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Sex-specific associations of cardiorespiratory fitness and galectin-3 in the general population

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Abstract

Aims Low cardiorespiratory fitness (CRF) is associated with greater mortality and morbidity. Galectin-3 (Gal-3) is a prognostic biomarker for fibrosis and heart failure. Gal-3 is also associated with a greater risk for cardiovascular mortality. Whether CRF is related with Gal-3 is unclear. The objective of this study was to assess the sex-specific associations of CRF and Gal-3 levels in the general population.

Methods Gal-3 concentrations were determined using a sandwich enzyme immunoassay in the population-based Study of Health in Pomerania (SHIP-TREND-0). Sex-stratified linear regression models adjusted for age, current smoking status, and renal function were used. Individuals with left ventricular ejection fraction (LVEF) <40%, previous myocardial infarction, atrial fibrillation, chronic lung disease, severe renal disease (estimated glomerular filtration rate <30 mL/min/mm^2), a history of cancer, and extreme values for Gal-3 (<1st percentile; >99th percentile) were excluded.

Results A total of n = 1515 participants with a median age of 49 (IQR: 39–60 years, 48% males) were included. In men, a 1 L/min greater VO$_2$peak was significantly related to 0.50 ng/mL (95% CI −0.8068 to −0.1938, $P < 0.01$) less Gal-3. In males, a 1 mL/min/kg higher VO$_2$peak adjusted for body weight was associated with −0.0286 ng/mL (95% CI −0.0052 to −0.0005, P = 0.02) less Gal-3. When VO$_2$peak was adjusted for lean mass 1 mL/kg/min more was correlated with a −0.0022 ng/mL (95% CI −0.0043 to -0.0007, P = 0.04) less Gal-3. In women, VO$_2$peak (β −0.2046 95% CI −0.6541 to 0.2449, P = 0.37) and VO$_2$peak adjusted for lean mass (β −0.0019 95% CI −0.0421 to −0.0050, P = 0.12) were not related with Gal-3, whereas a 1 mL/min/kg higher VO$_2$peak adjusted for body weight was significantly associated with a −0.0064 ng/mL lower Gal-3 (95% CI −0.0092 to -0.0035, $P < 0.01$). There were no differences between pre-menopausal and post-menopausal women.

Conclusions VO$_2$peak was associated with Gal-3 only in men, but VO$_2$peak adjusted for body weight in women and men. Our results suggest that the adverse consequences of low CRF may be mediated by Gal-3. Further research is needed to understand the sex-specific association between CRF and Gal-3 and whether they are clinically relevant.

Introduction

Cardiovascular diseases are considered the most common cause of death worldwide.[1,2] Low levels of cardiorespiratory fitness (CRF) are related to a greater risk for cardiovascular diseases, mortality, and morbidity.[3,4] Further, a reduced CRF is a strong predictor of cardiovascular diseases and all-cause mortality.[5]

Galectin-3 (Gal-3) is a member of the lectin family containing a carbohydrate-recognition-binding domain. This domain enables the specific binding of ß-galactosides to regulate the activity of glycoproteins. Through this, Gal-3 exerts pleiotropic responses.[6] Gal-3 is secreted by macrophages into the extracellular space where an interaction with cell surface receptors takes place. This induces transmembrane signalling pathways.[7] Gal-3 influences cell proliferation, cell adhesion

and migration, apoptosis, angiogenesis, and especially organ specific and systemic fibrosis.[8] Recent research explores the role of Gal-3 as a prognostic biomarker for organ fibrosis and heart failure.[9] Higher Gal-3 levels are also associated with increased cardiovascular mortality.[10–12] More specifically with regard to heart failure, higher circulating Gal-3 levels were associated with greater mortality in acute and[13] compensated heart failure.[14] Therefore, Gal-3 may serve as an early biomarker for various diseases allowing for earlier prevention measures. The therapeutic use of Gal-3 inhibitors previously demonstrated potential for prevention of cardiovascular diseases.[15–17] Gal-3 inhibitors prevent cardiac remodelling by interfering with myocardial fibrogenesis attenuating myocardial fibrosis, left ventricular dysfunction, and potentially heart failure.[18] Interestingly, potentially sex-specific effects of Gal-3 have been suggested due to greater adipose tissue in women. In the general population, therefore, Gal-3 levels are higher in women compared with men. Albeit, this is not true in patients with heart failure.[19] If sex modifies the association of Gal-3 and cardiovascular endpoints is yet to be determined.

Whether low CRF is related with Gal-3 is unclear. The objective of this study was to explore the association of CRF with Gal-3 in a large sample from the population-based Study of Health in Pomerania (SHIP-TREND-0). Parameters for CRF were peak oxygen uptake (VO_2peak), VO_2peak per kg body weight (VO_2peak/kg), and VO_2peak per kg lean mass ($VO_2peak/lean\ mass$).

Methods

Study design and participants

We used data of the population-based Study of Health in Pomerania (SHIP-TREND-0) from Northeast Germany. Recruitment strategy and study design have been reported elsewhere.[20] Briefly, SHIP-TREND-0 was carried out between 2008 and 2012. A stratified random sample of 8826 individuals aged 20–79 years was drawn from population registries. A total of 4420 individuals participated in the baseline examination. The study was approved by the ethics committee of the University of Greifswald and complies with the Declaration of Helsinki. All study participants provided informed written consent prior to participation.

Initially all subjects who chose to participate in cardiopulmonary exercise testing (CPET) were included. Individuals with left ventricular ejection fraction (LVEF) <40% (n = 18), previous myocardial infarction (n = 31), atrial fibrillation (n = 86), chronic lung disease (n = 183), severe renal disease (estimated glomerular filtration rate [eGFR] < 30 mL/min/mm^2) (n = 36), a history of cancer (n = 111), and extreme values for Gal-3 (<1st percentile; >99th percentile) (n = 21) were excluded (*Figure 1*).

Figure 1 Flow chart of the analysis sample.
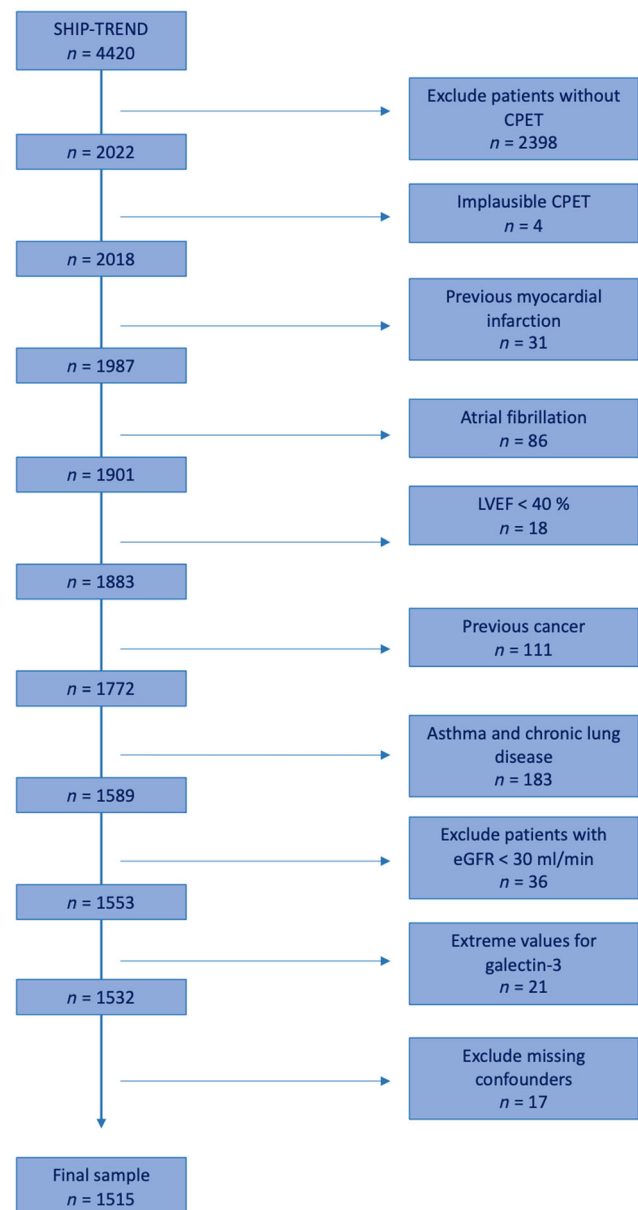
Interview and medical and laboratory examination

Data on age, sex, and medical histories were obtained by standardized computer-assisted personal interviews. All participants underwent an extensive standardized medical examination. Anthropometric measurements included height and weight based on recommendations of the World Health Organization (WHO). Body mass index (BMI) was calculated by dividing weight (kg) by height (m) to the square. A non-fasting venous blood sample was drawn from all subjects

in supine position (between 7 a.m. and 1 p.m.). Samples were stored at −80°C in the Integrated Research Biobank (Liconic, Liechtenstein) of the University Medicine of Greifswald[21] and were used in accordance with its regulations. Plasma Gal-3 concentrations were determined using a quantitative sandwich enzyme immunoassay (R&D Systems, Abingdon, UK). The estimated glomerular filtration rate (eGFR) was calculated according to Levey *et al*. [eGFR = 186 × (plasma creatinine concentration × $0.0113118)^{-1.154}$ × $age^{-0.203}$] multiplied by 0.742 for female subjects and expressed as mL/min/1.73 m^2.[22] Menopause status was assessed with a questionnaire regarding absence of menorrhoea. Diabetes mellitus was defined as a glycosylated haemoglobin A1c level >6.5%, anti-diabetic medication [anatomic, therapeutic, and chemical (ATC) code: A10] or as self-reported based on the question of whether a physician had ever diagnosed diabetes mellitus. Systolic and diastolic blood pressures were assessed after a resting period of 5 min in a sitting position on the right arm. With 3-min rest in between, the blood pressure measurements were taken three times. The average of the second and third measurements is reported. Trained and certified staff used a digital blood pressure monitor (HEM-750CP, Omron Corporation, Tokyo, Japan). Hypertensive patients were identified by either self-reported antihypertensive medication (ATC: C02, C03, C07, C08, and C09) or a systolic blood pressure above 140 mmHg or a diastolic value of more than 90 mmHg. Two-dimensional, M-Mode echocardiography was performed using the Vivid-I system (GE Medical Systems, Waukesha, WI, USA) as described in detail elsewhere.[20] Measurement of the LVEF was performed according to the guidelines of the American Society of Echocardiography.[23]

Exercise testing

CRF parameters were measured using standardized CPET on a bicycle ergometer (Ergoselect 100, Ergoline, Bitz, Germany) according to a modified Jones protocol.[24,25] In short, 3 min of rest was followed by 1 min of unloaded cycling (20 W) at 60 rpm. Afterwards, the workload was increased in steps of 16 W every minute. Prior to the test, subjects were encouraged to reach maximal exhaustion, whereas no encouragement was provided during exercise. Exercise testing was terminated by the subject due to exhaustion or by the attending physician due to ECG abnormalities.

Gas exchange variables

During CPET, breath-by-breath gas exchanges were measured by using an Oxycon Pro with a Rudolf's mask (JÄGER/VIASYS Healthcare System, Hoechberg, Germany). The following parameters were assessed: tidal volume (VE), oxygen uptake (VO_2), and carbon dioxide uptake (VCO_2). Furthermore, CPET is coupled continuously with pulse oximetry, blood pressure, and electrocardiogram. The VO_2peak was defined as the highest 10 s average of VO_2 during late exercise or early recovery.

Statistics

Age-specific VO_2peak quartiles are used to describe the male and female study population, respectively. For the age-specific quartiles, we stratified the study population by 10-year age strata and calculated the quartiles for each stratum. Continuous data are presented as median (25th quartile; 75th quartile). Nominal data are given as percentages. The response variable was CRF, whereas the outcome was Gal-3. Sex-specific linear regression models were used to relate CRF parameters and serum Gal-3. All models were adjusted for age, current smoking, and eGFR (*Figure 2*). The normality and homoscedasticity of residuals were assessed using histograms, kernel density plots, Q-Q plots, and residuals-vs.-fitted plots. Potential non-linear associations were tested with restricted cubic splines.[27] To assess whether the observed sex differences were related to menopause status, a sensitivity analysis that stratified female study participants

Figure 2 Directed acyclic graph for the potential association between cardio-respiratory fitness and galectin-3. BMI, body mass index; CRF, cardio-respiratory fitness; eGFR, estimated glomerular filtration rate; Gal-3, galectin 3; LVEF, left ventricular ejection fraction.[26]
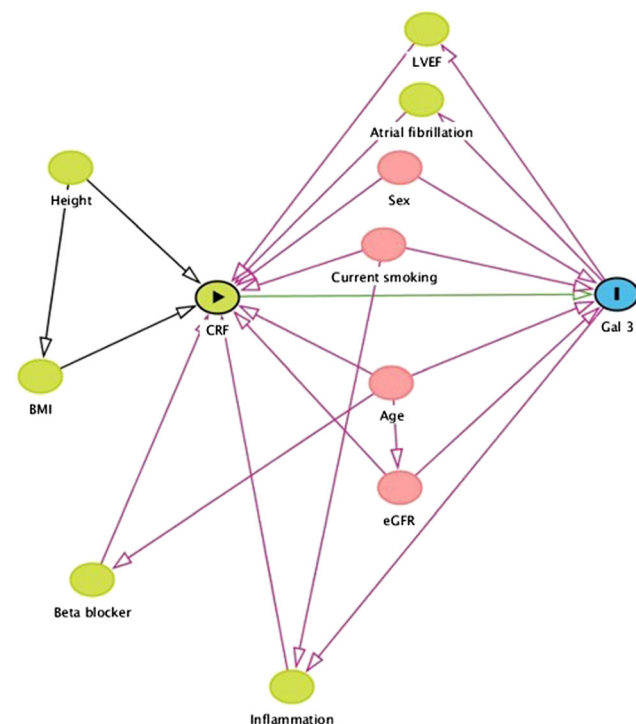
based on their menopause status was performed. All the calculations were done in SAS 9.4 (SAS Institute, Cary, NC, USA). Statistical significance was defined as $P < 0.05$.

Results

General characteristics

A total of 1515 participants with a median age of 49 (IQR: 39–59 years, male 48%) were included in the analysis. The population description according to VO_2peak sex-specific and age-specific quartiles for men and women are presented in *Tables 1* and *2*, respectively. Study participants with low VO_2peak showed significantly greater levels of physical inactivity, had a greater BMI, and smoked more often independent of sex. In addition, higher VO_2peak was also related to more lean mass. Differences in VO_2peak were not related to hypertension, eGFR, or metabolic syndrome. In men, VO_2peak was not correlated to fat mass, whereas higher VO_2peak levels were associated with greater fat mass in women. Furthermore, plasma Gal-3 levels in women were generally higher than in men.

The association between CRF and Gal-3

The results of the linear regression analysis are shown in *Table 3*. In men, VO_2peak was inversely associated with Gal-3. Specifically, a 1 L/min greater VO_2peak was significantly related to 0.50 ng/mL (95% CI -0.8068 to -0.1938, $P < 0.01$) less Gal-3. Similarly, a 1 mL/min/kg higher VO_2peak adjusted for body weight in males was associated to −0.0286 ng/mL (95% CI −0.0052 to −0.0005, $P = 0.02$) less Gal-3. When VO_2peak was adjusted for lean mass one ml/kg/min more was correlated with a −0.0022 ng/mL (95% CI −0.0043 to -0.0007, $P = 0.04$) lower Gal-3. With regard to workload, a 1 W greater resistance was associated with −0.0078 ng/mL (95% CI −0.1174 to −0.0038, $P < 0.01$) less Gal-3. When workload was adjusted for body weight, a 1 W per kg greater was related with 0.3983 ng/mL (95% CI -0.6920 to −0.1046, $P < 0.01$) less Gal-3.

We found no significant association of VO_2peak (β −0.2046 95% CI −0.6541 to 0.2449, $P = 0.37$) and VO_2peak adjusted for lean mass (β −0.0019 95% CI −0.0421 to 0.0050, $P = 0.12$) with Gal-3 in women. Contrary, a 1 mL/min/kg higher VO_2peak adjusted for body weight was significantly inversely associated with a −0.0064 ng/mL lower Gal-3 (95% CI −0.0092 to −0.0035, $P < 0.01$). With respect to the maximum power output a 1 W higher resistance was associated with a −0.0049 ng/mL less Gal-3 (95% CI −0.0011 to 0.0007, $P = 0.09$). But when normalized for body weight, a 1 W higher resistance adjusted for body weight was

related to a 0.8718 ng/mL (95% CI −1.2145 to −0.5292, $P < 0.01$).

Effect of menopause on the association between CRF and Gal-3

The results of the linear regression analysis for the association between CRF and Gal-3 in women stratified by menopause status are presented in *Table 4*. Overall, 367 women were pre-menopause and 421 were post-menopause. In pre-menopausal women, a 1 L for minute higher VO_2peak was not related to Gal-3 (β 0.3737 95% CI −0.5205 to 0.5950, $P = 0.90$). When VO_2peak was adjusted for body weight a 1 mL/min/kg higher CRF was related to a −0.0640 ng/mL lower Gal-3 (95% CI −0.0099 to −0.0293, $P < 0.01$). Adjusted of VO_2peak for lean mass in pre-menopausal women resulted in a non-significant relationship between CRF and Gal-3 (β −0.0194 95% CI −0.0049 to 0.0103, $P = 0.20$). In these women, maximal workload was also not related to Gal-3 (β −0.0021 95% CI −0.0095 to 0.0053, $P = 0.58$), whereas adjusted workload for body weight was significantly associated with a −0.9412 ng/mL lower Gal-3 (95% CI −1.3733 to −0.5090, $P < 0.01$).

In post-menopausal women VO_2peak was not associated with Gal-3 (β −0.2095 95% CI −0.9331–0.5140, $P = 0.57$). A 1 mL/kg/min higher VO_2peak adjusted for body weight was related to a −0.0460 ng/mL lower Gal-3 (95% CI −0.0927 to 0.009, $P = 0.05$). Adjustment for lean mass nullified this association (β −0.0054 95% CI −0.0420 to 0.0313, $P = 0.77$). Maximal workload was not related to Gal-3 (β −0.0036 95% CI −0.0012 to 0.0050, $P = 0.41$). A 1 W/kg higher workload corrected for body weight was significantly associated with a −0.5748 ng/mL (95% CI −1.1125 to −0.0372, $P = 0.04$) less Gal-3.

Discussion

Several studies have demonstrated a significant association of Gal-3 and cardiovascular risk factors. However, very few studies have assessed the relationship between CRF and Gal-3. Most studies concentrated on subjects with overt diseases like heart failure.[8–12] Other studies included patients with pulmonary,[16,28,29] kidney,[15] or liver fibrosis[14] as well as with an increased risk for chronic kidney diseases.[15] In contrast, we used data from a community-based cohort and excluded subjects with several manifest diseases to assess the relationship between CRF and Gal-3. After adjustment for body weight and other confounding factors, we found an inverse association between CRF and Gal-3 in men and women. We also report that the observed associations in women are independent of menopause status. Interestingly, a previous

Table 1 Population descriptions according to age-specific and sex-specific VO$_2$peak quartiles for males

| | | VO$_2$ peak quartiles | | | |
		I 1687–2200	II 2100–2633	III 2363–2968	IV 2813–3447	P for trend
	mL/min					
n		178	177	188	184	
Age (years)		49 (39; 59)	48 (39;59)	50 (40;60)	49 (39; 59)	0.91
Galectin-3 (ng/mL)		7.31 (5.37; 9.07)	7.02 (5.60: 8.49)	7.02 (5.66;8.30)	6.63 (5.32; 7.96)	0.12
Height (cm)		175 (170; 180)	176 (172; 180)	177 (174; 181)	180 (175; 184)	<.01
Weight (kg)		81.9 (75.1; 91.5)	82.4 (76.9; 92.7)	86.8 (79.8; 95.6)	88.9 (81.6; 98.6)	<.01
Waist circumference (cm)		93.0 (86.2; 102.3)	93.0 (85.6; 99.4)	94.1 (87.0; 104.0)	94.0 (86.6; 101.5)	0.59
Hip circumference (cm)		99.5 (95.5; 103.9)	99.5 (94.5; 104.0)	100.8 (96.6; 106.2)	101.1 (97.3; 107.8)	<.01
Risk factors	eGFR (mL/min/1.72 mm^2)	89.5 (88.7; 110.7)	99.4 (91.0; 109.2)	98.9 (91.1; 106.3)	97.6 (88.9; 108.4)	0.64
	Hypertension (%)	47.46	52.54	49.20	40.76	0.15
	Diabetes (%)	8.99	7.91	7.98	5.98	0.75
	Metabolic syndrome (%)	35.84	26.86	32.80	22.95	0.03
	Physical inactivity (%)	44.38	24.86	26.06	16.30	<.01
	BMI (kg/m^2)	27.0 (24.5; 29.5)	27.1 (24.8; 29.4)	27.7 (25.5; 30.7)	27.8 (25.3; 30.4)	0.04
	HbA1c (%)	5.3 (4.9; 5.7)	5.3 (5.0; 5.6)	5.3 (5.0; 5.5)	5.2 (4.9; 5.6)	0.30
Smoking status	Non-smoker (%)	21.91	28.81	29.79	44.57	<.01
	Ex-smoker (%)	36.52	46.33	49.47	46.20	<.01
	Smoker (%)	41.57	24.86	20.74	9.24	<.01
BIA	Fat mass (kg)	19.2 (15.2; 23.8)	19.3 (15.6; 24.4)	20.8 (15.5; 25.4)	19.7 (15.6; 24.8)	0.42
	Lean mass (kg)	63.3 (58.2; 68.4)	64.3 (59.7; 70.6)	67.4 (63.0; 72.5)	69.5 (64.8; 74.7)	<.01
CPET	Watt max	164 (132; 180)	196 (164; 228)	212 (180; 244)	244 (212; 276)	<.01
	HR max	154 (137; 171)	166 (150; 181)	166 (147; 179)	171 (162; 181)	<.01
	VO$_2$@AT (mL/min)	900 (850; 1,000)	1,100 (1,000; 1,250)	1,200 (1,100; 1,350)	1,400 (1,300; 1,550)	<.01
	VE/CO$_2$	35 (31; 40)	35 (31; 38)	35 (31; 38)	35 (31; 38)	0.28
	VE/CO2@AT	27 (25; 30)	26 (24; 28)	25 (24; 28)	25 (23; 27)	<.01
	VE/CO$_2$ max	30 (27; 33)	30 (27; 29)	30 (26; 32)	30 (27;33)	0.32
	VE/CO$_2$ slope	28 (25; 30)	27 (24; 29)	26 (24; 29)	26 (24;28)	<.01

BIA, body impedance analysis; BMI, body mass index; eGFR, estimated glomerular filtration rate; HR max, maximal heart rate; VO$_2$@AT, maximal oxygen consumption at the anaerobic threshold.
Values presented as median (25th and 75th percentile) for continuous variables. For categorical variables, percentage is provided.

Table 2 Population descriptions according to age-specific and sex-specific VO$_2$peak quartiles for females

		VO$_2$ peak quartiles				
	mL/min	I 1104–1373	II 1390–1650	III 1559–1878	IV 1882–2200	P for trend
n		195	194	198	201	
Age (years)		49 (39; 60)	48 (39; 59)	49 (39; 60)	49 (39; 60)	0.98
Galectin-3 (ng/mL)		7.34 (6.01; 9.32)	7.33 (5.86; 8.83)	7.78 (6.14; 9.05)	7.50 (6.24; 9.15)	0.52
Height (cm)		163 (158; 167)	164 (159; 168)	165 (161; 169)	167 (163; 171)	<.01
Weight (kg)		64.8 (57.4; 73.6)	68.5 (62.3; 75.2)	73.0 (63.6; 80.7)	74.7 (66.4; 83.0)	<.01
Waist circumference (cm)		78.5 (71.7; 87.5)	79.5 (72.5; 87.7)	81.6 (75.0; 91)	82.8 (75.1; 92.0)	<.01
Hip circumference (cm)		96.0 (90.8; 104.4)	98.0 (93.5; 106.5)	101.5 (94.0; 108.0)	101.5 (94.0; 108.0)	<.01
Risk factors	eGFR (mL/min/1.72 mm^2)	98.5 (89.1; 108:5)	99.1 (87.0; 109.1)	97.4 (86.4; 106.4)	97.3 (84.9; 107.4)	0.42
	Hypertension (%)	33.33	29.53	33.84	30.35	0.74
	Diabetes (%)	4.62	7.22	8.08	2.99	0.11
	Metabolic syndrome (%)	15.38	15.71	16.92	11.50	0.46
	Physical inactivity (%)	40.51	26.29	24.75	12.94	<.01
	BMI (kg/m^2)	24.3 (21.8; 27.8)	25.7 (23.1; 28.1)	26.4 (23.4; 30.1)	26.9 (24.0; 30.6)	<.01
	HbA1c (%)	5.1 (4.8; 5.4)	5.1 (4.8; 5.4)	5.2 (4.8; 5.6)	5.2 (4.8; 5.5)	0.28
Smoking status	Non-smoker (%)	40.00	48.45	47.98	48.26	0.06
	Ex-smoker (%)	28.72	30.93	32.83	32.84	0.06
	Smoker (%)	31.28	20.62	19.19	18.91	0.06
BIA	Fat mass (kg)	20.7 (15.4; 26.6)	22.7 (17.6; 27.1)	24.9 (18.3; 31.4)	25.8 (19.7; 31.4)	<.01
	Lean mass (kg)	44.1 (41.0; 47.7)	46.5 (43.6; 48.5)	47.2 (44.5; 51.5)	49.3 (46.5; 52.6)	<.01
CPET	Watt max	116 (84; 116)	132 (116; 132)	148 (116; 148)	164 (148; 180)	<.01
	HR max	155 (133; 169)	160 (142; 173)	164 (146; 173)	164 (151; 176)	<.01
	VO2@AT (mL/min)	700 (650; 800)	800 (750; 900)	900 (800; 950)	1,050 (900; 1,200)	<.01
	VE/CO$_2$	35 (31; 38)	35 (32; 40)	35 (31; 37)	35 (31;38)	0.18
	VE/CO2@AT	28 (25; 30)	27 (24; 29)	26 (25; 28)	26 (24;28)	<.01
	VE/CO$_2$ max	30 (27;33)	29 (26; 33)	29 (26; 32)	29 (26; 31)	0.02
	VE/CO$_2$ slope	28 (25; 30)	27 (25; 29)	27 (24; 28)	26 (24;28)	<.01

BIA, body impedance analysis; BMI, body mass index; eGFR, estimated glomerular filtration rate; HR max, maximal heart rate; VO$_2$@AT, maximal oxygen consumption at the anaerobic threshold.

Values presented as median (25th and 75th percentile) for continuous variables. For categorical variables, percentage is provided.

Table 3 Association of cardiorespiratory fitness with Galectin-3 levels for males and females

	Men			Women		
	Estimate	95% CI	P value	Estimate	95% CI	P value
VO$_2$peak (L/min)	−0.5003	−0.8068; −0.1938	<.01	−0.2046	−0.6541; 0.2449	0.37
VO$_2$peak/kg (mL/min/kg)	−0.0286	−0.0052; −0.0005	0.02	−0.0064	−0.0092; −0.0035	<.01
VO$_2$peak/lean mass (mL/min/kg)	−0.0022	−0.0043; −0.0007	0.04	−0.0019	−0.0421; 0.0050	0.12
Watt max (W)	−0.0078	−0.1174; −0.0038	<.01	−0.0049	−0.0011; 0.0007	0.09
Watt max/kg (W/kg)	−0.3983	−0.6920; −0.1046	<.01	−0.8718	−1.2145; −0.5292	<.01

Table 4 Association of cardiorespiratory fitness with Galectin-3 levels for pre-menopausal and post-menopausal women

	Pre-menopause			Post-menopause		
	Estimate	95% CI	P value	Estimate	95% CI	P value
VO$_2$peak (L/min)	0.3737	−0.5202; 0.5950	0.90	−0.2095	−0.9331; 0.5140	0.57
VO$_2$peak/kg (mL/min/kg)	−0.0640	−0.0099; −0.0293	<.01	−0.0460	−0.0927; 0.0009	0.05
VO$_2$peak/lean mass (mL/min/kg)	−0.0194	−0.0049; 0.0103	0.20	−0.0054	−0.0420; 0.0313	0.77
Watt max (W)	−0.0021	−0.0095; 0.0053	0.58	−0.0036	−0.0012; 0.0050	0.41
Watt max/kg (W/kg)	−0.9412	−1.3733; −0.5090	<.01	−0.5748	−1.1125; −0.0372	0.04

randomized controlled clinical trial in post-menopausal women showed that high-intensity interval training significantly reduced whole blood Gal-3 gene expression compared with moderate continuous exercise training.[30] However, in both exercise groups, Gal-3 decreased compared with baseline, whereas Gal-3 increased in the control group. Hence, lower Gal-3 concentrations due to exercise training could be a potential mechanism for the anti-fibrotic effects of exercise. In the baseline characteristics of the HF-Action trial, lower CRF was related to higher Gal-3.[31] In addition to the previously mentioned positive effects of exercise training, the findings of the HF-Action trial could highlight an additional mechanism for the adverse fibrotic effects of low CRF potentially mediated by Gal-3. Unfortunately, whether exercise induced changes in VO$_2$peak are related to Gal-3 has not been reported for the HF-Action trial. In endurance athletes, which usually have a higher CRF compared with the general population, Gal-3 levels are within normal range but higher than in healthy sedentary control subjects.[32] This agrees with the notion that long-term high-level exercise training can increase the risk for cardiac fibrosis. In patients with chronic heart failure, exercise training increased CRF, but this increase was not associated with changes in Gal-3.[33] The authors even concluded that the inconsistent independent associations between CRF and Gal-3 limit the incremental utility for patient monitoring. Overall, our results and previous reports potentially support the notion of Gal-3 as a biomarker for CRF. However, this relationship may be influenced by sex, training, and disease status.

The sex-specific associations between CRF and Gal-3 are especially intriguing. A previous study also reported sex-related differences in associations of Gal-3 with incident heart failure.[34] The analysis used data from four community-based longitudinal cohorts with 22 756 participants. Plasma concentrations of Gal-3 were more strongly associated with heart failure in women than in men. Another study investigated the relationship between the severity of sleep apnoea and plasma levels of Gal-3, because sleep apnoea is associated with increased risk for cardiovascular diseases.[35] The cohort of the cross-sectional study included 471 Mexican-Americans. They found significantly higher Gal-3 levels in women with moderate to severe sleep apnoea, but not in men. We show that CRF, independent of parameter, is inversely associated with Gal-3 in men, whereas in women only adjustment for body weight revealed significantly inverse associations between CRF and Gal-3. Hence, our results further support that Gal-3 is potentially a sex-specific marker with regard to cardiovascular risk factors like CRF and sleep apnoea. A specific biological mechanism underlying our observations is unclear. There are several differences between women and men that may influence the identified associations like body composition, fat distribution, muscle composition, or sex hormones.[36] Further, we found that Gal-3 levels in women are generally higher than in men. Although one may suggest that sex hormones could play a role in the sex-specific associations of Gal-3 and cardiovascular outcomes, we found no evidence for differences between pre-menopausal and post-menopausal women. Overall, the sex-specific associations between cardiovascular risk and Gal-3 identified by others[34] and ourselves should be further explored in the future.

As mentioned above, Gal-3 is generally considered a marker for organ-specific as well as systemic fibrosis. More recent evidence suggests that sex-specific differences with regard to systemic and organ-specific fibrosis are present.[37] There is rather strong evidence that the underlying biology

for this observation is driven by sex hormones. Although we also found sex-specific associations between CRF and the fibrosis marker Gal-3, we found no evidence that this observation was due to menopause status because we found no differences between pre-menopausal and post-menopausal women. Exercise is well known to increase CRF and thereby improve cardiac health. The mechanisms underlying these observational findings have been supported by animal models.[38] However, a large drawback is that most research was carried out in male animals. Hence, future research should employ more female animals to improve our understanding of the potentially sex-related importance of Gal-3.

The strengths of our study design are the large sample size (n = 1515) and the population-based design. This may allow drawing inference for the general population from our results. In addition, we employed a highly standardized quality control during the course of the study. However, the results of this study need to be interpreted in the context of some limitations. Based on the cross-sectional analysis of observational data, we cannot conclusively determine the direction of the investigated association. Another limitation is that the results are not directly applicable to other ethnicities, because SHIP consists mainly of Caucasians. Finally, we cannot exclude possible additional residual confounding that could influence the results.

In conclusion, we report that CRF is inversely associated with Gal-3 in a sample from the general population, excluding several manifest diseases. In men, absolute values of VO$_2$peak were inversely related to Gal-3, although body weight normalized VO$_2$peak was inversely associated with Gal-3 independent of sex. Our findings may be of interest for preventive cardiology. Specifically, exercise training is well known to improve VO$_2$peak as well as reduce fibrosis.[38] Our results suggest that lower Gal-3 concentrations could be a potential mechanism underlying this observation.

Further research is required to confirm and fully understand potential sex-specific associations and their underlying mechanisms between CRF and Gal-3. Overall, our results suggest that Gal-3 deserves further examination as a potentially sex-specific cardiovascular risk factor.

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Conflict of interest

None declared.

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