


# Vitamin D levels correlate with exercise capacity in adults with CHD

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## Original Article

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### Abstract

**Introduction:** Vitamin D is crucial for normal organ function, vascular health and exercise performance, yet its deficiency is widespread. Patients with CHD often exhibit reduced exercise capacity. Limited research exists on vitamin D in CHD. **Methods:** This study investigates serum 25-hydroxy vitamin D levels in 55 adult CHD patients (median age 31 years) compared to 55 age- and gender-matched controls without cardiac disease and examines associations with exercise capacity, peripheral microvascular function, muscle strength and biventricular function in CHD. Therefore, patients underwent fingertip arterial tonometry, transthoracic echocardiography, muscle strength measurements and cardiopulmonary exercise testing. **Results:** Results indicated that 93% of CHD patients and 91% of controls had 25-hydroxy vitamin D levels <30 ng/ml, with both groups showing varying values depending on the season in which the studies were conducted. No significant difference in 25-hydroxy vitamin D levels was found between patients and controls. While vitamin D levels in CHD patients did not significantly correlate with age, body mass index, blood pressure, peripheral microvascular function, high-sensitivity C-reactive protein, cholesterol levels, N-terminal-pro hormone B-type natriuretic peptide, ventricular function or muscle strength, a significant correlation was found with percent-predicted peak oxygen consumption ( $\rho=0.41$ ,  $p=0.005$  and  $\rho=0.34$ ,  $p=0.02$  for reference values following Wasserman and the LowLands registry, respectively), even after adjusting for season ( $p=0.03$  and  $0.05$ , respectively). **Conclusions:** In conclusion, vitamin D levels were similar between CHD patients and controls, but vitamin D insufficiency is common and linked to reduced exercise capacity in CHD. Further research is needed to determine whether vitamin D supplementation combined with exercise could be beneficial in CHD with vitamin D insufficiency.

### Introduction

CHDs encompass a broad spectrum of cardiac malformations.<sup>1</sup> While medical and surgical advancements have greatly improved survival rates,<sup>2,3</sup> CHD patients still face challenges such as lower physical fitness,<sup>3–5</sup> reduced quality of life<sup>6</sup> and a worse prognosis<sup>7–9</sup> compared to their healthy counterparts. Heart failure remains a primary concern for morbidity and mortality in this population.<sup>10,11</sup> Achieving advancements in therapeutic modalities and preventive strategies necessitates a better comprehension of the underlying pathophysiological mechanisms.<sup>12</sup>

25-hydroxy vitamin D deficiency is a prevalent condition.<sup>13</sup> Vitamin D is a fat-soluble vitamin<sup>14</sup> and is synthesised in the skin from 7-dehydro-cholesterol following exposure to ultraviolet radiation (cholecalciferol or D3). Only a small percentage is exogenous originating from food (ergocalciferol, D2).<sup>15</sup> Vitamin D is crucial not only for bone health, calcium homeostasis and skeletal mineralisation, but also has immune-modulatory properties<sup>14,16</sup> and plays a significant role in cardiovascular health.<sup>15–17</sup> The activated form of vitamin D, i.e., 1,25(OH)<sub>2</sub> vitamin D, is essential for maintaining cardiovascular function and is involved in the structural remodelling of cardiac muscle and vascular tissue.<sup>16–18</sup> An insufficiency in vitamin D has been associated with increased arterial stiffness and endothelial dysfunction.<sup>15</sup> Furthermore, studies have demonstrated that vitamin D significantly influences skeletal muscle physiology.<sup>15</sup> It is critical for sustaining effective performance in everyday tasks, and a lack of vitamin D can potentially impair exercise capacity.<sup>15</sup> While it is well known that exercise capacity is reduced in patients with CHD,<sup>4</sup> literature on vitamin D in patients with CHD is limited. A few studies report lower serum vitamin D levels in children with CHD.<sup>14,19</sup> Moreover, vitamin D levels seem to decrease with age.<sup>19,20</sup> In Fontan patients, vitamin D deficiency is associated with skeletal muscle deficits.<sup>21</sup> However, the relationship between vitamin D levels on the one hand and exercise capacity and peripheral microvascular function on the other in CHD has never been investigated before.

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Therefore, the aim of this study was to evaluate serum 25-hydroxy vitamin D levels in adults with CHD compared to controls without cardiac disease and to investigate associations with peripheral microvascular function and exercise capacity. Additionally, a potential correlation with muscle strength and ventricular function was also investigated.

## Materials and method

### Study population

Fifty-five adult (age range 18–65 years) patients with CHD, NYHA class I–II, visiting the out-patient clinic at the Antwerp University Hospital, were prospectively enrolled between 2021 and 2023. Exclusion criteria were smoking, body mass index  $>35$  kg/m<sup>2</sup>, professional endurance athlete, presence of macrovascular coronary artery disease, diabetes mellitus or a systemic disease (e.g. malignancies, acute and chronic inflammatory diseases in the preceding 3 months). For each CHD patient, an age- and gender-matched control without cardiac disease was included. The same exclusion criteria were applied. The study was carried out according to the principles of the Declaration of Helsinki and the Research and Ethics committee of the Antwerp University Hospital approved the study protocol (Belgian number: B3002020000298). Written informed consent was obtained from all subjects.

### Study protocol

Both the CHD and control groups were tested in the morning following an overnight fasting period. Participants were instructed to refrain from consuming high-fat substances, caffeine or alcohol and to avoid engaging in strenuous physical activity for a period of 24 h prior to the examination. The patients underwent the following examinations consecutively: assessment of peripheral microvascular function, transthoracic Doppler echocardiography, blood sampling, cardiopulmonary exercise testing and muscle strength measurements. In the control group, only blood samples were taken.

### Assessment of peripheral microvascular function

Patients were examined in a quiet, temperature-controlled room (21–24°C). The examinations were carried out in a supine position. Blood pressure measurements were acquired utilising an automated blood pressure apparatus (Digital ProBPTM 2000, Welch Allyn) across all participants. Assessment of peripheral artery function at the microvascular level was exclusively conducted within the CHD patient cohort, employing the Endo-PAT2000® device (Itamar Medical, software version 3.2.4), as previously described.<sup>12</sup> Reactive hyperemia index and Framingham modified reactive hyperemia index<sup>22</sup> were computed utilising specialised software (Itamar Medical).

### Transthoracic Doppler echocardiography

A conventional two-dimensional transthoracic echocardiogram was performed on patients positioned in the left lateral decubitus posture, using an EPIQ7 ultrasound system (Philips Medical Systems, Best, the Netherlands). Assessment of left ventricular systolic function was accomplished through the evaluation of left ventricular ejection fraction (Simpson biplane) and left ventricular global longitudinal strain, combining data from the three left ventricular chamber views. Right ventricular function was assessed

by measuring right ventricular fractional area change, right ventricular tricuspid annular plane systolic excursion and right ventricular tissue Doppler imaging systolic velocity, all documented in the four-chamber view. The terminology “LV” and “RV” denotes the morphological left ventricle and right ventricle, respectively.

### Blood sampling

Fasting peripheral blood was collected using ethylenediaminetetraacetic acid and serum vacuette tubes (BD Vacutainer®, Canada). Ethylenediaminetetraacetic acid and serum samples were analysed, respectively, using a Sysmex XN-9100 (Sysmex, Germany) and Atellica® IM/CH Analyzer (Siemens Healthcare, Germany). 25-hydroxy vitamin D levels, white blood cell counts, high-sensitivity C-reactive protein, cholesterol levels, and N-terminal-pro hormone B-type natriuretic peptide concentrations were quantified.

### Cardiopulmonary exercise testing

A cardiopulmonary exercise test was performed in the CHD patient group using a continuously incrementing ramp protocol until maximal exhaustion, as previously described.<sup>12</sup> Peak oxygen consumption (pVO<sub>2</sub>) was determined as the mean VO<sub>2</sub> during the final 30 s of exercise. Subsequently, percent-predicted peak oxygen consumption (%ppVO<sub>2</sub>) was calculated (reference values following Wasserman *et al.*<sup>23</sup> and the LowLands registry<sup>24</sup>). Only cardiopulmonary exercise test values from patients who performed a maximal metabolic exercise test, defined as a respiratory exchange ratio  $\geq 1.10$ , were included in the analysis.

### Muscle strength measurements

The one-repetition maximum was measured on fitness machines (BioCircuit Series 4, TechnoGym®, Benelux<sup>25</sup>) for four different exercises (chest press, vertical traction, low row and leg press) targeting major muscle groups.

### Statistical analysis

Statistical analysis was performed using SPSS version 29.0 (IBM Corp. 2023, NY). Normality of continuous variables was evaluated using histograms, Q–Q plots and the Shapiro–Wilk test. Data are presented as mean  $\pm$  standard deviation or median (Q1–Q3) depending on the normality of the data. If the lab results showed a “less than” value (N-terminal-pro hormone B-type natriuretic peptide  $< 35$  or high-sensitivity C-reactive protein  $< 0.16$ ), this value was replaced with the respective number (respectively 35 and 0.16). Subsequently, this variable was considered as “non-normally distributed” for the entire study group. Groups were compared using the independent sample *t*-test for normally distributed data and the Mann–Whitney *U* test in case of non-normal distribution. Spearman correlation coefficient was used for univariable correlation analysis. In the patient group, correlations between 25-hydroxy vitamin D levels and %ppVO<sub>2</sub>, reactive hyperemia index and Framingham modified reactive hyperemia index were investigated as primary endpoints. In addition, correlations between 25-hydroxy vitamin D levels on the one hand and age, body mass index, blood pressure, inflammatory markers (high-sensitivity C-reactive protein and white blood cells), cholesterol levels, N-terminal-pro hormone B-type natriuretic peptide, echocardiographic parameters of ventricular function and muscle strength measurements on the other were also examined as secondary endpoints. A two-tailed  $p < 0.05$  was considered

significant. To correct for a seasonal effect in vitamin D levels, a linear regression model was constructed with %ppVO<sub>2</sub> as dependent variable, 25-hydroxy vitamin D level as independent variable and season as a confounding factor. Model assumptions were checked by means of residual plots. Seasons were defined as follows: Winter (21<sup>th</sup> of December–20<sup>th</sup> of March) versus non-Winter (21<sup>th</sup> of March–20<sup>th</sup> of December).

## Results

### Characteristics and between-group comparisons

Patients differed from controls without cardiac disease in systolic and diastolic blood pressure, white blood cells, N-terminal-pro hormone B-type natriuretic peptide levels and medical treatment (Table 1). The patient population consisted of a diverse group of adults with various types of CHD, with the specific cardiac defects at birth summarised in Table S1 of the supplementary material. Thirty patients (55%) had a history of surgical intervention for CHD, while eight patients (15%) received exclusively percutaneous treatment. The remaining 17 patients were managed clinically without prior cardiac interventions.

### Vitamin D levels in CHD and controls

Fifty-one of the 55 patients (93%) and 50 of the 55 controls (91%) had low 25-hydroxy vitamin D levels (< 30 ng/ml) (Figure 1a–b). Vitamin D deficiency (< 20 ng/ml) was present in 36 patients (66%) and in 34 controls (62%) and severe deficits (< 10 ng/ml) occurred in 4 patients (7%) and 5 controls (9%). There was no statistically significant difference in serum levels of 25-hydroxy vitamin D between the CHD patients and control group (Figure 1c). In both groups, varying 25-hydroxy vitamin D values were observed depending on the season in which the studies were conducted (Figure 2).

### Vitamin D levels and patient characteristics, inflammation and cholesterol levels

Vitamin D levels in blood of adults with CHD were not significantly correlated with age, body mass index or systolic and diastolic blood pressure values, which are indirect measures of arterial stiffness (Table 2). Furthermore, no significant correlations were observed with high-sensitivity C-reactive protein or cholesterol levels (Table 2). In contrast, there was a significant negative correlation between white blood cells and 25-hydroxy vitamin D levels (Table 2).

### Vitamin D levels and peripheral microvascular function

Reactive hyperemia index and Framingham modified reactive hyperemia index could not be obtained in one patient due to frequent ectopic beats. 25-hydroxy vitamin D levels did not exhibit significant correlations with reactive hyperemia index and Framingham modified reactive hyperemia index (Table 2).

### Vitamin D levels and ventricular function

Due to poor echogenicity, not all echocardiographic parameters were obtainable for every CHD patient. Reduced ventricular function, defined as left ventricular ejection fraction < 50% and right ventricular fractional area change < 35%, was present in 8 out of 52 (15%) and 11 out of 52 patients (21%), respectively. No significant correlations were found between 25-hydroxy vitamin D

levels and echocardiographic parameters of left ventricular or right ventricular function, nor with levels of N-terminal-pro hormone B-type natriuretic peptide (Table 2).

### Vitamin D levels and muscle strength

No muscle strength measurement correlated significantly with vitamin D levels (Table 2). Not all maximal strength measurements could be conducted in all patients due to medical restrictions (e.g., aortic dilatation) or injury limiting articular range of motion.

### Vitamin D levels and exercise capacity

Forty-six patients achieved a respiratory exchange ratio  $\geq 1.10$ . A diminished exercise capacity, defined as %ppVO<sub>2</sub> < 85%, was evident in 22 of 46 patients (48%) based on the predicted values from Wasserman et al.<sup>23</sup> (%ppVO<sub>2(Wasserman)</sub>). However, according to the LowLands values<sup>24</sup> (%ppVO<sub>2(LowLands)</sub>), 39 patients (85%) had a reduced exercise capacity. Exercise capacity correlated significantly with vitamin D levels in adults with CHD (Table 2). Even after adjusting for season as a confounding factor, the relationship between vitamin D levels and exercise capacity remained statistically significant ( $p = 0.03$  for %ppVO<sub>2(Wasserman)</sub>;  $p = 0.05$  for %ppVO<sub>2(LowLands)</sub>).

## Discussion

In this study, serum levels of 25-hydroxy vitamin D were investigated in adults with CHD and controls without cardiac disease. Low vitamin D levels (< 30 ng/ml) were found in 93% of the patients and 91% of the controls, with no significant difference between both groups. Moreover, exercise capacity correlated significantly with vitamin D levels in adults with CHD, even after adjustment for season.

### Prevalence of vitamin D deficiency and seasonal variations

Vitamin D deficiency is highly prevalent, with some considering it the most common medical condition worldwide.<sup>26</sup> Globally, 47.9% of the population has been reported to have serum 25-hydroxy vitamin D levels below 20 ng/ml.<sup>13</sup> In Western Europe, vitamin D deficiency affects 30–60% of individuals, with over 10% having severe deficiency,<sup>27</sup> which are values similar to those observed in our CHD patients and controls. Moreover, endogenous vitamin D production decreases drastically in winter due to reduced UVB radiation, whereas summer provides sufficient UVB exposure for synthesis.<sup>15</sup> This seasonal variation in vitamin D levels is a well-documented phenomenon. In our two study groups as well, varying 25-hydroxy vitamin D values were observed depending on the season in which the studies were conducted.

### Vitamin D in CHD

In contrast to our findings in adults with CHD, previous studies have demonstrated lower mean serum vitamin D levels in children with CHD compared to controls.<sup>14,19,28</sup> Potential causes of vitamin D deficiency in these patients may include increased metabolism with higher consumption of vitamins and disease-related sedentary lifestyle with reduced outdoor activities and longer hospital stays resulting in limited ultraviolet-induced vitamin D production in the skin.<sup>14</sup> Additionally, while children with CHD exhibited a decline in vitamin D with age,<sup>19,20</sup> our study in adult CHD patients revealed a borderline positive correlation between vitamin D levels and age.

**Table 1.** Characteristics, markers of inflammation, cholesterol levels, peripheral microvascular function, ventricular function, muscle strength and exercise capacity in CHD patients and controls

Variable	CHD patients (n = 55)	Controls (n = 55)	P-value
<b>Characteristics</b>			
Age (years)	31 (24–42)	31 (25–42)	0.96
Gender (male/female)	27/28	27/28	1.00
BMI (kg/m <sup>2</sup> )	24.72 ± 3.99	24.19 ± 3.81	0.48
Systolic blood pressure (mmHg)	115 (107–125)	121 (113–129) <sup>1</sup>	<b>0.02*</b>
Diastolic blood pressure (mmHg)	73 (70–77)	79 (70–85) <sup>1</sup>	<b>0.008**</b>
Medication			/
• Antiplatelet/Anticoagulant	14 (25%)	2 (4%)	
• ACE I/ARB	11 (20%)	2 (4%)	
• Beta blocker	15 (27%)	2 (4%)	
• Calcium channel blocker	3 (5%)	1 (2%)	
• Diuretics	1 (2%)	0 (0%)	
• Statin	1 (2%)	1 (2%)	
<b>Inflammation and cholesterol levels</b>			
WBC (x10 <sup>9</sup> /L)	6.48 (5.65–7.66) <sup>2</sup>	5.81 (4.52–6.46)	<b>0.02*</b>
hs-CRP (mg/L)	0.84 (0.43–2.00)	0.84 (0.32–1.80) <sup>3</sup>	0.76
Total cholesterol (mg/dL)	181 (159–210)	181 (160–206)	0.90
LDL (mg/dL)	127 (96–153)	121 (96–147)	0.83
HDL (mg/dL)	54 (45–65)	56 (49–71)	0.18
Triglycerides (mg/dL)	87 (67–121)	94 (72–121)	0.64
<b>Peripheral microvascular function</b>			
RHI	2.16 ± 0.66 <sup>2</sup>	/	/
fRHI	0.71 ± 0.47 <sup>2</sup>	/	/
<b>Ventricular function</b>			
LVEF (%)	58 (52–62) <sup>2</sup>	/	/
LV GLS (%)	−19 ± 3 <sup>2</sup>	/	/
RV FAC (%)	43 (37–49) <sup>2</sup>	/	/
RV TAPSE (mm)	21 (16–25) <sup>2</sup>	/	/
RV TDI S' (cm/s)	10.7 ± 2.8 <sup>2</sup>	/	/
NT-proBNP (pg/mL)	78 (41–180) <sup>4</sup>	48 (35–90) <sup>4</sup>	<b>0.002*</b>
<b>Muscle strength</b>			
Chest press (kg)	47.00 (32.75–63.75) <sup>2</sup>	/	/
Vertical traction (kg)	50.73 ± 16.54 <sup>2</sup>	/	/
Low row (kg)	57.12 ± 18.22 <sup>2</sup>	/	/
Leg press (kg)	157.89 ± 57.70 <sup>2</sup>	/	/
<b>Exercise capacity</b>			
%ppVO <sub>2</sub> (Wasserman)	85.30 ± 18.07 <sup>5</sup>	/	/
%ppVO <sub>2</sub> (LowLands)	70.11 ± 14.41 <sup>5</sup>	/	/

Data are expressed as mean ± standard deviation, median (Q1–Q3) or n (%).

\*/\*\*The significance level is 0.05/0.01 (2-tailed).

<sup>1</sup>These values were only available in 52 controls.

<sup>2</sup>These values were not available in all patients (n = 54 for WBC, RHI and fRHI, n = 52 for LVEF and RV FAC, n = 51 for RV TAPSE, n = 50 for RV TDI S', n = 48 for leg press, n = 47 for low row, n = 46 for chest press and vertical traction, n = 44 for LV GLS).

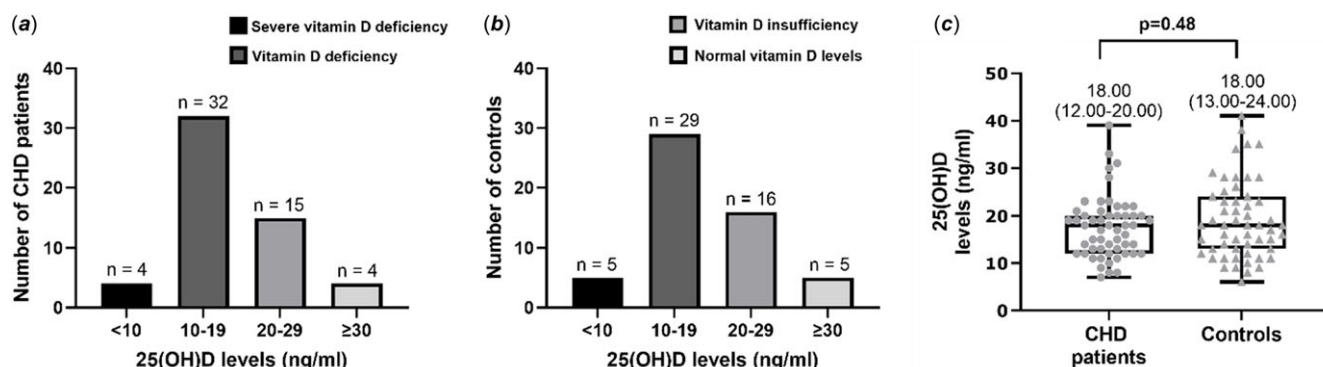
<sup>3</sup>hs-CRP < 0.16 mg/L in 3 controls (5%).

<sup>4</sup>NT-proBNP < 35 pg/mL in 6 patients (11%) and 19 controls (35%).

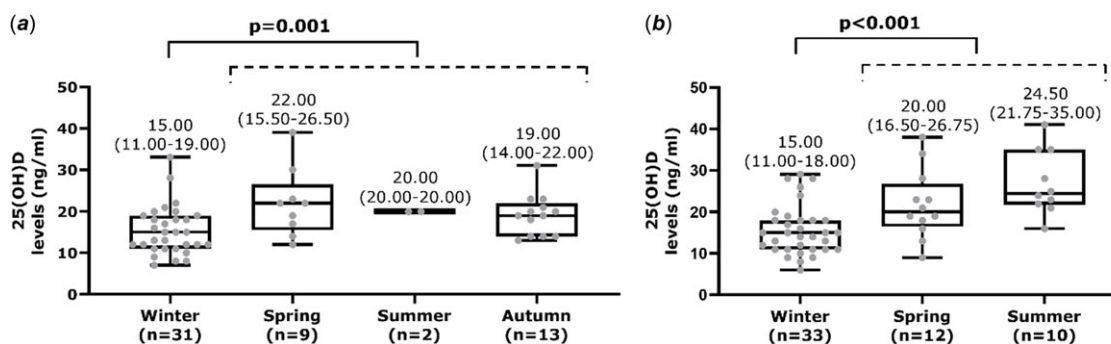
<sup>5</sup>Results for patients (n = 46) who performed a maximal metabolic cardiopulmonary exercise test (i.e. respiratory exchange ratio ≥ 1.10).

ACE I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; bpm = beats per minute; BMI = body mass index; FAC = fractional area change; GLS = global longitudinal strain; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LV = left ventricle; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal-pro hormone B-type natriuretic peptide; (%p)ppVO<sub>2</sub> = (percent-predicted) peak oxygen consumption; (f)RHI = (Framingham modified) reactive hyperaemia index; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; TDI S' = tissue Doppler imaging systolic velocity; WBC = white blood cell count.





**Figure 1.** Distribution of vitamin D levels in adults with CHD (a) and controls (b) and comparison of vitamin D levels between CHD and controls (c). Data are presented as median (Q1–Q3), whisker plots indicate min-max. 25(OH)D = 25-hydroxy vitamin D.



**Figure 2.** Comparison of vitamin D levels according to the season in which the studies were conducted in adults with CHD (a) and controls (b). Data are presented as median (Q1–Q3), whisker plots indicate min-max. 25(OH)D = 25-hydroxy vitamin D.

### Vitamin D is a pleiotropic hormone

Vitamin D is important for the proper functioning of multiple organ systems.<sup>29</sup> Beyond its well-known role in bone physiology and calcium homeostasis, there is emerging evidence that vitamin D exerts a plethora of additional effects on most tissues regulating the musculoskeletal, cardiovascular, and immune systems, and energy homeostasis.<sup>15</sup>

### Vitamin D and the cardiovascular system

Although the mechanisms of vitamin D signalling in cardiomyocytes and the vascular wall have not been fully elucidated, existing evidence indicates that 1,25(OH)<sub>2</sub> vitamin D is crucial for proper cardiac and vascular function.<sup>16–18</sup> Vitamin D receptors and 1 $\alpha$ -hydroxylase, which is essential to form active vitamin D, are expressed in human cardiomyocytes, fibroblasts, endothelial cells and vascular smooth muscle cells.<sup>15–18,30,31</sup> In addition to its direct effects, vitamin D may also influence the cardiovascular system indirectly by modulating various cardiovascular risk factors.<sup>31</sup>

1,25(OH)<sub>2</sub> vitamin D has been shown to exert anti-hypertrophic, anti-proliferative and anti-fibrotic effects on cardiomyocytes and thereby contributes to cardiac muscle remodelling.<sup>16,18,31,32</sup> Moreover, vitamin D accelerates myocyte relaxation essential for normal diastolic function and promotes myocyte contractility.<sup>15,30–32</sup> In adult patients with CHD and heart failure, serum parathyroid hormone and 25-hydroxy vitamin D levels were found to correlate with several clinical markers of heart failure, indicating that vitamin D deficiency may exacerbate heart function in CHD.<sup>33</sup> However, in our study of adult CHD patients, no significant relationship was found

between 25-hydroxy vitamin D levels and N-terminal-pro hormone B-type natriuretic peptide levels or echocardiographic parameters of left ventricular and right ventricular function. Nevertheless, it is noteworthy that our study exclusively encompassed patients classified as NYHA class I and II, with reduced left and right ventricular function observed in 15 and 21% of patients only, respectively.

In addition to its effects on the heart muscle, 1,25(OH)<sub>2</sub> vitamin D offers several benefits to the vascular system. It plays a role in vascular tissue remodelling, supports endothelial repair, regulates vascular tone and improves blood pressure.<sup>15,16,18,31</sup> Moreover, strong evidence from experimental studies in genetically engineered mice indicates that ablation of vitamin D signalling is associated with endothelial dysfunction.<sup>18</sup> Additionally, in humans, vitamin D insufficiency has been found to be related to endothelial dysfunction in the conductance and resistance blood vessels.<sup>15</sup> However, in this study, we could not establish a significant correlation between vitamin D levels and blood pressure or peripheral microvascular function in adults with CHD. Finger plethysmography (EndoPAT<sup>®</sup>), used to assess flow-dependent endothelium-mediated peripheral artery function<sup>34</sup>, is the most widely used technique to investigate peripheral microvascular function in CHD.<sup>35</sup>

### Vitamin D, adipocyte physiology and inflammation

Vitamin D receptors have also been identified in most immune cells, including macrophages, dendritic cells and activated T cells.<sup>16</sup> Vitamin D also inhibits oxidative stress and atherogenesis<sup>15,17</sup> and exhibits anti-inflammatory and immunomodulating effects.<sup>15,16,36</sup>

**Table 2.** Correlations of vitamin D levels in blood of adults with CHD and patient characteristics, markers of inflammation, cholesterol levels, peripheral microvascular function, ventricular function, muscle strength and exercise capacity

Variable	Spearman correlation	
	$\rho$	<i>p</i> -value
<b>Patient characteristics</b>		
Age (years)	0.23	0.10
BMI (kg/m <sup>2</sup> )	0.01	0.93
Systolic blood pressure (mmHg)	−0.13	0.33
Diastolic blood pressure (mmHg)	−0.03	0.86
<b>Inflammation and cholesterol levels</b>		
WBC (x10 <sup>9</sup> E/L)	<b>−0.31*</b>	<b>0.02</b>
hs-CRP (mg/L)	0.02	0.89
Total cholesterol (mg/dL)	0.01	0.93
LDL (mg/dL)	−0.04	0.77
HDL (mg/dL)	0.20	0.15
Triglycerides (mg/dL)	−0.23	0.09
<b>Peripheral microvascular function</b>		
RHI	0.18	0.19
fRHI	0.20	0.16
<b>Ventricular function</b>		
LVEF (%)	0.16	0.25
LV GLS (%)	−0.25	0.10
RV FAC (%)	−0.09	0.53
RV TAPSE (mm)	0.21	0.13
RV TDI S' (cm/s)	0.19	0.18
NT-proBNP (pg/mL)	−0.02	0.90
<b>Muscle strength</b>		
Chest press (kg)	0.11	0.47
Vertical traction (kg)	0.09	0.55
Low row (kg)	0.13	0.38
Leg press (kg)	0.15	0.30
<b>Exercise capacity</b>		
%ppVO <sub>2</sub> (Wasserman) <sup>1</sup>	<b>0.41**</b>	<b>0.005</b>
%ppVO <sub>2</sub> (LowLands) <sup>1</sup>	<b>0.34*</b>	<b>0.02</b>

\*/\*\*Correlation is significant at the 0.05/0.01 level (2-tailed).

<sup>1</sup>Results for patients (*n* = 46) who performed a maximal metabolic cardiopulmonary exercise test (i.e. respiratory exchange ratio  $\geq$  1.10).

BMI = body mass index; FAC = fractional area change; GLS = global longitudinal strain; HDL = high-density lipoprotein; hs-CRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LV = left ventricle; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal-pro hormone B-type natriuretic peptide; (%p)VO<sub>2</sub> = (percent-predicted) peak oxygen consumption; (f)RHI = (Framingham modified) reactive hyperemia index; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; TDI S' = tissue Doppler imaging systolic velocity; WBC = white blood cell count;  $\rho$  = Spearman's rho.

Moreover, it influences adipocyte physiology and shows an inverse relationship with body mass index and body fat percentage,<sup>15</sup> which in turn contributes to systemic chronic low-grade inflammation and inversely affects neuromuscular performance.<sup>15</sup> Despite the absence of a significant correlation with body mass

index, cholesterol levels or high-sensitivity C-reactive protein, our study revealed a significant negative association between white blood cells and 25-hydroxy vitamin D levels among adult CHD patients, though the relevance of this finding remains undetermined due to insufficient data.

#### Vitamin D and exercise capacity

Through its impact on cardiac output, vascular tone and endothelial function, vitamin D also affects the supply of oxygen and nutrients to the muscles. These cardiovascular effects, along with its influence on inflammation, skeletal muscle,<sup>37,38</sup> bones and lungs, make vitamin D vital for both aerobic and anaerobic exercise performance, and even for the ability to perform efficiently during the normal daily activities.<sup>15</sup> In athletes, seasonal variations in exercise performance often parallel those of vitamin D levels.<sup>15</sup> While most authors attribute the improved athletic performance observed in summer to higher vitamin D levels, others consider these two phenomena as parallel but independent.<sup>15</sup> Although we did not observe a significant association with muscle strength, serum 25-hydroxy vitamin D levels exhibited a significant correlation with %ppVO<sub>2</sub> in our diverse adult CHD population, which remained significant after adjusting for season. Moreover, exercise capacity was diminished in 48% and even in 85% of patients depending on the reference values used, underscoring the importance of enhancing exercise capacity in CHD patients. Since the globally utilised reference values by Wasserman et al.<sup>23</sup> are derived from an American cohort and are not applicable to female subjects, we also considered the reference values from the LowLands registry.<sup>24</sup> These values, sourced from a more recent Dutch and Flemish cohort that includes both men and women, are significantly higher than other reference values. Consequently, they offer a more accurate interpretation of maximal oxygen uptake in the Western European population.<sup>24</sup>

#### Vitamin D supplementation

Based on the results of the present study, it is advisable to regularly monitor serum levels of 25-hydroxy vitamin D in adults with CHD and to initiate supplementation if an insufficiency is detected. The goal of the treatment is to normalise vitamin D levels, countering the negative effects of low vitamin D levels on multiple organ systems,<sup>15,39</sup> particularly on the heart, blood vessels and exercise capacity in adults with CHD. However, to date, there are no studies evaluating vitamin D supplementation in CHD patients.

Current literature shows inconsistent results on the effects of vitamin D supplementation on vascular function, arterial stiffness and cardiac function, with no strong evidence supporting its use to reduce cardiovascular risk in the general population.<sup>17</sup> Furthermore, while most existing research indicates potential benefits of vitamin D supplementation for physical activity and performance in physically active individuals or athletes, these effects are only observed when pre-treatment levels are insufficient. For individuals with adequate levels of vitamin D, additional supplementation at supra-physiological levels does not appear to enhance physical capabilities further.<sup>15,38</sup>

Variations in vitamin D dosage and treatment regimens across studies have led to inconsistent outcomes,<sup>15</sup> leaving no established "ideal" schedule. In addition, safety findings from healthy populations or other diseases may not apply directly to CHD patients due to their unique metabolic demands, organ dysfunctions and known or unknown genetic abnormalities that may make them more or less susceptible to vitamin D toxicity.<sup>29</sup> The current

lack of clinical trials evaluating supplementation in CHD prevents evidence-based recommendations, highlighting the need for studies on the efficacy and safety of different vitamin D schedules in CHD. Further research should investigate whether substitution in case of vitamin D insufficiency benefits exercise capacity in CHD patients, ideally in combination with diverse training programs incorporating both aerobic training and strength exercises.

### Study limitations

This study has several limitations. First, the sample size was relatively small, especially for parameters not available in all CHD patients, potentially affecting the statistical significance of certain correlations. Second, the inclusion of only CHD patients classified as NYHA class I and II may limit the generalisability of the results to the entire CHD population. Third, subgroup analyses for specific CHD types were not feasible due to the small study group. Fourth, several cardiovascular effects of vitamin D may also be mediated by parathyroid hormone.<sup>17</sup> However, in our study, only serum 25-hydroxy vitamin D levels were measured without assessing serum levels of parathyroid hormone, calcium, phosphate and calcitonin. Fifth, although our study demonstrated a significant correlation between vitamin D levels and exercise capacity in adults with CHD, we cannot infer causality from these findings. For instance, individuals who spend more time outdoors and engage in more physical activity may naturally have higher vitamin D levels, which could be associated with improved cardiorespiratory fitness, confounding the observed relationship. While we accounted for seasonality as a confounding factor in our linear regression model, other potential confounders, such as physical activity levels and daily ultraviolet exposure, were not assessed. Finally, many correlations were explored without correction for multiple testing. Future research with larger sample sizes and diverse CHD types is needed to validate and expand upon the findings of this study.

### Conclusion

Vitamin D insufficiency is prevalent in adults with CHD and correlates with exercise intolerance. Serum levels of 25-hydroxy vitamin D did not significantly differ between adults with CHD and controls without cardiac disease. It remains to be elucidated whether substitution combined with exercise is beneficial in CHD in the case of vitamin D insufficiency.

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**Competing interests.** The authors declare no conflict of interest.

**Ethical standard. Institutional Review Board Statement:** The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics committee of the Antwerp University Hospital (study protocol – Belgian number: B3002020000298; date of approval: 18/01/2021).

**Informed Consent Statement:** Informed consent was obtained from all subjects involved in the study.

**Data Availability Statement:** The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

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