and postoperative (early in- and outpatient)
75 rehabilitation. Furthermore, the program is multidisciplinary, including guidance from a physical
76 therapist, dietician, and psychologist, which has been suggested to be an effective approach to
77 promote cardiac health and optimize surgical outcomes [21, 22].

78 Studies evaluating preoperative or early postoperative inpatient rehabilitation mainly focus on
79 the effects of a certain protocol, but often do not reflect on the actual capabilities or performance of
80 the patients while executing that protocol. The actual frequency, intensity, and duration of total body
81 exercises are very important for improving physical capacity. Though, it is still unclear what is
82 feasible for this patient group, this is especially true since they may have a greater risk of sudden
83 cardiac death during exercise [12]. Thus, the knowledge gap is that information about the feasibility,
84 including the executed training characteristics and compliance, of a preoperative and postoperative
85 program with total body exercises is scarce, while this may have a great impact on the efficacy of
86 such a program [5, 11–15, 18–20, 23].

87 The aim of this study was therefore to evaluate the feasibility of the Heart-ROCQ-pilot
88 program. Feasibility was assessed through evaluating the compliance and the characteristics of
89 bicycle and strength training sessions during the Heart-ROCQ-pilot program. We hypothesized that
90 patients awaiting cardiac surgery were able to safely exercise pre- and postoperatively and improve
91 the actual bicycle and strength training characteristics (i.e., duration and intensity) during the Heart-
92 ROCQ-pilot program.

93

94 **Methods**

95 **Patients**

96 Data were analysed of a cohort of all consecutive patients (≥ 18 years) scheduled for elective open
97 heart surgery, including coronary artery bypass graft surgery, valve surgery, aortic surgery, or
98 combinations of these surgeries in the University Medical Center Groningen (UMCG), the
99 Netherlands, between March 2015 and August 2016 and who were invited to participate in the Heart-
100 ROCQ-pilot program. Patients from regional hospitals are referred to the Heart Center of Groningen
101 for Heart Team consultation immediately after diagnosis. This process normally takes 2-3 days.
102 After the Heart Team makes a decision about the treatment, the referring cardiologist is notified the
103 same day and the patient is placed on the waiting list within one week for surgery at the UMCG and
104 concomitantly for inclusion in the Heart-ROCQ-pilot program. Patients were excluded if they had
105 comorbidities that prevented participation in one of the program elements (e.g., disorders to the
106 nervous or musculoskeletal system that limit exercise capacity, severe COPD with GOLD
107 classification ≥ 3 , non-coping behaviour, addiction, serious psychological illness) or if exercise was
108 deemed undesirable (i.e., hypertrophic cardiomyopathy, unstable angina, advice from a cardiologist).
109 Furthermore, patients were excluded if they were unable to understand or read Dutch instructions.
110 Patients who did not give permission to use data or who followed an adapted program (i.e., not able
111 to follow bicycle training) were also excluded from the analysis. Data were collected from existing
112 databases and medical records. All collected data were anonymised in according with the Dutch
113 Privacy Law. Ethical approval and consent for the study were waived by the Medical Ethics Board of
114 the UMCG. Since this was a feasibility study, no sample size calculation was done.

115

116 **Heart-ROCQ-pilot program**

117 The Heart-ROCQ-pilot program consists of three phases: preoperative outpatient (PRE phase:
118 minimum of 4 weeks until surgery, 3x/wk.), early postoperative inpatient (POST-in phase: 3 weeks,

119 5x/wk. during a working week), and postoperative outpatient (POST-out phase: 4 weeks, 2x/wk.)
120 rehabilitation (Fig. 1). Key elements of the program were bicycle and strength training (Fig. 1). In
121 order to estimate the individual, initial intensity of bicycle and strength training, different physical
122 tests were performed [12]. Preoperatively, a submaximal bicycle test and six to ten repetition
123 maximum (RM) of six strength exercises (triceps dips, rowing, chest press, seated leg press, seated
124 leg curl, leg extension) were conducted (Fig. 1). The submaximal bicycle test used a 5-25 W/min
125 ramp protocol and was ended when 70% of expected heart rate or expected workload was reached, or
126 standard indications to terminate a test occurred [12]. Postoperatively, at the end of the POST-in
127 phase, a symptom limited ergometer test with a 5-25 W/min ramp protocol and cardiopulmonary
128 measurements was performed (Fig. 1). Expected workload was calculated based on gender, age, and
129 height. The value of the expected workload defined the height of the steps of the ramp protocol.
130 After establishing the initial intensity during the first bicycle training session, training sessions were
131 based on the rate of perceived exertion (RPE; Fig. 1). All bicycle and strength sessions were
132 conducted under the supervision of two physical therapists specialized in cardiac rehabilitation.
133 During bicycle training patients were monitored with continuous 3-wire lead ECG. Additional
134 elements of this multidisciplinary program were swimming, sports and games, inspiratory muscle
135 training, and guidance from a dietician, a psychologist, an occupational health consultant, and a stop-
136 smoking consultant. These elements were not evaluated in the current study.

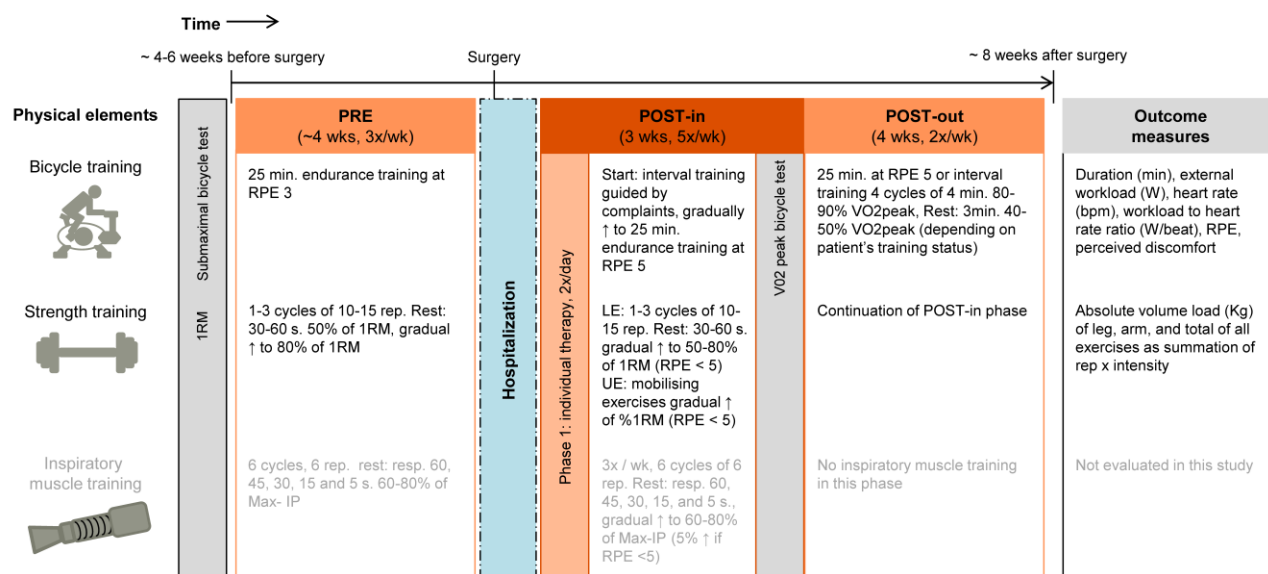


Fig. 1 Overview of the physical elements of the Heart-ROCQ-pilot program. ↑: An increase; LE: lower extremities; Max-IP: Maximum inspiratory pressure; rep: repetitions; RM: repetition maximum; RPE: rate of perceived exertion (Borg scale 0-10); UE: upper extremities; VO2: oxygen uptake

Feasibility

Compliance

Compliance (%) was defined as the number of actual bicycle and strength training sessions completed by the patients relative to the number of offered sessions. The offered sessions were those planned and presented to the patients. The sessions according to the protocol were as prespecified in the protocol (Fig. 1). It was assumed that patients completed a session when data of the training equipment was available. When malfunctioning of the equipment occurred (i.e., no absence was recorded in the patient rehabilitation planning systems, but no data was available for any of the scheduled patients for that session), the patient was assumed to be present during that session. The reasons for not offering a session according to the protocol and a patient's absence were also evaluated.

154

155 **Training characteristics**

156 The training characteristics for bicycle training were duration (min), external workload (W), heart
157 rate (bpm), workload to heart rate ratio (W/HR-ratio [W/beat]), and a subjective evaluation (Fig. 1).
158 Subjective evaluation was assessed on the Borg scale 0-10, with higher scores indicating a higher
159 level of the three components: RPE of fatigue and shortness of breath, and perceived discomfort
160 [24]. The isopower ergometers with ECG (Corival IV Rehab and Lode ECG streamer, Lode)
161 monitored (5 Hz) the external workload and the heart rate. For strength training, the absolute volume
162 load (Kg) of leg (VL-leg, i.e., seated leg press, seated leg curl, and leg extension), arm (VL-arm, i.e.,
163 triceps dips, rowing, and chest press), and total of all exercises (VL-total) were evaluated (Fig. 1).
164 Equipment for strength training (Enraf-Nonius) monitored the training characteristics in sets,
165 repetitions, and intensity.

166

167 **Data analyses**

168 Data of bicycle training was exported using the LCRM software (v2.15.0, Lode). MATLAB
169 (vR2018a, Mathworks) was used to interpolate and filter (8th order low-pass Butterworth, cut-off
170 frequency: 0.1 Hz) the heart rate data. Subsequently, the mean values of external workload and heart
171 rate of the training phase (excluding warm-up and cooling down) over each session were calculated.
172 W/HR-ratio was calculated by dividing the mean external workload by the mean heart rate of the
173 training phase over each session. Data of strength training was exported from the En-Track software
174 (v6.29.4, Enraf-Nonius EN-track). Per session, the VL-arm, VL-leg, and VL-total (Formula 1) were
175 calculated using STATA statistical software (v15.0, StataCorp).

176

177 Formula 1:
$$\sum_{iExercise}^{nExercise} (\sum_{iSet}^{nSet} Repetitions_{iSet} \times Intensity_{iSet})_{iExercise}.$$

178 With iExercise is the number of the exercise and iSet is the number of sets of the exercise [25].

179

180 **Statistical analyses**

181 Statistical analyses were performed using IBM SPSS statistics software (v23). Descriptive statistics
182 were used to present patient characteristics, compliance, RPE, and perceived discomfort. Repeated
183 measures analyses were performed to analyse differences in training characteristics for each
184 rehabilitation phase separately, using external workload, heart rate, W/HR-ratio, VL-leg, VL-arm,
185 and VL-total as dependent variables. The within subject factor was the first and last session of each
186 phase. The analyses were repeated with the last session in the POST-out phase and the first and last
187 sessions in the PRE phase as the within subject factor. Patients were excluded from the analysis of a
188 phase due to missing data when data from only one session in a phase was available or when there
189 were only two sessions available either at the beginning or at the end of a phase. When the data
190 consisted of different sample sizes, separate repeated measures analyses (or paired samples t-tests)
191 were performed. Non-parametric equivalents were performed when the assumption of normal
192 distribution was not met. All statistical tests were two-sided and P-values < 0.05 were considered
193 statistically significant.

194

195 **Results**

196 **Patients**

197 Of the eligible patients, 56% (n = 74) participated in the Heart-ROCQ-pilot program (Fig. 2). Of
198 those excluded, 41% (n = 24) did not meet the exclusion criteria and 59% (n = 35) declined
199 participation mostly due to lack of motivation (n = 25). A further five patients were excluded from
200 the analyses, because the program needed to be adapted (n = 3), they objected to the use of data (n =
201 1) or they underwent congenital surgery (n = 1). The characteristics of the 69 analysed patients are
202 shown in Table 1. Of the included patients, 58% of the surgeries were an isolated CABG and 17%

203 were another surgical procedure than a CABG. Of the remaining proportion, the surgeries were a
204 combination of two interventions (22% of the patients) or three interventions (3% of the patients),
205 which could also be a combination including a CABG. Only six patients underwent an isolated mitral
206 valve surgery, and as institutional policy, isolated mitral valve surgery is performed via minimally
207 invasive right anterolateral thoracotomy at our department.

208

209 **Feasibility**

210 **Compliance**

211 Figure 2 also shows the number of patients included in the analyses of the three rehabilitation phases
212 and the reasons for drop out. Figure 3 shows the number of bicycle and strength training sessions in
213 each rehabilitation phase and the reasons why a session was not planned or completed. All 69
214 patients completed on average 9 and 8 sessions of respectively bicycle and strength training in the
215 PRE phase, which represented a compliance rate of respectively 86.7% and 81.8%. During this
216 phase, one patient was admitted to the hospital due to an infected wound seroma. The surgery of two
217 patients changed from elective to a more urgent basis because of unstable angina pectoris. One of
218 these patients participated for 2.5 weeks in the PRE phase and for the other patient the duration of
219 the PRE phase was 11 weeks (prolonged because of a consultation with a urologist). Postoperatively,
220 eight patients (12%) were readmitted to the hospital (median: 4 days, IQR: 1-8 days), of whom two
221 were readmitted twice. The reasons for readmissions were arrhythmias, dyspnoea, fever, superficial
222 sternal wound infection, and collapsing. After readmissions all patients were able to continue in the
223 same but extended phase ($n = 7$) or the subsequent phase ($n = 1$). The compliance rates of the
224 postoperative rehabilitation phases for both bicycle and strength training were also above 80% (Fig.
225 3). On average across the rehabilitation phases, patients completed 88% and 83% of the offered
226 sessions of bicycle and strength training, respectively.

227

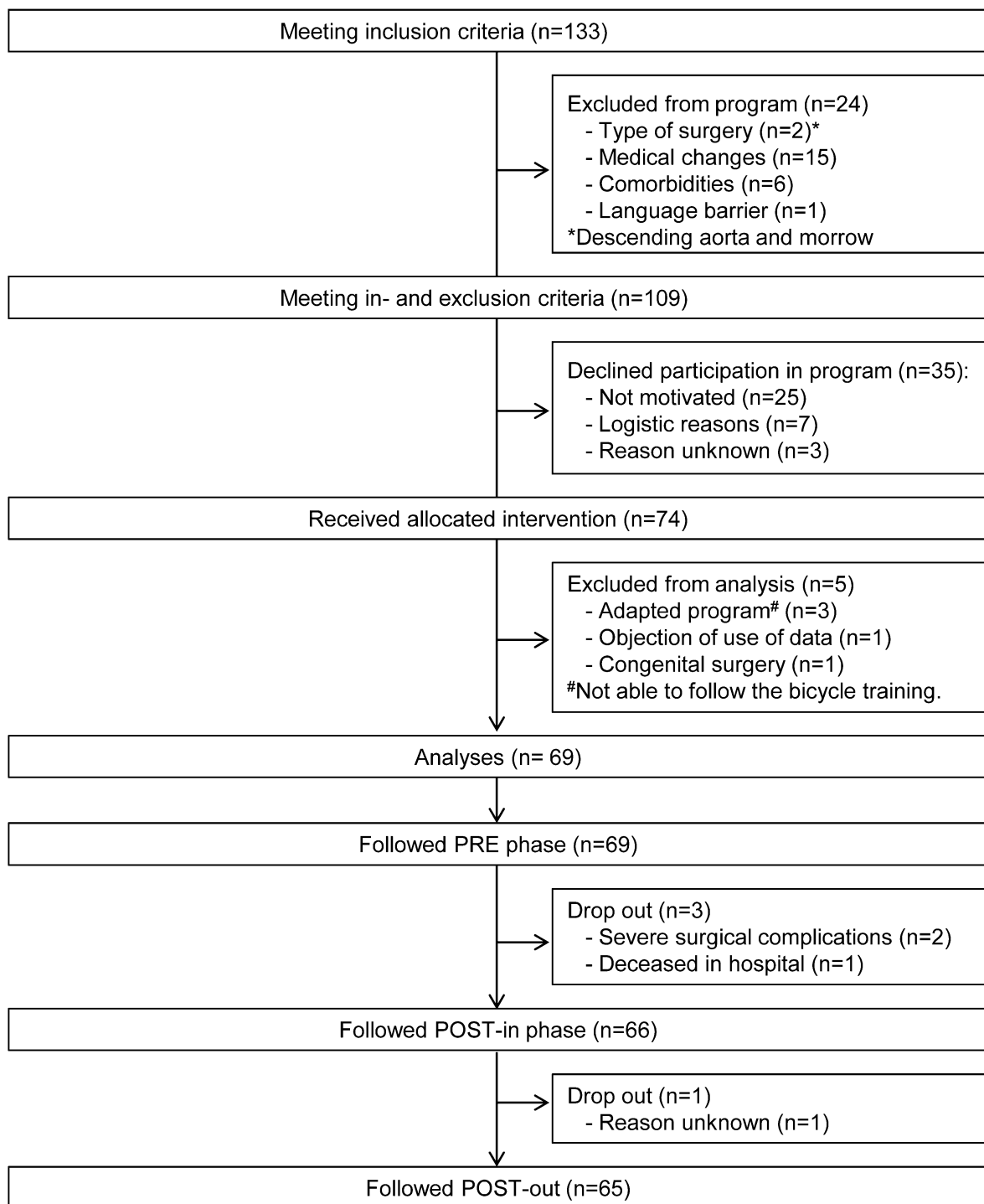


Fig. 2 Consort flow diagram of patients in- and excluded in the Heart-ROCQ-pilot program and drop-outs during the three rehabilitation phases

233 **Table 1** Patient and in-hospital characteristics

Patient preoperative characteristics	Heart-ROCQ-pilot program (n = 69)
Age (years)	65 ± 9.0
Male	53 (77)
Body mass index (Kg/m ²)	27.7 ± 5.0
Left ventricular function (LVF)	
Poor LVF (< 31%)	2 (3)
Moderate LVF (31-50%)	20 (29)
Good LVF (> 50%)	47 (68)
NYHA class	
Class I	4 (6)
Class II	45 (65)
Class III	18 (26)
Class IV	2 (3)
Atrial fibrillation/flutter	13 (19)
Diabetes mellitus	16 (23)
Chronic lung disease ^a	5 (7)
Recent myocardial infarction	6 (9)
Previous percutaneous coronary intervention	19 (28)
Previous cardiac surgery	3 (4)
History of stroke	4 (6)
logistic EuroSCORE II	1.3 (0.9-2.2)
In-hospital characteristics	
Type of surgery	
CABG isolated	40 (58)
Single, non-CABG	12 (17)
- Valve procedure	11 (92)
- Aorta surgery	1 (8)
Two interventions	15 (22)
Three interventions	2 (3)
On-pump surgery	37 (54)
Bypass time (min)	160.3 ± 87.0
Cross clamp time (min)	105.4 ± 69.7
Surgery time (min)	237.1 ± 93.9
Prolonged mechanical ventilation > 24u	5 (7)
Prolonged ICU stay ^b	11 (16)
Re-admission ICU	5 (7)
Hospital stay (days, median (IQR))	6 (6-10)
Hospital mortality	1 (1)

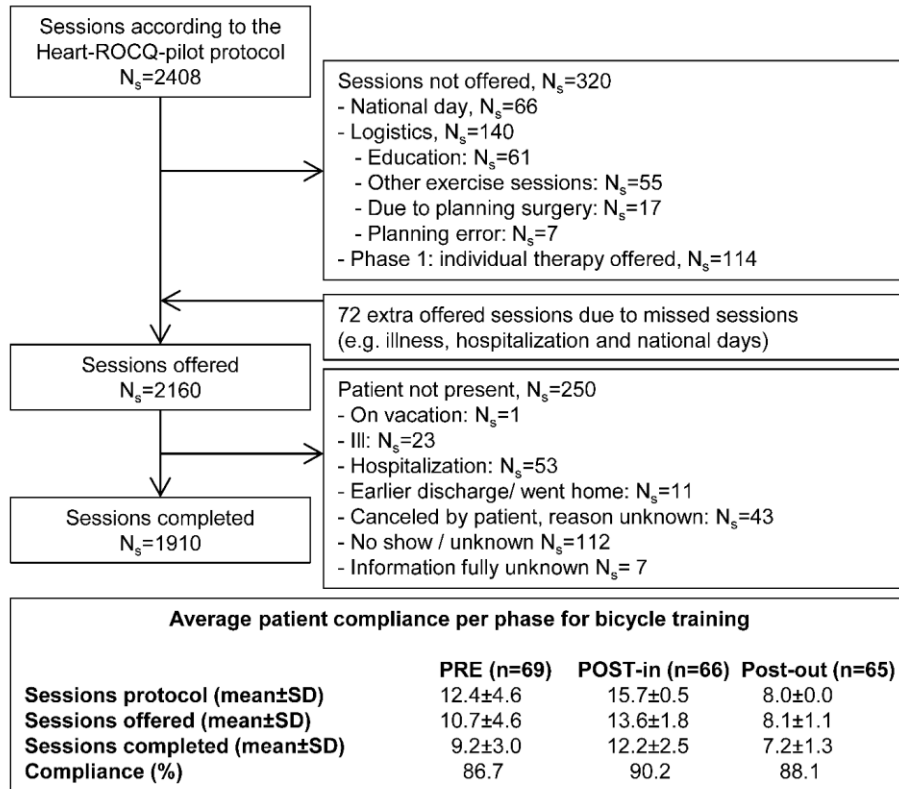
234 Values expressed as mean ± SD or n (% yes), unless otherwise noted. CABG: Coronary artery

235 bypass graft; ICU: Intensive care unit.

236 ^aLong-term use of bronchodilators or steroids for lung disease.

237 ^bTwo or more calendar days from ICU admission to discharge.

A



B

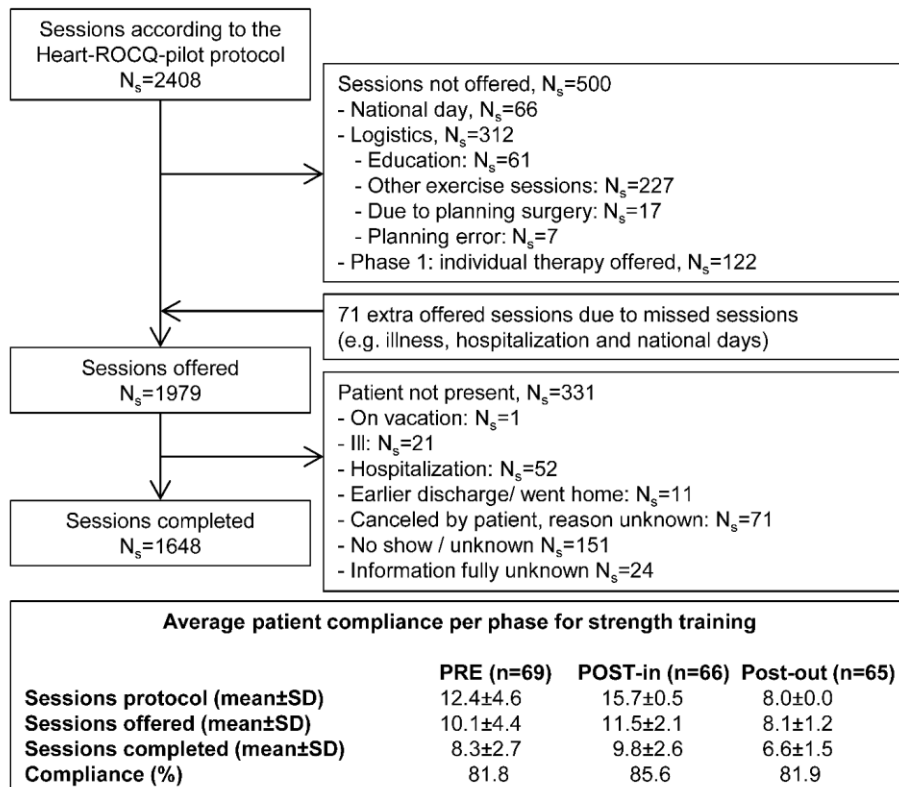


Fig. 3 Number of bicycle (A) and strength (B) training sessions in the three rehabilitation phases according to the protocol, offered to and actually completed by the patients. n: number of patients; Ns: number of sessions

242

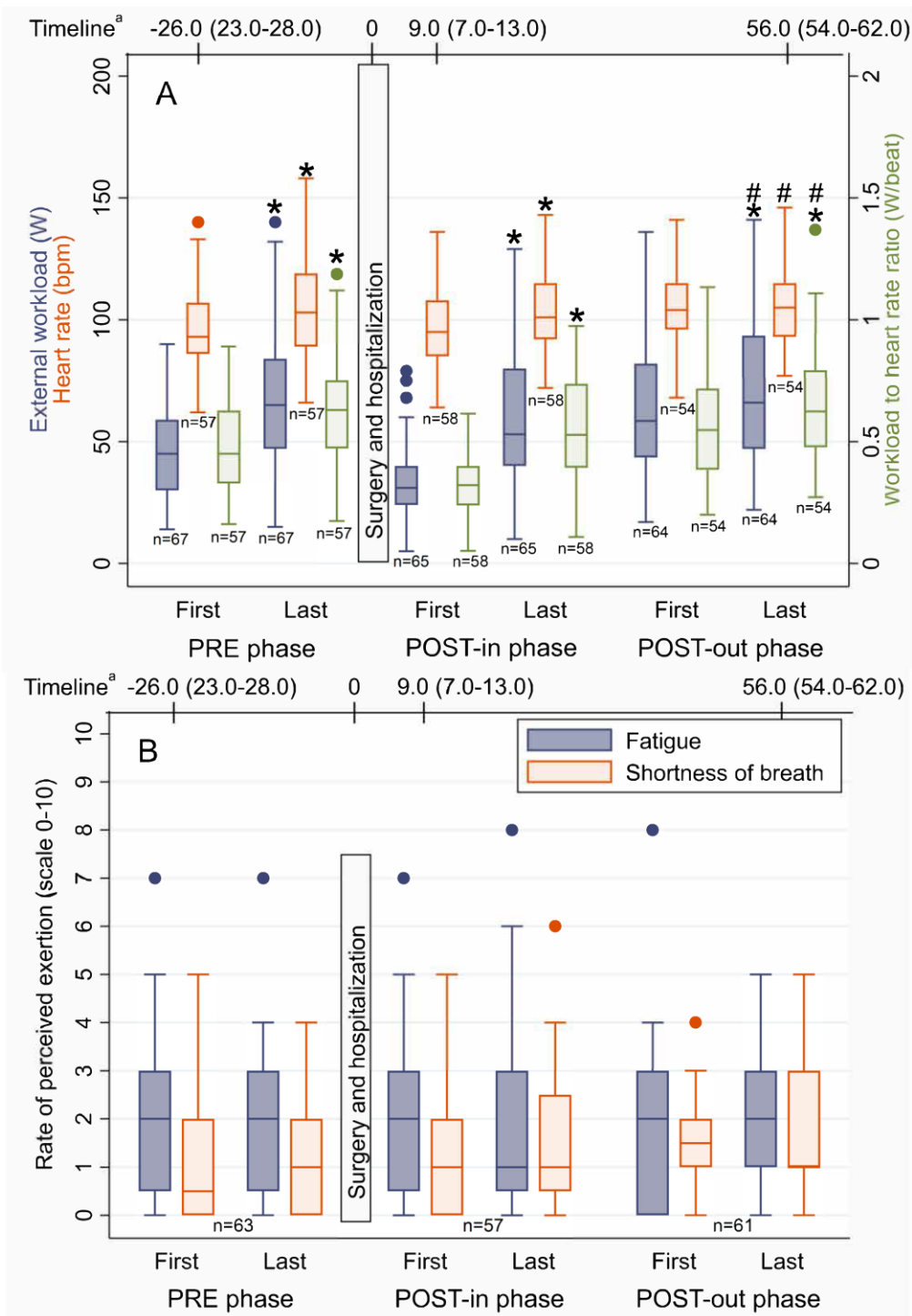
243 **Training characteristics**

244 The median duration of the PRE phase from the initial bicycle test was 38 days (IQR: 37-42) during
245 a waiting time with a median duration of 55 days (IQR: 50-66) (from the day of acceptance to
246 surgery). At the start of the POST-in phase, patients received individual therapy for a median of 2
247 days (IQR: 1-2) with a maximum of 6 days. Patients started at a median of 8 days (IQR: 7-12) after
248 surgery with group sessions of bicycle and strength training. Details about the physical tests to
249 determine the individual, initial training intensity are shown in S1 Table (see Additional file 1).

250 The results of the bicycle training are shown in Fig. 4 and S2 Table (see Additional file 2). In
251 the PRE- and POST-in phases, external workload, heart rate, and W/HR-ratio significantly increased
252 ($P < 0.05$). In the POST-out phase, external workload increased ($P < 0.001$), while heart rate
253 remained the same ($P = 0.642$), which was reflected in an increase in the W/HR-ratio ($P < 0.001$).
254 These three outcome measures were significantly higher during the last postoperative session
255 compared to the first preoperative session ($p < 0.001$), but similar to the last preoperative session (P
256 > 0.05). Figure 4B shows that the median for RPE of fatigue and shortness of breath was below three
257 in the first and last session in each rehabilitation phase. Patients reported a perceived discomfort
258 score of 0 (scale 0-10, with higher scores indicating a higher level of discomfort) during the majority
259 of all bicycle sessions in the three rehabilitation phases (range of 80-86% across the phases), a
260 discomfort score of 0.5 to 2 in 11-16% of the sessions, and in 3-5% of the sessions a discomfort
261 score of 3 to 4 was reported. In less than 1% of the sessions a score of 5 to 6 for discomfort was
262 reported. The highest level of discomfort was seven, which was reported once during the PRE phase
263 due to pain between the shoulder blades. In 6% of the sessions, no score of perceived discomfort was
264 reported at all.

265

266



267

268 **Fig. 4** Training load of bicycle training at the first and last session of the three rehabilitation phases.

269 (A) External workload, heart rate, and workload to heart rate ratio; (B) Rate of perceived exertion.

270 Differences paired samples t-tests: *first vs. last session in a rehabilitation phase; #first session of

271 PRE phase vs. last session of POST-out phase; +last session of PRE phase vs. last session of POST-

272 out phase. ^a days (Median (IQR)) relative to the surgery

273

274 The median durations of the first and last session of bicycle training of all phases were 25
275 min (excluding warm-up and cooling down), except for the first session of the POST-in phase which
276 had a median of 21 minutes (IQR: 14-25). Because of knee complaints, one patient switched to
277 another ergometric device and was therefore excluded from these analyses. Another patient was
278 excluded from the PRE phase analysis, because only one session was available.

279 Strength training results are shown in Fig. 5 and S3 Table (see Additional file 3) and show
280 significant increases in VL-leg, VL-arm, and VL-total in each rehabilitation phase ($P < 0.05$), except
281 for VL-leg in the PRE phase ($P = 0.124$). The VL-leg during the last postoperative session was
282 significantly higher than the first preoperative session ($P = 0.033$) and was comparable with the last
283 preoperative session ($P = 0.658$). For VL-arm and VL-total the last postoperative session was
284 significantly lower than the first and last preoperative session ($P < 0.05$). At the start of the POST-in
285 phase, patients performed the arm exercises with a median of 2 days (IQR: 0-3) later than the leg
286 exercises. In total, nine patients (PRE: $n = 1$, POST-in: $n = 5$, POST-out: $n = 3$) were excluded from
287 the analysis of that particular phase since only two sessions either at the beginning or at the end of a
288 phase or just one session was available.

289 Due to the introduction of newly developed exercise equipment some additional missing
290 values were present in the first and last session of a training phase. Therefore, in 12% of the sessions
291 the adjacent session was chosen for analysis. In 2% of the cases there was no external workload
292 available in the first, last, or adjacent session, thus the first or last session from which data was
293 available was used. Heart rate data was missing in 31 sessions since it was not completely recorded
294 ($n = 5$) or a high variability was present with no indication of atrial fibrillation ($n = 26$). All analyses
295 of external workload and W/HR-ratio showed similar statistical results when patients with atrial
296 fibrillation were excluded.

297

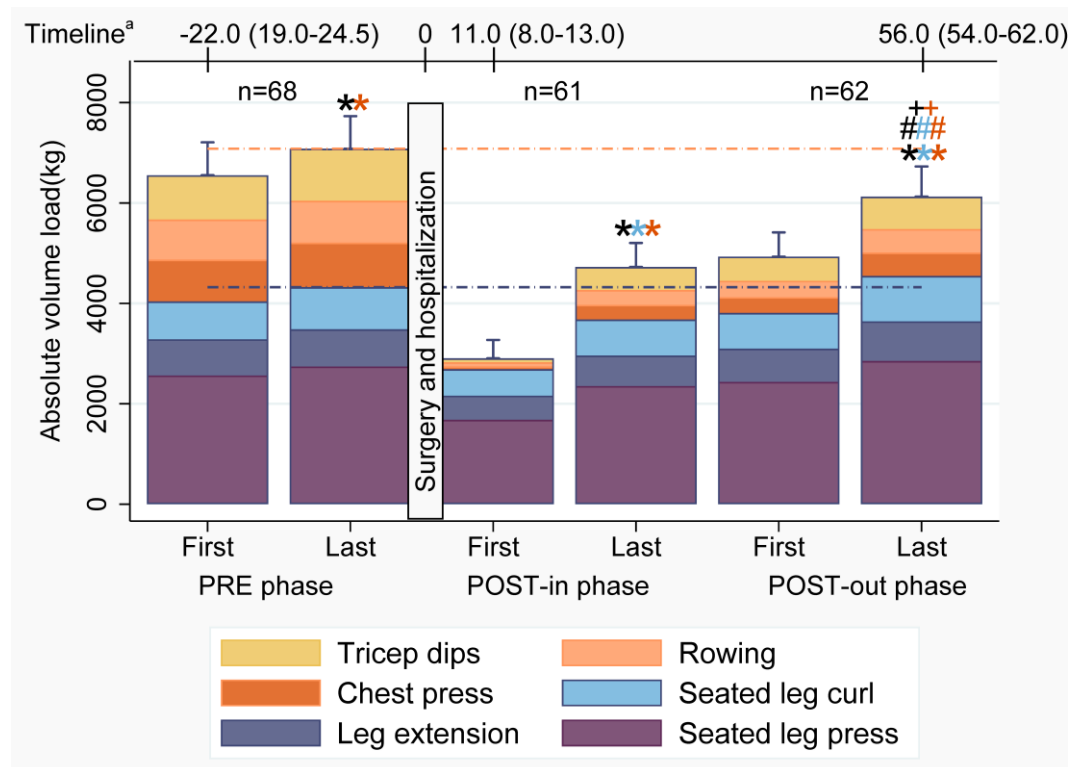


Fig. 5 Absolute volume load (sets*repetitions*intensity) of the strength training at the first and last session of the three rehabilitation phases. Mean with upper limit of 95% confidence interval are shown. Differences of repeated measures analyses of all exercises (black), leg exercises (blue), and the arm exercises (orange): *first vs. last session in a rehabilitation phase; #first session of PRE phase vs. last session of POST-out phase; +last session of PRE phase vs. last session of POST-out phase. ^a days (Median (IQR)) relative to the surgery

Discussion

The purpose of this study was to determine the feasibility of the Heart-ROCQ-pilot program with preoperative and postoperative (in- and outpatient) physical rehabilitation in elective cardiac surgery patients. The results showed that 56% of eligible patients participated in the program. Patients completed on average 88% and 83% of the offered sessions of bicycle and strength training, respectively. In each phase the external workload and W/HR-ratio during bicycle training increased significantly. The same applied to the VL-total during strength training. During the majority of the sessions (80-86% in the three rehabilitation phases) no discomforts (score 0) were reported and patients rarely (< 1% of the sessions) reported discomfort scores of 5 to 6 (scale 0-10, with higher scores indicating a higher level of discomfort).

The sample of this study was representative with respect to patient characteristics compared to the Dutch population undergoing cardiac surgery [26]. Furthermore, the enrolment in the Heart-ROCQ-pilot program was comparable to usual care cardiac rehabilitation in the Netherlands [17] and the United States [27], and other prehabilitation studies [5, 18, 19, 23]. Remarkably, patients included in the Heart-ROCQ-pilot program underwent higher-risk surgeries as well (seen as a wide range in EuroSCORE), compared to previous prehabilitation studies [5, 18, 19]. Despite the additional types of sessions due to the multidisciplinary nature and intensive postoperative inpatient program when compared to other prehabilitation programs, patients were very compliant to the Heart-ROCQ-pilot program [5, 18, 23]. These findings suggest that this program is well suitable for “all-comers” undergoing cardiac surgery.

To our knowledge, this is the first study that present detailed information about the training characteristics and trainability of patients before and early after cardiac surgery. Evaluating training characteristics provided insights into the capabilities and performance of patients during physical cardiac rehabilitation. This is paramount for the efficacy of any such cardiac rehabilitation program. The results of the training characteristics of the bicycle sessions (increases in W/HR-ratio and

workload in each of the three rehabilitation phases, but without changes in heart rate in the POST-out phase and RPE values in all three phases) indicate better cardiac functioning and thereby improved exercise tolerance. Furthermore, these findings suggest that patients listed for cardiac surgery are able to improve their training load. Within eight weeks after surgery, patients improved their training load during bicycle training and leg strength exercises compared to the first session preoperatively. Patients were, however, not able to recover to their preoperative load regarding arm exercises. This is probably because of the healing process of the sternotomy in the first six to eight weeks after surgery, where patients trained at lower frequencies and intensities to accommodate [11, 12]. Bicycle and strength training, especially leg exercises, were thus feasible components of the Heart-ROCQ-pilot program.

Since cardiac surgery patients may have a greater risk of sudden cardiac death during exercise, safety is very important [12]. To ensure safety, several measures have been included in the Heart-ROCQ-pilot program. In close collaboration with the supervising cardiologists, only patients without unstable angina or progressions in complaints were referred to the Heart-ROCQ-pilot program. Moreover, all patients underwent bicycle ergometry preoperatively to obtain information on their capability to exercise. In addition, all bicycle sessions were conducted under the supervision of two physical therapists specialized in cardiac rehabilitation and with continuous ECG monitoring. The majority of the patients reported no perceived discomfort and patients rarely reported a score of 5 or higher for perceived discomfort. A previous study suggested that patients participated safely in the preoperative part of the Heart-ROCQ-pilot program and were not at higher risk for postoperative complications, while it might even prevent postoperative atrial fibrillation [28]. Thus, despite their heart disease, our selection of patients were able to safely exercise in the Heart-ROCQ-pilot program prior to and early after cardiac surgery.

This feasibility study was initiated to acquire more insight into the trainability of patients listed for cardiac surgery as a preparation for the design of the Heart-ROCQ PROBE study [29].

357 Little is known about the trainability of patients before (and early) after cardiac surgery, because
358 prehabilitation studies mainly focused on inspiratory muscle training [10] and measurement of
359 maximal exercise capacity is complex in this patient group due to potential medical contra-
360 indications and occurrence of kinesiophobia [12]. The strength of this study is that we circumvented
361 these aspects by evaluating the actual performed training load (W) in combination with how the body
362 responded physiologically (heart rate) and the patient's subjective experience (RPE and perceived
363 discomfort). Patients experienced the strain of bicycle training lower than expected (Fig. 4, RPE
364 medians < 3). Changing the stop criteria of the preoperative submaximal ergometry test from 70 to
365 90% of the expected maximal heart rate will possibly improve the tailoring of the initial training load
366 to the individual. Nevertheless, the external workload during bicycle training in the preoperative
367 phase and at the end of the early postoperative inpatient phase was comparable to those seen in two
368 other studies that showed an improvement in quality of life and a reduced hospital stay in their
369 patient group [5, 13]. Moreover, improvements in training characteristics were shown with the
370 current exercise intensity. The Heart-ROCQ-pilot program could, therefore, possibly reduce physical
371 and psychological risk factors and work as a means of secondary prevention as well by promoting a
372 healthy lifestyle. Our currently ongoing randomized controlled trial, the Heart-ROCQ PROBE study,
373 will show whether these improvements in training characteristics will lead to an enhanced recovery
374 after cardiac surgery [29]. The Heart-ROCQ PROBE study determines the effects of this program on
375 physical and psychological functioning, as well as on the cost-effectiveness and lifestyle risk factors,
376 in comparison to postoperative cardiac rehabilitation provided in usual care [29].

377 This study had some limitations. When interpreting the results, it should be considered that
378 the use of medication, such as beta-blockers, may have changed during the rehabilitation program. In
379 addition, the presence of missing values could have influenced the results. Even though there is
380 always a risk of interferences when using ECG, newly developed exercise equipment showed many
381 interferences in the ECG signals at the start of this study. By improving this equipment, the number

of interferences and thus missing values in heart rate during the study was reduced. Because we used a 3-wire ECG lead, it was not reliable to evaluate ECG changes during the bicycle sessions. A 3-wire ECG lead is, however, easier to use for patients during cardiac rehabilitation. Our study included a relatively small convenience sample of selected group of patients (44% of eligible patients was not included), which in itself impacts the study's generalizability. Characteristics of the group of excluded patients are unknown, though they could possibly be less compliant, since 25 patients were excluded on the basis of a lack of motivation. Patients might be more motivated to participate in a home-based rehabilitation program, especially when rehabilitation centers are far away from where patients live. Therefore, future research should also investigate the feasibility of home-based rehabilitation programs for higher-risk patients as well, such as those awaiting cardiac surgery, while also providing proper monitoring in order to evaluate the trainability and to ensure safety [30]. Moreover, the effect of the program in different types of patients (e.g., in terms of gender or type of underlying disease and its consequent surgery) is unclear and this is deemed to be of interest for future research. The percentage of postoperative readmissions in this study (12% of the patients) was lower compared to earlier reported figures in cardiac surgery (15-25% of the patients) [31]. Since no control group was included, we could not investigate whether this was due to the selected patient group or a better recovery.

Conclusions

The Heart-ROCQ-pilot program was feasible for patients awaiting cardiac surgery. Despite their heart disease, patients were very compliant and were able to safely increase the training load before surgery and regain it within eight weeks after surgery. More research is needed on this promising program to evaluate the effects of preoperative and postoperative physical rehabilitation on surgical outcomes, overall functioning, and health in order to further improve clinical care before and after cardiac surgery.

407

408 **List of abbreviations**

409	POST-in	Early postoperative inpatient rehabilitation
410	POST-out	Postoperative outpatient rehabilitation
411	PRE	Preoperative rehabilitation
412	RM	Repetition maximum
413	RPE	Rate of perceived exertion
414	UMCG	University Medical Center Groningen
415	VL-arm	Absolute volume load for arm exercises
416	VL-leg	Absolute volume load for leg exercises
417	VL-total	Absolute volume load for all exercises
418	W/HR-ratio	Workload to heart rate ratio

419

420 **Supplementary information**

421 The online version contains supplementary material available at [https://doi.org/10.1186/s13102-023-](https://doi.org/10.1186/s13102-023-00786-1)
422 00786-1.

423 Supplementary S1 Table. Test outcomes used to determine the individual, initial training intensity of
424 the Heart-ROCQ-pilot program

425 Supplementary S2 Table. Differences in the characteristics of external workload, heart rate and their
426 ratio of bicycle training at the first and last session in the three rehabilitation phases

427 Supplementary S3 Table. Differences in the characteristics of the absolute volume load of strength
428 training at the first and last session in the three rehabilitation phase

429

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434

435 **Author contributions**

436 Conceptualization: SD, JH, PvdH, JF, LHVvdW, MAM; Formal Analysis, and Methodology: SD,
437 JH, LHVvdW; Investigation and project administration: SD, JH; Data curation: SD, JH; Writing –
438 Original draft: SD, JH; Visualization: JH; Writing -Review and Editing: SD, JH, JF, LHVvdW,
439 MAM; Supervision: JF, LHVvdW, PvdH, MAM; Funding Acquisition: SD, JH, MAM; All authors
440 read and approved the final manuscript.

441

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445 St. Jude Medical Nederland B.V.) [to JH]. The funders had no role in the study design, data
446 collection and analysis, decision to publish, or preparation of the manuscript.

447

448 **Data availability**

449 All data generated or analysed during this study are included in this published article [and its
450 supplementary information files].

451

452 **Declarations**

453 **Ethics approval and consent to participate**

454 All collected data were anonymised in according with the Dutch Privacy Law. Ethical approval and
455 consent for the study were waived by the Medical Ethics Board of the UMCG. The study was
456 conducted according to the principles of the Declaration of Helsinki.

457

458 **Consent for publication**

459 Not applicable.

460

461 **Competing interests**

462 SD, JH, and MAM report grants from “Stichting Beatrixoord Noord-Nederland”, Edwards
463 Lifesciences SA, and Abbott (formerly St. Jude Medical Nederland B.V.). MAM reports consultancy
464 from AtriCure, Getinge, and LivaNova. The remaining authors have nothing to disclose.

465

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1 **Title**

2 **HEART** Rehabilitation in patients awaiting **O**pen heart surgery targeting to prevent **C**omplications
3 and to improve **Q**uality of life (Heart-ROCQ): study protocol for a **P**rospective, **R**andomised, **O**pen,
4 **B**linded **E**ndpoint (PROBE) trial

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29 ABSTRACT

30 Introduction

31 The rising prevalence of modifiable risk factors (eg, obesity, hypertension and physical inactivity) is
32 causing an increase in possible avoidable complications in patients undergoing cardiac surgery. This
33 study aims to assess whether a combined preoperative and postoperative multidisciplinary cardiac
34 rehabilitation (CR) programme (Heart-ROCQ programme) can improve functional status and reduce
35 surgical complications, readmissions and major adverse cardiac events (MACE) as compared with
36 standard care.

37 Methods and analysis

38 Patients (n=350) are randomised to the Heart-ROCQ programme or standard care. The Heart-ROCQ
39 programme consists of a preoperative optimisation phase while waiting for surgery (three times per
40 week, minimum of 3 weeks), a postoperative inpatient phase (3 weeks) and an outpatient CR phase
41 (two times per week, 4 weeks). Patients receive multidisciplinary treatment (eg, physical therapy,
42 dietary advice, psychological sessions and smoking cessation). Standard care consists of 6 weeks of
43 postsurgery outpatient CR with education and physical therapy (two times per week). The primary
44 outcome is a composite weighted score of functional status, surgical complications, readmissions and
45 MACE, and is evaluated by a blinded endpoint committee. The secondary outcomes are length of stay,
46 physical and psychological functioning, lifestyle risk factors, and work participation. Finally, an
47 economic evaluation is performed. Data are collected at six time points: at baseline (start of the waiting
48 period), the day before surgery, at discharge from the hospital, and at 3, 7 and 12 months postsurgery.

49 Ethics and dissemination

50 This study will be conducted according to the principles of the Declaration of Helsinki (V.8, October
51 2013). The protocol has been approved by the Medical Ethical Review Board of the UMCG (no
52 2016/464). Results of this study will be submitted to a peer-reviewed scientific journal and can be
53 presented at national and international conferences.

54 **Trial registration number:** NCT02984449.

55 **Strength and limitations of this study**

- 56 • This is a prospective, randomised, open, blinded endpoint trial.
- 57 • This study is a comparison of a unique multidisciplinary preoperative and postoperative cardiac
58 rehabilitation (CR) programme with a standard care postoperative outpatient CR programme.
- 59 • This study is patient-oriented; primary and secondary outcomes provide a comprehensive and
60 clinically relevant evaluation of patients' recovery from surgery (eg, on physical, psychological
61 and social domains).
- 62 • Both short-term and long-term effects of the CR programmes are included.
- 63 • This is a single-centre study, although patients are referred from four hospitals.

64 INTRODUCTION

65 The leading cause of death in Western countries is ischaemic heart disease.(1) One of the treatments
66 for severe ischaemic heart disease is cardiac surgery. The risk of postoperative complications related
67 to cardiac surgery is substantial; pulmonary complications (up to 33%), delirium (~26%), and
68 arrhythmias (~30%) have been reported to occur.(2–4) These complications are associated with
69 prolonged hospitalisation, increased adverse events (ie, readmission, stroke, myocardial infarction and
70 mortality), reduced health-related quality of life (HRQoL) and higher healthcare costs.(5–10) Patients
71 with poor dietary habits (present in ~80% of the candidates for cardiac surgery), who are physically
72 inactive (~45%), who smoke (22%), or who experience depression and/or anxiety disorders (~30%)
73 are at higher risk for postoperative complications and are at risk for lack of functional benefits after
74 cardiac surgery.(8,11–19)

75 Over the last decades risk factors such as age, obesity, diabetes, hypertension and
76 dyslipidaemia have steadily increased in patients undergoing cardiac surgery.(20,21) Despite their
77 adverse effects on treatment outcomes, reducing the burden of modifiable risk factors is currently not
78 part of standard clinical care before and after cardiac surgery. Before cardiac surgery, patients often
79 have a preoperative period of several weeks on the waiting list in which they receive little or no
80 guidance. This waiting period has been associated with increased psychological stress, feelings of
81 anxiety and reduced functional status.(22,23) With respect to inactivity during hospitalisation after
82 cardiac surgery, research has shown that during the 8-11 days of hospitalisation, patients spent the
83 majority of their time sitting or in a supine position.(24,25) In-hospital physical inactivity is a predictor
84 of a longer hospital stay and rehospitalisation.(24,26,27) It causes a decrease in muscle strength and
85 aerobic capacity, both fundamental in the performance of activities of daily living.(28,29) This reduced
86 physical capacity may seriously impact independence, especially since these patients are often elderly
87 and the functioning of their entire physiological system is already reduced.(30)

88 The goal of cardiac rehabilitation (CR) is to improve the preoperative and postoperative status
89 of patients undergoing cardiac surgery. CR aims 'to favourably influence the underlying cause of
90 cardiovascular disease, as well as to provide the best possible physical, mental, and social

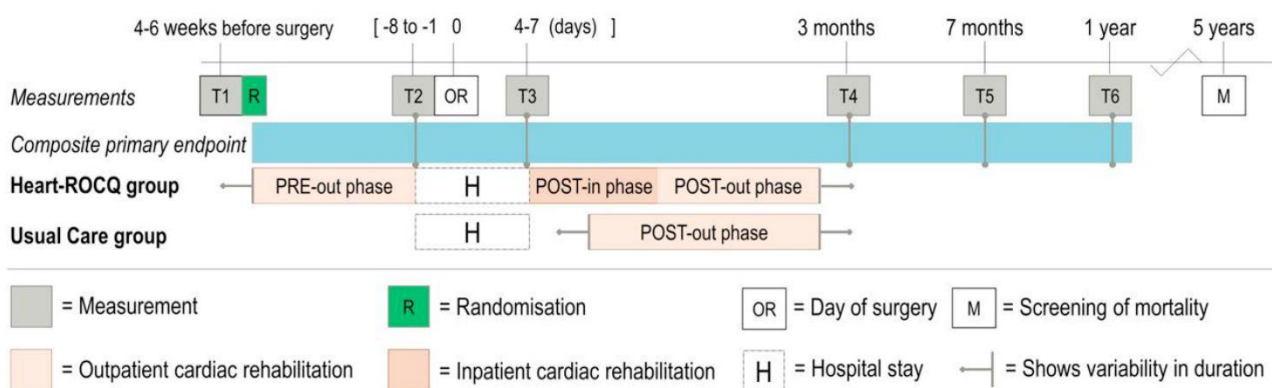
91 conditions'.(31) Postoperative CR is already an essential part of standard care in the Netherlands,
92 although many hospitals in the Netherlands provide a phase II outpatient CR programme starting 3-6
93 weeks after cardiac surgery.(32,33) Benefits of postoperative CR are reported for a variety of cardiac
94 patients(34); however, the evidence in patients undergoing cardiac surgery is still lacking with regard
95 to patient-relevant outcomes and mortality.(35) In addition to postoperative CR, small trials suggested
96 that preoperative CR is effective in reducing postoperative pulmonary complications, duration of
97 hospital stay, improving HRQoL and physical fitness, and increasing the compliance to postoperative
98 CR.(23,36,37) However, long-term effects and the effects on other complications remain unclear.
99 Furthermore, most studies investigated the effect of preoperative CR or postoperative CR, but not the
100 effect of both CR methods combined. The hypothesis is that a combined preoperative and
101 postoperative CR programme is more beneficial when compared with a separate preoperative CR
102 programme or a single postoperative CR programme.

103 The aim of the Heart-ROCQ (Heart Rehabilitation in patients awaiting Open heart surgery
104 targeting to prevent Complications and to improve Quality of life) study is to determine the effect of a
105 comprehensive preoperative and postoperative CR programme (the Heart-ROCQ programme) on
106 functional status, postoperative surgical complications, readmissions to hospital and major adverse
107 cardiac events (MACE) compared with a regular Dutch postoperative outpatient CR programme (the
108 standard care CR programme).(32) In addition, the effect of the Heart-ROCQ programme on physical
109 and psychological functioning, including HRQoL, lifestyle risk factors, work participation and cost-
110 effectiveness, is evaluated in comparison with the standard care CR programme. To assess who will
111 benefit from CR and why the CR programme is effective, moderator and mediator analyses are
112 performed.

METHODS AND ANALYSIS

Study design and organisation

This investigator-initiated, prospective, randomised, open, blinded endpoint trial is executed in a single centre (University Medical Center Groningen (UMCG)). Patients from three referral hospitals (Ommelander Hospital Groningen, Martini Hospital Groningen and Wilhelmina Hospital Assen) who are accepted for cardiac surgery at the UMCG are also approached to participate. Patients are randomly assigned to a combined preoperative and postoperative multidisciplinary CR programme (the Heart-ROCQ group) or a regular phase II outpatient CR programme after surgery (the Standard Care group).(32) Figure 1 provides an overview of the study design.



123

124 Figure 1 Research design of the Heart-ROCQ prospective, randomised, open, blinded endpoint trial.

125 The phases of both cardiac rehabilitation programmes and the measurements are shown relative to
126 the moment of surgery. Heart-ROCQ, Heart Rehabilitation in patients awaiting Open heart surgery
127 targeting to prevent Complications and to improve Quality of life.

128

Ethical considerations and dissemination

130 The study has been registered at ClinicalTrials.gov If applicable, substantial amendments will be
131 notified to the Medical Ethical Review Board (METc) for approval, and changes will be written into
132 articles describing the results of the study. Results of this study will be submitted to a peer-reviewed
133 scientific journal and can be presented at national and international conferences.

134

135 Participants

136 Patients (≥ 18 years) admitted for elective coronary artery bypass grafting (CABG), valve surgery, aortic
137 surgery or combined procedures are eligible. Patients accepted for congenital procedures,
138 transcatheter aortic valve implantations, aortic dissections or aortic descending repair are excluded.
139 Other exclusion criteria are inability to participate in all programme elements of the Heart-ROCQ
140 programme due to disorders of the nervous or musculoskeletal system that limit exercise capacity,
141 chronic obstructive pulmonary disease with Global Initiative for Chronic Obstructive Lung Disease
142 criteria classification 3 or 4,(38) addiction to alcohol or drugs, a serious psychiatric illness (ie, recently
143 experienced psychosis, bipolar disorder, diagnosis of schizophrenia, serious cognitive or neurological
144 problems, and acute suicidal ideations or behaviour), or when it is undesirable to exercise (ie,
145 hypertrophic cardiomyopathy, unstable angina, advice from cardiologist); any treatment which is
146 planned during one of the CR programmes and which is expected to interrupt attendance to the CR
147 programme (eg, planned organ transplantation, preoperative endocarditis, planned chemotherapy and
148 so on); playing a sport at the (inter)national level; and being unable to read, write or understand Dutch.

149

150 Study enrolment, randomisation and registry

151 Figure 2 shows the flow chart of the Heart-ROCQ study. Patients on the waiting list of the thoracic
152 surgery department and meeting the study criteria for type of surgery are asked by their cardiologist to
153 participate. The cardiologist provides the patients with study information and an invitation to meet the
154 researcher at the preoperative consultation. At the preoperative consultation, the researcher will obtain
155 informed consent and conduct the baseline measurements. Eligible patients who have signed informed
156 consent and performed the baseline measurements are randomised to the Heart-ROCQ group or
157 Standard Care group. Randomisation (concealed group allocation in REDCap, random blocks of 2-4,
158 1:1 ratio) is stratified for weight of the surgery (isolated CABG, single non-CABG (ie, replacement or
159 repair of part of aortic or valve), two procedures or three procedures), gender and age (≥ 65 and < 65
160 years). Prior to the start of the study, the randomisation lists were created (using the 'ralloc' function
161 of Stata/SE V.13.0) and imported into the secure data collection tool REDCap (V.7.3.2) by an

162 independent researcher. Medical staff and researchers are not blinded to group allocation due to
163 logistic reasons. The primary endpoint is evaluated by an independent endpoint committee blinded to
164 group allocation.

165 Patients who are not willing to participate are asked to give written consent for using data that
166 are collected during routine care. The data are collected in the Heart-ROCQ study registry to increase
167 insight into potential differences between patients who participated in the study and patients who did
168 not. The Heart-ROCQ registry will thus provide more insights into the generalisability of the results.
169 Data from this registry are not used for the primary statistical analyses.

170

171 Intervention

172 *Heart-ROCQ group*

173 The Heart-ROCQ group receives a CR programme at the Centre for Rehabilitation of the UMCG
174 (Beatrixoord location, which is located 6 km from the hospital of the UMCG) consisting of three phases.
175 The first phase is an outpatient preoperative optimisation phase during the waiting period (three times
176 per week, minimum of 3 weeks). The second phase is a postoperative inpatient CR phase (3 weeks,
177 weekdays only), followed by the third phase, an outpatient CR phase (two times per week, for 4 weeks).
178 During each phase, all participants receive physical therapy including group sessions of inspiratory
179 muscle training,(39) strength training, aerobic cycling, breathing, coughing and relaxation. In addition,
180 patients have an assessment with a dietitian and a psychologist and take part, when indicated, in
181 individual sessions to optimise their health. In addition, different group education sessions are
182 organised regarding coping with stress, awareness of risk factors and maintaining a healthy lifestyle.
183 Two additional modules, namely coaching to stop smoking and to return to work, are available for
184 patients who, respectively, smoke or are employed. A detailed description of the CR programme is
185 given in the online supplementary information.

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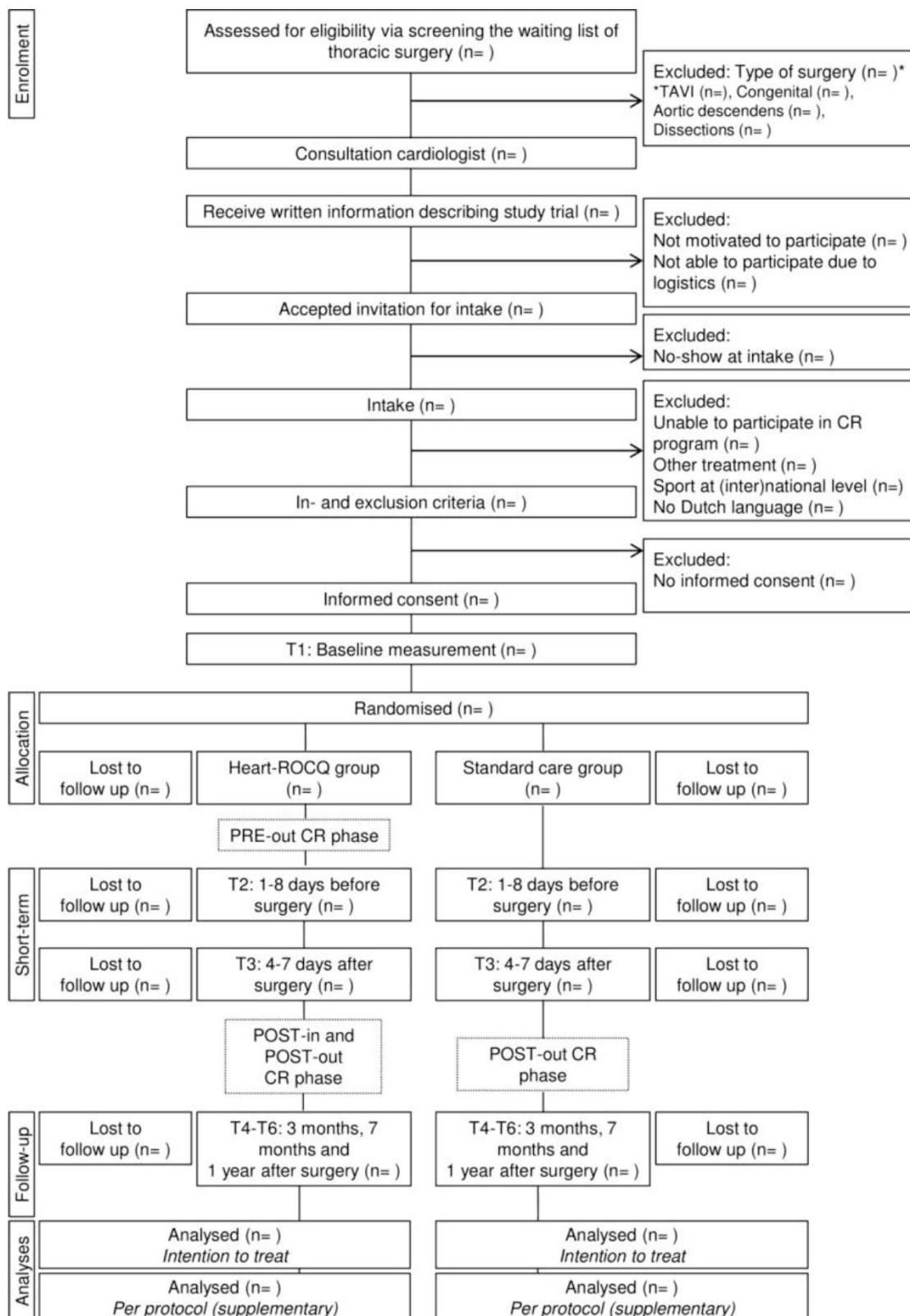


Figure 2 Flow chart of the Heart-ROCQ study. CR, cardiac rehabilitation; Heart-ROCQ, Heart Rehabilitation in patients awaiting Open heart surgery targeting to prevent Complications and to improve Quality of life; TAVI, transcatheter aortic valve implantation.

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Standard Care group

In the Netherlands, the current standard of care consists of a phase II outpatient CR programme which is conducted at the referred hospital.(32,33) In general, this CR programme starts 3-6 weeks after discharge from the hospital and lasts for 6 weeks. The programme consists of four educational sessions (regarding risk factors and retaining a healthy lifestyle) and physical therapy (two times per week: 30 min cycling, together with 30 min sports and games, relaxation therapy, or strength training). Furthermore, patients can be referred to a psychologist or a dietitian when needed. The content of this CR programme is based on the Dutch CR guidelines.(40)

Composite primary endpoint: functional status, complications and events

The primary outcome is a composite weighted score of functional status, postoperative surgical complications, readmissions to the hospital and MACE. Each event is scored (ranging from 1 to 3 points) separately. Table 1 shows an overview of the primary outcome and the scoring system.

The scores of all events are combined to calculate a total score. Only the most serious complication is counted per event (eg, when a percutaneous coronary intervention (score 1) is complicated by a stroke (score 2), the score will be 2 and not 3 (1+2)).

The concept of the composite weighted score is adapted from the African-American Heart Failure Trial.(41) Functional status is assessed through two health domains of the Medical Outcomes Study 36-item General Health Survey (RAND-36 V.2)(42): physical functioning and physical health problems. The primary endpoint is evaluated at 3 months (T4) and 1 year (T6) after surgery (figure 1). Deep wound infections and surgical re-explorations are screened up to 120 days after surgery. Other postoperative surgical complications are measured in the period between the surgery and when a patient meets the UMCG discharge criteria (box 1). Hospital admissions are checked between baseline and 1 year after surgery. To prevent bias (since the Heart-ROCQ group follows the inpatient CR phase after surgery), hospital admissions between the day of admission before surgery and 30 days after surgery are not included when determining the (calculated) primary endpoint.

219 Secondary outcomes

220 *Complications and events*

221 All individual components of the composite endpoint regarding the complications and events will be
222 analysed separately as secondary outcomes. Table 2 summarises the definitions of the secondary
223 complications and events, including at the time of screening.

224 All documents concerning the composite primary endpoint and the secondary complications
225 are encrypted and subsequently adjudicated by the independent endpoint committee. The endpoint
226 committee consists of four members (cardiologists and cardiothoracic surgeons) who are not employed
227 in the UMCG and are blinded to group allocation.

228

Table 1: Definitions and score of the components of the composite primary endpoint

Functional status	Score
Worsening in physical functioning (domain score of health-related quality of life, RAND-36 V.2).*	1
No change or improvement in physical functioning.*	0
Worsening in physical problem (domain score of health-related quality of life, RAND-36 V.2).*	1
No change or improvement in physical problem.*	0
A clinical relevant worsening is classified as minimal change according to Wyrwich et al.(59)	
(Serious) adverse events	
No serious adverse event.	0
Prolonged mechanical ventilation Mechanical ventilation longer than 24 hours.	1
Lung infection (1) A new lung radiographic infiltrate and (2) two signs that the infiltrate is of infectious origin – that is, (a) fever: body temperature >38°C or <36°C; (b) leucocytosis - white cell counts >10x10 ⁹ /L or <4x10 ⁹ /L ; (c) positive sputum culture; and/or (d) decline in oxygenation.	1
Delirium (1) A DOS (60) score ≥3 at hospital ward and/or (2) diagnosis confirmed by a psychiatrist, geriatrist, or supervising specialist according to the DSM-IV criteria resulting in treatment with medication.	1
Readmissions to intensive care unit Unrelated to a secondary endpoint.	1
Deep wound infection Deeper tissues are affected (muscle, sternum and mediastinum) and must include (1) surgical drainage/refixation or (2) an organism is isolated from culture of mediastina tissue or fluid, or (3) antibiotic treatment because of sternum wound.	2
Readmissions to hospital An unplanned hospital stay with different dates of admission and discharge with a medical indication (ie, clinical signs and symptoms or change of treatment).	1
Any cardiothoracic surgical interventions Graft or valve failure, CABG, valve, aortic or other cardiac surgery.†	2
Any percutaneous interventions PCI, TAVI and so on.	1
Myocardial infarction According to the third universal definition of myocardial infarction.‡	2
Cerebral vascular accident / stroke Acute neurological event of at least 24 hours in duration, with focal signs and symptoms and without evidence supporting any alternative explanation. Diagnosis of stroke requires confirmation by CT, MRI or pathological confirmation.	2
Sudden death survivor The sudden onset of symptoms, such as chest pain and cardiac arrhythmias, and ventricular tachycardia, which lead to the loss of consciousness and cardiac arrest followed by reanimation and does not lead to biological death.	2
Death All-cause mortality.	3
Total score = sum of physical status and SAE's at 3 months and 1 year (worst score of each event).	

230 In gray: postoperative complications can be scored ones.

231 *Compared with baseline.

232 † According to the definitions of the 'Begeleidingscommissie Hartinterventies Nederland'.

233 ‡ Thygesen et al.(61)

234 CABG, coronary arterial bypass graft; DOS, Delirium Observation Screening scale; DSM, Diagnostic and
 235 statistical manual of mental disorders; PCI: Percutaneous coronary intervention; RAND-36 V.2, Medical
 236 Outcome Study 36-item General Health Survey; SAE, serious adverse event; TAVI, Transcatheter aortic valve
 237 implantation.

238

239 *Box 1: Discharge criteria of the University Medical Center Groningen (UMCG)*

-
- 1) No drain, no external pacemaker lead, no infusion or oxygen present.
 - 2) Stable clinical conditions (stable lab results, X-ray and haemodynamic parameters).
 - 3) Able to perform basic activity of daily living activities (ie, going independently to the toilet).
-

240

241 *Table 2: Definitions of the secondary complications and events*

Definitions	Time of measure
Atrial fibrillation	
New onset of atrial fibrillation or atrial flutter requiring medical treatment or cardioversion.	Surgery to T3
Prolonged ICU stay	
When the number of calendar days is two or more from ICU admission to discharge.	Initial stay
Readmissions to hospital	
The number of unplanned hospital stays with different dates of admission and discharge with a medical indication (ie, clinical signs and symptoms or change of treatment).	Baseline to T6*
a. Directly related to a cardiac cause.	
b. Not directly related to a cardiac cause.	
Hospitalisation days	
Total number of days of hospitalisation	Baseline to T6*
a. Directly related to a cardiac cause.	
b) Not directly related to a cardiac cause.	
Cardiovascular death	
Any death due to proximate cardiac or cardiovascular cause (eg, myocardial infarct, low-output failure, fatal arrhythmia, death secondary to a cerebral vascular accident, pulmonary embolism, ruptured or dissecting aortic aneurysm, or other vascular diseases), unwitnessed death, and death of unknown cause, and all procedure-related deaths (eg, PCI, CABG), including those related to concomitant treatment†.	Baseline to 5 years after surgery
Non-cardiovascular death	
Any death not covered by above definition, such as death caused by infection, malignancy, sepsis, pulmonary causes, accident, suicide, or trauma.	Baseline to 5 years after surgery
Concerning safety	
Surgical re-exploration for bleeding/ tamponade	
Surgical incision into the sternum as a result of a bleeding or tamponade.	Surgery to T4
a. Acute: presented within 24 hours after surgery.	
b) Late: presented after 24 hours after surgery.	
Surgical re-exploration dehiscence	
Aseptic wound dehiscence	Surgery to T4

242 * Not measured between the day of admission before surgery and 30 days after surgery, because of POST-
 243 in phase of Heart-ROCQ programme.

244 † Specifically, any unexpected death even in patients with coexisting, potentially fatal non-cardiac disease
 245 (eg, cancer, infection) will be classified as cardiac death.

246 CABG, coronary arterial bypass graft; Heart-ROCQ, Heart Rehabilitation in patients awaiting Open heart
 247 surgery targeting to prevent Complications and to improve Quality of life; ICU, Intensive care unit; PCI,
 248 percutaneous coronary intervention; T4, follow-up at 3 months after surgery; T6, follow-up at 12 months
 249 after surgery.

250

251 *Questionnaires and physical tests*

252 Table 3 shows the physical tests and questionnaires of the secondary outcomes regarding physical
253 and psychological health, lifestyle risk factors, and the economic evaluation. Physical tests and
254 questionnaires are completed at six assessment points (figure 1). The preoperative measurements
255 (T1 and T2) are conducted at the start (preoperative consultation) and the end (1-8 days before
256 surgery) of the waiting period. The third measurement (T3) is performed when patients meet the UMCG
257 discharge criteria (box 1). The follow-up measurements (T4, T5 and T6) are at 3, 7 and 12 months
258 after surgery. Patients are asked to fill in questionnaires online, or when requested on paper prior to
259 the visits for the physical tests. All adverse events reported spontaneously by the patient or observed
260 by the investigator are recorded. In addition, serious adverse events are reported to the METc. Data
261 are stored in REDCap and on a secure drive at the CardioResearch department in the UMCG. Two
262 times per year, the study is monitored by a trained research monitor from another department of the
263 UMCG. Details of procedures, data collection, management and monitoring can be found in the Trial
264 Master File of the Heart-ROCQ study (can be obtained by the investigators). On 12 June 2018, the
265 study was audited and certified for ISO 9001:2015 independently by DNV GL.

266

267 Potential moderators

268 Preoperative risk profile (ie, Euroscore II, medical history, lifestyle risk factors, and physical and mental
269 status), surgery parameters and demographics are collected from the medical record and baseline
270 measurements. The content of the CR programme is described in terms of compliance, duration of CR
271 programme, type of treatment, frequency and training load (ie, for bicycle training: external workload,
272 heart rate response, and rate of perceived exertion using the Borg Scale; and for strength training:
273 sets, repetitions, and intensity) for both the Heart-ROCQ group and the Standard Care group.

274 **Table 3: Time of measure, physical tests and questionnaires of the secondary outcomes**

Secondary outcomes	Measure	Time of measure
<i>Physical health</i>		
Cardiorespiratory fitness	6MWT(62)	T1-T4, T6
Muscle strength	STS-10, grip and leg strength(63,64)	T1-T4, T6
Independence in ADL	KATZ(65,66)	T1, T4, T6
<i>Psychological health</i>		
General anxiety	GAD-7(67)	T1, T2, T4, T6
Feelings of depression	PHQ-9(68,69)	T1, T2, T4, T6
Health-related quality of Life	Rand-36 V.2(42)	T1, T4, T6
<i>Lifestyle risk factors</i>		
Physical activity	iPAQ(70) and Actigraph*(71)	T1, T4, T6
Obesity indices	BMI, waist to hip ratio	T1, T4, T6
Smoking behaviour	Number of cigarettes per day	T1, T4, T6
<i>Economic evaluation</i>		
Healthcare use and related medical costs	iMCQ(72)	T1, T4-T6
Work participation [†]	iPCQ(73)	T1, T4-T6
QALYs	EQ-5D-5L(52)	T1, T4-T6
<i>Potential mediators</i>		
Cardiac self-efficacy	CSE(45)	T1, T2, T4, T6
Illness representations	IPQ-R(43)	T1, T2, T4, T6

* Patients are asked to wear the Actigraph during waking hours for one consecutive week.

[†] Health-related productivity losses of paid work and unpaid work

ADL, activities of daily living; BMI, body mass index; CSE, cardiac self-efficacy; EQ-5D-5L, EuroQol Five-Dimensional Questionnaire; GAD-7, Generalised Anxiety Disorder 7-item scale; iMCQ, iMTA Medical Cost Questionnaire; iPAQ, International Physical Activity Questionnaire; iPCQ, iMTA Productivity Cost Questionnaire; IPQ-R, Illness Perception Questionnaire, Revised; KATZ, Katz Index of Independence in Activities of Daily Living; 6MWT, 6 min walking test; PHQ-9, Patient Health Questionnaire 9-item scale; QALY, quality-adjusted life years; RAND-36 V.2, Medical Outcome Study 36-item General Health Survey; STS-10, 10 times sit to stand test; T1, begin of waiting time; T2, 1–8 days before surgery; T3, moment that patients meet the University Medical Center Groningen discharge criteria; T4–T6, follow-up at 3, 7 and 12 months after surgery.

Potential mediators

Illness perceptions (ie, patients' mental representations of their illness based on different sources of information) are measured with three subscales (personal control, treatment control and consequences) of the Revised Illness Perception Questionnaire.(43) These subscales are chosen because of their sensitivity to change and because of their relation to psychological distress.(44) The Cardiac Self-Efficacy (CSE) Scale(45) is used to measure CSE (ie, patients' confidence to perform a specific task related to cardiac disease).

294 Statistical analyses

295 *Sample size*

296 Assuming a normal distribution, the mean weighted score of the primary endpoint is estimated at 1.0
297 with a SD of 0.9 at 1 year after surgery. This estimation is based on historical data of the UMCG, an
298 unpublished ongoing pilot study in the UMCG, the Dutch registration database(46) and data reported
299 in the literature.(6,47–49) A decrease of 0.3 is expected in the Heart-ROCQ group, based on previous
300 studies comparing CR with standard care(36,48,50) (ie, no CR), and is considered to be clinically
301 relevant (ie, on average a 30% decrease in complications/events or worsening in functional status, or
302 10%-20% decrease in MACE or death). To detect this decrease and achieve 80% power (significance
303 level of 5%), a group of 286 patients (143 in the Heart-ROCQ group and 143 in the Standard Care
304 group) is needed. To incorporate a withdrawal of $\pm 20\%$, a total sample size of 350 is needed at
305 baseline.

306

307 *Interim analysis*

308 An interim analysis will be conducted when 40% of the included patients have had the measurements
309 1 year after surgery. The study will be terminated prematurely when the primary outcome of one of the
310 CR programmes is obviously ($p < 0.001$) different from the other CR programme.

311

312 *Primary and sensitivity analyses*

313 All endpoints are primarily analysed according to the 'intention-to-treat' principles, and missing values
314 are counted as worst-case score (nominal variables) or estimated using maximum likelihood estimation
315 (interval variables). As supplementary analyses, the endpoints are analysed on a per-protocol principle
316 with and without using imputation methods for missing values. In all analyses, a two-sided $p < 0.05$ is
317 considered statistically significant.

318 The total score of the primary endpoint will be handled as a continuous variable. All continuous
319 variables will be analysed using linear mixed models to determine 'time x group' differences. Significant
320 interactions will be further explored using the Bonferroni post-hoc test to determine differences
321 between each time point. Non-parametric tests will be used if the assumptions of normal distribution

are violated. More information about the statistical methods and clinical relevance are written in the research protocol (ClinicalTrials.gov: NCT02984449).

Economic evaluation

For the evaluation of healthcare utilisation, standard prices published in the Dutch costs guidelines are used.⁽⁵¹⁾ To compare the costs with quality-adjusted life years (QALYs), QALYs are estimated with the use of the EuroQol Five-Dimensional Questionnaire (EQ-5D-5L).⁽⁵²⁾ Utility values for the EQ-5D-5L are calculated based on the new Dutch tariff.⁽⁵³⁾ Results from the analysis are reported as an incremental cost-effectiveness ratio, dividing the difference in effect by the difference in costs. Bootstrap resampling will be performed, and cost-effectiveness acceptability curves will be plotted, to estimate the probability that the Heart-ROCQ programme is cost-effective when compared with standard care. A societal perspective is applied.

Study status

From May 2017 to December 2018, 75 patients were enrolled. In the following years we expect that the enrolment will increase to 85 patients per year. The last patient is expected to be included in July 2021.

Patient and public involvement

In a pilot study (to be submitted), patient satisfaction and feasibility (in terms of accessibility, compliance, training load and safety) of the Heart-ROCQ programme have been evaluated. Patients were very satisfied with the programme, scoring it 8 out of 10; therefore, we did not change the content of the programme. However, patients' rate of perceived exertion was generally quite low and no serious adverse events occurred during the bicycle training. For safety reasons the intensity was not increased. However, in order to estimate the maximum load more accurately and better tailor the programme to the individual, we decided to change one of the stop criteria of the preoperative submaximal ergometry test from 70% to 90% of the expected maximal heart rate. Furthermore, our outcomes are, among others, based on the reasons why patients recommended the programme to other patients. For

350 example, patients reported that their self-efficacy and physical capacity were improved, so we added
351 the CSE questionnaire and physical tests to objectively measure these outcomes. In this way the
352 results were taken into account in the further development of the Heart-ROCQ programme and the
353 protocol of this study. The results of this trial will be distributed by various information channels (eg,
354 websites of cardiac patient organisations, social media). Two to three times a year, we provide a
355 newsletter about the progress, and (in the end) the results of the study are sent to patients who are
356 interested.

357 DISCUSSION

358 The Heart-ROCQ study is the first randomised clinical trial evaluating the effect of a combination of
359 preoperative and postoperative CR programme compared with a postoperative CR programme. Unlike
360 the vast majority of CR programmes in previous studies, the current programme is multidisciplinary,
361 targeting different aspects of surgical outcomes in patients undergoing cardiac surgery. Because
362 different aspects are targeted, a composite weighted score will better reflect the treatment benefits
363 than a single outcome. Therefore, the primary endpoint is a composite endpoint of functional status,
364 postoperative surgical complications, readmissions to the hospital and MACE. The components of the
365 endpoint are of clinical importance to patients undergoing cardiac surgery and reflect a comprehensive
366 representation of the recovery of the patient.

367 Both the ideas of the combined primary endpoint and the weighting of the individual
368 components were derived from other studies.(41,54,55) Assigning different weights to the components
369 was needed for more accurate comparison. Since the components are not equal in clinical importance,
370 equal weights would lead to inaccurate statistical analysis.(55) In the current study, the weighted score
371 of HRQoL is lower (1 point instead of 2 points) to minimise bias due to patients' knowledge of group
372 allocation. Therefore, improvements in quality of life are not counted in the primary endpoint to prevent
373 bias in a positive direction. This also prevents that a score in quality of life and an adverse event cancel
374 each other out (eg, when a patient experiences an improvement in quality of life (+2 points) and has a
375 stroke (-2 points), then the total score is 0). The scores of all-cause mortality, stroke, myocardial
376 infarction and revascularisation are in line with the results shown by Tong and colleagues.(55) A
377 disadvantage of composite endpoints is that the effect may be driven by complications that occur with
378 the greatest frequency.(56) Therefore, postoperative complications which occur frequently, such as
379 atrial fibrillation, are evaluated separately as secondary endpoint. The primary endpoint is evaluated
380 by an endpoint committee, which is blinded to group allocation and consists of four independent
381 cardiologists and cardiothoracic surgeons.

382 Previous preoperative CR studies were primarily focused on short-term effects; only one
383 preoperative CR study and a few postoperative CR studies have determined long-term

384 effects.(23,35,36,57) In contrast to previous preoperative CR studies, the Heart-ROCQ study sets out
385 to investigate both short-term and long-term effects of the CR programmes.(23,35,36) Due to the
386 trends in, among others, increasing age, obesity and physical inactivity, patients undergoing cardiac
387 surgery are becoming more complex. The Heart-ROCQ programme aims to address these issues,
388 which makes the programme clinically relevant for all cardiac surgery patients. Therefore, we chose to
389 include different types of cardiac surgery. Since different moderators and mediators are assessed
390 before, during and after CR, we can explore which factors are associated with better outcomes and
391 which working mechanisms contribute to its effectiveness. These findings may provide a more indepth
392 understanding of who benefits the most from CR in both the short and long term and the underlying
393 mechanisms of CR, which are still not fully understood in patients undergoing cardiac surgery.(35) In
394 addition, the present study is thought to considerably contribute to the evidence to further develop
395 guidelines for clinical practice, especially regarding the preoperative CR programme.(58)

396 The Heart-ROCQ programme is expected to be cost-effective in the long term, which is also of
397 interest for policymakers and healthcare providers. Therefore, an economic evaluation is performed to
398 assess the cost-effectiveness of CR, since little is known about the cost-effectiveness of CR.(48) A
399 societal perspective of this economic evaluation is chosen, meaning that healthcare costs and patient-
400 related and productivity-related costs and benefits are taken into account. If the Heart-ROCQ
401 programme is proven to be effective, it might be advisable to include a supportive prevention-oriented
402 waiting period prior to surgery as an integral part of the treatment for patients undergoing elective
403 cardiac surgery. This implies a paradigm shift from curative care following cardiac surgery to an
404 additional preventive care attitude before surgery. Extensions of rehabilitation options in or in the
405 vicinity of cardiac centres will then be required.

406 The Heart-ROCQ study is the first randomised clinical trial comparing the effect of a combined
407 preoperative and postoperative CR programme with a regular Dutch phase II postsurgery outpatient
408 rehabilitation CR programme in a population undergoing elective cardiac surgery. This study is
409 expected to provide new understanding of the effectiveness and underlying working mechanisms of
410 CR, and subsequently to improve value-based healthcare.

411 Supplemental material

412 Supplementary information associated with this article can be found online at
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414

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424

425 Contributors

426 Conception and design of the study: JH, FB, MJLD, MFR, WD, JF, LHVvdW, PVdH and MAM.
427 Methodology: JH, FB, SD, MJLD, MFR and PVdH. Acquisition of data: JH, FB and SD. Writing - original
428 draft, tables and figures: JH. Writing - reviewing and editing: FB, SD, MJLD, MFR, WD, ICCvdH, JF,
429 LHVvdW, PVdH and MAM. Supervision: MJLD, MFR, WD, JF, ICCvdH, LHVvdW, PVdH and MAM.
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432

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437

438 Competing interests

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442 PvdH have nothing to disclose.

443 Patient consent for publication

444 Not required

445

446 Ethics approval

447 This study is conducted according to the principles of the Declaration of Helsinki (V.8, October 2013)
448 and according to the research code of the UMCG. The protocol (V.2, 19 December 2016) has been
449 approved by the Medical Ethical Review Board (METc) of the UMCG (no 2016/464).

450

451 Provenance and peer review

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453

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Title

Physical activity in free-living conditions and its association with handgrip strength in patients awaiting cardiac surgery – a cross-sectional analysis.

Authors

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Abstract

Background: Physical activity in free-living conditions and handgrip strength are suggested important factors, each individually and associated with better cardiac surgery outcomes. However, limited information is available how these two factors are related to each other in the preoperative stage. Therefore, this study aims to cross-sectionally evaluate preoperative subjective and objective physical activity levels in free-living conditions and handgrip strength, and to explore their association in patients awaiting cardiac surgery.

Methods: This study is a single-centered cross-sectional subanalysis of 139 patients awaiting elective cardiac surgery. Physical activity was evaluated subjectively with a validated activity questionnaire (IPAQ) and objectively with the Actigraph accelerometer. Handgrip strength was assessed with a Jamar handheld dynamometer. Multiple regression analyses were performed for the association of subjective (duration of walking, moderate and vigorous activities per week) and objective (duration of light to very vigorous activities per valid day) physical activity with handgrip strength (maximum force across three trials) while corrected for possible confounders.

Results: The study showed that in this cardiac patient population the duration of subjectively reported total physical activity varied widely (median 637.5 minutes per week IQR: 332.5-1192.5), whereas objectively measured physical activity was predominantly of light intensity, with an average total physical activity duration of 286 ± 70 min per day. The durations of vigorous activity were minimal measured by both subjective (median 0 minutes per week IQR: 0-0) and objective (median 0 min/valid day IQR: 0-0) method. Handgrip strength was higher in males (45 ± 8 kgf) than females (26 ± 7 kgf). Subjective physical activity showed no significant association with handgrip strength, whereas objective physical activity did show a near-significant association with handgrip strength when corrected for confounders ($p=0.076$, $n=94$).

Conclusions: Among patients awaiting cardiac surgery, durations of subjective physical activity varied widely, whereas most objective physical activity consisted of light activities. Furthermore, only higher levels of objectively measured physical activity in free-living conditions showed a trend towards higher handgrip strength corrected for confounders. Subjective and objective assessment of physical activity seem to grasp different elements of the physical activity construct. Such multimodal assessment of physical activity and handgrip strength should be considered when evaluating preoperative health, which may help tailoring prehabilitation and improve care of cardiac surgery patients.

Introduction

Poor physical condition in patients awaiting cardiac surgery is associated with adverse surgical outcomes and impaired postoperative recovery.^{1,2} Approximately 28% of these patients have sarcopenia³, a multifactorial geriatric syndrome characterized by progressive and generalised loss of skeletal muscle strength, muscle mass, and physical performance.⁴ In addition, cardiac surgery patients are expected to be less physically active and live a more sedentary life. Indeed, sedentary behaviour is known as a risk factor for the development and progression of cardiac disease.⁵ Physical activity (PA) is defined as “any bodily movement produced by skeletal muscles that results in energy expenditure”.⁶ Assessment of PA and muscle strength in this vulnerable patient group provides information about the patient’s current health status, with both factors likely to impact outcomes of cardiac surgery.

Muscle strength is an element of physical fitness, which is defined as “a set of attributes that are either health- or skill-related. The degree to which people have these attributes can be measured with specific tests. The health-related components of physical fitness are (a) cardiorespiratory endurance, (b) muscular endurance, (c) muscular strength, (d) body composition, and (e) flexibility.”⁶ The skill-related attributes consist of agility, balance, coordination, speed, power and reaction time.⁶ An indication of overall skeletal muscular strength can be given by measuring handgrip strength (HGS). HGS can be measured relatively easy and is indicative for sarcopenia.⁷ HGS has been assessed in cardiac patients to evaluate interventions or used as an easy preoperative screening tool to assess physical condition and its prognostic value for recovery after surgery.^{8–10} Higher preoperative HGS was associated with better health after cardiac surgery in terms of mortality, morbidity, length of hospital stay, and functional status.^{8,9} Similarly, an increase in HGS between pre- and postoperative assessment was associated with better health-related quality of life after cardiac surgery.¹⁰

In addition to HGS, preoperative PA has also been linked to better health outcomes in cardiac patients, including mental well-being, the operative risk of death, postoperative inflammatory response, major adverse cardiac and cerebrovascular events, and hospitalization.^{11–13} Structured preoperative exercise training programmes, including total body exercises and commonly referred to as prehabilitation, have shown promising results in improving recovery and reducing complications in cardiac surgery patients.^{14–16} While prehabilitation represents a more targeted and probably more intensive exercise intervention than general PA in free-living conditions, these findings suggest that increasing PA in the preoperative phase, whether structured or unstructured, may be beneficial.^{6,14–16} Thus, both higher levels of HGS and PA prior to surgery are suggested to be associated with better functional outcomes and potential reduction of the risks of cardiac surgery.

PA can be determined subjectively with questionnaires or objectively through body-worn accelerometric devices.^{17,18} These two approaches are considered complementary in nature rather than interchangeable, as they reflect different aspects of PA behaviour.¹⁹ Subjective PA represents a ‘brain-filtered’ perception of PA, influenced by experience, memory, interpretations, and context.^{17,18} In contrast, accelerometric PA devices provide algorithm-based estimates of energy expenditure derived from bodily accelerations.^{17,18} However, current evidence of the effect of preoperative physical activity on postoperative complications in cardiac surgery patients is mixed and primarily based on self-reported subjective data, while objective assessments in free-living conditions remain scarce.¹³

Despite the clinical relevance of PA and HGS, information about the association between these factors in patients awaiting cardiac surgery is limited, especially using both subjective and objective PA measurement. Investigating this association is useful as it provides insight into the relationship between PA and muscle strength, which is relevant for understanding patients’ physical condition prior to surgery, optimising preoperative screening,

and exploring the potential of preoperative interventions. This relationship is likely to be complex and influenced by a range of potential confounding factors among a diverse sample of cardiac patients. Demographic factors, such as age, gender and body composition are well-documented factors associated with both PA^{11,12,20-24} and HGS²⁵⁻²⁷ across various cardiac populations. Clinical indicators of disease severity, including the operative risk of death, surgical complexity, cardiac function, and New York Heart Association (NYHA) classification, may also relate to handgrip strength²⁶⁻²⁹ and physical activity^{12,22,24,30} in cardiac patients. Additionally, the presence of atrial fibrillation is known to impair exercise capacity, thereby potentially affecting both PA and HGS.³¹⁻³⁴ Thus the levels of both HGS and PA in itself are influenced by many factors in cardiac patients; this in turn may impact the potential association between PA and HGS. Therefore, adjusting for these potentially confounding factors is essential for better understanding the association between PA and HGS, specifically in patients awaiting cardiac surgery.

In order to address the knowledge gap around preoperative PA in free-living conditions and HGS among patients awaiting cardiac surgery, the aims of this cross-sectional study are 1) to evaluate preoperative subjective and objective PA levels and HGS, and 2) to examine the associations between (both subjective and objective) PA and HGS in a typical group of cardiac patients awaiting cardiac surgery when corrected for confounders.

Methods

Design

This cross-sectional study employed baseline data from the Heart-ROCQ PROBE study, a randomised, open, blinded endpoint trial evaluating a pre- and postoperative multidisciplinary cardiac rehabilitation programme compared to regular outpatient rehabilitation after cardiac

surgery (explained in detail elsewhere).³⁵ The Heart-ROCQ PROBE study was approved by the medical ethics committee of the University Medical Centre Groningen (METc UMCG 2016/464). After the referral from the cardiologist and after signing informed consent, confirming voluntary participation, baseline data was obtained during preoperative consultation. During this preoperative consultation, among others, physical tests for muscle strength were performed and patients were asked to fill in the questionnaire (including the IPAQ for assessing subjective PA) at home and patients were asked to wear the Actigraph (a wearable PA monitor) for the following week. Patients were randomised after completing the questionnaires and most physical tests for baseline measurement. However, for practical reasons, two baseline measurements were obtained after randomization but still prior to the start of prehabilitation, namely the continued wearing of the activity monitor and the six-minute walk test. Medical history and demographics were extracted from medical records and confirmed during the preoperative consultation. The standardised measurements and study administration were conducted by trained research staff.

Patients

Eligible patients for this study, similar to the Heart-ROCQ PROBE study³⁵, were individuals aged 18 years or older and who were scheduled for elective coronary artery bypass grafting (CABG), valve surgery, aortic surgery or combined procedures. Patients were excluded when scheduled for congenital procedures, transcatheter aortic valve implantations, aortic dissections or aortic descending repairs.³⁵ Additionally, patients were excluded when having limitations to participate in the rehabilitation programme due to disorders affecting the nervous system or musculoskeletal systems limiting exercise capacity, or when they had COPD GOLD classification 3 or 4. Furthermore, patients were excluded when having an

alcohol or drug addiction or a serious psychiatric illness (such as recent psychosis, bipolar disorder, schizophrenia, serious cognitive or neurological impairments, and acute suicidal ideations or behaviours). For more details, see the design paper of the Heart-ROCQ PROBE study.³⁵

Sample size

The sample size of 140 patients was based on the power calculation for the interim analyses of the Heart-ROCQ PROBE study³⁵, at the same time this was also the patient group before the onset of the COVID-19 pandemic.

Subjective physical activity

Subjective PA was assessed with the long version of the International Physical Activity Questionnaire (IPAQ).³⁶ This is assumed a valid and reliable tool in middle-aged adults in twelve countries and also in comparison with activity monitors in cardiac rehabilitation patients.^{36,37} For this study the Dutch translation of the IPAQ long version was used, which has been translated following guidelines from the official IPAQ website and can be downloaded from this website.³⁸ The IPAQ consists of a series of questions regarding the past seven days. These questions capture information about the frequency (days per week), duration (in minutes), and intensity (moderate or vigorous) of physical activities performed in specific domains of life (form), including work-related activities, transportation, domestic and gardening, and leisure-time activities. In addition to physical activity behaviour, patients were asked to report the amount of time they spend sitting during a typical weekday and a typical weekend day. The self-administered questionnaire was filled in online using the secured

database REDCap (Research Electronic Data Capture, v15.0.15, Vanderbilt University, Nashville, TN, USA) and on request on paper (n=6).

Data analysis subjective PA

Data of PA and HGS were exported from the REDCap database and were processed in Stata (SE 18.0, StataCorp LLC, College Station, TX, USA). Data of subjective PA was analysed according to the standardized IPAQ scoring protocol³⁹, except for the minimum values for duration of activity, since nowadays every bout of activity counts⁴⁰, and the truncation rule of three hours per day. After cleaning the data for missing and out-of-range values (>6719 minutes of total PA per week), the data collected from the questionnaire were summed within each physical activity domain to estimate the total time spent in the specific domains as stated in the scoring protocol of the IPAQ.³⁹ Patients filling in “I don’t know” in minutes per week were excluded from analysis of that variable. Data were then used to estimate total weekly PA by weighting the reported minutes per week within each activity category by a MET energy expenditure estimate assigned to each category of activity (for walking 3.3 METs, moderate activity 4.0 METs, vigorous activity 8.0 METs, cycling 6.0 METs, exceptions of domestic and yard activities: vigorous 5.5 METs, moderate yard 4.0 METs, moderate indoors 3.0 METs). The weighted MET-minutes per week (MET·min/week) were calculated with the multiplication of duration, frequency per week, and MET intensity, which were summed across activity domains and across intensity level. Duration of total subjective PA was calculated by the summation of the durations of walking, moderate and vigorous activities per week (min/week, thus not the MET·min/week) and used in the statistical analysis.

Objective physical activity

Objective PA was evaluated in free-living conditions using the Actigraph activity monitor (model wGT3X-BT; Actigraph LLC, Pensacola, FL, USA). The Actigraph is a triaxial accelerometer that records accelerations in the three orthogonal planes, providing accurate and continuous data on PA and sedentary behaviour. The Actigraph is assumed a valid and reliable tool for measuring PA in the general population, but only limited research is available for patients attending cardiac rehabilitation or with cardiovascular disease.^{37,41} The device was worn with a waist belt on the right hip on top of the anterior superior iliac spine and was secured using a comfortable adjustable band, ensuring a proper fit to minimize movement artifacts and maximize data accuracy. Patients were asked to wear the device for one consecutive week, leaving it off during the night and during water-based activities. This period was chosen to capture patients' daily PA patterns and account for possible day-to-day variation. Also, for each day, patients were asked to fill in a diary with certain activities the monitor does not capture very adequately (i.e., bicycling, walking the stairs, strength training), and in addition the time patients start and end wearing the device on that day.

Data analysis objective PA

The Actigraph was set to record acceleration data at a sampling rate of 30 Hz. Data collected by the monitor were stored on the device's internal memory. When the device was returned to the UMCG, the acceleration data were downloaded onto a computer using the ActiLife software (version 6.13.3, Actigraph LLC, Pensacola, FL, USA). Raw acceleration data were processed using this software and algorithms to derive PA outcomes, using the following settings which are consistent with other studies among cardiovascular patients.⁴¹ Acceleration data were collected in epochs with a length of 60s. These epochs were categorized in different intensity levels (sedentary, light, moderate, vigorous, and very vigorous) based on the cut-off points of Freedson et al., 1998.⁴² Only data were used from patients who wore the Actigraph

for four or more valid days, with a valid day being defined as ten hours or more of wear time. Following the algorithm of Troiano et al. (2007), non-wear time was defined as a period of 60 consecutive minutes or more of zero activity counts, with an allowance of up to two consecutive minutes of counts between 1 and 100.⁴³ Given this selection criterion, we did not expect large variation in wear time between patients. Therefore, wear time was not included as a confounder in the multiple regression analysis. The export from ActiLife to an Excel file included the weekly totals of all valid days of for each PA parameters. This file was imported into Stata. In Stata, the values of weekly totals were divided by the number of valid days. Total duration of objective PA was used in the analysis, and this was the summation of the intensity categories from light to very vigorous (min/valid day).

Handgrip strength

Handgrip strength was measured using the Jamar Hydraulic handheld dynamometer (model 5030J1, Patterson Medical, now known as Performance Health, Warrenville, IL, USA), which is a reliable and responsive measure for patients in cardiac rehabilitation.⁴⁴ The dynamometer width was set at level II. Patients were instructed to hold the dynamometer in a seated position with the shoulder in an adducted neutral position, the elbow flexed at 90°, and the forearm and wrist in a neutral position. Three trials per hand were conducted, with a minimum rest of one minute between trials. Patients initiated each trial when ready and were instructed to squeeze as hard as possible. The researcher watched the dial during the handgrip strength test to determine the maximum force exerted (Kg displayed by the device, which reports kg-force (kgf)), offering consistent encouragement for each attempt: “come one, come on, come on” [in Dutch]. For HGS, Stata was used to select the maximum force of the three trials of the dominant hand. This maximum force of HGS (kgf) of these three attempts was used in the

analysis, as it is less affected by the number of trials compared to the mean.⁴⁵ Moreover, normative data are available of this measure.⁴⁵

Patient characteristics

Patient characteristics included demographic data, disease severity, comorbidities, medical history, and lifestyle-related risk factors. Demographic data included age, gender, randomisation group, and referral from a peripheral hospital. Disease severity was assessed using the planned complexity of surgery, the logistic European System for Cardiac Operative Risk Evaluation II (EuroSCORE II), left ventricular function, and NYHA-class. Comorbidities included reduced mobility, chronic lung disease, and diabetes mellitus. Reduced mobility was defined as chronic illness that negatively impacts mobility of the patient and was divided into three body parts (i.e., thorax, upper, and lower extremities). Reduced mobility was assessed by the researcher and was not the same variable as used in the EuroSCORE II, which is filled in by the medical staff and stated as a severe impairment of mobility secondary to musculoskeletal or neurological dysfunction. Both measures are subjective evaluations of mobility. Medical history covered pacemaker/implantable cardioverter-defibrillator, atrial fibrillation/flutter, betablocker use, and prior event such as myocardial infarction, percutaneous coronary intervention, cardiac/lung/kidney surgery, delirium, or cerebral vascular accident. Lifestyle-related risk factors included smoking status, body mass index (BMI), and peak power output (W) measured during a standardized submaximal bicycle ergometer test. Based on international literature, the following patient characteristics were used as confounders in the multiple regression analysis: age (yrs.), gender (male=1, female=0), BMI, reduced mobility (yes, one of all body parts=1, no =0), and atrial fibrillation/flutter (yes=1, no=0).^{11,12,31–34,20–27}

Statistical Analysis

Statistical analyses were performed using Stata/SE 18.0 (StataCorp LLC, Lakeway, TX, USA). The descriptive statistics of all relevant patient characteristic variables were analysed. To explore the association of subjective and objective total PA and HGS scatterplots were generated of all available, valid data. In these plots, potential confounders were visualised using colour-coding. Separate plots were created for gender, age-group, presence of reduced mobility, BMI-group, and presence of atrial fibrillation.

Multiple regression analyses were performed on patients with complete data for all variables to examine the association between the duration of subjective total activity(min/week; walking, moderate, and vigorous activities), the duration of objective total activity (min/valid day; light to very vigorous levels) and the response variable maximum handgrip strength (kgf). Univariate regression analyses were also conducted, relating subjective and objective total activity separately to HGS. Multiple regression analyses were performed after checking if the assumptions of normal distribution (except for the IPAQ, since it is already expected to be not normally distributed⁴⁰), homoscedasticity, linearity, and no multi-collinearity were met. Model 1 assessed the association between potential confounders (age, gender, BMI, reduced mobility, atrial fibrillation) and HGS. Models 2 and 3 were used for the role of PA by adding objective PA and subjective PA, respectively. Model 4 was the most comprehensive and included all variables from model 1-3 simultaneously (i.e., objective PA, subjective PA, and confounders). All statistical tests were two-sided and a p-value of <0.05 was considered statistically significant.

294 Results

295 **Table 1:** Patient characteristics. The following variables were used in the multiple regression
 296 analysis: age, sex, BMI, reduced mobility, atrial fibrillation/flutter.

	Cardiac surgery patients (n=139)
Age (yrs.) ^a	65.5 ± 8.4
Sex n (% men) ^a	98 (71%)
BMI (mean ± SD) ^a	27.3 ± 4.3
Planned complexity of surgery	
CABG isolated	54 (39%)
One intervention (non-CABG)	48 (35%)
Two interventions	31 (22%)
Three interventions or more	6 (4%)
Logistic EuroSCORE II	1.4 (0.9-2.4)
Left ventricular function	
Poor LVEF (<31%)	1 (1%)
Moderate LVEF (31-50%)	40 (29%)
Good LVEF (>50%)	98 (71%)
NYHA-class	
Class I	6 (4%)
Class II	42 (30%)
Class III	75 (54%)
Class IV	16 (12%)
Reduced mobility ^{a,b}	37 (27%)
Thorax	14 (10%)
Upper extremities	15 (11%)
Lower extremities	25 (18%)
Chronic lung disease ^c	17 (12%)
Diabetes mellitus	20 (14%)
Atrial fibrillation/flutter ^a	29 (21%)
Pacemaker or implantable cardioverter-defibrillator	4 (3%)
Previous myocardial infarction	22 (16%)
Previous percutaneous coronary intervention	23 (17%)
Previous cardiac surgery	3 (2%)
Previous lung surgery	2 (1%)
Previous kidney surgery	1 (1%)
Previous delirium	4 (3%)
History of cerebral vascular accident	12 (9%)
Use of beta blocker	79 (57%)
Smoking	
Currently smoking	14 (10%)
Stopped smoking	80 (58%)
Never smoked	45 (32%)
Peak power output (W)	102 ± 34
Randomisation (%new intervention)	70 (50%)
From peripheral hospital	85 (61%)

297 ^a Included as confounders in the multiple regression analysis

^b Chronic illness that negatively impacts mobility of the patient, divided into thorax, upper and lower extremities, patients could be included in multiple categories.

^c Long-term use (> 3 months) of bronchodilators or steroids for lung disease.

Values are shown as n (% yes) or mean $\pm$ standard deviation or median (IQR) or otherwise stated. Abbreviations; AVR: aortic valve replacement; BMI: Body mass index; CABG: coronary artery bypass graft; ICU: intensive care unit; LVEF: Left ventricular function; NYHA: New York Heart Association; TAVI: transcatheter aortic valve implantation.

Patients

The flowchart of the included patients is shown in Figure 1 and characteristics of the included patients are shown in Table 1. Of the patients that met the in- and exclusion criteria, 38% were enrolled and randomized in the study. One patient withdrew consent from the study and so that eventually 139 patients were analysed in the current cross-sectional study. Due to missing data, the number of patients included in each analysis varied per variable (Table 2-4). For the multiple regression analyses (Table 5), only 94 patients with complete, valid data on PA and HGS were included. Exclusions from the multiple regression analyses, due to missing data or invalid measurements, are presented in Figure 1. The preoperative consultation was conducted 32 ± 25 days before surgery. Patients in our study presented with several chronic conditions that reduced mobility (n=37), the most common being osteoarthritis, rheumatoid arthritis, joint degeneration, hernia, and peripheral artery disease, conditions frequently observed in older populations. All chronic conditions that reduced mobility were used in the multiple regression analysis.

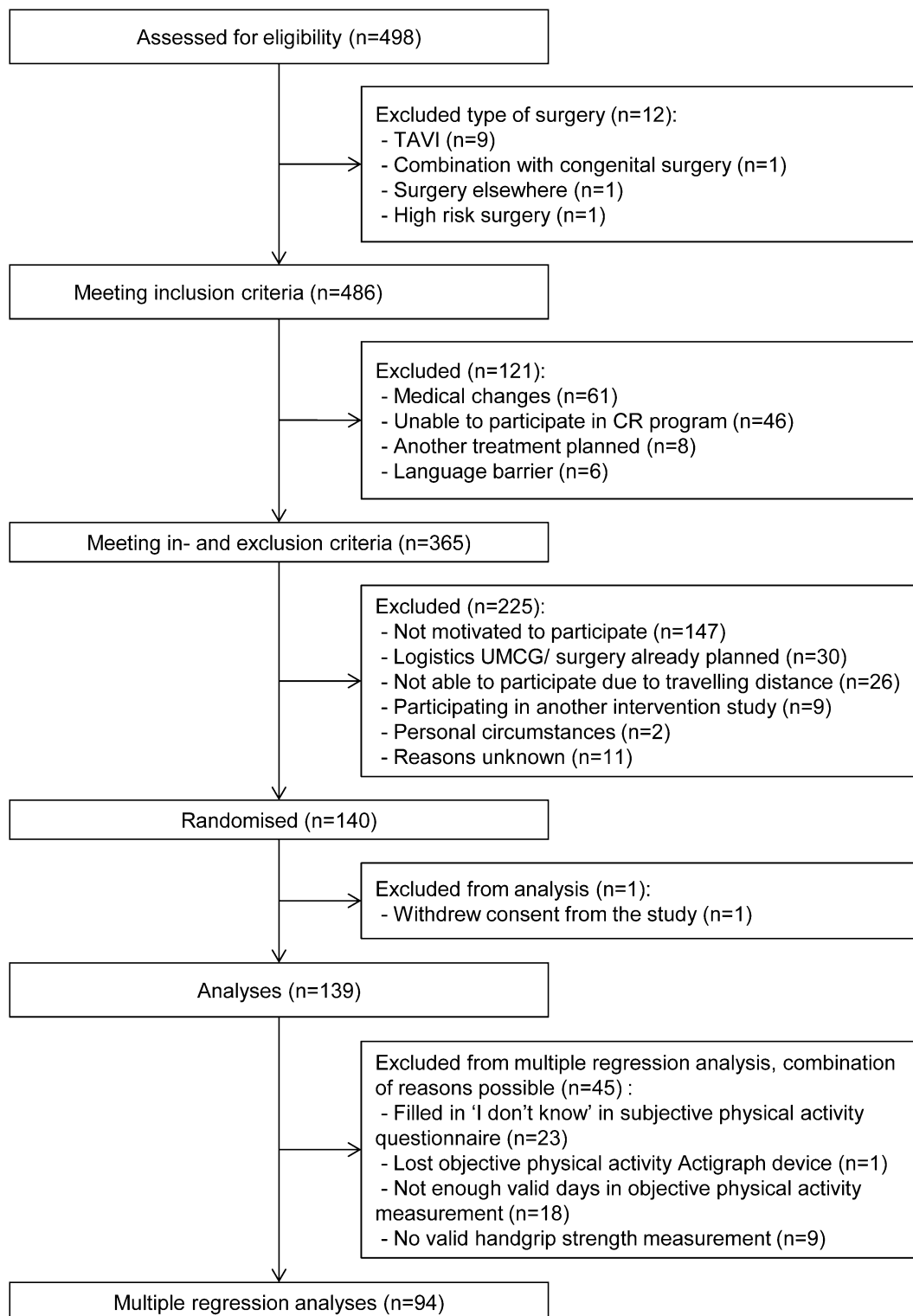


Figure 1: Consort flow diagram of patients in- and excluded in the Heart-ROCQ PROBE study until 140 randomised patients, and patients in- and excluded in the analyses and multiple regression analyses.

Subjective physical activity

Table 2 shows information about subjective PA in terms of the domain, frequency, duration, and intensity. The median total duration of subjective PA was 672.5 minutes per week (IQR: 332.5-1192.5; n=116), indicating substantial variability between patients. In addition, the durations per week of all reported activities varied widely across different domains. Of the patients, 43% were currently working or performed voluntary work. The majority of patients reported performing moderate activities for domestic, gardening (60% of all patients outdoors and 71% of all patients indoors). Furthermore, bicycling (53% of all patients) and walking (70% of all patients) was often reported as modes for transportation and during leisure time. In addition, 39% of patients participated in moderate leisure time activities. Overall, fewer vigorous activities were reported by the patients, with proportions ranging from 10% to 23% across different vigorous intensity activity variables. One patient was excluded from the analyses of subjective PA because of being an outlier (total minutes of physical activity > 6719 minutes per week), according to the IPAQ scoring protocol³⁹. For subjective PA, patients could indicate that they could not estimate the number of minutes of physical activity per question. There were 23 patients that used this option (not including the variables for sitting, since this variable is not used in the duration of total activity) and therefore were not included in the multiple regression analysis.

Table 2: Results of subjective physical activity (N=138, excluded one outlier). Subjective total all PA in duration per week (min/week) was used in the multiple regression analysis.

	Number of patients (n (%))	Frequency (days/week)	Duration per week (min/week)	Met-minutes (MET*min/week)
Work-related (n=60)				
Moderate	28 (20)	4 (2-5)	240 (65-510)	960 (260-2040)
Vigorous	19 (14)	4 (3-5)	150 (40-540)	1200 (320-4320)
Walking	35 (25)	4 (3-5)	240 (90-500)	792 (297-1650)
Total				
Transportation				
Motorised vehicle	108 (78)	4 (3-6)	240 (120-480)	NA
Bicycle	73 (53)	3 (2-5)	90 (40-180)	540 (240-1080)
Walking	97 (70)	3 (2-6)	105 (60-200)	346.5 (198-660)
Domestic, gardening				
Moderate	83 (60)	2 (1-4)	90 (45-180)	360 (180-720)
Vigorous	32 (23)	1.5 (1-3)	60 (30-180)	330 (165-990)
Moderate indoors	98 (71)	3 (2-5)	90 (60-210)	270 (180-630)
Leisure time				
Walking	88 (64)	3 (2-4)	90 (45-190)	297 (148.5-627)
Moderate	54 (39)	2.5 (2-4)	90 (45-180)	360 (180-720)
Vigorous	14 (10)	1 (1-2)	67.5 (30-120)	540 (240-960)
Sitting				
Weekdays	123 (89)	NA	1500 (1200-2400)	NA
Weekend	119 (86)	NA	720 (480-960)	NA
days				
Total	118 (86)	NA	2260 (1680-3480)	NA
Total^b				
Walking	116 (84)	NA	210 (47.5-420)	693 (156.75-1386)
Moderate	116 (84)	NA	350 (120-802.5)	1520 (442.5-3225)
Vigorous	116 (84)	NA	0 (0-0)	0 (0-0)
All PA	116 (84)	NA	672.5 (332.5-1192.5) ^a	2644.5 (1257-4538)

^a Variable used in the multiple regression analysis

^b Only from patients of whom all variables for PA, excluding sitting, were filled in and patients did not fill in "I don't know". Otherwise, patients filling in "I don't know" in minutes per week were excluded from analysis of that specific variable.

Median (IQR) were presented. Abbreviations; NA: not applicable.

Objective physical activity

Results of objective PA are shown in Table 3. The majority of the week when being awake was spent sedentary, and when they performed activities, it was mostly at light intensity. The average duration of objective total PA was 286 ± 70 min/valid day (n=120). The median duration of objective moderate activities was 18 min/valid day (IQR: 9-32; n=120). Vigorous activities had a median duration of 0 min/valid day (IQR: 0-0; n=120). One patient lost the device of the Actigraph monitor and data of 18 patients did not contain enough valid days (>4 days of >10h); these patients were excluded from the analysis. Of the patients with more than 4 valid days (n=120), the median number of valid days was 6(IQR:6-6) with an average wear time of $14h \pm 1.0$ per valid day.

Table 3: Results of objective physical activity. Duration of total physical activity was used in the multiple regression analysis.

Objective physical activity	Number of patients (n)	Results
Energy expenditure (kcal /valid day)	120	359 (228-546)
Sedentary (min/valid day)	120	543 ± 67
Light (min/valid day)	120	263 ± 68
Moderate (min/valid day)	120	18 (9-32)
Vigorous (min/valid day)	120	0 (0-0)
Very Vigorous (min/valid day)	120	0 (0-0)
MVPA (min/valid day)	120	18 (9-32)
Total PA (min/valid day) ^a	120	286 ± 70
Step count (n/valid day)	120	5214 (4314-6696)

^a Variable used in the multiple regression analysis

Mean $\pm$ STD for normal distribution, otherwise median (IQR) were presented. Abbreviations; MVPA: moderate to very vigorous physical activity. PA: physical activity.

Handgrip strength

Results of HGS can be found in Table 4. Higher levels of HGS are observed in male (45 ± 8 kgf; $n=92$) compared to female patients (26 ± 7 kgf; $n=38$). One patient could only perform one measurement of HGS of his right hand, due to pain because of arthrosis; this value was now used as the maximum score. Unfortunately, in a certain period the dynamometer was not measuring HGS in a valid way and required calibration. Therefore, for nine patients the values of handgrip strength were not used in the analysis.

Table 4: Results of the maximum handgrip strength of the dominant hand. The maximum handgrip strength in kgf was used in the multiple regression analysis.

Handgrip strength	Number of patients (n)	Results
Handedness (% right-handed) ^b	130	115 (88%)
Maximum grip strength (kgf) ^a	130	39 ± 12
Men	92	45 ± 8
Women	38	26 ± 7
Maximum grip strength (kgf per weight)	130	0.47 (0.37-0.58)
Men	92	0.52 (0.43-0.62)
Women	38	0.36 (0.28-0.45)

^a Variable used in the multiple regression analysis

^b One patient was bimanual, the maximum value of the maximum of left and right was used in the analysis as dominant hand which was the right hand.

Mean $\pm$ STD for normal distribution, median (IQR) for non-normal distribution or stated otherwise were presented.

Association between subjective and objective physical activity and handgrip strength

In univariate regression analyses, subjective total PA was significantly associated with HGS ($p=0.044$), whereas objective total PA was just below statistical significance ($p=0.087$). The explained variance was low in the univariate analyses (subjective $R^2 = 0.0433$, objective $R^2 = 0.0315$) but increased in the multivariate analyses. The results of multiple regression analyses

are shown in Table 5 and visually plotted in Figures 2-4. All models showed acceptable levels of multicollinearity, with variance inflation factor (VIF) values remaining below 2.0 for all predictors. Adding objective PA to the model with confounders (model 1 vs. model 2) model fit improved (adjusted R^2 model 1 = 0.5998 model 2 = 0.6097), and the likelihood ratio test showed a near-significant improvement ($p=0.0644$). The combination of subjective and objective PA in model 4 showed a nearly significant contribution of objective PA, a non-significant role for subjective PA and an overall model of again +1% compared to model 1 (non-significant), a slightly stronger and nearly significant better model than model 3 ($p=0.0755$), though not significantly better than model 2 ($p=0.8374$). Thus, including subjective PA, either alone (model 3) or jointly with objective PA (model 4) and confounders, did not result in a significant improvement of the model, and with minimal changes in coefficients.

Changes in confounding effect in coefficients and p-values between models 1 and 2 were small, with slight changes in the values of the constant, BMI, and AF. The coefficient of gender in model 2 was 17.8, comparable to the difference in mean HGS (Table 4). The standardized Beta values of model 2 showed that the largest significant adjusted contributor to the model was gender, followed by reduced mobility, and age (Table 5). Objective total activity was associated nearly significant ($p=0.076$) with HGS in model 2.

412 **Table 5:** Results of multiple regression analyses for the association between subjective and objective total physical activity durations and
413 maximum handgrip strength of the dominant hand (N=94)

Model	Predictor	Coefficient	Standardized Beta	p-value	VIF	R ²	Adjusted R ²	LR test vs smaller model
1	Constant	47.05271	.	<0.001*	.	0.6213	0.5998	
	Age (yrs.)	-0.2258902	-0.164	0.015*	1.02			
	Gender (if male)	18.09914	0.692	<0.001*	1.10			
	BMI	-0.1474623	-0.056	0.394	1.01			
	Reduced mobility (if yes)	-4.421958	-0.161	0.021*	1.09			
	Atrial fibrillation/flutter (if yes)	-0.6713464	-0.022	0.740	1.03			
2	Constant	40.33623	.	<0.001*	.	0.6349	0.6097	0.0644 ^a
	Objective total activity (min/valid day)	0.0184794	0.119	0.076	1.05			
	Age (yrs.)	-0.2252721	-0.164	0.014*	1.02			
	Gender (if male)	17.84025	0.682	<0.001*	1.11			
	BMI	-0.0886575	-0.034	0.610	1.05			
	Reduced mobility (if yes)	-4.524689	-0.165	0.017*	1.09			
	Atrial fibrillation/flutter (if yes)	-0.3704408	-0.012	0.854	1.03			
3	Constant	46.8347	.	<0.001*	.	0.6226	0.5965	0.5815 ^a
	Subjective total activity (min/week)	0.000476	0.036	0.597	1.08			
	Age (yrs.)	-0.2241466	-0.163	0.016*	1.03			
	Gender (if male)	17.87189	0.683	<0.001*	1.16			
	BMI	-0.1529824	-0.059	0.379	1.01			

Model	Predictor	Coefficient	Standardized Beta	p-value	VIF	R ²	Adjusted R ²	LR test vs smaller model
	Reduced mobility (if yes)	-4.416119	-0.161	0.021*	1.09			
	Atrial fibrillation/flutter (if yes)	-0.80663	-0.027	0.694	1.04			
4	Constant	40.10005	.	<0.001*	.	0.6350	0.6053	0.1770 ^a
	Objective total activity (min/valid day)	0.0193688	0.125	0.090	1.25			0.8374 ^b
	Subjective total activity (min/week)	-0.0001901	-0.014	0.845	1.28			0.0755 ^c
	Age (yrs.)	-0.2259387	-0.164	0.015*	1.03			
	Gender (if male)	17.91855	0.685	<0.001*	1.16			
	BMI	-0.0836226	-0.032	0.636	1.07			
	Reduced mobility (if yes)	-4.531966	-0.165	0.017*	1.09			
	Atrial fibrillation/flutter (if yes)	-0.301928	-0.010	0.883	1.07			

414 ^a vs. model 1 ^b vs. model 2 ^c vs. model 3

415 * significant result p<0.05. LR test = Likelihood ratio, lower <0.05 suggest bigger model is better.

In Figure 2, subjective total PA is plotted against HGS, although the association was not statistically significant in the multiple regression analyses. Figures 3 and 4 shows a visual representation of the near-significant association between objective PA and HGS stratified by certain confounders. In line with the coefficients of model 2 in Table 5, Figure 3 shows that higher levels of HGS were observed in patients with higher levels of objective total activity (except for female younger than the mean and male with reduced mobility), in younger patients, male patients, and patients without having reduced mobility. Figure 4 shows that patients with lower BMI than the mean and patients with AF had a less steep slope, though these factors were not significant in model 2.

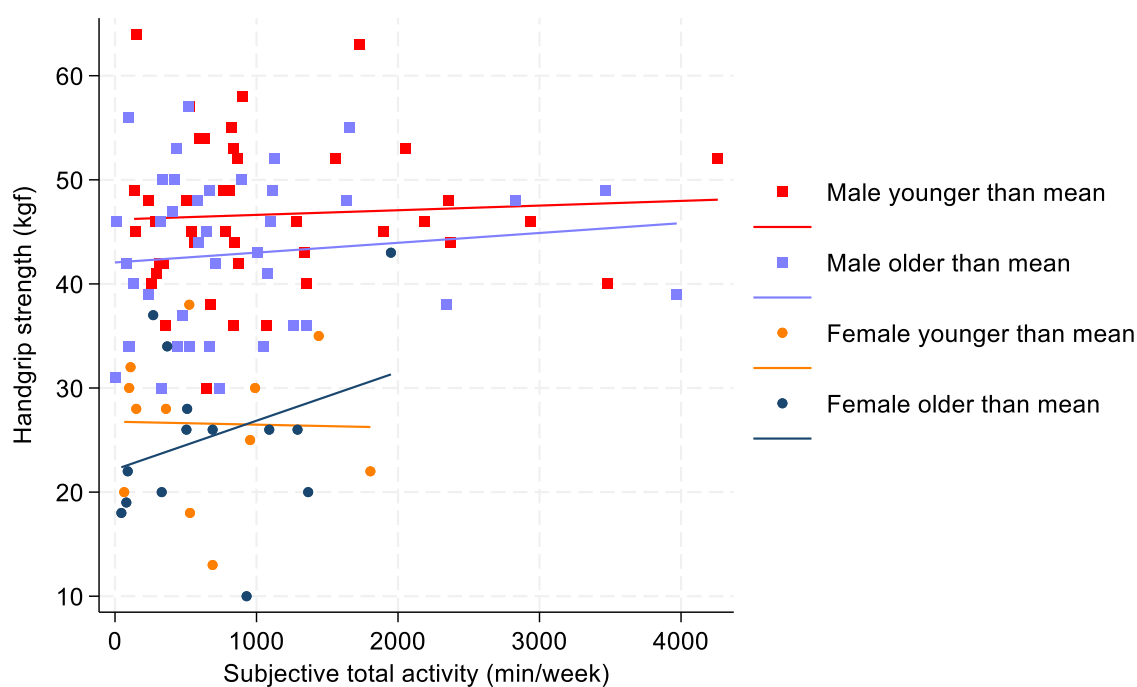


Figure 2: Association between subjective total activity and handgrip strength stratified by gender and age-group.

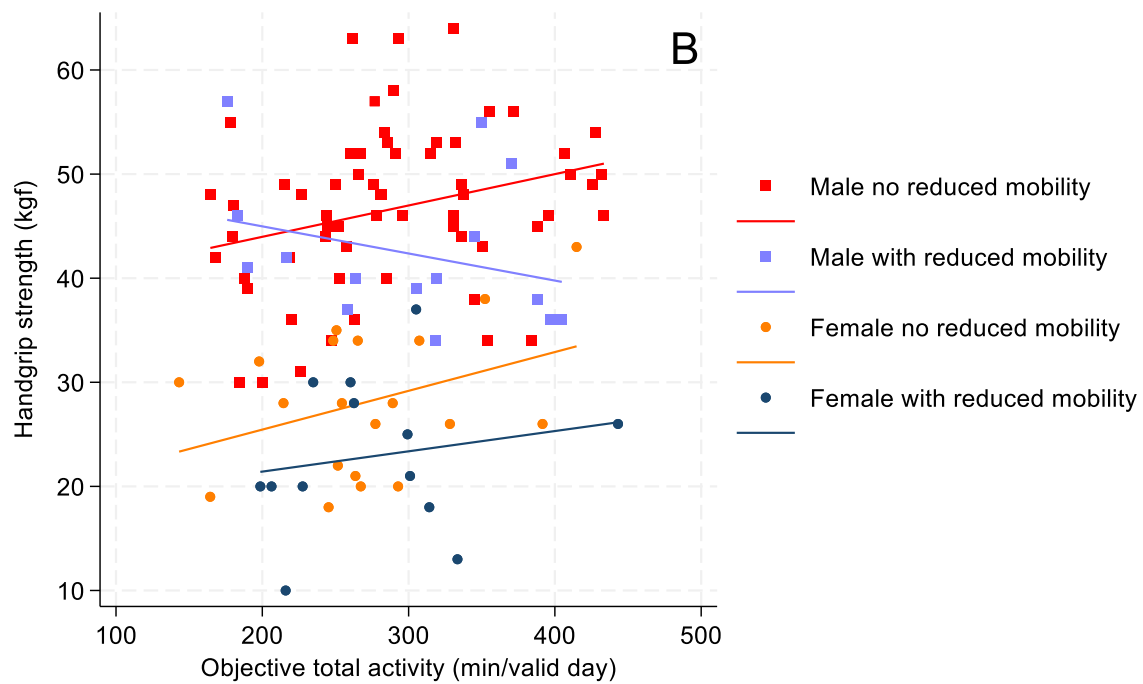
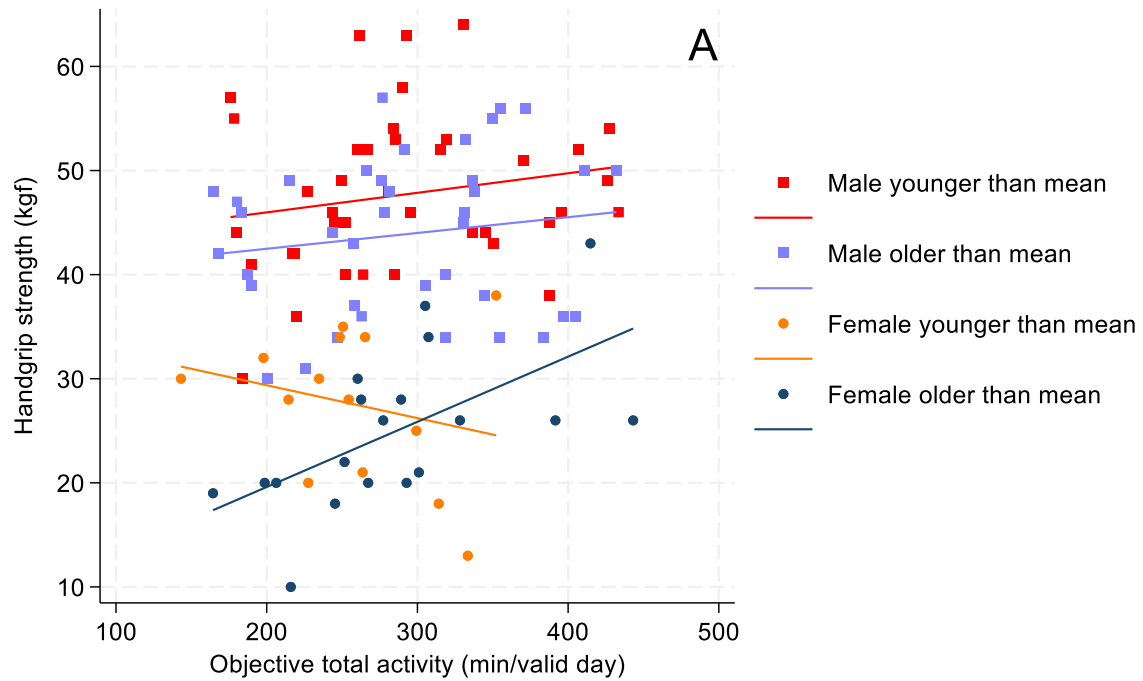


Figure 3: Association between objective total activity and handgrip strength stratified by gender and age-group (A) and stratified by gender and reduced mobility (B).

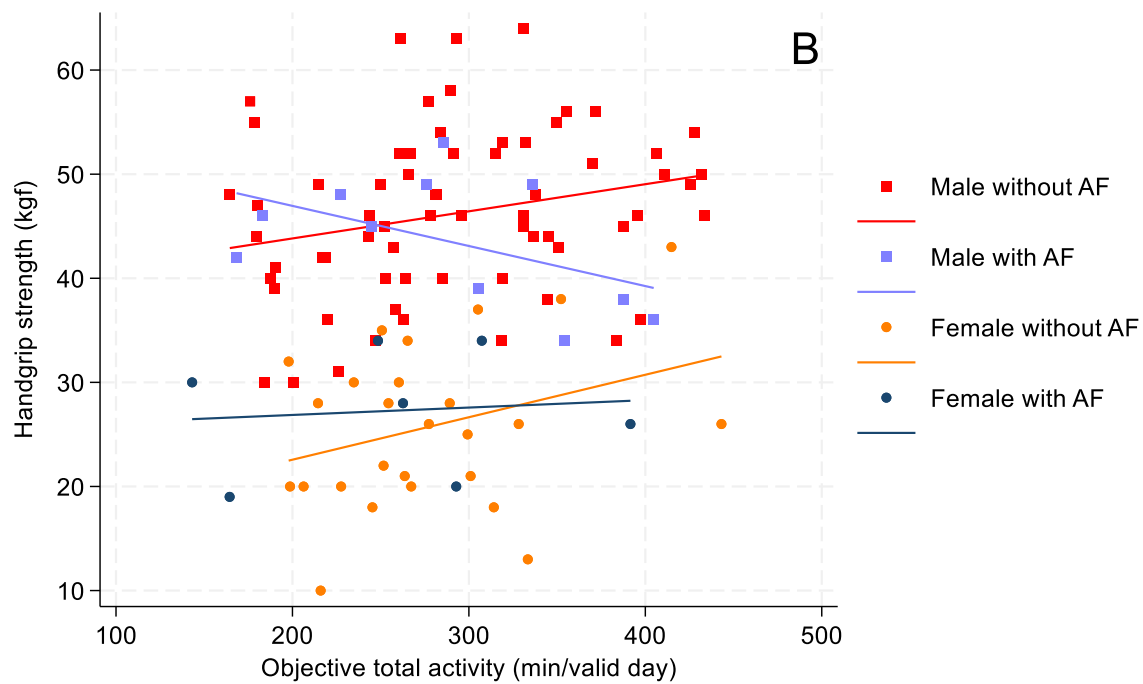
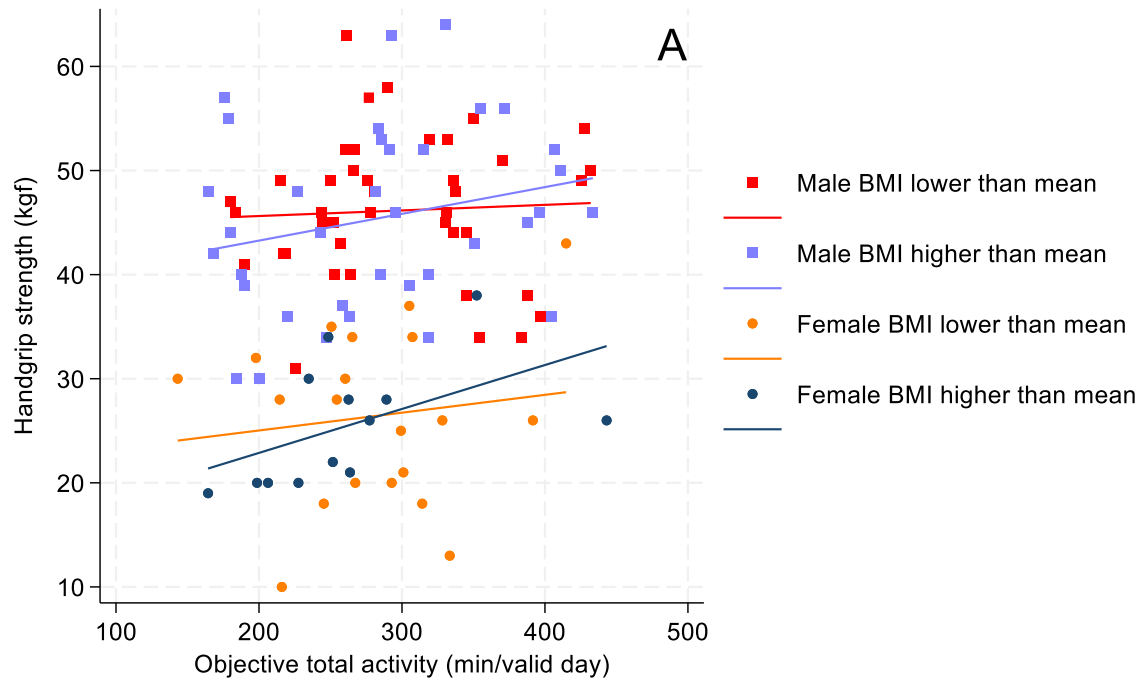


Figure 4: Association between objective total activity and handgrip strength stratified by gender and BMI (A) and stratified by gender and atrial fibrillation or flutter (AF) (B).

Additional analyses were performed to verify the robustness of the findings. First, a log transformation of subjective total PA was applied to reduce skewness but did not improve the linearity or residual distribution. Therefore, the original variable was retained in the model. Second, sample size of female participants (n=24) was too small to make robust statements with separate models for gender. While exploring the multiple regression analyses of males (n=70), it showed that all models were near-significant (p-values ranging from 0.0513 to 0.1104) and had lower R^2 values (< 0.15) compared with the models including gender (~ 0.63 , Table 5). In all these models, neither subjective nor objective physical activity was significantly associated with handgrip strength ($p > 0.05$) and none approached statistical significance. Third, interaction between factors were explored continuing with Model 2 (especially since figures suggested possible difference in relationship between gender and BMI and gender and reduced mobility on HGS); almost all interactions revealed not to be significant in the regression model and showed a non-significant LR test, suggesting no improvement in model fit. The only exception was the interaction between objective total PA and reduced mobility. As expected, the inclusion of the interaction term substantially increased VIF values (> 15.00) due to collinearity with the main effects. Compared to Model 2, this model slightly improved model fit ($R^2 = 0.6473$, adjusted $R^2 = 0.6186$, LR-test $p = 0.0712$). In this model, objective total PA remained significant (standardized Beta = 0.176, $p = 0.019$) and the interaction term was near-significant (standardized Beta = -0.463, $p = 0.085$). The main effect of reduced mobility was no longer significant (standardized Beta = 0.279, $p = 0.294$), while age (standardized Beta = -0.167, $p = 0.012$) and gender (standardized Beta = 0.681, $p < 0.001$) remained significant compared to Model 2.

Discussion

This cross-sectional study aimed to evaluate both subjective and objective physical activity (PA) levels in free-living conditions and handgrip strength (HGS), and to examine the association between PA and HGS in patients awaiting cardiac surgery. The findings showed that the duration of subjective reported total PA varied widely (median 637.5 minutes per week IQR: 332.5-1192.5), whereas objectively measured PA was predominantly of light intensity, with an average total PA duration of 286 ± 70 min per day. Virtually no vigorous activities were recorded, either with the subjective (median 0 minutes per week IQR: 0-0) or the objective (median 0 min/valid day IQR: 0-0) method. As expected, HGS was higher in males (45 ± 8 kgf) than females (26 ± 7 kgf). While no significant association was observed between subjective total PA and HGS, a near-significant positive association was found between objective total PA and HGS when adjusted for confounders.

Cardiac patients

The study population, consisting mainly of older male patients with comorbidities, is representative of a typical cardiac surgery population. This is a complex group, not only due to advanced age, but also because of the presence of common comorbidities.⁴⁶⁻⁴⁸ These factors likely contribute to reduced levels of PA and HGS, as observed in various cardiac populations.^{11,12,20-27} Moreover, patients awaiting cardiac surgery may adopt a more cautious approach to movement and exertion, potentially out of fear of provoking chest pain, breathlessness or worse.²¹ Such understandable behavioural adaptation may lead to underperformance in free-living PA and during functional tests, such as HGS. Reduced activity levels have also been reported during the COVID-19 pandemic, due to societal restrictions and behavioural changes.⁴⁹ Since the current cohort was enrolled just before the

onset of the pandemic, the observed levels of PA and HGS are more likely a result of patient characteristics and behavioural adaptations related to cardiac disease.

Comparison previous studies

Physical activity

Although durations of self-reported subjective PA varied widely, the majority of the participants reported walking (70%) and cycling (53%) for transportation, as well as engaging in moderate domestic activities and gardening (60% and 71% indoors). A substantial proportion of the patients also took part in moderate leisure activities (39%) according to the subjective measurement. Virtually no vigorous activities were recorded by either measurement method. Objective PA predominantly consisted of light-intensity activities, with a considerable duration of total PA (286 ± 70 min per day). We included light activities and short-duration movements in total PA. While this approach may differ from other studies, it aligns with emerging evidence underscoring the importance of transitioning from sedentary behaviour to any physical activity level, including light activities.⁴⁰

Compared to patients with coronary artery disease, similar findings were observed in subjective total PA using the IPAQ.²⁰ Step counts in our study were lower than the pedometer results of another study²⁰, also reflecting reduced walking activity in the IPAQ. Objective PA in our cohort was similar to that of heart failure patients with NYHA class III using the Sensewear device, which includes accelerometry and physiological sensors.²² Compared to another study in the same patient population, we observed substantially higher values for both subjective total PA (twice as high using the same questionnaire) and objective total PA (seven times higher using a different accelerometer).¹¹ This discrepancy may be attributed to differences in patient selection (e.g. inclusion of urgent patients, surgery complexity, or other personal characteristics), cultural context, or measurement timing. In our

study, 'baseline' was defined as the start of the waiting period before prehabilitation and cardiac surgery, whereas in the other study, baseline may have referred to hospital admission. PA is likely lower when monitored closer to surgery due to patients' mental state, including emotional stress, perceived fatigue or increased intentional rest. Additionally, compared to another study²⁴ using a different accelerometer in the same patient population, our study found lower moderate to very vigorous physical activity (MVPA), more light PA, and slightly less sedentary time, resulting in a higher total PA. Physical activity outcomes vary substantially across countries, reflecting cultural and contextual differences in activity patterns, with differences more pronounced in objectively measured compared to subjectively measured data.⁵⁰ These findings underscore what has also been reported in a review; that differences in measurement methods, timing, cultural context, and clinical patient selection, can lead to considerable variation in PA outcomes and make direct comparisons among studies challenging.¹³ In summary, despite the differences in measurement and context, our cohort demonstrates physical activity patterns within the expected range for similar populations, largely driven by light-intensity activity.

Handgrip strength

HGS levels in our study population were comparable to that of healthy individuals of similar age⁴⁵ and even exceeded those reported in another study among patients awaiting cardiac surgery²⁶, despite the higher complexity of surgery and largely similar patient characteristics (except for a lower proportion of diabetes in our sample). Although the Jamar handheld dynamometer is widely used for assessing HGS, it has some disadvantages, including the analogue measurement which is susceptible to reading errors, as well as the influence of the dynamometer width, weight and positioning.^{45,51} Furthermore, HGS can vary across different countries and cultural contexts due to differences in physical and environmental factors,

which should be considered when comparing results internationally.⁵² Taken together, these findings suggest that, despite the potential methodological and contextual influences, our study population demonstrates HGS levels within the normal range, even though it consisted of patients awaiting cardiac surgery with a risk of sarcopenia (which implies low muscle strength).³

Association of subjective and objective PA with HGS

Although subjective PA initially appeared to have a significant association with HGS, this effect disappeared in the multivariate analysis, suggesting that the other confounding factors play a more important role. In contrast, objective PA was not significantly associated with HGS in the univariate analysis, but showed a near-significant association with HGS ($p=0.076$) when adjusted for confounders in the multiple regression analysis. Including objective PA in the model slightly improved overall model fit compared with the model including only confounders (+1%; $p=0.0644$). A considerable proportion of the variance of HGS was explained in this model (63%). When both subjective and objective PA were included in the model, objective PA again showed a near-significant association, while subjective PA remained non-significant. These findings align with other studies, showing there was no association between subjective PA and physical fitness outcome.¹² Our model including both subjective and objective PA improved by 1% compared to the model consisted of only confounders though non-significant ($p=0.1770$), was near-significant better than the model including only subjective PA ($p=0.0755$), and was not significantly better than the model including only objective PA ($p=0.8374$). These results suggest that trends in subjective and objective PA in this patient population are apparently not identical.

In the current study, both subjective and objective PA methods were used to assess PA and were included in the multiple regression analysis, as they are assumed to capture different

but complementary aspects of PA behaviour.^{19,53} Subjective PA, measured with the IPAQ questionnaire, reflects the perceptions of patients, while the objective data were derived from accelerometry (though not the gold standard¹⁸) providing quantifiable movement-based insights. Including both measures aligns with recent recommendations for multimodal assessment¹⁹, and was supported by low VIF-values indicating no multicollinearity. Although the subjective IPAQ data are known to be not normally distributed⁴⁰, the use of parametric regression analysis was considered justified in this context due to the complementary value of the two methods.

The minimal changes in most confounder coefficients after adding objective PA suggest a potentially independent, though limited, contribution of objective PA to HGS. Notably, the coefficients for BMI and atrial fibrillation changed more markedly, indicating possible shared explained variance with objective PA. An association between prehabilitation and atrial fibrillation has previously been reported.⁵⁴ Future research should explore whether similar associations for BMI, atrial fibrillation, and objective PA in free-living conditions exist among patients awaiting cardiac surgery. Furthermore, the negative interaction of objective total PA and reduced mobility suggests that the benefit of PA may be slightly smaller in patients with mobility limitations. However, given the exploratory nature of this analysis and the borderline significance, these findings should be interpreted cautiously and requires further investigation.

Clinical implications

While objective PA may be associated with HGS, it might also relate to other clinical characteristics in this patient group relevant for preoperative care. Moving forward the challenge is to determine which parameters are most useful for identifying patients during preoperative screening, either for risk stratification of surgical recovery⁴⁶⁻⁴⁸ or for enrolment

in prehabilitation programmes¹⁵. Assessments of PA and HGS may complement each other in characterising patient status, as less active patients also tend to have lower handgrip strength, and both factors are potentially modifiable. Integrating valid measures of PA and muscle strength into preoperative screening may offer a more comprehensive picture of baseline health and help tailor interventions more effectively.^{46–48}

Study limitations

To our knowledge, this is the first cross-sectional study investigating preoperative associations between PA, especially through objective measurement, and HGS in this patient group. However, several limitations must be acknowledged. The sample size was relatively small and included a wide range of surgical complexity, which may affect both the generalisability and variability of the findings. Comorbidities were common, their potential confounding effect on test performance could not be fully accounted for. Disease severity, known to affect both PA and HGS, could not be included in our multiple regression model due to the number of categories and lack of gradual build-up of complexity. Selection bias may also have occurred, as patients willing to participate in prehabilitation may represent a more motivated or health-conscious subgroup, particularly inclined towards PA, potentially skewing results. In addition, the process of randomisation may also have influenced patient motivation. Control patients, for instance, may have felt disappointed when, during the period they were wearing the activity monitor, they were informed that they would not receive prehabilitation, which could have reduced their motivation to wear the activity monitor consistently and correctly. Future research could investigate day-to-day variation in PA, as well as the impact of motivation and mental wellbeing on PA levels and HGS in this patient group. Overall, these factors may have influenced the observed associations and limit the generalisability of our results.

Beyond the characteristics of the patients, several methodological limitations should be considered. The fixed order of the tests may have influenced outcomes, although this standardization ensured consistency across all participants and at all measurement time points in the longitudinal study.³⁵ With regard to the duration of total PA, subjective and objective methods were not directly comparable (e.g. subjective PA did not capture light-intensity activity). Therefore, differences between the two methods were not analysed. Moreover, data processing algorithms in objective PA (e.g., Chojs vs Troiano method, epoch length) as well as in the subjective method can impact the derived PA metrics.⁴¹ Yet validation studies are limited, especially for patient-specific groups, who may behave differently than the healthy population.¹⁹ For subjective PA, we used the total duration in minutes per week rather than MET minutes per week to improve interpretability and avoid assumptions derived from healthy populations. For objective PA, we chose to use total duration of physical activity rather than energy expenditure, since the monitor was not worn during the night, energy expenditure was not the primary focus of the longitudinal Heart-ROCQ PROBE study³⁵, and energy expenditure was not normally distributed in the current cohort.

For muscle strength, only HGS was assessed in this study. While lower extremity strength may be more sensitive to (in)activity, sedentariness and/or hospital immobilisation⁵⁵, such tests⁵⁶ are less practical in routine clinical practice in the hospital, though feasible in clinical research settings such as the Heart-ROCQ PROBE study³⁵. Although simple tests, such as the sit-to-stand test, may provide less accurate measurements of lower extremity strength, they may offer a feasible and practical alternative for use in clinical practice.⁵⁷

Finally, the cross-sectional design prevents conclusions about causality and directionality of the observed associations, which may also change over time. In addition, model fit may differ between subgroups, for example based on gender. Unfortunately, the final sample size for the regression analysis was substantially reduced due to missing data

across multiple variables, which could not be foreseen. This limited the power to investigate subgroup differences, such as gender-specific associations between PA and HGS. A supplementary analysis in men only (n=70) suggested that gender differences may partly drive the observed associations, highlighting the need for larger subgroup studies. In the main model (which included gender and objective PA as predictors) a considerable proportion of the variance in HGS (~37%) remained unexplained, indicating that additional factors (e.g., psychosocial, nutritional, disease-specific) should be further explored as well.

Future research

Future research should address the discussed limitations and further explore the utility of PA and HGS measures in the diverse cardiac surgery population. Specifically, larger prospective studies are needed to monitor changes in PA and HGS over time to evaluate their predictive value for postoperative outcomes. Given that PA is a multifactorial and dynamic construct, it remains challenging to capture accurately with a single method. The choice of assessment tools and data processing techniques can significantly impact outcomes, underscoring the need for validated, context-specific methodologies.¹³ Moreover, exercise intervention trials, particularly part of prehabilitation programmes, could determine whether targeted, structured training improves PA, muscle strength, functional capacity, and recovery in cardiac surgery patients. Advances in wearable technology and data algorithms, especially those tailored to clinical populations, will further improve measurement accuracy and clinical applicability. Finally, incorporating PA and HGS assessments into prehabilitation strategies could contribute to improved recovery and support long-term health and well-being.

Conclusions

Among patients awaiting cardiac surgery, durations of subjective physical activity varied widely, whereas most objective physical activity consisted of light activities. Values of preoperative handgrip strength were comparable to the healthy population in the same age group. In this cross-sectional study among patients awaiting cardiac surgery, there was a trend that higher levels of objectively measured physical activity in free-living conditions were associated with an increase in handgrip strength when corrected for confounders. Multiple tests for assessing objective and subjective physical activity and muscle strength should be considered in the evaluation of patients' preoperative health status, which could be helpful for tailoring prehabilitation and improving recovery in patients awaiting cardiac surgery.

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General Discussion

Cardiac surgery can significantly impact the physical health and quality of life (QoL) of patients with cardiovascular disease.^{1–8} At the same time, this procedure also carries risks of complications, especially in frail patients with sarcopenia.^{1–3,9–12} Preoperative physical and mental health conditions are considered important factors that influence the outcome of surgery. As for physical health, there are indications that both preoperative handgrip strength and physical activity are important predictors of postoperative recovery.^{13–19} Therefore, the first aim of this thesis was to investigate the preoperative condition, the relationship between handgrip strength, physical activity, and health-related quality of life (HR-QoL) in patients awaiting cardiac surgery. Secondly, this thesis explored the potential role of preoperative rehabilitation (prehabilitation) combined with postoperative rehabilitation within the Heart-ROCQ-pilot programme to optimise patient physical and mental health before and after surgery. This final chapter aims to summarize the main findings in the current literature context and to reflect on their overall contribution to knowledge about enhancing rehabilitation care of cardiac surgery patients. Furthermore, it reflects on methodological choices, as well as on potential clinical implications and future perspectives.

Summary of findings

The goal of Chapter 2 was to determine trajectories of handgrip strength and their association with postoperative HR-QoL in patients undergoing Coronary Artery Bypass Grafting (CABG) surgery. Results of this prospective cohort study suggested that male patients following the less favourable handgrip strength trajectory showed to have more preoperative risk factors than the other distinct trajectory. Patients in both trajectories showed to recover or improve at six months after surgery to preoperative levels of handgrip strength. Although handgrip strength trajectories by themselves were not associated with postoperative HR-QoL, a change in handgrip strength did appear to be related to postoperative HR-QoL.

Chapter 3 was a prospective pilot study aimed to evaluate the levels of preoperative subjective physical activity, and its effects on handgrip strength and postoperative outcomes including QoL and cognitive functioning among patients undergoing CABG surgery. Findings from this study suggested that CABG patients who reported being inactive had

surgeries with higher risk of death, lower preoperative QoL and higher inflammation status compared to active patients. However, these differences did not translate into postoperative differences in QoL, complications, or cognitive functioning. In addition, handgrip strength was also not associated with higher cardiac risk scores nor with postoperative cognitive decline.

The focus of Chapter 4 was on the evaluation of both subjective and objective physical activity levels and their dose-characteristics under free-living conditions in patients awaiting CABG surgery. This cross-sectional subanalysis of Chapter 3 showed that according to the outcomes of both the subjective and objective physical activity methods, the majority of the CABG patients met the Dutch guideline of healthy activity prior to surgery. The self-reported, subjective method indicated longer durations of moderate to vigorous physical activity compared with the objective accelerometer-based method. Agreement between the two methods for assessing physical activity was limited and decreased with higher levels of activity.

Next to physical activity in free-living conditions, physical exercise in a structured rehabilitation programme was also explored in this thesis. The goal of Chapter 5 was to examine the feasibility of the Heart-ROCQ-pilot programme, consisting of pre- and postoperative rehabilitation in patients undergoing cardiac surgery. High compliance to bicycle and strength training was observed. Workload increased in each rehabilitation phase with low discomfort scores. Patients could recover to preoperative levels of workload for both bicycle training and leg strength exercises. The findings from this study suggested that the physical components of this programme were feasible and safe for patients undergoing elective cardiac surgery.

Chapter 6 described the protocol of the randomised controlled trial evaluating the Heart-ROCQ programme compared to usual care. The findings from Chapter 5 were integrated into this protocol. This protocol used a primary combined endpoint of functional status, complications, and events, represented by a composite weighted score that extended beyond mortality to capture recovery after surgery from a broader perspective. Secondary outcomes focused on physical (cardiorespiratory fitness, muscle strength, independence in ADL), mental (general anxiety, feelings of depression, HR-QoL), and social (healthcare use, work participation, QALYs) well-being, together with lifestyle risk factors (physical activity, obesity indices, smoking behaviour) and potential mediators (cardiac self-efficacy, illness

representations), and complications and events. With this study design factors and mechanisms that were responsible for the efficacy of this pre- and postoperative rehabilitation programme in cardiac surgery patients could be explored in the future.

Chapter 7 incorporated initial baseline results from the Heart-ROCQ study set-up described in the previous Chapter 6, and evaluated both preoperative subjective and objective physical activity and handgrip strength, and their cross-sectional association in patients awaiting cardiac surgery. The results showed that values of physical activity and handgrip strength were in the ‘normal’ or expected range regarding age, gender, and compared to similar patients. When corrected for confounders, subjective physical activity was not associated with handgrip strength, while higher levels of objective physical activity were nearly significantly associated with higher levels of handgrip strength in patients awaiting cardiac surgery.

Main insights and theoretical reflections

This section discusses four main insights that emerged across the different studies included in this thesis and reflects on their theoretical implications. Each finding is discussed in a separate subsection below.

Clinical relevance of changes in handgrip strength

In this thesis, we chose to use handgrip strength as an outcome measure for muscle strength as part of the overall assessment of physical fitness, because of its practical applicability in the clinical setting and its predictive value regarding recovery from surgery.^{13,14,20–22} Furthermore handgrip strength is a simple, objective and widely used measure of muscle strength and is often used as an indicator of frailty and sarcopenia.^{21,23–25} Frailty, sarcopenia and cardiovascular disease are all strongly related to age. With the aging population, the number of elderly patients requiring cardiac surgery is expected to increase, making handgrip strength a particularly relevant measure in this population.²⁶

Although handgrip strength trajectories alone were not associated with postoperative HR-QoL, changes in handgrip strength did appear to be related to postoperative HR-QoL (Chapter 2), consistent with previous research in older adults.²³ Surprisingly, a single

preoperative value of handgrip strength was not associated with higher cardiac risk scores nor with postoperative cognitive decline (Chapter 3).^{13,27,28} These findings (Chapter 2 and 3) suggest, in line with another study²², that handgrip strength may represent a modifiable aspect of physical fitness that might be monitored over time and considered as a dynamic measure in the evaluation of patients awaiting cardiac surgery. Handgrip strength assessments could therefore not only be used as a prognostic indicator, but also as a practical tool to monitor trainability in patients undergoing cardiac surgery when measured longitudinally.^{13,14,22,27,29,30}

However, differences between studies in patient population (e.g., complexity of surgery, presence of comorbidities, and demographic factors)^{9,31–34}, used method (e.g., device type, timing, and positioning)^{35,36} and context (i.e., country and cultural background)³⁷, impacts handgrip strength outcomes and thereby making comparisons more difficult. These relevant associated factors might be considered in higher-powered studies involving a larger and more diverse population of patients undergoing cardiac surgery, preferably through multicentre collaboration. Such studies are still needed to improve our understanding of handgrip strength, to identify subgroups, and evaluate longitudinal changes. Findings from these studies in patients undergoing cardiac surgery could further help in evaluating the effectiveness of (p)rehabilitation programmes and contribute to the development of more tailored, personalised care.

Levels of physical activity and their impact on clinical outcomes

The second main finding of this thesis concerned the levels and assessment of physical activity in patients undergoing cardiac surgery. While physical inactivity is a major risk factor for cardiovascular disease,³⁸ the majority of the patients included in this thesis met the Dutch guideline of healthy activity or had physical activity levels within the normal or expected range (Chapters 3, 4 and 7). Notably, differences in self-reported, subjective physical activity between inactive and active CABG patients did not translate into postoperative differences in complications nor in cognitive functioning (Chapter 3), which was contrary to previous findings.^{15,16} In addition, subjective physical activity was not associated with handgrip strength, while objective physical activity was nearly significantly associated with handgrip strength in cardiac surgery patients (Chapter 7). Furthermore, agreement between the subjective and objective methods for assessing physical activity decreased with higher levels of physical activity in CABG patients (Chapter 4). Taken together, these findings indicate that

assessing physical activity in cardiac surgery patients is complex: subjective and objective measures provide different, sometimes conflicting information, and subjective activity levels do not appear to predict postoperative outcomes. This underscores the importance of considering both methods in evaluating physical activity, as will be further addressed in the subsequent text.

General clinical practice in the hospital understandably focuses on treating complaints and symptoms, and cardiac surgery patients mainly undergo tests to assess the function of the heart, which is both important and necessary for the decision to operate.^{4-7,26} However, overall physical health, including information about physical activity, is important to consider, especially since it is a major risk factor in this patient group.³⁸ Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure,²⁰ and can be described in the following dose characteristics; context, form, duration, frequency, and intensity. Dose-characteristics of physical activity in this patient group are important for the understanding of the construct of physical activity in patients, are useful for evaluating individual scores and to determine the dose-characteristics needed to individually tailor structured physical activity in prehabilitation.³⁹ Physical activity can be assessed subjectively through questionnaires and objectively by using portable activity monitors. Although the relevance of physical activity in cardiac populations is well-known, information about objectively measured physical activity among patients awaiting cardiac surgery remains limited.^{38,40}

By incorporating both subjective and objective assessments, this thesis shows that these methods offer complementary value and different perspectives of patients' physical activity behaviour (Chapter 4 and 7), which was also emphasized by a review.⁴¹ Subjective methods, such as questionnaires, can provide information on dose-characteristics in terms of context, form, duration, frequency and intensity, however these reflect the perceived, brain-filtered activity behaviour.^{42,43} In addition, subjective methods are subject to recall bias and influenced by socially desirable answers, potentially resulting in less accurate outcomes.^{42,43} Furthermore, cardiac surgery patients might experience physical activity differently, possibly more intense, than the healthy population.⁴⁴ It could be possible that these more frail, vulnerable patients experience even light activity levels as moderate activity.

Our findings (Chapter 4 and 7) highlight the importance of including light activities in the duration of total activity, which is consistent with the current WHO guidelines emphasizing

that even a shift from sedentary to light activities is beneficial for health.⁴⁵ This idea that some activity, even at light intensity, is better than nothing, is already mentioned in 1994 by William Haskell.⁴⁶ However, only current guidelines for physical activity, including the one of WHO, mentioned the importance of both light and short duration activities, illustrating that it can take a long time before an idea is implemented in practice.

While subjective questionnaires provide information about form and context of physical activity, this is often not possible to capture with the objective methods, such as accelerometers. On the other hand, these objective methods, estimate energy expenditure from body movement and can give more detailed information about duration, frequency and intensity for each minute of the day.^{42,43} In contrast to subjective methods, this information from objective methods is not influenced by the perception of patients, although they are subject to observation bias and possibly are more burdensome.^{42,43}

Therefore, it is assumed that the subjective and objective method both provide relevant complementary information and possibly reflect different aspects of the construct of physical activity. The lower agreement observed between the two methods (Chapter 4 and 7) may be due to differences in measurement focus and perspective, or to the fact that the methods have not been specifically validated for patient groups. Both methods still rely on validation and algorithms developed in healthy populations, whereas it may be more accurate to tailor them specifically to certain patient populations.^{41,47} Ideally, these algorithms are customised to provide more personalised care for each individual, so that physical activity can be estimated as accurately as possible. Integrating both subjective and objective assessments into clinical practice help obtain a more complete understanding of physical activity in cardiac surgery patients.

Feasibility of pre- and postoperative rehabilitation

Because patients with cardiovascular disease are at increased risk of sudden death during exercise⁴⁸, safe and individually tailored interventions are required. Currently there are no guidelines for preoperative exercise for patients awaiting cardiac surgery, so it is important to evaluate their exercise performance during an intervention.⁴⁹ Patients in the Heart-ROCQ-pilot programme showed high compliance to the physical components despite the multidisciplinary approach (Chapter 5), which was more comprehensive than previous prehabilitation studies.^{50–52} Evaluating actual protocol adherence, such as compliance and

workload during bicycle and strength training, is important in the context of training physiology for programme effectiveness, yet rarely examined.³⁹ In the Heart-ROCQ-pilot programme, workload and cardiac functioning improved throughout the programme (Chapter 5). Overall, pre- and postoperative (in- and outpatient) rehabilitation, including both bicycle and strength training, is considered feasible and safe for patients undergoing elective cardiac surgery (Chapter 5).

Results of the feasibility study were used to refine the randomised study (Chapter 6), illustrating the value of conducting feasibility studies first. Future results of the protocol of the randomised trial proposed in this thesis (Chapter 6) may be more conclusive with a more robust analysis of whether participation in pre- and postoperative rehabilitation reduces complications and improves recovery from cardiac surgery compared to usual care. Also, in line with the ICF model, the secondary outcomes of this protocol (Chapter 6) focus on physical, social and mental well-being, so that we can understand the mechanisms of potential confounders.⁵³ Eventually, preventive measures, such as the prehabilitation programme, may contribute not only to better individual outcomes, but also to reduce the pressure on (and costs of) the health care system by using available human and financial resources more efficiently and effectively. Cost-effectiveness will be assessed according to the protocol described in Chapter 6, and selecting patients who require additional care may further improve overall cost-effectiveness.

Impact on postoperative quality of life

Cardiac surgery is a procedure which can be viewed as an important life-event, often accompanied by negative emotions and affecting QoL.^{4,54} The findings of this thesis indicate that higher levels of handgrip strength (Chapter 2) and physical activity (Chapter 3), which were nearly significantly associated with each other (Chapter 7), was related with reduced preoperative risk factors (Chapter 2 and 3). In addition, higher levels of handgrip strength and physical activity were also related to higher levels of HR-QoL in cardiac surgery patients (Chapter 2 and 3). This supports the idea that physical and mental health are closely linked, which are indeed parts of the broader construct of health following the WHO definition and ICF model.⁵³

However, the definition of health being used can influence the interpretation of these findings. Although the WHO definition and ICF model are widely used in research and

clinical practice and offer standard methods for assessing well-being and functioning, Huber's concept of Positive Health offers an additional perspective.⁵⁵ It emphasizes the ability to adapt and manage oneself in the context of physical, emotional, and social challenges⁵⁵, integrating resilience and QoL, aspects that may be particularly relevant for patients undergoing cardiac surgery.

Furthermore, although no differences were observed between active and inactive CABG patients in postoperative HR-QoL or cognitive functioning, preoperative HR-QoL was significantly lower in inactive compared to active patients ([Chapter 3](#)). This could mean that subjective physical activity impacts the preoperative health state, but other factors might be of higher influence for the postoperative health state.

Physical exercise, which can be viewed similar to physical activity, but in a far more structured goal-oriented approach²⁰, will be further investigated in the protocol described in this thesis ([Chapter 6](#)), which aims to evaluate a pre- and postoperative rehabilitation programme on, among others, HR-QoL and mental well-being. The hypothesis is that participating in structured exercise in the Heart-ROCQ programme reflects in higher subjective physical activity before surgery, which was associated with a lower inflammatory response to surgery and better preoperative HR-QoL ([Chapter 3](#)). Additionally, this might reflect in higher objective physical activity possibly associated with higher levels of handgrip strength ([Chapter 7](#)). Given the observed improvements in workload during strength training in the Heart-ROCQ pilot programme ([Chapter 5](#)), it seems plausible that these gains may be reflected in higher handgrip strength values and better change scores of handgrip strength, which could in turn relate to more favourable postoperative HR-QoL outcomes ([Chapter 2](#)). Patient enrolment for this study has recently been completed, and all follow-up results are currently being finalised. Future research on this Heart-ROCQ programme may help to further explore these hypotheses.

Methodological reflections

The strengths and limitations of the studies are described in more detail in the separate chapters in the thesis. Three overarching methodological issues are discussed here: research methods, generalizability and sample size, and outcome measures.

Research methods

The current thesis applied research methods within a clinical setting, balancing measurement accuracy with patient burden and practicality. In practice this meant that the ideal designs, such as randomised controlled trials (except for [Chapter 6](#)), were often difficult to implement due to clinical workload, patient flow, and ethical considerations. An important reflection concerns the data availability. Due to the pressure of clinical care, data collection is often limited to information already gathered for patient management and with potentially more missing data, making repeated collection for research purposes less feasible.

However, the choice for longitudinal observational studies ([Chapters 2, 3, and 5](#)) was not only pragmatic, but also necessary to ensure that data collection interfered as little as possible with routine care, though limiting causal inference. Cross-sectional studies ([Chapters 4 and 7](#)) were used to understand the potential associations between key factors within a group at a specific point in time, limiting conclusions about how these relationships might evolve or change within individuals over time. Next to differences in research design, also different statistical approaches were used depending on the research aim, ranging from data-driven techniques in [Chapter 2](#) to literature-guided modelling in [Chapter 7](#).

These methodological compromises demonstrate how clinical limitations influence research design, but also showed that meaningful insights can still be gained when methods are carefully tailored to the clinical context. With the combination of all these different methods, we were able to not only approach the research aims within the boundaries of daily practice, but also demonstrate what is needed for future work. The findings from such studies can give guidance to the development of larger, more controlled studies and provide an important basis for the design of future prehabilitation programmes.

Generalizability and sample size

The challenge for research into physical activity, exercise, and physical fitness lies in patient selection which affects both the representativeness and applicability of the findings. First, as common in clinical research, in- and exclusion criteria were applied to ensure patient safety and valid outcome assessment, resulting in the exclusion of higher-risk patients. Second, the patients who chose to participate may have been somewhat more motivated or in better physical condition than the broader cardiac surgery population, which could be related to the

study focus. As such, there was a tendency of lower values of handgrip strength and HR-QoL in drop-outs in [Chapter 2](#). Third, female patients were underrepresented, reflecting the typical composition of this patient group in the Netherlands⁵⁶, but limiting exploration of potential gender differences. Finally, small sample sizes reduce statistical power and further restrict generalizability. If participants were indeed more physically fit, our outcomes could have been more favourable than in the broader, more vulnerable population, precisely the group that probably benefits most from targeted interventions.

These findings suggest multicentre collaboration for clinical research in cardiac surgery patients to collect data of a larger and broader patient group, including more female patients and provide the potential to evaluate subgroups with sufficient power.⁵⁷ The Netherlands Heart Registration (NHR) collects extensive data on cardiac surgery patients across the country⁵⁶; however, information on handgrip strength or physical activity levels is currently not included. Institutional databases, such as Cardiolines⁵⁸ (cardiovascular patients) and Rehabilines⁵⁹ (rehabilitation medicine patients, in collaboration with the national ‘Stichting Revalidatie Impact’) at the UMCG or Lifelines databank (research into healthy aging among participants from the northern Netherlands), may provide complementary information. In addition, the RIVM collects data on physical activity behaviour of the Dutch population via the Health Monitor, for evaluation of the Dutch guideline of healthy activity.⁶⁰ Examples of multicentre studies about physical activity are the Rehabilitation, Sports and Active lifestyle (ReSpAct) study, aimed to evaluate a tailored counselling programme in inpatients and outpatients in the Dutch rehabilitation care in the target population of people with a physical disability and/or chronic disease.⁶¹ In summary, examples of multicentre collaboration exists in similar populations, however, there is no specific database or multicentre study that focuses specifically on measuring the combination of subjective and objective physical activity and handgrip strength in patients undergoing cardiac surgery. Expanding these data sources and developing larger multicentre datasets could facilitate the use of big-data approaches to explore predictors of recovery including physical fitness and activity levels, identify high-risk patients, and optimize personalized pre- and postoperative rehabilitation strategies to improve the recovery of cardiac surgery patients.

Outcome measures

Both physical fitness and physical activity are broad, complex constructs that need to be evaluated in different domains.²⁰ In this thesis, handgrip strength was assessed using the Jamar hand-held dynamometer. Although this device is widely used, it is susceptible to reading errors.³⁶ Future studies may benefit from digital dynamometers, for example the Smedley, which is less biased by reading errors.³⁶ However, different devices for assessing handgrip strength resulted in different outcomes, showing the need for standardization of assessing handgrip strength.³⁶ Next to handgrip strength, physical fitness may be further investigated on other elements, for example with regard to leg muscle strength and functional exercise capacity, which are indeed evaluated in the randomised controlled trial described in Chapter 6. Although these alternative physical tests may be less suitable in daily clinical practice, particularly due to time constraints and limited familiarity with physical exercise testing in the hospital, it can offer added value in the research context and/or rehabilitation settings. This is especially relevant because leg muscle strength, compared to handgrip strength, may be more affected by inactivity and hospital immobilisation⁶², and is more closely related to activities of daily living such as walking, climbing the stairs, and bicycling⁶³. Therefore, muscle strength in larger muscle groups in the legs may have a stronger association with cardiovascular health and HR-QoL.

Bicycle tests are used for assessing cardiorespiratory functioning, though measurement of maximum exercise capacity is complex when evaluating frail patients especially with heart disease because of the contraindications.⁴⁸ To ensure safety, preoperative bicycle tests in cardiac surgery patients are submaximal and have additional stop criteria.⁴⁸ After the feasibility study described in Chapter 5 stop criteria of the submaximal bicycle test had been expanded from 70% to 90% of expected heart rate for specific surgery indications for better tailoring of the initial training load to the individual. These stop criteria have been used in the randomised controlled trial described in Chapter 6. In our hospital, oxygen uptake measurement was not part of a regular preoperative bicycle test for cardiac surgery patients, limiting the estimation of peak aerobic oxygen uptake and cardiorespiratory functioning. As an alternative for submaximal exercise testing, we evaluated the actual performed workload in combination with heart rate (W/HR-ratio) and patients' subjective experience (i.e., rate of perceived exertion and perceived discomfort), which provided information about the patients' dose-response to exercise during pre- and postoperative rehabilitation (Chapter 5). These results thus offered an alternative indication of cardiac functioning and exercise tolerance, which improved throughout the Heart-ROCQ programme. When financial resources allow

the use cardiopulmonary equipment evaluation during the preoperative bicycle test, this will benefit our understanding of cardiorespiratory functioning in our cardiac patient group. Ideally, standardization in exercise bicycle tests takes place, with every patient undergoing the same test and employing a fixed time protocol with individualised steps in workload. However, determining the factors that influence workload is complex. In this thesis, during the preoperative bicycle test (Chapter 5 and 6), expected workload was estimated based on gender, age, and height, though this could be refined in the future. Studies in wheelchair users have shown that individualized protocols, taking into account both aerobic and anaerobic capacity, can provide more accurate and relevant results.⁶⁴ Applying such a personalized approach in our patient group would require extensive data collection and analysis of patient-specific data. To further improve preoperative testing, it would be valuable to understand each patient's peak isometric strength and anaerobic exercise capacity.

The 6 minute walking test is an alternative test, which is commonly used and is a simple, though a submaximal test for assessing functional capacity.⁶⁵ Functional capacity in this context reflects the ability to perform activities of daily living that require strength and (an)aerobic activity and involving all the body systems involved for exercise capacity.⁶⁵ Much research has stressed the relevance of the 6 minute walking test for people with at least moderately severe impairment and had been used for the evaluation of interventions such as cardiac surgery and cardiac rehabilitation.^{65–68}

For physical activity, the use of varying analysing techniques makes it difficult to evaluate the impact of physical activity on postoperative outcomes.⁴⁰ More consensus on reliable and valid methods is needed, especially for vulnerable populations, such as cardiac surgery patients.⁴¹ These patients often have poorer physical and mental functioning, including fear of shortness of breath, reduced cardiovascular functioning, and higher levels of depression and anxiety.^{4,44,54} As a result, they differ markedly from healthy individuals in both their physical activity behaviours and experiences.

Moreover, as discussed earlier in this chapter, it is believed that this multidimensional construct of physical activity cannot be fully assessed using device-based tools alone.⁴¹ As such, subjective and objective methods are ideally measured simultaneously, as they seem much more complementary and additive to each other instead of identical measures for physical activity. Each method seems to offer unique insights that, when combined, potentially provide a more comprehensive understanding of patients' activity levels and

behaviour. Studies on the methodology of the physical activity construct and its measurement are heavily required for various patient groups in the clinical, cardiac and rehabilitation domains.^{41,47}

Clinical implications

Despite widespread knowledge about risk factors for cardiovascular disease, physical activity and muscle strength are not yet taken into account structurally enough in preoperative care of cardiac surgery patients.^{4-7,26,69} The aim of this thesis was to explore the relevance of handgrip strength, physical activity, QoL, and pre- and postoperative results in cardiac surgery patients. While handgrip strength trajectories and physical activity were not always directly related to traditional postoperative outcomes such as complications, they were associated with aspects of recovery, including HR-QoL ([Chapter 2 and 3](#)). Furthermore, this thesis demonstrated that the pre- and postoperative rehabilitation programme was feasible for this population and that patients were able to improve their workload and cardiac functioning based on submaximal exercise testing ([Chapter 5](#)). This argues for the implementation of prehabilitation in broader, higher-risk patient populations, with attention to feasibility, safety, and adequate monitoring.

Integrating multimodal assessment of physical activity, muscle strength, and fitness in the preoperative screening could offer a more comprehensive evaluation of patients' health status before cardiac surgery ([Chapter 4, 6 and 7](#)). Together with the identification of relevant patient subgroups (e.g., based on physical parameters and gender), such assessment may facilitate the development of targeted, tailored, individualised interventions within this heterogeneous patient group.^{4-6,26,69-71} Incorporating such multimodal assessment into routine care of cardiac surgery patients could contribute across different levels of prevention. This means not only for the treatment of existing disease (secondary) and the prevention of complications or deterioration (tertiary), but also offer opportunities for primary prevention by identifying risk factors and promoting a healthy lifestyle.⁷²

Future results from the protocol of the Heart-ROCQ programme ([Chapter 6](#)) also include an analysis of the cost-effectiveness of this pre- and postoperative rehabilitation programme, which may provide further insight into its implementation in clinical practice. These considerations are in line with the evolving concept of the Care Economy, which emphasizes

that investments in prevention, physical fitness, and recovery do not only benefit individual patients, but are essential for sustaining future healthcare workforce and ensuring the long-term economic viability of healthcare systems.⁷³ Moreover, this concept emphasizes the importance of structured data collection, monitoring of functional health, and integrated rehabilitation programmes for sustainable healthcare.⁷⁴ Thus, integrating these insights of the relevance of handgrip strength, physical activity, and QoL into standard clinical practice may help shift the focus from just surviving cardiac surgery to achieving higher HR-QoL and better recovery, while simultaneously reducing the burden on the healthcare system.

Future perspectives

Future research may focus on further refining measurement methods for physical activity and physical fitness in the context of cardiac surgery. This includes that measurement tools, such as activity monitors and questionnaires are properly validated and reliable for use in specific patient groups, like our heterogeneous group of elderly cardiac patients with comorbidities. Since these measurement tools are usually validated in healthy populations, they may not fully capture accurate responses in cardiac surgery patients, who often have reduced physical work capacity, fear of exercise-induced chest pain, or breathlessness, and might experience higher perceived fatigue.⁴⁴ In addition, more insight is needed into the underlying mechanisms of both physical and mental recovery following surgery, and how preoperative interventions can address this. The ongoing randomized controlled trial will further evaluate the effects of the pre- and postoperative rehabilitation programme for cardiac surgery patients on the composite endpoint, which is becoming increasingly common in cardiovascular research⁷⁵. In addition, this study will evaluate the effects on secondary outcomes, including measures of physical, mental, and social well-being. Follow-up studies may benefit from including larger and more diverse cohorts with specific attention to females; the latter are often underrepresented due to a lower prevalence of females undergoing cardiac surgery⁵⁶, as seen in this thesis. Multicentre collaboration could be helpful for including a broader, more representative, patient group. When combined with a powerful study design, it could allow for the evaluation of relationships between patient characteristics and outcomes, as well as subgroup analyses based on gender, disease characteristics, age-cohorts or differences in physical activity behaviour and/or fitness, since patient characteristics and outcomes may vary between centers.^{56,57}

As the burden of the healthcare system forces the use of more cost-effective interventions or to reduce costs, home-based care solutions are emerging¹⁸. This is especially relevant with an ageing population and more complex patients^{26,70,71} with perhaps more difficulties reaching the hospital or rehabilitation centres. The COVID-19 pandemic have accelerated the development in remote health care, since physical contact and appointments with healthcare providers were not allowed during a certain time in the Netherlands⁷⁶. My experience during this period is that hospitals were looking for ways to help patients from home with regard to cardiac rehabilitation. For example, apps on smartphones have been developed to provide information and access to medical records, fill in questionnaires, or enable accessible digital contact with medical staff, such as the app currently used in the UMCG. Special attention may be given to the Wilhelmina hospital Assen, which was one of the first centres (based on our contact with the centres regarding cardiac rehabilitation described in Chapter 6) to implement apps for remote care; the so called *BeterDichtbij*-app (contact with healthcare providers), and now also have implemented the *Thuismeten*-app (guidance on an active and healthy lifestyle, including videos, fill in measurements for example about the lifestyle, tiredness after physical activity, blood pressure and heart rate).⁷⁷

For remote approaches, the monitoring of physical activity and exercise load, and patient safety is expected to play a key role in supporting prehabilitation outside the rehabilitation centres.¹⁸ With proper safety measures, this approach can reach a broader patient group, which is particularly relevant now given the growing trend of treating more complex cardiosurgical patients in fewer more specialised hospital, by definition more distant from an average home.^{26,70,71} As it is expected that remote approaches and monitoring continue to develop, it will be increasingly important to understand their effects on patients' health status, including the social domain, which may be negatively affected by reduced contact with peers and medical staff. Technological innovations for monitoring cardiovascular health and muscle function are needed and are likely to continue to develop through wearable devices, sensors, and mobile applications.^{78,79} This may include improvements in tracking the health status (e.g., mental wellbeing, symptoms such as arrhythmias or hypertension) and continuous monitoring and managing of physical activity, exercise and QoL.⁷⁸ While tracking the health status and physical activity level are already implemented in commercial smart devices used in general public⁷⁸, there is also growing interest in developing wearables that track muscle function during training.⁷⁹

The challenge then is to combine all these types of sensors and data in relevant outcomes using complex logarithms, which are also properly validated and reliable in specific patient populations. Artificial Intelligence (AI) will also play a major role in this.^{78,79} Opportunities of AI may support more accurate identification of frail patients, who are at higher risk, help to determine optimal workload to improve individualised training, and enable algorithms that screen for safety issues. These applications can assist medical decision-making and are particularly relevant in home-based prehabilitation.^{78,79} In this way, there may be a shift from providing care at the group level to care that is better tailored to individual characteristics. Finally, future studies could focus on comparing different models of personalised prehabilitation, including home-based or new technologies, which vary in dose-characteristics (context, form, duration, intensity, and frequency), to help the development of widely applicable evidence-based clinical guidelines.

Concluding remarks

The key message of this thesis is that physical activity and handgrip strength are important dynamic, modifiable factors in the preoperative phase that influence the physical and mental health of patients undergoing cardiac surgery. Handgrip strength provides a simple, objective measure of muscle strength, with longitudinal measurements being important for evaluating recovery after cardiac surgery and responsiveness to interventions. Physical activity may be assessed both subjectively and objectively, providing a comprehensive understanding of patients' overall physical health prior to surgery. Furthermore, physical exercise in the pre- and postoperative rehabilitation programme (Heart-ROCQ-pilot) was feasible among patients undergoing cardiac surgery, with improvements in exercise capacity and muscle strength. Although preoperative handgrip strength and physical activity were not consistently associated with traditional postoperative outcomes, they were associated with recovery-related measures, such as HR-QoL. At the same time, the measurement of physical activity and physical fitness requires more attention, especially in the context of preoperative health assessment in cardiac surgery patients. This thesis highlights the need for reliable measurements, safe monitoring with multimodal assessments, and personalized cardiac rehabilitation to meet the diverse patient needs and for supporting a future-resistant healthcare system that continues to be under strain.

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