The clinical utility of preoperative functional assessment

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Nearly 17% of patients undergoing elective surgery have an in-hospital complication, and 0·5% are estimated to die during the admission for surgery.[1] With more than 300 million operations occurring per annum, this equates to 50 million complications and 1·5 million deaths annually.[2] Preoperative risk assessment is the cornerstone on which subsequent safe surgical care is provided, and functional capacity is entrenched in preoperative cardiovascular assessment. The subjective assessment of functional capacity is a critical decision node in preoperative cardiovascular algorithms,[3,4] yet the evidence supporting this practice is limited.

The inclusion of functional capacity in the original American College of Cardiology/American Heart Association guidelines on preoperative cardiovascular assessment was based on the philosophy that data showing increased risk in non-surgical patients, would translate to the surgical environment. Some surgical clinical research was subsequently published supporting an association between poor functional status and perioperative cardiac risk.[5,6] However, the veracity of the evidence from these studies was poor, based on multiple comparisons,[5] and highly fragile results (fragility index of 1 for cardiovascular complications,[5] and 4 for mortality).[6] Furthermore, a subjective assessment of poor functional capacity for preoperative cardiovascular risk stratification is limited by the low prevalence in preoperative patients. This limitation can result in substantial misclassification of risk, and thus most patients who die or have a myocardial infarction within 30 days of surgery were categorised as having good functional status (or in a low-risk category).[7,8] The more objective assessment of functional capacity with cardiopulmonary exercise testing (CPET) has been associated with several postoperative complications, but its association specifically with cardiovascular complications remains tenuous.[9] Cardiac risk stratification based on preoperative B-type natriuretic peptides has been shown to be useful in non-cardiac surgical patients over and above standard risk stratification protocols.[10] Thus, although functional status is embedded in the American and European preoperative cardiovascular assessment algorithms, the Canadian Cardiovascular Society guidelines recommend risk stratification based on B-type natriuretic peptides rather than functional status in preoperative cardiovascular assessment.[11]

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The controversy surrounding preoperative assessment of functional status for preoperative cardiovascular risk assessment therefore requires a head-to-head comparison of a subjective assessment of function, the Duke Activity Status Index (DASI), CPET, and B-type natriuretic peptides. In *The Lancet*, Duminda Wijeysundera and colleagues[12] provide these comparative data for the primary outcome of 30-day mortality and myocardial infarction in the Measurement of Exercise Tolerance before Surgery (METS) study.[12] The results might prompt a review of preoperative risk assessment algorithms. First, the primary outcome was not associated with the subjective assessment of functional capacity but was associated only with DASI scores (adjusted odds ratio 0·96, 95% CI 0·83–0·99; p=0·03). Furthermore, results from the METS study confirmed[8] that a subjective assessment of functional capacity resulted in a substantial misclassification of high-risk patients as low-risk, based on an assessment of good functional capacity[8] (calculations not shown). Therefore, a measure such as the DASI should replace a subjective assessment of functional capacity for preoperative cardiac risk assessment. However, the optimum DASI scores necessary to appropriately discriminate between good and bad outcomes are unknown.

Second, although preoperative serum N-terminal pro-B-type natriuretic peptide concentrations were not associated with 30-day death and myocardial infarction, they were associated with 30-day death and myocardial injury (as was the DASI score). Since myocardial injury after non-cardiac surgery has a similar prognosis to perioperative myocardial infarction, the measurement of preoperative B-type natriuretic peptide for cardiovascular risk assessment as stated in the Canadian guidelines[11] is supported by findings from Wijeysundera and colleagues' study.[12] Whether DASI scores or preoperative B-type natriuretic peptide risk stratification are preferable for preoperative cardiovascular risk stratification is unclear, but B-type natriuretic peptide risk stratification might be preferable as it was also associated with 1-year mortality.[12]

Finally, the commonly measured CPET variables of mean peak oxygen consumption and anaerobic threshold were not associated with the 30-day cardiovascular outcomes.[12] Instead, low preoperative peak oxygen consumption was associated with other common postoperative complications, including respiratory failure, pneumonia, surgical site infection, re-operation, and critical care admission.[12] These complications are common after non-cardiac surgery, and are associated with subsequent postoperative mortality.[1] The study suggests that commonly used CPET risk predictors should not be used for preoperative cardiovascular risk assessment, but rather for other important postoperative complications. The challenge now is to develop a sensible and streamlined preoperative algorithm that can be used to determine the risk for postoperative cardiovascular complications and other important complications associated with mortality.

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I declare no competing interests.

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Addressing the unfinished agenda on sexual and reproductive health and rights in the SDG era

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The autonomy and empowerment of women are essential not only for their own health and wellbeing but also for those of their families and communities and, ultimately, for sustainable development. Sexual and reproductive health are, in turn, fundamental for women's full participation in society. Recognising this, in 1994 in Cairo, Egypt, the International Conference on Population and Development (ICPD) formally recognised that reproductive rights were linked to human rights already protected under international law, created a definition of reproductive health that explicitly relied on the ability of individuals to decide if, and when, to reproduce, and compiled a list of essential elements of reproductive health care.[1]

12 years on from ICPD, *The Lancet* published its first Series on sexual and reproductive health.[2] The Series highlighted the historical neglect of sexual and reproductive health and its initial omission from

Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study

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Summary

Background Functional capacity is an important component of risk assessment for major surgery. Doctors' clinical subjective assessment of patients' functional capacity has uncertain accuracy. We did a study to compare preoperative subjective assessment with alternative markers of fitness (cardiopulmonary exercise testing [CPET], scores on the Duke Activity Status Index [DASI] questionnaire, and serum N-terminal pro-B-type natriuretic peptide [NT pro-BNP] concentrations) for predicting death or complications after major elective non-cardiac surgery.

Methods We did a multicentre, international, prospective cohort study at 25 hospitals: five in Canada, seven in the UK, ten in Australia, and three in New Zealand. We recruited adults aged at least 40 years who were scheduled for major non-cardiac surgery and deemed to have one or more risk factors for cardiac complications (eg, a history of heart failure, stroke, or diabetes) or coronary artery disease. Functional capacity was subjectively assessed in units of metabolic equivalents of tasks by the responsible anaesthesiologists in the preoperative assessment clinic, graded as poor (<4), moderate (4–10), or good (>10). All participants also completed the DASI questionnaire, underwent CPET to measure peak oxygen consumption, and had blood tests for measurement of NT pro-BNP concentrations. After surgery, patients had daily electrocardiograms and blood tests to measure troponin and creatinine concentrations until the third postoperative day or hospital discharge. The primary outcome was death or myocardial infarction within 30 days after surgery, assessed in all participants who underwent both CPET and surgery. Prognostic accuracy was assessed using logistic regression, receiver-operating-characteristic curves, and net risk reclassification.

Findings Between March 1, 2013, and March 25, 2016, we included 1401 patients in the study. 28 (2%) of 1401 patients died or had a myocardial infarction within 30 days of surgery. Subjective assessment had 19·2% sensitivity (95% CI 14·2–25) and 94·7% specificity (93·2–95·9) for identifying the inability to attain four metabolic equivalents during CPET. Only DASI scores were associated with predicting the primary outcome (adjusted odds ratio 0·96, 95% CI 0·83–0·99; p=0·03).

Interpretation Subjectively assessed functional capacity should not be used for preoperative risk evaluation. Clinicians could instead consider a measure such as DASI for cardiac risk assessment.

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Introduction

International clinical practice guidelines emphasise the assessment of preoperative cardiopulmonary fitness, or functional capacity, as an important component of estimating patients' risks for major morbidity and mortality after surgery.[1,2] For example, the American College of Cardiology and American Heart Association recommend that patients proceed directly to elective intermediate and major non-cardiac surgery if they are capable of more than four metabolic equivalents of tasks of activity without symptoms.[1] The usual standard of care for assessing preoperative functional capacity involves doctors assessing patients, then making subjective estimates of their fitness (ie, subjective assessment). Although these estimates are easily implementable into clinical practice, subjective assessment has limitations, including little agreement with validated measures of functional capacity,[3] and poor accuracy when used to predict postoperative death or complications.[4,5] These limitations point to the need for better alternatives to assess preoperative functional capacity.

Possible alternative options are cardiopulmonary exercise testing (CPET), which has been described as a gold standard non-invasive assessment of exercise tolerance, and the Duke Activity Status Index (DASI),[6] which is a standardised questionnaire correlated with gold-standard measures of functional capacity. Additionally, although no blood test can directly measure functional capacity, N-terminal pro-B-type natriuretic peptide (NT pro-BNP) concentrations might indirectly fulfil this role.[7]

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Research in context

Evidence before this study
Estimation of cardiopulmonary fitness, or functional capacity, is an important component of risk assessment before major non-cardiac surgery. This estimation typically involves subjective assessment, where doctors interview patients and make a subjective judgment of their fitness. To assess the validity of this commonly used measure of functional capacity, we used the terms [("prediction" OR "preoperative evaluation" OR "risk prediction") AND ("surgery" AND "complications") AND ("exercise capacity" OR "activities of daily living" OR "functional capacity")] to search the PubMed database for English-language articles on relevant studies published before Dec 31, 2017. The search was supplemented with hand-searches of reference lists from relevant reviews and practice guidelines. Previous research was limited to single-centre studies with small sample sizes or a high risk of bias. In these studies, subjective assessment showed poor agreement with validated questionnaires, and an inconsistent association with postoperative complications.

Added value of this study
Our multicentre prospective cohort study (Measurement of Exercise Tolerance before Surgery) assessed patients before they underwent major elective non-cardiac surgery and compared the prognostic accuracy of subjective assessment against three alternative measures: the Duke Activity Status Index (DASI) questionnaire, cardiopulmonary exercise testing (CPET) to measure peak oxygen consumption, and serum N-terminal pro-B-type natriuretic peptide (NT pro-BNP) concentrations. In a sample of 1401 adult participants at 25 hospitals, lower DASI scores predicted 30-day death or myocardial infarction, and 30-day death or myocardial injury; higher NT pro-BNP concentrations predicted 30-day death or myocardial injury, and 1-year death; and lower peak oxygen consumption predicted complications. Subjective assessment did not predict any outcomes.

Implications of all the available evidence
Subjective assessment of functional capacity should not be used for preoperative risk assessment. This commonly used practice does not accurately identify patients with poor fitness or those at increased risk for postoperative morbidity and mortality. As alternatives, clinicians could consider more objective measures, such as DASI questionnaires and NT pro-BNP testing to assess perioperative cardiac risk, and perhaps CPET to predict complications after major elective non-cardiac surgery.

Increased NT pro-BNP concentrations are integrated markers of cardiac dysfunction, including myocardial stretch and ischaemia. We therefore did a study to compare preoperative subjective assessment, CPET, DASI, and NT pro-BNP for predicting death or complications after major elective non-cardiac surgery.

Methods

Study design and participants

We did a multicentre, international, prospective cohort study (Measurement of Exercise Tolerance before Surgery [METS]) at 25 hospitals: five in Canada, seven in the UK, ten in Australia, and three in New Zealand. The study's objectives, design, and methods have been previously reported.[8] Details of the methods are in the appendix.

See Online for appendix

Participants were aged 40 years or older, scheduled for elective non-cardiac surgery under general or regional anaesthesia (or both) with a minimum of one overnight hospital stay, and deemed to have at least one risk factor for cardiac complications or at least one risk factor for having coronary artery disease (appendix). All participants provided written informed consent, and each centre obtained research ethics board approval before commencing recruitment.

Procedures

During the period from recruitment to 1 day before surgery, participants underwent symptom-limited incremental CPET on a computer-controlled, electromagnetically braked cycle ergometer using a standardised protocol (appendix).[8] This assessment usually occurred during a separate hospital visit after the date of recruitment. On the basis of a prespecified assessment of the plotted CPET data, trained investigators at each centre determined patients' peak oxygen consumption and anaerobic threshold.

Participants also underwent three other preoperative assessments of functional capacity. First, responsible anaesthesiologists in the preoperative assessment clinic (on the date of recruitment) or operating theatre (on the day of surgery) were asked to make a subjective judgment of participants' functional capacity after assessing their usual preoperative history. Subjectively assessed functional capacity was classified as poor (<4 metabolic equivalents), moderate (4–10 metabolic equivalents), or good (>10 metabolic equivalents). The poor category included cases where anaesthesiologists were uncertain about patients' functional capacity, typically due to pre-existing conditions such as arthritis or peripheral arterial disease.[1] Second, participants completed the DASI questionnaire on the date of recruitment (appendix). Third, blood samples were drawn at any point between recruitment and surgery to measure serum NT pro-BNP concentrations. These samples were stored at –70°C to –80°C at each study site, then analysed at the Aberdeen Royal Infirmary (Aberdeen, UK) using the Siemens Vista immunoassay analyser (Siemens Healthcare Diagnostics, Frimley, UK). Participants, health-care providers, and outcome adjudicators were masked to CPET and NT pro-BNP results, and health-care providers and outcome adjudicators were masked to DASI scores; specifically, the study's central laboratory, exercise testing facilities, and exercise testing laboratories did not report these specific measurements to masked individuals. The exceptions were cases of myocardial ischaemia or substantial new arrhythmias during CPET, in which case these specific findings, but not peak oxygen consumption or anaerobic threshold results, were revealed to health-care providers.

After surgery, participants underwent daily electrocardiograms and blood sampling to measure troponin and creatinine concentrations, until the third post-operative day or hospital discharge (whichever came first). Research personnel followed participants each day throughout their hospital stay to ascertain the presence of specific complications (appendix). The severity of complications was categorised as mild, moderate, severe, or fatal using a modified Clavien-Dindo classification scheme.[9,10] After hospital discharge, participants were contacted at 30 days and 1 year after surgery to ascertain vital status. Details of the follow-up process are in the appendix.

Outcomes

The primary outcome was death or myocardial infarction within 30 days after surgery. The secondary outcome was death within 1 year after surgery. Myocardial infarction was diagnosed by an adjudication committee that used the third universal definition of myocardial infarction[11] while remaining masked to CPET, DASI, and NT pro-BNP results. Other outcomes of interest were death or myocardial injury within 30 days after surgery, and moderate or severe (including fatal) complications during the index admission to hospital. Myocardial injury was defined as postoperative troponin concentrations exceeding both the 99th percentile of the normal reference population, and the threshold at which the assay coefficient of variation was 10%. Moderate or severe complications were included as an endpoint because these events have been associated with poor preoperative functional capacity, especially when measured objectively by CPET.[12,13]

Statistical analysis

The sample size calculation was based on comparing the area under the curve (AUC) of the receiver-operating-characteristic (ROC) curves for peak oxygen consumption versus subjective assessment with respect to predicting myocardial infarction or death within 30 days of surgery. During the design of the study, we initially calculated that a sample size of 1180 was required on the basis of underlying assumptions of an outcome event rate of 8%, correlation of 0·5 between peak oxygen consumption and subjective assessment,[6] an AUC of 0·65 for subjective assessment, an AUC of 0·75 for peak oxygen consumption, and 90% power to detect this difference in AUC values (two-sided α of 0·05). To account for 10% of participants not undertaking CPET or surgery, we aimed to recruit 1312 participants. After recruiting about half the original planned sample size, this calculation was reassessed based on two factors identified in the accumulating study data. First, we noted that about 20% of participants did not either undertake CPET or undergo their planned surgeries. Second, the event rate for the primary outcome was instead projected to be approximately 5%. The overall sample size was therefore increased to 1723 participants to account for up to 20% of recruited individuals not being eligible for the primary analysis, and a primary outcome event rate of 5%, while retaining the power of 80%. We remained masked to all data on the principal exposures (ie, CPET results, DASI scores, and NT pro-BNP concentrations) during the sample size re-estimation.

All participants who undertook both CPET and surgery were included in the primary analysis; CPET performance was characterised by peak oxygen consumption. For each outcome of interest, we built separate nested logistic regression models that sequentially included baseline clinical characteristics followed by the exposure of interest

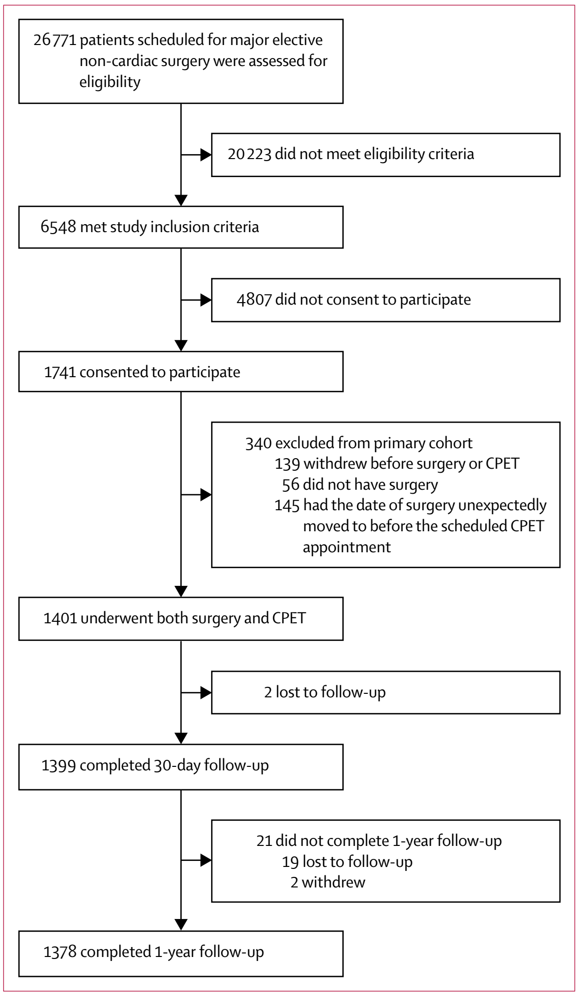

Figure 1: **Participant screening, recruitment, and follow-up**
CPET=cardiopulmonary exercise testing.

	Full cohort (n=1401)	Missing data
Demographic characteristics		
Age (years)	65 (57–72)	··
Female sex	548 (39%)	··
Comorbidities		
Coronary artery disease	165 (12%)	··
Heart failure	20 (1%)	··
Cerebrovascular disease	59 (4%)	··
Peripheral arterial disease	42 (3%)	··
Diabetes mellitus	264 (19%)	··
Hypertension	779 (56%)	··
Current or recent smoker*	216 (15%)	··
Obstructive lung disease†	181 (13%)	··
Significant arthritis‡	289 (21%)	··
Significant malignancy§	597 (43%)	··
Preoperative renal function¶		49
eGFR ≥60 mL/min per 1·73 m²	1195 (88%)	··
eGFR 30–59 mL/min per 1·73 m²	125 (9%)	··
eGFR <30 mL/min per 1·73 m² or dialysis	31 (2%)	··
Composite risk scales		
ASA-PS classification		3
Class 1	103 (7%)	··
Class 2	818 (59%)	··
Class 3	457 (33%)	··
Class 4	20 (1%)	··
Revised Cardiac Risk Index||		··
Class 1	624 (45%)	··
Class 2	635 (45%)	··
Class 3	115 (8%)	··
Class 4	27 (2%)	··
Preoperative medications		
β blocker	232 (17%)	··
Dihydropyridine calcium channel blocker	248 (18%)	··
Diltiazem or verapamil	27 (2%)	··
ACE inhibitor or ARB	529 (38%)	··
Furosemide	55 (4%)	··
Aspirin	334 (24%)	··
Other antiplatelet medication	35 (3%)	··

(Table 1 continues in next column)

	Full cohort (n=1401)	Missing data
(Continued from previous column)		
Operative characteristics		
Procedure type		··
Vascular	26 (2%)	··
Intrathoracic	31 (2%)	··
Intraperitoneal or retroperitoneal	464 (33%)	··
Urological or gynaecological	417 (30%)	··
Head and neck	93 (7%)	··
Orthopaedic	336 (24%)	··
Other	30 (2%)	··
Laparoscopic or thoracoscopic assistance	499 (36%)	··
Anaesthesia type		··
General anaesthesia alone	758 (54%)	··
Regional anaesthesia alone	210 (15%)	··
General plus regional anaesthesia	433 (31%)	··
Intraoperative haemodynamic monitoring		··
Arterial line	687 (49%)	7
Central venous line	212 (15%)	7
Cardiac output monitor	95 (7%)	8
Postoperative disposition		··
Critical-care unit or monitored bed unit	331 (24%)	1

Data are median (IQR), n (%), or ··=not applicable. eGFR=estimated glomerular filtration rate. ASA-PS=American Society of Anesthesiologists Physical Status. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. *Current smoker or quit within previous 1 year. †Previous diagnosis of asthma, reactive airways disease, chronic obstructive lung disease, chronic bronchitis, or emphysema. ‡Previous or scheduled major joint replacement surgery. §Indication for surgery was for treatment of cancer. ¶eGFR was calculated using the preoperative serum creatinine concentration and Chronic Kidney Disease Epidemiology Collaboration equation. ||Revised Cardiac Risk Index scores were calculated using the original definitions of diabetes (ie, requirement for insulin therapy) and renal insufficiency (ie, creatinine concentration >176 μmol/L).[15] When determining Revised Cardiac Risk Index scores, any individual with missing preoperative creatinine concentration data was assumed to have a concentration of 176 μmol/L or less.

Table 1: **Baseline characteristics of study cohort**

(ie, subjective assessment, peak oxygen consumption, anaerobic threshold, DASI scores, or NT pro-BNP). We modelled NT pro-BNP concentrations using a logarithmic transformation to reduce the potential effect of extreme values within its highly skewed distribution. The statistical significance of prognostic information from additional predictors was based on the increase in log likelihood of the larger model. For the models predicting the primary and secondary outcomes, the baseline variable was the validated Revised Cardiac Risk Index (RCRI) score.[14,15] In the model predicting death or myocardial injury by 30 days, the baseline variables were age, sex, and RCRI score. The baseline variables in the model predicting moderate-or-severe complications were age, sex, and high-risk surgery, which was defined as intraperitoneal, intrathoracic, or suprainguinal vascular procedures.[14] These covariates were selected a priori based on previous evidence, their inclusion in guideline-recommended assessment algorithms,[1,16] and the need to prevent model overfitting. Additionally, the covariates mirror clinically sensible factors typically considered during preoperative assessment. We calculated the area under the ROC curve of models with successively more predictors, and models with only the individual exposure of interest (eg, peak oxygen consumption). Prognostic information from these models was compared using the continuous net reclassification improvement (NRI) statistic and area under the ROC curve.[17]

To address whether preoperative functional capacity might have better prognostic value in more invasive surgical procedures, a post-hoc subset analysis was done in some patients undergoing body cavity surgery, which was defined as intrathoracic, intraperitoneal, retroperitoneal or pelvic (ie, urological or gynaecological) procedures.

Analyses were done with R (version 3.4.0), statistical significance was defined by a two-tailed p value of less than 0·05, and no adjustments were made for multiple comparisons.[18] Because missing data were uncommon, a complete case analysis was done. Additionally, these missing data pertained to baseline information that was likely missing completely at random.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 1, 2013, and March 25, 2016, 1741 patients (23% of eligible patients who consented to participate) were recruited at 25 hospitals, with 1401 (81%) undergoing CPET and surgery (figure 1). Of these 1401 participants in the primary cohort, 1399 (99·9%) completed a 30-day follow-up and 1378 (98%) completed a 1-year follow-up. Participants' median age was 65 years (IQR 57–72), 39% were female, and 91% were classified as American Society of Anesthesiologists Physical Status (ASA-PS) 2 or 3 (table 1). Most participants underwent major abdominal, pelvic, or orthopaedic procedures. Data were missing for less than 4% of participants.

The CPET exercise protocol was terminated early in 11% of participants, with the most common reasons being inability to pedal, fatigue, or a safety-based indication (table 2). Mean peak oxygen consumption was 19·2 mL/kg per min (SD 6·5) and mean anaerobic threshold was 12·6 mL/kg per min (4·1). 110 (8%) of participants had adverse events during CPET (table 2), with 27 cases meeting criteria for unmasking. The clinical sequelae of these events are in the appendix.

Additionally, 1351 (96%) participants underwent subjective assessment of functional capacity, 1396 (99·6%) completed DASI questionnaires, and 1347 (96%) had NT pro-BNP concentrations measured (appendix). 107 (8%) participants were subjectively judged to have poor preoperative functional capacity, 230 (16%) had a peak oxygen consumption value of less than 14 mL/kg per min (equivalent to <4 metabolic equivalents), and 426 (30%) had an anaerobic threshold below the suggested high-risk threshold of 11 mL/kg per min.[19] The characteristics of participants within strata defined by peak oxygen consumption values is in the appendix. A subjective assessment of poor functional capacity had a sensitivity of 19·2% (95% CI 14·2–25·0) for identifying peak oxygen consumption of less than 14 mL/kg per min, while its specificity was 94·7% (93·2–95·9).

When stratified by subjectively assessed functional capacity, peak oxygen consumption and DASI values were generally lower in individuals judged to have poor functional capacity, but there was substantial within-stratum variation (figure 2). Peak oxygen consumption was positively correlated with DASI scores (figure 2; Spearman ρ 0·43, p<0·0001), and negatively correlated with NT pro-BNP concentrations (Spearman ρ –0·21, p<0·0001). There was also a negative correlation between DASI scores and NT pro-BNP concentrations (Spearman ρ –0·25, p<0·0001; appendix).

	Overall cohort (n=1401)
Interval to CPET to surgery (days)	9 (5–21)
Early termination of CPET	157 (11%)
Reasons for early termination of CPET	
Safety-based indication	23 (2%)
Fatigue	31 (2%)
Shortness of breath	11 (<1%)
Unable to pedal	76 (5%)
Unable to tolerate mouthpiece or mask	12 (<1%)
Technical problems with equipment	4 (<1%)
Measurable peak oxygen consumption	1356 (97%)
Measurable AT	1275 (91%)
Adverse events during CPET	
Any adverse event	110 (8%)
Ischaemic ECG changes	25 (2%)
Chest pain	2 (<1%)
Significant new arrhythmias	14 (1%)
Significant hypertension	43 (3%)
Significant drop in blood pressure	28 (2%)
Syncope	3 (<1%)
Significant decrease in oxygen saturation	10 (<1%)

Data are median (IQR) or n (%). CPET=cardiopulmonary exercise testing. AT=anaerobic threshold. ECG=electrocardiogram.

Table 2: **Characteristics of CPET assessments**

After surgery, 194 (14%) participants had in-hospital moderate-or-severe complications.

By 30 days after surgery, five (<1%) participants had died, 24 (2%) had a myocardial infarction, 28 (2%) had the primary outcome of death or myocardial infarction, and 176 (13%) had died or had a myocardial injury. By 1 year after surgery, 38 participants (3%) had died. Of the moderate or severe complications, the more frequent events were respiratory failure, pneumonia, surgical site infection, re-operation, and unexpected critical care unit admission (appendix).

Subjectively assessed preoperative functional capacity had no significant adjusted association with the four main study outcomes (appendix). A significant adjusted association and significant risk reclassification with peak oxygen consumption was observed only with respect to moderate or severe complications (table 3). Anaerobic threshold showed no significant association or risk reclassification with the main outcomes. DASI scores showed significant adjusted associations with the primary outcome of death or myocardial infarction by

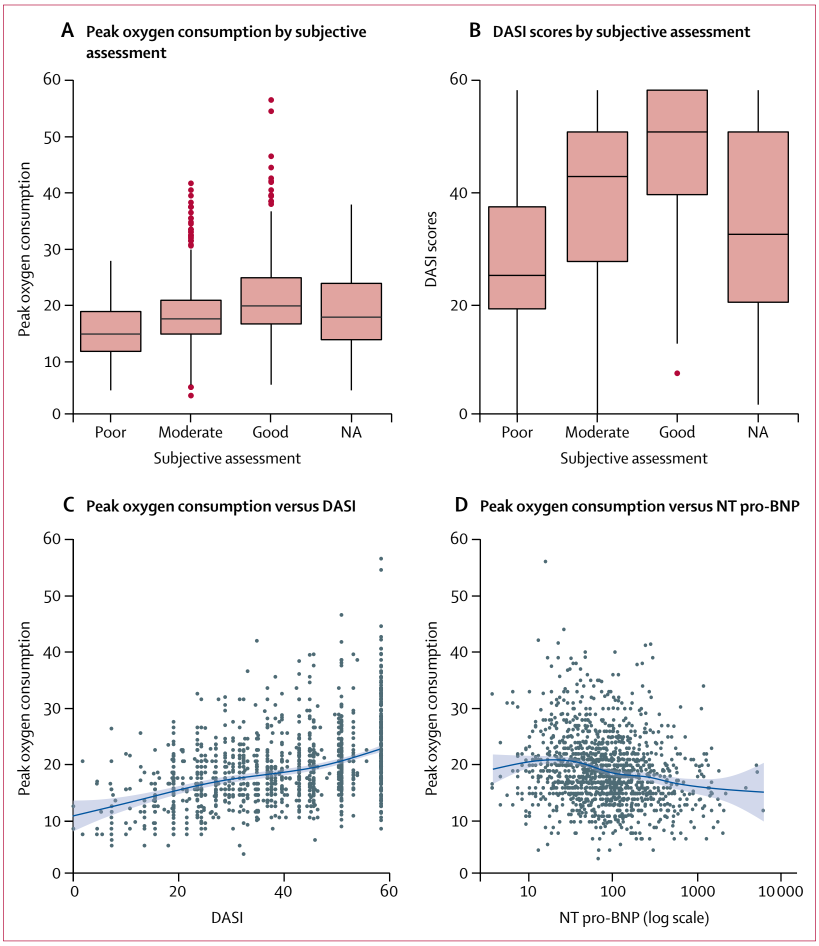

Figure 2: **Correlation between measures of preoperative functional capacity**
(A) is a boxplot presenting the distributions of peak oxygen consumption within strata defined by subjectively assessed preoperative functional capacity, categorised as poor (<4 metabolic equivalents), moderate (4–10 metabolic equivalents) or good (>10 metabolic equivalents). The horizontal line within each box denotes the median, and the top and bottom of each box indicate the IQR. Vertical lines at the top and bottom of each box extend to the 5th and 95th percentiles, and solid circles indicate outliers. 4 metabolic equivalents correspond to a peak oxygen consumption of 14 mL/kg per min, and 10 metabolic equivalents correspond to a peak oxygen consumption of 35 mL/kg per min. The boxplot on the right (denoted as not applicable [NA]) presents the peak oxygen consumption distribution among the 50 participants with missing subjective assessments. B is a boxplot presenting the distributions of scores on the Duke Activity Status Index (DASI) within strata defined by subjectively assessed preoperative functional capacity. The minimum possible DASI score is 0 and the maximum possible score is 58·2. The boxplots on the right (denoted as NA) presents the DASI score distribution among the 50 participants with missing subjective assessments. The wide-ranging distribution in panels (A) and (B) for participants with missing assessments suggests that these values were missing completely at random. (C) is a scatter plot presenting the association of peak oxygen consumption (y axis) and DASI scores (x axis). The Spearman correlation coefficient between DASI scores and peak oxygen consumption was 0·41 (p<0·0001). (D) is a scatter plot presenting the association of peak oxygen consumption (y axis) and N-terminal pro-B-type natriuretic peptide (NT pro-BNP) concentrations (x axis on a log_{10} scale). The Spearman correlation coefficient between NT pro-BNP and peak oxygen consumption was –0·21 (p<0·0001). In both panels C and D, the line of best fit is shown in blue (estimated using cubic regression splines), and the grey shaded zones represent its 95% CIs.

30 days after surgery and with death or myocardial injury by 30 days after surgery. Additionally, DASI scores showed significant risk reclassification with death or myocardial injury by 30 days. NT pro-BNP concentrations showed significant adjusted associations and significant risk reclassification with death by 1 year after surgery and death or myocardial injury by 30 days after surgery. When the main study analyses were repeated in the post-hoc subset, the results remained qualitatively unchanged (appendix).

Discussion

Preoperative subjective assessment neither accurately identified patients with poor cardiopulmonary fitness nor predicted postoperative morbidity and mortality. The DASI questionnaire improved prediction of 30-day myocardial infarction or death, and 30-day myocardial injury or death; and NT pro-BNP concentrations improved prediction of 30-day myocardial injury or death, and 1-year death. Formal assessment of cardiopulmonary fitness, based on peak oxygen consumption during CPET, improved prediction of moderate or severe postoperative complications.

In our study, subjective assessment of preoperative functional capacity consistently performed poorly. Although it had construct validity, in that peak oxygen consumption was generally lower in patients judged to be less fit, subjective assessment correctly identified only 16% of patients who achieved a peak less than 14 mL/kg per min, which is consistent with less than 4 metabolic equivalents. Further, subjective assessment did not predict postoperative myocardial infarction, myocardial injury, or myocardial complications, confirming findings from a single-centre retrospective cohort study that relied on an administrative database for outcome ascertainment.[5] Based on these findings, subjective assessment should not be used to assess patients' risks of major postoperative cardiac complications.

Notably, more objective assessment of cardiopulmonary fitness with CPET did not improve most aspects of preoperative risk assessment. Consistent with previous evidence,[12] peak oxygen consumption measured during CPET was predictive of postoperative complications; however, most of these events were pulmonary complications, surgical site infections, unexpected critical care unit admissions, and re-operations. By contrast, peak oxygen consumption and anaerobic threshold were not associated with postoperative myocardial infarction or myocardial injury, somewhat contradicting the emphasis of practice guidelines on functional capacity for preoperative cardiac risk evaluation.[1,2] These findings occurred within the context of our study addressing several important limitations in the current evidence base,[20] in that it masked CPET results (unlike most previous studies), and implemented standardised outcome surveillance in a large, generalisable, multicentre sample. There are several possible explanations for our results. First, the previous evidence supporting a link between fitness and perioperative cardiac risk had limitations; eg, many of the studies were done more than 30 years ago, and have limited generalisability to contemporary patients and surgeries.[21,22] Other studies had few outcome events or associations of only weak magnitudes.[23,24] Second, low peak oxygen consumption or anaerobic threshold might not be the ideal CPET-based indicator of the underlying causal mechanisms for perioperative myocardial infarction. Other metrics, such as an exaggerated exercise-mediated heart rate response,[25] might be better indicators of perioperative cardiac risk.

The DASI questionnaire had construct validity as a measure of functional capacity in surgical patients, consistent with previous research,[26] and also improved prediction of postoperative myocardial infarction and myocardial injury. Our findings confirmed non-operative data indicating enhanced risk prediction using this questionnaire,[27] supported guideline suggestions for using objective scales to assess functional capacity,[1] and indicate opportunities for straightforward improvements in clinical practice. Specifically, the simple DASI questionnaire can be easily implemented into most perioperative practice settings, although further studies are needed to define optimal risk-specific thresholds in DASI scores, and develop reliable non-English versions of the questionnaire.[28] An important area of residual uncertainty is why DASI scores were associated with postoperative cardiac events, yet peak oxygen consumption was not. Given the only moderate correlation between DASI scores and peak oxygen consumption, a possible explanation is that DASI also measures somewhat different constructs, such as musculoskeletal strength, frailty, and self-imposed physical limitations.[29]

Confirming results from a previous individual patient data meta-analysis,[30] increased preoperative NT pro-BNP concentrations were associated with increased risks of postoperative 30-day death or myocardial injury in the METS study cohort; additionally, increased concentrations also predicted increased 1-year mortality. These findings support recommendations in recent practice guidelines to incorporate natriuretic-peptide testing into preoperative risk assessment strategies.[16] We noted only slight-to-fair correlation between NT pro-BNP concentrations and measures of exercise capacity (ie, peak oxygen consumption and DASI). This low correlation suggests that NT pro-BNP measures are a construct distinct from exercise capacity, and raises the possibility of enhancing preoperative assessment by combining measures of functional capacity and NT pro-BNP in future risk prediction models.

Our study had several limitations. First, despite increasing the original projected sample size, the primary and secondary outcomes occurred fewer times than anticipated. To some extent, the risks of death within 30 days of surgery (ie, 0·4%) and 30-day death or myocardial infarction (ie, 2·0%) in our study are representative of risks for contemporary elective major non-cardiac surgery in high-income countries, as suggested by several studies published after the design of our study. For example, in the ISOS prospective cohort study of 44 814 adults having elective inpatient surgery across 27 high-income and middle-income countries, the risk of in-hospital 30-day death was 0·5%.[10] Similarly, in the VISION prospective cohort study of 15 133 patients having inpatient non-cardiac surgery in eight high-income and middle-income countries, the risk of 30-day mortality after elective surgery was 1·2%. In this same cohort, the overall risk of myocardial infarction was about 3·3%.[31] Since 14% of the cohort had emergency surgery, which is associated with a three-times higher risk of myocardial infarction,[32] the risk of myocardial infarction after elective surgery in the VISION study was probably about 2·6%. Thus, the event rates in our study were consistent with other contemporary major non-cardiac surgery samples. Nonetheless, to help to address this reduced statistical power, we analysed the association

	Adjusted odds ratio (95% CI)	AUC*	Net reclassification improvement index†		
			Events	Non-events	Overall
30-day death or myocardial infarction					
Baseline model‡		0·59			
Plus peak oxygen consumption	0·90 (0·71–1·16; p=0·45)§	0·62	0·04	−0·04	0·01 (p=0·98)
Plus AT	0·96 (0·66–1·41; p=0·84)§	0·59	−0·24	−0·12	−0·36 (p=0·10)
Plus DASI	0·91 (0·83–0·99; p=0·03)§	0·67	0·07	0·21	0·28 (p=0·14)
Plus NT PRO-BNP	1·88 (0·89–3·96; p=0·09)¶	0·65	0·11	0·14	0·25 (p=0·19)
30-day death or myocardial injury					
Baseline model‖		0·70			
Plus peak oxygen consumption	1·03 (0·92–1·14; p=0·62)§	0·70	−0·07	0·16	0·09 (p=0·26)
Plus AT	1·12 (0·96–1·31; p=0·16)§	0·71	0·17	−0·08	0·09 (p=0·27)
Plus DASI	0·96 (0·92–0·99; p=0·05)§	0·71	0·05	0·19	0·23 (p=0·004)
Plus NT PRO-BNP	1·78 (1·21–2·62; p=0·003)¶	0·71	0·07	0·13	0·20 (p=0·02)
In-hospital moderate or severe complications					
Baseline model**		0·72			
Plus peak oxygen consumption	0·86 (0·78–0·97; p=0·007)§	0·74	0·21	−0·004	0·21 (p=0·008)
Plus AT	0·87 (0·74–1·02; p=0·08)§	0·69	0·17	−0·08	0·09 (p=0·27)
Plus DASI	0·97 (0·93–1·01; p=0·16)§	0·72	−0·17	0·15	−0·02 (p=0·80)
Plus NT PRO-BNP	1·10 (0·77–1·57; p=0·61)¶	0·72	0·03	0·08	0·12 (p=0·12)
1-year death					
Baseline model‡		0·65			
Plus peak oxygen consumption	0·94 (0·77–1·15; p=0·56)§	0·66	0·20	−0·06	0·14 (p=0·39)
Plus AT	1·03 (0·76–1·40; p=0·56)§	0·64	0·13	0·15	0·28 (p=0·12)
Plus DASI	0·94 (0·87–1·02; p=0·13)§	0·69	0·00	0·16	0·16 (p=0·34)
Plus NT PRO-BNP	2·91 (1·54–5·49; p=0·001)¶	0·72	0·17	0·23	0·39 (p=0·02)

AUC=area under the curve. AT=anaerobic threshold. DASI=Duke Activity Status Index. NT PRO-BNP=N-terminal pro-B-type natriuretic peptide. *AUC of the receiver operating characteristic curve for the relevant logistic regression model. †The weighed net proportion of individuals whose predicted probability of the outcome of interest improved with inclusion of a specific additional covariate in the regression model (eg, peak oxygen consumption). Improved predicted probability implies a higher predicted probability in individuals who had the outcome event of interest, and a lower predicted probability in individuals who did not. Negative statistic values indicate net worsening of predicted probabilities (eg, higher predicted probability in individuals who did not have the outcome of interest). This statistic has an associated p value. ‡Covariate in this baseline model was the Revised Cardiac Risk Index score. §Adjusted odds ratios (OR) expressed with respect to 1 metabolic equivalent increase in peak oxygen consumption (per 3·5 mL/kg per min), AT (per 3·5 mL/kg per min), or DASI scores (per 3·5 points). ¶Adjusted OR expressed with respect to 1 $\log_{10}$ increase in NT pro-BNP concentrations ‖Covariates in this baseline model were age, sex, and Revised Cardiac Risk Index score. **Covariates in this baseline model were age, sex, and high-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular procedures).

Table 3: Predictive performance of different measures of preoperative functional capacity

of the exposures of interest with two more frequent outcomes: myocardial injury and moderate or severe postoperative complications. Myocardial injury and postoperative complications are clinically and prognostically important outcomes.[32–34] Our general findings with respect to prediction of 30-day myocardial infarction or death were qualitatively unchanged in the complementary analysis pertaining to 30-day myocardial injury or death.

Second, despite significant efforts by research personnel and study investigators, the consent rate among otherwise eligible patients in our study was only 27%. Nonetheless, this consent rate is somewhat unsurprising when viewed from the perspective of the study setting (ie, anxious patients awaiting major surgery within a short timeframe) and procedures (ie, strenuous exercise testing solely for research purposes). The consent rate is also consistent with several large contemporary prospective studies in surgical patients that had arguably more straightforward study procedures. For example, consent rates were 30% in the POISE-2 trial of aspirin and clonidine in non-cardiac surgery,[35] and 36% in the ATACAS trial in cardiac surgery.[36]

Third, our primary analyses relied on peak oxygen consumption and anaerobic thresholds determined by trained investigators at each individual centre. It is possible that central adjudication of CPET results might have led to different determinations of these measures. Nonetheless, given that our study was designed to be pragmatic and generalisable, our main analyses better represent the prognostic accuracy of peak oxygen consumption or anaerobic thresholds in real world clinical practice. Fourth, the preoperative predictive models in this study had generally low-to-moderate discrimination, with AUC values of 0·74 or lower. This observation could be partly explained by the lower-than-expected outcome event rate, which limited the number of covariates included in regression models. Nonetheless, the discrimination of these models is similar to those from other studies, such as a prospective cohort study where the combination of RCRI score and preoperative coronary CT angiography had an AUC of 0·66 for predicting 30-day death or myocardial infarction.[37] Fifth, each hospital used its own preferred troponin assay to detect myocardial infarction or myocardial injury. This pragmatic approach is consistent with many multicentre perioperative studies.[35,38] Furthermore, variation in troponin assays does not affect the prognostic importance of myocardial infarction or myocardial injury,[32,33] and should not have biased the association between the study exposures and outcomes.

Combined with previous data, the results of our study suggest that DASI scores and natriuretic peptides, such as NT pro-BNP, should supplant subjective assessment for the estimation of perioperative cardiac risk for major non-cardiac surgery. More research is required to define optimum thresholds for these measures and determine how they should be used in combination with other prognostically important information, including alternative preoperative biomarkers (eg, high-sensitivity troponin).[39] These other biomarkers might also help to partly address the limitations of NT pro-BNP as a prognostic biomarker in the presence of obesity,[40] chronic renal kidney,[41] or heart failure with preserved ejection fraction.[42]

Our findings also indicate that CPET, specifically peak oxygen consumption, can be used to identify patients at increased risk for postoperative complications. Research is needed to define optimal thresholds in peak oxygen consumption, determine the role of central expert adjudication in improving its prognostic accuracy, assess novel CPET-derived metrics of cardiopulmonary fitness (eg, heart rate recovery), and assess possible inter-relationships of CPET-derived metrics with prognostically important comorbidities. For example, lower haemoglobin concentrations are associated with both increased perioperative risk and reduced peak oxygen consumption.[43,44]

In conclusion, preoperative subjective assessment of functional capacity should not be used in clinical practice because it does not accurately identify patients with poor fitness or those at increased risk for morbidity and mortality after major elective non-cardiac surgery. Clinicians could instead consider more objective measures, such as DASI questionnaires and NT pro-BNP testing for assessing perioperative cardiac risk, and perhaps CPET to predict complications after major elective non-cardiac surgery.

Contributors

DNW, RMP, MAS, TEFA, BLC, JTG, KET, MPWG, PSM, and BHC contributed to the conception and design of the study. DNW, RMP, MAS, TEFA, ET, AA, BLC, JTG, KET, MPWG, CF, PSM, and BHC contributed to the acquisition, analysis, and interpretation of the data. DNW wrote the first draft of the manuscript. DNW, RMP, MAS, TEFA, ET, AA, BLC, JTG, KET, MPWG, CF, PSM, and BHC revised the manuscript critically for important intellectual content. All authors read and approved the final version of the manuscript.

Declaration of interests

TEFA reports grants from the UK Medical Research Council and other funding from the UK National Institute of Health Research (NIHR) Clinical Research Network, and is a committee member of the Perioperative Exercise Testing and Training Society. DNW reports grants and personal fees from Canadian Institutes of Health Research and grants from Heart and Stroke Foundation of Ontario, Ontario Ministry of Health and Longterm Care, and the Ontario Ministry of Research, Innovation and Science. PSM reports grants from the Australian and New Zealand College of Anaesthetists and Monash University. JTG has received research funding from Bayer, Pfizer, and Actelion, and has served on steering, safety, and adjudication committees for Actelion, United Therapeutics, and Bellepheron. RMP reports grants and personal fees from Edwards Lifesciences, Nestle Health Sciences, and BBraun, grants from Intersurgical, and personal fees from Medtronic and GlaxoSmithkline. MPWG reports grants from Sphere Medical and Pharmacosmos, and personal fees from Sphere Medical and Edwards Lifesciences. KET, MAS, ET, BHC, AA, BLC, and CF declare no competing interests.

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Duke Activity Status Index

PROVIDENCE
Heart and Vascular Institute

The Duke Activity Status Index is a self-administered questionnaire that measures a patient's functional capacity. It can be used to get a rough estimate of a patient's peak oxygen uptake.

		Yes	No
1	**Can you take care of yourself (eating, dressing, bathing or using the toilet)?**	2.75	0
2	**Can you walk indoors, such as around your house?**	1.75	0
3	**Can you walk a block or two on level ground?**	2.75	0
4	**Can you climb a flight of stairs or walk up a hill?**	5.50	0
5	**Can you run a short distance?**	8.00	0
6	**Can you do light work around the house, such as dusting or washing dishes?**	2.70	0
7	**Can you do moderate work around the house, such as vacuuming, sweeping floors or carrying in groceries?**	3.50	0
8	**Can you do heavy work around the house, such as scrubbing floors or lifting and moving heavy furniture?**	8.00	0
9	**Can you do yard work, such as raking leaves, weeding or pushing a power mower?**	4.50	0
10	**Can you have sexual relations?**	5.25	0
11	**Can you participate in moderate recreational activities, such as golf, bowling, dancing, doubles tennis or throwing a baseball or football?**	6.00	0
12	**Can you participate in strenuous sports, such as swimming, singles tennis, football, basketball or skiing?**	7.50	0

Duke Activity Status Index (DASI) = sum of “Yes” replies ___________

VO2peak = (0.43 x DASI) + 9.6

VO2peak = ___________ ml/kg/min ÷ 3.5 ml/kg/min = __________ METS

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Functional capacity and preoperative risk evaluation

I wish to draw attention to two methodological issues that might affect the interpretation of findings in Duminda Wijeysundera and colleagues' Measurement of Exercise Tolerance before Surgery (METS) study (June 30, 2018, p 2631).[1]

First, the small number of primary outcome events (death and myocardial infarction) limits the power of any predictive analyses. To avoid overfitting, the investigators seem to have excluded several variables that are important for prognosis from their regression models. For example, age and high-risk surgery are "clinically sensible factors typically considered during preoperative assessment"[1] and should arguably be part of any model for predicting 30-day death or myocardial infarction and excluding them might produce misleading results. Further, the sequential inclusion of highly correlated variables (eg, Duke Activity Status Index [DASI] and plasma concentrations of N-terminal pro-B-type natriuretic peptide [NT-pro-BNP]) might further reduce the predictive power of the regression model by increasing the mean square error of the estimates.[2]

Second, patients were categorised as having poor functional capacity when anaesthesiologists were "uncertain about patients' functional capacity, typically due to pre-existing conditions such as arthritis or peripheral arterial disease".[1] Patients scheduled for orthopaedic or vascular surgery constituted over a quarter of participants in the study, and this categorisation approach could have resulted in substantial misclassification of their functional capacity. This assumption is supported by the investigators' data on the main study outcomes within strata defined by subjectively assessed functional capacity. Although the proportion of patients categorised as having moderate or good functional capacity who had events was commensurate with perceived risk, the proportion in those classified as having poor functional capacity was unexpectedly low. It is unclear whether excluding these patients might have produced different results. Moreover, the objectively assessed measures of functional capacity (DASI and NT-pro-BNP) were included as continuous variables, thereby increasing statistical power, but without discrete categorisation (low, moderate, or good functional capacity), they are not useful in the clinical setting.

Given these limitations, the results of this study should be considered inconclusive. It might be premature to discard preoperative functional capacity (assessed both objectively and subjectively) as an important predictor of perioperative death or myocardial infarction in patients undergoing non-cardiac surgery.

I declare no competing interests.

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1 Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* 2018; **391:** 2631–40.
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Duminda Wijeysundera and colleagues' prospective cohort study[1] challenges concepts of preoperative risk assessment, showing that neither subjective assessments of fitness nor exercise testing were correlated with important cardiopulmonary outcomes. Instead, the structured Duke Activity Status Index (DASI) questionnaire and the predictive assessment of complications through measuring serum concentrations of N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) were better correlated with the outcomes.

The METS investigators modelled the relationship of the tests with the outcomes of interest using the Revised Cardiac Risk Index (RCRI) as a baseline model. For predicting 30-day death or myocardial injury, age, sex, and RCRI already performed well (area under the curve [AUC] of 0·70) and improved too little when the DASI or the NT-pro-BNP were added (AUC 0·71 for both). For predicting 1-year mortality, the NT-pro-BNP showed a greater improvement from the base model than did the DASI (AUC 0·65 in baseline model to 0·72 in NT-pro-BNP model). Unsurprisingly, the RCRI alone had already performed well as a single explanatory variable.

However, we should consider that tools for risk stratification need to be implemented to improve patient care.

These tools must be easily applicable at the bedside and should reflect the comorbidities and surgical traumas of the patient. For instance, we developed a model to predict 30-day mortality that considers age, American Society of Anesthesiologists Physical Status, nature of surgery (elective or urgent), and surgical severity, which are all variables that are picked up at the bedside. This model performs well with 85·2% sensitivity and 81·7% specificity.[2] A similar model (SORT)[3] that uses the same variables to predict 30-day mortality was validated in a UK cohort and had an AUC of 0·72. Thus, although the METS study investigators recommend using the DASI and the NT-pro-BNP to improve risk stratification, perhaps scores that are simpler to calculate because they use only bedside information merit more investment.

We declare no competing interests.

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1 Wijeysundera DN, Pearse RM, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* 2018; **391:** 2631–40.
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We commend Duminda Wijeysundera and colleagues[1] for testing the prognostic value conferred by assessment of subjective functional capacity in non-cardiac surgery and read the results with interest. We raise two issues with the published data.

First, the investigators reported that neither assessment of subjective functional capacity nor objective performance on cardiopulmonary exercise testing predisposed patients to cardiovascular complications. Regardless, the Duke Activity Status Index (DASI) score happened to confer a higher risk, which was significant (adjusted odds ratio 0·96, 95% CI 0·83–0·99; p=0·03). Although the authors highlighted this discrepancy, a chance of a type II error in calculation of risk using the DASI score was not mentioned. This omission is pertinent given the somewhat tenuous risk association of DASI, with an upper confidence interval that approaches 1·00. Primarily, this trial demonstrates that subjective and objective functional performance does not predict the occurrence of adverse cardiovascular events. Based on the weight of the evidence in the study, it might be premature to infer that the DASI could be the suitable replacement for clinical subjective assessment of functional capacity.

Second, it is notable that ten (41%) of 24 myocardial infarction events occurred in patients with a clinically significant postoperative complication. It would be of interest to assess whether significant differences existed in the results of preoperative functional exercise testing between the myocardial infarction cohorts with and without a postoperative complication. The variable performance of preoperative risk stratification tools and functional status might reflect the pathophysiological heterogeneity that underpins perioperative cardiovascular complications.[2] Therefore, future development of models of risk prediction that integrate putative risk factors, biomarkers, and non-invasive imaging are essential.

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1 Wijeysundera DN, Pearse RP, Shulman MA, et al. Assessment of functional capacity before major non-cardiac surgery: an international, prospective cohort study. *Lancet* 2018; **391:** 2631–40.
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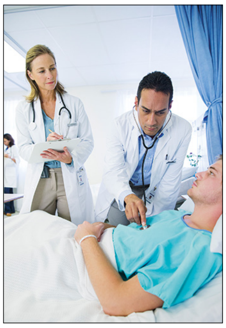
Authors' reply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We thank the correspondents for their interest in our study.[1]

Ganesan Karthikeyan raises concerns about our analytic approach and potential misclassification of subjectively assessed functional capacity. He is correct that the low number of primary outcome events (death or myocardial infarction within 30 days of surgery) in our study limits the statistical power of our analysis. Although the proportion of patients with these events was consistent with another study on elective non-cardiac surgery,[2] we do clearly acknowledge this limitation in our Article. Despite this limitation, our analysis did adjust for important risk factors when calculating Revised Cardiac Risk Index (RCRI) scores. The RCRI includes high-risk surgery but not advanced age, which is often excluded from guideline algorithms.[3,4] Additionally, the results of our secondary analysis of more frequent cardiovascular endpoints (30-day death or myocardial injury), which adjusted for more risk factors (ie, age, sex, and RCRI), produced similar results to our primary analysis. Although inclusion of highly correlated covariates in regression models might indeed lead to multicollinearity, this issue does not affect our analyses of predictive performance of preoperative functional capacity measures because the principal exposures (Duke Activity Status Index [DASI], plasma concentrations of N-terminal pro-B-type natriuretic peptide, and mean peak oxygen consumption) were evaluated in separate models with otherwise similar covariates. Karthikeyan also raised concerns about categorising participants as having poor functional capacity if anaesthesiologists reported uncertain subjective assessments. We do not believe that this issue affected our study. Of 107 participants in the poor functional capacity category, anaesthesiologists reported uncertain subjective assessments for only 15 (14%) patients. Furthermore, these 15 participants had similar distributions of mean peak oxygen consumption and DASI scores to the remaining 92 participants who anaesthesiologists rated as certainly having poor functional capacity. For all these reasons, we believe Karthikeyan's final statement to be markedly overstated. Indeed, the consistently poor performance of subjective assessment in predicting outcomes identifies the need for better approaches towards preoperative risk evaluation.

Anoop Koshy and colleagues raise concerns about whether our results support the incorporation of the DASI questionnaire in preoperative risk assessment. We certainly agree that further validation of the DASI is needed in the perioperative setting. In the interim, our findings are sufficiently robust to support replacing subjective assessment with the DASI questionnaire during preoperative evaluation. The questionnaire demonstrated prognostic utility in the study cohort across two cardiovascular endpoints and two statistical measures (net risk reclassification index and logistic regression model coefficients).

We agree with Jairo Dussán-Sarria and colleagues that tools for estimating simple bedside risk have the potential to improve patient care. However, the METS study did not seek to develop such a tool; rather, its narrower focus was to identify optimal approaches for using preoperative functional capacity to inform risk estimation. The METS study thus complements work done by Stefani and colleagues,[5] because it identifies the optimal measures of functional capacity that might be included in indices of risk stratification.

We declare no competing interests.

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Orphan drugs

Lucio Luzzatto and colleagues[1] (Sept 1, 2018, p 791) have called for collaboration from EU member states on negotiation of orphan drug prices to take advantage of the fact that with 500 million inhabitants, the EU is the largest customer for any new drug. Low-income and middle-income countries (LMICs), with more than 6 billion inhabitants and 360–480 million patients with rare diseases,[2] are in need of orphan drugs and should join forces in this area.

Rare diseases cannot continue to be neglected in developing countries, and international collaboration among these countries is vital to change the situation. Screening programmes should be introduced for more diseases, and educational programmes for doctors (especially paediatricians and general practitioners) and nurses should be implemented; these would raise the number of diagnoses and reduce misdiagnoses. Most importantly, more patients with rare diseases for which drugs are available should be treated.

Legislations, regulations, and policies for orphan drugs should be drafted and implemented (a review article[3] failed to identify any pertinent legislation in Latin American and African countries). Patient organisations should be created in LMICs and should play a prominent role in increasing awareness and urging governments to provide treatment for rare diseases, particularly for children. Provision of antiretrovirals to HIV-infected patients in LMICs was considered impossible on economic grounds 20 years ago, and became a reality in 2010; a joint effort from patient organisations and governments could make the provision of orphan drugs to patients in need in the same countries a reality.

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