Independent and joint association of physical activity and sedentary behavior on all-cause mortality

Wei Zhou[1,2], Wei Yan[3], Tao Wang[1,2], Ling-Juan Zhu[1,2], Yan Xu[3], Jun Zhao[3], Ling-Ling Yu[4], Hui-Hui Bao[1,2,4], Xiao-Shu Cheng[1,2,4]

[1]Center for Prevention and Treatment of Cardiovascular Diseases, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China;
[2]Jiangxi Provincial Cardiovascular Disease Clinical Medical Research Center, Nanchang, Jiangxi 330006, China;
[3]Chronic Disease Prevention and Control Institute, Jiangxi Province Center for Disease Control and Prevention, Nanchang, Jiangxi 330006, China;
[4]Department of Cardiovascular Medicine, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi 330006, China.

Abstract

Backgrounds: Physical activity (PA) and sedentary behavior (SB) have been associated with mortality, while the joint association with mortality is rarely reported among Chinese population. We aimed to examine the independent and joint association of PA and SB with all-cause mortality in southern China.

Methods: A cohort of 12,608 China Hypertension Survey participants aged ≥35 years were enrolled in 2013 to 2014, with a follow-up period of 5.4 years. Baseline self-reported PA and SB were collected via the questionnaire. Kaplan–Meier curves (log-rank test) and Cox proportional hazards regression were performed to evaluate the associations of PA and SB on all-cause mortality.

Results: A total of 11,744 eligible participants were included in the analysis. Over an average of 5.4 years of follow-up, 796 deaths occurred. The risk of all-cause mortality was lower among participants with high PA than those with low to moderate level (5.2% *vs.* 8.9%; hazards ratio [HR]: 0.75, 95% confidence interval [CI]: 0.61–0.87). Participants with SB ≥ 6 h had a higher risk of all-cause mortality than those with SB <6 h (7.8% *vs.* 6.0%; HR: 1.37, 95% CI: 1.17–1.61). Participants with prolonged SB (≥6 h) and inadequate PA (low to moderate) had a higher risk of all-cause mortality compared to those with SB < 6 h and high PA (11.2% *vs.* 4.9%; HR: 1.67, 95% CI: 1.35–2.06). Even in the participants with high PA, prolonged SB (≥6 h) was still associated with the higher risk of all-cause mortality compared with SB < 6 h (7.0% *vs.* 4.9%; HR: 1.33, 95% CI: 1.12–1.56).

Conclusions: Among Chinese population, PA and SB have a joint association with the risk of all-cause mortality. Participants with inadequate PA and prolonged SB had the highest risk of all-cause mortality compared with others.

Keywords: Physical activity; Sedentary behavior; All-cause mortality; Joint association

Introduction

The lack of physical activity (PA) is a primary risk factor for mortality.[1] Previous studies indicated that over 5 million deaths worldwide each year are due to inadequate PA.[2] High amounts of sedentary behavior (SB) are associated with increased risks for chronic diseases and mortality.[3-5] Furthermore, self-reported SB in several domains such as sitting,[6] driving a car,[7] and TV viewing,[8,9] is positively associated with mortality. A study on the dose-response association between sitting time and both all-cause and cardiovascular disease mortality revealed that people who reported sitting almost the whole time had a 54% higher risk than those who reported sitting almost no time.[10] SB was nearly responsible for 3.8% of all-cause mortality based on a meta-analysis involving 54 countries.[11] Unfortunately, SB is very widespread. According to objective monitoring, adults in western countries spend an average of 9 to 11 h for daily sedentary.[12,13] Meanwhile, several studies emphasized that a large proportion of the global population still present with high levels of SB and low levels of PA.[14-16] A multi-center study conducted in ten countries including China found that the mean sedentary time of adults aged 18 to 66 years was 8.7 h/day.[17] The largest study involving 1,005,791 participants to date examined the joint associations of SB and PA with mortality, and the result indicated that the relative risks (RRs) associated with SB were higher among the population who were physically inactive, and high levels of PA might attenuate the harmful effects associated with prolonged SB.[18]

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001730

Wei Zhou and Wei Yan contributed equally to the work.

Correspondence to: Xiao-Shu Cheng, Department of Cardiovascular Medicine, The Second Affiliated Hospital of Nanchang University, No. 1 Minde Road, Nanchang, Jiangxi 330006, China
E-Mail: xiaoshumenfan126@163.com

Chinese Medical Journal 2021;134(23)
Received: 24-03-2021 **Edited by:** Jing Ni

To our knowledge, the associations of PA and SB with mortality have been examined in quite a few studies from western countries. However, the availability of similar data is rare among Chinese population. Therefore, in the present study, we aimed to prospectively examine the independent and joint associations of PA and SB with all-cause mortality in Jiangxi Province of China.

Methods

Ethical approval

All participants were from the China Hypertension Survey,[19] which was approved by the Ethics Committee of the Second Affiliated Hospital of Nanchang University and the Fuwai Cardiovascular Hospital in Beijing, China (Approval No. 2012-402). Written informed consent was obtained from each participant.

Study design and participants

The cross-sectional epidemiological investigation, a community-based study, aimed to assess the prevalence of hypertension in China, of which a subset was conducted from November 2013 to August 2014 in Jiangxi Province in southern China. Participants living in Jiangxi Province for 6 months and aged 15 years or older were randomly recruited in the study. Details regarding the method and design of the survey have been published previously.[20,21] Briefly, a stratified, multistage random sampling method was used to obtain a nationally representative sample of the general Chinese population aged ≥15 years. The first stage of sampling was to select four cities in urban areas and four counties in rural areas within Jiangxi Province by the probability proportional to size method. Then, by a simple random sampling method, two districts or two townships were selected within each city or rural area, and three communities or villages were chosen within each district or township, respectively. In the final stage of sampling, a given number of participants from each stratum based on sex and age were selected from communities or villages using lists compiled from local government registers of households.

In the present longitudinal study, 12,608 participants aged ≥ 35 years were followed up from July 2019 to October 2020. After excluding those with missing data on PA ($n = 66$) and SB ($n = 798$), a final total of 11,744 eligible participants were included in the analysis.

Exposure variables

Self-reported PA was assessed with the International Physical Activity Questionnaire (IPAQ), which was supported by the WHO and the American Centers for Disease Control and Prevention.[22,23] The categoric analysis divided participants into groups of performing low, moderate, or high PA, according to the questionnaire scoring rule (standard for scoring: http://www.ipaq.ki.se). The detailed definition of the categories is as follows: (1) Low: meet neither "moderate" nor "high" criteria. (2) Moderate: meet any of the following three criteria: 3 days of high-intensity activity for ≥20 min/day; 5 days of moderate-intensity activity or walking of >30 min/day for >10 min each time; or 5 days of any combination of walking, moderate-intensity, or high-intensity activities, achieving ≥600 metabolic equivalents of task (MET)-minutes per week (MET-min per week). At rest or sitting idly, 1 MET equals:1 kilocalorie per kilogram of body weight times minutes of activity, or 3.5 milliliters of oxygen per kilogram of body weight times minutes of activity. (3) High: meet either of two criteria: (a) high-intensity activity for >3 days per week and accumulating ≥1500 MET-min per week, or (b) >5 days of any combination of walking, moderate-intensity, or high-intensity activities, achieving ≥3000 MET-min per week.

SB is defined as any waking behavior with an energy expenditure ≤1.5 METs, while in a sitting or reclining posture. Self-reported SB was obtained with the following question from the long-form of IPAQ: "How long do you spend in your SB every day, such as sitting or reclining, including reading, watching TV, or working online?"

Potential confounders

Potential confounders at baseline were shown as: demographic characteristics including sex (male and female), education (0–6 years of school, 7–9 years of school, and 10 years of school or more), residence (urban and rural), employment status (employed, retired, student, and unemployed), marital status (unmarried, married, divorced, or widowed). Lifestyle including current smoking (defined as a "yes" responding to the question: "Have you smoked at least one cigarette per day during the past 30 days?"), current drinking (assessed based on the responses to the question: "Have you had at least one drink per week during the past 30 days?"), sleep duration (relied on the response to the question: "On average, how many hours of sleep do you get in a 24-h period on workdays and nonwork days, respectively?" and calculated as [average sleep duration on weekdays × 5+average sleep duration on weekends × 2]/7). Diseases history including self-reported history of stroke (assessed by the question: "Have you ever been told by a doctor or other health professional that you had a stroke?" and verified with medical or hospital records), self-reported myocardial infarction (MI, obtained with the question: "Have you been diagnosed with MI by a hospital?" and verified with medical or hospital records), hypertension (defined as systemic blood pressure [SBP] ≥140 mm Hg and/or diastolic blood pressure [DBP] ≥90 mmHg, and use of antihypertensive drugs within 2 weeks).[24,25] Body measurement index including body mass index (BMI) (calculated as weight/height^2), basal metabolism rate (BMR), and visceral fat rate (VAI) which was measured by bioelectrical impedance methods using Omron body fat and weight measurement device (V-BODY HBF-371, OMRON, Kyoto, Japan).

Outcome ascertainment

All-cause deaths were collected through telephone interviews, consultations to the local public health doctor and village doctors, and also ascertained from the Jiangxi

Province Center for Disease Control and Prevention, which is responsible for the provincial cause-of-death monitoring, and results from different approaches were mutually verified. Information on death time, location, cause, and diagnostic institution were collected.

Statistical analysis

Data were analyzed using the statistical packages R (http://www.r-proje.ct.org) and Empower (R) (www.empow.erstats.com, X&Y Solutions Inc., Boston, MA, USA). Data are presented as mean ± standard deviation or median (interquartile range) for continuous variables and as frequency (%) for categorical variables. The baseline characteristics of the different groups were compared using one-way analysis of variance, Kruskal-Wallis H tests (continuous variables) or χ^2 tests (categorical variables). The associations of PA and SB on all-cause mortality were evaluated using Kaplan-Meier curves (log-rank test) and Cox proportional hazards models (hazards ratio [HR] and 95% confidence interval [CI]) with survival time (in years) as the time from baseline to death or the censor date (October 1, 2020), with adjustment for major covariables including age, education, residence, employment status, marital status, current smoking, current drinking, sleeping duration, MI, stroke, hypertension, BMI, BMR, and VAI. The joint association between PA and SB by deriving a combined variable with four groups, where the combined high PA and SB of <6 h served as the reference category. Relative excess risk due to interaction (RERI), attributable proportion (AP), and synergy index (S),[26,27] and their 95% CIs, were calculated to evaluate the additive interaction between PA and SB on all-cause mortality. Excel sheets for calculation of CIs around RERI, AP, and S can be found elsewhere.[28,29] When RERI and AP were equal to 0 and S was equal to one, or 0 was within the 95% CI of RERI and AP or one was within the 95% CI of S, there was no additive interaction. In addition, modifications of potential variables (e.g. PA) on the association between SB and all-cause mortality were also evaluated by stratified analyses. A two-tailed $P < 0.05$ was considered to be statistically significant.

Results

The present study included 11,744 eligible participants. The average age of all participants was 58.9 ± 13.3 years; 4813 were men (41.0%). Mean sedentary time was 3.8 ± 2.6 h. There were 1781 (15.2%), 3171 (27.0%), and 6792 (57.8%) participants engaged in low, moderate, and high PA, respectively. The characteristics of participants are presented in Table 1. SB (<6 h, ≥6 h) and PA (low to moderate, high) were crosswise combined into four groups of high PA and SB < 6 h, high PA and SB ≥ 6 h, low to moderate PA and SB < 6 h, and low to moderate PA and SB ≥ 6 h. Compared to the other three groups, participants with low to moderate PA and SB ≥ 6 h had the highest age, VAI, SB, SBP, DBP, the largest proportion of male, current smoking, hypertension, stroke, education ≥10 years, urban residents, unemployed, the lowest BMI, and the lowest proportion of married participants. Characteristics of participants stratified by SB (<6 h, ≥6 h) and PA (low to moderate, high) were also presented in Supplementary Table 1, http://links.lww.com/CM9/A739.

During an average of 5.4 years of follow-up (median: 5.6 years; interquartile range: 5.3–5.7 years), there were totally 796 deaths, including 133 stroke deaths, 240 cardiovascular deaths, 68 cancer deaths, 109 respiratory failure deaths, and 246 other deaths. The risk of all-cause mortality was lower among participants with high PA than those with low to moderate level (5.2% *vs*. 8.9%) and higher (7.8% *vs*. 6.0%) among participants with SB ≥6 h compared to those with <6 h.

Table 2 presented the independent association of PA and SB with all-cause mortality by the Cox proportional hazards regression analysis. There was a statistically positive linear association between SB (continuous) and all-cause mortality (HR: 1.04, 95% CI: 1.02–1.06). When SB <4 h group was assessed as the reference group, the HR (95% CI) values in groups of 4 h ≤ SB < 6 h, 6 h ≤ SB < 8 h, and SB ≥ 8 h were 0.97 (0.78–1.15), 1.28 (1.03–1.59), and 1.46 (1.17–1.83), respectively. There was no significant difference on HR values between SB < 4 h group and 4 h ≤ SB < 6 h group. Therefore, the SB was finally combined into <6 h group and ≥6 h group. High SB (≥6 h) was associated with a greater risk of all-cause mortality compared with low SB (<6 h); the HR (95% CI) was 1.37 (1.17–1.61) in the all-adjusted model (Model II). Compared with low PA group, the HR for all-cause mortality was not significant in the moderate PA group. Thus, SB was divided into low to moderate PA group and high PA group. After adjustment for pertinent covariates, participants with high PA had a lower risk of all-cause mortality than participants with low to moderate PA (HR: 0.75, 95% CI: 0.61–0.87). Sensitivity analysis showed that the independent association of PA and SB with all-cause mortality remained statistically significant in participants excluding those who died in the first 2 years of follow-up [Supplementary Table 2, http://links.lww.com/CM9/A739].

When PA and SB were assessed together, the Kaplan–Meier curves [Figure 1] showed that the cumulative hazards of all-cause mortality significantly differed among the four groups (log-rank $P < 0.001$). Based on RERI of −0.090 (95% CI: −0.175 to −0.005), AP of −0.054 (95% CI: −0.076 to −0.032), and S of 0.881 (95% CI: 0.874–0.889), the analyses revealed an interaction on the additive scale between SB and PA on all-cause mortality. There was a significant interaction between PA (low to moderate, high) and SB (<6 h, ≥6 h) on all-cause mortality. A stronger positive association between SB and all-cause mortality was found in low to moderate PA group (HR: 1.74, 95% CI: 1.18–2.28) compared with in high PA group (HR: 1.28 [95% CI: 1.04–1.57], $P_{\text{interaction}} = 0.023$) [Supplementary Figure 1, http://links.lww.com/CM9/A739].

Table 3 showed that the highest risk of all-cause mortality was in the group with prolonged SB (≥6 h) and inadequate PA (low to moderate), with an HR of 1.67 (95% CI: 1.35–2.06). Among participants with high PA, compared with SB < 6 h, prolonged SB (≥6 h) was still associated with a higher all-cause mortality (7.0% *vs*. 4.9%; HR: 1.33, 95%

Table 1: Baseline characteristics of study participants stratified by PA and SB.

Characteristics	High PA, SB < 6 h	High PA, SB ≥ 6 h	Low to moderate PA, SB < 6 h	Low to moderate PA, SB ≥ 6 h	Statistics	*P* value
N	5768	1024	3699	1253		
Age, years	57.7 ± 12.2	57.5 ± 13.3	60.1 ± 14.1	62.2 ± 15.1	53.991*	<0.001
BMI, kg/m^2	23.2 ± 3.5	23.1 ± 3.7	23.1 ± 3.7	22.9 ± 3.8	18.488*	0.014
BMR, kcal/day	1222.0 (1117.0– 1370.0)	1209.0 (1116.0–1350.0)	1220.0 (1109.0– 1381.0)	1213.0 (1110.0–1399.0)	0.870‡	0.351
VAI, %	7.7 (5.0–10.0)	7.3 (4.7–9.0)	7.7 (5.0–10.0)	7.8 (4.5–10.0)	2.548‡	0.017
Sleeping duration, h	7.5 (6.6–8.0)	8.0 (6.6–8.0)	7.7 (6.5–8.0)	7.5 (6.6–8.0)	2.603‡	0.431
SB, h	2.8 ± 1.3	7.6 ± 2.3	2.8 ± 1.4	8.0 ± 3.1	524.579*	<0.001
SBP, mmHg	126.8 ± 19.1	127.1 ± 19.7	129.2 ± 20.3	129.4 ± 19.6	14.130*	<0.001
DBP, mmHg	74.3 ± 10.7	75.5 ± 10.7	75.1 ± 10.8	76.0 ± 11.3	10.939*	<0.001
Male	2180 (37.8)	378 (36.9)	1638 (44.3)	617 (49.2)	83.233†	<0.001
Current smoking	1077 (18.7)	203 (19.8)	775 (21.0)	279 (22.3)	12.437†	0.006
Current drinking	1520 (26.4)	265 (25.9)	916 (24.8)	288 (23.0)	7.506†	0.057
Hypertension	1844 (32.0)	314 (30.7)	1343 (36.3)	508 (40.5)	48.161†	<0.001
MI	35 (0.6)	6 (0.6)	36 (1.0)	8 (0.6)	4.699†	0.195
Stroke	92 (1.6)	11 (1.1)	70 (1.9)	40 (3.2)	18.195†	<0.001
Education, years					99.898†	<0.001
0 to 6	3417 (59.2)	538 (52.5)	2204 (59.6)	727 (58.0)		
7 to 9	2223 (38.5)	445 (43.5)	1364 (39.6)	436 (34.8)		
≥10	128 (2.2)	41 (4.0)	131 (3.5)	90 (7.2)		
Residence					507.669†	<0.001
Urban	2439 (42.3)	668 (65.2)	1716 (46.4)	913 (72.9)		
Rural	3329 (57.7)	356 (34.8)	1983 (53.6)	340 (27.1)		
Employment status					79.126†	<0.001
Employed	2058 (35.7)	340 (33.2)	1308 (35.4)	358 (28.6)		
Retired	893 (15.5)	190 (18.6)	441 (11.9)	181 (14.4)		
Student	85 (1.5)	5 (0.5)	45 (1.2)	9 (0.7)		
Unemployed	2732 (47.4)	489 (47.8)	1905 (51.5)	705 (56.3)		
Marital status					98.683†	<0.001
Unmarried	50 (0.9)	19 (1.9)	45 (1.2)	25 (2.0)		
Married	5134 (89.0)	876 (85.5)	3114 (84.2)	1001 (79.9)		
Divorced or widowed	584 (10.1)	129 (12.6)	540 (14.6)	227 (18.1)		

Data are presented as *n* (%), mean ± standard deviation or median (interquartile range). *F value. †χ^2 values. ‡H values. BMI: Body mass index; BMR: Basal metabolism rate; DBP: Diastolic blood pressure; MI: Myocardial infarction; PA: Physical activity; SBP: Systemic blood pressure; SB: Sedentary behavior; VAI: Visceral fat rate.

CI: 1.12–1.56). Consistent results were found among participants excluding those who died in the first 2 years of follow-up [Supplementary Table 3, http://links.lww.com/CM9/A739].

Discussion

In recent years, the association of PA and SB with health outcomes is an object of intense concern. Our study lends further evidence to the increasing literature pointing to PA and SB as independent predictors of all-cause mortality. We found that Chinese participants with adequate PA (high) had lower mortality risk, while those with prolonged SB (≥6 h) had higher mortality, and participants with prolonged SB (≥6 h) combining with inadequate PA (low to moderate) had the highest risk of all-cause mortality.

Previous studies demonstrated the inverse association of self-reported PA with all-cause mortality. Samitz *et al*[30] pooled data of 1,338,143 participants and found that RR for mortality was 0.65 (95% CI: 0.60–0.71) comparing highest with lowest levels of PA. Investigating different intensity categories of PA with all-cause mortality, Lollgen *et al*[31] reported highly active men and women had a 22% (RR: 0.78, 95% CI: 0.72–0.84) and 31% (RR: 0.69, 95% CI: 0.53–0.90) lower risk of all-cause mortality, respectively. An increasing number of papers comprising the literature documented the positive association between self-reported SB and all-cause mortality. Biswas *et al*[32] found a significant HR association of prolonged SB with all-cause mortality (HR: 1.24, 95% CI: 1.09–1.41). Matthews *et al*[33] revealed that black adults with SB > 12 h/day had a 20% to 25% increased risk of all-cause mortality than those with SB < 5.8 h/day. In recent decades for China, there has been a substantial transformation from a labor-intensive lifestyle to more sedentary and physically inactive lifestyle, which is close to the Western lifestyle. However, the status of PA and SB and the associations with mortality risk were unclear.[34] Our study made efforts in this regard. In agreement with the above results mainly in Western countries, consistent conclusions were found in our study among Chinese population.

Similar results were also reported in prior studies relying on objective measurements. A study on 7-day waist-worn

Table 2: The association of PA and SB on all-cause mortality.

Variables	*N*	All-cause death (%)	All-cause mortality, HR (95% CI)		
			Crude	Model I	Model II
SB, h					
As continuous variable	11,744	796 (6.8)	1.04 (1.02–1.06)	1.04 (1.02–1.07)	1.04 (1.02–1.06)
As categories variable (4 groups)					
<4	6738	406 (6.0)	1.00	1.00	1.00
≥4 to 6	2727	178 (6.5)	1.08 (0.90–1.28)	0.99 (0.82–1.18)	0.97 (0.81–1.16)
≥6 to 8	1253	112 (8.9)	1.48 (1.20–1.82)	1.33 (1.08–1.65)	1.28 (1.03–1.59)
≥8	1026	100 (9.7)	1.64 (1.31–2.04)	1.53 (1.23–1.91)	1.46 (1.17–1.83)
As categories variable (2 groups)					
<6	9467	584 (6.2)	1.00	1.00	1.00
≥6	2277	212 (9.3)	1.52 (1.30–1.78)	1.43 (1.22–1.68)	1.37 (1.17–1.61)
PA					
As categories variable (3 groups)					
Low	1781	187 (10.5)	1.00	1.00	1.00
Moderate	3171	253 (8.0)	0.75 (0.62–0.91)	0.93 (0.77–1.12)	0.95 (0.78–1.15)
High	6792	356 (5.2)	0.48 (0.40–0.57)	0.69 (0.58–0.83)	0.73 (0.61–0.87)
As categories variable (2 groups)					
Low to moderate	4952	440 (8.9)	1.00	1.00	1.00
High	6792	356 (5.2)	0.57 (0.50–0.66)	0.72 (0.63–0.83)	0.75 (0.61–0.87)

Model I: adjusted for sex; age; education; residence; marital status; employment status; Model II: adjusted for sex; age; education; residence; marital status; employment status; current smoking; current drinking; sleeping duration; BMI; BMR; VAI; SBP; DBP; hypertension; MI; stroke. BMI: Body mass index; BMR: Basal metabolism rate; CI: Confidence interval; DBP: Diastolic blood pressure; HR: Hazards ratio; MI: Myocardial infarction; SB: Sedentary behavior; SBP: Systemic blood pressure; VAI: Visceral fat rate.

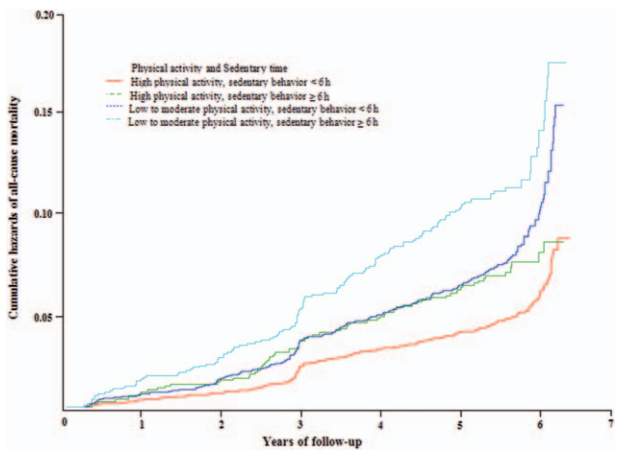

Figure 1: Kaplan–Meier curves of cumulative hazards of all-cause mortality by PA (low to moderate *vs.* high) and SB (<6 h, ≥6 h). PA: Physical activity; SB: Sedentary behavior.

accelerometry data of 1906 participants aging ≥50 years from the U.S. nationally representative National Health and Nutrition Examination Survey 2003 to 2004 with 2.8 years of follow-up, indicated that participants in the fourth of SB quartile had a 5.94 times higher risk of mortality than those in the lowest quartile.[35] Lee *et al*[36] reported that among 16,741 women with PA measured by wearing a triaxial accelerometer on the hip for 7 days, during a follow-up of 2.3 years, there was a 60.0% to 70.0% of risk reduction for the fourth quartile *vs*. the first quartile of PA. A subset of the European Prospective Investigation Into Cancer and Nutrition-Norfolk study prospectively investigated 5249 adults 40 to 79 years of age wearing an accelerometer on the right hip for 1 week; strongly inverse and positive linear associations were, respectively, observed for PA and SB with mortality.[37] Comparing to accelerometry measurements, self-report measurements have not quantified PA and SB, but they had

Table 3: Joint associations of PA (low to moderate, high) and SB Levels (<6 h, ≥6 h) on all-cause mortality.

Combined variables	*N*	All-cause death (%)	All-cause mortality, HR (95% CI)		
			Crude	Model I	Model II
High PA, SB<6 h	5768	284 (4.9)	1.00	1.00	1.00
High PA, SB≥6 h	1024	72 (7.0)	1.43 (1.10–1.85)	1.39 (1.18–1.64)	1.33 (1.12–1.56)
Low to moderate PA, SB<6 h	3699	300 (8.1)	1.70 (1.45–2.00)	1.51 (1.17–1.97)	1.43 (1.10–1.86)
Low to moderate PA, SB≥6 h	1253	140 (11.2)	2.35 (1.92–2.88)	1.77 (1.44–2.18)	1.67 (1.35–2.06)
P for trend			<0.001	<0.001	<0.001

Model I: adjusted for sex; age; education; residence; marital status; employment status; Model II: adjusted for sex; age; education; residence; marital status; employment status; current smoking; current drinking; sleeping duration; BMI; BMR; VAI; SBP; DBP; hypertension; MI; stroke. BMI: Body mass index; BMR: Basal metabolism rate; CI: Confidence interval; DBP: Diastolic blood pressure; HR: Hazards ratio; MI: Myocardial infarction; SB: Sedentary behavior; SBP: Systemic blood pressure; VAI: Visceral fat rate.

longer follow-up durations to reflect long-term patterns and could be accessed easily. The two assessment approaches overlapped, but each would provide unique information.[38] Further studies should effectively integrate them to explore a more comprehensive estimation of PA, SB, and their associations with all-cause mortality.

Although recommendations on minimizing SB have begun to appear in public health guidelines,[5] few quantitative guidelines exist for SB. Previous cut-off duration of daily SB required to minimize mortality was inconsistent. A meta-analysis including 13 studies (all self-reported measures) indicated that ≥4 h/day in SB resulted in an increased risk of all-cause mortality.[18] Based on six studies (five self-reported *vs*. one device-based), Chau *et al*[4] revealed that SB of >7 h/day was associated with increased mortality risk. Basing on studies with device-based measures, Ku *et al*[39] reported that the appropriate daily SB cut-off duration in adults was around 9 h. In our study, we found the significant cut-off duration of self-reported SB was 6 h/day. After considering the report indicating that the subjective assessment might lead to an underestimation of daily SB in the range of 2 to 3.5 h,[40] it is our inference that the specific duration of SB for recommendations in China needs further study.

Some mechanisms may explain the association of SB and PA with health. SB has been significantly associated with metabolic risk factors including fasting glucose, triglycerides, and high-density lipoprotein cholesterol,[41,42] which may be a part of the explanation for the higher risk of mortality. Moreover, SB would lead to mitochondrial dysfunction, dysregulation of cellular redox status, and increased inflammation, and also may alter mitochondrial DNA deletions or mutations and increase reactive oxygen species-mediated toxicity. Finally, this chain of factors results in cellular senescence and cell death.[43] Nevertheless, more study is necessary for the mechanisms underlying the harmful influence of SB on health. Possible mechanisms underlying the benefit of PA on mortality involve the favorable alterations in glucose tolerance, lipid levels, blood pressure, and BMI.[44,45] Recent studies have demonstrated the direct vascular deconditioning and conditioning effect of PA, which may contribute to decreased health risk.[46] Furthermore, PA has other potential benefits on health covering attenuation of plaque progression, improvement of endothelial cell function, reduction of myocardial oxygen and thrombosis, stabilization of vulnerable plaques, and strengthened collateralization.[47,48] This may explain how adequate PA attenuates the harmful influence of SB.

The strengths of our study include a Chinese population-based design, a large random sample size, and strict adjustment to minimize residual confounders. Several limitations should be noted. First, we did not objectively quantify PA and SB, so the association of PA and SB with mortality might be underestimated in questionnaire- based studies, possibly due to recall bias when relying on imprecise PA and SB self-reports.[20,49,50] Second, although a range of confounding covariates we adjusted, the influence of potential confounding effects could not be excluded entirely. Third, all participants included in our study were from southern China, so it would be difficult to generalize to other populations.

Conclusions

A significant and independent association of prolonged SB on all-cause mortality appeared among participants with high PA. High amounts of PA effectively attenuate the risk of SB on mortality. In conclusion, PA and SB have been among the leading modifiable risk factors for all-cause mortality not only in Western countries but also in China. Reduction of SB will be an effective strategy, ancillary to increasing PA, for preventing all-cause mortality in physically inactive or sedentary populations.

Acknowledgements

The authors thank to all the investigators and subjects who participated in the Chinese Hypertesion Survey.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 81760049), the Jiangxi Science and Technology Innovation Platform Project (No. 20165BCD41005), the National Key R&D Program of China (No. 2018YFC1312902), the Science and Technology Plan of Health Commission of Jiangxi Province (No. 20185215), and the Key Project of Education Department of Jiangxi Province (No. GJJ170013).

Conflicts of interest

None.

References

1. Wen CP, Wai JPM, Tsai MK, Yang YC, Cheng TYD, Lee MC, *et al*. Minimum amount of physical activity for reduced mortality and extended life expectancy: A prospective cohort study. Lancet 2011;378:1244–1253. doi: 10.1016/S0140-6736(11)60749-6.
2. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, *et al*. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012;380:219–229. doi: 10.1016/S0140-6736(12)61031-9.
3. Grontved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. JAMA 2011;305:2448–2455. doi: 10.1001/jama.2011.812.
4. Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE, *et al*. Daily sitting time and all-cause mortality: a meta-analysis. PLoS One 2013;8:e80000. doi: 10.1371/journal.pone.0080000.
5. Young DR, Hivert MF, Alhassan S, Camhi SM, Ferguson JF, Katzmarzyk PT, *et al*. Sedentary behavior and cardiovascular morbidity and mortality: a science advisory from the American Heart Association. Circulation 2016;134:e262–e279. doi: 10.1161/CIR.0000000000000440.
6. Patel AV, Bernstein L, Deka A, Feigelson HS, Campbell PT, Gapstur SM, *et al*. Leisure time spent sitting in relation to total mortality in a prospective cohort of US adults. Am J Epidemiol 2010;172:419–429. doi: 10.1093/aje/kwq155.
7. Warren TY, Barry V, Hooker SP, Sui X, Church TS, Blair SN. Sedentary behaviors increase risk of cardiovascular disease mortality in men. Med Sci Sports Exerc 2010;42:879–885. doi: 10.1249/MSS.0b013e3181c3aa7e.
8. Dunstan DW, Barr ELM, Healy GN, Salmon J, Shaw JE, Balkau B, *et al*. Television viewing time and mortality: the Australian diabetes, obesity and lifestyle study (AusDiab). Circulation 2010;121:384–391. doi: 10.1161/circulationaha.109.894824.

9. Wijndaele K, Brage S, Besson H, Khaw KT, Sharp SJ, Luben R, *et al*. Television viewing time independently predicts all-cause and cardiovascular mortality: the EPIC Norfolk study. Int J Epidemiol 2011;40:150–159. doi: 10.1093/ije/dyq105.
10. Katzmarzyk PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. Med Sci Sports Exerc 2009;41:998–1005. doi: 10.1249/MSS.0b013e3181930355.
11. Rezende LFM, Sa TH, Mielke GI, Viscondi JYK, Rey-Lopez JP, Garcia LMT. All-cause mortality attributable to sitting time: analysis of 54 countries worldwide. Am J Prev Med 2016;51:253–263. doi: 10.1016/j.amepre.2016.01.022.
12. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, *et al*. Amount of time spent in sedentary behaviors in the United States, 2003-2004. Am J Epidemiol 2008;167:875–881. doi: 10.1093/aje/kwm390.
13. Colley RC, Garriguet D, Janssen I, Craig CL, Clarke J, Tremblay MS. Physical activity of Canadian adults: accelerometer results from the 2007 to 2009 Canadian Health Measures Survey. Health Rep 2011;22:7–14. doi: 10.1016/j.yspm.2011.03.006.
14. Lavie CJ, Arena R, Swift DL, Johannsen NM, Sui X, Lee DC, *et al*. Exercise and the cardiovascular system: clinical science and cardiovascular outcomes. Circ Res 2015;117:207–219. doi: 10.1161/CIRCRESAHA.117.305205.
15. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting physical activity and exercise: JACC Health Promotion Series. J Am Coll Cardiol 2018;72:1622–1639. doi: 10.1016/j.jacc.2018.08.2141.
16. Wisloff U, Lavie CJ. Taking physical activity, exercise, and fitness to a higher level. Prog Cardiovasc Dis 2017;60:1–2. doi: 10.1016/j.pcad.2017.06.002.
17. Van Dyck D, Cerin E, De Bourdeaudhuij I, Hinckson E, Reis RS, Davey R, *et al*. International study of objectively measured physical activity and sedentary time with body mass index and obesity: IPEN adult study. Int J Obes (Lond) 2015;39:199–207. doi: 10.1038/ijo.2014.115.
18. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, *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;388:1302–1310. doi: 10.1016/S0140-6736(16)30370-1.
19. Wang Z, Chen Z, Zhang L, Wang X, Hao G, Zhang Z, *et al*. Status of hypertension in China: results from the China hypertension survey, 2012-2015. Circulation 2018;137:2344–2356. doi: 10.1161/CIRCULATIONAHA.117.032380.
20. Yu L, Liang Q, Zhou W, Huang X, Hu L, You C, *et al*. Sedentary behavior and the risk of cardiac-cerebral vascular diseases in southern China. Medicine (Baltimore) 2018;97:e12838. doi: 10.1097/MD.0000000000012838.
21. Wang Z, Zhang L, Chen Z, Wang X, Shao L, Guo M, *et al*. Survey on prevalence of hypertension in China: background, aim, method and design. Int J Cardiol 2014;174:721–723. doi: 10.1016/j.ijcard.2014.03.117.
22. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, *et al*. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–1395. doi: 10.1249/01.MSS.0000078924.61453.FB.
23. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, *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;116:1081–1093. doi: 10.1161/CIRCULATIONAHA.107.185649.
24. Writing Group of 2010 Chinese Guidelines for the Management of Hypertension. 2010 Chinese guidelines for the management of hypertension. Chin J Cardio 2011;39:579–616. doi:10.3760/cma.j.issn.0253-3758.2011.07.002.
25. Lenfant C, Chobanian AV, Jones DW, Roccella EJ. Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. Hypertension 2003;41:1178–1179. doi: 10.1161/01.HYP.0000075790.33892.AE.
26. Jager DJD, Mutsert RD, Jager KJ, Zoccali C, Dekker FW. Reporting of interaction. Nephron Clin Pract 2011;119:c158–c161. doi: 10.1159/000327598.
27. Knol MJ, Tweel IVD, Grobbee DE, Numans ME. Estimating interaction on an additive scale between continuous determinants in a logistic regression model. Int J Epidemiol 2007;36:1111–1118. doi: 10.1093/ije/dym157.
28. Richardson DB, Kaufman JS. Estimation of the relative excess risk due to interaction and associated confidence bounds. Am J Epidemiol 2009;169:756–760. doi: 10.1093/aje/kwn411.
29. Andersson T, Alfredsson L, Kllberg H, Zdravkovic S, Ahlbom A. Calculating measures of biological interaction. Eur J Epidemiol 2005;20:575–579. doi: 10.1007/s10654-005-7835-x.
30. Samitz G, Egger M, Zwahlen M. Domains of physical activity and all-cause mortality: systematic review and dose-response meta-analysis of cohort studies. Int J Epidemiol 2011;40:1382–1400. doi: 10.1093/ije/dyr112.
31. Lollgen H, Bockenhoff A, Knapp G. Physical activity and all-cause mortality: an updated meta-analysis with different intensity categories. Int J Sports Med 2009;30:213–224. doi: 10.1055/s-0028-1128150.
32. Biswas A, Oh PI, Faulkner GE, Bajaj RR, Silver MA, Mitchell MS, *et al*. Sedentary time and its association with risk for disease incidence, mortality, and hospitalization in adults: a systematic review and meta-analysis. Ann Intern Med 2015;162:123–132. doi: 10.7326/M14-1651.
33. Matthews CE, Cohen SS, Fowke JH, Han X, Xiao Q, Buchowski MS, *et al*. Physical activity, sedentary behavior, and cause-specific mortality in black and white adults in the Southern Community Cohort Study. Am J Epidemiol 2014;180:394–405. doi: 10.1093/aje/kwu142.
34. Bennett DA, Du H, Clarke R, Guo Y, Yang L, Bian Z, *et al*. Association of physical activity with risk of major cardiovascular diseases in Chinese men and women. JAMA Cardiol 2017;2:1349–1358. doi: 10.1001/jamacardio.2017.4069.
35. Koster A, Caserotti P, Patel KV, Matthews CE, Berrigan D, Domelen DRV, *et al*. Association of sedentary time with mortality independent of moderate to high physical activity. PLoS One 2012;7:e37696. doi: 10.1371/journal.pone.0037696.
36. Lee IM, Shiroma EJ, Evenson KR, Kamada M, Lacroix AZ, Buring JE. Accelerometer-measured physical activity and sedentary behavior in relation to all-cause mortality: the Women's Health Study. Circulation 2018;137:203–205. doi: 10.1161/CIRCULATIONAHA.117.031300.
37. Dempsey PC, Strain T, Khaw KT, Wareham NJ, Brage S, Wijndaele K. Prospective associations of accelerometer-measured physical activity and sedentary time with incident cardiovascular disease, cancer, and all-cause mortality. Circulation 2020;141:1113–1115. doi: 10.1161/CIRCULATIONAHA.119.043030.
38. Troiano RP, Pettee GK, Welk GJ, Owen N, Sternfeld B. Reported physical activity and sedentary behavior: why do you ask? J Phys Act Health 2012;9 Suppl 1:S68–S75. doi: 10.1123/jpah.9.s1.s68.
39. Ku PW, Steptoe A, Liao Y, Hsueh MC, Chen LJ. A cut-off of daily sedentary time and all-cause mortality in adults: a meta-regression analysis involving more than 1 million participants. BMC Med 2018;16:74. doi: 10.1186/s12916-018-1062-2.
40. Gupta N, Christiansen CS, Hanisch C, Bay H, Burr H, Holtermann A. Is questionnaire-based sitting time inaccurate and can it be improved? A cross-sectional investigation using accelerometer-based sitting time. BMJ Open 2017;7:e013251. doi: 10.1136/bmjopen-2016-013251.
41. Renninger M, Hansen BH, Steene-Johannessen J, Kriemler S, Froberg K, Northstone K, *et al*. Associations between accelerometry measured physical activity and sedentary time and the metabolic syndrome: a meta-analysis of more than 6000 children and adolescents. Pediatr Obes 2020;15:e12578. doi: 10.1111/ijpo.12578.
42. Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet P, *et al*. Objectively measured sedentary time, physical activity, and metabolic risk: the Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care 2008;31:369–371. doi: 10.2337/dc07-1795.
43. Safdar A, Hamadeh MJ, Kaczor JJ, Raha S, Debeer J, Tarnopolsky MA. Aberrant mitochondrial homeostasis in the skeletal muscle of sedentary older adults. PLoS One 2010;5:e10778. doi: 10.1371/journal.pone.0010778.
44. Rossi A, Dikareva A, Bacon SL, Daskalopoulou SS. The impact of physical activity on mortality in patients with high blood pressure: a systematic review. J Hypertens 2012;30:1277–1288. doi: 10.1097/HJH.0b013e3283544669.

45. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. Circulation 2007;116:2110–2118. doi: 10.1161/CIRCULATIONAHA.107.729939.
46. Thijssen DHJ, Maiorana AJ, O'Driscoll G, Cable NT, Hopman MTE, Green DJ. Impact of inactivity and exercise on the vasculature in humans. Eur J Appl Physiol 2010;108:845–875. doi: 10.1007/s00421-009-1260-x.
47. Moyna NM, Thompson PD. The effect of physical activity on endothelial function in man. Acta Physiol Scand 2004;180:113–123. doi: 10.1111/j.0001-6772.2003.01253.x.
48. Bowles DK, Laughlin MH. Mechanism of beneficial effects of physical activity on atherosclerosis and coronary heart disease. J Appl Physiol (1985) 2011;111:308–310. doi: 10.1152/japplphysiol.00634.2011.
49. Blond K, Brinklov CF, Ried-Larsen M, Crippa A, Grontved A. Association of high amounts of physical activity with mortality risk: a systematic review and meta-analysis. Br J Sports Med 2020;54:1195–1201. doi: 10.1136/bjsports-2018-100393.
50. Celis-Morales CA, Perez-Bravo F, Ibanez L, Salas C, Bailey ME, Gill JMR. Objective vs. self-reported physical activity and sedentary time: effects of measurement method on relationships with risk biomarkers. PLoS One 2012;7:e36345. doi: 10.1371/journal.pone.0036345.

How to cite this article: Zhou W, Yan W, Wang T, Zhu LJ, Xu Y, Zhao J, Yu LL, Bao HH, Cheng XS. Independent and joint association of physical activity and sedentary behavior on all-cause mortality. Chin Med J 2021;134:2857–2864. doi: 10.1097/CM9.0000000000001730