Cardiorespiratory Fitness, Sedentary Time, and Cardiovascular Risk Factor Clustering

JAVAID NAUMAN[1,2], DORTHE STENSVOLD[1,2], JEFF S. COOMBES[3], and ULRIK WISLØFF[1,2]

[1]*The K.G. Jebsen Center of Exercise in Medicine, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, NORWAY;* [2]*Department of Circulation and Medical Imaging, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, NORWAY;* [3]*School of Human Movement Studies, The University of Queensland, St. Lucia, Queensland, AUSTRALIA*

ABSTRACT

NAUMAN, J., D. STENSVOLD, J. S. COOMBES, and U. WISLØFF. Cardiorespiratory Fitness, Sedentary Time, and Cardiovascular Risk Factor Clustering. *Med. Sci. Sports Exerc.*, Vol. 48, No. 4, pp. 625–632, 2016. **Purpose**: Prolonged sedentary time (ST) is associated with cardiovascular risk factors (CV-RF) independent of physical activity (PA). Whether a high level of cardiorespiratory fitness (CRF) can modify the deleterious health consequences related to high ST is not known. **Methods**: We performed a cross-sectional study of 12,274 men and 14,209 women (≥20 yr) without known cardiovascular disease. Self-reported ST measurements during a regular day were divided into three sex-specific equally sized groups (≤4, 5 to <7, and ≥7 $h \cdot d^{-1}$). CRF was estimated (eCRF) using a previously validated nonexercise model. Using logistic regression analyses, adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated for the association of ST with CV-RF clustering and for the potential modifying effect of eCRF. **Results**: Each hour increase in ST was associated with 5% and 4% greater likelihood of having CV-RF clustering independent of PA in men and women, respectively. Among the participants with higher levels of eCRF, the adjusted OR values associated with ≥7 $h \cdot d^{-1}$ of ST were 0.92 (0.56–1.51) for men and 1.16 (0.49–2.74) for women, compared with men and women with low ST (≤4 $h \cdot d^{-1}$) and high eCRF levels. In combined analyses of eCRF, PA, and ST, compared with the reference group of participants meeting the recommendations, ≤4 $h \cdot d^{-1}$ of ST and high eCRF, the OR values were 0.63 (0.27–1.44) and 0.65 (0.14–3.07) in fit men and women with ≥7 $h \cdot d^{-1}$ of ST, which did not meet the recommendations. Men and women meeting the PA recommendations, but were unfit, had significantly increased odds of having CV-RF clustering across levels of ST. **Conclusion**: High levels of eCRF abolished the increased odds of having CV-RF clustering associated with high ST, even among those individuals who did not meet the current PA recommendations. **Key Words:** SEDENTARY TIME, CARDIORESPIRATORY FITNESS, PHYSICAL ACTIVITY, CARDIOVASCULAR RISK FACTORS, PREVENTION

Time spent in sedentary behavior has shown detrimental associations with various cardiovascular risk factors (CV-RF) (6,13,14,22,36) and has been recognized as an independent risk factor for all-cause mortality (7,34,37,39). Sedentary behavior is defined as activities during sitting or lying incurring no more than 1.5 METs (1 MET ≈ 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$). Sedentariness is generally considered distinct from inactivity, which refers to a lack of physical activity (PA) of ≥3 METs (31).

Recent studies have suggested a positive association between sedentary time (ST) and CV-RF independent of moderate- to vigorous-intensity PA (12,32,33,39). Importantly, the risk of dying from all-cause and cardiovascular diseases associated with high ST persisted, even among the participants who met the public health guidelines for PA (15,24,37).

Cardiorespiratory fitness (CRF) has an independent protective effect against cardiovascular morbidity and mortality, and seems to be the single best predictor of mortality and cardiovascular health (5,16,20,21,25,26). In fact, CRF was more strongly associated with all-cause mortality than PA, and fit individuals had lower risk of death whether or not they met the PA recommendations (21). Interestingly,

Address for correspondence to: Javaid Nauman, The K.G. Jebsen Center of Exercise in Medicine, Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Post Box 8905, Medisinsk Teknisk Forskningssenter, 7491 Trondheim, Norway; E-mail: javaid.nauman@ntnu.no.
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in men and women who met the recommended level of PA, but were unfit, the relative risks of mortality were not significantly lower than the reference group that did not meet the recommended PA levels and was unfit (21).

A few studies have examined the combined association of PA and ST (23,36), and others have examined the interaction between ST and CRF (18,33), showing a favorable effect of a high fitness level on the risk related to sedentary behavior. Given the ubiquitous nature and significant increased trends of sedentariness in modern society, it is important to investigate whether a high level of fitness can modify the deleterious health consequences related to high ST. In addition, the optimal amounts of PA to potentially mitigate the adverse effects of ST need to be assessed.

Therefore, we examined the associations of ST with clustering of CV-RF and the potential modifying effect of CRF and PA in a large population-based cohort of apparently healthy men and women.

METHODS

Study population. The third wave of the Nord-Trøndelag Health Study (the HUNT study) in Norway was carried out between October 2006 and June 2008. All inhabitants of the Nord-Trøndelag county 20 yr and older (n = 94,194) were invited, and 50,805 individuals (54%) accepted the invitation. Respondents filled in the questionnaire that was included in the invitation and later attended a clinical examination conducted by trained nurses. All participants provided written informed consent before volunteering to participate. Details about the HUNT study have been described elsewhere (17).

Among the participants who attended the clinical examination and returned the questionnaire, we excluded those who reported a history of heart disease (myocardial infarction, angina pectoris, stroke, prevalent diabetes mellitus, or regular use of blood pressure medication), motion impairment, or somatic disease resulting in long-term functional impairment. A total of 15,070 participants with these conditions were excluded from the analyses. In addition, 910 participants who failed to return the questionnaire with information about PA and 3140 participants with missing values for sedentary status were excluded. We further excluded 5202 participants that we did not have information about CV-RF and smoking status. Therefore, a total of 26,483 (12,274 men and 14,209 women) were included in the analyses of this study (Fig. 1).

Clinical measures and questionnaire-based information. The clinical examination was conducted by trained personnel and consisted of standardized measurements of height, weight, blood pressure, and resting HR (RHR) (17,27). A self-administered questionnaire provided information about leisure time PA, smoking habits, alcohol consumption, marital status, family history of disease, and attained education. PA questions were related to frequency, intensity, and duration. From these three questions, we constructed a previously published PA summary index (PA-I) (3,19).

Information on sedentary behavior was based on self-reported data. The main exposure variable, time spent sitting, was assessed with the following question: "On a regular day, how many hours do you spend sitting?" This question is similar to the sitting measure of the commonly used International Physical Activity Questionnaire, which has shown acceptable reliability and validity (8,37).

Estimated CRF. A nonexercise prediction model that was derived and cross-validated in a subsample of healthy participants with a similar age range was used to estimate CRF (29,30). The sex-specific models consisted of age,

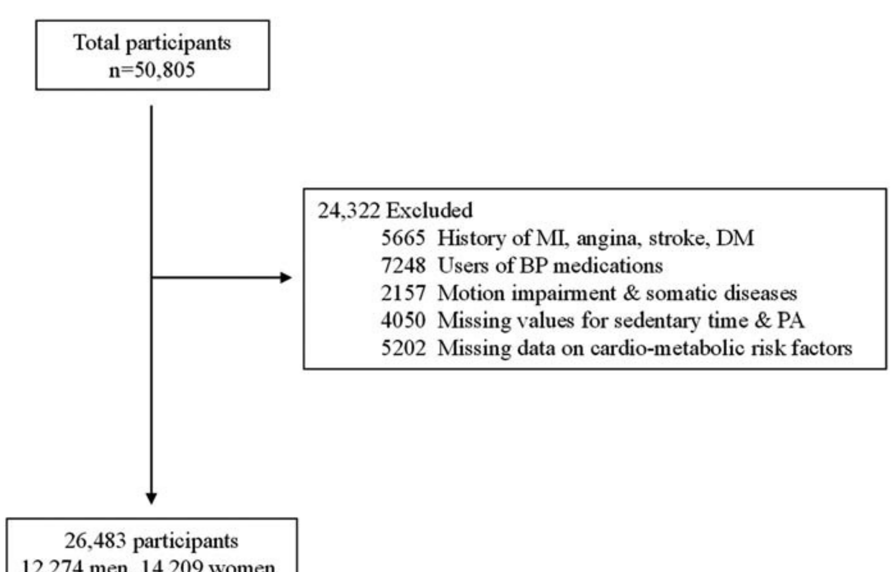

FIGURE 1—Flow of participants in the study cohort.

waist, PA-I, and RHR. These algorithms were used to predict each individual's CRF in this study:

$$\text{women}\left(R^2\,0.56,\ \text{SEE}\,5.1\right):\ 74.74 - (0.247\,\text{AGE}) - (0.259\,\text{WAIST}) - (0.114\,\text{RHR}) + (0.198\,\text{PA-I})$$

$$\text{men}\left(R^2\,0.61,\ \text{SEE}\,5.7\right):\ 100.27 - (0.296\,\text{AGE}) - (0.369\,\text{WAIST}) - (0.155\,\text{RHR}) + (0.226\,\text{PA-I})$$

Statistical analyses. The ST measurements were divided into three sample and sex-specific equally sized groups (tertiles). Descriptive data are presented as mean (SD) and percentages for continuous variables and categorical variables across the ST tertiles.

The clustering of CV-RF was defined as a waist circumference of 94 cm or wider in men and 80 cm or wider in women, combined with HDL cholesterol <1.0 mmol·L^{-1} in men and <1.3 mmol·L^{-1} in women, systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, and serum triglycerides ≥1.7 mmol·L^{-1}, on the basis of the definition of the metabolic syndrome (2,3). We used logistic regression analyses to estimate the association of ST with CV-RF clustering. Our basic models were age adjusted, and in further analyses, we adjusted for PA, smoking status, and nonfasting serum glucose. Results were expressed as odds ratios (OR), and precision of the estimates was assessed by 95% confidence intervals (CI).

On the basis of the PA questionnaire, we divided participants in accordance with recommendations of PA (1) and assessed the association of time spent sedentary with CV-RF clustering. Thus, exercise at high intensity for 30 min or more for at least two to three times per week and/or exercise of medium intensity for 30 min or more almost every day were according to the recommendations.

We assessed the combined associations of ST with estimated CRF for clustering of CV-RF. For this purpose, estimated CRF was classified into three sex-specific categories: low fitness level was defined as the least fit 20%, moderate fitness level as the next fit 40%, and high fitness level as the most fit 40%, as previously suggested (21). Results are reported as OR (95% CI) for each third of ST combined with each category of fitness, where participants in the high fitness category (the most fit 40%) and lowest third of ST served as the reference group. In a separate analysis, we also assessed the combined associations of ST with PA and estimated CRF. Participants with high fitness levels, meeting the current recommendations of PA, and low ST were used as the referent. We also investigated the potential effect modification by age for the association of ST and clustering of CV-RF and found no evidence.

We performed sensitivity analyses to assess the robustness of our findings. For example, we investigated the combined association of ST with estimated CRF for individual risk factors and reported the results as marginal means for each third of ST combined with each fitness level. Furthermore, we compared exercise at a high-intensity short-duration level and at a moderate-intensity long-duration level in relation to measurements of estimated CRF. In a separate analysis, we used data from HUNT fitness study (3), where CRF was directly measured running on a treadmill. All statistical tests were two-sided, and a P value of less than 0.05 was considered significant.

TABLE 1. Descriptive characteristics of participants according to ST.

	Sedentary Behavior[a] (h·d^{-1})		
	≤4 (*n* = 10,151)	**4 to <7 (*n* = 7787)**	**≥7 (*n* = 8545)**
Women, no. (%)	5662 (39.8)	4297 (30.2)	4250 (29.9)
Age, mean (range) (yr)	47.5 (20–90)	48.8 (20–93)	45.9 (20–100)
Waist circumference, mean (SD) (cm)	90.7 (11.2)	92.0 (11.8)	92.1 (12.0)
Systolic blood pressure, mean (SD) (mm Hg)	126.5 (16.5)	128.2 (17.1)	126.8 (16.1)
Diastolic blood pressure, mean (SD) (mm Hg)	71.9 (10.6)	72.8 (11.0)	72.9 (10.8)
Total cholesterol, mean (SD) (mmol·L^{-1})	5.5 (1.1)	5.5 (1.1)	5.4 (1.1)
HDL cholesterol, mean (SD) (mmol·L^{-1})	1.4 (0.3)	1.4 (0.3)	1.3 (0.3)
Glucose, mean (SD) (mmol·L^{-1})	5.3 (1.0)	5.3 (1.1)	5.4 (1.2)
Triglycerides, mean (SD) (mmol·L^{-1})	1.5 (0.9)	1.6 (1.0)	1.6 (1.0)
RHR, mean (SD) (bpm)	69.8 (10.8)	70.3 (11.0)	69.3 (11.2)
BMI, mean (SD) (kg·m^{-2})	26.3 (3.9)	26.6 (4.1)	26.6 (4.2)
Obesity status (BMI ≥ 30.0), no. (%)	1596 (15.7)	1429 (18.4)	1583 (18.5)
PA recommendations, no. (%)			
No	5083 (39.0)	3872 (29.7)	4074 (31.3)
Yes	5068 (37.7)	3915 (29.1)	4471 (33.2)
Smoking, no. (%)			
Never	4571 (38.1)	3371 (28.1)	4056 (33.8)
Former	2872 (37.2)	2376 (30.9)	2462 (31.9)
Current	1875 (41.0)	1418 (30.9)	1284 (28.1)
Occasional	833 (37.9)	622 (28.3)	743 (33.8)
CRF,[b] no. (%)			
Low	1703 (36.7)	1641 (35.3)	1301 (28.0)
Moderate	4225 (39.5)	3179 (29.7)	3289 (30.7)
High	4223 (37.9)	2967 (26.6)	3955 (35.4)

[a]Sample-specific tertiles of ST.
[b]Low, moderate, and high fitness levels were defined as the least fit 20%, the next fit 40%, and the most fit 40%, respectively.

EPIDEMIOLOGY

TABLE 2. OR values for CV-RF clustering according to ST.

	Men			Women		
	CV-RF (n)			CV-RF (n)		
	No	Yes	OR (95% CI)	No	Yes	OR (95% CI)
ST[a] ($h \cdot d^{-1}$)						
≤4	4261	228	1.00 (reference)	5436	226	1.00 (reference)
5 to <7	3279	211	1.19 (0.98 to 1.45)	4058	239	1.31 (1.09 to 1.59)
≥7	3994	301	1.41 (1.18 to 1.68)	4047	203	1.27 (1.05 to 1.55)
P trend			<0.001			0.01
Per 1 h	11,534	740	1.05 (1.03 to 1.08)	13,541	668	1.04 (1.01 to 1.07)

CV-RF clustering was a waist circumference ≥94 cm in men and ≥80 cm in women, combined with HDL cholesterol <1.0 $mmol \cdot L^{-1}$ in men and <1.3 $mmol \cdot L^{-1}$ in women, systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, and serum triglycerides ≥1.7 $mmol \cdot L^{-1}$.
Adjusted for age, PA, smoking status, and nonfasting serum glucose.
[a]Sex-specific tertiles of ST.

The statistical analyses were conducted using Stata (version 13.1 StataCorp).

RESULTS

The baseline characteristics of the study cohort are presented in Table 1. Of the 26,483 healthy participants, 53.7% were women, 17.4% were obese, 38.3% reported sitting ≤4 $h \cdot d^{-1}$, and 32.3% reported ≥7 h of sitting during an average day. Participants with ST ≤ 4 $h \cdot d^{-1}$ had a smaller waist circumference, lower body mass index (BMI), were more likely to be meeting the PA recommendations, and were more likely to have high estimated CRF.

ST and CV-RF clustering. Table 2 shows the OR for CV-RF clustering according to the tertiles of ST adjusted for various confounders. Compared with the reference group (ST, ≤4 $h \cdot d^{-1}$), men reporting an ST of ≥7 $h \cdot d^{-1}$ had 41% higher odds of having CV-RF clustering ($P < 0.01$ for the trend). In women, there was a corresponding 27% increased odds of CV-RF clustering associated with ≥7 $h \cdot d^{-1}$ of ST ($P = 0.01$ for the trend).

Effect of PA upon ST and CV-RF clustering. In participants meeting the current recommendations for PA, the risk of CV-RF clustering was 25% higher in those with ≥7 $h \cdot d^{-1}$ of ST compared with ≤4 $h \cdot d^{-1}$ of ST (OR, 1.25; 95% CI, 1.01–1.55), as shown in Table 3. The corresponding risk of CV-RF clustering was significantly higher among those with ≥7 $h \cdot d^{-1}$ of ST and not meeting the recommendations of PA (OR, 2.38; 95% CI, 1.96–2.89).

Modifying effect of estimated fitness upon ST and CV-RF clustering. The modifying effect of estimated fitness for the prevalence of risk factor clustering appeared more substantial than PA (Fig. 2). In comparison with men with a high fitness level (the fittest 40%: $\dot{V}O_{2peak}$ >43.3 $mL \cdot kg^{-1} \cdot min^{-1}$) and low ST (≤4 $h \cdot d^{-1}$), men with a low fitness level (the least 20%: $\dot{V}O_{2peak}$ <35.7 $mL \cdot kg^{-1} \cdot min^{-1}$) and high ST (≥7 $h \cdot d^{-1}$) were 28 times more likely to have clustering of risk factors (OR, 27.90; 95% CI, 18.18–42.81). Among the women with a low fitness level ($\dot{V}O_{2peak}$ <28.4 $mL \cdot kg^{-1} \cdot min^{-1}$) and ≥7 $h \cdot d^{-1}$ of ST, the adjusted OR was 48.44 (95% CI, 25.25–92.93) compared with the women with a high fitness level ($\dot{V}O_{2peak}$ >35.2 $mL \cdot kg^{-1} \cdot min^{-1}$) and ≤4 $h \cdot d^{-1}$ of ST. Among the participants with higher levels of estimated fitness, the adverse effects of prolonged ST upon CV-RF clustering were completely abolished. The adjusted OR values associated with ≥7 $h \cdot d^{-1}$ of ST were 0.92 (95% CI, 0.56–1.51) for men and 1.16 (95% CI, 0.49–2.74) for women with high estimated fitness levels.

Combined analysis of PA levels and estimated fitness upon ST and CV-RF clustering. The combined association analyses showed that fit men and women were protected against CV-RF clustering associated with ST, whether or not they met the PA recommendations (Table 4). In fit men ($\dot{V}O_{2peak}$ >43.3 $mL \cdot kg^{-1} \cdot min^{-1}$) with ≥7 $h \cdot d^{-1}$ of ST, the adjusted OR values were 0.6 (95% CI, 0.3–1.4) in those not meeting the recommendations and 1.0 (95% CI, 0.5–1.8) among those meeting the recommendations of PA, compared with fit men with ≤4 $h \cdot d^{-1}$ of ST and meeting the recommendations. Among the fit women ($\dot{V}O_{2peak}$ >35.2 $mL \cdot kg^{-1} \cdot min^{-1}$) with ≥7 $h \cdot d^{-1}$ of ST, the corresponding OR values were 0.7 (95% CI, 0.1–3.1) in those not meeting the PA recommendations and 1.2 (95% CI, 0.5–3.3) among those meeting the PA recommendations. Men and women meeting the PA recommendations, but were unfit

TABLE 3. OR values for CV-RF clustering according to ST in participants meeting and not meeting PA recommendations.

	Meeting Recommendations			Below Recommendations		
	CV-RF (n)			CV-RF (n)		
	No	Yes	OR (95% CI)	No	Yes	OR (95% CI)
ST[a] ($h \cdot d^{-1}$)						
≤4	4898	170	1.00 (reference)	4799	284	1.62 (1.33 to 1.97)
5 to <7	3738	177	1.33 (1.07 to 1.65)	3599	273	2.02 (1.66 to 2.46)
≥7	4291	180	1.25 (1.01 to 1.55)	3750	324	2.38 (1.96 to 2.89)

CV-RF clustering was a waist circumference ≥94 cm in men and ≥80 cm in women, combined with HDL cholesterol <1.0 $mmol \cdot L^{-1}$ in men and <1.3 $mmol \cdot L^{-1}$ in women, systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, and serum triglycerides ≥1.7 $mmol \cdot L^{-1}$.
Adjusted for age, sex, smoking status, and nonfasting serum glucose.
[a]Sex-specific tertiles of ST.

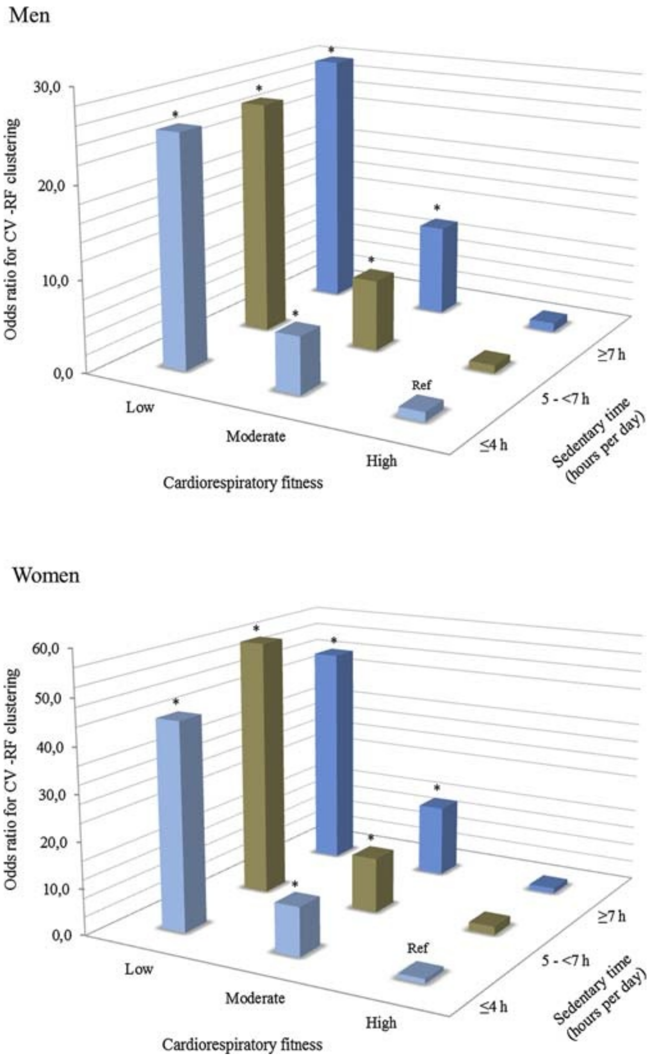

FIGURE 2—Adjusted OR (A) of clustering (B) of CV-RF in combined categories of fitness and ST. A. Adjusted for age, nonfasting serum glucose, and smoking status. B. CV-RF clustering was a waist circumference ≥94 cm in men and ≥80 cm in women combined with HDL cholesterol <1.0 mmol·L^{-1} in men and <1.3 mmol·L^{-1} in women, systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, and serum triglycerides ≥1.7 mmol·L^{-1}. Low, moderate, and high fitness levels were defined as the least fit 20%, the next fit 40%, and the most fit 40%, respectively. CRF values were <35.7 for low, 35.7–43.3 for moderate, and >43.3 mL·kg^{-1}·min^{-1} for high fitness levels in men, and <28.4 for low, 28.4–35.2 for moderate, and >35.2 mL·kg^{-1}·min^{-1} for high fitness levels in women. * Denotes significant difference (*P* < 0.05) from reference category.

($\dot{V}O_{2peak}$ <35.7 mL·kg^{-1}·min^{-1} for men and $\dot{V}O_{2peak}$ <28.4 mL·kg^{-1}·min^{-1} for women), had significantly increased odds of having CV-RF clustering across different levels of ST. For example, unfit men with ≤4 h·d^{-1} of ST and following the PA recommendations had an OR of 27.2 (95% CI, 14.2–52.0) compared with the reference group of fit men with ≤4 h·d^{-1} of ST who were meeting the recommendations.

Sensitivity analyses. Time spent sedentary was positively associated with waist circumference, diastolic blood pressure, nonfasting serum glucose, and triglycerides, whereas HDL cholesterol was negatively associated with ST (see Table, Supplemental Digital Content 1, association between ST and cardiometabolic risk factors, http://links.lww.com/MSS/A599). However, higher values of CRF were associated with lower values of waist circumference, systolic blood pressure, triglycerides, and significantly higher values of HDL cholesterol across the tertiles of ST (see Figure, Supplemental Digital Content 2, age-adjusted marginal means for combined associations of ST and CRF, http://links.lww.com/MSS/A600). When examining the association between CRF and total exercise time combined with intensity of exercise (see Figure, Supplemental Digital Content 3, CRF according to total exercise duration and exercise intensity, http://links.lww.com/MSS/A601), we found that men with less than 75 min·wk^{-1} (mean, 52 min) of high-intensity exercise (corresponding to ≈87.5% of $\dot{V}O_{2peak}$ [28,40]) had a $\dot{V}O_{2peak}$ of 47.6 mL·kg^{-1}·min^{-1} compared with a $\dot{V}O_{2peak}$ of 45.6 mL·kg^{-1}·min^{-1} among the men who reported more than 150 min·wk^{-1} of exercise (mean, 202 min) at moderate intensity (corresponding to ≈75% of $\dot{V}O_{2peak}$ [28,40]). The $\dot{V}O_{2peak}$ values for women were 37.8 mL·kg^{-1}·min^{-1} when reporting less than 75 min·wk^{-1} (mean, 50 min) at high intensity and 37.4 mL·kg^{-1}·min^{-1} for those with more than 150 min·wk^{-1} (mean, 206 min) at moderate intensity. In a separate analysis using directly measured CRF data (n = 4386), the results were similar to those when using estimated fitness (see Figure, Supplemental Digital Content 4, OR of CV-RF clustering in combined categories of ST and directly measured CRF, http://links.lww.com/MSS/A602). Compared with the reference group of men with a high fitness level (the fittest 40%: $\dot{V}O_{2peak}$ >46.5 mL·kg^{-1}·min^{-1}) and low ST (≤4 h·d^{-1}), the OR for CV-RF clustering was 6.37 (95% CI, 2.24–18.08) among the men with a low fitness level (the least 20%: $\dot{V}O_{2peak}$ <36.0 mL·kg^{-1}·min^{-1}) and high ST (≥7 h·d^{-1}). The adjusted OR associated with ≥7 h·d^{-1} of ST was 0.52 (95% CI, 0.14–1.85) in men with high levels of fitness.

DISCUSSION

The main findings of the present study were that 1) time spent sedentary is associated with CV-RF clustering independent of PA, and 2) high levels of estimated fitness abolished the increased odds of having clustering of CV-RF associated with high ST, even among those individuals who did not meet the current PA recommendations.

Our results of combined analyses of ST and the recommended amounts of PA are consistent with previous studies showing an independent association of time spent sedentary with clustering of CV-RF in participants who met the current recommendations of regular PA (12,32). In a population of healthy Australian adults who met the public health guidelines for PA, TV viewing time was positively associated with a number of metabolic risk variables (12). A recent analysis of 15,235 Danish adults demonstrated that higher amounts of ST were associated with a greater risk of having a metabolic syndrome, even among the participants who reported moderate to vigorous PA (32). Furthermore,

TABLE 4. OR values (95% CI)[a] for CV-RF clustering in combined associations of CRF, the recommended PA, and ST.

	PA and ST (h·d^{-1})					
	Meeting PA Recommendations			Below PA Recommendations		
	≤4	5 to <7	≥7	≤4	5 to <7	≥7
CRF[b]						
Men						
Low (<35.7 mL·kg^{-1}·min^{-1})	27.2 (14.2 to 52.0)	31.9 (17.1 to 59.6)	24.2 (12.7 to 46.3)	23.7 (13.8 to 40.5)	22.4 (13.1 to 38.4)	27.8 (16.6 to 46.6)
Moderate (35.7–43.3 mL·kg^{-1}·min^{-1})	6.4 (3.5 to 11.59)	8.7 (4.9 to 15.4)	10.3 (6.0 to 17.6)	5.7 (3.4 to 9.5)	6.8 (4.0 to 11.5)	9.1 (5.5 to 15.1)
High (>43.3 mL·kg^{-1}·min^{-1})	Reference	1.1 (0.6 to 2.1)	1.0 (0.5 to 1.8)	0.9 (0.4 to 1.8)	0.4 (0.1 to 1.2)	0.6 (0.3 to 1.4)
Women						
Low (<28.4 mL·kg^{-1}·min^{-1})	48.6 (21.9 to 108.1)	45.7 (20.6 to 101.4)	36.0 (15.3 to 84.6)	40.1 (18.9 to 84.8)	55.0 (26.2 to 115.8)	49.1 (23.1 to 104.3)
Moderate (28.4–35.2 mL·kg^{-1}·min^{-1})	11.6 (5.4 to 24.8)	14.5 (6.8 to 31.2)	16.4 (7.7 to 34.9)	8.2 (3.8 to 17.5)	8.5 (3.9 to 18.4)	12.7 (5.9 to 27.1)
High (>35.2 mL·kg^{-1}·min^{-1})	Reference	2.1 (0.8 to 5.2)	1.2 (0.5 to 3.3)	0.7 (0.2 to 2.8)	0.8 (0.2 to 3.8)	0.7 (0.1 to 3.1)

CV-RF clustering was a waist circumference ≥94 cm in men and ≥80 cm in women, combined with HDL cholesterol <1.0 mmol·L^{-1} in men and <1.3 mmol·L^{-1} in women, systolic blood pressure ≥130 mm Hg and/or diastolic blood pressure ≥85 mm Hg, and serum triglycerides ≥1.7 mmol·L^{-1}.
[a]Adjusted for age, smoking status, and nonfasting serum glucose.
[b]Sex-specific low, moderate, and high fitness levels were defined as the least 20%, the next 40%, and the most fit 40%, respectively.

our findings are supported by previous studies (6,9,13,14,36), also indicating an association between ST and CV-RF, independent of PA (12,32,33,39). We observed that each hour increase in ST was associated with 5% and 4% greater likelihood of having CV-RF clustering in men and women, respectively. These findings are of clinical significance because prevalence of CV-RF clustering or a metabolic syndrome is a large and growing public health problem. In fact, individuals with a metabolic syndrome have been found to have an increased risk of diabetes (10), a strong association with all-cause and cardiovascular disease mortality, and an increased incidence of cardiovascular and ischaemic heart disease and stroke compared with individuals who do not have a metabolic syndrome (9,11).

Our results substantially extend findings in previous studies (18,33) regarding the association of ST, CV-RF clustering, and CRF by showing that high levels of estimated fitness (>43.3 mL·kg^{-1}·min^{-1} in men and >35.2 mL·kg^{-1}·min^{-1} in women) compensate for the deleterious health consequences related to ≥7 h·d^{-1} of ST. This is important because finding effective ways of preventing CV-RF clustering is a major aim in preventive medicine and an important goal of the current recommendation for PA. Arguably, PA is probably the most important factor determining CRF (20), and increasing adults' PA to meet guidelines has been suggested to reduce health care expenditures (4). Our results indicate that the recommendation for PA should focus on activities that increase CRF.

In the analysis examining the association between CRF and total exercise time combined with intensity of exercise, we observed that $\dot{V}O_{2peak}$ among the participants reporting a considerably smaller total volume of exercise at high intensity (<75 min·wk^{-1}: corresponds to not meeting the current recommendations of PA) was comparable with those who reported ≥150 min·wk^{-1} at moderate-intensity exercise. In fact, men and women exercising <75 min (average, 51 min) per week but at high intensity obtained $\dot{V}O_{2peak}$ that was about 1 MET above the average in those categorized to be fit (the fittest 40%). Our data are in line with clinical studies showing that high-intensity exercise is more effective for increasing $\dot{V}O_{2peak}$ than moderate-intensity exercise, even when the duration of exercise is adjusted to achieve the same amount of caloric expenditure (28,35,38). Future studies are warranted to assess the optimal dose of exercise volume and intensity to achieve maximal gains in CRF, which would be important for primary and secondary prevention.

The strengths of the present study include the large sample size of representative adult men and women who were free from known heart diseases and the detailed information on various CV-RF. The limitation of this study is that ST was self-reported, which is subject to either over- or underreporting because of recall bias. Although the ST questionnaire was similar to the sitting measure of the commonly used International Physical Activity Questionnaire, which has shown acceptable reliability and validity (8), objective monitoring of sedentary behavior through accelerometers would have been preferable. In addition, the estimation of CRF through a nonexercise model could be a limitation; however, we observed similar results in a subpopulation where fitness was directly measured. Moreover, the fitness algorithm that was used in the present study has been shown to predict long-term risk of premature all-cause and cardiovascular mortality with an accuracy that was similar to what has been obtained using directly measured fitness (30). Future studies are warranted using objective measurements of both ST and CRF to confirm the combined effect of these variables on the prevalence of CV-RF clustering.

In conclusion, our findings provide novel evidence of the modifying effect of CRF on the relationship of ST with CV-RF clustering. Higher levels of fitness abolished the adverse health outcomes associated with high ST, regardless of meeting the recommended amounts of PA. These results contribute to the mounting evidence that public health programs should focus on increasing PA that result in improved fitness levels and also the inclusion of ST guidelines in public health recommendations for cardiovascular disease prevention.

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J. N. had full access to all of the data in the study and take responsibility for the integrity of the data. J. N. analyzed the data, interpreted the results, and wrote the article. D. S. interpreted the results and wrote the article. J. S. C. interpreted the results and wrote the article. U. W. interpreted the results and wrote the article, and is the guarantor of the study.

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The regional committee for ethics in medical research approved the study.

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