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Isotemporal Substitution of Time Between Sleep and Physical Activity: Associations With Cardiovascular Risk Factors in Early Rheumatoid Arthritis

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Objective. We aimed to determine relationships between objectively measured nightly sleep, sedentary behavior (SB), light physical activity (LPA), and moderate to vigorous physical activity (MVPA) with risk factors for cardiovascular disease (CVD) in patients with early rheumatoid arthritis (RA). Furthermore, we aimed to estimate consequences for these risk factors of theoretical displacements of 30 minutes per day in one behavior with the same duration of time in another.

Methods. This cross-sectional study included 78 patients with early RA. Nightly sleep, SB, LPA, and MVPA were assessed by a combined heart rate and accelerometer monitor. Associations with risk factors for CVD were analyzed using linear regression models and consequences of reallocating time between the behaviors by isotemporal substitution modeling.

Results. Median (Q1-Q3) nightly sleep duration was 4.6 (3.6-5.8) hours. Adjusted for monitor wear time, age, and sex, 30-minutes-longer sleep duration was associated with favorable changes in the values β (95% confidence interval [CI]) for waist circumference by –2.2 (–3.5, –0.9) cm, body mass index (BMI) by –0.9 (–1.4, –0.4) kg/m^2, body fat by –1.5 (–2.3, –0.8)%, fat-free mass by 1.6 (0.8, 2.3)%, sleeping heart rate by –0.8 (–1.5, –0.1) beats per minute, and systolic blood pressure by –2.5 (–4.0, –1.0) mm Hg. Thirty-minute decreases in SB, LPA, or MVPA replaced with increased sleep was associated with decreased android fat and lower systolic blood pressure levels. Replacement of SB or LPA with MVPA yielded lower BMIs.

Conclusion. Shorter sleep during the night is common among patients with early RA and is associated with adverse risk factors for CVD.

INTRODUCTION

Rheumatoid arthritis (RA) is a common chronic autoimmune disease, manifested by joint inflammation. Stiffness and pain are typical symptoms, leading to sleep disturbances (1), activity limitations, and decreased quality of life (2). Furthermore, the disease is associated with several comorbidities, including cardiovascular disease (CVD), which is a major cause of death in these patients (3,4). The systemic inflammation as well as the increased prevalence of cardiovascular (CV) risk factors seen in patients with RA, play a substantial role in the exacerbated CV risk (5,6).

Studies in the general population show a significant link between risk factors for CVD and the time spent in different activity behaviors such as sleep, sedentary behavior (SB), light physical activity (LPA), and moderate to vigorous physical activity (MVPA) (7,8). The different activity behaviors can be defined by the energy required for performing the activity. Commonly used cutoff points are 0.9 metabolic equivalents (METs ≈ resting energy expenditure) for sleep, 1 to 1.5 METs for SB, 1.6 to 2.9 METs for LPA, and 3 or more METS for MVPA (9). In SB, the person is awake but in a sitting or reclining position (9). A large meta-analysis demonstrated an increased risk in a dose-dependent manner for all CV events and all-cause mortality with less than 7 hours of sleep (10).

To our knowledge, associations between sleep duration and CV health are yet to be investigated in patients with RA, although sleep disturbances are known to be common in these patients (1), with less than 20% reporting good sleep quality in a study by Goes et al (11). SB has been linked to increased long-term CVD risk in those with RA, even after adjustments for MVPA (12). The importance of physical activity and exercise in RA is well established (13). Along with its beneficial effects on joint and muscle function, aerobic capacity, and psychological health, a higher level of physical activity is associated with a more beneficial CV risk profile (14–16) and arterial function (17–19). Exercise interventions improve risk factors (20–22) and decrease long-term risk for CVD (23). Even LPA shows beneficial associations with cardiovascular health (24). In earlier publications on the same cohort as in the present study, advantageous relationships with risk factors for CVD were demonstrated for higher levels of physical activity (25) and aerobic capacity (26).

However, studying the association between different activity behaviors and risk of CVD poses some challenges. Because the total time available in a day is fixed, less time spent in one behavior implies more time spent in another. Consequently, the relative distribution of time spent in the various activity behaviors during a 24-hour period is interesting and should be taken into consideration when analyzing the relationship between activity and health. Spending less time being sedentary could be an important strategy to prevent CVD, but the potential beneficial effects should be mirrored not only by the reduction of time spent being sedentary but also by the behavior it is replaced with. The isotemporal substitution model makes it possible to analyze the association between one behavior and the different health outcomes, whereas the other behaviors are kept constant. It also theoretically analyzes the effect of substituting sedentary time with the same amount of time in sleep, LPA, or MVPA (27,28). The aim of this cross-sectional study was to determine the relationship between the objectively measured sleep, SB, LPA, and MVPA in a 24-hour day with CV risk factors in patients with early RA. Furthermore, we

aimed to estimate the consequences of theoretical reallocations of 30 minutes spent in one behavior with the same duration of time spent in another, on the aforementioned variables.

PATIENTS AND METHODS

Patients. Patients were recruited from the early arthritis cohort at the Department of Rheumatology, University Hospital of Umeå, Sweden. Figure 1 shows the inclusion and exclusion process for the study. Participants included all patients with early RA (with a disease duration of 12-24 months) who were diagnosed between 2013 and 2016 (symptomatic for <12 months before diagnosis (29)). Patients aged over 75 years and those with severe diseases, or functional limitations that hinder physical activity to a higher extent than the limitations caused by RA, were excluded. One participant did not fulfil the 2010 criteria for RA (29) but fulfilled the 1988 criteria (30). However, the results did not change with this patient being omitted from the analyses, so the patient was thereby included. Nine patients were eventually excluded because of invalid data registrations on physical
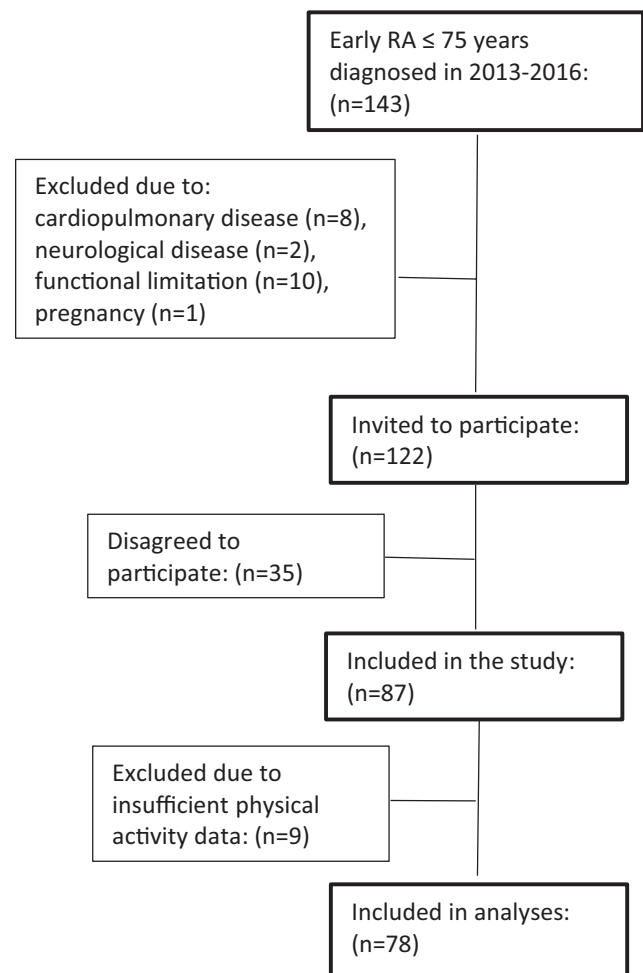
Figure 1. Flowchart of the inclusion and exclusion process in the present study.

activity. Seventy-eight patients were included in the final analyses (Figure 1). No differences were found in the age, sex, disease activity, or functional ability between the 44 excluded and the 78 patients who participated. Data were collected during the years 2015 to 2017 as previously described (25,26). The patients provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the University in Umeå, Sweden (Dnr 2014/356-31).

Methods. *Nightly sleep, SB, and physical activity.* Activity behaviors were measured, day and night, for seven consecutive days using the waterproof monitor Actiheart (CamNTech), which was applied using two standard electrocardiogram (ECG) electrodes (Red Dot 2560, 3M) to the left side of the chest (31). The monitor obtained samples of ECG signals and uniaxial trunk accelerations in 30-second intervals, which were stored. Prior to performing long-term recordings, a signal test was performed as per the instructions of the manufacturer (32). The patients were instructed to change the ECG electrodes at least once during the week and to continue with their habitual activities, including those in water.

The data were cleaned to remove potential measurement noise, and the following variables included in the analyses were calculated: night sleep, SB, LPA, MVPA, and total wear time. Night sleeping time was visually identified on the time-series plots for every patient as a prolonged period of minimal movement and concurrent low heart rate (HR) as described by Collings et al (33). Two examiners (KH and CS) independently examined 10 randomly selected plots, for which disagreements were discussed and consensus was reached for the identification of sleeping time. Sedentary time was defined as the interval of valid HR data with zero accelerometer counts per minute during the wakeful state. The HR $\geq 1.75 \times$ the resting HR represented an energy expenditure of 3 or more METs (34) and was determined as a cutoff between LPA and MVPA. Resting HR was defined as the median of the 30 lowest HR values registered for every 24 hours. Sleeping HR was determined as the highest HR registered, during the 30-minute interval with the lowest heart rates, for every 24 hours. At least 600 minutes of valid HR recording were required for the day to be included in the analyses.

CV risk factors. Levels of cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and glucose from fasting blood samples were analyzed according to standard protocol. Hypertension (defined as the prescription of antihypertensive drugs), tobacco use, diabetes mellitus, and history of CVD (myocardial infarction or stroke) were registered based on patients' report and verified by medical records.

Body composition was measured by dual-energy X-ray absorptiometry (Lunar Prodigy X-ray Tube Housing Assembly, Brand BX-1L, Model 8743 and Lunar iDXA Forma, GE Medical Systems) (35), and the variables included in the analyses were body weight, BMI, body fat, android fat, gynoid fat and fat-free mass. Waist circumference was measured midway between the lower costal margin and the iliac crest. The measurement was performed at the end of a normal expiration while the patient was standing with their arms hanging freely (36).

Pulse wave analysis (Arteriograph Type TL2 v. 3.0.0.3, Tensio-Med Ltd), was used to measure blood pressure: systolic (SBP), diastolic (DBP), aortic systolic (SBPao), and pulse pressure (PPao) (37). The patients rested supine in a quiet room for 10 minutes, after which three measurements were taken in the right arm, the average values of which were noted.

Disease activity and subject characteristics. Rheumatoid factor and anticyclic citrullinated peptide antibody were analyzed using enzyme-linked immunoassays. Erythrocyte sedimentation rate (ESR) and C-reactive proteins (CRP) were also measured using routine methods, and disease activity was calculated as Disease Activity Score (38). Disease duration, defined as time since diagnosis, and current medication were noted. Assessment of pain (Visual Analogue Scale) and functional ability (Stanford Health Assessment Questionnaire) (39) were performed.

Statistics. Data were presented as means with ±1 standard deviation, median with interquartile range (Q1-Q3), or as number with a percentage (%), depending on the distribution of data. Differences between groups were tested by the independent samples t test or χ^2 test. Pearson correlation test or Spearman rank correlation test were used to analyze correlations between daily activity behaviors and association between behaviors and covariates. Linear regression modeling—adjusted for total Actiheart wear time, age, and sex—was performed to examine associations of the individual daily activity behaviors (independent variables) with CV risk factors (dependent variables). Nonnormally distributed data were analyzed both in its original as well as log transformed forms. However, because the results were comparable, the original variables were chosen for the analyses to facilitate the interpretation of the results.

To analyze the theoretical consequences of replacing 30 minutes of one behavior with the same amount of time spent in another behavior, isotemporal substitution modeling was performed as described by Mekary et al (27). Using linear regression modeling, the statistical method controls not only for the confounding effect of other behaviors but also for the fact that daily time is limited. Thus, more time spent in one behavior inevitably leads to less time spent in another. The variables sleep, SB, LPA, MVPA, and total Actiheart wear time were recalculated from 1-minute to 30-minute intervals. Thereby, the β coefficient in the linear regression models represented the effect of reallocating 30 minutes between the behaviors. Independent variables entered in these linear regression models were three of the four behavior variables—sleep, SB, LPA, and MVPA—together with total Actiheart wear time, sex, and age. By adding the "total time" variable, the model limits the available time in a day, ie, the model is isotemporal. For example, when

Table 1. Descriptive data and measures reflecting disease activity, risk factors for CVD, and daily activity behaviors in 78 patients with early rheumatoid arthritis

	All patients (n = 78)	Women (n = 54)	Men (n = 24)
Age, y	55.4 (±14.4)	53.0 (±14.7)	60.8 (±12.4)
Disease duration, y	1.4 (±0.4)	1.4 (±0.4)	1.4 (±0.4)
ACPA pos, n (%)	54 (69%)	38 (70%)	16 (67%)
RF pos, n (%)	59 (76%)	44 (81%)	15 (62%)
DAS 28	2.76 (±1.35)	3.02 (±1.38)	2.18 (±1.12)
ESR, mm/h	13.9 (±10.0)	15.0 (±8.6)	11.5 (±12.4)
Pain, VAS, 0-100 mm	28.0 (±24.8)	30.8 (±25.8)	21.9 (±21.5)
HAQ, 0-3	0.38 (0.0-0.75)	0.50 (0.0-0.88)	0.13 (0.0-0.38)
Treatment			
csDMARDs, n (%)	73 (94%)	49 (91%)	24 (100%)
bDMARDs, n (%)	12 (15%)	9 (17%)	3 (12%)
Corticosteroids, n (%)	20 (26%)	14 (26%)	6 (25%)
Blood lipids			
Cholesterol, mmol/L	5.1 (±1.1)	5.1 (±1.0)	5.0 (±1.2)
Triglycerides, mmol/L	1.3 (±0.7)	1.3 (±0.8)	1.3 (±0.6)
HDL, mmol/L	1.5 (±0.5)	1.6 (±0.5)	1.4 (±0.4)
LDL, mmol/L	3.0 (±0.9)	3.0 (±0.9)	3.0 (±1.0)
Blood glucose, mmol/L	5.8 (±1.4)	5.8 (±1.5)	5.7 (±0.7)
Current smoker, n (%)	9 (12%)	4 (7%)	5 (21%)
Diabetes mellitus, n (%)	5 (6%)	4 (7%)	1 (4%)
History of CVD, n (%)	2 (3%)	0 (0%)	2 (8%)
Hypertension, treated n (%)	27 (35%)	14 (26%)	13 (54%)
Body composition			
Body weight, kg	76.3 (±16.3)	72.9 (±15.9)	83.9 (±14.8)
BMI, kg/m^2	27.2 (±5.4)	27.2 (±5.9)	27.0 (±4.2)
Waist circumference, cm	95.6 (±15.3)	93.0 (±15.7)	101.6 (±12.6)
Body fat, %	38.2 (±9.9)	41.4 (±9.1)	31.2 (±7.6)
Android fat, %	44.6 (±11.4)	46.2 (±12.0)	41.0 (±9.0)
Gynoid fat, %	41.7 (±10.1)	46.0 (±8.2)	31.8 (±6.4)
Fat-free mass, %	63.6 (±10.7)	60.1 (±9.0)	69.9 (±7.4)
Pulse wave analysis			
SBP, mm Hg	131.1 (±16.9)	129.8 (±17.4)	134.1 (±15.7)
DBP, mm Hg	78.5 (±9.6)	77.0 (±9.4)	82.0 (±9.4)
SBP ao, mm Hg	128.8 (±19.3)	128.1 (±20.4)	130.5 (±16.7)
PP ao, mm Hg	50.0 (±12.3)	50.7 (±13.2)	48.4 (±9.9)
Sleeping HR, beats/min	60.9 (±7.5)	61.0 (±7.9)	60.7 (±6.4)
Actiheart wear time			
Minutes per 24 hours	1160 (995-1248)	1160 (1020-1248)	1147 (949-1245)
Sleep			
Minutes per night	276 (213-345)	264 (213-331)	302 (189-357)
SB			
Percent of awake wear time	43 (35-50)	42 (35-51)	43 (35-49)
Minutes per day	356 (275-446)	356 (271-446)	354 (277-443)
LPA			
Percent of awake wear time	51 (40-56)	51 (40-57)	51 (39-56)
Minutes per day	421 (338-471)	422 (332-471)	410 (341-479)
MVPA			
Percent of awake wear time	5 (1-11)	5 (1-10)	4 (1-12)
Minutes per day	42 (11-86)	43 (11-82)	30 (11-115)

Note. Data are presented as mean with standard deviation (± SD), median with interquartile range (Q1-Q3) or as number with percent (%) as appropriate. Disease duration is the years since diagnosis.

Abbreviations: ACPA, anticitrullinated protein antibodies; bDMARDs, biological disease-modifying antirheumatic drugs; BMI, body mass index; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CVD, cardiovascular disease; DAS28, Disease Activity Score; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire; HDL, high-density lipoprotein; HR, heart rate; LPA, light physical activity; LDL, low-density lipoprotein; MVPA, moderate to vigorous physical activity; PP ao, aortic pulse pressure; RF, rheumatoid factor; SB, sedentary behavior; SBP, systolic blood pressure; SBP ao, aortic SBP; VAS, Visual Analogue Scale.

estimating the consequence of replacing 30 minutes of SB with 30 minutes of sleep, LPA, or MVPA, the variable SB was omitted from the model. By including total Actiheart wear time and omitting SB, the β coefficients for sleep, LPA, and MVPA represent the theoretical consequence of replacing SB with that activity for 30 minutes, respectively. Dependent variables in the models included CV risk factors that had significant associations with any activity behavior. Isotemporal substitution modeling requires a linear relationship between the variables. However, sleep has shown a U-shaped association with CV risk factors with the lowest risk at about 7 hours of sleep (10). Because only four patients had a mean sleep duration of more than 7 hours per night and none had more than 8 hours, sleep duration was considered to have a linear relation to the variables included in the analyses. Complementary linear regression analyses were performed after the exclusion of patients on medication, including corticosteroids or antihypertensive drugs. Furthermore, analyses of body composition were carried out for women and men separately. Statistical calculations were undertaken using the Statistical Package for Social Sciences for Windows (SPSS), version 26 (IBM Corp) and a value of $p < 0.05$ was considered statistically significant.

RESULTS

The median number of valid days with acceptable Actiheart recordings was 5.0 (3.0-6.0) days. The median sleep duration at night was 276 minutes, ie, 4.6 hours, for the whole group (Table 1). Patients on corticosteroids revealed no differences statistically in median sleep duration when compared with the other patients (median [Q1-Q3]: 279 [225-359] minutes per night). SB showed a moderate correlation with LPA and MVPA ($r_s = -0.341$ and $r_s = -0.333$, respectively, both $p < 0.01$). No significant relationships were found between sleep and other activity behaviors or between LPA and MVPA (data not shown). Furthermore, no correlations were found between activity behaviors and disease activity, measured as ESR, CRP, or DAS 28 (data not shown).

Associations between activity behaviors and risk factors for CVD. The most pronounced associations between daily activity behaviors (independent variables) and individual variables reflecting CV risk factors (dependent variables) were found with sleeping duration (Table 2). After adjustments for Actiheart wear time, age, and sex, longer sleep duration was associated with more favorable values of body composition, sleeping HR, and blood pressure. On the contrary, more time spent sedentary was associated with higher proportion of body fat and lower fat-free mass. No significant associations were found between LPA or MVPA with CV risk factors (Table 2). When the analyses were performed after exclusion of patients medicated with corticosteroids, the results were similar (data not shown). In separate analyses for men and women for associations between behavior and variables reflecting body composition, no significant associations were found for men, whereas apart from numerically higher β values, women showed the same results as for the whole group (data not shown).

Isotemporal substitution models. The theoretical consequences of reallocating 30 minutes per day of one behavior with an equal amount of time in another on CV risk factors are presented in Table 3. Replacing sleep with SB, LPA, or MVPA was

Table 2. Linear regression analyses of variables reflecting the risk factors for CVD in relation to increase of sleep, sedentary behavior, light physical activity, and moderate to vigorous physical activity by 30 minutes per day in 78 patients with early RA

	Sleep β (95% CI)	SB β (95% CI)	LPA β (95% CI)	MVPA β (95% CI)
Cholesterol, mmol/L	−0.02 (−0.12, 0.08)	0.00 (−0.06, 0.07)	0.02 (−0.04, 0.08)	−0.01 (−0.07, 0.05)
Triglycerides, mmol/L	−0.03 (−0.10, 0.04)	0.03 (−0.02, 0.07)	0.01 (−0.03, 0.06)	−0.02 (−0.06, 0.02)
HDL, mmol/L	0.02 (−0.03, 0.07)	−0.02 (−0.05, 0.01)	−0.01 (−0.04, 0.02)	0.02 (−0.01, 0.05)
LDL, mmol/L	−0.02 (−0.11, 0.06)	0.01 (−0.04, 0.07)	0.02 (−0.03, 0.07)	−0.02 (−0.07, 0.03)
Blood glucose, mmol/L	−0.01 (−0.16, 0.14)	0.04 (−0.07, 0.16)	0.02 (−0.09, 0.12)	−0.04 (−0.14, 0.06)
Body weight, kg	**−2.53 (−3.94, −1.12)**	0.50 (−0.48, 1.48)	0.69 (−0.22, 1.59)	−0.19 (−1.07, 0.69)
BMI, kg/m^2	**−0.90 (−1.38, −0.40)**	0.31 (−0.02, 0.65)	0.20 (−0.12, 0.52)	−0.14 (−0.44, 0.17)
Waist circumference, cm	**−2.21 (−3.51, −0.91)**	0.79 (−0.09, 1.67)	0.49 (−0.34, 1.32)	−0.35 (−1.15, 0.45)
Body fat, %	**−1.53 (−2.27, −0.79)**	**0.59 (0.08, 1.10)**	−0.23 (−0.72, 0.26)	0.25 (−0.22, 0.72)
Android fat, %	**−1.88 (−2.82, −0.93)**	0.63 (−0.02, 1.29)	−0.20 (−0.82, 0.42)	0.30 (−0.30, 0.90)
Gynoid fat, %	**−1.08 (−1.79, −0.38)**	**0.49 (0.02, 0.96)**	−0.36 (−0.80, 0.08)	0.30 (−0.13, 0.73)
Fat-free mass, %	**1.56 (0.83, 2.28)**	**−0.60 (−1.10, −0.09)**	0.23 (−0.25, 0.72)	−0.25 (−0.72, 0.21)
Sleeping HR, beats/min	**−0.80 (−1.49, −0.10)**	0.37 (−0.08, 0.83)	0.32 (−0.11, 0.74)	−0.32 (−0.73, 0.08)
SBP, mm Hg	**−2.49 (−3.95, −1.04)**	0.31 (−0.69, 1.32)	0.44 (−0.50, 1.38)	0.17 (−0.73, 1.08)
DBP, mm Hg	**−1.22 (−2.04, −0.39)**	0.13 (−0.44, 0.69)	0.21 (−0.31, 0.73)	0.11 (−0.39, 0.61)
SBP ao, mm Hg	**−2.18 (−3.69, −0.68)**	0.25 (−0.77, 1.27)	0.36 (−0.59, 1.31)	0.19 (−0.72, 1.10)
PP ao, mm Hg	**−0.99 (−1.90, −0.08)**	0.10 (−0.50, 0.71)	0.18 (−0.38, 0.75)	0.08 (−0.46, 0.62)

Note. Adjusted for Actiheart wear time, age, and sex.
Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HR, heart rate; LDL, low-density lipoprotein; LPA, light physical activity; MVPA, moderate to vigorous physical activity; PP ao, aortic pulse pressure; RA, rheumatoid arthritis; SB, sedentary behavior; SBP, systolic blood pressure; SBP ao, aortic SBP.
Significant results ($p < 0.05$) are marked in bold.

Table 3. Isotemporal substitution modeling demonstrating consequences of replacing 30 minutes per day of one behavior with another behavior for an equal amount of time on variables reflecting cardiovascular risk in 78 patients with early rheumatoid arthritis

	Sleep β (95% CI)	SB β (95% CI)	LPA β (95% CI)	MVPA β (95% CI)
Body weight, kg	*Replaced*	**2.93 (1.40, 4.46)**	**3.32 (1.68, 4.96)**	**2.33 (0.88, 3.78)**
	−2.93 (−4.46, −1.40)	*Replaced*	0.40 (−0.63, 1.42)	−0.60 (−1.66, 0.46)
	−3.32 (−4.96, −1.68)	−0.40 (−1.42, 0.63)	*Replaced*	**−0.99 (−1.94, −0.04)**
	−2.33 (−3.78, −0.88)	0.60 (−0.46, 1.66)	**0.99 (0.04, 1.94)**	*Replaced*
BMI, kg/m^2	*Replaced*	**1.13 (0.61, 1.66)**	**1.14 (0.57, 1.70)**	**0.76 (0.26, 1.26)**
	−1.13 (−1.66, −0.61)	*Replaced*	0.00 (−0.35, 0.36)	**−0.37 (−0.74, −0.01)**
	−1.14 (−1.70, −0.57)	−0.00 (−0.36, 0.35)	*Replaced*	**−0.38 (−0.70, −0.05)**
	−0.76 (−1.26, −0.26)	**0.37 (0.01, 0.74)**	**0.38 (0.05, 0.70)**	*Replaced*
Waist circumference, cm	*Replaced*	**2.80 (1.40, 4.20)**	**2.80 (1.30, 4.30)**	**1.86 (0.53, 3.19)**
	−2.80 (−4.20, −1.40)	*Replaced*	−0.00 (−0.94, 0.94)	−0.94 (−1.91, 0.03)
	−2.80 (−4.30, −1.30)	0.00 (−0.94, 0.94)	*Replaced*	**−0.94 (−1.81, −0.07)**
	−1.86 (−3.19, −0.53)	0.94 (−0.03, 1.91)	**0.94 (0.07, 1.81)**	*Replaced*
Body fat, %	*Replaced*	**1.71 (0.89, 2.52)**	**1.32 (0.45, 2.20)**	**1.40 (0.62, 2.17)**
	−1.71 (−2.52, −0.89)	*Replaced*	−0.38 (−0.93, 0.16)	−0.31 (−0.88, 0.25)
	−1.32 (−2.20, −0.45)	0.38 (−0.16, 0.93)	*Replaced*	0.07 (−0.44, 0.58)
	−1.40 (−2.17, −0.62)	0.31 (−0.25, 0.88)	−0.07 (−0.58, 0.44)	*Replaced*
Android fat, %	*Replaced*	**2.06 (1.01, 3.11)**	**1.72 (0.59, 2.84)**	**1.74 (0.75, 2.74)**
	−2.06 (−3.11, −1.01)	*Replaced*	−0.34 (−1.05, 0.36)	−0.32 (−1.04, 0.41)
	−1.72 (−2.84, −0.59)	0.34 (−0.36, 1.05)	*Replaced*	0.03 (−0.62, 0.68)
	−1.74 (−2.74, −0.75)	0.32 (−0.41, 1.04)	−0.03 (−0.68, 0.62)	*Replaced*
Gynoid fat, %	*Replaced*	**1.18 (0.40, 1.95)**	0.73 (−0.10, 1.56)	**0.99 (0.26, 1.73)**
	−1.18 (−1.95, −0.40)	*Replaced*	−0.44 (−0.96, 0.08)	−0.18 (−0.72, 0.35)
	−0.73 (−1.56, 0.10)	0.44 (−0.08, 0.96)	*Replaced*	0.26 (−0.22, 0.74)
	−0.99 (−1.73, −0.26)	0.18 (−0.35, 0.72)	−0.26 (−0.74, 0.22)	*Replaced*
Fat-free mass, %	*Replaced*	**−1.74 (−2.54, −0.94)**	**−1.36 (−2.22, −0.50)**	**−1.42 (−2.18, −0.67)**
	1.74 (0.94, 2.54)	*Replaced*	0.38 (−0.15, 0.92)	0.32 (−0.24, 0.87)
	1.36 (0.50, 2.22)	−0.38 (−0.92, 0.15)	*Replaced*	−0.07 (−0.56, 0.43)
	1.42 (0.67, 2.18)	−0.32 (−0.87, 0.24)	0.07 (−0.43, 0.56)	*Replaced*
Sleeping HR, beats/min	*Replaced*	**1.15 (0.41, 1.89)**	**1.16 (0.37, 1.96)**	0.59 (−0.11, 1.30)
	−1.15 (−1.89, −0.41)	*Replaced*	0.01 (−0.49, 0.51)	**−0.56 (−1.07, −0.04)**
	−1.16 (−1.96, −0.37)	−0.01 (−0.51, 0.49)	*Replaced*	**−0.57 (−1.04, −0.11)**
	−0.59 (−1.30, 0.11)	**0.56 (0.04, 1.07)**	**0.57 (0.11, 1.04)**	*Replaced*
SBP, mm Hg	*Replaced*	**2.62 (1.01, 4.23)**	**3.01 (1.27, 4.74)**	**2.45 (0.92, 3.98)**
	−2.62 (−4.23, −1.01)	*Replaced*	0.39 (−0.70, 1.47)	−0.17 (−1.29, 0.95)
	−3.01 (−4.74, −1.27)	−0.39 (−1.47, 0.70)	*Replaced*	−0.56 (−1.56, 0.44)
	−2.45 (−3.98, −0.92)	0.17 (−0.95, 1.29)	0.56 (−0.44, 1.56)	*Replaced*
DBP, mm Hg	*Replaced*	**1.26 (0.34, 2.17)**	**1.46 (0.48, 2.45)**	**1.21 (0.34, 2.08)**
	−1.26 (−2.17, −0.34)	*Replaced*	0.21 (−0.41, 0.82)	−0.04 (−0.68, 0.59)
	−1.46 (−2.45, −0.48)	−0.21 (−0.82, 0.41)	*Replaced*	−0.25 (−0.82, 0.32)
	−1.21 (−2.08, −0.34)	0.04 (−0.59, 0.68)	0.25 (−0.32, 0.82)	*Replaced*
SBP ao, mm Hg	*Replaced*	**2.27 (0.59, 3.94)**	**2.61 (0.82, 4.41)**	**2.16 (0.58, 3.75)**
	−2.27 (−3.94, −0.59)	*Replaced*	0.35 (−0.78, 1.47)	−0.10 (−1.26, 1.06)
	−2.61 (−4.41, −0.82)	−0.35 (−1.47, 0.78)	*Replaced*	−0.45 (−1.49, 0.59)
	−2.16 (−3.75, −0.58)	0.10 (−1.06, 1.26)	0.45 (−0.59, 1.49)	*Replaced*
PP ao, mm Hg	*Replaced*	**1.03 (0.01, 2.04)**	**1.21 (0.12, 2.30)**	**0.98 (0.02, 1.95)**
	−1.03 (−2.04, −0.01)	*Replaced*	0.18 (−0.51, 0.86)	−0.04 (−0.75, 0.66)
	−1.21 (−2.30, −0.12)	−0.18 (−0.86, 0.51)	*Replaced*	−0.22 (−0.85, 0.41)
	−0.98 (−1.95, −0.02)	0.04 (−0.66, 0.75)	0.22 (−0.41, 0.85)	*Replaced*

Note. Every model includes three behaviors, total wear time, age, and sex.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; LPA, light physical activity; MVPA, moderate to vigorous physical activity; PP ao, aortic pulse pressure; SB, sedentary behavior; SBP, systolic blood pressure; SBP ao, aortic systolic blood pressure.
Significant results ($p < 0.05$) are marked in bold.

associated with detrimental changes in several variables of body composition and blood pressure. For example, after adjustments for age and sex, 30 minutes of shorter sleep duration per night was associated with 2.1%, 1.7%, and 1.7% increase in android fat when replaced with 30 minutes of increased sedentary time, LPA, or MVPA, respectively. Furthermore, it also resulted in an SBP higher by 2.6, 3.0, and 2.5 mm Hg and a DBP higher by 1.3, 1.5, and 1.2 mm Hg when replaced by SB, LPA, or MVPA, respectively (Table 3). When 30 minutes of SB was replaced with 30 minutes of MVPA, BMI and sleeping HR decreased, whereas replacement of LPA with MVPA was associated with lower values for BMI, body weight, waist circumference, and sleeping HR

(Table 3). Subgroup analyses of the patients without corticosteroids yielded similar results (data not shown).

DISCUSSION

In this study on patients with early RA, sleep duration at night was, surprisingly, the behavior that had the strongest association with risk factors for CVD. After adjustments for Actiheart wear time, age, and sex, shorter sleep duration was associated with a higher proportion of body fat, with a higher β value for the proportion of android fat than that of gynoid fat. Shorter sleep duration also demonstrated a higher sleeping HR as well as a higher aortic SBP and a higher brachial SBP and DBP.

Impairment of sleep quality and sleep duration is a frequent finding in RA (1,11,40,41), with McKenna et al (42,43) demonstrating an objectively measured sleep duration of mean 5.7 hours in 32 patients with low to moderate disease activity. In the present study, objectively estimated sleep duration was even lower, with a median of 4.6 hours per night. Only four of our participants exceeded 7 hours, and none exceeded 8 hours of sleep. Because of the cross-sectional design of our study, we could not evaluate causal relationships, but it might be noted that the impact of sleep on CV health is widely acknowledged in prospective studies in the general population (10,44,45). Shorter sleep duration is associated with diabetes, hypertension, obesity, CVD, and mortality (44), with the latter shown to be more apparent in people with overweight or obesity (45). A large dose-response meta-analysis that included a healthy population revealed a U-shaped association, with increased CV morbidity and mortality in those with shorter as well as longer than approximately 7 hours of sleep duration (10). The pooled relative risk for CV events and all-cause mortality increased by 5% to 7% for every hour of reduction of sleep, and by 5% to 18% for every additional hour of sleep (10).

Some of the previously suggested mechanisms that explain the negative effect of sleep deprivation on CV risk include a slowing down of the glucose metabolism in combination with reduced levels of leptin, which signals satiety to the brain, and increased levels of ghrelin, which signals hunger to the brain (46). Increased sympathetic activation and levels of inflammatory markers as CRP, interleukin-6, and tumor necrosis factor in the general population, are also related to shorter sleep duration (46). However, in our study on patients with a chronic inflammatory disease, no significant associations were found between sleep duration and disease activity measured using DAS28, ESR, or CRP.

In the present study, more time spent sedentary was associated with a higher proportion of body fat and lower fat-free mass. The relationship between SB and CV risk in RA has been denoted in previous publications (12,16), although the unfavorable association of SB on BMI, blood pressure, and HDL previously described by Khoja et al (24) did not reach statistical significance in our analysis. Elkan et al (15) compared measures of body composition between tertiles of self-assessed total physical activity and found

no difference between patients in the lowest and highest tertiles of physical activity. Differences in methodology may partly explain the differences in results.

We performed the well-established method of isotemporal substitution modeling (27), which allows adjustments for other behaviors and makes it possible to analyze the theoretical effect of substituting 30 minutes of time in one behavior with the same duration of time in another. Our findings suggest that replacing 30 minutes of SB with 30 minutes of sleep has a beneficial impact on body composition and blood pressure, which are factors known to decrease the risk for CVD. On the other hand, replacing sleep with SB, or even with LPA or MVPA, theoretically implied a worse CVD risk profile. As far as we know, there are no previous publications using isotemporal substitution in patients with RA, but during the last decade, the method has been used in other studies to increase knowledge on the relationships between the 24-hour activity behaviors and CV health (7). In concordance with our results, a recently published study of older women presented a favorable effect on waist circumference and BMI with a reallocation of time from SB to sleep for the subgroup with shorter sleep duration (<8 hours) (47). In a study conducted in 200 000 participants followed up on for 4.2 years, Stamatakis et al revealed lower all-cause mortality when replacing sitting time with sleep or with physical activity in participants sleeping 7 or fewer hours per day (48). Furthermore, Buman et al showed that replacing 30 minutes of LPA with the same amount of time in MVPA or replacing SB or LPA with sleep was associated with lower waist circumference (8). It also led to changes of the β coefficient of HDL cholesterol and triglycerides by reallocation of time between the behaviors (8), yet this relationship did not reach statistical significance in the present analyses. Associations between SB and physical activity on risk factors for CVD have been presented in a number of studies among patients with RA (12,13,23–25); however, the results of the isotemporal substitution performed here highlight the importance of sleep for CV health and contribute to the knowledge of behavioral change recommendations.

The major strength of this study was the inclusion of patients with RA from the only referral center in our county, thereby including essentially all patients with RA diagnosed during the relevant time period. There were no differences in age, sex, disease activity, or functional ability between participants and nonparticipants; therefore, included individuals must be regarded as representative of an adult population with early RA without severe comorbidities. In addition, we used objective measures of sleep, sedentary, and active behaviors over 24 hours, which is a less biased method compared with self-assessments (49). The major limitation of this study was the cross-sectional design, which did not allow conclusions about causality. Furthermore, median time with activity registrations was 19.3 h/d, which have obviously biased the estimates of time spent in different behaviors, including the time registered for falling asleep and waking up. However, sleep duration was visually identified on the time-series plots for every patient

as a prolonged period of minimal movement and concurrent low heart rate and periods with missing data during sleeping time was registered as sleep. Also, it must be noted that our measure of sleep only includes sleep during the night and not any naps nor any sleep during the day. Nonetheless, our results indicate that patients with RA have issues with sleep. Also, it must be noted that the isotemporal substitution method merely indicated the theoretical consequences of changing the amount of time spent in the different behaviors during the day. Longitudinal studies with real displacements of time are warranted to validate our results and to add to the knowledge about this topic. In our analyses, we used 30-minute intervals to make the findings easy to translate into clinical practice and to facilitate comparison with other studies as this time frame was the most commonly used (7). To address missing data during the measurements of activity and sleep, we used available time monitored as "total discretionary time" for the isotemporal substitution models. Another limitation in the substitution models was collinearity between the different activity behaviors, which was due to the nature of the fixed time period in a day.

CONCLUSION

To our knowledge, this is the first study among patients with RA to report associations between sleep duration at night and risk factors for CVD as well as to present the possible consequences of reallocating time between different activity behaviors on CV risk factors by performing isotemporal substitution modeling. Sleep deprivation was common and associated with unfavorable values for CV risk factors in these patients with early RA. Theoretical reallocation of time from SB, LPA, or MVPA to sleep was associated with beneficial changes of body composition, sleeping HR, and blood pressure. The risk for CVD is significantly increased in patients with RA, and the results of our study highlight the importance of managing sleep impairment as a part of CVD prevention. Future studies are needed to clarify the causal relationships between sleep and CV health and to explore the longitudinal effects of sleep deprivation among these patients.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.
Study conception and design. Hörnberg, Sandberg, Södergren and Sundström.
Acquisition of data. Hörnberg, Sandberg, Ångström, Sundström.
Analysis and interpretation of data. Hörnberg, Pomeroy, Södergren, Sundström.

REFERENCES

1. Benlidayi IC. Sleep impairment: an obstacle to achieve optimal quality of life in rheumatoid arthritis. Rheumatol Int 2018;38:2183–92.

2. Uutela T, Kautiainen H, Järvenpää S, Salomaa S, Hakala M, Häkkinen A. Patients with rheumatoid arthritis have better functional and working ability but poorer general health and higher comorbidity rates today than in the late 1990s. Scand J Rheumatol 2015;44:173–81.

3. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690–7.

4. Wållberg-Jonsson S, Johansson H, Ohman ML, Rantapää-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. J Rheumatol 1999;26:2562–71.

5. Crowson CS, Rollefstad S, Ikdahl E, Kitas GD, van Riel PL, Gabriel SE, et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. Ann Rheum Dis 2018;77:48–54.

6. Innala L, Möller B, Ljung L, Magnusson S, Smedby T, Södergren A, et al. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. Arthritis Res Ther 2011;13:R131.

7. Grgic J, Dumuid D, Bengoechea EG, Shrestha N, Bauman A, Olds T, et al. Health outcomes associated with reallocations of time between sleep, sedentary behaviour, and physical activity: a systematic scoping review of isotemporal substitution studies. Int J Behav Nutr Phys Act 2018;15:69.

8. Buman MP, Winkler EA, Kurka JM, Hekler EB, Baldwin CM, Owen N, et al. Reallocating time to sleep, sedentary behaviors, or active behaviors: associations with cardiovascular disease risk biomarkers, NHANES 2005–2006. Am J Epidemiol 2014;179:323–34.

9. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett DR Jr, Tudor-Locke C, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. Med Sci Sports Exerc 2011;43:1575–81.

10. Yin J, Jin X, Shan Z, Li S, Huang H, Li P, et al. Relationship of sleep duration with all-cause mortality and cardiovascular events: a systematic review and dose-response meta-analysis of prospective cohort studies. J Am Heart Assoc 2017;6:e005947.

11. Goes AC, Reis LA, Silva MBG, Kahlow BS, Skare TL. Rheumatoid arthritis and sleep quality. Rev Bras Reumatol Engl Ed 2017;57:294–8.

12. Fenton SA, Veldhuijzen van Zanten JJ, Kitas GD, Duda JL, Rouse PC, Yu CA, et al. Sedentary behaviour is associated with increased long-term cardiovascular risk in patients with rheumatoid arthritis independently of moderate-to-vigorous physical activity. BMC Musculoskel Dis 2017;18:131.

13. Verhoeven F, Tordi N, Prati C, Demougeot C, Mougin F, Wendling D. Physical activity in patients with rheumatoid arthritis. Joint Bone Spine 2016;83:265–70.

14. Metsios GS, Stavropoulos-Kalinoglou A, Panoulas VF, Wilson M, Nevill AM, Koutedakis Y, et al. Association of physical inactivity with increased cardiovascular risk in patients with rheumatoid arthritis. Eur J Cardiovasc Prev Rehabil 2009;16:188–94.

15. Elkan AC, Håkansson N, Frostegård J, Hafström I. Low level of physical activity in women with rheumatoid arthritis is associated with cardiovascular risk factors but not with body fat mass - a cross sectional study. BMC Musculoskelet Disord 2011;12:13.

16. Hammam N, Ezeugwu VE, Rumsey DG, Manns PJ, Pritchard-Wiart L. Physical activity, sedentary behavior, and long-term cardiovascular risk in individuals with rheumatoid arthritis. Phys Sportsmed 2019;47:463–70.

17. Byram KW, Oeser AM, Linton MF, Fazio S, Stein CM, Ormseth MJ. Exercise is associated with increased small HDL particle concentration and decreased vascular stiffness in rheumatoid arthritis. J Clin Rheumatol 2018;24:417–21.

18. Fenton SA, Sandoo A, Metsios GS, Duda JL, Kitas GD. Veldhuijzen van Zanten JJ. Sitting time is negatively related to microvascular

endothelium-dependent function in rheumatoid arthritis. Microvasc Res 2018;117:57–60.

19. Crilly MA, Wallace A. Physical inactivity and arterial dysfunction in patients with rheumatoid arthritis. Scand J Rheumatol 2013;42:27–33.

20. Metsios GS, Moe RH, van der Esch M, Veldhuijzen van Zanten JJ, Fenton SA, Koutedakis Y, et al. The effects of exercise on cardiovascular disease risk factors and cardiovascular physiology in rheumatoid arthritis. Rheumatol Int 2020;40:347–57.

21. Cooney JK, Ahmad YA, Moore JP, Sandoo A, Thom JM. The impact of cardiorespiratory fitness on classical cardiovascular disease risk factors in rheumatoid arthritis: a cross-sectional and longitudinal study. Rheumatol Int 2019;39:1759–66.

22. Hörnberg K, Ångström L, Wållberg-Jonsson S. Benefits of spinning exercise on cardiovascular risk factors in Rheumatoid Arthritis: A pilot study. Cardiopulm Phys Ther J 2014;25:68–74.

23. Stavropoulos-Kalinoglou A, Metsios GS, Veldhuijzen van Zanten JJCS, Nightingale P, Kitas GD, Koutedakis Y. Individualised aerobic and resistance exercise training improves cardiorespiratory fitness and reduces cardiovascular risk in patients with rheumatoid arthritis. Ann Rheum Dis 2013;72:1819–25.

24. Khoja SS, Almeida GJ, Wasko MC, Terhorst L, Piva SR. Association of light intensity physical activity with lower cardiovascular risk factor burden in rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68:424–31.

25. Hörnberg K, Pomeroy J, Sandberg C, Södergren A, Angström L, Sundström B, et al. Physical activity in rheumatoid arthritis: relationship to cardiovascular risk factors, subclinical atherosclerosis, and disease activity. Scand J Rheumatol 2020;49:112–21.

26. Ångström L, Hörnberg K, Sundström B, Jonsson SW, Södergren A. Aerobic capacity is associated with disease activity and cardiovascular risk factors in early rheumatoid arthritis. Physiother Res Int 2020;25:e1833.

27. Mekary RA, Willett WC, Hu FB, Ding EL. Isotemporal substitution paradigm for physical activity epidemiology and weight change. Am J Epidemiol 2009;170:519–27.

28. Mekary RA, Ding EL. Isotemporal substitution as the gold standard model for physical activity epidemiology: why it is the most appropriate for activity time research. Int J Environ Res Public Health 2019;16:797.

29. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010;69:1580–8.

30. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.

31. Brage S, Brage N, Franks PW, Ekelund U, Wareham NJ. Reliability and validity of the combined heart rate and movement sensor Actiheart. Eur J Clin Nutr 2005;59:561–70.

32. The Actiheart user manual, version 5.0.29. Cambridgeshire, UK: CamNtech Ltd; 2019.

33. Collings PJ, Wijndaele K, Corder K, Westgate K, Ridgway CL, Dunn V, et al. Levels and patterns of objectively-measured physical activity volume and intensity distribution in UK adolescents: the ROOTS study. Int J Behav Nutr Phys Act 2014;11:23.

34. Assah FK, Brage S, Ekelund U, Wareham NJ. The association of intensity and overall level of physical activity energy expenditure with a marker of insulin resistance. Diabetologia 2008;51:1399–407.

35. Pietrobelli A, Formica C, Wang Z, Heymsfield SB. Dual-energy X-ray absorptiometry body composition model: review of physical concepts. Am J Physiol 1996;271:E941–51.

36. Douketis JD, Paradis G, Keller H, Martineau C. Canadian guidelines for body weight classification in adults: application in clinical practice to screen for overweight and obesity and to assess disease risk. CMAJ 2005;172:995–8.

37. Horváth IG, Németh A, Lenkey Z, Alessandri N, Tufano F, Kis P, et al. Invasive validation of a new oscillometric device (Arteriograph) for measuring augmentation index, central blood pressure and aortic pulse wave velocity. J Hypertens 2010;28:2068–75.

38. Prevoo ML, van 't Hof MA, Kuper HH, van Leeuwen MA, van de Putte LB, van Riel PL. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995;38:44–8.

39. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137–45.

40. Løppenthin K, Esbensen BA, Jennum P, Østergaard M, Tolver A, Thomsen T, et al. Sleep quality and correlates of poor sleep in patients with rheumatoid arthritis. Clin Rheumatol 2015;34:2029–39.

41. Grabovac I, Haider S, Berner C, Lamprecht T, Fenzl KH, Erlacher L, et al. Sleep quality in patients with rheumatoid arthritis and associations with pain, disability, disease duration, and activity. J Clin Med 2018;7:336.

42. McKenna S, Tierney M, O'Neill A, Fraser A, Kennedy N. Sleep and physical activity: a cross-sectional objective profile of people with rheumatoid arthritis. Rheumatol Int 2018;38:845–53.

43. McKenna S, Tierney M, O'Neill A, Fraser A, Kennedy N. Correction to: Sleep and physical activity: a cross-sectional objective profile of people with rheumatoid arthritis. Rheumatol Int 2018;38:2165.

44. Itani O, Jike M, Watanabe N, Kaneita Y. Short sleep duration and health outcomes: a systematic review, meta-analysis, and meta-regression. Sleep Med 2017;32:246–56.

45. Xiao Q, Keadle SK, Hollenbeck AR, Matthews CE. Sleep duration and total and cause-specific mortality in a large US cohort: interrelationships with physical activity, sedentary behavior, and body mass index. Am J Epidemiol 2014;180:997–1006.

46. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. Prog Cardiovasc Dis 2009;51:294–302.

47. Full KM, Gallo LC, Malhotra A, Bellettiere J, Kerr J, Arredondo E, et al. Modeling the cardiometabolic benefits of sleep in older women: exploring the 24-hour day. Sleep 2020;43:zsz205.

48. Stamatakis E, Rogers K, Ding D, Berrigan D, Chau J, Hamer M, et al. All-cause mortality effects of replacing sedentary time with physical activity and sleeping using an isotemporal substitution model: a prospective study of 201,129 mid-aged and older adults. Int J Behav Nutr Phys Act 2015;12:121.

49. Dowd KP, Szeklicki R, Minetto MA, Murphy MH, Polito A, Ghigo E, et al. A systematic literature review of reviews on techniques for physical activity measurement in adults: a DEDIPAC study. Int J Behav Nutr Phys Act 2018;15:15.