Maastricht University

Sedentary Behavior, Physical Activity, and Fitness-The Maastricht Study

Document status and date:
Published: 01/08/2017

DOI:
10.1249/MSS.0000000000001262

Document Version:
Publisher's PDF, also known as Version of record

Document license:
Taverne

Please check the document version of this publication:

• A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
• The final author version and the galley proof are versions of the publication after peer review.
• The final published version features the final layout of the paper including the volume, issue and page numbers.

Link to publication

Download date: 08 Jan. 2021

Sedentary Behavior, Physical Activity, and Fitness—The Maastricht Study

JEROEN H. P. M. VAN DER VELDE[1,2,3,4], ANNEMARIE KOSTER[5,6], JULIANNE D. VAN DER BERG[5,6,7], SIMONE J. S. SEP[4,8], CARLA J. H. VAN DER KALLEN[4,8], PIETER C. DAGNELIE[4,6,9], MIRANDA T. SCHRAM[4,8,10], RONALD M. A. HENRY[4,8,10], SIMONE J. P. M. EUSSEN[4,6,9], MARTIEN C. J. M. VAN DONGEN[6,9], COEN D. A. STEHOUWER[4,8], NICOLAAS C. SCHAPER[3,4,6], and HANS H. C. M. SAVELBERG[1,2]

[1]Department of Human Movement Sciences, Maastricht University, Maastricht, THE NETHERLANDS; [2]NUTRIM School for Nutrition and Translational Research in Metabolism, Maastricht University, Maastricht, THE NETHERLANDS; [3]Division of Endocrinology, Department of Internal Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, THE NETHERLANDS; [4]CARIM School for Cardiovascular Diseases, Maastricht University, Maastricht, THE NETHERLANDS; [5]Department of Social Medicine, Maastricht University, Maastricht, THE NETHERLANDS; [6]CAPHRI School for Public Health and Primary Care, Maastricht University, Maastricht, THE NETHERLANDS; [7]Radboud Institute for Health Sciences, Radboud University Medical Center, Nijmegen, THE NETHERLANDS; [8]Department of Internal Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, THE NETHERLANDS; [9]Department of Epidemiology, Maastricht University, Maastricht, THE NETHERLANDS; and [10]Heart and Vascular Centre, Maastricht University Medical Centre (MUMC+), Maastricht, THE NETHERLANDS

ABSTRACT

VAN DER VELDE, J. H. P. M., A. KOSTER, J. D. VAN DER BERG, S. J. S. SEP, C. J. H. VAN DER KALLEN, P. C. DAGNELIE, M. T. SCHRAM, R. M. A. HENRY, S. J. P. M. EUSSEN, M. C. J. M. VAN DONGEN, C. D. A. STEHOUWER, N. C. SCHAPER, and H. H. C. M. SAVELBERG. Sedentary Behavior, Physical Activity, and Fitness—The Maastricht Study. *Med. Sci. Sports Exerc.*, Vol. 49, No. 8, pp. 1583–1591, 2017. **Purpose**: This cross-sectional study examined the mutual independent associations of sedentary behavior, lower intensity physical activity (LPA) and higher intensity physical activity (HPA) (an approximation of moderate to vigorous physical activity with cardiorespiratory fitness (CRF). **Methods**: Two thousand twenty-four participants were included from The Maastricht Study (mean ± SD age, 59.7 ± 8.1 yr; 49.6% men). With the activPAL3 activity monitor, we assessed sedentary time (ST), sedentary pattern variables (number of sedentary breaks, average sedentary bout duration, and number of prolonged sedentary bouts [$\geq$30 min]), LPA, and HPA. CRF was calculated as maximum power output per kilogram body mass ($W_{max} \cdot kg^{-1}$) estimated from a submaximal cycle ergometer test. Linear regression analyses and isotemporal substitution analyses were used to examine associations of ST, sedentary pattern variables, and HPA with CRF. Analyses were stratified by sex. **Results**: One hour of ST per day was associated with a lower $W_{max} \cdot kg^{-1}$: $B_{men} = -0.03$ (95% confidence interval [CI], -0.05 to -0.01) and $B_{women} = -0.02$ (95% CI, -0.04 to 0.00), independent of HPA. No statistically significant associations between sedentary patterns variables and CRF were observed. LPA was associated with a higher $W_{max} \cdot kg^{-1}$: $B_{men} = 0.12$ (95% CI, 0.07–0.17) and $B_{women} = 0.12$ (95% CI, 0.07–0.18). HPA was associated with a higher $W_{max} \cdot kg^{-1}$: $B_{men} = 0.48$ (95% CI, 0.38–0.58) and $B_{women} = 0.27$ (95% CI, 0.18–0.36). Replacing ST with LPA (B_{men}, 0.08; 95% CI, 0.03–0.14; B_{women}, 0.10; 95% CI, 0.05–0.16) or with HPA (B_{men}, 0.49; 95% CI, 0.39–0.59; B_{women}, 0.28; 95% CI, 0.19–0.36), but not with standing was associated with higher CRF. **Conclusions**: Modest associations between sedentary behavior and CRF were observed. Replacing ST with LPA was associated with higher CRF, which could be of particular importance for individuals who cannot engage in HPA. Nonetheless, replacing ST with HPA was associated with greatest estimated change in CRF. **Key Words**: SEDENTARY LIFE-STYLE, SEDENTARY PATTERNS, ACCELEROMETRY, HIGH-INTENSITY PHYSICAL ACTIVITY, PHYSICAL FITNESS

Cardiorespiratory fitness (CRF), defined as the capacity of the cardiovascular and respiratory systems to supply fuel and oxygen during sustained physical activity (PA), has shown to be an important determinant of health. Impaired CRF has been recognized in the etiology of the metabolic syndrome and cardiovascular disease (CVD), and may predict premature mortality (6,16,17,21). Although CRF is determined to a certain extent by factors such as sex, genetics and environment, PA has been identified as a key modifiable determinant (7). Specifically, more time engaged in moderate-to-vigorous PA (MVPA), has been associated with higher CRF (20,22).

EPIDEMIOLOGY

Despite the well-documented health benefits of MVPA, PA guidelines are frequently not met (32) and the majority of the adult population appears to be sedentary most time of the day (25). In addition, even individuals who do regularly engage in MVPA may spend the majority of the day in sedentary behavior. Sedentary behavior is defined as any waking behavior that is characterized by an energy expenditure ≤1.5 METs while in a sitting or reclining position (29). More daily sedentary time (ST) has been associated with several adverse health outcomes including an increased risk for the metabolic syndrome, type 2 diabetes mellitus (T2DM) and CVD (9,38). Importantly, these associations were observed independent of MVPA. Even individuals who do adhere to PA guidelines appear to be at increased risk for detrimental health effects from sitting too much (25). These findings are supported by the observation that MVPA may not compensate the detrimental associations of ST on markers of metabolic health (12).

Not only total ST has shown to be a determinant of several adverse health outcomes but also the pattern in which ST is accumulated may be relevant as well. Patterns of ST can be expressed by sedentary breaks (interruptions of periods of sitting), the length of sedentary bouts (uninterrupted periods of ST) and the mean duration of a sedentary bout. For instance, more sedentary breaks have been associated with favorable cardiometabolic outcomes (11,15). Because both sedentary behavior and CRF have been associated with detrimental health, associations between these constructs should be examined. Possibly, the positive effect of MVPA on CRF may be attenuated by increased amounts of ST. To date, only a few studies have considered the associations of sedentary behavior with CRF. Studies using self-reported measures of ST observed that larger amounts of ST were associated with lower CRF (13,33). One study that used objectively measured ST and CRF in a population age 12 to 49 yr, also found that more ST was associated with a lower CRF (19).

To obtain a better insight into the associations between sedentary behavior and CRF, we examined the mutually independent associations of objectively measured ST, sedentary behavior patterns and PA with CRF in a large adult population. PA was divided into lower-intensity PA (LPA) and higher-intensity PA (HPA) (corresponding approximately with MVPA). We hypothesized that more daily ST, a longer average sedentary bout duration and more prolonged sedentary bouts per day would be associated with lower CRF. On the other hand, more daily sedentary breaks and more time engaged in LPA and HPA would be associated with higher CRF.

METHODS

Population. We used data from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously (28). In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of T2DM and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals age between 40 and 75 yr and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency. The present report includes cross-sectional data from a selection of the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. For this study, data were available for 2024 participants. Main reasons for missing data were: medical exclusion for the submaximal cycle ergometer test ($n = 425$), invalid ergometer test ($n = 180$), missing or invalid accelerometry data ($n = 629$) and missing data in covariates ($n = 193$). The examinations of each participant were performed within a time window of 3 months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

Accelerometry: ST, patterns of sedentary behavior, and HPA. Daily activity levels were measured using the activPAL3™ PA monitor (PAL Technologies, Glasgow, UK). The activPAL3 is a small ($53 \times 35 \times 7$ mm), lightweight (15 g) triaxial accelerometer that records movement in the vertical, anteroposterior and mediolateral axes, and also determines posture (sitting or lying, standing and stepping) based on acceleration information. The device was attached directly to the skin on the front of the right thigh with transparent 3M Tegaderm™ tape, after the device had been waterproofed using a nitrile sleeve. Participants were instructed to wear the accelerometer for eight consecutive days, without removing it at any time. To avoid inaccurately identifying nonwear time, participants were asked not to replace the device once removed. Data were uploaded using the activPAL software and processed using customized software written in MATLAB R2013b (MathWorks, Natick, MA). Data from the first day were excluded from the analysis because participants performed physical function tests at the research center after the device was attached. In addition, data from the final wear day providing ≤14 waking hours of data were excluded from the analysis. Participants were included if they provided at least one valid day (≥10 h of waking data).

The total amount of ST was based on the sedentary posture (sitting or lying), and calculated as the mean time spent in a sedentary position during waking time per day. The method used to determine waking time has been described elsewhere (37). The number of sedentary breaks during waking time was determined as each transition from a sitting or lying position to standing or stepping with a duration of at least 1 min, and the mean number of breaks per day was calculated. Sedentary time accumulated in a consecutive period ≥30 min was defined as a prolonged sedentary bout, and the mean number of prolonged sedentary bouts during waking time per day was calculated. Average bout duration was calculated by dividing total ST by total number of sedentary bouts of any duration. The total amount of standing time was based on the

standing posture, and calculated as the mean time spent standing during waking time per day. The total amount of stepping (PA) was based on the stepping posture, and calculated as the mean time stepping during waking time per day. Stepping time (PA) was further classified into HPA (minutes with a step frequency >110 steps per minute during waking time) and LPA (minutes with a step frequency ≤110 steps per minute during waking time) (35).

Submaximal cycle ergometer test: CRF. As an objective measure of CRF estimated maximum power output adjusted for body mass ($W_{max} \cdot kg^{-1}$) was used (8,30). W_{max} was estimated from a graded submaximal exercise protocol performed on a cycle ergometer system (CASE^{TM} version 6.6 in combination with e-bike; GE Healthcare, Milwaukee, WI). Participants were excluded from the submaximal cycle ergometer test if they had experienced cardiovascular complications in the preceding 3 months, had an abnormal resting ECG, were known with cardiovascular complications such as pericarditis and hypertrophic cardiomyopathy, had severe hypertension (SBP ≥180 and/or DBP ≥110), renal failure or an ICD/pacemaker. Participants eligible for the test were fitted with a blood pressure cuff on the upper left arm (Tango+; SunTech Medical, Inc., Morisville, NC) and electrodes on the thorax to provide continuously a 12-leads ECG.

The protocol consisted of a short warm-up period and at most seven stages with increasing work load. Participants were instructed to cycle at a cadence of 60–70 rotation per minute (rpm) during a short familiarization period without any external workload. For the first exercise stage, external workload was set at 25 W. Every consecutive 2 min external workload was increased with 25 W. At the end of each stage, HR and blood pressure were measured. Further, the participant was asked to provide a RPE on the 15-point Borg-scale; an interval scale ranging from 6 ("no exertion at all") up to 20 ("maximal exertion"). The exercise protocol was considered as "completed" when HR reached ≥85% of the estimated maximum HR (220 − age) or when a RPE ≥ 17 was scored by the participant. If HR < 85% or RPE < 17 by the end of stage 7 (work load of 175 W), the test was also stopped. The test could also be prematurely terminated on medical grounds or when the participant was unwilling to continue.

Submaximal values of HR and RPE with workload from each stage were extrapolated to 100% of maximum HR or an RPE of 20 and corresponding workload (W_{max}) using individual linear regression models. Using RPE to predict W_{max} overcomes the issue that certain medical conditions, such as autonomous neuropathy and medication use (e.g., beta blockers) may affect the linear association of HR with power output. Consequently, this protocol is suitable for participants who otherwise would have been excluded from exercise testing (27). Analyses demonstrated that estimated W_{max} using HR ($W_{maxHR85\%}$) was comparable to W_{max} based on RPE ($W_{maxRPE17}$) in this study (see document, Supplemental Digital Content 1, Comparison of W_{max} based on HR and W_{max} based on RPE, http://links.lww.com/MSS/A891).

W_{max} was calculated from HR values if the test was completed based on HR, that is, HR ≥ 85% of estimated HR$_{max}$ ($W_{maxHR85\%}$; N = 1201). W_{max} was calculated from RPE values if the test was completed based on RPE, that is, RPE ≥ 17 ($W_{maxRPE17}$; N = 350). In addition to completed tests, W_{max} from uncompleted tests was calculated from HR if ≥75% of HR$_{max}$ was achieved ($W_{maxHR75\%}$; N = 375) and W_{max} was calculated from RPE values if an RPE ≥ 15 was scored ($W_{maxRPE15}$; N = 98). Estimations of W_{max} from these lower ranges of HR and RPE were found to be similar to completed tests (methods and results of the analyses between $W_{maxHR85\%}$ vs $W_{maxHR75\%}$ and $W_{maxRPE17}$ vs $W_{maxRPE15}$ are shown as text and tables in Supplemental Digital Content 2, Estimations of W_{max} from lower ranges of HR, http://links.lww.com/MSS/A892. Tests where both 75% of HR$_{max}$ and RPE15 were not achieved were considered as invalid.

Covariates. The following variables were considered as potential confounders: BMI, age, education level, alcohol use, smoking status, CVD, energy intake, mobility limitations, beta-blocker use, and T2DM. BMI was calculated from weight and height measured in a physical examination to the nearest of 0.5 kg or 0.1 cm. Questionnaires were conducted to collect information on age (in years), sex, educational level, smoking status, alcohol consumption, CVD history, energy intake, and mobility limitations. Educational level was divided into low, middle, and high. Smoking status was divided into current, former, and never smokers. Alcohol consumption was divided into three categories: non-consumers, low consumers (for women ≤7 glasses alcohol per week; for men ≤14 glasses alcohol per week), and high consumers (for women >7 glasses per week; for men >14 glasses alcohol per week) (14). CVD history was derived from the Rose questionnaire and defined as a self-reported history of any of the following conditions: myocardial infarction, cerebrovascular infarction or hemorrhage, percutaneous artery angioplasty of, or vascular surgery on, the coronary, abdominal, peripheral, or carotid arteries. Energy intake was derived from a food frequency questionnaire, which was developed for The Maastricht Study, and calculated as the mean energy intake per day (kcal). Mobility limitation was acquired from the Dutch version of the Short Form Health Survey and was defined as having difficulty with stair climbing and/or walking 500 m (1). The use of diabetes medication and beta blockers was obtained from a medication interview. To determine glucose metabolism status, all participants (except those who use insulin or with a fasting plasma glucose > 11.0 mmol·L^{-1}) underwent a standardized seven-point oral glucose tolerance test after an overnight fast as described elsewhere (28). Glucose metabolism was defined according to the World Health Organization 2006 criteria, and participants were categorized as having a normal glucose metabolism, prediabetes, T2DM, or type 1 diabetes mellitus (and other types). Participants on diabetes medication and without type 1 diabetes were also considered as having T2DM (39).

Statistical analyses. CRF ($W_{max} \cdot kg^{-1}$) was used as a continuous measure and was categorized into tertiles (low,

medium, and high fit) based on sex and age (40–49, 50–59, 60–69, and >70 yr). Descriptive statistics are presented for the total population and by sex. Normally distributed variables are presented as mean (SD), skewed variables are presented as median (interquartile range, 25%–75%]. Percentages are provided for categorical variables.

Linear regression analyses were performed to assess the association between ST, sedentary breaks, average sedentary bout duration, number of prolonged sedentary bouts, LPA and HPA with estimated $W_{max} \cdot kg^{-1}$. Associations were expressed as regression coefficients (B) with 95% confidence intervals. The associations in models 1 were adjusted for waking time, age, education level, and T2DM (to account for oversampling in the study design). In models 2 HPA was added to the model describing ST, and vice versa. ST and HPA were both added in the models describing sedentary breaks, average sedentary bout duration and number of prolonged sedentary bouts. In models describing LPA no other activity was added due to collinearity. Models 3 were additionally adjusted for BMI, alcohol use, smoking status, CVD, beta-blocker use, energy intake and mobility limitations. Interaction terms with sex were significant for ST, prolonged sedentary bouts and HPA ($P < 0.10$). Analyses were therefore stratified by sex. Additional analyses were performed with participants that provided four or more valid days of activPAL data ($n = 1940$) and with participants that had complete ergometer tests ($n = 1551$).

An isotemporal substitution modeling approach was applied to explore the effect of theoretical replacement of ST to other types of activity. For this, three models were created: a single effect model for each type of activity (no adjustments for other activities, nor waking time), a partition model (each type of activity was adjusted for all other activities, but not waking time), and a substitution model (dropping ST from the model and introducing waking time). By doing so, in the substitution model, the regression coefficient of each type of activity represents the (independent) estimated change in $W_{max} \cdot kg^{-1}$ of replacing 1 h of ST (the only type of activity not included in the model) by this activity. The associations in all models were adjusted for age, education level, and T2DM, BMI, alcohol use, smoking status, CVD, beta-blocker use, energy intake and mobility limitations. In these substitution models, there was no indication for collinearity (all VIF <1.5, Pearson correlation coefficients between exposures: standing LPA, 0.35; standing HPA, 0.17; LPA-HPA, 0.22).

All analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY).

RESULTS

Compared with the excluded population ($N = 1427$), the included population of this study was generally healthier. For instance, the study population had a lower BMI and there were fewer participants with T2DM, a history of CVD and mobility limitations (data not tabulated). This was largely due to the exclusion criteria applied for the exercise test. Table 1 presents the characteristics of the total study population ($N = 2024$) and stratified by sex. The participants, of whom 49.3% were men, had a mean ± SD age of 59.7 ± 8.1 yr. More than 95% of the study population provided four or more valid days

TABLE 1. Descriptive characteristics of the total study population, and according to sex.

	Total Population ($n = 2024$)		Men ($n = 997$)		Women ($n = 1027$)	
Age (yr)	59.7	(8.1)	60.9	(7.9)	58.6	(8.2)
Education level (%)						
High	39.6		43.5		35.8	
Medium	28.5		29.0		27.9	
Low	31.9		27.5		36.2	
Smoking status (% current smokers)	12.1		13.1		11.1	
Alcohol consumption (% high consumers)	25.4		23.1		27.8	
Energy intake (kcal·d^{-1})	2167.7	(596.4)	2358.8	(618.5)	1981.6	(509.9)
Mobility limitation (% with limitation)	17.1		15.2		18.9	
BMI (kg·m^{-2})	26.7	(4.3)	27.4	(3.9)	26.0	(4.5)
(History of) CVD (%)	13.9		15.9		12.0	
Glucose metabolism status (%)						
Normal glucose metabolism	58.3		47.3		68.8	
Prediabetes	15.5		16.5		14.4	
T2DM	25.3		35.3		15.6	
Type 1 diabetes or other	0.9		0.8		1.2	
Antihypertensive medication (β-blockers) (%)	15.8		19.9		11.9	
No. valid days						
<4 valid days (%)	4.2		4.8		3.5	
≥4 valid days (%)	95.8		95.2		96.5	
Waking time (h·d^{-1})	15.7	(0.9)	15.8	(0.9)	15.7	(0.9)
ST (h·d^{-1})	9.3	(1.6)	9.8	(1.5)	8.8	(1.6)
Total PA (h·d^{-1})	2.0	(0.7)	2.0	(0.7)	2.1	(0.6)
HPA (min·d^{-1})	19.5	[9.9–32.0]	14.7	[7.2–26.9]	23.5	[14.5–35.3]
Sedentary breaks (N per day)	37.6	(8.5)	37.8	(9.0)	37.4	(8.1)
Average sedentary bout duration (min)	11.1	(3.5)	11.7	(3.7)	10.5	(3.1)
Sedentary bouts ≥30 min (N per day)	4.8	(1.5)	5.1	(1.6)	4.5	(1.4)
CRF (W_{max})	164.8	(48.3)	191.3	(46.6)	139.2	(34.1)
CRF adjusted for body mass ($W_{max} \cdot kg^{-1}$)	2.14	(0.58)	2.26	(0.60)	2.02	(0.52)

Values are means (SD), median (25%–75%), or percentages. BMI, body mass index; W_{max}, estimated maximum work load (W).
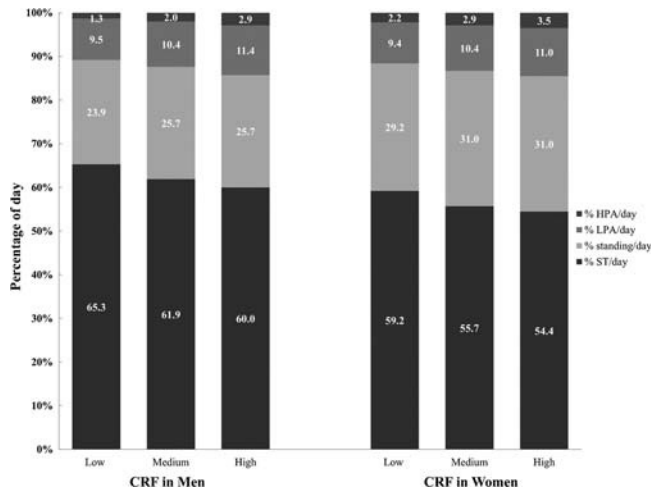
FIGURE 1—Percentage ST, standing time, LPA, and HPA per day, according to CRF category (low, medium, and high) and sex.

of activPAL data with, on average, 15.7 h of waking time. With 9.8 ± 1.5 h, men spent on average 1 h·d^{-1} more in a sedentary position during waking hours than women. Men had a higher estimated W_{max} than women: 2.62 ± 0.60 versus 2.02 ± 0.52 W·kg^{-1}.

Figure 1 presents the proportion of the day spent sedentary, standing, in LPA and HPA for each (age specific) CRF category. Proportion of time per day spent in a sedentary position was 65.3% for men and 59.2% for women with low level of CRF. This was 60.0% for men and 54.4% for women with high CRF. Standing time was higher in men and lower in women with increasing CRF level. Both men and women in the highest CRF category spent more time in LPA and HPA compared with those with lower CRF level.

Table 2 presents the waking time adjusted associations of ST and sedentary behavior pattern variables with CRF (W_{max}·kg^{-1}) stratified by sex. More ST per day was associated with lower CRF after adjustment for waking time, age, education level, T2DM, and HPA (model 2): $B_{men} = -0.05$ W·kg^{-1} (95% confidence interval [CI], -0.07 to -0.03) and $B_{women} = -0.03$ W·kg^{-1} (95% CI, -0.05 to -0.01). As we adjusted for waking time and HPA, these regression coefficients should be interpreted as the associations of engaging 1 h in ST instead of standing and/or LPA. After

adjustment for BMI, alcohol use, smoking status, CVD, beta-blocker use, energy intake, and mobility limitations (model 3) associations remained statistically significant. More sedentary breaks per day were associated with higher CRF independent of HPA and ST (model 2): $B_{men} = 0.04$ W·kg^{-1} (0.01; 0.08) and $B_{women} = 0.06$ W·kg^{-1} (0.02; 0.09). A longer average sedentary bout duration was associated with lower CRF independent of HPA and ST (model 2): $B_{men} = -0.02$ W·kg^{-1} (95% CI, -0.03 to -0.01) and $B_{women} = -0.02$ W·kg^{-1} (95% CI, -0.03 to -0.01). After adjustment for additional potential confounders (model 3), these associations became statistically nonsignificant. Associations between prolonged sedentary bouts and CRF were statistically significant in model 1, but this was no longer seen after additional adjustment for HPA and ST (model 2); $B_{men} = -0.02$ W·kg^{-1} (95% CI, -0.05 to 0.01) and $B_{women} = -0.03$ W·kg^{-1} (95% CI, -0.06 to 0.00).

Table 3 presents the waking time adjusted associations of LPA and HPA with CRF (W_{max}·kg^{-1}) stratified by sex. More time spent in LPA and HPA were associated with higher CRF. Statistically significant associations between LPA and CRF were observed after adjustment for all potential confounders (model 3): $B_{men} = 0.12$ W·kg^{-1} (95% CI, 0.07–0.17) and $B_{women} = 0.12$ W·kg^{-1} (95% CI, 0.07–0.18). Associations between HPA and CRF in models 3 were: $B_{men} = 0.48$ W·kg^{-1} (95% CI, 0.38–0.58) and $B_{women} = 0.27$ W·kg^{-1} (95% CI, 0.18–0.36). One may interpret these regression coefficients as the associations of engaging 1 h in LPA and HPA, respectively, as a replacement for engaging in an activity not included in the model.

Table 4 shows that each type of activity was associated with CRF in the single effect models (similar as in Tables 2 and 3 but without adjustment for waking time). Further, it shows that, when all activities were adjusted for each other (partition model), only LPA and HPA were associated with CRF. The substitution model shows the effect on CRF of the theoretical replacement of ST by other types of activity (standing, LPA and HPA). After adjustment for potential confounders, replacing 1 h of ST with standing was not associated with higher CRF. Replacing 1 h of ST with 1 h of LPA was associated with higher CRF: $B_{men} = 0.08$ W·kg^{-1} (95% CI, 0.03–0.14) and $B_{women} = 0.10$ W·kg^{-1} (95% CI, 0.05–0.15). Replacing 1 h of ST with 1 h of HPA was

TABLE 2. Associations of ST and sedentary behavior pattern variables with estimated CRF (W·kg^{-1}) stratified by sex.

		ST		Sedentary Breaks (10 per day)		Average Sedentary Bout Duration (min)		Prolonged Sedentary Bouts (n per day)	
		B	(95% CI)	B	(95% CI)	B	(95% CI)	B	(95% CI)
Men	Model 1	**−0.08**	**(−0.10 to −0.06)**	**0.09**	**(0.05 to 0.13)**	**−0.03**	**(−0.04 to −0.02)**	**−0.07**	**(−0.09 to −0.05)**
	Model 2	**−0.05**	**(−0.07 to −0.03)**	**0.04**	**(0.01 to 0.08)**	**−0.02**	**(−0.03 to −0.01)**	−0.02	(−0.05 to 0.01)
	Model 3	**−0.03**	**(−0.05 to −0.01)**	0.02	(−0.02 to 0.05)	−0.01	(−0.02 to 0.00)	−0.01	(−0.04 to 0.02)
Women	Model 1	**−0.06**	**(−0.08 to −0.04)**	**0.08**	**(0.04 to 0.11)**	**−0.03**	**(−0.04 to −0.02)**	**−0.06**	**(−0.08 to −0.04)**
	Model 2	**−0.03**	**(−0.05 to −0.01)**	**0.06**	**(0.02 to 0.09)**	**−0.02**	**(−0.03 to −0.01)**	−0.03	(−0.06 to 0.00)
	Model 3	**−0.02**	**(−0.04 to 0.00)**	0.02	(−0.01 to 0.06)	−0.01	(−0.02 to 0.00)	−0.01	(−0.04 to 0.02)

Results are presented as unstandardized regression coefficients (B), with 95% CI. The associations in models 1 adjusted for: waking time, age, education level, and T2DM. Model 2: model 1 + HPA for ST; + HPA and ST for sedentary breaks, mean bout duration and prolonged sedentary bouts. Model 3: model 2 + BMI, alcohol use, smoking status, CVD, beta-blocker use, energy intake and mobility limitations. Bold fonts indicate statistical significance $P < 0.05$.

TABLE 3. Associations of lower intensity activity and higher intensity physical with estimated CRF ($W \cdot kg^{-1}$) stratified by sex.

		LPA ($h \cdot d^{-1}$)		HPA ($h \cdot d^{-1}$)	
		B	**(95% CI)**	**B**	**(95% CI)**
Men	Model 1	**0.22**	**(0.16–0.27)**	**0.68**	**(0.58–0.79)**
	Model 2	n.a.		**0.61**	**(0.50–0.72)**
	Model 3	**0.12**	**(0.07–0.17)**	**0.48**	**(0.38–0.58)**
Women	Model 1	**0.20**	**(0.14–0.25)**	**0.45**	**(0.36–0.54)**
	Model 2	n.a.		**0.40**	**(0.31–0.50)**
	Model 3	**0.12**	**(0.07–0.18)**	**0.27**	**(0.18–0.36)**

Results are presented as unstandardized regression coefficients (*B*), with 95% CI. The associations in models 1 adjusted for: waking time, age, education level, and T2DM. Model 2: model 1 + ST. n.a.: No additional adjustment for other type(s) of activity in the model for LPA due to collinearity. Model 3: model 2 + BMI, alcohol use, smoking status, CVD, beta-blocker use, energy intake, and mobility limitations. Bold fonts indicate statistical significance $P < 0.05$.

associated with higher CRF: $B_{men} = 0.49$ $W \cdot kg^{-1}$ (95% CI, 0.39–0.59) and $B_{women} = 0.28$ $W \cdot kg^{-1}$ (95% CI, 0.10–0.36).

Results were similar when analyses were repeated after excluding participants with les than four valid days of activPAL measurement (data not shown). Additionally, results were similar after excluding participants where W_{max} was calculated from completed ergometer tests (data not shown).

DISCUSSION

This study is one of the first to evaluate the mutually independent associations of objectively measured ST, sedentary behavior patterns, LPA, and HPA with CRF. Our results show that more ST per day was associated with lower CRF, independent from HPA. Sedentary breaks and average sedentary bout duration were associated also with CRF. However, these associations were attenuated and no longer statistically significant in the fully adjusted models. Further, both daily LPA and HPA were positively associated with CRF, independent of potential confounders. The theoretical replacement of ST with HPA or with LPA was associated with higher CRF. The greatest estimated change in CRF was observed when ST was replaced with HPA.

In our study, one additional hour of ST corresponded with, on average, approximately 1.2% lower $W_{max} \cdot kg^{-1}$ for men and approximately 0.9% lower $W_{max} \cdot kg^{-1}$ for women. The strength of these associations is clearly less than strength of the association observed between LPA and HPA with CRF; reducing 1 h of ST approximately resembles an increase of 5 min of HPA. However, small improvements in CRF have been associated with reduced risk for CVD and mortality in particularly the least-fit part of the adult population (5). Therefore, reductions in ST may improve CRF, which could be beneficial for health. This conclusion is supported by the results from the isotemporal substitution analyses that show that replacing ST with LPA was associated with higher CRF (independent of time engaged in standing and HPA). Of note, replacing ST with HPA was associated with a greater estimated change in CRF. Consequently, engaging in HPA is most important for CRF than increasing time spent with LPA. However, for many people (elderly or those with functional limitations). replacing ST by LPA may be more feasible than replacing ST by HPA.

To our knowledge, only two studies have previously reported on associations between objectively measured ST and CRF in adults (19,26). In the study by Kulinski et al. (19), a small, but statistically significant inverse association between objectively measured ST and CRF was reported in a population age 12 to 49 yr, after adjustment for MVPA. In the study by Prince et al. (26), an inverse association between ST and CRF was reported in a postcardiac rehabilitation population. Both studies are in line with our findings. Several other studies have evaluated the association between ST and CRF using self-reported measures of ST. Results from these studies were inconsistent. Tucker et al. (33) reported that female frequent TV viewers had a lower CRF, but after adjustment for PA and BMI, this effect was attenuated and no longer statistically significant. A large-scale population based study by Eriksen et al. (13) reported inverse associations between ST and CRF in participants who reported low levels of PA, while no association between ST and CRF was reported in those who were classified as being moderately or vigorously

TABLE 4. Single, partition, and isotemporal substitution models examining the associations of ST, standing time, lower- and higher-intensity physical activities with CRF and the theoretical replacement of 1 h ST with other activities, stratified by sex.

		ST		Standing		LPA		HPA	
		B	**(95% CI)**	**B**	**(95% CI)**	**B**	**(95% CI)**	**B**	**(95% CI)**
Men	Single[a]	**−0.04**	**(−0.11 to −0.06)**	**0.03**	**(0.01 to 0.06)**	**0.14**	**(0.09 to 0.19)**	**0.53**	**(0.43 to 0.63)**
	Partition[b]	0.02	(−0.0 to 0.06)	0.03	(−0.00 to 0.07)	**0.11**	**(0.05 to 0.17)**	**0.52**	**(0.41 to 0.62)**
	Substitution[c]		Dropped	0.01	(−0.02 to 0.04)	**0.08**	**(0.03 to 0.14)**	**0.49**	**(0.39 to 0.59)**
Women	Single[a]	**−0.02**	**(−0.04 to −0.01)**	**0.02**	**(0.00 to 0.04)**	**0.14**	**(0.09 to 0.19)**	**0.32**	**(0.23 to 0.40)**
	Partition[b]	0.03	(0.00 to 0.06)	0.03	(0.00 to 0.06)	**0.13**	**(0.08 to 0.20)**	**0.31**	**(0.22 to 0.40)**
	Substitution[c]		Dropped	−0.00	(−0.02 to 0.02)	**0.10**	**(0.05 to 0.16)**	**0.28**	**(0.19 to 0.36)**

[a]No adjustment for other type of activity nor for wear time.
[b]Each activity was adjusted for all other types of activity, no adjustment for wear time.
[c]ST was dropped from the model, and additionally adjusted for wear time.
The associations in all models were adjusted for age, education level, and T2DM, BMI, alcohol use, smoking status, CVD, beta-blocker use, energy intake, and mobility limitations.

active. Lastly, Barlow et al. (3) found a detrimental association between more self-reported sitting time and CRF in women independent of levels of PA.

This study is, to the best of our knowledge, the first to examine pattern variables of sedentary behavior with CRF. Sedentary breaks have previously been associated with improved cardiometabolic health in some studies (11,15). In our study, an association was observed between sedentary breaks and CRF independent of ST and HPA, but not independent of health related variables in model 3. Similar results were observed for average sedentary bout duration. Prolonged sedentary bouts lasting ≥ 30 min were not associated with CRF independent of HPA and ST. Although it has been suggested that long uninterrupted periods of ST are detrimental for health (11,12), it is unknown at what duration a prolonged sedentary bout becomes detrimental. Possibly this is not at 30 min, but after 60 or 90 min or even longer. Based on our results, total ST seems to be more important for CRF than SB patterns. The mechanisms through which sedentary behavior affects CRF are not yet fully understood. Partly it could be explained by vascular changes in response to sedentary behavior. The pathways, through which these changes occur, appear to be distinct from pathways that are involved in vascular changes in response to PA (31). Clearly, more research in this area is warranted to further investigate how sedentary behavior affects CRF.

Our finding that LPA and HPA were strongly associated with CRF elaborates on the existing body of evidence linking PA to CRF (20,22). Mechanisms through which HPA improves CRF have been studied comprehensively and include vascular, muscular, and respiratory adaptations (24). These responses are found to be largest when PA is of higher intensity and/or longer duration. In our study, one additional hour of HPA per day corresponded with, on average, approximately 21% higher $W_{max}\cdot kg^{-1}$ for men and ~13% higher $W_{max}\cdot kg^{-1}$ for women. Similar amounts have been associated with reduced mortality risk (17). The difference between men and women in our study may be explained by a larger range in W_{max} for men compared with women, because men are physiologically capable of achieving higher levels of W_{max}.

A strength of this study was the use of a posture based accelerometer in a large sample of adults. The activPALP3 has been found to accurately measure (patterns of) sedentary behavior (4,18,23). Therefore, our estimations of ST were probably better than those in previous studies using other types of accelerometers. Further, CRF was estimated from a submaximal exercise protocol incorporating both HR and RPE. Extrapolating submaximal values of RPE, similarly as HR, has been shown to be an alternative and valid method to estimate CRF (10). By incorporating RPE in addition to HR, estimates of CRF were also obtained from individuals who otherwise would have been excluded from exercise testing due to medication use or medical conditions. Nevertheless, exclusion for exercise testing based on medical condition has introduced selection bias in this study, though to a lesser extent than in many other epidemiological studies measuring CRF. It should be noted that the analyses to compare W_{maxHR} with W_{maxRPE} (see document, Supplemental Digital Content 1, Comparison of W_{max} based on HR and W_{max} based on RPE, http://links.lww.com/MSS/A891) were only performed in a subset of the Maastricht Study population. Furthermore, the use of a submaximal exercise test instead of a maximal exercise test to estimate W_{max} may be considered as a limitation, since this may have resulted in underestimation or overestimation of actual W_{max}. Nevertheless, high correlations ($r = 0.76$–0.98) between estimated CRF and measured CRF have been reported in previous studies (2). Further, the associations in this study were adjusted for a series of potential confounders. As The Maastricht Study is enriched with participants with T2DM, adjustments were made for T2DM in the associations of model 1. However, T2DM may lie in the pathway between sedentary behavior and CRF, as ST has previously been associated with increased odds for T2DM in this population (36). Consequently, these adjustments may have resulted in over adjustment bias. Overadjustment may also be an issue in the fully adjusted models (models 3). For instance, sedentary behavior has been associated with increased BMI and increased risk for CVD, which both have been associated with lower CRF. Consequently, the strength of the associations as reported in this study may actually be greater.

Some other limitations should be considered as well. Most importantly, the cross-sectional design of the study requires caution with regard to causal inferences. In addition, at least one valid day of accelerometer wear time was considered sufficient in this study, but 1 d may not be representative for habitual behavior. However, 95% of the study population provided at least four valid days of accelerometer data, and results were similar when participants with less than four valid days of wear time were excluded from analyses. Further, LPA and HPA was based on step frequency which may be less precise to determine intensity levels compared with estimations of LPA and HPA based on acceleration data. However, we used a step frequency of >~100 steps per minute which has been reported to correspond to a MET score of approximately 3.0 (a frequently used cutoff value for moderate to vigorous PA) (34). Finally, our study population consisted of a relatively healthy population of predominantly whites from European descent with well controlled participants with T2DM. Therefore, generalizability of our results may be limited.

In conclusion, more daily ST appeared to be modestly associated with lower CRF, independent of HPA. Both LPA and HPA were associated with higher CRF. Replacing ST with LPA was associated with a positive estimated change in CRF, which is particularly helpful for people who are unable to engage in HPA. Further, replacing ST with HPA was associated with greatest estimated change in CRF. Therefore, engaging regularly in HPA appears to be the best strategy to improve CRF.

REFERENCES

1. Aaronson NK, Muller M, Cohen PD, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol*. 1998;51(11):1055–68.

2. Akalan C, Roberg RA, Kravitz L. Prediction of VO2max from an individualized submaximal cycle ergometer protocol. *J Exerc Physiol Online*. 2008;11(2):1–17.

3. Barlow CE, Shuval K, Balasubramanian BA, Kendzor DE, Pettee Gabriel K. Sitting time, physical activity and cardiorespiratory fitness: Cooper Center Longitudinal Study Cohort. *J Phys Act Health*. 2016;13(1):17–23.

4. Berendsen BA, Hendriks MR, Meijer K, Plasqui G, Schaper NC, Savelberg HH. Which activity monitor to use? Validity, reproducibility and user friendliness of three activity monitors. *BMC Public Health*. 2014;14:749.

5. Blair SN, Connelly JC. How much physical activity should we do? The case for moderate amounts and intensities of physical activity. *Res Q Exerc Sport*. 1996;67(2):193–205.

6. Blair SN, Kampert JB, Kohl HW 3rd, et al. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA*. 1996;276(3): 205–10.

7. Bouchard C, Rankinen T. Individual differences in response to regular physical activity. *Med Sci Sports Exerc*. 2001;33(6 Suppl): S446–51, discussion S52–3.

8. Bovens AM, Van Baak MA, Vrencken JG, Wijnen JA, Saris WH, Verstappen FT. Maximal aerobic power in cycle ergometry in middle-aged men and women, active in sports, in relation to age and physical activity. *Int J Sports Med*. 1993;14(2):66–71.

9. Brocklebank LA, Falconer CL, Page AS, Perry R, Cooper AR. Accelerometer-measured sedentary time and cardiometabolic biomarkers: a systematic review. *Prev Med*. 2015;76:92–102.

10. Coquart JB, Garcin M, Parfitt G, Tourny-Chollet C, Eston RG. Prediction of maximal or peak oxygen uptake from ratings of perceived exertion. *Sports Med*. 2014;44(5):563–78.

11. Dunstan DW, Kingwell BA, Larsen R, et al. Breaking up prolonged sitting reduces postprandial glucose and insulin responses. *Diabetes Care*. 2012;35(5):976–83.

12. Duvivier BM, Schaper NC, Bremers MA, et al. Minimal intensity physical activity (standing and walking) of longer duration improves insulin action and plasma lipids more than shorter periods of moderate to vigorous exercise (cycling) in sedentary subjects when energy expenditure is comparable. *PLoS One*. 2013;8(2):e55542.

13. Eriksen L, Grønbaek M, Helge JW, Tolstrup JS. Cardiorespiratory fitness in 16 025 adults aged 18–91 years and associations with physical activity and sitting time. *Scand J Med Sci Sports*. 2016;26(12):1435–43.

14. Health Council of the Netherlands. Guidelines for a healthy diet 2006. The Hague: Health Council of the Netherlands, 2006; publication no. 2006/21.

15. Healy GN, Dunstan DW, Salmon J, et al. Breaks in sedentary time: beneficial associations with metabolic risk. *Diabetes Care*. 2008; 31(4):661–6.

16. Katzmarzyk PT, Church TS, Blair SN. Cardiorespiratory fitness attenuates the effects of the metabolic syndrome on all-cause and cardiovascular disease mortality in men. *Arch Intern Med*. 2004;164(10):1092–7.

17. Kodama S, Saito K, Tanaka S, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: a meta-analysis. *JAMA*. 2009;301(19):2024–35.

18. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson PS. Validation of wearable monitors for assessing sedentary behavior. *Med Sci Sports Exerc*. 2011;43(8):1561–7.

19. Kulinski JP, Khera A, Ayers CR, et al. Association between cardiorespiratory fitness and accelerometer-derived physical activity and sedentary time in the general population. *Mayo Clin Proc*. 2014;89(8):1063–71.

20. Laukkanen JA, Laaksonen D, Lakka TA, et al. Determinants of cardiorespiratory fitness in men aged 42 to 60 years with and without cardiovascular disease. *Am J Cardiol*. 2009;103(11): 1598–604.

21. Lee DC, Artero EG, Sui X, Blair SN. Mortality trends in the general population: the importance of cardiorespiratory fitness. *J Psychopharmacol*. 2010;24(4 Suppl):27–35.

22. Lin X, Zhang X, Guo J, et al. Effects of exercise training on cardiorespiratory fitness and biomarkers of cardiometabolic health: A systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2015;4(7):e002014.

23. Lyden K, Kozey Keadle SL, Staudenmayer JW, Freedson PS. Validity of two wearable monitors to estimate breaks from sedentary time. *Med Sci Sports Exerc*. 2012;44(11):2243–52.

24. McArdle WD, Katch FI, Katch VL. *Exercise Physiology: Nutrition, Energy, and Human Performance*. Baltimore, MD: Lippincott Williams & Wilkins; 2010. pp. 451–75.

25. Owen N, Healy GN, Matthews CE, Dunstan DW. Too much sitting: the population health science of sedentary behavior. *Exerc Sport Sci Rev*. 2010;38(3):105–13.

26. Prince SA, Blanchard CM, Grace SL, Reid RD. Objectively-measured sedentary time and its association with markers of cardiometabolic health and fitness among cardiac rehabilitation graduates. *Eur J Prev Cardiol*. 2016;23:818–25.

27. Sartor F, Vernillo G, de Morree HM, et al. Estimation of maximal oxygen uptake via submaximal exercise testing in sports, clinical, and home settings. *Sports Med*. 2013;43(9): 865–73.

28. Schram MT, Sep SJ, van der Kallen CJ, et al. The Maastricht Study: an extensive phenotyping study on determinants of type 2 diabetes, its complications and its comorbidities. *Eur J Epidemiol*. 2014;29(6):439–51.

29. Sedentary Behaviour Research Network. Letter to the editor: standardized use of the terms "sedentary" and "sedentary behaviours." *Appl Physiol Nutr Metab*. 2012;37(3):540–2.

30. Storer TW, Davis JA, Caiozzo VJ. Accurate prediction of VO2max in cycle ergometry. *Med Sci Sports Exerc*. 1990;22(5): 704–12.

EPIDEMIOLOGY

31. Thijssen DH, Green DJ, Hopman MT. Blood vessel remodeling and physical inactivity in humans. *J Appl Physiol (1985)*. 2011; 111(6):1836–45.

32. Tucker JM, Welk GJ, Beyler NK. Physical activity in U.S.: adults compliance with the physical activity guidelines for Americans. *Am J Prev Med*. 2011;40(4):454–61.

33. Tucker LA, Arens PJ, LeCheminant JD, Bailey BW. Television viewing time and measured cardiorespiratory fitness in adult women. *Am J Health Promot*. 2015;29(5):285–90.

34. Tudor-Locke C, Craig CL, Brown WJ, et al. How many steps/ day are enough? For adults. *Int J Behav Nutr Phys Act*. 2011;8:79.

35. Tudor-Locke C, Rowe DA. Using cadence to study free-living ambulatory behaviour. *Sports Med*. 2012;42(5):381–98.

36. van der Berg JD, Stehouwer CD, Bosma H, et al. Associations of total amount and patterns of sedentary behaviour with type 2 diabetes and the metabolic syndrome: the Maastricht Study. *Diabetologia*. 2016;59(4):709–18.

37. van der Berg JD, Willems PJ, van der Velde JH, et al. Identifying waking time in 24-h accelerometry data in adults using an automated algorithm. *J Sports Sci*. 2016;34(19):1867–73.

38. Wilmot EG, Edwardson CL, Achana FA, et al. Sedentary time in adults and the association with diabetes, cardiovascular disease and death: systematic review and meta-analysis. *Diabetologia*. 2012; 55(11):2895–905.

39. World Health Organization. *Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia*. Geneva, Switzerland: World Health Organization; 2006. pp. 1–3.

EPIDEMIOLOGY