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Replacing sedentary time with physical activity and sleep: Associations with cardiometabolic health markers in adults

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This study aimed to examine the associations of sedentary time, and substituting sedentary time with physical activity and sleep, with cardiometabolic health markers while accounting for a full 24 h of movement and non-movement behaviors, cardiorespiratory fitness (CRF), and other potential confounders. The participants were 4585 members of the Northern Finland Birth Cohort 1966, who wore a hip-worn accelerometer at the age of 46 years for 14 consecutive days. Time spent in sedentary behaviors, light-intensity physical activity (LPA), and moderate-to-vigorous-intensity physical activity (MVPA) were determined from the accelerometer and combined with self-reported sleep duration to obtain the 24-h time use. CRF was estimated from the peak heart rate in a submaximal step test. An isotemporal substitution paradigm was used to examine how sedentary time and substituting sedentary time with an equal amount of LPA, MVPA, or sleep were associated with adiposity markers, blood lipid levels, and fasting glucose and insulin. Sedentary time was independently and adversely associated with the markers of cardiometabolic health, even after adjustment for CRF, but not in partition models including LPA, MVPA, sleep, and CRF. Substituting 60, 45, 30, and 15 min/day of sedentary time with LPA or MVPA was associated with 0.2%–13.7% favorable differences in the cardiometabolic health markers after accounting for LPA, MVPA, sleep, CRF, and other confounders. After adjustment for movement and non-movement behaviors within the 24-h cycle, reallocating additional time to both LPA and MVPA was beneficially associated with markers of cardiometabolic health in middle-aged adults regardless of their CRF level.

KEYWORDS
adiposity, dyslipidemias, isotemporal substitution, metabolic diseases

1 | INTRODUCTION

The relationships of sedentary time, light-intensity physical activity (LPA), moderate-to-vigorous-intensity physical activity (MVPA), and sleep duration with cardiometabolic health markers have typically been examined in isolation.[1] However, changes in any given movement or non-movement behaviors are likely to modify the health effects of other movement or non-movement behaviors.[1,2] In recent years, a paradigm shift has occurred toward using 24-h isotemporal substitution modeling techniques to investigate the combined associations of movement and non-movement behaviors with health outcomes.[2] Studies examining the associations of 24-h movement and non-movement behaviors have consistently shown that more sedentary time could be detrimental to markers of cardiometabolic health and several other health indicators,[3–5] even after accounting for time spent in physical activities and sleep.[3–5] However, replacing this ubiquitous behavior with physical activity of any intensity or even sleep is likely to lead to better cardiometabolic health.[3,5] Nevertheless, a limitation of research to date is that the relationship of the 24-h behaviors with cardiometabolic health markers was investigated without accounting for cardiorespiratory fitness (CRF).

CRF is an important indicator of cardiometabolic health in adults.[6,7] A complex interrelationship exists between sleep, sedentary time, and physical activity as behaviors and CRF as a physiological outcome.[6–8] In addition to physical activity, CRF could be influenced by several factors, such as age and genetics, and it is also likely that CRF and MVPA have overlapping effects on cardiometabolic health.[7,9] This may be partially because increasing the time spent on MVPA could generate cardiorespiratory benefits and accordingly lead to better cardiometabolic health.[6,7] However, the interrelationships between sedentary time and CRF remain largely unclear, especially after accounting for sleep and physical activities.

Overall, sedentary physiology is a less well-established discipline than physical activity research.[1] Few studies have investigated the combined associations of sedentary time and CRF with cardiometabolic health and mortality risk. These studies have generally suggested that the detrimental relationship between the total sedentary time and the cardiometabolic risk is less pronounced when considering CRF.[10–12] Still, the main limitation of these studies is that they have overlooked the implications of sleep and LPA on cardiometabolic health and have not accounted for the full 24-h movement and non-movement behaviors.[7,9–12] The relationships between sedentary time and the cardiometabolic health markers, after accounting for other physical activities, sleep, and CRF, are even less clear. More research is therefore needed to understand how substituting sedentary time with physical activity or sleep could contribute to cardiometabolic health after accounting for CRF. This study aimed to use a 24-h isotemporal substitution paradigm to examine how sedentary time and substituting sedentary time with an equal amount of LPA, MVPA, or sleep are associated with adiposity markers, blood lipid levels, and fasting glucose and insulin in a large sample of middle-aged adults while accounting for CRF.

2 | MATERIALS AND METHODS

2.1 | Study population and design

Data for this study were collected from the population-based Northern Finland Birth Cohort 1966 study (NFBC1966). NFBC1966 ($N = 12\,058$) is a life course study involving participants whose date of birth was expected to be in 1966 in Northern Finland. The cohort members have been regularly monitored prospectively with a comprehensive set of clinical measurements, interviews, and postal questionnaires. Further information about the NFBC1966 study, recruitment, and follow-ups is presented elsewhere.[13] This cross-sectional study includes individuals from the NFBC1966 who participated in the latest follow-up session performed at the age of 46 years (during 2012–2014) and who agreed to wear an accelerometer to measure their daily activity. The data collection in the 46-year follow-up also included completing postal questionnaires, attending a clinical examination day to collect fasting blood samples, and taking anthropometric measurements.

2.2 | Measurements

2.2.1 | Sedentary time, physical activity intensities, and self-reported sleep

Daily activities were monitored with a hip-worn accelerometer (Hookie AM20; Traxmeet Ltd.). Participants were instructed to wear the accelerometer during all waking activities, except water-based activities, for 14 consecutive days. Raw acceleration signals were collected and stored at 100 Hz. The accelerometer data were first segmented into 6-s epochs, and mean amplitude deviation (MAD) values were computed.[14] The agreement between MAD values from the Hookie and the commonly used ActiGraph GTX3 accelerometer is shown to be excellent.[15] Based on the 6-s epochs, accelerometer non-wear intervals were detected and removed with a widely used approach for count-based data with a 30-s threshold.[16]

The wear time intervals were then cross-referenced with self-reported sleep times, and all the accelerometer data overlapping with a sleep interval were removed. Sleep times were captured with two questions: "At what time do you normally go to bed?" and "At what time do you normally get out of bed?" The remaining 6-s epochs were classified as sedentary (<1.5 metabolic equivalents [MET] in sitting or lying posture), standing still (<1.5 MET in standing posture), LPA (1.5–3.0 MET), or MVPA (≥3 MET) using a previously validated algorithm for posture detection and validated thresholds for MAD values.[14,17] The number of minutes per day in each activity category was obtained by dividing the time spent in each activity by the number of valid days. Differentiation between standing still and sitting or lying postures was performed using a recently validated approach for posture estimation from hip-based raw acceleration data, which has shown good to excellent accuracy (89.2%) compared with thigh-worn posture classification under free-living conditions.[17] Participants were required to provide four or more valid days of accelerometry. A valid day was defined as ≥10 h of monitor wear time. For this study, LPA constituted the sum of all minutes per day spent standing still and in LPA. Sleep duration was self-reported in response to the question, "How many hours do you sleep on average per day?" The values were converted to minutes per day asleep.

2.2.2 | Cardiometabolic health

Participants attended the clinical examination after fasting for 12 h overnight and abstained from smoking and drinking coffee. Trained nurses measured height, weight, and waist circumference, and body mass index (BMI) was calculated. Body composition was measured by bioelectrical impedance analysis (InBody720; InBody, Seoul, Korea), and body fat and fat mass were obtained. Fasting blood samples were taken and analyzed for plasma glucose, serum insulin, total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides, as described elsewhere.[18] The ratios of total to HDL (total/HDL cholesterol ratio) and LDL to HDL (LDL/HDL cholesterol ratio) cholesterol levels were computed, as they could be better predictors of cardiovascular disease risk than lipid and lipoprotein levels alone.[19]

2.2.3 | Confounders

Sex and birthweight were extracted from medical records. CRF was measured on the clinical examination day by a submaximal 4-min single-step test with continuous heart rate measurement (RS800CX, Polar Electro, Finland) and expressed as peak heart rate during the step test.[18] The submaximal step test heart rate is an acceptable method for indirectly estimating maximal oxygen uptake in the general adult population.[20] Participants self-reported their education level, employment status, marital status, and household income and provided information about lifestyle (smoking habits and alcohol consumption), health-related quality of life, and use of medication for hypertension, high cholesterol, and diabetes.

2.3 | Statistical analyses

The analyses were conducted in accordance with published methods for isotemporal substitution analyses.[21,22] Multiple linear regression was used to investigate the associations of sedentary time, LPA, MVPA, and sleep duration with cardiometabolic health markers in single-variable, partition, and isotemporal substitution models.[21] Interpreting the results of these models (and the reallocation of time) requires the assumption of linearity among the exposure and outcome variables.[21,22] Sedentary time, LPA, and MVPA are assumed to be linearly related to cardiometabolic health markers. However, the shape of the relationships for sleep duration may differ across different cardiometabolic markers, with a linear relationship for some markers and a U-shaped relationship for others.[23] To test the possibility of a U-shaped relationship, we included sleep duration in regression models with each cardiometabolic marker, and the relationship was considered linear if the association was significant ($p < 0.05$). If the association was insignificant, a quadratic term for sleep duration was included and the model was rerun. When the quadratic term was significant ($p < 0.10$), the relationship between sleep duration and the cardiometabolic health marker was considered U-shaped, and the analysis for that outcome was stratified by sleep duration. The analysis was stratified by ≤7.5 and >7.5 h/day asleep for the cardiometabolic markers displaying a U-shaped relationship. This cut point corresponds to the mean sleep duration for all study participants and is within the recommended sleep duration for adults (7 to 9 h per night).[23]

Before regression analyses, all the outcomes were log-transformed to better represent a normal distribution for linear regression.[24] Initially, the overall associations of 24-h movement and non-movement behaviors with cardiometabolic health markers were examined using single-variable models. Time spent in sedentary behaviors, LPA, MVPA, and sleep were included in separate models with each cardiometabolic marker. Partition models were then used to examine the independent associations of 24-h movement and non-movement behaviors with cardiometabolic health markers. The partition

model included sleep, sedentary time, LPA, and MVPA into one model for each cardiometabolic outcome. Inclusion of all movement and non-movement behaviors in the same model may lead to the problem of multicollinearity among exposures.[21,22] The presence of multicollinearity among the exposure variables (sedentary time, LPA, MVPA, and sleep) in partition models was therefore examined by computing the variance inflation factor (VIF). VIF greater than 5 was considered as indicator of high multicollinearity.[25] All the models and tests for U-shaped relationships were controlled for age, sex, birthweight, education, marital status, employment, income, lifestyle factors (smoking habits and alcohol consumption), health-related quality of life,[26] and medication use. All models were run twice, with and without adjustment for CRF, to understand the role of CRF.

Isotemporal substitution analyses were conducted to model the effects of substituting sedentary time with LPA, MVPA, or sleep, after accounting for all potential confounders and CRF. First, the total wear time was computed by adding all the time variables (i.e., total time = sedentary + LPA + MVPA + sleep). MVPA, LPA, sleep duration, and total wear time were included in the same model, while sedentary time was dropped to model the effects of substituting sedentary time with other activities. Dropping sedentary time from the regression models that, in addition to sleep duration, LPA, and MVPA, include total wear time allows interpretation of the differences in cardiometabolic outcomes associated with substituting sedentary time with an equal amount of time spent in other activities.[21,22] This is because including a total wear time variable in the model while excluding one of the movement or non-movement behaviors (in this case, sedentary time) would hold the time invariant. Time-invariant regression models can be used to understand the cross-sectional associations of cardiometabolic health markers with reducing the mean time spent in one of the movement or non-movement behaviors by equivalently increasing the mean time spent in another movement or non-movement behavior.[21,22] Results are reported for substituting 60, 45, 30, and 15 min/day of sedentary time with MVPA, LPA, and sleep. The associations of sedentary behaviors, physical activity at different intensity levels, and sleep duration are generally prone to the problem of reverse causality bias.[27] To ascertain the robustness of the results, we conducted a sensitivity analysis. We repeated the regression analyses for the participants who slept according to current recommendations for sleep duration (7–9 h/night)[23] and had no hypertension, heart problems (i.e., congenital heart disease, congestive heart failure, and/or coronary artery disease), or diabetes. All statistical analyses were performed using R version 3.6.2 (R Core Team, Vienna, Austria).

3 | RESULTS

A total of 5840 NFBC1966 cohort members (48% of the 12 058 original cohort members and 57% of the 10 321 cohort members who lived in Finland and were invited to participate in the 46-year follow-up) participated in the 46-year follow-up. Of those participating in the follow-up, 4585 participants provided valid acceleration data, in addition to self-reported sleep questions that were needed for this study. Full descriptive statistics of the cohort members participating in the 46-year follow-up and the subsample with valid data by sleep categories are shown in Table 1. Compared with those participating in the follow-up, a similar percentage of participants with valid accelerometry data were men (44.1% vs 42.8%), married/cohabiting (78.8% vs 79.5%), non-smokers (53.8% vs 54.3%), and with a polytechnic/university degree (25.5% vs 29.5%). The mean (SD) values of accelerometer wear time and self-reported sleep duration for the participants were 854.0 (59.5) and 450.1 (55.1) min/day (equivalent to 14.2 (1.0) and 7.5 (0.9) h/day), respectively.

The results of the tests for U-shaped associations between sleep duration and cardiometabolic outcomes are shown in Table S1. Evidence for U-shaped relationships (significant quadratic term with $p < 0.10$) was observed for fasting serum insulin and fasting glucose. The distribution of CRF is shown in Figure S1, indicating that CRF was normally distributed.

3.1 | Single-variable models

The results from the single-variable models are shown in Table 2. In single-variable Model 1, higher sedentary time was associated with higher total/HDL cholesterol ratio (β = 0.027), LDL/HDL cholesterol ratio (β = 0.038), triglycerides (β = 0.45), body fat (β = 0.049), BMI (β = 0.022), and fat mass (β = 0.075). Higher sleep duration was associated with higher total/HDL cholesterol ratio (β = 0.017), LDL/HDL cholesterol ratio (β = 0.022), and triglycerides (0.024). In single-variable Model 1, LPA and MVPA were each significantly and inversely associated with the total/HDL cholesterol ratio (β = −0.030 and −0.116), LDL/HDL cholesterol ratio (β = −0.041 and −0.164), triglycerides (β = −0.063 and −0.181), body fat (β = −0.050 and −0.184), BMI (β = −0.022 and −0.071), fat mass (β = −0.076 and −0.256), and fasting insulin (sleep duration ≤7.5 h/day: β = −0.080 and −0.276; sleep duration >7.5 h/day:

TABLE 1 Characteristics of the study population overall and by sleep duration categories

Variable	Full sample (n = 5840)	Analytical sample (N = 4585)	Sleep duration ≤7.5 h/day (N = 2546)	Sleep duration >7.5 h/day (N = 2039)
Demographics				
Age, years	46.6 (0.6)	46.6 (0.5)	46.6 (0.5)	46.6 (0.5)
Sex				
Male	2565 (44.1%)	1962 (42.8%)	1215 (47.7%)	747 (36.6%)
Female	3257 (55.9%)	2623 (57.2%)	1331 (52.3%)	1292 (63.4%)
Education				
Comprehensive school	383 (7.1%)	128 (2.9%)	78 (3.2%)	50 (2.5%)
Vocational/college level education	3455 (64.3%)	3006 (67.6%)	1719 (69.8%)	1287 (65.0%)
Polytechnic/university degree	1531 (25.5%)	1310 (29.5%)	667 (27.1%)	643 (32.5%)
Employment status				
Employed	4672 (88.2%)	3891 (88.9%)	2216 (91.2%)	1675 (86.0%)
Unemployed	295 (5.6%)	241 (5.5%)	118 (4.9%)	123 (6.3%)
Other (e.g., student, homemaker)	333 (6.3%)	245 (5.6%)	95 (3.9%)	150 (7.7%)
Marital status				
Married/cohabiting	4348 (78.8%)	3632 (79.5%)	2007 (79.0%)	1625 (80.1%)
Divorced/Widowed	555 (10.1%)	452 (9.9%)	263 (10.4%)	189 (9.3%)
Unmarried	615 (11.1)	485 (10.6%)	270 (10.6%)	215 (10.6%)
Household income (€ per year)				
≤50 000	2149 (42.8%)	1715 (41.6%)	973 (42.2%)	742 (40.8%)
50 001 to 100 000	23.5 (45.9%)	1925 (46.7%)	1073 (46.5%)	852 (46.9%)
>100 000	564 (11.2%s)	485 (10.6%)	261 (11.3%)	224 (12.3%)
Birth weight, kg		3.5 (0.5)	3.4 (0.5)	3.5 (0.5)
Lifestyle factors, medication use, and health-related quality of life				
Alcohol consumption, grams/day	10.7 (17.3)	10.4 (16.8)	11.0 (16.7)	9.6 (16.9)
Health-related quality of life score	0.9 (0.1)	0.92 (0.06)	0.91 (0.06)	0.92 (0.06)
Smoking status				
Nonsmoker	2941 (53.8%)	2469 (54.3%)	1289 (51.0%)	1180 (58.5%)
Former smoker	1485 (27.1%)	828 (18.2%)	514 (20.4%)	314 (15.6%)
Current smoker	1045 (17.9%)	1246 (27.4%)	722 (28.6%)	524 (26.0%)
Diabetes, cholesterol, and/or hypertension medication				
Yes	943 (17.0%)	799 (21.6%)	443 (21.7%)	356 (21.6%)
No	4597 (83.0%)	2894 (78.4%)	1603 (78.3%)	1291 (78.4%)
Cardiorespiratory fitness and cardiometabolic markers				
Cardiorespiratory fitness, bpm	147.6 (15.4)	147.4 (15.5)	146.8 (15.6)	148.2 (15.3)
Total/HDL cholesterol ratio	3.6 (1.0)	3.6 (1.0)	3.6 (1.0)	3.6 (1.0)
LDL/HDL cholesterol ratio	2.4 (0.9)	2.4 (0.9)	2.4 (0.9)	2.4 (0.9)
Triglycerides, mmol/L	1.3 (0.8)	1.2 (0.8)	1.2 (0.8)	1.3 (0.9)
Fasting insulin, pmol/L	9.8 (8.8)	9.5 (8.2)	9.5 (8.7)	9.6 (7.6)
Fasting glucose, mmol/L	5.5 (0.9)	5.5 (0.8)	5.5 (0.8)	5.5 (0.9)
Body fat, %	28.9 (9.3)	28.8 (9.1)	28.2 (9.3)	29.6 (9.0)
BMI, kg/m2	26.9 (4.9)	26.8 (4.9)	26.8 (4.9)	26.7 (4.8)

(Continues)

TABLE 1 (Continued)

Variable	Full sample (n = 5840)	Analytical sample (N = 4585)	Sleep duration ≤7.5 h/day (N = 2546)	Sleep duration >7.5 h/day (N = 2039)
Fat mass, kg	23.1 (10.7)	23.0 (10.7)	22.7 (10.8)	23.2 (10.4)
Total daily volumes				
Wear time, min/day	-	854.0 (59.5)	869.1 (60.1)	835.1 (52.9)
Sedentary time, min/day	-	435.7 (89.3)	442.2 (91.6)	427.6 (85.6)
LPA time, min/day	-	341.1 (81.7)	347.8 (83.3)	332.8 (78.8)
MVPA time, min/day	-	45.4 (24.7)	46.7 (26.1)	43.7 (22.7)
Sleep duration, min/day		450.1 (55.1)	412.1 (37.7)	497.5 (31.8)

Note: A total of 5840 cohort members participated in the 46-year follow-up (full sample). Of those participating in the follow-up, 4585 participants provided valid acceleration data, in addition to self-reported sleep questions that were needed for this study (analytical sample). Values are mean (SD) or count (%).

Abbreviations: BMI = body mass index, bpm = beats per minute, HDL = high-density lipoprotein, HOMA-IR = homeostatic model assessment of insulin resistance, LDL = low-density lipoprotein, SD = standard deviation.

β = −0.084 and −0.315). These significant associations for sedentary time, LPA, MVPA, and sleep, although generally moderated, were all retained in single-variable Model 2 after further adjustment for CRF. However, sedentary time, LPA, and MVPA were not associated with fasting glucose in single-variable Model 2 after further adjustment for CRF; only the association between sleep duration and fasting glucose in those who slept >7.5 h/night was significant (β = 0.018).

3.2 | Partition models

The results from the partition models are shown in Table 3. Partition models simultaneously accommodating 24-h movement and non-movement behaviors (sedentary time, LPA, MVPA, and sleep) showed no signs of multicollinearity (VIF <5). In partition Model 1, higher sedentary time was associated with higher body fat (β = 0.010), BMI (β = 0.016), and fat mass (β = 0.001), and higher sleep duration was associated with higher values of the total/HDL cholesterol (β = 0.011) and LDL/HDL cholesterol ratios (β = 0.016). LPA and MVPA were each significantly and inversely associated with the total/HDL cholesterol ratio (β = −0.020 and −0.1), LDL/HDL cholesterol ratio (β = −0.023 and −0.139), triglycerides (β = −0.069 and −0.165), body fat (β = −0.030 and −0.153), BMI (β = −0.012 and −0.057), fat mass (β = −0.042 and −0.205), and fasting insulin (β = −0.058 and −0.235 in those who slept ≤7.5 h/day). Partition Model 1 also indicated an inverse association of MVPA with fasting insulin in those who slept >7.5 h/night (β = −0.243) and fasting glucose in those whose sleep duration was ≤7.5 h/day (β = −0.018). In partition Model 2, the associations for LPA and MVPA tended to remain significant after further adjustment for CRF, but the associations for sedentary time and sleep duration did not reach the significance level.

3.3 | Isotemporal substitution of sedentary time with MVPA, LPA, and sleep

The effects of substituting sedentary time with MVPA, LPA, and sleep are shown in Figures 1 and 2. Regardless of the shape of the association with sleep duration, substituting sedentary time with MVPA and LPA was consistently associated with favorable differences in the cardiometabolic health outcomes. For instance, substituting 60, 45, 30, and 15 min of sedentary time with MVPA was associated with 7.9% (95% confidence interval [CI] = −9.0 to −6.7), −6.0% (95% CI = −6.8 to −5.1), −4.0% (95% CI = −4.6 to −3.4), and −2.0% (95% CI = −2.3 to −1.7) lower total/HDL cholesterol ratio, respectively. Substituting 60, 45, 30, and 15 min of sedentary time with LPA was associated with −1.8% (95% CI = −2.2 to −1.4), −1.4% (95% CI = −1.7 to −1.1), −0.9% (95% CI = −1.1 to −0.7), and −0.5% (95% CI = −0.6 to −0.4) lower total/HDL cholesterol ratio, respectively.

Substituting sedentary time with sleep was associated with unfavorable, minor differences in the total/HDL cholesterol ratio, LDL/HDL cholesterol ratio, triglycerides, and fasting glucose. For instance, substituting 60 min of sedentary time with sleep was associated with a 1.1% (95% CI = 0.5 to 1.8) higher total/HDL cholesterol ratio. In the sensitivity analysis (see Figure S2), the differences associated with substituting sedentary time with sleep, LPA, and MVPA were generally moderated when the isotemporal modeling was performed with participants who slept 7–9 h/night and had no hypertension, heart disease, or diabetes, but the association patterns were unchanged. The only difference was that substituting sedentary time with

TABLE 2 Single-variable models for associations of sedentary time, light-intensity physical activity (LPA), moderate-to-vigorous physical activity (MVPA), and self-reported sleep duration with cardiometabolic health markers

		Sedentary time		LPA		MVPA		Sleep	
Cardiometabolic markers	***n***	**β (95% CI)**	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***
Outcomes displaying a linear relationship with sleep duration									
Total/HDL cholesterol ratio									
Single variable Model 1	2911	**0.027 (0.023, 0.030)**	**<0.001**	**−0.030 (−0.033, −0.026)**	**<0.001**	**−0.116 (−0.127, −0.104)**	**<0.001**	**0.017 (0.012, 0.022)**	**0.001**
Single variable Model 2	2584	**0.018 (0.014, 0.021)**	**<0.001**	**−0.022 (−0.026, −0.018)**	**<0.001**	**−0.089 (−0.101, −0.076)**	**<0.001**	**0.016 (0.010, 0.021)**	**0.005**
LDL/HDL cholesterol ratio									
Single variable Model 1	2913	**0.038 (0.033, 0.043)**	**<0.001**	**−0.041 (−0.046, −0.035)**	**<0.001**	**−0.164 (−0.181, −0.146)**	**<0.001**	**0.022 (0.014, 0.030)**	**0.005**
Single variable Model 2	2585	**0.027 (0.022, 0.033)**	**<0.001**	**−0.030 (−0.036, −0.025)**	**<0.001**	**−0.127 (−0.146, −0.109)**	**<0.001**	**0.021 (0.012, 0.029)**	**0.014**
Triglycerides									
Single variable Model 1	2913	**0.045 (0.039, 0.051)**	**<0.001**	**−0.063 (−0.070, −0.057)**	**<0.001**	**−0.181 (−0.202, −0.159)**	**<0.001**	**0.024 (0.015, 0.034)**	**0.010**
Single variable Model 2	2585	**0.025 (0.018, 0.031)**	**<0.001**	**−0.049 (−0.056, −0.042)**	**<0.001**	**−0.110 (−0.133, −0.088)**	**<0.001**	**0.028 (0.018, 0.038)**	**0.005**
Body fat									
Single variable Model 1	2873	**0.049 (0.045, 0.052)**	**<0.001**	**−0.050 (−0.054, −0.046)**	**<0.001**	**−0.184 (−0.197, −0.171)**	**<0.001**	0.010 (0.004, 0.016)	0.095
Single variable Model 2	2553	**0.026 (0.023, 0.030)**	**<0.001**	**−0.030 (−0.034, −0.026)**	**<0.001**	**−0.089 (−0.102, −0.077)**	**<0.001**	0.009 (0.003, 0.014)	0.131
BMI									
Single variable Model 1	2924	**0.022 (0.020, 0.024)**	**<0.001**	**−0.022 (−0.024, −0.020)**	**<0.001**	**−0.071 (−0.079, −0.064)**	**<0.001**	0.002 (−0.002, 0.005)	0.618
Single variable Model 2	2594	**0.009 (0.007, 0.011)**	**<0.001**	**−0.010 (−0.012, −0.007)**	**<0.001**	**−0.021 (−0.028, −0.014)**	**0.003**	0.003 (0.0, 0.006)	0.373
Fat mass									
Single variable Model 1	2873	**0.075 (0.069, 0.080)**	**<0.001**	**−0.076 (−0.082, −0.070)**	**<0.001**	**−0.256 (−0.275, −0.237)**	**<0.001**	0.014 (0.006, 0.023)	0.101
Single variable Model 2	2553	**0.040 (0.035, 0.046)**	**<0.001**	**−0.044 (−0.050, −0.039)**	**<0.001**	**−0.117 (−0.135, −0.098)**	**<0.001**	0.015 (0.007, 0.024)	0.061
Outcomes displaying a U-shaped relationship with sleep duration									
Fasting insulin									
Sleep duration ≤7.5 h/day									
Single variable Model 1	1605	**0.076 (0.066, 0.086)**	**<0.001**	**−0.080 (−0.091, −0.070)**	**<0.001**	**−0.276 (−0.310, −0.243)**	**<0.001**	−0.012 (−0.036, 0.012)	0.624
Single variable Model 2	1430	**0.034 (0.024, 0.044)**	**0.001**	**−0.042 (−0.052, −0.031)**	**<0.001**	**−0.130 (−0.164, −0.096)**	**<0.001**	−0.015 (−0.038, 0.009)	0.538
Sleep duration >7.5 h/day									
Single variable Model 1	1249	**0.088 (0.077, 0.100)**	**<0.001**	**−0.084 (−0.096, −0.071)**	**<0.001**	**−0.315 (−0.359, −0.272)**	**<0.001**	0.054 (0.022, 0.085)	0.088
Single variable Model 2	1098	**0.048 (0.036, 0.059)**	**<0.001**	**−0.053 (−0.066, −0.041)**	**<0.001**	**−0.158 (−0.201, −0.114)**	**<0.001**	0.058 (0.027, 0.090)	0.064
Fasting glucose									

(Continues)

TABLE 2 (Continued)

Cardiometabolic markers	*n*	Sedentary time		LPA		MVPA		Sleep	
		β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Sleep duration ≤7.5 h/day									
Single variable Model 1	1599	0.004 (0.002, 0.006)	0.051	−0.004 (−0.007, −0.002)	0.067	**−0.020 (−0.027, −0.013)**	**0.005**	0.0 (−0.005, 0.005)	0.968
Single variable Model 2	1424	−0.003 (−0.005, −0.001)	0.165	0.0 (−0.002, 0.003)	0.862	−0.006 (−0.013, 0.002)	0.433	0.001 (−0.004, 0.006)	0.860
Sleep duration >7.5 h/day									
Single variable Model 1	1242	**0.009 (0.007, 0.012)**	**<0.001**	**−0.010 (−0.013, −0.007)**	**<0.001**	**−0.027 (−0.037, −0.018)**	**0.004**	0.013 (0.006, 0.020)	0.054
Single variable Model 2	1091	0.004 (0.002, 0.007)	0.105	−0.005 (−0.008, −0.002)	0.095	−0.007 (−0.017, 0.003)	0.5	**0.018 (0.011, 0.025)**	**0.012**

Note: Sedentary time, LPA, MVPA, and self-reported sleep duration were separately included in regression model with each cardiometabolic health marker. Model 1 was adjusted for age, sex, birthweight, education, marital status, employment, income, lifestyle factors (smoking status and alcohol consumption), health-related quality of life, and medication use, and Model 2 was further adjusted for cardiorespiratory fitness. Beta coefficients reflect associations for 60 min of sedentary time, LPA, MVPA, and self-reported sleep duration. Significant associations are shown in bold.

sleep was associated with favorable differences in body fat, BMI, and fat mass.

4 | DISCUSSION

This study followed a 24-h isotemporal substitution data analysis approach to examine how sedentary time and replacing sedentary time with physical activity of different intensities and sleep are associated with markers of cardiometabolic health in a large sample of middle-aged adults, while simultaneously accounting for CRF. The distribution of CRF, estimated by peak heart rate during a 4-min submaximal step test, was normal and comparable to the values reported in previous studies.[28] Sedentary time was adversely associated with the markers of cardiometabolic health in single-variable models. However, there were no significant associations between sedentary time and cardiometabolic health markers in partition models accommodating all movement and non-movement behaviors after adjustment for CRF. Nevertheless, according to the isotemporal substitution analyses, replacing sedentary time with both LPA and MVPA were associated with favorable differences in the cardiometabolic health markers after accounting for CRF.

Our results show that LPA and MVPA are both beneficially associated with markers of cardiometabolic health, after accounting for all other movement and non-movement behaviors within the 24-h cycle. The beneficial associations for LPA and MVPA slightly attenuated after adjustment for CRF. Consistent with our results, previous studies have shown that after adjustment for CRF and sedentary time, higher levels of MVPA are associated with better cardiometabolic health.[6,12,29] However, although evidence is accumulating that adults may gain cardiometabolic health benefits by performing more LPA,[3,5,30–33] it remains unclear whether this intensity of movement would lead to better cardiometabolic health irrespective of CRF. Our findings, while supporting the robust evidence for the health benefits of MVPA,[1,34] further indicate that physical activity from light intensity upward is beneficially associated with markers of cardiometabolic health, even after accounting for 24-h movement and non-movement behaviors and CRF.

Most adverse associations observed between sedentary time and cardiometabolic health markers were changed to nonsignificant when models were adjusted for CRF and the 24-h movement and non-movement behaviors. Currently, the biological pathways through which sedentary time adversely affects cardiometabolic health remain unclear. Even less is known about the mediating role of CRF in this pathway.[9] While few population-based studies have reported that the associations between accelerometer-measured

TABLE 3 Partition models for associations of sedentary time, light-intensity physical activity (LPA), moderate-to-vigorous physical activity (MVPA), and self-reported sleep duration with cardiometabolic health markers

		Sedentary time			LPA			MVPA			Sleep		
	n	β (95% CI)	*p*	VIF	β (95% CI)	*p*	VIF	β (95% CI)	*p*	VIF	β (95% CI)	*p*	VIF
Outcomes displaying a linear relationship with sleep duration													
Total/HDL cholesterol ratio													
Partition model 1	2911	0.005 (0.0, 0.010)	0.362	3.08	**−0.020 (−0.026, −0.014)**	**<0.001**	2.99	**−0.1 (−0.112, −0.088)**	**<0.001**	1.23	**0.011 (0.006, 0.017)**	**0.033**	1.19
Partition model 2	2584	−0.001 (−0.007, 0.005)	0.892	3.09	**−0.019 (−0.025, −0.013)**	**0.001**	2.96	**−0.083 (−0.096, −0.070)**	**<0.001**	1.25	0.011 (0.005, 0.016)	0.064	1.19
LDL/HDL cholesterol ratio													
Partition model 1	2913	0.011 (0.003, 0.020)	0.163	3.08	**−0.023 (−0.032, −0.015)**	**0.007**	2.99	**−0.139 (−0.157, −0.120)**	**<0.001**	1.23	**0.016 (0.008, 0.025)**	**0.045**	1.19
Partition model 2	2585	0.005 (−0.004, 0.013)	0.598	3.09	**−0.022 (−0.032, −0.013)**	**0.015**	2.96	**−0.116 (−0.135, −0.096)**	**<0.001**	1.25	0.015 (0.007, 0.024)	0.080	1.19
Triglycerides													
Partition model 1	2913	−0.016 (−0.026, −0.007)	0.096	3.08	**−0.069 (−0.080, −0.059)**	**<0.001**	2.99	**−0.165 (−0.188, −0.143)**	**<0.001**	1.23	0.006 (−0.004, 0.016)	0.567	1.19
Partition model 2	2585	**−0.033 (−0.043, −0.023)**	**0.002**	3.09	**−0.072 (−0.083, −0.061)**	**<0.001**	2.96	**−0.119 (−0.142, −0.095)**	**<0.001**	1.25	0.008 (−0.002, 0.019)	0.419	1.19
Body fat													
Partition model 1	2873	**0.015 (0.009, 0.021)**	**0.010**	3.11	**−0.030 (−0.036, −0.023)**	**<0.001**	3.03	**−0.153 (−0.167, −0.140)**	**<0.001**	1.23	0.003 (−0.003, 0.009)	0.649	1.20
Partition model 2	2553	0.004 (−0.002, 0.010)	0.512	3.10	**−0.024 (−0.031, −0.018)**	**<0.001**	2.98	**−0.079 (−0.092, −0.066)**	**<0.001**	1.25	0.003 (−0.003, 0.009)	0.587	1.19
BMI													
Partition model 1	2924	**0.008 (0.005, 0.012)**	**0.016**	3.09	**−0.012 (−0.016, −0.009)**	**0.001**	3.01	**−0.057 (−0.064, −0.049)**	**<0.001**	1.23	−0.001 (−0.004, 0.003)	0.807	1.19
Partition model 2	2594	0.003 (0.0, 0.006)	0.352	3.10	−0.006 (−0.010, −0.003)	0.064	2.97	**−0.016 (−0.024, −0.009)**	**0.028**	1.25	0.002 (−0.001, 0.005)	0.583	1.19
Fat mass													
Partition model 1	2873	**0.029 (0.020, 0.037)**	**0.001**	3.11	**−0.042 (−0.052, −0.033)**	**<0.001**	3.03	**−0.205 (−0.225, −0.185)**	**<0.001**	1.23	0.005 (−0.003, 0.014)	0.543	1.20
Partition model 2	2553	0.013 (0.004, 0.021)	0.144	3.10	**−0.031 (−0.040, −0.022)**	**0.001**	2.98	**−0.096 (−0.116, −0.077)**	**<0.001**	1.25	0.010 (0.001, 0.019)	0.249	1.19
Outcomes displaying a U-shaped relationship with sleep duration													
Fasting insulin													
Sleep duration ≤7.5 h/day													
Partition model 1	1605	0.015 (−0.001, 0.031)	0.347	2.98	**−0.058 (−0.074, −0.041)**	**0.001**	2.86	**−0.235 (−0.270, −0.200)**	**<0.001**	1.24	−0.011 (−0.034, 0.013)	0.650	1.10
Partition model 2	1430	−0.006 (−0.023, 0.010)	0.694	2.98	**−0.044 (−0.061, −0.027)**	**0.010**	2.84	**−0.124 (−0.159, −0.088)**	**0.001**	1.25	−0.015 (−0.039, 0.009)	0.535	1.11
Sleep duration >7.5 h/day													
Partition model 1	1249	0.050 (0.031, 0.070)	0.011	3.36	−0.028 (−0.049, −0.007)	0.182	3.29	**−0.243 (−0.289, −0.198)**	**<0.001**	1.25	0.048 (0.016, 0.079)	0.129	1.13
Partition model 2	1098	0.014 (−0.006, 0.034)	0.476	3.38	−0.036 (−0.057, −0.015)	0.083	3.26	**−0.133 (−0.179, −0.087)**	**0.004**	1.27	0.048 (0.016, 0.080)	0.132	1.10
Fasting glucose													
Sleep duration ≤7.5 h/day													
Partition model 1	1599	0.0 (−0.003, 0.004)	0.970	2.97	−0.003 (−0.007, 0.0)	0.362	2.84	**−0.018 (−0.026, −0.011)**	**0.016**	1.24	0.0 (−0.005, 0.005)	0.953	1.10
Partition model 2	1424	**−0.008 (−0.011, −0.004)**	**0.024**	2.97	−0.005 (−0.009, −0.002)	0.119	2.82	−0.011 (−0.019, −0.004)	0.136	1.25	0.0 (−0.005, 0.005)	0.946	1.11

(Continues)

TABLE 3 (Continued)

	n	Sedentary time			LPA			MVPA			Sleep		
		β (95% CI)	*p*	VIF	β (95% CI)	*p*	VIF	β (95% CI)	*p*	VIF	β (95% CI)	*p*	VIF
Sleep duration >7.5 h/day													
Partition model 1	1242	0.006 (0.001, 0.010)	0.201	3.35	−0.004 (−0.008, 0.001)	0.426	3.28	−0.019 (−0.029, −0.009)	0.062	1.25	0.012 (0.005, 0.019)	0.076	1.13
Partition model 2	1091	0.004 (0.0, 0.009)	0.352	3.37	0.0 (−0.005, 0.004)	0.928	3.25	−0.002 (−0.013, 0.009)	0.863	1.28	**0.019 (0.011, 0.026)**	**0.013**	1.10

Note: Partition models accommodated sedentary time, LPA, MVPA, and self-reported sleep duration simultaneously. Model 1 was adjusted for age, sex, birthweight, education, marital status, employment, income, lifestyle factors (smoking status and alcohol consumption), health-related quality of life, and medication use, and Model 2 was further adjusted for cardiorespiratory fitness. Beta coefficients reflect associations for 60 min of sedentary time, LPA, MVPA, and self-reported sleep duration. Significant associations are shown in bold.

Abbreviations: VIF = variance inflation actor.

sedentary time and poor cardiometabolic health may be independent of CRF and MVPA,[35,36] several studies indicate a substantially less pronounced association between sedentary time and cardiometabolic health markers after adjustment for CRF and MVPA levels.[10–12] Studies reporting that the associations between sedentary time and cardiometabolic health markers are likely to be independent of CRF have generally accounted for a partial of movement or non-movement behaviors, typically sedentary time and MVPA, but not sleep and LPA.[35,36] According to most recent studies, improper adjustments for 24-h movement and non-movement behaviors when examining the health associations of daily activities are likely to lead to biased results and findings.[1,2] Future studies examining the associations of sedentary time with health indicators may therefore consider accounting for the full spectrum of movement and non-movement behaviors and CRF. Based on the results of this study, it appears that sedentary time is not associated with markers of cardiometabolic health after adjustment for the full spectrum of 24-h movement and non-movement behaviors and CRF.

Although most adverse associations between sedentary time and cardiometabolic health markers did not remain in the partition models adjusting for 24-h movement and non-movement behaviors and CRF, reallocating additional time to LPA and MVPA from daily time spent sedentary was associated with favorable differences in most cardiometabolic health markers examined here. The size of these beneficial differences was comparable to those reported in the existing literature.[3–5,32,37] In recent years, the combination of device-based measurement of daily activities and 24-h analytical approaches has led to an improved understanding of the interplay among movement behaviors.[1,2] Evidence continues to accumulate that any duration of physical activity is better than none, especially when more physical activity is performed at the expense of sedentary behaviors.[3,30–32,37,38] Regarding the intensity of movement, it appears that MVPA is the most potent health-enhancing intensity of movement.[1,3–5,34,37] However, replacing sedentary time with LPA also appears to be associated with better cardiometabolic health and reduced risk of mortality.[3,5,37,38] Such findings have shifted the emphasis from exercise training to active living, and updated guidelines have accordingly been proposed for physical activity and sedentary behaviors with an emphasis on performing more physical activity of any intensity and duration.[39] Our results provide further support for the current guidelines,[39] confirming that adults may be encouraged to limit their daily sedentary time by performing more physical activity of any duration and intensity for better cardiometabolic health, regardless of their CRF level.

Self-reported sleep duration was generally not associated with cardiometabolic health markers in partition

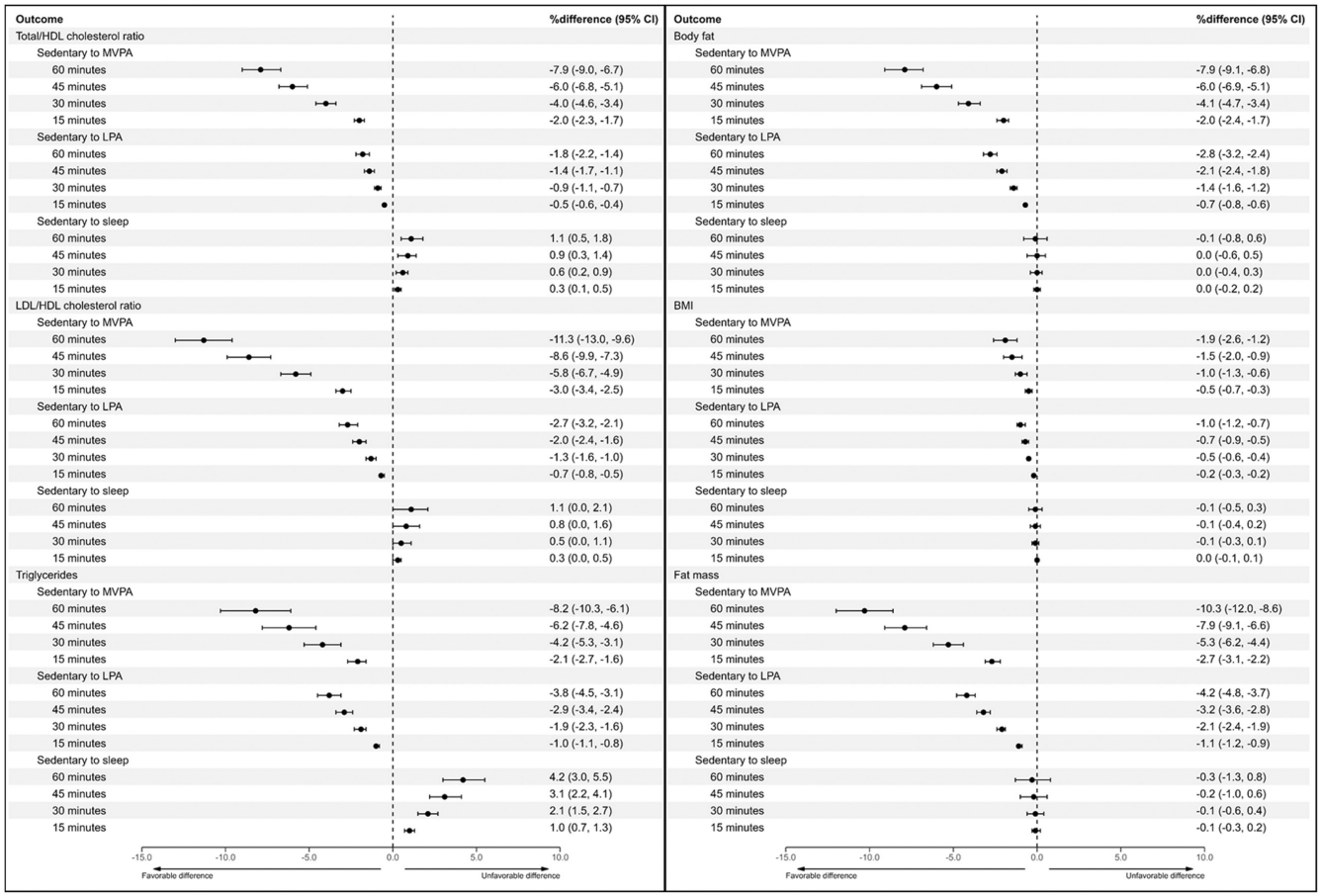

FIGURE 1 Percent difference (with 95% confidence interval) associated with substituting 60, 45, 30, and 15 min/day of sedentary time with moderate-to-vigorous-intensity (MVPA), light-intensity physical activity (LPA), or self-reported sleep duration in cardiometabolic health markers displaying a linear relationship with self-reported sleep duration. Percent difference can be interpreted as expected changes in the outcomes, when mean sedentary time would be replaced with sleep, LPA, or MVPA. For example, reallocation of 60 min of sedentary time to MVPA is estimated to be associated with 7.9% lower total/HDL cholesterol ratio, compared to total/HDL cholesterol ratio with current level of sedentary time, LPA, MVPA, and sleep. Isotemporal substitution model including LPA, MVPA, and sleep, and total time. All models were adjusted for age, sex, birthweight, education, marital status, employment, income, lifestyle factors (smoking status and alcohol consumption), health-related quality of life, medication use, and cardiorespiratory fitness.

models adjusting for CRF and 24-h movement and non-movement behaviors. However, replacing sedentary time with self-reported sleep was unfavorably associated with total/HDL and LDL/HDL cholesterol ratios but not with adiposity measures, fasting blood glucose, and insulin. Similar to our results, previous studies based on 24-h data have tended to report nonsignificant associations between sleep duration and cardiometabolic health markers,[5,37,40] with no apparent differences associated with substituting sedentary time with sleep for most cardiometabolic health markers such as fasting blood glucose and insulin levels.[5,37,40] Still, the findings of previous studies regarding time reallocation from sedentary behaviors to sleep appear to be somewhat mixed. For instance, a study of adults using isotemporal substitution modeling reported that while substituting sedentary time with sleep may be beneficial for BMI, this substitution does not affect other cardiometabolic markers.[5] Hence, this study reported that a similar substitution was detrimentally associated with a composite cardiovascular risk score computed based on smoking, diet, BMI, blood pressure, total cholesterol, and fasting glucose.[5] The inconclusive findings of previous studies may be related to inaccurate estimation of both sedentary time and sleep duration,[41,42] even in studies with 24-h device-based activity measurements.[43] Measuring actual sleep duration appears most complex among the 24-h daily activity behaviors, while measuring sleep quality, onset, and timing is even more complex.[1,43] Additionally, sedentary time and sleep have different physiology but appear to be correlational.[1,4] The diverse results across different markers of cardiometabolic health may therefore indicate a complex interplay between these two behaviors. More research is therefore needed to better understand the potential interaction between sleep duration and sedentary time and their potential combined and interactive association with cardiometabolic health markers.

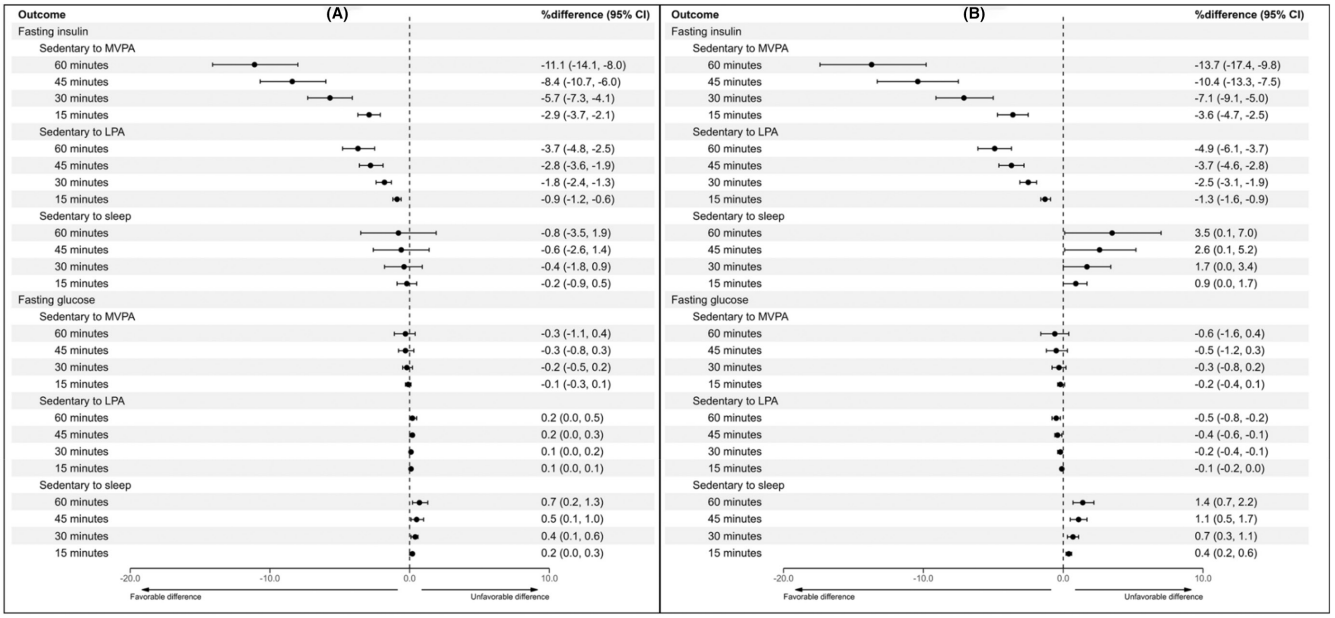

FIGURE 2 Percent difference (with 95% confidence interval) associated with substituting 60, 45, 30, 15 min/day of sedentary time with moderate-to-vigorous-intensity (MVPA), light-intensity physical activity (LPA), or self-reported sleep duration in cardiometabolic health markers displaying a U-shaped relationship with self-reported sleep duration. (A) Percent difference for substituting sedentary time with MVPA, LPA, or self-reported sleep duration in individuals with sleep duration ≤7.5 h/day, and (B) in individuals with sleep duration >7.5 h/day. Percent difference can be interpreted as expected changes in the outcomes, when mean sedentary time would be replaced with sleep, LPA, or MVPA. For example, reallocation of 60 min of sedentary time to MVPA is estimated to be associated with 11.1% lower fasting insulin in individuals with sleep duration ≤7.5 h/day, compared to fasting insulin with current level of sedentary time, LPA, MVPA, and sleep. Isotemporal substitution model including LPA, MVPA, and sleep, and total time. All models were adjusted for age, sex, birthweight, education, marital status, employment, income, lifestyle factors (smoking status and alcohol consumption), health-related quality of life, medication use, and cardiorespiratory fitness.

This study has several strengths. Measurement of daily activities was device-based for 14 days with raw accelerometry. Another strength is the large population-based sample of adults.[5] We examined the associations after accounting for CRF, which is an important predictor of cardiometabolic health,[7,8] but has generally been neglected in previous studies examining the associations between movement and non-movement behaviors and cardiometabolic health markers.[3,32]

This study has some limitations. Because of the birth cohort setting, the study sample was homogeneous in terms of age and ethnicity. Although beneficial for reducing the probability of confounding the associations, this may limit the generalizability of the study results to more diverse populations. Due to the observational and cross-sectional study design, inferences about the causality of associations cannot be determined. To address the problem of reverse causality, we repeated the isotemporal substitution models with participants who had appropriate sleep duration and no hypertension, heart disease, or diabetes. When repeating the analysis, the differences associated with time reallocations from sedentary time to LPA or MVPA remained unchanged. Still, undiagnosed diseases remain an issue, and the possibility of inverse causality cannot be completely excluded. CRF was expressed as peak heart rate during a 4-min submaximal step test. Although this is a widely acceptable and validated method for estimating CRF,[20] this surrogate measure probably provides a less accurate estimate of the true CRF than the gold standard of assessing maximal oxygen uptake. To address the nonlinearity in sleep duration, we tested for possible U-shaped relationships between sleep duration and cardiometabolic health markers and, when necessary, stratified the analyses by short and long sleep duration. Still, the VIF for sleep and sedentary time in partition models were slightly higher than 2.5 for some of the cardiometabolic markers, which although acceptable, appear to be higher than those that were reported in previous studies.[44,45] To confirm our findings, future studies may consider assessing the associations with alternative statistical methodologies capable of solving the problem of collinearity such as partial least square model.[2] Sleep duration was self-reported, so is likely to be less accurate than the estimates of other movement and non-movement behaviors. Still, self-reported duration appears the most common methodology for estimating sleep duration in epidemiological studies; it also correlates reasonably well with device-based estimates of sleep duration.[41]

5 | PERSPECTIVE

This population-based study of middle-aged adults showed that after adjustment for 24-h movement and non-movement behaviors, CRF, and other potential confounders, reallocating sedentary time to LPA and MVPA was beneficially associated with markers of cardiometabolic health. Regardless of their CRF level, adults may be encouraged to maintain an active lifestyle by performing more physical activity and reducing sedentary time.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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