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RESEARCH ARTICLE

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Aerobic capacity is associated with disease activity and cardiovascular risk factors in early rheumatoid arthritis

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Abstract

Objectives: The aim of this study was to investigate aerobic capacity and its associations with disease activity and risk factors for cardiovascular disease (CVD) in early rheumatoid arthritis (RA).

Methods: This cross-sectional study included 67 patients with early RA. Aerobic capacity was estimated with the Åstrand submaximal test adjusted according to the Nord-Tröndelag Health Study formula. The following were also assessed: subclinical atherosclerosis by carotid intima-media thickness and pulse wave analysis; body composition by dual X-ray absorptiometry; estimated CVD mortality risk by the Systematic Coronary Risk Evaluation; disease activity by the Disease Activity Score 28, C-reactive protein and erythrocyte sedimentation rate; blood lipids by total cholesterol, low-density lipoproteins, high-density lipoproteins, and triglycerides; and functional ability by the Stanford health assessment questionnaire. Univariate and multiple linear regression analyses were performed to explore the associations between variables.

Results: The mean (*SD*) aerobic capacity was 31.6 (8.7) ml O_2^{-1} kg min^{-1}. Disease activity and risk factors for CVD were more favourable for patients with aerobic capacity above the median value. Aerobic capacity was associated with ESR and several CVD risk factors, independent of age and sex. In a multiple regression model that was adjusted for age and sex, aerobic capacity was significantly associated with per cent body fat (β = −0.502, 95% CI [−0.671, −0.333]) and triglycerides (β = −2.365, 95% CI [−4.252, −0.479]).

Conclusions: Disease activity and risk factors for CVD were in favour for patients with a higher aerobic capacity. Aerobic capacity was associated with disease activity and several risk factors for CVD, independent of age and sex. In RA, these findings may provide insights into the benefits of using aerobic capacity as a marker to prevent CVD.

KEYWORDS
aerobic capacity, disease activity, cardiovascular disease, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a systemic and inflammatory disease that is associated with an increased morbidity and mortality due to cardiovascular disease (CVD; Wallberg-Jonsson, Ohman, & Dahlqvist, 1997; Avina-Zubieta, 2008; Avina-Zubieta, Thomas, Sadatsafavi, Lehman & Lacaille, 2012). This may be due to traditional CVD risk factors and to chronic inflammation (Innala et al., 2011; Solomon et al., 2010). Patients with RA have accelerated subclinical atherosclerosis (Ambrosino et al., 2015) and altered body composition, characterized by increased body fat mass and reduced muscle mass (Wolfe & Michaud, 2012).

Low aerobic capacity is one of the strongest independent risk factors for CVD and all-cause mortality in the general population (Myers et al., 2002; Gulati et al., 2003; Kodama et al., 2009). Values below 9 METs (~31.5 ml O_2) for women and 10 METs (~35 ml O_2) for men were related to an increased mortality risk in one report, regardless of age (Blair et al., 1989). Previous studies on aerobic capacity in patients with RA have shown somewhat contradictory results. Low values have been described in two cross-sectional studies (Metsios et al., 2015; Stavropoulos-Kalinoglou et al., 2013), and test values similar to reference data or comparable with healthy controls have also been reported (Bilberg, Ahlmen, & Mannerkorpi, 2005; Eurenius & Stenstrom, 2005; Hornberg, Sundstrom, Innala, Rantapaa-Dahlqvist, & Wallberg-Jonsson, 2017). Therefore, further studies in this area are needed. Low aerobic capacity has been related to a worse cardiovascular profile and to an increased risk over 10-year for CVD mortality in patients with long-standing RA (Metsios et al., 2015). Consequently, low aerobic capacity might represent an additional risk factor for CVD in the RA population. There are, however, few reports on populations with early RA and associations between aerobic capacity and other CVD risk factors (Zoli et al., 2017).

The aim of the present cross-sectional study was to investigate aerobic capacity in patients with early RA as well as the associations between aerobic capacity and disease activity and risk factors for CVD.

2 | METHODS

2.1 | Participants

This study is a part of a continuing structured programme on early RA at the Department of Rheumatology, University Hospital of Umeå, Sweden. All eligible patients (n = 143), during 2013–2016, being symptomatic for no longer than 12 months before diagnosed with RA, were considered to be invited to the study. Inclusion criteria were either sex, aged between 18 to 75 years, and diagnosed with RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria (Aletaha et al., 2010). Exclusion criteria were severe functional limitations, severe cardiopulmonary, and/or neurological disease or prescription of beta-blocking agents thus restricting the patient from performing the aerobic capacity test. Forty-one patients were excluded. Finally, 102 patients were invited, and 67 agreed to participate, 51 women and 16 men. The inclusion and exclusion process is described in Figure 1. All included patients provided their informed consent before assessments, after they were given verbal and written information about the study, in accordance with the tenets of the Declaration of

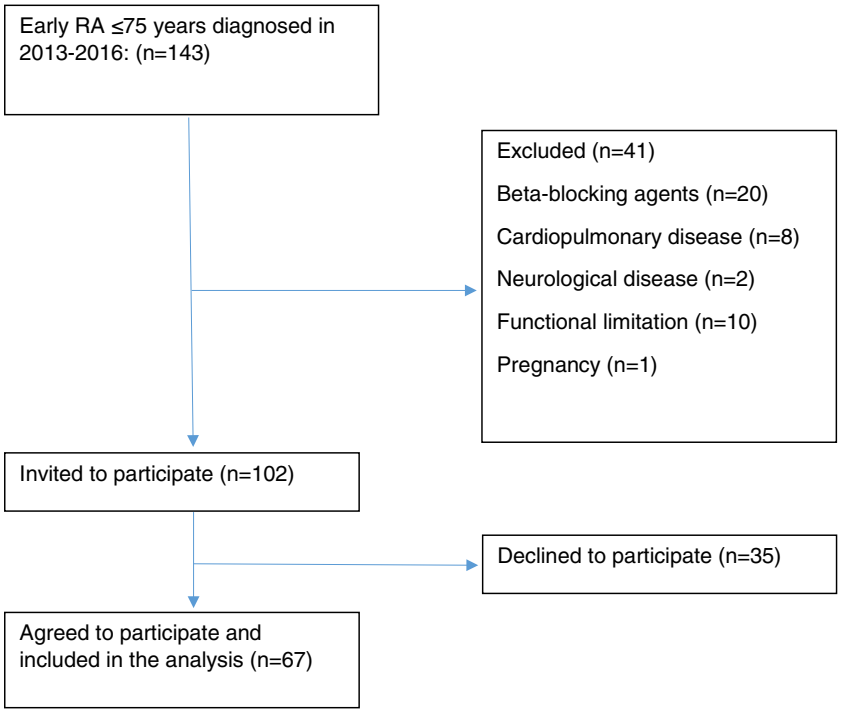

FIGURE 1 Flowchart of the inclusion and exclusion process

Helsinki. The study was approved by the Ethics Committee at Umeå University (Dnr 2014/356-31).

Descriptive data in relation to the sex of the patient, including estimated aerobic capacity data according to the Åstrand (1960) test, which was adjusted with the Nord-Tröndelag Health Study (HUNT) formula (Nes, Janszky, Wisløff, Støylen, & Karlsen, 2013), are presented in Table 1. All patients were treated in accordance to standard clinical practices. A total of 63 (94%) patients were treated with disease modifying antirheumatic drugs, whereas biological agents and corticosteroids were used by 12 (18%) and 16 (24%) patients, respectively.

2.2 | Assessments

Aerobic capacity was estimated using the Åstrand submaximal cycle test (Astrand, 1960; Astrand & Ryhming, 1954), which has shown to be valid in comparison with a maximal aerobic capacity test in patients with RA (Nordgren et al., 2014). The HUNT formula, $211 - 0.64 \times$ age (Nes et al., 2013), has been reported to better predict the maximal age-related heart rate than the original Åstrand age prediction; thus, the HUNT formula was used to further improve estimation of aerobic capacity (Nordgren et al., 2014). Subjects were instructed to refrain from exercise for 24 hr preceding the test, as well as heavy meals and tobacco for at least 2 hr before the test. The same cycle ergometer (Monark 928 G3) was used for all tests.

Subclinical atherosclerosis was estimated through assessment of bilateral carotid intima-media thickness (cIMT) in the right and left carotid artery by ultrasound (Sequoia 512 Ultrasound System, Siemens, Upplands-Väsby, Sweden; O'Leary & Bots, 2010). Measurements were taken along 1-cm-long longitudinal segments of the common carotid artery proximal to the carotid bulb on three diastolic images (defined by R wave on an attached 3 lead ECG), and mean values were recorded.

To further assess subclinical atherosclerosis, the pulse wave analysis (Horváth et al., 2010) was recorded using an Arteriograph TL2 (v.3.0.0.1 TensioMed Ltd, Budapest Hungary) after the patient rested in a supine position in a quiet room for 10 min. This measurement showed peripheral systolic blood pressure (SBP) and diastolic blood pressure (DBP), central systolic blood pressure aorta (SBPao), and a measurement of arterial stiffness, the pulse wave velocity (PWV). Three measurements were performed in the right arm, and the average values were noted. Measurements of cIMT and PWV are both predictors of CVD events in patients with RA (Kerekes et al., 2012).

The 10-year mortality risk percentage in CVD was estimated using the Systematic Coronary Risk Evaluation (SCORE; Arts et al., 2016). This is an index comprising age, sex, total cholesterol, SBP, and current smoking status and was further adjusted in accordance with the recommendations of the EULAR using a 1.5 multiplier (Agca et al., 2017).

Body composition, that is, fat-free mass (g) and fat mass (%), was assessed by dual energy X-ray absorptiometry (Lunar Prodigy X-ray Tube Housing Assembly, Brand BX-11, Model 8743; GE Medical Systems, Madison, WI, USA; Toombs, Ducher, Shepherd, & De Souza, 2012). The percentage of fat-free mass was calculated by dividing fat-free mass (g) by the total mass (g). Waist circumference was assessed with the patient in a standing position, the arms hanging freely, and the measuring tape placed midway between the lower costal margin and the iliac crest. The measurement was made to the nearest 5 mm at the end of a normal expiration (Douketis, Paradis, Keller, & Martineau, 2005).

Disease activity was calculated with the Disease Activity Score 28 (DAS 28; Prevoo et al., 1995), which includes the number of tender and swollen joints (of 28 joints), the erythrocyte sedimentation rate (ESR), and the patient's global health as measured on a visual analogue scale. The range of the DAS 28 is 0–9.4, where lower values indicate lower disease activity. C-reactive protein, ESR and total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein were analysed using clinical routine laboratory methods. Functional ability was assessed by the Stanford

TABLE 1 Descriptive data for 67 patients with early rheumatoid arthritis, shown for the entire group and according to patient sex

Variable	All patients, *n* (%)	Women, *n* (%)	Men, *n* (%)
Participants	67 (100)	51 (76)	16 (24)
Age, years	53.1 (14.4)	51.6 (14.4)	57.8 (13.7)
Aerobic capacity, ml O_2^{-1} kg min^{-1}	31.6 (8.7)	31.7 (9.4)	31.3 (6.1)
Aerobic capacity, L O_2 min^{-1}	2.3 (0.6)	2.2 (0.6)	2.7 (0.5)
Current smoker, *n* (%)	7 (10)	5 (10)	2 (12)
Positive ACPA, *n* (%)	47 (70)	38 (74)	9 (56)
Positive RF, *n* (%)	52 (78)	42 (82)	10 (62)
ESR, mm hr^{-1}	13.3 (9.1)	14.6 (8.7)	9.3 (9.5)
CRP, mg L^{-1}	3.2 (2.8)	3.3 (2.7)	2.8 (1.1)
DAS 28, (0–9.4), unit	2.8 (1.3)	2.9 (1.4)	2.4 (1.1)
HAQ, (0–3), unit	0.38 (0–0.88)	0.50 (0–0.88)	0.13 (0–0.38)
Disease duration, months	16 (4.4)	16 (3.9)	17 (5.6)
Cholesterol, mmol L^{-1}	5.1 (1.1)	5.1 (1.1)	5.0 (1.1)
Triglycerides, mmol L^{-1}	1.3 (0.8)	1.3 (0.8)	1.2 (0.6)
HDL, mmol L^{-1}	1.5 (0.5)	1.6 (0.5)	1.4 (0.4)
LDL, mmol L^{-1}	2.9 (0.9)	2.9 (0.9)	3.0 (0.9)
SCORE, %	1.5 (0.0–3.0)	0.0 (0.0–1.5)	2.2 (1.5–5.6)
cIMT, mm	0.7 (0.2)	0.7 (0.2)	0.8 (0.2)
SBP, mmHg	130 (17)	130 (18)	132 (16)
SBPao, mmHg	127 (20)	128 (21)	126 (16)
DBP, mmHg	78 (10)	77 (10)	81 (10)
PWV, m s^{-1}	9.3 (2.4)	9.3 (2.5)	9.2 (2.2)
Body fat mass, %	38.1 (10)	40.9 (9.3)	29.4 (7.6)
Fat-free mass, %	63.0 (9)	60.5 (9.1)	71.7 (7.4)
Waist circumference, cm	93 (15)	91 (15)	99 (14)

Note. Data are presented as mean (*SD*) or as median (Q1–Q3).
Abbreviations: ACPA, anticitrullinated protein antibodies; cIMT, carotid intima-media thickness; CRP, C-reactive protein; DAS 28, Disease Activity Score 28; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PWV, pulse wave velocity; RF, rheumatoid factor; SBP, systolic blood pressure; SBPao, systolic blood pressure aorta; SCORE, Systematic Coronary Risk Evaluation.

health assessment questionnaire, including eight categories of functional activities. The range of the health assessment questionnaire is 0–3, where higher values indicate a higher degree of disability (Fries, Spitz, Kraines, & Holman, 1980). All patients were interviewed by medical staff to collect additional data on risk factors for CVD, previous CVD events, chronic diseases, and current medication. All cardiovascular events were validated through revision of patient medical files.

2.3 | Statistical analysis

Descriptive statistics are presented as numbers with percentages, as mean values (*SD*) or as median values (Q1–Q3), depending on the variable and on the distribution of the data. Patients were dichotomised into two groups with low- and high-aerobic capacity based on the median value, 29.7 ml O_2^{-1} kg min^{-1}. Additionally, patients were divided into three subgroups, based on tertiles of aerobic capacity, to further investigate differences between groups. The Student's independent *t* test, the Mann–Whitney *U* test, and the chi-squared test were used to investigate differences between groups based on data type and distribution. Associations between the dependent variable, namely, aerobic capacity and the independent variables related to subclinical atherosclerosis, body composition, estimated CVD mortality risk, and disease activity were analysed using linear regression analysis before and after adjustment for age and sex. Multiple linear regression analyses were performed, based on statistically significant variables in the unadjusted univariate analysis, to find the best fitting model to explain the variability in aerobic capacity. The interpretation of the linear regression analysis assumes that a positive β-coefficient indicates that as the independent variable increases with one unit, the dependent variable increases. A negative β-coefficient indicates that with each unit increase in the independent variable, the dependent variable decreases. The multiple linear regression modelling assumes on holding other variables in the model constant which allows to estimate the effect of each variable isolated from the others. Further, the Bonferroni's post hoc test to counteract Type 1 errors was applied. We used R^2 = .2 for sample size calculations. A test to test R^2 deviation from zero in a linear regression model was used to calculate the required sample size, that is, the sample size needed to reject R^2 = 0. The calculations suggested that a sample size of at least 34 was needed to achieve a power of 80% with a significance level of 0.05. The sample size calculation was determined using G*Power (version 3.1.9.2, University of Dusseldorf, Germany). All other statistical calculations were performed using the Statistical Package of Social Sciences (SPSS, version 26, IBM, Armonk, NY, USA).

3 | RESULTS

Table 2 shows the descriptive data related to aerobic capacity for patients with aerobic capacity below and above the median value of 29.7 ml O_2^{-1} kg min^{-1}. There were significant differences in the following variables between patients with aerobic capacity below versus above the median value: RA specific variables, traditional CVD risk factors, and disease activity. The group with a higher aerobic capacity showed more favourable values. When the patient group was subdivided into three groups, based on tertiles in aerobic capacity, there were similar differences between the groups, in favour of the groups with a higher aerobic capacity (Supporting Information). There were 35 patients who declined to participate in the study: 27 (77%) women and eight (23%) men. These patients did not differ from those who participated regarding the proportions of women and men, disease activity, and blood pressure (data not shown). The mean age (*SD*) of 50 (15) years, was lower in the group that declined participation ($p < .05$).

3.1 | Associations between aerobic capacity, disease activity, and cardiovascular risk factors

We performed a univariate linear regression analysis, with aerobic capacity as the dependent variable. Table 3 (column A) shows unadjusted analyses. Aerobic capacity was positively associated with HDL and fat-free mass percentage. Negative associations were seen between aerobic capacity and age, cIMT, PWV, SBP, SBPao, DBP, ESR, CRP, DAS 28, triglycerides, body fat percentage, waist circumference, and estimated 10-year CVD mortality risk. After adjustments for age and sex (Table 3, column B), all but DAS 28, CRP, cIMT, and PWV remained significant. In a multiple linear regression model, aerobic capacity was negatively associated with body fat percentage and triglycerides, even after adjustments for age and sex (Table 4). This model explained 62.2% of the variation in aerobic capacity.

4 | DISCUSSION

The main findings from this study of patients with early RA were that descriptive data showed consistent and biologically plausible differences in several important CVD risk factors and disease activity measurements between patient groups with aerobic capacity above versus below the median value. Patients with a higher aerobic capacity had more favourable values of measurements. Furthermore, aerobic capacity was associated with disease activity and several CVD risks factors. Although there were significant differences in age between the groups, the associations between aerobic capacity and SBP, SBPao, DBP, measurements of body composition, triglycerides, HDL, and ESR remained after adjusted analyses, independent of age and sex. To exemplify these associations (Table 3, column B), adjusted analyses indicated that 0.26 ml higher aerobic capacity was associated with 1 mm hr^{-1} lower ESR. Further, 0.21 ml higher aerobic capacity was associated with 1 mmHg lower SBP. These relatively robust associations may be clinically important and support the use of aerobic capacity testing to improve patient outcome.

The mean (*SD*) value of aerobic capacity was 31.6 (8.7) ml O_2^{-1} kg min^{-1} in the studied group, which was rather similar to the

TABLE 2 Descriptive data for 67 patients with early rheumatoid arthritis, shown for the entire group and for aerobic capacity subgroups based on the median value

Variable	All patients (*n* = 67)	Aerobic capacity <29.7 ml kg^{-1} min^{-1} (*n* = 33)	Aerobic capacity <29.7 ml kg^{-1} min^{-1} (*n* = 34)	*p* value
Female sex, *n* (%)	51 (76)	25 (76)	26 (76)	.946
Age, years	53 (14.4)	59 (10.7)	47 (15.4)	**.001**
Current smoker, *n* (%)	7 (10)	5 (15)	2 (6)	.257
Positive ACPA, *n* (%)	47 (72)	24 (73)	23 (68)	.656
Positive RF, *n* (%)	52 (81)	26 (79)	26 (76)	.823
ESR, mm hr^{-1}	13.3 (9.1)	17 (8.8)	7 (8.3)	**.002**
CRP, mg L^{-1}	3.2 (2.8)	3.8 (2.9)	2.5 (2.5)	**.025***
DAS 28 (0–9.4), unit	2.8 (1.3)	3.3 (1.2)	2.2 (1.4)	**.033***
HAQ (0–3), unit	0.38 (0.0–0.88)	0.38 (0.0–0.88)	0.38 (0.0–0.63)	.670
Disease duration, months	16 (4.4)	16 (3.6)	16 (5.0)	.743
Cholesterol, mmol L^{-1}	5.1 (1.1)	5.6 (1.2)	4.8 (1.0)	.836
Triglycerides, mmol L^{-1}	1.3 (0.8)	1.5 (0.9)	0.8 (0.6)	**.025***
HDL, mmol L^{-1}	1.5 (0.5)	1.5 (0.4)	1.6 (0.5)	.231
LDL, mmol L^{-1}	2.9 (0.9)	2.9 (0.9)	2.9 (0.9)	.962
SCORE, %	1.5 (0.03.0)	1.5 (0.0–3.8)	0.0 (0.0–1.9)	**.02***
cIMT, mm	0.7 (0.2)	0.8 (0.16)	0.6 (0.22)	.154
SBP, mmHg	130 (17)	135 (13)	118 (19)	**.015***
SBPao, mmHg	124 (114-142)	128 (121-144)	118 (107-134)	**.01***
DBP, mmHg	78 (10)	81 (8)	72 (12)	.157
PWV, m s^{-1}	8.9 (7.2-10.6)	9.2 (8.0-11.8)	7.4 (6.9-10.4)	**.01***
Body fat mass, %	38.1 (10)	45.9 (9.3)	33.4 (9.2)	**<.001**
Fat-free mass, %	63.0 (0.1)	55.7 (0.1)	67.7 (0.1)	**<.001**
Waist circumference, cm	93 (15)	103 (14)	83 (12)	**<.001**

Note. Data are presented as mean (*SD*) or as median (Q1–Q3). Significant *p* values are highlighted in bold.
Abbreviations: ACPA, anticitrullinated protein antibodies; cIMT, carotid intima-media thickness; DAS 28, disease Activity Score 28; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; HDL, high-density lipoprotein; LDL, low-density lipoprotein; PWV, pulse wave velocity; RF, rheumatoid factor; SBP, systolic blood pressure; SBPao, systolic blood pressure aorta; SCORE, Systematic Coronary Risk Evaluation; WC, waist circumference.
*Value not statistically significant after the Bonferroni correction.

mean value of approximately 33 ml O_2^{-1} kg min^{-1}, reported from the Swedish general population, age 35–74 years (Ekblom-Bak et al., 2019). Some previous studies reported that patients with early RA have low levels of aerobic capacity (Häkkinen, Sokka, Kotaniemi, & Hannonen, 2001; Zoli et al., 2017). Other has reported test values that are similar to the general population (Bilberg et al., 2005). Alarmingly low values have been reported in patients with long-standing RA (Metsios et al., 2015); other studies have reported values similar like those in the present study (Eurenius & Stenstrom, 2005; Hornberg et al., 2017). These differences may be due to different inclusion criteria, to different traditions of recreational physical activity, and possibly to different standard advice regarding physical activity given by the health care providers.

Maintaining or improving aerobic capacity over time has shown to be associated with lower all-cause and CVD mortality risk in the general population (de Lannoy, Sui, Lavie, Blair, & Ross, 2018; Lee et al., 2011). Also, epidemiological data (Myers et al., 2002; Gulati et al., 2003; Kodama et al., 2009; Nes, Vatten, Nauman, Janszky, & Wisloff, 2014) report that each increase of metabolic equivalent task (1 MET~3.5 ml O_2^{-1} kg min^{-1}) is associated with a 12–21% reduction of all-cause and CVD mortality risk in women and men. In the general population, patients with the lowest aerobic capacity seem to have the greatest potential to reduce mortality risk by increasing their aerobic capacity (Berry et al., 2011; Ross et al., 2016). Because aerobic capacity is approximately equally dependent on genetics and physical activity (Bouchard et al., 1999), it is reasonable to suggest that an increased aerobic capacity can be a meaningful protector for CVD in early RA.

Interestingly, the present study reports inverse associations between aerobic capacity and disease activity, measured as ESR, CRP, and DAS 28. The association with ESR remained significant, also after adjustments for age and sex. Because RA is a systemic inflammatory

TABLE 3 Linear regression analysis of the 67 patients with early rheumatoid arthritis

	A		B	
Variable	***β***	**95% CI**	***β***	**95% CI**
Sex	0.47	−4.56, 5.51	n.a.	n.a.
Age, year	**−0.32**	**−0.45**, **−0.19**	n.a.	n.a.
ESR, mm hr^{-1}	**−0.39**	**−0.60**, **−0.17**	**−0.26**	**−0.47**, **−0.02***
CRP, mg L^{-1}	**−1.12**	**−1.87**, **−0.38***	−0.06	−1.28, 0.14
DAS 28/unit	**−1.90**	**−3.5**, **−0.34***	−1.15	−2.6, 0.29
Triglycerides, mmol L^{-1}	**−4.39**	**−7.0**, **−1.76**	**−3.24**	**−5.6**, **−0.87***
HDL, mmol L^{-1}	**4.57**	**0.08**, **9.06***	**4.15**	**0.20**, **8.1***
SCORE, %	**−1.41**	**−2.40**, **−0.43***	n.a	n.a.
cIMT, mm	**−15.6**	**−26.3**, **−4.9***	−1.76	−13.5, 9.9
SBP, mmHg	**−0.28**	**−0.38**, **−0.17**	**−0.21**	**−0.31**, **−0.11**
SBPao, mmHg	**−0.24**	**−0.33**, **−0.15**	**−0.16**	**−0.26**, **−0.05***
DBP, mmHg	**−0.39**	**−0.58**, **−0.20**	**−0.28**	**−0.46**, **−0.08***
PWV, m s^{-1}	**−1.38**	**−2.21**, **−0.56**	−0.25	−1.26, 0.75
Body fat mass, %	**−0.48**	**−0.66**, **−0.30**	**−0.55**	**−0.72**, **−0.39**
Fat-free mass, %	**0.49**	**0.31**, **−0.67**	**0.56**	**0.40**, **0.74**
WC, cm	**−0.36**	**−0.48**, **−0.24**	**−0.31**	**−0.42;−0.21**

Note. Aerobic capacity was the dependent variable. A: unadjusted analysis; B: analysis adjusted for age and sex. Significant values are highlighted in bold.
Abbreviations: cIMT, carotid intima-media thickness; CRP, C-reactive protein; DAS 28, Disease Activity Score 28; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; n.a., not applicable; PWV, pulse wave velocity; SBP, systolic blood pressure; SBPao, systolic blood pressure aorta; SCORE, Systematic Coronary Risk Evaluation; WC, waist circumference.
*Value not statistically significant after the Bonferroni correction.

TABLE 4 Multiple linear regression model with aerobic capacity as the dependent variable, of the 67 patients with early rheumatoid arthritis

Variable	***β***	**95% CI**
Body fat mass, %	**−0.502**	**−0.671**, **−0.333**
Triglycerides, mmol L^{-1}	**−2.365**	**−4.252**, **−0.479**
Age, year	**−0.230**	**−0.330**, **−0.129**
Sex, female	**5.14**	**1.37**, **8.914**

Note. R^2 for the model: 62.2. Significant values are highlighted in bold.

disease, this might indicate a positive effect of improved aerobic capacity on inflammation, as shown in a meta-analysis of studies that investigated the effects of exercise on inflammatory diseases (Sveaas, Smedslund, Hagen, & Dagfinrud, 2017). The inverse association between aerobic capacity and inflammation in early RA was also found in a study by Zoli et al. (2017). In addition, and possibly interrelated to the previously described association, aerobic capacity was inversely associated with body fat per cent and waist circumference. In the general population, the amount of body fat is associated with the increased systemic inflammation, which may lead to an increased risk of CVD (Berg & Scherer, 2005).

The associations found in the present study confirmed our postulation that a higher aerobic capacity would be associated with more favourable measurements of several CVD risk factors and estimated CVD risk. Relationships between aerobic capacity and atherosclerosis (Ferreira, Twisk, Stehouwer, van Mechelen, & Kemper, 2003; Scholl, Bots, & Peters, 2015), body composition (Ekblom-Bak, Hellenius, Ekblom, Engstrom, & Ekblom, 2009; Wientzek et al., 2014), CVD mortality risk (Ekblom-Bak et al., 2009; Gulati et al., 2003; Kodama et al., 2009; Myers et al., 2015), and measures of inflammation (Church, 2002; Kondo, Nomura, Nakaya, Ito, & Ohguro, 2005) have also been found in the general population. Also, in populations with other chronic diseases, there are inverse associations between aerobic capacity and mortality risk (Kavanagh et al., 2003; Lyerly et al., 2009; Martin et al., 2013). Several biological mechanisms have been suggested underlying the impact of aerobic capacity on mortality, including improvements of blood pressure, blood lipids, glucose levels, body composition, and markers of inflammation (Lee, Artero, Sui, & Blair, 2010). In patients with long-standing RA, one study reported inverse associations between aerobic capacity and body fat per cent, estimated CVD mortality risk, and disease activity (Metsios et al., 2015).

The associations between aerobic capacity and markers of atherosclerosis (cIMT and PWV) did not remain statistically significant after adjustments for age and sex; however, this could be expected because cIMT and PWV are known to increase with age. Notably, the associations between aerobic capacity and blood pressure, a variable that increases with age, remained statistically significant even after adjustments for age and sex.

The present study reports an inverse association between aerobic capacity and the SCORE risk predictor, which implicates the importance of aerobic capacity for risk classification also in RA. Common scores for predicting the risk of CVD, like the SCORE (Arts et al., 2016), the Framingham risk score (D'Agostino et al., 2008), and the Reynolds score (Ridker, Paynter, Rifai, Gaziano, & Cook, 2008), were developed for the general population. These scores seem to underestimate cardiovascular risk in patients with RA (Arts et al., 2016; Crowson et al., 2017). Notably, the RA-specific risk tools, the expanded risk score, the Q-risk II, and the EULAR multiplier for SCORE do not predict cardiovascular events or CVD mortality in RA better than general risk scores (Arts et al., 2015; Crowson et al., 2017; Wahlin et al., 2019). None of these scores include aerobic capacity as a component. Several publications support the idea that the addition of aerobic capacity would improve traditional risk classification in the general population, both in the short term and in the long term (Gupta et al., 2011; Stamatakis, Hamer, O'Donovan, Batty, & Kivimaki, 2013; Wickramasinghe et al., 2014). Our results are in accordance with these findings.

5 | STRENGTHS AND LIMITATIONS

The main strength of this study was the well-defined population. The study was well-powered, and the study population was representative of early RA in terms of age and the proportions of women and men. The results should therefore be applicable to other populations with early RA. We estimated the aerobic capacity with the Åstrand submaximal test, which has been reported to be valid in RA (Nordgren et al., 2014) and in other populations (Ekblom, Engstrom, & Ekblom, 2007). To further improve aerobic capacity estimation, we used the HUNT formula (Nes et al., 2013), which may provide a better estimate of age-related maximal heart rate and increase the validity of the Åstrand original estimation (Nordgren et al., 2014). Maximal aerobic capacity testing, which progressively increases the test load until exhaustion, is accepted as the most precise measurement of cardiopulmonary capacity. However, in patients with chronic diseases, it can be difficult to reach a maximal effort due to patient motivation, pain, and the tester's ability to push against exhaustion; therefore, a submaximal test can be recommended (Hurkmans et al., 2011). The main limitation of this study was the exclusion of patients with functional limitations, with cardiopulmonary or neurological disease or patients treated with beta-blockers. This might have led to selection bias, because we may not have tested the patients with the lowest aerobic capacity. The cross-sectional design also limited us from drawing conclusions regarding causality between the variables.

6 | CONCLUSIONS AND CLINICAL IMPLICATIONS

Consistent associations between aerobic capacity, disease activity, and several important risk factors for CVD were evident in this report. Measurements related to disease activity and risk factors for CVD were favourable for the group of patients with aerobic capacity that was above the median value, a clinically important application. These findings suggest that aerobic capacity may be a useful indicator for CVD risk in early RA, and assessment of this variable is encouraged in clinical practice as it may improve screening for CVD risk. Altogether, these results extend current evidence of the relationship between aerobic capacity and important risk factors for CVD in populations with chronic diseases and in general populations. Longitudinal studies are warranted to investigate if long-term changes in aerobic capacity is associated with mortality risk in patients with RA.

ETHICS APPROVAL

All the included patients provided their informed consent, after they were given verbal and written information about the study, in accordance with the tenets of the Declaration of Helsinki. The study was approved by the Ethics Committee at Umeå University (Dnr 2014/356-31).

AVAILABILITY OF DATA AND MATERIALS

The dataset used and analysed in the current study is available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

Lars Ångström, Solveig Wållberg Jonsson, and Anna Södergren participated in the conception and design of the study. Lars Ångström and Kristina Hörnberg collected the data and coordinated with the project administration. Lars Ångström, Björn Sundström, and Anna Södergren did the interpretation of data. Kristina Hörnberg, Björn Sundström, Solveig Wållberg Jonsson, and Anna Södergren critically revised the manuscript for important intellectual content. Lars Ångström wrote the manuscript. All authors, where possible, read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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