SPECIAL FOCUS ISSUE: CARDIOVASCULAR HEALTH PROMOTION

Sitting Time, Physical Activity, and Risk of Mortality in Adults

Emmanuel Stamatakis, PhD,[a] Joanne Gale, PhD,[a] Adrian Bauman, PhD,[a] Ulf Ekelund, PhD,[b] Mark Hamer, PhD,[c] Ding Ding, PhD[a]

ABSTRACT

BACKGROUND It is unclear what level of moderate to vigorous intensity physical activity (MVPA) offsets the health risks of sitting.

OBJECTIVES The purpose of this study was to examine the joint and stratified associations of sitting and MVPA with all-cause and cardiovascular disease (CVD) mortality, and to estimate the theoretical effect of replacing sitting time with physical activity, standing, and sleep.

METHODS A longitudinal analysis of the 45 and Up Study calculated the multivariable-adjusted hazard ratios (HRs) of sitting for each sitting-MVPA combination group and within MVPA strata. Isotemporal substitution modeling estimated the per-hour HR effects of replacing sitting.

RESULTS A total of 8,689 deaths (1,644 due to CVD) occurred among 149,077 participants over an 8.9-year (median) follow-up. There was a statistically significant interaction between sitting and MVPA only for all-cause mortality. Sitting time was associated with both mortality outcomes in a nearly dose-response manner in the least active groups reporting <150 MVPA min/week. For example, among those reporting no MVPA, the all-cause mortality HR comparing the most sedentary (>8 h/day) to the least sedentary (<4 h/day) groups was 1.52 (95% confidence interval: 1.13 to 2.03). There was inconsistent and weak evidence for elevated CVD and all-cause mortality risks with more sitting among those meeting the lower (150 to 299 MVPA min/week) or upper (≥300 MVPA min/week) limits of the MVPA recommendation. Replacing sitting with walking and MVPA showed stronger associations among high sitters (>6 sitting h/day) where, for example, the per-hour CVD mortality HR for sitting replaced with vigorous activity was 0.36 (95% confidence interval: 0.17 to 0.74).

CONCLUSIONS Sitting is associated with all-cause and CVD mortality risk among the least physically active adults; moderate-to-vigorous physical activity doses equivalent to meeting the current recommendations attenuate or effectively eliminate such associations. (J Am Coll Cardiol 2019;73:2062–72) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

P hysical activity has established protective effects on health, and its potential benefits span across the prevention, management, and treatment of cardiovascular disease (CVD) (1). Sedentary behavior (SB) represents the lowest end of the physical activity spectrum and is commonly defined as a low energy expenditure of <1.5 metabolic equivalents (MET) in a sitting or reclining posture during waking hours (2). The links among SB, mortality, and cardiovascular disease are not always well understood (3,4). For example, a meta-analysis of 9 prospective studies reported a nonlinear association between sitting time and CVD events with increased risk appearing at >10 h of sitting/day when physical activity was taken into account (5). A large individual participant pooled analysis that examined the joint associations of sitting and physical activity (6) found that the association between sitting and all-cause and CVD mortality risk was gradually attenuated with increased physical activity, to the point that it was effectively nullified at amounts equivalent to >60 to 75 min of moderate-intensity physical activity a day. Neither of these studies considered that a 24-h day is finite, and an increase in any type of physical activity or SB would displace another activity or sleep.

Evidence-based guidelines are the cornerstone of public health and clinical practice (7). Understanding the joint associations and the health-enhancing potential of various physical activity alternatives to sitting is important for the development of such guidelines. Due to the absence of such evidence, SB guidelines are currently nonspecific and are not always evidence-based (4,8). Considering the paucity of randomized controlled trials with mortality and other hard endpoints in the broader field of physical activity research (9), well-designed observational longitudinal studies provide the best available evidence for public health guidelines development (4). The recent 2018 U.S. Physical Activity Guidelines Advisory Committee Scientific Report identified the paucity of prospective studies on the interactive effects of physical activity and sedentary behavior on all-cause and CVD mortality as a major evidence gap (10,11).

The main aim of this study was to examine the joint associations of sitting and physical activity with all-cause and CVD mortality in a large population sample of middle-age and older Australian adults. An extension of this aim was to examine the associations between sitting and mortality separately in each physical activity stratum. The secondary aim was to estimate the theoretical effects of replacing sitting with standing, physical activity, and sleep on mortality risk.
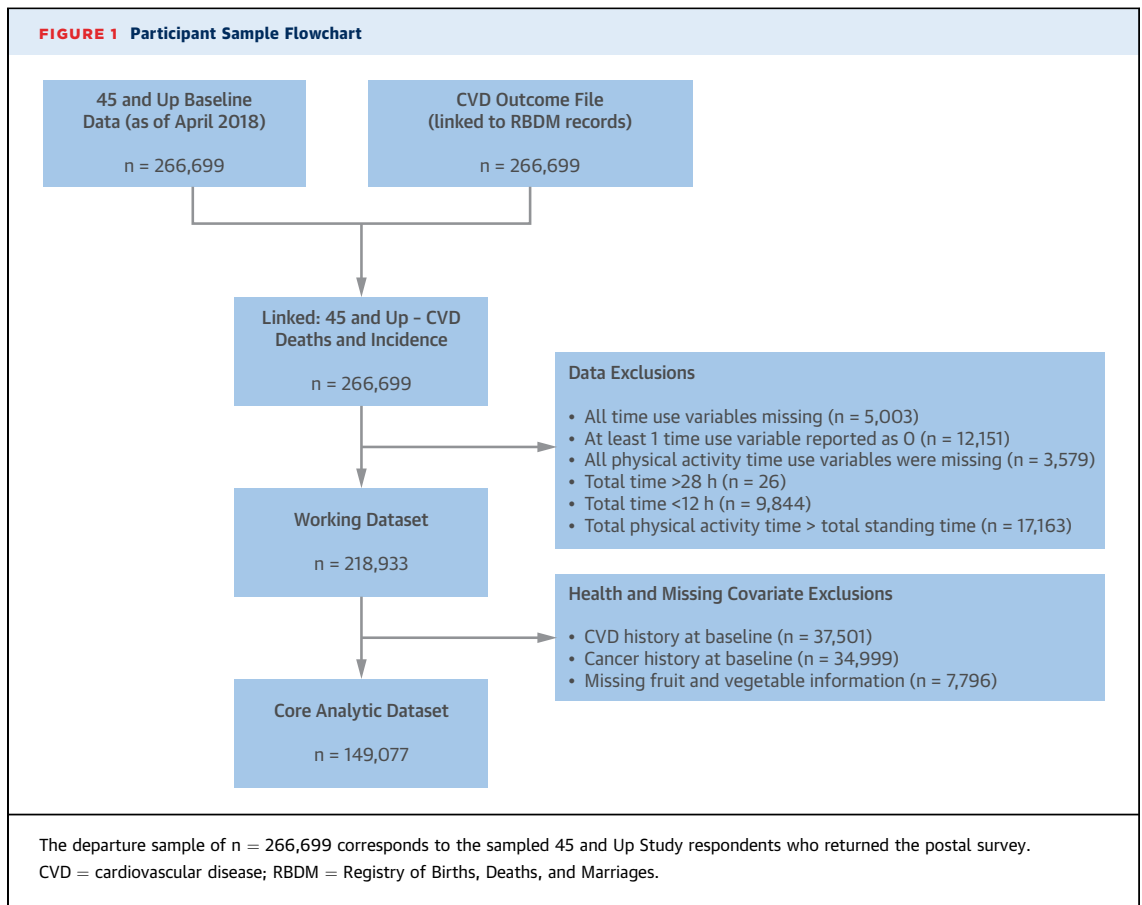
METHODS

SAMPLE. The analyses are based on data from the 45 and Up Study (12), in which participants completed a baseline questionnaire from January 2006 through December 2009. The 45 and Up Study is a large-scale (N = 267,119) prospective cohort of men and women age 45 years or older living in the state of New South Wales, Australia. Participants were randomly sampled from the Department of Human Services enrollment database. Eligible individuals were asked to complete and mail the questionnaire and consent forms to the study center. The 45 and Up Study received ethics approval from the University of NSW Human Research Ethics Committee. Approval to use data from the 45 and Up Study for this paper was obtained from the NSW Population and Health Services Ethics Committee (reference 2010/05/234).

EXPOSURE VARIABLES. The sitting, standing, and sleeping variables were assessed using the question "About how many hours in each 24-h day do you usually spend doing the following?" (13,14). The responses to these questions were recorded as h/day. Such questions are in line with the sitting questions in the International Physical Activity Questionnaire, which have shown acceptable validity against accelerometry (coefficients ranging between 0.33 to 0.34) (15). Total weekly time for walking for recreation or exercise, moderate intensity physical activity (MPA), and vigorous physical activity (VPA) was assessed using the Active Australia Survey questions: "If you add up all the time you spent doing each activity last week, how much time did you spend altogether doing each type of activity?" For MPA and VPA, there was additional explanation to define what each intensity means (e.g., "that made you breathe harder or puff and pant, …" for VPA) as well as examples of common activities. These questions have been shown to have acceptable reliability (coefficients between 0.56 to 0.64) and validity (coefficient of 0.52) (16,17).

POTENTIAL CONFOUNDERS. Potential confounders were similar to previous 45 and Up Study SB analyses (13,14): sex, age (5-year bands), educational level (12 years of school or less, >12 years of school), marital status (married or de facto, single/divorced/separated/widowed), urban/rural residence, body mass index (BMI) (calculated as self-reported weight/[self-reported height squared]), smoking status (current/previous/never smoker), self-rated health (poor/fair/good/very good/excellent), help with daily tasks,

FIGURE 1 Participant Sample Flowchart

The departure sample of n = 266,699 corresponds to the sampled 45 and Up Study respondents who returned the postal survey.

CVD = cardiovascular disease; RBDM = Registry of Births, Deaths, and Marriages.

psychological distress (Kessler 10 scale [18]), servings of fruit and vegetables per day (19), and previous physician diagnoses of diabetes mellitus.

OUTCOME ASCERTAINMENT. All-cause mortality to June 2017 was ascertained from the New South Wales Registry of Births, Deaths, and Marriages. CVD related mortality to December 2015 was ascertained from the Cause of Death Unit Record File held by the Ministry of Health. Linkage to of the 45 and Up Study to the above databases was undertaken by the Centre for Health Record Linkage (CHeReL). Classification of a CVD-related death was based on a ICD codes I00 to I99, as defined earlier (20).

DATA HANDLING. A detailed account of data cleaning, handling, and preparatory statistical testing procedures is described elsewhere (Additional File 1 in Stamatakis et al. [14]). In summary, we used multiple imputation and the Expectation-Maximisation algorithm (30 imputations) (21) to impute missing data for participants who had at least 1 of the time use behavioral variables missing. The multiple imputation model included age, sex, and nonmissing time use variables as covariates. We examined the missing

at random assumption of sitting variables, and no apparent violations were noted. For the joint and stratified analyses, daily sitting time categorization was the same as in recent studies (6,22): <4, 4 to <6, 6 to 8, and >8 h. Weekly MVPA was categorized into no physical activity (inactive), 1 to 149 min (insufficiently active), 150 to 299 min (sufficiently active at the lower Australian physical activity recommendations limit) (23), 300 to 419 min (sufficiently active at the upper limit) (23), and ≥420 min (corresponding to roughly 35.5 MET-h/week, previously identified as the threshold that eliminates mortality risks of sitting [6,22]).

To satisfy the isotemporal substitution modelling (ISM) assumption of linearity between independent and dependent variables (14), we treated sleeping as a piecewise variable with a breakpoint at 7 h (≤7 and >7 h/day). For the same reason, we treated sitting time as a piecewise variable with a breakpoint at 6 h. This 6-h/day cutpoint coincides with the recently identified minimum sitting threshold for raised CVD death risk (24). As per standard practice in epidemiological studies (25), for the calculation of total MVPA volume, each minute of VPA counted as 2 min of

TABLE 1 Distribution of Demographic, Behavioral, and Health Status Factors of the 45 and Up Participants by Amount of Time Spent Sitting Daily (n = 149,077)

	Category	Total*	0-6 h Sitting	>6 h Sitting	0-4 h Sitting	4-6 h Sitting	6-8 h Sitting	8+ h Sitting
Sex	Female	82,695 (55.5)	62,848 (57.0)	18,323 (50.2)	27,374 (58.4)	24,303 (56.6)	21,975 (53.5)	7,519 (47.5)
Age group, yrs	<60	87,371 (58.6)	61,377 (55.7)	24,618 (67.4)	27,787 (59.3)	22,535 (52.5)	24,169 (58.9)	11,504 (72.6)
Education status	Degree or higher	40,282 (27.3)	26,484 (24.3)	13,230 (36.6)	10,569 (22.8)	10,291 (24.3)	12,575 (30.9)	6,279 (40.0)
Marital status	Married/de facto	116,608 (78.6)	86,704 (79.1)	28,101 (77.3)	37,270 (80.0)	33,609 (78.7)	31,827 (77.9)	12,099 (76.7)
Employment status	Work in some capacity	93,043 (62.6)	64,593 (58.8)	26,895 (73.8)	28,867 (61.8)	23,931 (56.0)	26,059 (63.6)	12,631 (79.9)
Remoteness	Major cities	77,728 (53.2)	54,424 (50.4)	22,038 (61.5)	22,314 (48.6)	21,283 (50.5)	22,863 (56.7)	10,002 (64.3)
BMI category	Obese	29,908 (21.5)	21,061 (20.5)	8,339 (24.2)	8,426 (19.3)	8,346 (20.9)	8,868 (23.0)	3,760 (25.1)
MVPA category, min	0	6,707 (4.5)	4,621 (4.2)	1,909 (5.2)	1,976 (4.2)	1,779 (4.1)	1,854 (4.5)	921 (5.8)
	<150	23,604 (15.8)	16,339 (14.8)	6,846 (18.8)	6,687 (14.3)	6,433 (15.0)	6,799 (16.6)	3,266 (20.6)
	150–299	24,576 (16.5)	17,046 (15.5)	7,144 (19.6)	7,017 (15.0)	6,678 (15.6)	7,151 (17.4)	3,344 (21.1)
	300–420	17,835 (12.0)	12,673 (11.5)	4,884 (13.4)	5,192 (11.1)	4,896 (11.4)	5,308 (12.9)	2,161 (13.6)
	>420	76,355 (51.2)	59,498 (54.0)	15,722 (43.1)	25,978 (55.4)	23,145 (53.9)	19,943 (48.6)	6,154 (38.8)
Smoking status	Never smoked	87,565 (58.7)	64,733 (58.8)	21,401 (58.6)	27,980 (59.7)	25,110 (58.5)	23,684 (57.7)	9,360 (59.1)
Self-rated health	Excellent	27,676 (18.8)	20,731 (19.1)	6,498 (18.0)	9,500 (20.6)	7,631 (18.0)	7,316 (18.0)	2,782 (17.7)
Needs help with a disability		4,029 (2.8)	2,733 (2.5)	1,238 (3.5)	995 (2.2)	1,115 (2.7)	1,258 (3.1)	603 (3.9)
Physician-diagnosed diabetes (self-report)		9,798 (6.6)	7,138 (6.5)	2,502 (6.9)	2,758 (5.9)	2,899 (6.8)	2,888 (7.0)	1,095 (6.9)
Psychological distress: K10 category score	High (scores 22–50)	9,438 (6.8)	6,699 (6.5)	2,578 (7.4)	2,945 (6.8)	2,468 (6.2)	2,629 (6.8)	1,235 (8.1)

Values are n (%). *2,384 participants had missing sitting time data.

BMI = body mass index.

MPA. Missing covariates data ranged from 0.4% (employment status) to 6.5% (BMI). For the core analyses, we adopted a missing indicator approach for all categorical covariates, which involved creating a dummy category to denote missingness.

STATISTICAL ANALYSES. Analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, North Carolina). The association between sitting and risk of mortality was analyzed using Cox proportional hazards regression models with survival time (in years) as the time from baseline to death or the censor point. We examined the joint association between physical activity and sitting by deriving a combined variable with 20 groups (6), where the combined lowest sitting (<4 h/day) and highest MVPA (≥420 min/week) served as the reference category. We also ran Cox models of sitting and mortality within each physical activity stratum in a similar fashion to the recent pooled analysis (22). Effect modification was tested by fitting an interaction term between sitting and MVPA groups. To reduce the possibility of spurious associations due to reverse causation, we repeated all analyses after excluding all participants who died from any cause (n = 835) or CVD causes (n = 241) in the first 24 months of follow-up. In another set of sensitivity analyses, we repeated all models in the sample that had valid data in all covariates (n = 123,031).

We estimated the classical partition model which generate estimates of changes in risk/h of sitting increase, which assumes that the exposure is added to the daily time rather than substituting another activity (14,26). The partition model is the standard type of Cox analysis that has been used in the vast majority of epidemiological studies in the field. The ISM analyses make a more realistic assumption that an increase in one behavior will be accompanied by a decrease of equal duration (isotemporal) in another behavior while total time in all behaviors is kept constant. For example, to estimate the effect of substituting 1 h of sitting with walking, walking is removed from a model adjusted for all individual behavior components (sleep, MPA, standing, and so on) as well as total time spent in all activities (14,26). Sitting was modelled in 1-h intervals in both sitting groups (≤6 and >6 h/day). Although nondomain-specific screen time was included in the ISM analyses, we did not report its replacement effect estimates due to the limited clinical value of such information.

RESULTS

A total of 218,913 participants were initially considered, after excluding those with an invalid date of recruitment and implausible covariate or exposure variable values (n = 47,975) (**Figure 1**). Following further exclusions of 63,735 participants who had heart disease, stroke, or cancer at baseline and 6,121 participants who had missing fruit and vegetable

CENTRAL ILLUSTRATION Joint Associations of Sitting and Physical Activity Time and All-Cause Mortality Events
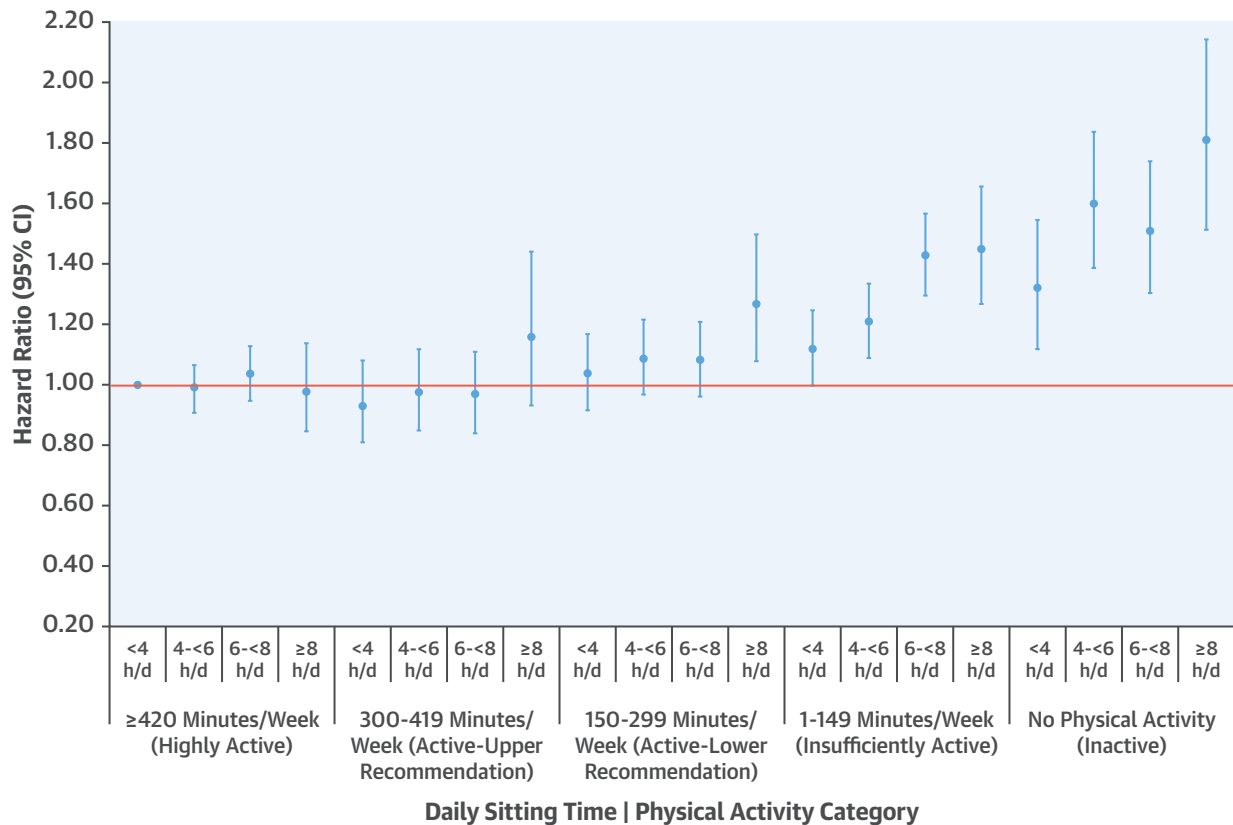
Stamatakis, E. et al. J Am Coll Cardiol. 2019;73(16):2062–72.

Multivariable-adjusted analysis; n = 149,077, n events = 8,689. Adjusted for age, sex, education, marital status, remoteness, body mass index, smoking, self-rated health, help for disability, psychological distress, fruit and vegetable consumption, and diabetes. CI = confidence interval.
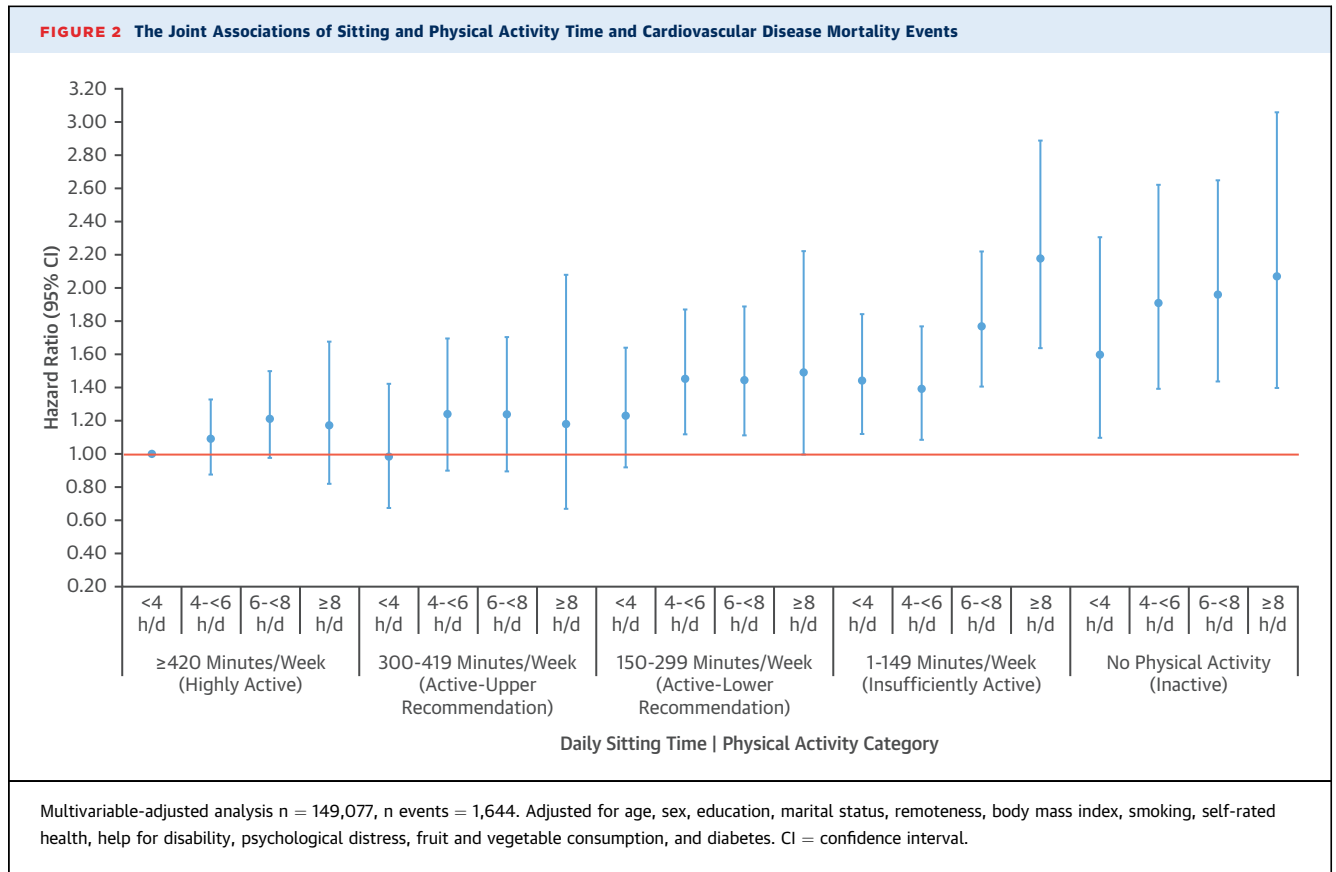
consumption information, the core analytic sample size was 149,077. The median follow-up for all-cause mortality was 8.9 years, corresponding to 1,355,574 person-years and 8,689 deaths, and for CVD mortality was 7.4 years, corresponding to 1,144,279 person-years and 1,644 deaths. **Table 1** presents the characteristics of the core analytic sample by sitting times. Online Table 1 presents the reported mean daily times of sedentary behavior, physical activity, and sleep by sitting time groups. Online Figure 1 presents the splines describing the overall curves of sitting and physical activity variables with CVD mortality.

JOINT AND STRATIFIED ASSOCIATIONS OF SITTING AND PHYSICAL ACTIVITY WITH MORTALITY RISK. Online Table 2 presents the events count and sample size across categories of the joint sitting-MVPA variable. The sitting × MVPA group interaction test in both the imputed and unimputed models was

statistically significant for ACM (p < 0.001) but not for CVD mortality (imputed model p = 0.478).

In both the joint and stratified analyses, with a few exceptions, sitting was mostly associated with the mortality outcomes among the least physically active groups only. In the joint MVPA-sitting analyses, combinations of higher sitting time and lower MVPA were deleteriously associated with ACM risk in the physically inactive and insufficiently active groups (**Central Illustration**). Across groups that met any physical activity recommendation, only sitting for >8 h/day and meeting the lower physical activity recommendation was associated with increased risk (hazard ratio [HR]: 1.27; 95% confidence interval [CI]: 1.08 to 1.50). For CVD mortality, there was a dose response with higher sitting and lower MVPA among the inactive and insufficiently active groups (**Figure 2**). Among those meeting the lower physical

FIGURE 2 The Joint Associations of Sitting and Physical Activity Time and Cardiovascular Disease Mortality Events

Multivariable-adjusted analysis n = 149,077, n events = 1,644. Adjusted for age, sex, education, marital status, remoteness, body mass index, smoking, self-rated health, help for disability, psychological distress, fruit and vegetable consumption, and diabetes. CI = confidence interval.
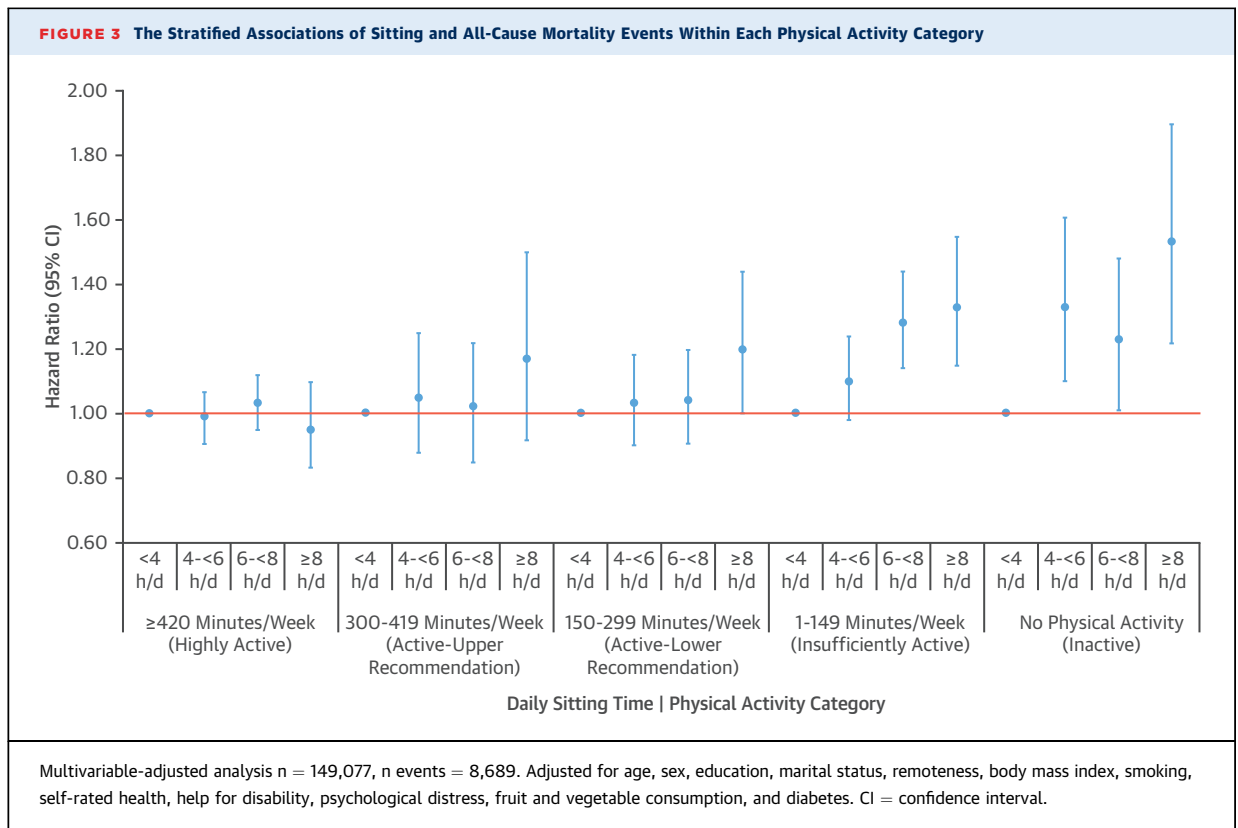
activity recommendation, all sitting groups had elevated risk (for example, HR: 1.45; 95% CI: 1.12 to 1.88 for the 4 to 6 h/day sitting group), although there was no evidence for a dose-response (**Figure 2**). The results of the analyses stratified by MVPA group were in broad agreement with the joint analyses: associations between sitting and ACM (**Figure 3**) and CVD mortality risk (**Figure 4**) were largely limited to the 2 least active groups. Unlike the joint analyses, however, sitting was not associated with elevated CVD mortality risk among those meeting the lower physical activity recommendation. The detailed data used in Online Figures 2 to 13 are presented in Online Tables 3 to 14. Removing events occurring in the first 24 months of follow-up did not appreciably change the joint or stratified associations (Online Figures 2 to 5). Repeating analyses in the unimputed dataset of participants who had valid data for all covariates (n = 123,031; 6,161 ACM events; 1,077 CVD mortality events) led to some attenuation of the associations (in both magnitude and gradient) across several sitting-MVPA combinations (Online Figures 6 and 7) and strata of MVPA (Online Figures 8 and 9). For example, the HR for ACM for those who met the

lower physical activity recommendation and reported sitting for >8 h/day was attenuated to 1.18 (95% CI: 0.98 to 1.42). No appreciable differences were observed when those who died in the first 24 months of follow-up were excluded (Online Figures 10 to 13). Across all main and sensitivity joint analyses, the combination of highly active (>420 MVPA min/week) and 6 to 8 h sitting/day tended to point toward increased CVD mortality risk, although it did not reach statistical significance.

REPLACEMENT EFFECTS OF SITTING TIME WITH PHYSICAL ACTIVITY, STANDING, AND SLEEP. **Tables 2 and 3** present the multivariable-adjusted per-hour estimates of ACM and CVD risk stratified by low (≤6 h/day) and high (>6 h/day) sitting level. In the partition models, each additional hour of daily sitting was associated with increased ACM risk among high sitters only (HR: 1.04; 95% CI: 1.02 to 1.06) (**Table 2**). Replacing sitting with standing was associated with a small reduction in ACM risk among low sitters only (HR: 0.97; 95% CI: 0.96 to 0.99). Replacing sitting with walking and VPA (but not with MPA) was associated with ACM risk reduction, in particular among

FIGURE 3   The Stratified Associations of Sitting and All-Cause Mortality Events Within Each Physical Activity Category

Multivariable-adjusted analysis n = 149,077, n events = 8,689. Adjusted for age, sex, education, marital status, remoteness, body mass index, smoking, self-rated health, help for disability, psychological distress, fruit and vegetable consumption, and diabetes. CI = confidence interval.

high sitters; for example, the HR per substituted hour of sitting for walking was 0.78 (95% CI: 0.70 to 0.87). There was little evidence for replacement effects of sitting with sleeping on ACM mortality among low sleepers (≤7 h/day); in contrast, there were relatively large increases in ACM risk (7% to 14%/h) when sitting was replaced with sleeping in high sleepers (>7 h/day).

Each additional hour of daily sitting was associated with increased CVD death risk among high sitters only (HR: 1.07; 95% CI: 1.03 to 1.12) (**Table 3**). Replacing sitting with standing was associated with a reduction in CVD risk among low sitters only (HR: 0.94; 95% CI: 0.91 to 0.98). Replacing sitting with MPA and VPA (but not walking) was associated with lower CVD mortality risk in both sitting groups, although the replacement effects were more pronounced among high sitters (HR: 0.80; 95% CI: 0.70 to 0.93 for MPA; HR: 0.36; 95% CI: 0.17 to 0.74 for VPA). The CVD mortality ISM estimates for replacing sitting with sleeping were broadly comparable to the equivalent ACM mortality estimates described in the previous text.

Removing deaths occurring in the first 24 months of follow-up, repeating analyses in the sample with valid data in all covariates, or imputing BMI values

had no material impact on the partition and ISM estimates (Online Tables 15 to 19).

DISCUSSION

This is the first study on sitting and mortality risk to use a comprehensive analytic approach involving joint MVPA-sitting effects, stratification by MVPA, and replacement effects. We found that higher sitting times were associated with higher ACM and CVD mortality risk, but these associations were in most cases restricted to those not meeting the physical activity recommendations (**Central Illustration**).

Compared with the lowest risk category of the joint analysis of 20 mutually exclusive categories (>420 min of MVPA and <4 h of sitting/day), the gradient of the sitting-ACM and -CVD associations progressively leveled off with higher levels of physical activity (**Central Illustration, Figure 2**). Meeting even the lower 150 to 299 min/week physical activity recommendation eliminated the association of sitting with ACM risk, where estimates only in the top sitting category (>8 h/day) reached statistical significance. Our results support continued efforts to promote physical activity in those segments of the population that are physically inactive. Lower daily

FIGURE 4 **The Stratified Associations of Sitting and Cardiovascular Disease Mortality Events Within Each Physical Activity Category**
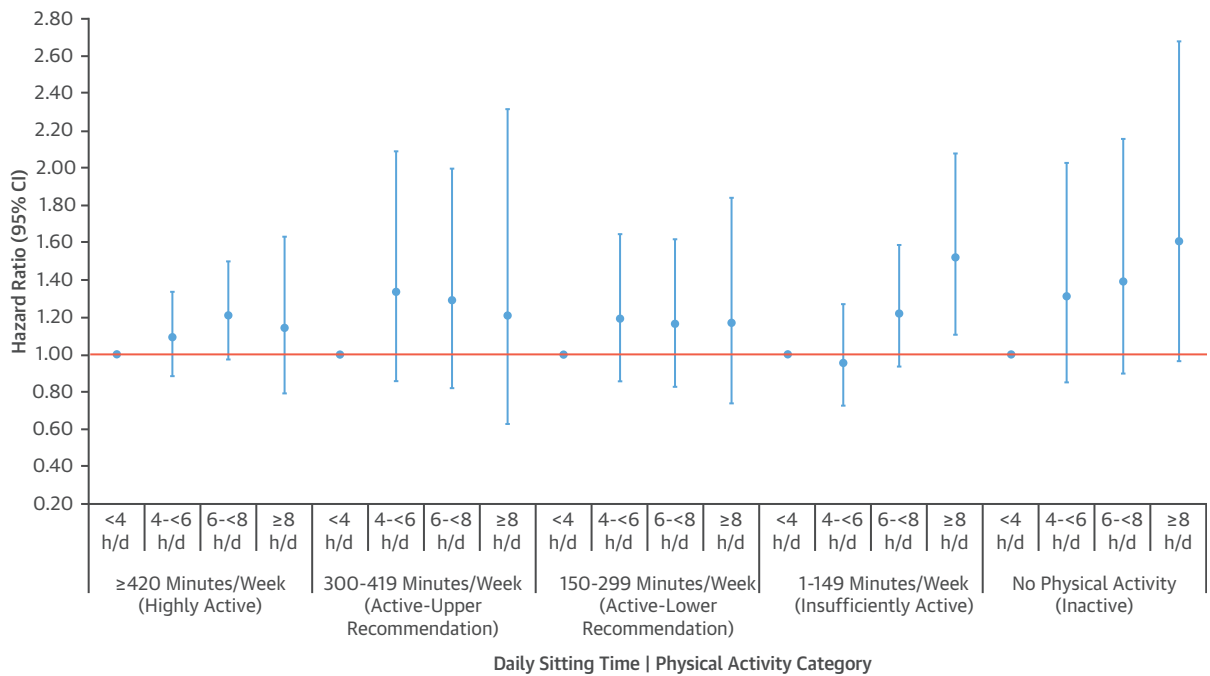
Multivariable-adjusted analysis n = 149,077, n events = 1,644. Adjusted for age, sex, education, marital status, remoteness, body mass index, smoking, self-rated health, help for disability, psychological distress, fruit and vegetable consumption, and diabetes. CI = confidence interval.

sitting time reduced the risk among those who reported >8 h of sitting/day, although risks remained substantially elevated compared with the reference group, who were highly active and sat for <4 h/day (e.g., 60% and 44% higher risk in the groups with <4 h of sitting who were physically inactive and insufficiently active, respectively). Such findings suggest that in the absence of some physical activity, reducing sitting times may be insufficient for optimal health benefit.

Several prospective studies have found that the associations of sitting time with fatal or nonfatal CVD risk are dependent on MVPA levels (27-29). Although our interaction test was not statistically significant for CVD death, our results in their totality are broadly consistent with recent large joint (6) and stratified (22) analyses of sitting and ACM (6) and CVD (6,22) mortality. In both studies, which arose from the same pooled harmonized dataset, a dose-response association between sitting time and ACM and CVD mortality was observed in the lowest quartiles of physical activity (<2.5 MET-h/week) where, for example, CVD mortality was 32% higher in those who sat for >8 h/day compared with the lowest

sitting group (<4 h/day) (22). Although the associations of sitting with both mortality outcomes was less consistent across the other physical activity strata, clearer evidence for elimination of the sitting effects was seen in the most active group (>35.5 MET-h/week) (4), which is roughly equivalent to ≥420 min. Our results differ in that adherence to the lower physical activity limit (150 to 299 min/week) largely offset the increased risk of sitting except in those who reported very high sitting time, while adherence to the upper limit of at least 300 min/week eliminated the associations. Our findings offer support for this unique "upper limit" aspect of the 2014 Australian and, more recently, the 2018 U.S. (11) physical activity guidelines.

The modeled effects of sitting on mortality risk varied considerably by sitting level: replacing sitting with standing was associated with risk reduction in low sitters, but replacing sitting with physical activity had more consistent protective associations in high sitters (**Tables 2 and 3**). These findings corroborate the outcomes from 2 nonisotemporal meta-analyses that showed nonlinear association between sedentary time and risk of CVD events only

TABLE 2 Independent* and Replacement Effects of Sitting With Physical Activity, Sleeping on ACM Mortality

1. Isotemporal Substitution Model† *Replace 1 h of*:		With 1 h of:						2. Partition Model (HR and 95% CI per h of sitting)*
		A. Sleeping (≤7 h)	B. Sleeping (>7 h)	C. Standing	D. Walking	E. MPA	F. VPA	
All samples‡	Sitting (≤6 h)	1.01 (1.00–1.02)	1.07 (1.05–1.10)	0.97 (0.96–0.99)	0.97 (0.94–1.02)	0.99 (0.97–1.02)	0.92 (0.86–1.00)	1.01 (0.99–1.02)
	Sitting (>6 h)	1.00 (0.98–1.01)	1.14 (1.08–1.20)	0.98 (0.95–1.01)	0.78 (0.70–0.87)	0.97 (0.92–1.02)	0.69 (0.56–0.88)	1.04 (1.02–1.06)

Values are hazard ratio (95% confidence interval). Imputed data n = 149,077, n events = 8,689. *Adjusted for sex, age, educational level, marital status, urban or rural residence, body mass index, smoking status, self-rated health, fruit and vegetable consumption receiving help with daily tasks for a long-term illness or disability, prevalent diabetes at baseline, and psychological distress, and mutually adjusted for all activity classes. †Adjusted for sex, age, educational level, marital status, urban or rural residence, body mass index, smoking status, self-rated health, total fruit and vegetable consumption, receiving help with daily tasks for a long-term illness or disability, psychological distress, mutually adjusted for all activity classes, and total time in all activities classes. ‡Multiple imputation was used to replace missing time of the activity classes (based on age, sex, and non-missing other activity classes variables).

among those who reported sitting for >6 h/day (24) or 10 h/day (5). In our study, sitting level appeared to modify the magnitude of the associations when we modeled the effects of replacing sitting with standing and physical activity. For example, replacing 1 h of sitting with 1 h of standing was associated with 3% (ACM) and 6% (CVD) reduction in low sitters, but there was no such association in high sitters. While there is no biologically apparent explanation for this finding, it is noteworthy that low sitters reported almost double the standing (5.7 h/day vs. 3.1 h/day) compared with high sitters. Such large differences between the two sitting groups may reflect that standing is a proxy of ambulatory light intensity physical activity (30). Another possible explanation is that among the most sedentary groups replacing sitting with standing may not be sufficient for reducing health risks. In such groups substituting sitting for walking (which was associated with 10% to 12% reduction in mortality risk) may be a better option that is feasible for the majority of adults. We noted inconsistent replacement effects for substituting sitting for MPA, which showed clear associations only among high sitters (20% reduction in CVD mortality per replaced hour). The largest replacement effects were observed for VPA, for example, 31% (ACM) and 64% (CVD) risk reduction per hour replaced in high sitters (**Tables 2 and 3**). Although our findings are supported by

previous work showing that that participation in VPA maximizes the population benefits of physical activity (25), translation into tangible health messages for CVD and premature mortality prevention may be challenging. VPA, as reported in the 45 and Up Study, consisted mainly of exercise and sports, a class of physical activity that may not be immediately accessible to sedentary middle-age and older people who are not accustomed to physical exertion; and who may need to be supervised during exercise.

Replacing sitting with sleeping showed no clear associations with mortality risk in those sleeping ≤7 h/day and, like previously (14), deleterious associations in those sleeping >7 h/day. Our results contrast previous cross-sectional results with surrogate CVD outcomes, suggesting that replacing sedentary behavior with sleep is associated with favorable cardiometabolic profiles (31), although we acknowledge that interpretation of our findings is less straightforward due to the necessitated dichotomization of sleep and sitting variables.

An immediate implication of an independent biological mechanism for sitting would be a risk gradient by increasing sitting time across all MVPA groups. Although our study did not address biological mechanisms, both our findings and the data summarized in the previous text (4,22,27,29) offer little support to the 2016 Science Advisory from the American Heart Association report (3), which

TABLE 3 Independent* and Replacement Effects of Sitting With Physical Activity, Sleeping on CVD Mortality

1. Isotemporal Substitution Model† *Replace 1 h of*:		With 1 h of:						2. Partition Model (HR and 95% CI per h of Sitting)*
		A. Sleeping (≤7 h)	B. Sleeping (>7 h)	C. Standing	D. Walking	E. MPA	F. VPA	
All Sample‡	Sitting (≤6 h)	1.03 (1.00–1.05)	1.09 (1.03–1.15)	0.94 (0.91–0.98)	1.06 (0.97–1.16)	0.95 (0.89–1.01)	0.72 (0.56–0.91)	1.02 (0.99–1.04)
	Sitting (>6 h)	0.99 (0.95–1.03)	1.10 (0.99–1.22)	0.97 (0.92–1.03)	0.90 (0.73–1.12)	0.80 (0.70–0.93)	0.36 (0.17–0.74)	1.07 (1.03–1.12)

Imputed data n = 149,077, n events = 1,644. *Adjusted for sex, age, educational level, marital status, urban or rural residence, body mass index, smoking status, self-rated health, fruit and vegetable consumption receiving help with daily tasks for a long-term illness or disability, prevalent diabetes at baseline, psychological distress, and mutually adjusted for all activity classes. †Adjusted for sex, age, educational level, marital status, urban or rural residence, body mass index, smoking status, self-rated health, total fruit and vegetable consumption, receiving help with daily tasks for a long-term illness or disability, psychological distress, mutually adjusted for all activity classes, and total time in all activities classes. ‡Multiple imputation to replace missing time of the activity classes (based on age, sex, and nonmissing other activity classes variables).

concluded that SB influences cardiometabolic health in part independent of MVPA. Our findings also contrast the conclusions of a recent meta-analysis that reported an increased CVD hazard of 1% to 2%/h of sitting time "independent" of physical activity (24). Studies included in this review assessed independence by merely statistically adjusting for MVPA, an approach that is insufficient on its own, as it ignores evidence of effect modification (6,22,27,29).

STUDY STRENGTHS AND LIMITATIONS. The strengths of our study include one of largest population-based studies to date, our comprehensive statistical approach, the multiple measures we took to account for reverse causation, and the sitting level-specific ISM structure that revealed novel insights into possible differential replacement effects. In comparison to the recent larger pooled harmonized studies of similar scope (6,22), our study has several advantages, including the consistent measurements used and the individual-level analyses. A limitation of our work was that the exposures were only measured at baseline and our data did not reflect complete time-use as we lacked information on light-intensity physical activity (ambulatory activities 1.5 to 3 MET). Our ISM results are based on statistical modeling and not on actual replacements. The ISM approach is regression-based and could not handle complete 24-h data due to the unavoidable collinearity. Although we were able to adjust analyses for several key confounders, we cannot rule out the presence of unmeasured confounding. For example, we could not adjust for biomedical risk factors such as cholesterol and blood pressure, although these variables are less likely to be confounders and more likely to be on the intermediate causal pathway between physical activity, sitting, and mortality. While the 45 and Up Study response rate was relatively low (18% [12]), it is unlikely that our results were materially compromised as relative risks based on internal comparisons are not dependent on representativeness (32). A previous analysis that compared a broad range of exposure-outcome associations in the 45 and Up Study with another New South Wales population study with much higher response rate (~60%) found that the relative risk estimates in the 2 studies were almost identical in magnitude and direction (33). Although the published validity coefficients of the sitting measurement used in 45 and Up Study are of moderate strength (15), they are in line with the estimates of other self-report sitting questionnaires (34). Sitting and MVPA exposures were self-reported and are therefore likely prone to measurement error. Depending on the nature of such error in exposures and covariates (random vs. systematic), the reported estimates may be biased towards or away from the null. Assuming that the measurement error is random our results may under-estimate the true associations of sitting and mortality risk. Conversely, such measurement error in the effect modifier (MVPA) may have diminished effect modification and have made it harder to identify groups at higher risk.

CONCLUSIONS

Our comprehensive joint and stratified analyses on sitting, physical activity and mortality risk found that higher amounts of physical activity effectively eliminated the association of sitting time with ACM and CVD mortality risk. Replacing sitting with walking and VPA is associated with the most consistent risk reductions. Reduction of sitting time is an important strategy, ancillary to increasing physical activity, for preventing cardiovascular disease and premature mortality in physically inactive populations.

ADDRESS FOR CORRESPONDENCE: Dr. Emmanuel Stamatakis, D17, The Hub, Level 6, Charles Perkins Centre, The University of Sydney, 2006, NSW, Australia. E-mail: emmanuel.stamatakis@sydney.edu.au. Twitter: @M_Stamatakis.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Among relatively inactive middle-aged people, the amount of time spent sitting is associated with increased risks of both cardiovascular and all-cause mortality.

TRANSLATIONAL OUTLOOK: Future research should seek to define optimum physical activity regimens to prevent cardiovascular events and premature mortality among those who spend large amounts of time sitting.

REFERENCES

1. Bauman A, Alharbi M, Lowres N, Gallagher R, Stamatakis E. Exercise, physical activity, and cardiovascular disease. In: Vasan RSD, editor. The Encyclopedia of Cardiovascular Research and Medicine. Oxford: Elsevier, 2017:274–80.

2. Sedentary Behavior Research Network. Standardized use of the terms "sedentary" and "sedentary behaviours." Appl Physiol Nutr Metab 2012;37:540–2.

3. Young DR, Hivert MF, Alhassan S, et al. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. Circulation 2016;134:e262–79.

4. Stamatakis E, Ekelund U, Ding D, Hamer M, Bauman A, Lee IM. Is the time right for quantitative public health guidelines on sitting? A narrative review of sedentary behaviour research paradigms and findings. Br J Sports Med 2019;53:377–82.

5. Pandey A, Salahuddin U, Garg S, et al. Continuous Dose-response association between sedentary time and risk for cardiovascular disease: a meta-analysis. JAMA Cardiology 2016;1:575–83.

6. Ekelund U, Steene-Johannessen J, Brown WJ, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet 2016;388:1302–10.

7. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007;116:1081–93.

8. Department of Health. Start Active, Stay Active: A Report on Physical Activity for Health from the Four Home Countries' Chief Medical Officers. London: Department of Health, 2011.

9. Kujala UM. Is physical activity a cause of longevity? It is not as straightforward as some would believe. A critical analysis. Br J Sports Med 2018;52:914–8.

10. 2018 Physical Activity Guidelines Advisory Committee. Physical Activity Guidelines Advisory Committee Scientific Report. Washington, DC: U.S. Department of Health and Human Services, 2018: F2–33.

11. Piercy KL, Troiano RP, Ballard RM, et al. The physical activity guidelines for Americans. JAMA 2018;320:2020–8.

12. 45 & Up Study Collaborators. Cohort Profile: The 45 and Up Study. International J Epidemiology 2008;37:941–7.

13. Ding D, Rogers K, van der Ploeg H, Stamatakis E, Bauman AE. Traditional and emerging lifestyle risk behaviors and all-cause mortality in middle-aged and older adults: evidence from a large population-based Australian Cohort. PLOS Medicine 2015;12:e1001917.

14. Stamatakis E, Rogers K, Ding D, 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.

15. Rosenberg DE, Bull FC, Marshall AL, Sallis JF, Bauman AE. Assessment of sedentary behavior with the International Physical Activity Questionnaire. J Phys Act Health 2008;5 Suppl 1:S30–44.

16. Timperio A, Salmon J, Rosenberg M, Bull FC. Do logbooks influence recall of physical activity in validation studies? Med Sci Sports Exerc 2004;36: 1181–6.

17. Brown WJ, Burton NW, Marshall AL, Miller YD. Reliability and validity of a modified self-administered version of the Active Australia physical activity survey in a sample of mid-age women. Aust N Z J Public Health 2008;32:535–41.

18. Kessler RC, Andrews G, Colpe LJ, et al. Short screening scales to monitor population prevalences and trends in non-specific psychological distress. Psychological Med 2002;32:959–76.

19. Nguyen B, Bauman A, Gale J, Banks E, Kritharides L, Ding D. Fruit and vegetable consumption and all-cause mortality: evidence from a large Australian cohort study. Int J Behav Nutr Phys 2016;13:9.

20. Joshy G, Korda R, Abhayaratna W, Soga K, Banks E. Categorising major cardiovascular disease hospitalisations from routinely collected data. Public Health Res Pract 2015;25:e2531532.

21. Little R, Rubin D. Statistical Analysis with Missing Data. 2nd edition. New York: John Wiley & Sons, 2002.

22. Ekelund U, Brown WJ, Steene-Johannessen J, et al. Do the associations of sedentary behaviour with cardiovascular disease mortality and cancer mortality differ by physical activity level? A systematic review and harmonised meta-analysis of data from 850 060 participants. Br J Sports Med 2018 Jul 10 [E-pub ahead of print].

23. Department of Health. Australia's Physical Activity and Sedentary Behaviour Guidelines for Adults (18–64 years). Canberra, Australia: Australian Government, Department of Health, 2014.

24. Patterson R, McNamara E, Tainio M, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol 2018;33:811–29.

25. Gebel K, Ding D, Chey T, Stamatakis E, Brown WJ, Bauman AE. Effect of moderate to vigorous physical activity on all-cause mortality in middle-aged and older Australians. JAMA Intern Med 2015;175:970–7.

26. Mekary RA, Lucas M, Pan A, et al. Isotemporal substitution analysis for physical activity, television watching, and risk of depression. Am J Epidemiology 2013;178:474–83.

27. Chomistek AK, Manson JE, Stefanick ML, et al. Relationship of sedentary behavior and physical activity to incident cardiovascular disease: results from the Women's Health Initiative. J Am Coll Cardiol 2013;61:2346–54.

28. Herber-Gast GC, Jackson CA, Mishra GD, Brown WJ. Self-reported sitting time is not associated with incidence of cardiovascular disease in a population-based cohort of mid-aged women. Int J Behav Nutr Phys Act 2013; 10:55.

29. Petersen C, Bauman A, Gronbaek M, Helge J, Thygesen L, Tolstrup J. Total sitting time and risk of myocardial infarction, coronary heart disease and all-cause mortality in a prospective cohort of Danish adults. International J Behavioral Nutrition Physical Activity 2014;11:13.

30. Chastin SFM, De Craemer M, De Cocker K, et al. How does light-intensity physical activity associate with adult cardiometabolic health and mortality? Systematic review with meta-analysis of experimental and observational studies. Br J Sports Med 2019;53:370–6.

31. Buman MP, Winkler EA, Kurka JM, 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.

32. Ebrahim S, Davey Smith G. Commentary: should we always deliberately be non-representative? Int J Epidemiol 2013;42:1022–6.

33. Mealing NM, Banks E, Jorm LR, Steel DG, Clements MS, Rogers KD. Investigation of relative risk estimates from studies of the same population with contrasting response rates and designs. BMC Med Res Methodol 2010;10:26.

34. Prince SA, LeBlanc AG, Colley RC, Saunders TJ. Measurement of sedentary behaviour in population health surveys: a review and recommendations. PeerJ 2017;5:e4130.

KEY WORDS cardiovascular disease, epidemiology, exercise, mortality, physical activity, sedentary behavior

APPENDIX For supplemental figures and tables, please see the online version of this paper.