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Original Contribution

Reallocating Time to Sleep, Sedentary Behaviors, or Active Behaviors: Associations With Cardiovascular Disease Risk Biomarkers, NHANES 2005–2006

Matthew P. Buman*, Elisabeth A. H. Winkler, Jonathan M. Kurka, Eric B. Hekler, Carol M. Baldwin, Neville Owen, Barbara E. Ainsworth, Genevieve N. Healy, and Paul A. Gardiner

* Correspondence to Dr. Matthew P. Buman, Arizona State University, School of Nutrition and Health Promotion, 500 North Third Street, Mail code 3020, Phoenix, AZ 85004-2135 (e-mail: matthew.buman@asu.edu).

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Sleep and sedentary and active behaviors are linked to cardiovascular disease risk biomarkers, and across a 24-hour day, increasing time in 1 behavior requires decreasing time in another. We explored associations of reallocating time to sleep, sedentary behavior, or active behaviors with biomarkers. Data ($n = 2,185$ full sample; $n = 923$ fasting subanalyses) from the cross-sectional 2005–2006 US National Health and Nutrition Examination Survey were analyzed. The amounts of time spent in sedentary behavior, light-intensity activity, and moderate-to-vigorous physical activity (MVPA) were derived from ActiGraph accelerometry (ActiGraph LLC, Pensacola, Florida), and respondents reported their sleep duration. Isotemporal substitution modeling indicated that, independent of potential confounders and time spent in other activities, beneficial associations ($P < 0.05$) with cardiovascular disease risk biomarkers were associated with the reallocation of 30 minutes/day of sedentary time with equal time of either sleep (2.2% lower insulin and 2.0% lower homeostasis model assessment of β-cell function), light-intensity activity (1.9% lower triglycerides, 2.4% lower insulin, and 2.2% lower homeostasis model assessment of β-cell function), or MVPA (2.4% smaller waist circumference, 4.4% higher high-density lipoprotein cholesterol, 8.5% lower triglycerides, 1.7% lower glucose, 10.7% lower insulin, and 9.7% higher homeostasis model assessment of insulin sensitivity. These findings provide evidence that MVPA may be the most potent health-enhancing, time-dependent behavior, with additional benefit conferred from light-intensity activities and sleep duration when reallocated from sedentary time.

cardiovascular disease; isotemporal substitution; physical activity; sedentary behavior; sleep duration

Abbreviations: CVD, cardiovascular disease; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; HOMA-S, homeostasis model assessment of insulin sensitivity; HOMA-β, homeostasis model assessment of β-cell function; LDL, low-density lipoprotein; LIPA, light-intensity physical activity; MVPA, moderate-to-vigorous physical activity; NHANES, National Health and Nutrition Examination Survey; SB, sedentary behavior.

Across a 24-hour day, time is disproportionately distributed between sleep, sedentary behaviors, and active behaviors (1–3). Optimal sleep duration (i.e., 7–8 hours/day), moderate-to-vigorous physical activity (MVPA) (e.g., brisk walking, swimming, hard physical labor), and even light-intensity physical activity (LIPA) (i.e., lifestyle behaviors, such as leisurely walking or doing household chores) have been beneficially associated with markers of cardiovascular disease (CVD) risk (3–6). Conversely, sedentary behavior (SB) (i.e., sitting/reclining with low energy expenditure (7) as during television viewing or workplace sitting) and long (>8 hours) or short (<7 hours) sleep duration have been detrimentally associated with markers of CVD risk (3, 8).

Although there are distinct health consequences of sleep, SB, and active behavior, time is finite for individuals; thus, increasing time in 1 behavior inevitably requires decreasing time in another. The health impacts of sleep, SB, and active behavior depend not only on the behaviors themselves but also on the behaviors they displace (9). None of the literature reporting on sleep, SB, or physical activity has adequately accounted for the fixed-time nature in which these behaviors occur, or how varying distributions of sleep, SB, and active

behavior may affect CVD risk. Although the benefits of MVPA are well recognized, it is not feasible to participate at this activity level during all waking hours (10). Thus, understanding the potential health benefits of reallocating sedentary time to alternative activities (i.e., LIPA or sleep) is of substantial public health interest.

The isotemporal substitution paradigm explores associations of alternating allocations of time in 1 behavior with another while holding total time constant (9). Historically rooted in nutritional epidemiology (11), isotemporal substitution modeling has recently been applied to physical activity behaviors (of varying types and intensities) and weight change (9) and perceived physical and psychosocial health (12). The collection of objective measures of SB, LIPA, and MVPA, as well as self-reported sleep duration in the National Health and Nutrition Examination Survey (NHANES) from 2005–2006 has enabled us to examine for the first time the associations of alternating the allocations of time spent in sleep, SB, and active behavior with CVD risk biomarkers. Also, given that both short (<7 hours) and long (>8 hours) sleep durations among adults have been implicated in poor CVD risk profiles (6), we examined whether decreased sedentary time or increased active behaviors were protective or synergistic in the relationship between CVD risk biomarkers and varying levels of sleep duration.

METHODS

Study sample

The NHANES uses a complex sampling design to produce a representative sample of the US civilian noninstitutionalized population. The methods are described in detail elsewhere (13). The NHANES includes an in-person home interview and a visit to a mobile examination center where laboratory data are collected. The ethics review board of the Centers for Disease Control and Prevention (Atlanta, Georgia) approved the protocols, and informed consent was obtained for all subjects. These analyses include data from the 2005–2006 study cycle only because other study cycles did not include both accelerometry and sleep questionnaires. A total population-representative sample of 4,979 respondents who were 20 years of age or older was interviewed (74.4% response rate) and examined (71.5% response rate). Respondents with a diagnosed sleep disorder or those who were currently pregnant, lactating, or taking insulin were ineligible ($n = 1{,}945$). Participants without sufficient valid accelerometry data or those who had missing self-reported sleep duration, covariate, or biomarker data were excluded, leaving data from 2,185 adults available for the full sample (52.9% of eligible subjects) and 923 adults for the fasting subsample (22.3% of eligible subjects) (Web Figure 1, available at http://aje.oxfordjournals.org/).

Sociodemographic and health behavior/status covariates

Sociodemographic variables considered as potential confounders included sex; race/ethnicity (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or other/multiracial); marital status (married/living together, widowed, divorced, separated, or never married); education (<12 years, 12 years or equivalent, or some college or above); work status (not working, working part-time (<35 hours/week), or working full-time (≥35 hours/week)); and ratio of family income to poverty level (as a continuous variable) (range, 0 (lower income) to 5 (higher income)). Health behavior/status variables included smoking; depressive symptoms (14); 24-hour dietary recalls estimating intakes of total energy, saturated fat, caffeine, and alcohol (13); a general health rating (excellent to poor) (15); previous diagnosis of cancer or malignancy, CVD, or diabetes; and current use of diabetic, antihypertensive, lipidemic, or other CVD medication.

Sleep, sedentary time, and physical activity variables

Sleep duration was assessed with a single item with the following question: "How much sleep do you usually get at night on weekdays or workdays?" Acceptable values were whole integers from 1 to 24 hours, with values of 12 hours or more set at 12 hours. Sedentary and activity variables were derived from ActiGraph 7164 accelerometers (ActiGraph LLC, Pensacola, Florida), which were worn for 7 days. Details of the accelerometry protocol are described elsewhere (1, 2). We made additional scoring modifications including a) wear period interruptions to any 3 counts less than 50 counts/minute (16), and b) allowing nonwear periods to continue over the midnight hour. ("Counts/minute" refers to acceleration units observed during 1-minute epochs. Higher values indicate more intense activity.) Days with 10 or more hours of wear time were considered valid, and 4 or more valid days were needed to be included in the analyses. Standard count-per-minute thresholds were used to classify wear time as SB (<100 counts/minute) (1), LIPA (100–1,951 counts/minute), or MVPA (≥1,952 counts/minute) (17). Additional thresholds were explored to further delineate the light-intensity range (100–759 counts/minute to 760–1,951 counts/minute) but were not included in final analyses because of high multicollinearity with SB and MVPA. Nonwear accelerometer time was not used to estimate sleep duration because of other substantial sources of nonwear time (e.g., forgotten device, swimming/bathing, time in bed but not sleeping).

CVD risk biomarker outcomes

Clinically measured biomarkers included waist circumference and systolic and diastolic blood pressures. Laboratory-based nonfasting biomarkers included high-density lipoprotein (HDL) cholesterol and C-reactive protein. The fasting subsample measures were low-density lipoprotein (LDL) cholesterol, fasting triglycerides, plasma glucose, and insulin and were measured in the morning following a fast of more than 9 hours. Homeostasis model assessment of insulin sensitivity (HOMA-S) and homeostasis model assessment of β-cell function (HOMA-β) were derived using standard procedures (8). A full description of the methods is available elsewhere (13).

Data analysis

Statistical analyses in SAS Enterprise Guide, version 4.2, software (SAS Institute, Inc., Cary, North Carolina) used

linearized variance estimates and inverse probability weights to accommodate the complex survey design. The original NHANES weights were reweighted to correct for missing relevant data for this study (2). Biomarker variables were log-transformed to account for nonnormal distributions. Age (as a continuous variable and with a squared term if significant), sex, and race/ethnicity were included as confounders in all models; other potential confounders were retained in a backward elimination process in which *P* values were less than 0.2 (Web Table 1). Models showed no evidence of collinearity (i.e., variance inflation factor < 2), nonlinearity, nonnormality, or heteroscedasticity (assessed by scatterplots). Sleep duration, SB, LIPA, and MVPA were scaled to 30-minute/day units to improve interpretability of the results (4). Association parameters were expressed as relative rates for log-transformed outcomes. Three sets of regression models (discussed below) were fitted to assess associations of the exposure variables (sleep duration, SB, LIPA, and MVPA) with CVD risk biomarkers as depicted in Web Figure 2.

Single and partition models

Single-variable models were used to estimate the "total association" for each variable. These models depict the raw associations between each variable and the outcome, adjusted for confounders, but not for the other types of activity and without considering substitution or displacement of activities. Partition models were used to estimate the "unique association" of each exposure variable by holding time in all other variables constant. These models depict the unique associations of sleep duration, SB, LIPA, and MVPA with the outcome, independent of the other types of activity and confounders. Both single-variable and partition models were tested for linear and U-shaped relationships between sleep duration and biomarkers given the extant sleep literature suggesting that restricted (<7 hours) and extended (>8 hours) sleep durations have detrimental health effects (18).

Isotemporal substitution models

Isotemporal substitution models were used to estimate the "substitution association" of reallocating time from 1 exposure variable to an equal amount of time in another exposure variable (e.g., reallocating 30 minutes/day of SB to 30 minutes/day of MVPA). A full description of isotemporal substitution models is presented elsewhere (9). Briefly, all behaviors (i,e., sleep duration, LIPA, and MVPA), other than the behavior of interest (e.g., SB), plus a total assessment time variable (i.e., total time = sleep duration + SB + LIPA + MVPA) were entered into the models simultaneously. By including a total assessment time variable in the model, time is constrained (i.e., isotemporal) and allows direct associations to be made among exposure variables and the biomarker of interest. The regression estimates for the included behaviors (e.g., sleep duration, LIPA, MVPA) reflect the increase in mean levels of the biomarker in the population (in original units or in percent for relative rates) that is observed when the mean times spent in these behaviors are increased by 30 minutes/day because the mean time spent in the omitted behavior (e.g., SB) is decreased by 30 minutes/day. Importantly, because these data are cross-sectional, reallocations (e.g., from SB to sleep, LIPA, or MVPA) cannot be interpreted as temporal substitutions within individuals or as causal effects. Statistical significance was established at $P < 0.05$ for the single, partition, and isotemporal models.

Isotemporal models require linear relationships among exposure variables within a common metric (i.e., 30 minutes/day). When single or partition models showed U-shaped associations of sleep duration with biomarkers, isotemporal analyses were stratified so that associations could be examined separately for short (≤7 hours) and long (≥8 hours) sleepers, for whom each additional 30 minutes/day of sleep duration was expected to be beneficial or detrimental, respectively, in an approximately linear fashion.

Interaction analyses

To examine whether SB, LIPA, and MVPA were protective or synergistic in the strength of the relationship between sleep duration and CVD risk biomarkers, we performed interaction analyses. The sleep duration variable was recoded into the following 5 levels: ≤5 hours, 6 hours, 7 hours, 8 hours, or ≥9 hours. Sleep duration of 9 or more hours was collapsed with 8 hours in the fasting CVD risk biomarkers because of the small sample size ($n = 60$). Seven hours of sleep (median sleep duration) was used as the reference category for all comparisons. Accelerometry-derived variables were entered into the models continuously (adjusting for the main association of all confounding variables and the other accelerometry variables); however, results are presented graphically in quartiles to aid interpretation. Statistical significance was established at $P < 0.10$ for interactions given the exploratory nature of this research question and the focus on hypothesis generation for future studies (19).

RESULTS

The population-weighted sociodemographic, health behavior, and health status variables for the full sample and fasting subsample were each similar to the eligible sample (Table 1). Characteristics are also displayed by sleep duration for the full sample in Web Table 2. Differences for the accelerometry-derived variables and CVD risk biomarkers by sleep duration are displayed in Web Table 3. Spearman ρ correlations among accelerometry and sleep duration variables followed a simplex pattern (Web Table 4).

Single and partition models: total and adjusted associations with CVD biomarkers

Results from the single-activity and partition models are presented in Web Table 5. The strongest associations with biomarkers in the single-variable model were observed with MVPA. Here, moderate-to-strong beneficial associations were observed with all biomarkers except blood pressure and LDL cholesterol. LIPA had significant beneficial associations, and SB had significant detrimental associations with triglycerides, insulin, HOMA-β, and HOMA-S, with LIPA further showing significant beneficial associations with waist circumference and HDL cholesterol. By contrast,

Table 1. Characteristics of the Eligible, Full, and Fasting Samples, Weighted to the Population of US Adults Aged ≥20 Years by Total Sleep Time, National Health and Nutrition Examination Survey, 2005–2006

Characteristic	Eligible Sample[a,b] (*n* = 4,130)			Full Sample[c] (*n* = 2,185)			Fasting Subsample[d] (*n* = 923)		
	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%
Sociodemographic									
Age, years	46.6 (18.5)			46.6 (18.4)			46.6 (19.1)		
Female sex		2,050	49.4		1,028	51.9		492	47.6
Race/ethnicity									
Mexican American		772	7.9		430	8.0		183	8.0
Other Hispanic		123	3.4		67	3.5		34	4.1
Non-Hispanic white		1,987	72.1		1,159	72.2		474	71.1
Non-Hispanic black		906	11.2		449	11.5		189	11.1
Other/multiracial		154	5.3		80	4.8		43	5.7
Marital status									
Married/living together		2,402	65.4		1,418	67.1		614	67.4
Widowed		385	6.7		188	5.8		69	5.3
Divorced/separated		503	12.2		288	12.1		116	11.8
Never married/single		647	15.7		291	14.9		124	15.4
Education									
<12 years		1,095	17.7		552	15.3		220	15.0
12 years or equivalent		943	25.2		520	24.7		236	25.7
Some college or more		1,898	57.2		1,113	60.0		467	59.3
Work status[e]									
Not working		1,549	31.0		800	27.8		340	28.9
Part-time		314	8.8		182	9.6		84	10.7
Full-time		2,075	60.2		1,203	62.5		499	60.4
Family income to poverty ratio[f]	3.1 (1.9)			3.2 (1.7)			3.2 (1.7)		
Health behavior/status									
Smoking[g]									
Nonsmoker		2,953	72.9		1,674	75.1		715	75.2
Light smoker		216	5.6		108	5.2		42	5.4
Moderate smoker		479	13.3		245	12.2		98	11.7
Heavy smoker		294	8.2		158	7.5		68	7.7

Table continues

LIPA had a detrimental association and SB had a beneficial association with systolic blood pressure. Sleep duration had significant, beneficial linear associations with waist circumference and HOMA-β and significant, U-shaped associations with diastolic blood pressure, C-reactive protein, and LDL cholesterol, which showed excessive or too little sleep to be detrimental. The partition models showed similar, yet attenuated, associations compared with the single-activity models.

Isotemporal substitution models: reallocations of sleep, sedentary time, and active time

Isotemporal substitution models are highlighted in Figure 1 and displayed in full in Web Figures 3–5. Reallocating time to MVPA from other behaviors was beneficial for several biomarkers (Web Figure 3). Reallocating 30 minutes/day from sleep to MVPA was associated with significantly more favorable waist circumference (2.5% lower), C-reactive protein for short sleepers (25.3% lower), HDL cholesterol (4.4% higher), triglycerides (9.3% lower), glucose (1.7% lower), insulin (11.9% lower), and HOMA-S (9.7% higher). Reallocating 30 minutes/day of SB to MVPA was associated with significantly more favorable waist circumference (2.8% lower), HDL cholesterol (4.6% higher), triglycerides (9.5% lower), glucose (1.3% lower), insulin (14.5% lower) and HOMA-S (11.5% lower). Reallocating 30 minutes/day of LIPA to MVPA was associated with significantly more favorable waist circumference (2.6% lower), HDL cholesterol (4.3% higher), triglycerides (7.4% lower), glucose (1.5% lower) and insulin (11.7% lower). Reallocating time to LIPA had mixed results (Web Figure 4). Reallocating 30 minutes/day from sleep to LIPA had no significant association with biomarkers, whereas reallocating 30 minutes/day from SB to LIPA had the following significant beneficial

Table 1. Continued

Characteristic	Eligible Sample[a,b] (*n* = 4,130)			Full Sample[c] (*n* = 2,185)			Fasting Subsample[d] (*n* = 923)		
	Mean (SD)	No.	%	Mean (SD)	No.	%	Mean (SD)	No.	%
Depressive symptoms	2.4 (4.1)			2.2 (3.7)			2.4 (3.9)		
Total energy intake, MJ	9.3 (5.5)			9.2 (5.0)			9.1 (5.0)		
Saturated fat, % total energy intake	11.0 (4.9)			11.1 (4.5)			11.1 (4.4)		
Caffeine intake, g/day	190.4 (291.7)			196.3 (285.1)			190.1 (278.5)		
Alcohol intake[h]									
None		1,191	26.9		730	28.2		327	29.9
Light		1,489	43.7		930	44.3		388	44.2
Moderate		403	13.7		250	14.0		90	12.0
Heavy		506	15.7		275	13.6		118	13.9
General health rating[i]	2.6 (1.1)			2.5 (1.0)			2.6 (1.0)		
Previous diagnoses									
Cancer or malignancy		331	7.8		190	7.8		83	8.0
CVD		372	7.2		185	6.4		79	7.0
Diabetes		362	6.7		204	6.3		84	6.2
Current medication use									
Diabetic		241	4.2		143	4.3		58	4.1
Antihypertensive		214	4.9		125	4.8		44	3.8
Lipidemic		889	18.8		362	13.3		145	12.7
Other CVD		930	18.6		518	18.7		229	19.1

Abbreviations: CVD, cardiovascular disease; SD, standard deviation.
[a] Laboratory examination (in 2005–2006) weights were used.
[b] Actual *n* varies because of missing data.
[c] Laboratory examination (in 2005–2006) sample was reweighted for eligibility and missing data.
[d] Reweighted fasting subsample weight.
[e] Part-time = working <35 hours/week; full-time = working ≥35 hours/week.
[f] Scale is 0 (minimum) to 5 (maximum), with higher numbers reflecting higher income.
[g] Based on serum cotinine levels as follows: nonsmoker, <10 ng/dL; light smoker, 10–99 ng/dL; moderate smoker, 100–299 ng/dL, and heavy smoker, ≥300 ng/dL.
[h] Based on the following levels of alcohol consumption: light, <28 g/day for men or <14 g/day for women; moderate, 28–55 g/day for men or 14–27 g/day for women; heavy, ≥56 g/day for men or ≥28 g/day for women.
[i] Scale is 1 (excellent) to 5 (poor).

associations with some biomarkers, but to a lesser extent than when reallocating to MVPA: 1.9% lower triglycerides, 2.4% lower insulin, 2.3% lower HOMA-β, and 2.3% higher HOMA-S. Reallocating 30 minutes/day of SB to LIPA had the following significant, but weak, detrimental associations with blood pressure: 0.2% higher systolic blood pressure and 0.6% higher diastolic blood pressure (in long sleepers). Finally, reallocating 30 minutes/day from SB to sleep (Web Figure 5) had beneficial associations with insulin (2.3% lower), HOMA-S (2.0% higher), and HOMA-β (1.7% lower), as well as with LDL cholesterol in long sleepers only (4.8% lower).

Interactions: behavior-biomarker relationships across sleep duration categories

In general, the pattern of associations between sedentary or active behaviors and biomarkers was similar across sleep duration categories. For a few variables, however, the sedentary and active behavior relationships with biomarkers were more pronounced among short or long sleepers (Figures 2–4). For SB, significant interactions were present for systolic (Figure 2A) and diastolic (Figure 2B) blood pressures, such that associations in short sleepers (≤5 hours or 6 hours) were markedly different than in 7-hour sleepers. For LIPA, significant interactions were present for HDL cholesterol (Figure 3A), triglycerides (Figure 3B), HOMA-β (Figure 3C), and HOMA-S (Figure 3D). The interactions were typically such that the benefit of additional LIPA was most pronounced in those who slept 5 hours or less, whereas for triglycerides, the benefit of additional LIPA was consistent for all except 6-hour sleepers, for whom LIPA showed the least benefit. For MVPA, significant interactions were present for waist circumference (Figure 4A) (such that the benefits of additional MVPA appeared strongest in those who slept for 5 hours or less) and triglycerides (Figure 4B) (such that the benefit of

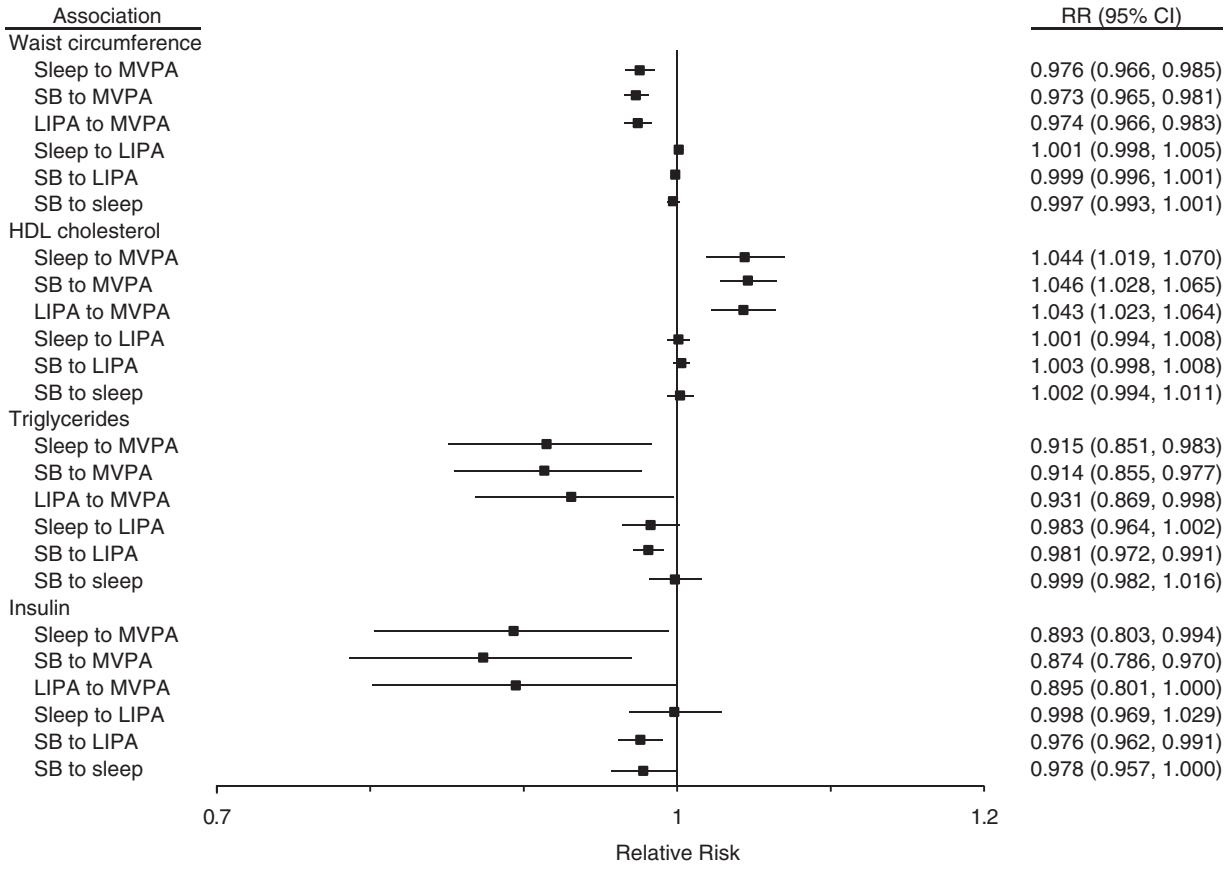

Figure 1. Population-weighted isotemporal substitution regression models for waist circumference, high-density lipoprotein (HDL) cholesterol, triglycerides, and insulin per a 30-minute/day reallocation of sleep duration, sedentary behavior (SB), and light-intensity physical activity (LIPA) to additional moderate-to-vigorous physical activity (MVPA), LIPA, or sleep in the National Health and Nutrition Examination Survey, 2005–2006. Nonfasting biomarkers included waist circumference and HDL cholesterol ($n = 2,187$); fasting biomarkers included triglycerides and insulin ($n = 923$). All models were adjusted for age (linear and age squared), sex, and race/ethnicity. Previous diagnosis of cancer or malignancy, cardiovascular disease, or diabetes; current diabetic, antihypertensive, lipidemic, or other cardiovascular disease medication; marital status; education; work status; poverty; smoking; depressive symptoms; intakes of energy and saturated fat; caffeine and alcohol use; and general health rating were included as covariates through backward elimination ($P < 0.2$). Total assessment time was entered as a covariate in all models. MVPA was defined as ≥1,952 counts/minute; LIPA was defined as 100–1,951 counts/minute; and SB was defined as <100 counts/minute. "Counts/minute" refers to acceleration units observed during 1-minute epochs. Higher values indicate more intense activity. Bars, 95% confidence interval (CI). RR, relative risk.

MVPA was most pronounced in 7-hour sleepers compared with short or long sleepers).

DISCUSSION

This study is unique because sleep, SB, and active behavior were examined for their synergistic associations with CVD risk biomarkers. Isotemporal substitution modeling is a key contribution because it acknowledges that sleep, SB, and active behavior take place during the same finite pool of available time and are interdependently linked. We applied this approach in a large, population-based sample examining CVD risk, and we explored a complementary hypothesis whereby sleep duration moderates the associations that sedentary and active behaviors may have with CVD biomarkers.

Key strategies advocated in public health include maintaining optimal sleep duration (20), reducing sedentary time (10), and increasing time in active behaviors (4); this investigation found support for each of these. However, we further found that reallocating time from sedentary behaviors, and in some cases from sleep and light activity to additional MVPA, was associated with more favorable values of CVD risk biomarkers related to adiposity, lipid metabolism, and glucose metabolism. In line with other studies examining weight change (9), metabolic risk (21), and self-rated physical health (12), this study found that reallocating time from SB to LIPA was beneficial for triglycerides, insulin, HOMA-β, and HOMA-S but weakly detrimental for systolic and diastolic blood pressures (within short sleepers only). Also, reallocating time from SB to sleep had beneficial associations with some biomarkers of lipid metabolism (LDL cholesterol in

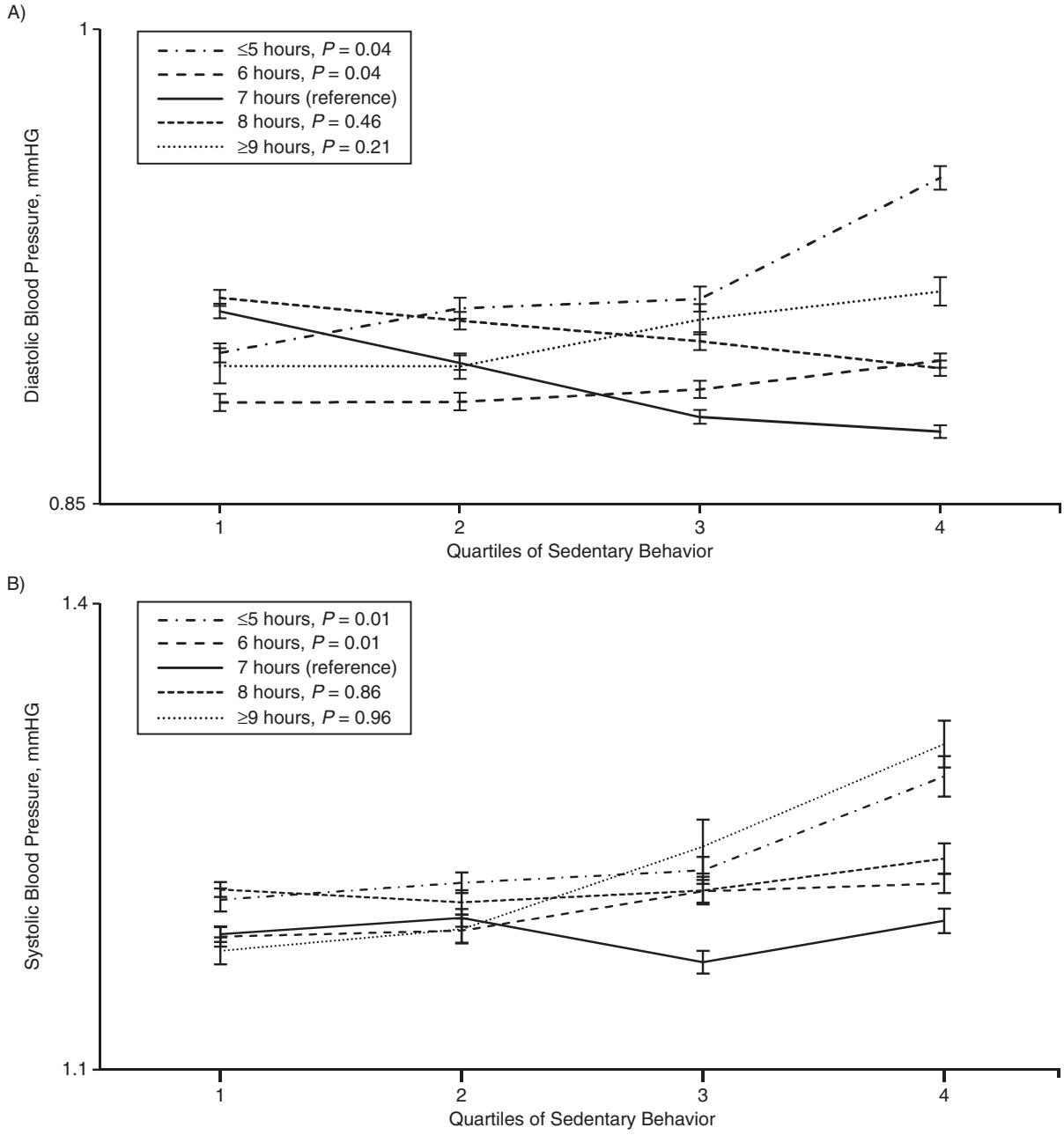

Figure 2. Population-weighted associations of sedentary behavior and A) systolic and B) diastolic blood pressures by categories of sleep duration ranging from ≤5 hours to ≥9 hours in the National Health and Nutrition Examination Survey, 2005–2006. Only associations for which a significant interaction ($P < 0.1$) was observed are shown. P values for interactions are 0.008 and 0.09 for systolic and diastolic blood pressures, respectively. Quartile thresholds for sedentary time are 7.00, 8.31, and 9.78 hours/day for the nonfasting sample ($n = 2,185$) and 6.86, 8.38, and 9.95 hours/day for the fasting sample ($n = 923$); outcomes are on a logarithmic scale.

long sleepers) and glucose metabolism (insulin, HOMA-β, and HOMA-S). These findings suggest that interventions targeting SBs may be able to expand beyond the typical replacement activities (e.g., exercise, sedentary breaks) to supporting healthful sleep time. Finally, with some notable exceptions discussed below, the potential benefit of less SB and more active behavior appeared to be similar across sleep duration categories, suggesting that recommendations (e.g., to reallocate sedentary time with sleep or active behaviors) can be considered generally for the population rather than needing to be tailored depending on sleep time.

Collectively, these findings provide preliminary evidence that MVPA may be the most potent health-enhancing behavior (2%–25% improvement per 30 minutes of reallocation),

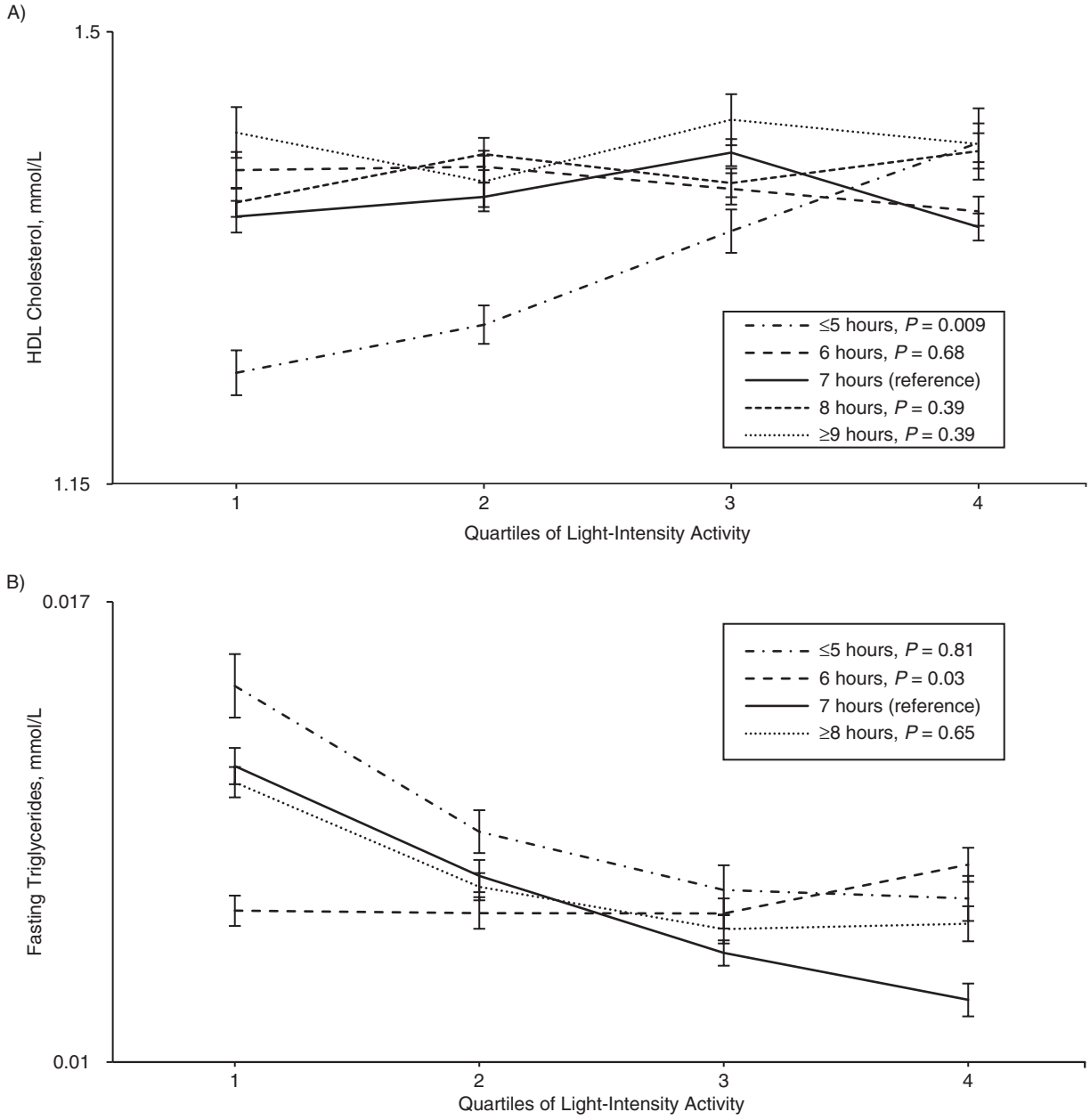

Figure 3. Population-weighted associations of light-intensity activity and A) high-density lipoprotein (HDL) cholesterol, B) fasting triglycerides, C) homeostatic model assessment of β-cell function (HOMA-β), and D) homeostatic model assessment of insulin sensitivity (HOMA-S) by categories of sleep duration ranging from ≤5 hours to ≥9 hours in the National Health and Nutrition Examination Survey, 2005–2006. Only associations for which a significant interaction ($P < 0.1$) was observed are shown. *P* values for interactions are 0.03, 0.09, 0.09, and 0.06 for HDL cholesterol, fasting triglycerides, HOMA-β, and HOMA-S, respectively. Quartile thresholds for light-intensity activity are 274.00, 342.75, and 416.71 minutes/day for the nonfasting sample ($n = 2,185$) and 266.83, 338.83, and 413.57 minutes/day for the fasting sample ($n = 923$); outcomes are on a logarithmic scale.

with some additional benefit conferred from LIPA (2%–4% improvement per 30 minutes of reallocation), and extended sleep duration (2%–4% improvement per 30 minutes of reallocation). To maximize benefits, it would appear that these activities should be reallocated primarily from sedentary time, because this produced the strongest associations. The clinical relevance of these improvements is most substantial with MVPA; however, the amount of time that might realistically be reallocated to MVPA is limited (10). Hence, the reallocations among the other activities (that comprise much more of a 24-hour period), such as sleep or LIPA, are also important and potentially clinically relevant, as long as sufficient time is reallocated. For example, based upon data presented here, the association for insulin of reallocating 3

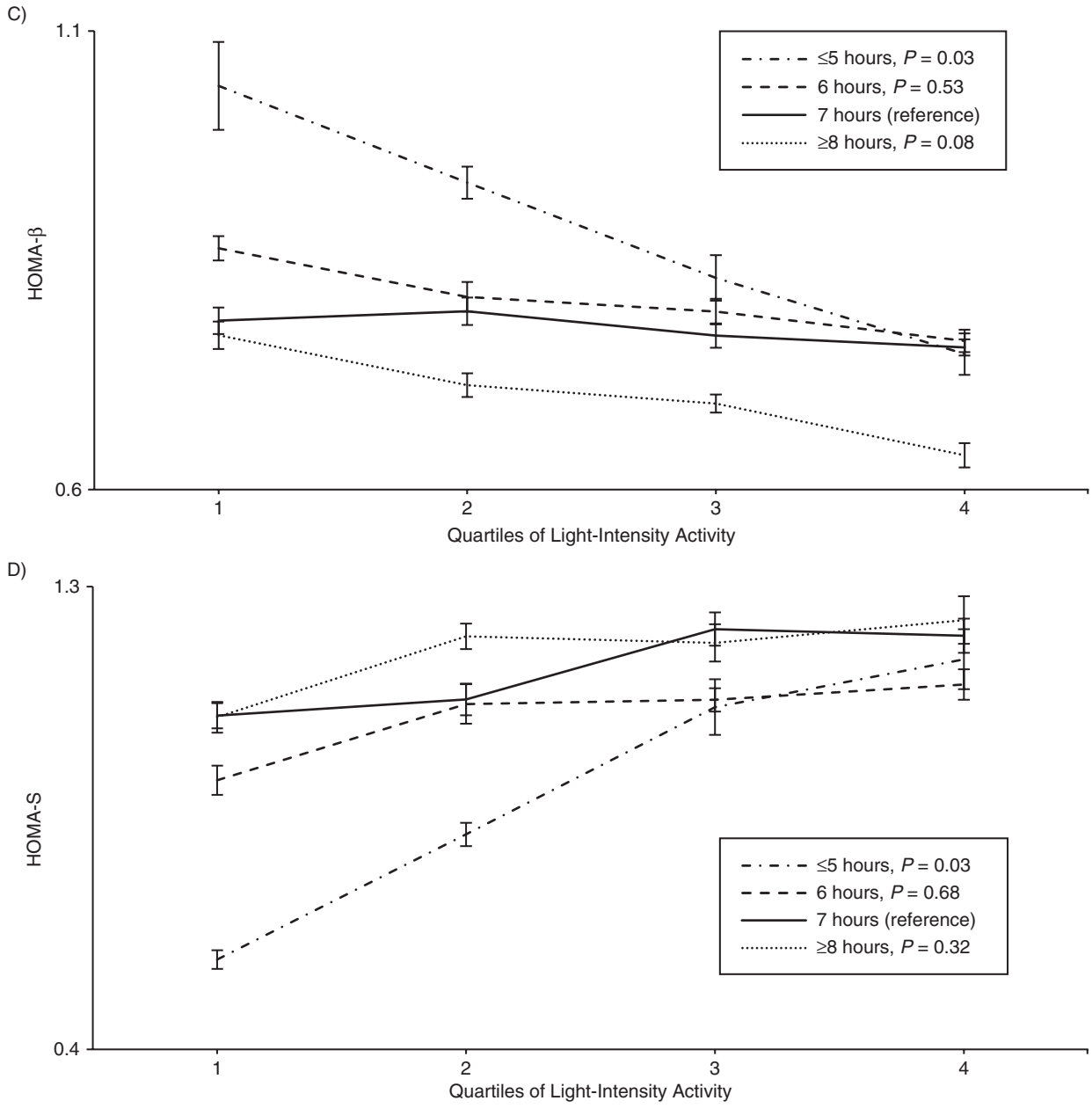

Figure 3. Continued

hours/day of sedentary time to LIPA is equivalent to reallocating 30 minutes/day of sedentary time to MVPA. In perspective, 3 hours/day represents a 52% increase in mean population-level LIPA time, whereas 30 minutes/day represents a more than 200% increase in mean population-level MVPA. More research is needed to determine which reallocations, and in what magnitudes, are most feasible to achieve and produce the most meaningful changes in risk biomarkers.

There are a number of potential mechanisms that may be driving the findings of this study. Each of the behaviors reported here (sleep, SB, and active behavior) has its own unique ecosystem of putative mechanistic actions on various metabolic functions, which may explain why some biomarkers were more or less consistently associated with reallocations of time from 1 behavior to another. Given the fixed-time nature of these analyses, more interesting are the potential interactive mechanisms of sleep, SB, and active behaviors. For example, increased physical activity may affect sleep via antidepressant, anxiolytic, thermoregulatory, and circadian phase–shifting mechanisms (22). Effects of sleep may be reciprocal, with optimal sleep duration and quality also increasing energy expenditure via increased energy and reduced fatigue (23). Finally,

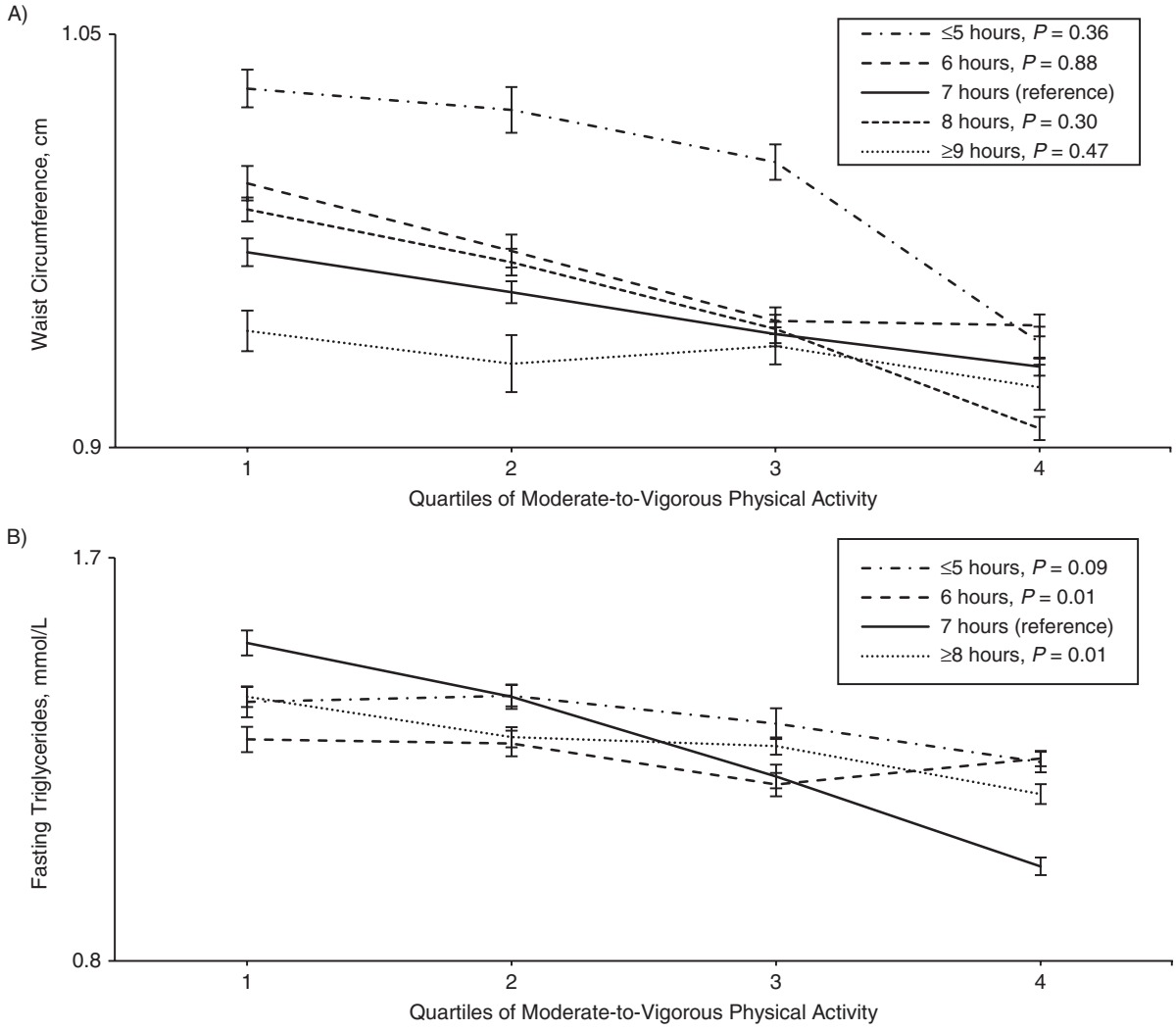

Figure 4. Population-weighted associations of moderate-to-vigorous physical activity and A) waist circumference and B) fasting triglycerides by categories of sleep duration ranging from ≤5 hours to ≥9 hours in the National Health and Nutrition Examination Survey, 2005–2006. Only associations for which a significant interaction ($P < 0.1$) was observed are shown. *P* values for interactions are 0.06 and 0.04 for waist circumference and fasting triglycerides, respectively. Quartile thresholds for moderate-to-vigorous physical activity are 6.43, 17.50, and 33.83 minutes/day for the nonfasting sample ($n = 2{,}185$) and 6.16, 17.57, and 35.29 minutes/day for the fasting sample ($n = 923$); outcomes are on a logarithmic scale.

although it would seem that fatigue and tiredness due to short sleep would lead to increased SB, no such relationships have been examined to our knowledge in adult populations.

In most cases, the potential association of sedentary and active behaviors on biomarkers was not shown to be different among short, normal, and long sleepers. Where there was some limited evidence of an interaction, it was typically such that the greatest benefits of less SB, more LIPA, and more MVPA were seen in very short sleepers (≤5 hours). In some cases, most notably for fasting triglycerides (Figures 3B and 4B), sleep and activity were synergistic in nature, with both normal sleep duration (i.e., 7 hours) and high levels of LIPA or MVPA needed for optimal benefit. The interactions with sleep duration may help to explain some of the large between-person heterogeneity of the associations of physical activity and SB with health outcomes (4). The interactions should be interpreted with caution, and future studies adequately powered to detect these relationships are needed.

Among its strengths, this study included a representative sample with objective measures of sedentary and active behaviors. Selection bias was unlikely to have affected conclusions given reweighting procedures that yielded an unbiased sample. Accelerometry is a more precise, less biased measure of habitual activity than are self-reported forms of measurement (24). Of note, the objective assessment allowed us to delineate LIPA (a particularly difficult behavior to capture through self-report (25)) from SB or MVPA and to explore unique associations of LIPA with CVD risk biomarkers. However, accelerometer use is not without its limitations. The appropriateness of standardized thresholds to classify time into intensity categories has

recently been questioned (26), and it is not clear what types/modalities of activities fit into these categories. Also, there is reason to suspect the accelerometers are better at classifying MVPA than LIPA or sedentary time (27), which may have contributed to the stronger associations for MVPA than for the other activities. Further, nonwear time (comprising sleep and other types of monitor removal) was estimated rather than measured, and estimations do not distinguish perfectly between nonwear and sedentary time, nor do they distinguish between napping from other forms of sleep.

Another limitation of this study was the self-report measure of sleep duration. Although common among large-scale population-based studies, self-reported habitual sleep duration has known biases (28). We attempted to control for some of these factors by adjusting for age, sex, race/ethnicity, and self-rated health, but it should be noted that total assessment time was associated with total sleep time, such that participants reporting shorter sleep durations also had less total assessment time, in some cases well below the expected 24-hour period (Web Table 3). Data from the United Kingdom Biobank (http://www.ukbiobank.ac.uk/) and the NHANES 2011–2012 cycle will largely overcome this limitation because participants are being instructed to wear the accelerometer on the wrist continuously throughout the 7-day period, allowing for concurrent measurement of objective daytime activity and sleep. Also, there have been differences noted in sleep duration and sleep problems by race/ethnicity (29) and age (30); therefore, future studies should explore these variations and their collective impact on CVD risk biomarkers. The cross-sectional design of this study limits the ability to make causal inferences. More specifically, because the isotemporal substitution findings refer to reallocation of time and not a true temporal substitution, the findings are more akin to population-level shifts in behavior than true activity replacement. Finally, it should be noted that these findings are in need of replication in other data sets given the possibility of false positive findings due to the large data set and number of analyses performed.

The present study adds to broader evidence that optimal sleep duration, less time in SBs, and greater time in active behaviors (both MVPA and LIPA) are associated with a reduced CVD risk profile. A key contribution of the present study is that, after holding all other time constant, reallocating sedentary time to MVPA and, in some cases, to LIPA and extended sleep duration, was associated with more favorable values for CVD risk biomarkers. Additionally, these findings appear to be relatively homogenous across individuals with varying levels of sleep duration, although for some biomarkers, less SB and more active behaviors were protective or synergistic in the context of short sleep duration. Continued investigation of the interrelated associations of sleep, SB, and active behaviors on health outcomes is needed, given that these behaviors are ultimately derived from the same finite pool of available time.

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Author affiliations: School of Nutrition and Health Promotion, College of Health Solutions, Arizona State University, Phoenix, Arizona (Matthew P. Buman, Jonathan M. Kurka, Eric B. Hekler, Barbara E. Ainsworth); School of Population Health, University of Queensland, Brisbane, Australia (Elisabeth A. H. Winkler, Genevieve N. Healy, Paul A. Gardiner); Center for World Health Promotion and Disease Prevention, College of Nursing and Health Innovation, Arizona State University, Phoenix, Arizona (Carol M. Baldwin); Baker IDI Heart and Diabetes Cancer Institute, Melbourne, Australia (Neville Owen, Genevieve N. Healy); Melbourne School of Population Health, University of Melbourne, Melbourne, Australia (Neville Owen); Central Clinical School, Monash University, Victoria, Australia (Neville Owen); School of Physiotherapy, Curtin University, Perth, Australia (Genevieve N. Healy); School of Population Health, University of Queensland, Brisbane, Australia (Paul A. Gardiner); and Translation Research Into Practice Centre, Mater Research Institute, Brisbane, Australia (Paul A. Gardiner).

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