Association between Physical Activity, Occupational Sitting Time and Mortality in a General Population: An 18-year Prospective Survey in Tanushimaru, Japan

Akiko Sakaue[1], Hisashi Adachi[1,2], Mika Enomoto[1], Ako Fukami[1], Eita Kumagai[1], Sachiko Nakamura[1], Yume Nohara[1], Shoko Kono[1], Erika Nakao[1], Nagisa Morikawa[1], Tomoko Tsuru[1], Hitoshi Hamamura[1], Noriko Yoshida[3], Yoshihiro Fukumoto[1]

1. Department of Internal Medicine, Division of Cardio-Vascular Medicine, Kurume University School of Medicine, Kurume, Japan
2. Department of Community Medicine, Kurume University School of Medicine, Kurume, Japan
3. Department of Sports Medicine and Science, Faculty of Human Health, Kurume University, Kurume, Japan

Abstract=250

Total word count=3,981

References=30

Six tables, four supplemental tables, and two supplemental figures

Running title: Physical activity, sitting time and mortality

Address for correspondence;

Hisashi Adachi, MD, PhD.

Department of Community Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, 830-0011, Japan

TEL: +81-942-31-7586, FAX: +81-942-31-7896

E-mail: hadac@med.kurume-u.ac.jp

Abstract

Aims: It is well known that a decline in physical activity is associated with an increase of all-cause death including cardiovascular events and cancer. Few studies have examined the association between occupational sitting time and mortality. Therefore, we investigated this issue in a general population.

Methods: Physical activity and occupational sitting time were measured using the Baecke physical activity questionnaire (BPAQ) in 1999. The questionnaire generated indices in three physical activity categories: work, sport and leisure-time. A total physical activity index was calculated by adding these three indices. The BPAQ was able to evaluate occupational sitting time. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox's proportional hazard regression models.

Results: We enrolled a total of 1,680 participants, who were followed up for 15.9±3.8 years. The final follow-up rate was 93%. During the follow-up period, 397 subjects died. A significant inverse association (p<0.0001) was found between physical activity and mortality after adjustment for age and

sex. Compared to lower levels of physical activity, the adjusted HR for mortality at higher levels of physical activity was 0.85 (95% CI: 0.78-0.92). Longer occupational sitting time was also significantly associated with higher mortality (p<0.01). The adjusted HR for mortality at longer occupational sitting time was 1.16 (95% CI: 1.05-1.27). These findings were observed in males, but not in females.

Conclusions: Our data demonstrated that higher levels of physical activity are associated with a reduced risk of cancer and cardiovascular death. Further, longer occupational sitting time is associated with increased mortality.

Key Words: Physical activity, Sitting time, Mortality, Epidemiology

Introduction

Several cohort studies have confirmed the overall benefit of physical activity in reducing morbidity and mortality [1]. Some studies have reported that a lower physical activity was associated with an increase in all-cause death, including cardiovascular events [2,3], breast and colorectal cancers [4]. Although various methods have been used to evaluate physical activity [5], none are yet well established. In this study, we evaluated individual physical activity using the Baecke physical activity questionnaire (BPAQ) [6], which is an effective way to evaluate both occupational and leisure physical activities. In modern society, prolonged sitting has become common in various areas of life, such as the workplace, home, and transportation, and such prolonged sitting is considered to be detrimental to health. Although prolonged sitting has been reported to be a risk factor for all-cause mortality independent of physical activity, only a few studies have been conducted [7,8]. The Danish Work Environment Cohort Study reported that there was no statistically significant association between sitting time and all-cause mortality [9], and another study in England suggested that sitting time was positively associated with all-cause

mortality in females, but not in males [10]. The Japan Public Health Centre-based prospective study (JPHC study) reported no significant association between occupational sitting duration and mortality in the overall population, whereas longer sitting duration was significantly associated with higher mortality in male workers in primary industries [11]. However, this issue is still controversial. Therefore, in the present study we examined the relationship between physical activity and mortality using a questionnaire. Moreover, we also examined the relationship between occupational sitting time and mortality in a Japanese general population, by means of a prospective 18-year follow-up study of 1,680 general inhabitants living in a farming district.

Methods

Study population

A periodic epidemiologic survey was performed in 1999 in the small farming community of Tanushimaru, Japan, which is one of the cohorts of the Seven Countries Study [12]. As previously reported, the demographic characteristics of the residents of this area were similar to those of the general Japanese population [13]. We performed epidemiological studies in

every 10 years and followed up the participants every year. In 1999, the total population aged over 40 years in this district was 3,463 persons (48.2% of men and 62.0% of women). A total of 1,920 subjects (794 males and 1,126 females; aged 40-95 years) were enrolled in this study, and physical activity and occupational sitting time were measured by the BPAQ [6]. We excluded 240 subjects from whom we were not able to collect a questionnaire. The remaining 1,680 (693 males and 987 females) subjects were finally included in this analysis, and the relationships among physical activity, occupational sitting time and mortality were examined. Exclusion criteria were 240 subjects from whom we were not able to collect a questionnaire.

Measurements

Baecke physical activity questionnaire (BPAQ)

The questionnaire consists of 16 questions organized into three sections: physical activity at work (Questions 1-8), sport during leisure time (Questions 9-12), and physical activity during leisure excluding sport (Questions 13-16) [6]. We defined total index as total physical activity

index, which were summed up of work, sport, and leisure-time index. Occupational sitting time could be assessed by Question 2, “At work I sit”. The questionnaire defined three levels of occupational/work physical activity, namely low (e.g., clerical work, driving, shop keeping, teaching, studying, housework, medical practice and all other occupations with a university education), middle (e.g., farming, factory work, and carpentry), and high (e.g., dock work, construction work, and sport). Similarly, the questionnaire categorized sports into three levels: low (e.g., billiards, sailing, bowling and golf: average energy expenditure 0.76MJ/h), middle (e.g., badminton, cycling, dancing, swimming, and tennis: average energy expenditure 1.26MJ/h), and high (e.g., boxing, basketball, rugby, football, and rowing: average energy expenditure 1.76MJ/h). A sport score was calculated from a combination of the intensity of the sport which was played, the amount of time per week playing that sport, and the proportion of the year in which the sport was played regularly. Questions in each of the three indices (work, sport, and leisure) were scored on a five-point Likert scale, ranging from “1 = never” to “5 = always” or “5 = very often”. Summing the three indices gives a total physical activity index [6, 14]. We

applied a five-point Likert scales to all of the three indices and only in sports index, we applied the combinations of intensity and duration.

Data collection

Medical history, smoking habits, and alcohol intake were ascertained by a questionnaire. Smoking and alcohol intake were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) was calculated as an index of obesity. Waist circumference was measured at the level of umbilicus in the standing position. Blood pressure (BP) was measured in the supine position twice at 3-minute intervals using a standard sphygmomanometer. The second BP was taken after 5 deep breaths, and that was used for analysis.

Blood was drawn from the antecubital vein in the morning after a 12-hour fast for determinations of lipids profiles (total cholesterol, triglycerides, high-density [HDL], and low-density lipoprotein cholesterol [LDL]), fasting plasma glucose (FPG), HbA_{1c} (NGSP), insulin, serum urea nitrogen, creatinine and uric acid. Fasting blood samples were centrifuged within 1 hour after collection, and measured at a commercially available

laboratory (Kyodo Igaku Laboratory, Fukuoka, Japan). The estimate of insulin resistance by homeostasis model assessment (HOMA) score was calculated with the formula: fasting insulin (μU/mL) × fasting glucose (mmol/L)/22.5 as described by Matthews et al. [15]. Insulin resistance was defined as HOMA ≥ 1.73 according to the diagnostic criteria used in Japan [16]. Estimated glomerular filtration rate (eGFR) was calculated according to the following estimation formula that has been recommended by the Japan Society of Nephrology: eGFR (mL/min/1.73^2) = (194 × Scr $^{-1.094}$ × age $^{-0.287}$) × (0.739 for females) [17].

The mean follow-up period was 15.9 years. The causes of death were determined based on a review of obituaries, medical records, death certificates, hospital charts, and interviews with primary care physicians or families of the deceased. Because many patients with cancer ultimately die from infection or other illnesses, care was taken to identify the underlying cause of death. The information was coded independently in accordance with the rules of the Seven Countries Study [12]. Follow-up data through the end of March 2017 were analyzed. The follow-up rate was 93%.

This study was approved by the Ukiha Branch of the Japan Medical

Association, by the City Council of Tanushimaru, and by the Ethics Committee of Kurume University. All participants gave informed consent.

Statistical analysis

Because of skewed distributions, natural logarithmic transformations were performed for HOMA index and triglycerides. Log-transformed values were used for the statistical calculation and reconverted to antilogarithm forms in the tables. The medications for hypertension, hyperlipidemia, and diabetes, sex, smoking habits, and alcohol intake were used as dummy variables.

First, we performed univariate regression analyses for correlates of physical activity and occupational sitting time at baseline in the cross-sectional study. Then, multivariate Cox’s proportional hazards regression model was used to estimate predictive physical activity, and occupational sitting time for all-cause mortality. Multivariable adjusted hazard ratios (HR) and 95% confidence intervals (CI) were calculated by using the models. Finally, Cox's proportional hazard regression model adjusted for age and sex was performed to obtain the survival function

estimation among total, work, sport, and leisure-time index quartiles and 5 groups of occupational sitting time. Statistical significance was defined as a *p* value less than 0.05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Cross-sectional study

1) Activity measurements

Table 1 showed the baseline characteristics of the 1,680 participants in the cross-sectional study, which was performed in 1999. The mean total physical activity index was 7.78, with a work index of 3.27, sport index of 2.00, and leisure-time index of 2.51. The mean occupational sitting time was 2.89. The total physical activity index showed a normal distribution with a peak score of 7-8 (**Supplemental Figure 1-A**). At the peak, the occupational sitting score was 3.0 (**Supplemental Figure 1-B**).

2) Correlation between activity and comorbidities

Univariate regression analysis for correlates of total physical activity index

146 at baseline was shown in **Table 2**. There was a significant relationship
147 between total physical activity index and age (p=0.037), male gender
148 (p=0.010), heart rate (p<0.0001; inversely), HOMA index (p=0.004;
149 inversely), occupational sitting time (p<0.0001; inversely), and alcohol
150 intake (p=0.015). Subjects with diabetes, hypertension and any other
151 cardiovascular diseases were not associated with total physical activity
152 index. Univariate regression analysis for correlates of occupational sitting
153 time at baseline was shown in **Table 3**. There was a significant relationship
154 between occupational sitting time and age (p=0.015; inversely), male
155 gender (p<0.0001; inversely), heart rate (p<0.0001), uric acid (p=0.007;
156 inversely), HOMA index (p=0.026), total physical activity index
157 (p<0.0001; inversely), work index (p<0.0001; inversely), and alcohol
158 intake (p=0.002; inversely). Multivariate linear regression analysis for
159 correlates of total index adjusted for age and sex at baseline was shown in
160 **Supplemental Table 1**. There was a significant relationship between total
161 physical activity index and systolic BP (p=0.042; inversely), heart rate
162 (p<0.0001; inversely), HOMA index (p=0.006; inversely), and
163 occupational sitting time (p<0.0001; inversely). Multivariate linear

164 regression analysis for correlates of occupational sitting time adjusted for
165 age and sex at baseline was shown in **Supplemental Table 2**. There was a
166 significant relationship between occupational sitting time and heart rate
167 (p=0.001), total physical activity index (p<0.0001; inversely), and work
168 index (p<0.0001; inversely).
169
170 **Prospective study**
171 We were able to ascertain the cause of death for 78% of the deceased. A
172 total of 397 (224 males and 173 females) subjects died: 118 (30%) of
173 cancer, 36 (9%) of cardiovascular disease, 30 (8%) of cerebrovascular
174 disease, 53 (13%) of infection, 24 (6%) of senility, 47 (12%) of others
175 causes, and 89 (22%) of unknown causes.
176 Multivariate Cox's proportional hazards regression analysis of
177 all-cause mortality adjusted for age and sex was shown in **Supplemental**
178 **Table 3**. HbA_{1c} (p=0.005), FPG (p=0.003), smoking (p<0.0001), and
179 occupational sitting time (p=0.002) were significant positive predictors of
180 all-cause mortality, whereas total cholesterol (p<0.0001), LDL-cholesterol
181 (p<0.0001), and total physical activity index (p<0.0001) were inversely

associated with all-cause mortality. Work index (p=0.018), sport index (p=0.033), and leisure-time index (p=0.003) were also inversely associated with all-cause mortality.

Table 4 showed the multivariate Cox's proportional hazards regression analysis of all-cause mortality adjusted for demographics and lifestyle factors. In the final model, total physical activity index (p=0.001) was inversely associated with mortality adjusted for age, sex, BMI, total cholesterol, systolic BP, FPG, and smoking. The leisure-time index (p=0.005) was also inversely associated with mortality. Work and sport indices were not statistically significant. In the final model, occupational sitting time (p=0.039) was also significantly associated with mortality adjusted for age, sex, BMI, total cholesterol, systolic BP, and total physical activity index. Occupational sitting time was a risk factor for all-cause mortality, independent of physical activity (**Table 5**). **Table 6** showed multivariate Cox's proportional hazards regression analysis of all-cause death adjusted for age stratified by sex. In males, but not in females, total physical activity index was a significant inverse predictor, and occupational sitting time was a significant positive predictor of all-cause death.

Cox's proportional hazard regression model adjusted for age and sex was performed to estimate the survival function. The cumulative survival rate was significantly decreased in the lowest total physical activity index (Q1) compared with the remaining higher groups (Q2-Q4) (**Supplemental Figure 2-A**), and significantly increased at the highest occupational sitting time (Score 5) compared with the lower groups (Score 1-4) (**Supplemental Figure 2-B**).

The multivariate Cox's proportional hazards regression analysis stratified by the cause of death adjusted for age and sex was shown in **Supplemental Table 4**. Total physical activity index was inversely associated with cancer and cardiovascular deaths. Occupational sitting time was significantly and positively associated with cardiovascular death, but not with cancer deaths.

Discussion

We found that higher levels of physical activity reduced mortality, and that the longer occupational sitting time increased mortality, irrespective of physical activity. These investigations were novel in Japan.

218

219 **Physical activity and clinical characteristics (cross-sectional study)**

220 The physical activity levels were high in elderly subjects, male gender,
221 with low heart rate, low HOMA index, and alcohol intake (**Table 2**). Total
222 physical activity index was gradually increased with age (Table 2), however,
223 there is no significant association between total physical activity index and
224 age groups (p=0.08). It was reported that exercise adherence reduced heart
225 rate in elderly women [18]. As for the inverse significance of HOMA index,
226 Holloszy suggested that regular exercise increased muscle insulin
227 sensitivity [19].

228 Previous studies have also revealed that physical activity was
229 associated with low mortality in the elderly [20] and that long-term regular
230 physical activity, including walking, was associated with better cognitive
231 function and less cognitive decline in elderly women [21], probably
232 because the retired elderly have time to do exercise and may have a strong
233 awareness of their health. To examine the relationship between physical
234 activity and alcohol intake, we performed univariate regression analysis for
235 correlates of alcohol intake. Alcohol intake was significantly and positively

associated with physical activity, especially work index and sport index, probably due to opportunities for elderly subjects to drink alcohol after hard labor and sports with their fellow workers or friends.

Physical activity measurement (cross-sectional study)

The 3 months test-retest reliability of the BPAQ was high in Dutch adults, work index (Pearson r = 0.88), sport index (Pearson r = 0.81), and leisure-time index (Pearson r = 0.74) [6]. The doubly labelled water method (DLW) is considered the gold standard in the assessment of physical activity. Due to its high cost, this method is used only in studies with small sample size but can provide accurate information about the average level of physical activity in terms of energy expenditure over a 1-3 week period. Therefore, this technique is useful in physical activity validation studies. The BPAQ showed a very high correlation with physical activity level from the DLW method ($r = 0.69$, $p < 0.001$) [22]. The validity of the questionnaire was also confirmed in a report by Sadeghisani M, et al. [23].

Sex-differences (prospective study)

254 The present study revealed that higher levels of physical activity reduced
255 all-cause mortality and longer occupational sitting time increased all-cause
256 mortality in males, but not in females (**Table 6**). As for the sex-difference,
257 four reasons may be considered. The difference can be explained by muscle
258 quantity and sex hormones. First, females have less muscle mass, lower
259 basal metabolism [24], and sweat less than males during the same physical
260 activity. Because the BPAQ contains items regarding sweat, the scores in
261 females might be lower than in males. Second, participants with hot flashes
262 among postmenopausal females may sweat more even at rest, so their
263 scores might be much higher than those who do not have hot flashes [25].
264 Third, physical activity was self-reported, and some misclassification of the
265 level of activity was inevitable. Finally, most physical activity
266 questionnaires have been developed and validated in males, but the
267 traditional activities in females such as housework may not be correctly
268 evaluated. On the other hand, Ono, et al. reported that the BPAQ was a
269 useful monitoring tool for assessing multiple domains of physical activity
270 with acceptable reliability and validity in adult women with hip disorders
271 [26].

272

273 **Physical activity and mortality (prospective study)**

274 The present study demonstrated that physical activity reduced cancer and
275 cardiovascular deaths (**Supplemental Table 4**). Several studies revealed an
276 inverse association between physical activity and cancer death, but this
277 issue remains controversial. O'Donovan, et al. followed more than 100,000
278 adults and found that the HR of cancer death in ex-smokers was 0.66
279 (95%CI: 0.52-0.84) in those who exercised compared to those who did not,
280 and that in current smokers the HR of cancer death was 0.69 (95%CI:
281 0.51-0.94) in those who exercised compared to those who did not [27].
282 Moore, et al. suggested that the increases in leisure-time physical activity
283 were associated with lower risks of 13 types of cancers [28]. However,
284 some studies did not show a significant association between physical
285 activity and cancer mortality [29, 30]. Thus, further studies will be needed
286 to clarify the association between physical activity and site-specific
287 cancers.

288

289 **Limitations**

290 This study had several limitations. First, we were unable to detect an
291 association between physical activity and all-cause death in females,
292 possibly because female participants tended to report lower and shorter
293 amounts of physical activity than males. Second, although we carefully
294 checked their causes of death, some asymptomatic subjects with
295 cardiovascular diseases might have been included. Similarly, we were not
296 able to exclude subjects with subclinical cancers. Third, we could not
297 clarify the cause of death in 89 participants (22%), and the number of
298 deaths might be insufficient to stratify by both sex and cause of deaths.
299 Fourth, although we have adjusted for a variety of clinical characteristics,
300 the possibility of residual confounding cannot be excluded. Fifth, we have
301 no data regarding the detailed educational level. Finally, we performed the
302 BPAQ only at baseline, and thus, we cannot negate the possibility of
303 misclassification of participants' score during the follow-up.
304

305 **Conclusion**

306 Our 18-year prospective study revealed that higher levels of
307 physical activity are associated with a reduced risk of cancer and

cardiovascular death. Further, these data demonstrated that longer duration of occupational sitting time is associated with increased mortality, irrespective of physical activity.

Acknowledgments

We are grateful to the members of the Japan Medical Association of Ukiha, the elected officials and residents of Tanushimaru, and the team of cooperating physicians for their help in performing the health examinations.

Funding

This study was supported in part by the Kimura Memorial Heart Foundation (Fukuoka, Japan).

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' contributions

Sakaue A was involved with data acquisition, performed the statistical analyses and interpretation, and drafted the manuscript. Adachi H and Fukumoto Y designed and conceptualized the study, directed its implementation, were involved with data acquisition and critically revised the manuscript. Enomoto M, Fukami A, Kumagai E, Nakamura S, Nohara Y, Kono S, Nakao E, Morikawa N, Tsuru T, Hamamura H, and Yoshida N contributed to data acquisition and critically revised the manuscript. All authors gave final approval of the version to be published and agreed to its submission.

References

1. Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh CC. Physical activity, all-cause mortality, and longevity of college alumni. N Engl J Med. 1986;314: 605-613.
2. Schnohr P, O'Keefe JH, Lange P, Jensen GB, Marott JL. Impact of persistence and non-persistence in leisure time physical activity on coronary heart disease and all-cause mortality: The Copenhagen City Heart Study. Eur J Prev Cardiol. 2017, 24: 1615-1623.
3. Ejlersen H, Andersen ZJ, von Euler-Chelpin MC, Johansen PP, Schnohr P, Prescott E. Prognostic impact of physical activity prior to myocardial infarction: Case fatality and subsequent risk of heart failure and death. Eur J Prev Cardiol. 2017, 24: 1112-1119.
4. Paffenbarger RS Jr, Hyde RT, Wing AL, Steinmetz CH. A natural history of athleticism and cardiovascular health. JAMA. 1984;252: 491-495.
5. Strath SJ, Kaminsky LA, Ainsworth BE, Ekelund U, Freedson PS, Gary RA, et al. Guide to the assessment of physical activity: Clinical and research applications: a scientific statement from the American Heart

355 Association. Circulation. 2013;128: 2259-2279.
356 6. Baecke JA, Burema J, Frijters JE. A short questionnaire for the
357 measurement of habitual physical activity in epidemiological studies.
358 Am J Clin Nutr. 1982;36: 936-942.
359 7. van der Ploeg HP, Chey T, Korda RJ, Banks E, Bauman A. Sitting time
360 and all-cause mortality risk in 222 497 Australian adults. Arch Intern
361 Med. 2012;172: 494-500.
362 8. Patel AV, Bernstein L, Deka A, Feigelson HS, Campbell PT, Gapstur
363 SM, et al. Leisure time spent sitting in relation to total mortality in a
364 prospective cohort of US adults. Am J Epidemiol. 2010;172: 419-29.
365 9. van der Ploeg HP, Møller SV, Hannerz H, van der Beek AJ, Holtermann
366 A. Temporal changes in occupational sitting time in the Danish
367 workforce and associations with all-cause mortality: results from the
368 Danish work environment cohort study. Int J Behav Nutr Phys Act.
369 2015;12: 71.
370 10. Stamatakis E, Chau JY, Pedisic Z, Bauman A, Macniven R, Coombs N,
371 Hamer M. Are sitting occupations associated with increased all-cause,
372 cancer, and cardiovascular disease mortality risk? A pooled analysis of

seven British population cohorts. PLoS One. 2013;8: e73753.

11. Kikuchi H, Inoue S, Odagiri Y, Inoue M, Sawada N, Tsugane S. Occupational sitting time and risk of all-cause mortality among Japanese workers. Scand J Work Environ Health. 2015;41: 519-528.

12. Adachi H, Hirai Y, Sasaki S, Enomoto M, Fukami A, Kumagai E, et al. Trends in dietary intakes and serum cholesterol levels over 50 years in Tanushimaru in Japanese men. Food Nutr Sci. 2011;2: 476-481.

13. Hino A, Adachi H, Toyomasu K, Yoshida N, Enomoto M, Hiratsuka A, et al. Very long chain N-3 fatty acids intake and carotid atherosclerosis: an epidemiological study evaluated by ultrasonography. Atherosclerosis. 2004;176: 145-149.

14. Oyeyemi AL, Moss SJ, Monyeki MA, Kruger HS. Measurement of physical activity in urban and rural South African adults: a comparison of two self-report methods. BMC Public Health. 2016;16 :1004.

15. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28: 412-419.

391 16. Ura N, Saitoh S, Shimamoto K. Clinical diagnosis of metabolic
392 syndrome 1: metabolic syndrome and insulin resistance. Intern Med.
393 2007;46: 1283-1284.
394 17. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al.
395 Collaborators developing the Japanese equation for estimated GFR.
396 Revised equations for estimated GFR from serum creatinine in Japan.
397 Am J Kidney Dis. 2009;53: 982-992.
398 18. Levy WC, Cerqueira MD, Harp GD, Johannessen KA, Abrass IB,
399 Schwarts RS, Stratton JR. Effect of endurance exercise training on heart
400 rate cariability at rest in healthy young and older men. Am J Cardiol.
401 1998;82: 1236-1241.
402 19. Holloszy JO. Exercise-induced increase in muscle insulin sensitivity. J
403 Appl Physiol. 2005;99: 338-343.
404 20. Hakim AA, Petrovitch H, Burchfiel CM, Ross GW, Rodriguez BL,
405 White LR, et al. Effects of walking on mortality among nonsmoking
406 retired men. N Engl J Med. 1998;338: 94-99.
407 21. Weuve J, Kang JH, Manson JE, Breteler MM, Ware JH, Grodstein F.
408 Physical activity, including walking, and cognitive function in older

409 women. JAMA. 2004;292: 1454-1461.
410 22. Philippaerts RM, Westerterp KR, Lefevre J. Doubly labelled water
411 validation of three physical activity questionnaires. Int J Sports Med.
412 1999;20: 284-289.
413 23. Sadeghisani M, Dehghan Manshadi F, Azimi H, Montazeri A. Validity
414 and reliability of the Persian version of Baecke habitual physical
415 activity questionnaire in healthy subjects. Asian J Sports Med. 2016;7:
416 e31778.
417 24. Abdel-Mageed SM, Mohamed EI. Total body capacitance for estimating
418 human basal metabolic rate in an Egyptian population. Int J Biomed Sci.
419 2016;12: 42-47.
420 25. Deecher DC, Dorries K. Understanding the pathophysiology of
421 vasomotor symptoms (hot flushes and night sweats) that occur in
422 perimenopause, menopause, and postmenopause life stages. Arch
423 Womens Ment Health. 2007;10: 247-57.
424 26. Ono R, Hirata S, Yamada M, Nishiyama T, Kurosaka M, Tamura Y.
425 Reliability and validity of the Baecke physical activity questionnaire in
426 adult women with hip disorders. BMC Musculoskelet Disord. 2007;8:

427 61.
428 27. O'Donovan G, Hamer M, Stamatakis E. Relationships between exercise,
429 smoking habit and mortality in more than 100,000 adults. Int. J. Cancer.
430 2017;140: 1819-1827.
431 28. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara
432 CM, et al. Association of leisure-time physical activity with risk of 26
433 types of cancer in 1.44 million adults. JAMA Intern Med. 2016;176:
434 816-825.
435 29. Kubota Y, Evenson KR, Maclehose RF, Roetker NS, Joshu CE, Folsom
436 AR. Physical activity and lifetime risk of cardiovascular disease and
437 cancer. Med Sci Sports Exerc. 2017;49: 1599-1605.
438 30. Mertens AJ, Sweeney C, Shahar E, Rosamond WD, Folsom AR.
439 Physical activity and breast cancer incidence in middle-aged women: a
440 prospective cohort study. Breast Cancer Res Treat. 2006;97: 209-21.

Supplemental Figure legends

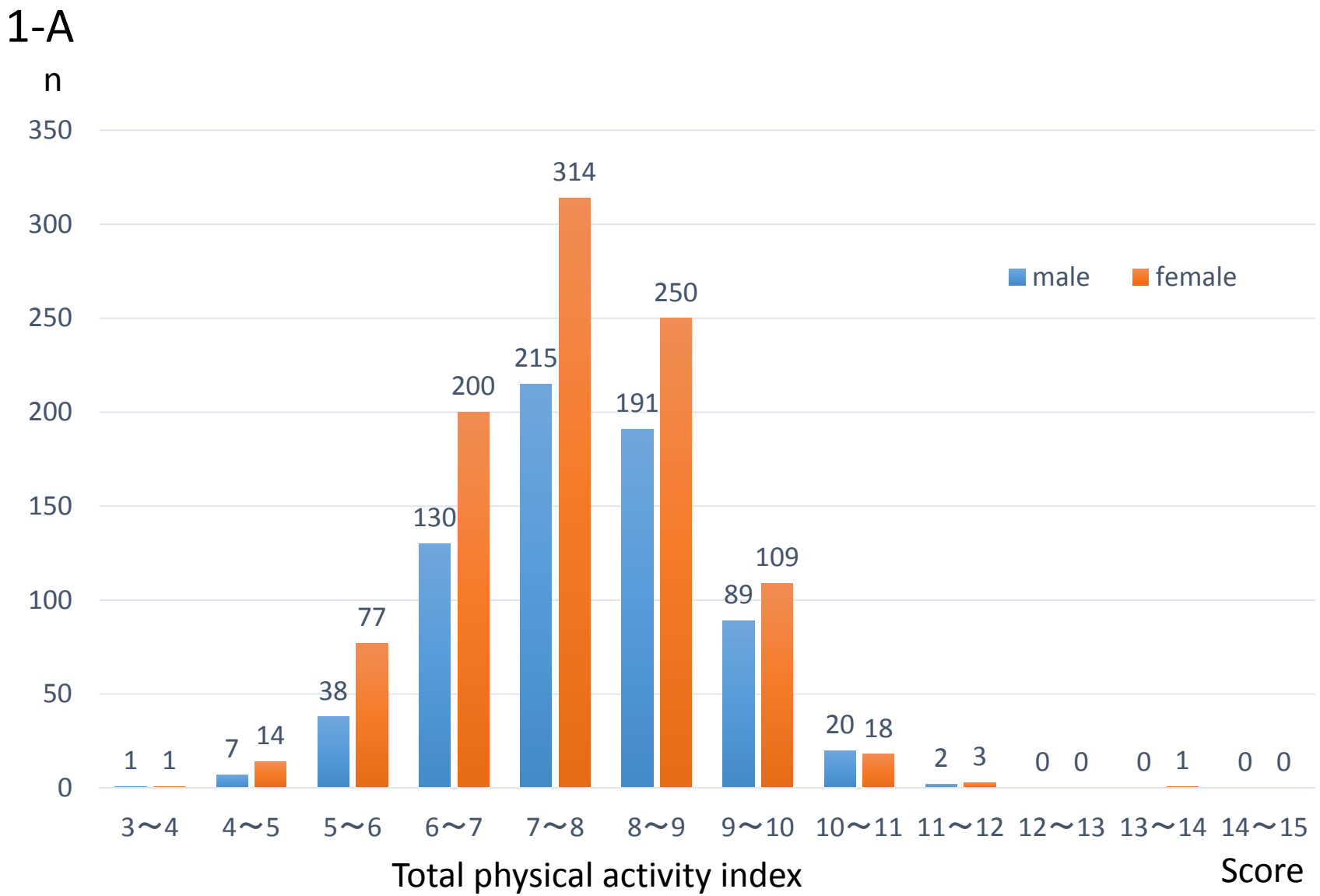
Supplemental Figure 1:

Score distribution

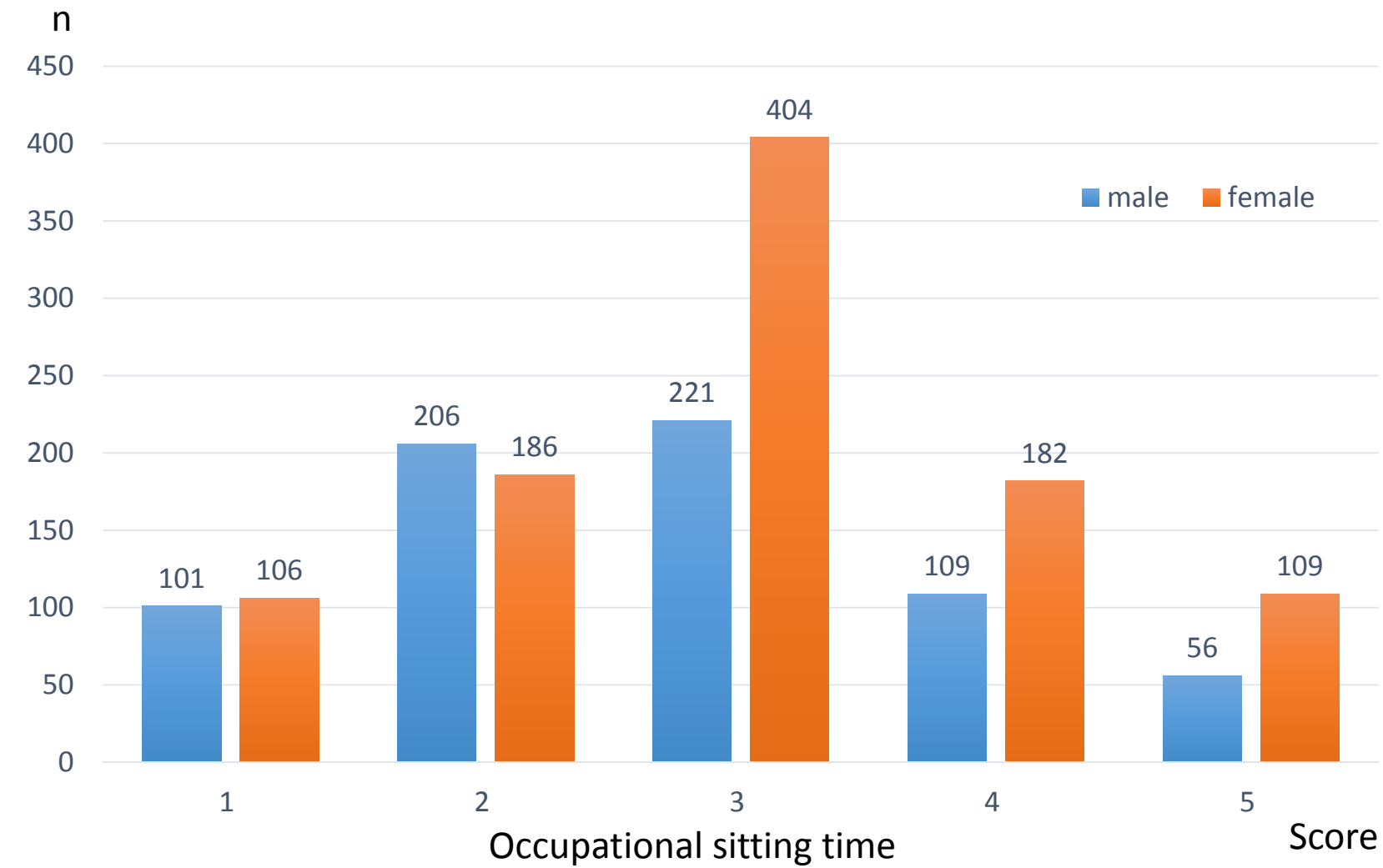
Supplemental Figure 2:

Survival function estimates

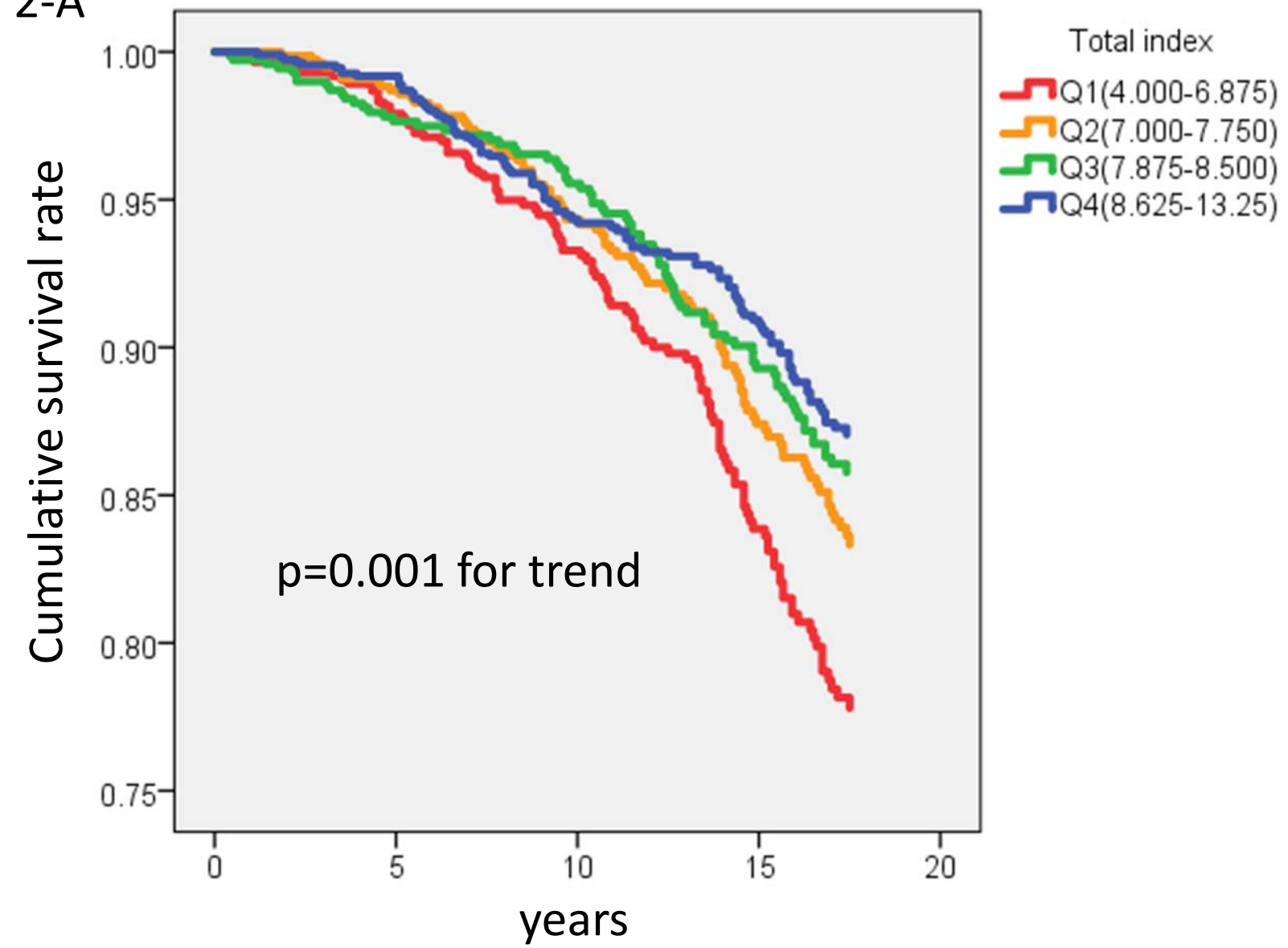
1-A


n
350
300
250
200
150
100
50
0
male
female
1 1
7 14
38 77
130 200
215 314
191 250
89 109
20 18
2 3
0 0
0 1
0 0
3～4
4～5
5～6
6～7
7～8
8～9
9～10
10～11
11～12
12～13
13～14
14～15
Total physical activity index
Score

1-B


n
450
400
350
300
250
200
150
100
50
0
male
female
101
106
206
186
221
404
109
182
56
109
1
2
3
4
5
Occupational sitting time
Score

2-A


Cumulative survival rate
1.00
0.95
0.90
0.85
0.80
0.75
0
5
10
15
20
years
p=0.001 for trend
Total index
Q1(4.000-6.875)
Q2(7.000-7.750)
Q3(7.875-8.500)
Q4(8.625-13.25)

2-B

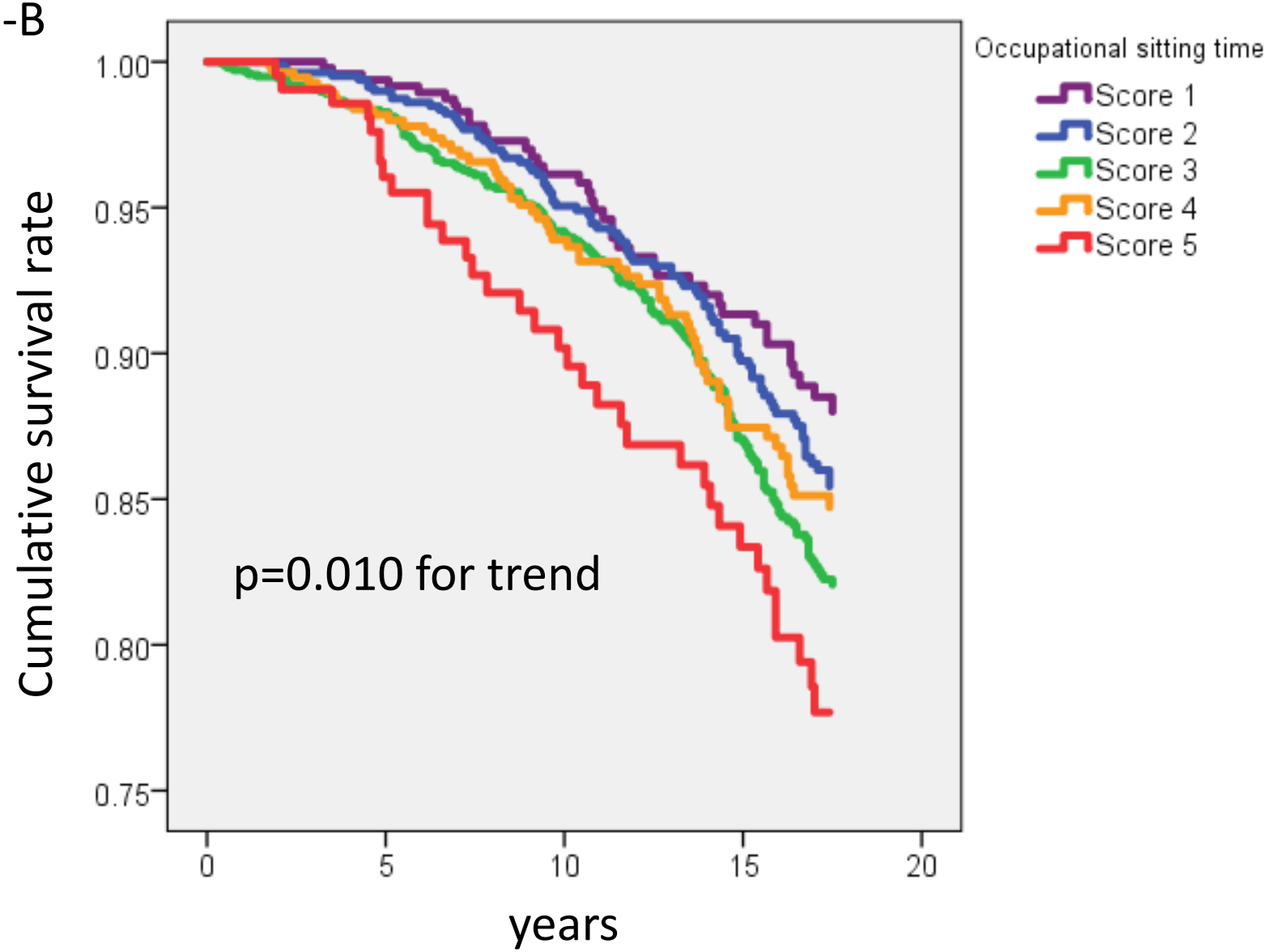

Cumulative survival rate
1.00
0.95
0.90
0.85
0.80
0.75
0
5
10
15
20
years
p=0.010 for trend
Occupational sitting time
Score 1
Score 2
Score 3
Score 4
Score 5

Table 1. Characteristics of the subjects at baseline

Variables	Male (n=693)	Female (n=987)	Total (n=1,680)
Age (year)	62.4±10.5**	61.0±10.5	61.6±10.6
40-49 years	n=97	n=171	n=268
50-59 years	n=171	n=255	n=426
60-69 years	n=235	n=327	n=562
≥70 years	n=190	n=234	n=424
Body mass index (kg/m^2)	23.3±3.0	23.1±3.2	23.2±3.1
Waist circumference (cm)	81.8±8.3***	73.7±8.4	77.1±9.3
Systolic blood pressure (mmHg)	135.1±20.5***	131.1±20.8	132.7±20.8
Diastolic blood pressure (mmHg)	81.2±12.0***	77.2±11.3	78.9±11.8
Heart rate (bpm/min)	61.2±9.6***	65.4±9.6	63.7±9.8
Estimated GFR (ml/min/1.73m^2)	63.7±11.9***	53.9±12.1	57.9±12.9
Uric acid (μmol/L)	345.0±83.3***	255.8±59.5	291.5±83.3
Total cholesterol (mmol/L)	4.9±0.9***	5.4±0.9	5.2±0.9
HDL-cholesterol (mmol/L)	1.4±0.4***	1.5±0.4	1.5±0.4
LDL-cholesterol (mmol/L)	2.9±0.8***	3.3±0.8	3.2±0.8
Triglycerides† (mmol/L) (range)	1.2(0.3-13.5)**	1.1(0.3-5.8)	1.1(0.3-13.5)
HbA_{1c} (%) (NGSP)	5.6±0.8	5.6±0.7	5.6±0.8
Fasting plasma glucose (mmol/L)	5.6±1.3***	5.3±0.9	5.4±1.1
HOMA-index†	1.0（0.2-23.6）**	1.2（0.2-24.9）	1.1（0.2-24.9）
Total index (①+②+③) (max score 15)	7.87±1.21**	7.71±1.23	7.78±1.22
① Work index (max score 5)	3.43±0.70***	3.16±0.68	3.27±0.70
② Sport index (max score 5)	2.01±0.57	1.98±0.54	2.00±0.56
③ Leisure-time index (max score 5)	2.42±0.71***	2.57±0.74	2.51±0.73
Occupational sitting time (max score 5)	2.73±1.14***	3.00±1.12	2.89±1.13
Smoking (%, yes)	40.0***	2.0	17.7
Alcohol intake (%, yes)	50.7***	3.4	22.9
Medication for hypertension (%, yes)	18.9	18.5	18.7
Medication for hyperlipidemia (%, yes)	2.6***	6.6	5.0
Medication for diabetes (%, yes)	3.5	2.4	2.9

Data are mean ± standard deviation, geometric mean, range, or percent.

Total index = Total physical activity index (①+②+③)

†: These variables were represented in the original scale after analysis using log (natural) transformed values. *: $p<0.05$, **: $p<0.01$, ***: $p<0.001$ (males vs females)

Table 2. Univariate regression analysis for correlates of total index at baseline

Variables	β	SE	*p*
Age	0.006	0.003	0.037
Sex (male=0, female=1)	-0.157	0.061	0.010
Body mass index (kg/m^2)	0.006	0.010	0.537
Waist circumference (cm)	0.003	0.003	0.293
Systolic blood pressure (mmHg)	-0.002	0.001	0.282
Diastolic blood pressure (mmHg)	-0.002	0.003	0.351
Heart rate (bpm/min)	-0.015	0.003	<0.0001
Estimated GFR (ml/min/1.73m^2)	0.003	0.002	0.235
Uric acid (μmol/L)	0.028	0.022	0.201
Total cholesterol (mmol/L)	-0.001	0.001	0.291
HDL-cholesterol (mmol/L)	0.002	0.002	0.258
LDL-cholesterol (mmol/L)	-0.001	0.001	0.591
Triglycerides†(mmol/L)	-0.073	0.062	0.239
HbA_{1c} (%)	0.022	0.036	0.537
Fasting plasma glucose (mmol/L)	0.001	0.002	0.554
HOMA-index†	-0.134	0.047	0.004
Occupational sitting time	-0.256	0.026	<0.0001
Smoking (no=0, yes=1)	-0.033	0.078	0.677
Alcohol intake (no=0, yes=1)	0.173	0.071	0.015
Medication for hypertension	-0.006	0.077	0.941
Medication for hyperlipidemia	0.085	0.138	0.537
Medication for diabetes	0.018	0.179	0.919

Total index = Total physical activity index (①+②+③)

†: These variables were represented in the original scale after analysis using log (natural) transformed values.

Table 3. Univariate regression analysis for correlates of occupational sitting time at baseline

Variables	β	SE	*p*
Age	-0.006	0.003	0.015
Sex (male=0, female=1)	0.272	0.056	<0.0001
Body mass index (kg/m^2)	-0.00004	0.009	0.997
Waist circumference (cm)	-0.005	0.003	0.094
Systolic blood pressure (mmHg)	-0.001	0.001	0.441
Diastolic blood pressure (mmHg)	-0.003	0.002	0.215
Heart rate (bpm/min)	0.011	0.003	<0.0001
Estimated GFR (ml/min/1.73m^2)	-0.004	0.002	0.061
Uric acid (μmol/L)	-0.054	0.020	0.007
Total cholesterol (mmol/L)	0.001	0.001	0.156
HDL-cholesterol (mmol/L)	0.0004	0.002	0.856
LDL-cholesterol (mmol/L)	0.001	0.001	0.496
Triglycerides†(mmol/L)	0.002	0.057	0.980
HbA_{1c} (%)	0.022	0.036	0.537
Fasting plasma glucose (mmol/L)	0.001	0.002	0.554
HOMA-index†	0.096	0.043	0.026
Total index (①+②+③)	-0.219	0.022	<0.0001
① Work index	-0.721	0.035	<0.0001
② Sport index	-0.015	0.050	0.765
③ Leisure-time index	0.061	0.038	0.110
Smoking (no=0, yes=1)	-0.034	0.072	0.639
Alcohol intake (no=0, yes=1)	-0.203	0.066	0.002
Medication for hypertension	-0.087	0.071	0.219
Medication for hyperlipidemia	0.143	0.128	0.264
Medication for diabetes	-0.122	0.166	0.461

Total index = Total physical activity index (①+②+③)

†: These variables were represented in the original scale after analysis using log (natural) transformed values.

Table 4. Multivariate Cox's proportional hazards regression analysis of all-cause death

Models	Variables	β	SE	HR (95%CI)	*p*
Model 1	Total index (①+②+③)	-0.167	0.042	0.85 (0.78-0.92)	<0.0001
	① Work index	-0.189	0.081	0.83 (0.71-0.97)	0.018
	② Sport index	-0.196	0.092	0.82 (0.68-0.99)	0.033
	③ Leisure-time index	-0.214	0.071	0.81 (0.70-0.93)	0.003
Model 2	Total index (①+②+③)	-0.151	0.042	0.86 (0.79-0.94)	0.0003
	① Work index	-0.178	0.081	0.84 (0.71-0.98)	0.028
	② Sport index	-0.174	0.093	0.84 (0.70-1.01)	0.060
	③ Leisure-time index	-0.193	0.072	0.83 (0.71-0.95)	0.008
Model 3	Total index (①+②+③)	-0.141	0.043	0.87 (0.80-0.95)	0.001
	① Work index	-0.151	0.083	0.86 (0.73-1.02)	0.070
	② Sport index	-0.135	0.096	0.87 (0.72-1.06)	0.160
	③ Leisure-time index	-0.213	0.076	0.81 (0.69-0.94)	0.005

Total index = Total physical activity index (①+②+③)

Model 1: adjusted for age and sex.

Model 2: adjusted for model 1 + body mass index, total cholesterol, and systolic blood pressure.

Model 3: adjusted for Model 2 + fasting plasma glucose, and smoking.

Table 5. Multivariate Cox's proportional hazards regression analysis of all-cause death

Models	Variables	β	SE	HR (95%CI)	*p*
Model 1	Occupational sitting time	0.145	0.048	1.16 (1.05-1.27)	0.002
Model 2	Occupational sitting time	0.133	0.048	1.14 (1.04-1.26)	0.006
Model 3	Occupational sitting time	0.092	0.050	1.10 (0.99-1.21)	0.068
Model 4	Occupational sitting time	0.102	0.049	1.11 (1.01-1.22)	0.039

Model 1: adjusted for age and sex.

Model 2: adjusted for model 1 + body mass index, total cholesterol, and systolic blood pressure.

Model 3: adjusted for model 2 + fasting plasma glucose, and smoking

Model 4: adjusted for model 2 + total physical activity index.

Table 6. Multivariate Cox's proportional hazards regression analysis of all-cause death adjusted for age stratified by sex

Males	β	SE	HR (95%CI)	*p*
Total index (①+②+③)	-0.251	0.054	0.78 (0.70-0.87)	<0.0001
① Work index	-0.294	0.102	0.75 (0.61-0.91)	0.004
② Sport index	-0.365	0.123	0.69 (0.54-0.89)	0.003
③ Leisure-time index	-0.289	0.096	0.75 (0.62-0.91)	0.003
Occupational sitting time	0.248	0.064	1.28 (1.13-1.46)	<0.0001
Females	β	SE	HR (95%CI)	*p*
Total index (①+②+③)	-0.048	0.065	0.95 (0.84-1.08)	0.456
① Work index	-0.038	0.127	0.96 (0.75-1.24)	0.766
② Sport index	0.033	0.139	1.03 (0.78-1.36)	0.810
③ Leisure-time index	-0.127	0.108	0.88 (0.71-1.09)	0.238
Occupational sitting time	0.017	0.071	1.02 (0.88-1.17)	0.806

Total index = Total physical activity index (①+②+③)

Supplemental table 1. Multivariate linear regression analysis for correlates of total index adjusted for age and sex at baseline

Variables	β	SE	*p*
Body mass index (kg/m^2)	0.006	0.010	0.523
Waist circumference (cm)	-0.0008	0.004	0.821
Systolic blood pressure (mmHg)	-0.003	0.002	0.042
Diastolic blood pressure (mmHg)	-0.004	0.003	0.125
Heart rate (bpm/min)	-0.014	0.003	<0.0001
Estimated GFR (ml/min/1.73m^2)	0.002	0.003	0.466
Uric acid (μmol/L)	-0.008	0.026	0.752
Total cholesterol (mmol/L)	-0.0004	0.001	0.687
HDL-cholesterol (mmol/L)	0.004	0.002	0.077
LDL-cholesterol (mmol/L)	-0.00006	0.001	0.950
Triglycerides†(mmol/L)	-0.094	0.062	0.131
HbA_{1c} (%)	-0.002	0.039	0.961
Fasting plasma glucose (mmol/L)	-0.0002	0.002	0.924
HOMA-index†	-0.129	0.047	0.006
Occupational sitting time	-0.250	0.026	<0.0001
Smoking (no=0, yes=1)	-0.151	0.091	0.095
Alcohol intake (no=0, yes=1)	0.115	0.085	0.177
Medication for hypertension	-0.047	0.079	0.556
Medication for hyperlipidemia	0.101	0.139	0.464
Medication for diabetes	-0.028	0.180	0.875

Total index = Total physical activity index (①+②+③)

†: These variables were represented in the original scale after analysis using log (natural) transformed values.

Supplemental table 2. Multivariate linear regression analysis for correlates of occupational sitting .time adjusted for age and sex at baseline

Variables	β	SE	*p*
Body mass index (kg/m^2)	0.001	0.009	0.952
Waist circumference (cm)	0.002	0.003	0.521
Systolic blood pressure (mmHg)	0.001	0.001	0.717
Diastolic blood pressure (mmHg)	-0.001	0.002	0.778
Heart rate (bpm/min)	0.009	0.003	0.001
Estimated GFR (ml/min/1.73m^2)	0.001	0.002	0.547
Uric acid (μmol/L)	0.001	0.024	0.971
Total cholesterol (mmol/L)	0.0002	0.001	0.837
HDL-cholesterol (mmol/L)	-0.002	0.002	0.380
LDL-cholesterol (mmol/L)	-0.0004	0.001	0.657
Triglycerides†(mmol/L)	0.039	0.057	0.487
HbA_{1c} (%)	0.031	0.036	0.398
Fasting plasma glucose (mmol/L)	0.002	0.002	0.166
HOMA-index†	0.083	0.043	0.053
Total index (①+②+③)	-0.211	0.022	<0.0001
① Work index	-0.729	0.036	<0.0001
② Sport index	-0.002	0.050	0.973
③ Leisure-time index	0.054	0.038	0.155
Smoking (no=0, yes=1)	0.159	0.083	0.057
Alcohol intake (no=0, yes=1)	-0.050	0.079	0.528
Medication for hypertension	-0.051	0.073	0.484
Medication for hyperlipidemia	0.105	0.127	0.410
Medication for diabetes	-0.066	0.165	0.690

Total index = Total physical activity index (①+②+③)

†: These variables were represented in the original scale after analysis using log (natural) transformed values.

Supplemental table 3. Multivariate Cox's proportional hazards regression analysis of all-cause death adjusted for age and sex

Variables	β	SE	HR (95%CI)	*p*
Body mass index (kg/m^2)	-0.024	0.018	0.98 (0.94-1.01)	0.167
Waist circumference (cm)	-0.004	0.006	1.00 (0.98-1.01)	0.476
Systolic blood pressure (mmHg)	0.004	0.003	1.00 (1.00-1.01)	0.083
Diastolic blood pressure (mmHg)	0.002	0.005	1.00 (0.99-1.01)	0.593
Heart rate (bpm/min)	0.009	0.005	1.01 (1.00-1.02)	0.063
Estimated GFR (ml/min/1.73m^2)	-0.003	0.004	1.00 (0.99-1.01)	0.552
Uric acid (μmol/L)	-0.025	0.041	0.98 (0.90-1.06)	0.549
Total cholesterol (mmol/L)	-0.008	0.002	0.99 (0.98-0.99)	<0.0001
HDL-cholesterol (mmol/L)	-0.004	0.004	1.00 (0.99-1.00)	0.308
LDL-cholesterol (mmol/L)	-0.008	0.002	0.99 (0.98-0.99)	<0.0001
Triglycerides†(mmol/L)	-0.139	0.118	0.87 (0.69-1.10)	0.237
HbA_{1c} (%)	0.175	0.062	1.19 (1.05-1.35)	0.005
Fasting plasma glucose (mmol/L)	0.006	0.002	1.00 (1.01-1.02)	0.003
HOMA-index†	0.104	0.077	1.11 (0.95-1.29)	0.180
Total index (①+②+③)	-0.167	0.042	0.85 (0.78-0.92)	<0.0001
① Work index	-0.189	0.081	0.83 (0.71-0.97)	0.018
② Sport index	-0.196	0.092	0.82 (0.68-0.99)	0.033
③ Leisure-time index	-0.214	0.071	0.81 (0.70-0.93)	0.003
Occupational sitting time	0.145	0.048	1.16 (1.05-1.27)	0.002
Smoking (no=0, yes=1)	0.813	0.140	2.25 (1.71-2.98)	<0.0001
Alcohol intake (no=0, yes=1)	-0.018	0.135	0.98 (0.75-1.29)	0.892
Medication for hypertension	0.099	0.117	1.10 (0.87-1.39)	0.396
Medication for hyperlipidemia	-0.055	0.243	0.95 (0.58-1.54)	0.819
Medication for diabetes	0.375	0.256	1.46 (0.87-2.43)	0.142

Total index = Total physical activity index (①+②+③)

†: These variables were represented in the original scale after analysis using log (natural) transformed values.

Supplemental table 4. Multivariate Cox's proportional hazards regression analysis of the cause of death adjusted for age and sex

Cause of deaths	Variables	β	SE	HR (95%CI)	*p*
Cancer death	Total index (①+②+③)	-0.193	0.075	0.82(0.71-0.96)	<0.0001
	① Work index	-0.091	0.143	0.91 (0.69-1.22)	0.525
	② Sport index	-0.158	0.167	0.85 (0.61-1.19)	0.346
	③ Leisure-time index	-0.394	0.131	0.67 (0.52-0.88)	0.003
	Occupational sitting time	0.092	0.086	1.10 (0.92-1.30)	0.286
Cardiovascular death	Total index (①+②+③)	-0.322	0.135	0.72 (0.55-0.95)	0.017
	① Work index	-0.583	0.253	0.56 (0.34-0.93)	0.021
	② Sport index	-0.461	0.314	0.63 (0.34-1.18)	0.143
	③ Leisure-time index	-0.209	0.234	0.81 (0.92-1.30)	0.372
	Occupational sitting time	0.330	0.159	1.39 (1.01-1.91)	0.038

Total index = Total physical activity index (①+②+③)