Martinez-Gomez, D., Cabanas-Sanchez, V., Yu, T., Rodriguez-Artalejo, F., Ding, D., Lee, I-M., Ekelund, U. (2022). Long-term leisure-time physical activity and risk of all-cause and cardiovascular mortality: Dose-response associations in a prospective cohort study of 210 327 Taiwanese adults. *British Journal of Sports Medicine, 56*, s. 919-926. http://dx.doi.org/10.1136/bjsports-2021-104961

Long-term leisure-time physical activity and risk of all-cause and cardiovascular mortality: dose-response associations in a prospective cohort study of 210,327 Taiwanese adults

Martinez-Gomez et al. Repeated measures of physical activity and mortality

David Martinez-Gomez, PhD[1,2], Veronica Cabanas-Sanchez, PhD[2], Tsung Yu, PhD[3], Fernando Rodriguez-Artalejo MD, PhD[1,2], Ding Ding, PhD[4+], I-Min Lee, MBBS, ScD[5,6+], Ulf Ekelund, PhD[7,8+]

[1]Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid, IdiPaz, and CIBERESP (CIBER of Epidemiology and Public Health), Madrid, Spain. [2]IMDEA-Food Institute, CEI UAM+CSIC, Madrid, Spain. [3]Department of Public Health, College of Medicine, National Cheng Kung University, Taiwan.[4]Prevention Research Collaboration, Sydney School of Public Health, The University of Sydney, Camperdown New South Wales, Australia. [5]Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [6]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA. [7]Department of Sports Medicine, Norwegian School of Sports Sciences, Oslo, Norway. [8]Department of Chronic Diseases, Norwegian Institute of Public Health, Oslo Norway. [+]Joint senior authors.

Correspondence: David Martinez Gomez, PhD. Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autonoma de Madrid, 28029, Madrid, Spain. E-mail: d.martinez@uam.es; Twitter: @dmg_pa

Word count: 3672

What is already known on this topic?

- Evidence on the association between physical activity and mortality is mainly limited by relying on a single measure of physical activity that assumes the stability of physical activity during follow-up.

What this study adds?

- We observed an inverse, nonlinear dose-response association between long-term physical activity obtained from repeated measures from at least two medical examinations for up to 20 years (median, IQR: 4.8 years, 2.3-9.0) and all-cause and cardiovascular mortality.
- Achieving the recommended amount or even less than recommended amount of physical activity over a long term lowered the risk of all-cause and cardiovascular mortality, whereas doing more activity beyond the recommendations was associated with a slight further reduction in all-cause mortality risk.
- The association between physical activity and risk of death was greater in magnitude when using repeated measures of physical activity compared with the associations between a single baseline measure of physical activity and risk of death.

How this might influence research, policy, or practice

- These results provide support and higher certainty of evidence for most of the recommendations and good practice statements included in the recently updated WHO guidelines and to inform future guidelines.

ABSTRACT

Objectives: Available evidence on the association between physical activity (PA) and mortality is limited by relying on a single measure of PA that assumes the stability of PA during follow-up. This study aimed to investigate the dose-response associations of long-term PA obtained from repeated measures with all-cause and cardiovascular disease (CVD) mortality outcomes in Taiwanese adults.

Methods: We included 210,327 participants, aged ≥18 years, with self-reported leisure-time PA at least in two medical examinations (867,968 data points) for up to 20 years (median, IQR: 4.8 years, 2.3-9.0). Dose-response relationships were modeled with restricted cubic spline functions and Cox regressions hazard ratios (95% confidence intervals) adjusted for socioeconomic characteristics, lifestyle behaviors, and chronic conditions.

Results: During up to 23 years of follow-up (3,655,734 person-years), 10,539 participants died, of which 1,919 from CVD. We observed an inverse, nonlinear dose-response association between long-term PA and all-cause and CVD mortality. Compared with the referent (0 metabolic equivalent of task [MET]-h/week), insufficient (0.01-7.49 MET-h/week), recommended (7.50-15.00 MET-h/week), and additional (>15 MET-h/week) amounts of PA had a lower mortality risk of 0.74 (0.69-0.80), 0.64 (0.60-0.70), and 0.59 (0.54-0.64) for all-cause mortality and 0.68 (0.60-0.84), 0.56 (0.47-0.67), and 0.56 (0.47-0.68) for CVD mortality, respectively. When using only baseline measures of PA, the corresponding mortality risk was 0.88 (0.84-0.93), 0.83 (0.78-0.88), and 0.78 (0.73-0.83) for all-cause, and 0.91 (0.81-1.02), 0.78 (0.68-0.89), and 0.80 (0.70-0.92) for CVD mortality.

Conclusion: Long-term PA, and even in less than recommended amounts, was associated with lower risks of all-cause and CVD mortality. The magnitude of risk reductions was larger when modelling repeated measures of PA compared with one measure of PA at baseline.

INTRODUCTION

The 2020 World Health Organization (WHO) guidelines on PA and sedentary behavior have provided new evidence-based public health recommendations on the amounts of PA required for health benefits (1-3). These recommendations are based on the most up-to-date evidence linking PA with health outcomes, such as mortality, cardiovascular disease (CVD), diabetes and some cancers. However, the certainty of evidence supporting these recommendations was rated as moderate by WHO Guidelines Review Committee because there is still a possibility that the ‘true effect’ (i.e., stronger) is substantially different from the estimated effect, and it has been recommended that further research on the precise dose-response associations between PA and health outcomes is needed (1,2,4).

Numerous studies have observed an association between higher levels of PA with lower risk of mortality (1-10). However, much of the available evidence is based on a single baseline measure of PA in middle-aged and older populations assuming stability of PA during the follow-up. Considering that PA changes across life stages (11) and that changes in PA affect survival (12-15), repeated measures of PA in younger populations taking into account changes over time may provide more robust effect estimates as well as more precise dose-response association between PA and risk of death (16,17). Also, there is a paucity of data on the association between PA taken into account its changes over time with risk of death in non-Caucasian populations, possibly limiting the generalizability of the current evidence.

Hence, the purpose of this study was to investigate the dose-response associations of long-term leisure-time PA obtained from up to 20 repeated measures with all-cause and CVD mortality in a cohort of more than 210,000 Taiwanese adults aged 18 years and older.

METHODS

Study design and participants

This study analyzed data from the Taiwan Mei Jau (MJ) cohort (18). Details of the MJ cohort and data collection procedures have been reported elsewhere (18,19). In brief, this is an open and dynamic cohort established by the MJ Health Management Institution, a private fee-for-service company, which offers comprehensive health medical screenings in Taiwan. The cost of each health examination was covered by the participants themselves or their employer's health insurance. Standardized protocols included physical examinations, laboratory tests and self-administered questionnaires applied to all individuals, following the ISO 9001 for quality management. The cohort was established as part of the health screening data management process, handled by the MJ Health Research Foundation (www.mjhrf.org), and has enrolled more than 600,000 participants all over Taiwan since 1994. Although study participants are mostly young and middle-aged adults, some of their offspring, parents or relatives in other age strata have also been included in the cohort. In addition, all participants were encouraged to repeat the medical examinations every year or when they considered it necessary, and around one in two participants had additional medical examinations.

For the present analysis, we included 210,327 apparently healthy men and women (figure S1), aged 18 years and above, with at least two data points on leisure-time PA between 1997 and 2016. All participants were free of cancer or CVD at the first medical examination, with a follow-up of at least 1 year between the last medical examination and the time when their vital status ascertained. Participants in the cohort signed a consent form authorizing MJ Health Management Institution to manage the data generated from their medical examinations. The present study was approved by the institutional review boards of the MJ Health Management Institution, the National Health Research Institutes and at National Cheng Kung University.

Leisure-time physical activity assessment

The time spent in leisure-time PA was assessed using the MJ PA Questionnaire in 1997 and subsequent medical examinations (11,20). Participants were asked to report the intensity, frequency, and duration of leisure-time PA during the last month, with several examples of activity types given in four intensity categories: light-moderate (e.g., slow walking), moderate (e.g., brisk walking), low-vigorous (e.g., jogging), or high-vigorous (e.g., running); a metabolic equivalent (MET; 3.5 ml/kg/min) value of 2.5, 4.5, 6.5, and 8.5 was assigned to each intensity, respectively. To calculate the total volume of PA (MET-h/week), the MET value for the reported intensity was multiplied by the frequency and duration. For participants who indicated activities in more than one intensity category, an averaged MET value was assigned. Since the PA questionnaire has been slightly modified over the years (table S1), all data were harmonized before pooling. To best represent long-term leisure-time PA, we calculated the cumulative average (i.e., average of repeated measures) with all available assessments (table S2), which reduces random measurement error and minimize within-person variations over time (17). Long-term leisure-time PA obtained from the cumulative average was truncated at 40.00 MET-h/week (99^{th} percentile in the first examination) to minimize the influence of outliers. Study participants were also categorized according to WHO PA guidelines as follows (1,2); 1) 'none' (0 MET-h/week), 2) 'insufficient' (0.01-7.49 MET-h/week), 3) 'recommended' (7.50-15.00 MET-h/week, equivalent to 150-300 min/week in moderate-intensity or 75-150 min/week in vigorous intensity), and 4) 'additional' (>15.00 MET-h/week, equivalent to >300 min/week in moderate-intensity or >150 min/week in vigorous-intensity).

Covariates

Information on covariates were assessed in each medical examination. Participants reported their age, educational attainment, and marital status during the interview. Smoking, alcohol intake and occupational PA based on standard questions was also self-reported. An optimal regular meal pattern (21) was defined as an affirmative answer to the following question: "Do you eat on time and in regular amounts?"; this question was shown to predict lower risk of biological cardiometabolic risk factors such as obesity, hypercholesterolemia, atherogenic dyslipidemia, metabolic syndrome, and type 2 diabetes (20). During the clinical examination, body weight and height were measured without shoes and wearing light indoor clothing, and body mass index was calculated as weight in kg divided by squared height in m. Hypertension was identified from the medical history or as systolic/diastolic blood pressure ≥140/≥90 mm Hg (22). Dyslipidemia was defined according to the National Cholesterol Education Program Adult Treatment Panel (ATP) III criteria as total cholesterol ≥240 mg/dl, low-density lipoprotein cholesterol ≥160 mg/dl, high-density lipoprotein cholesterol <40 mg/dl, or use of lipid-lowering drugs (24). Diabetes was defined as diagnosed diabetes or fasting blood glucose ≥126 mg/dl. A standard 12-lead 5-min resting electrocardiogram test was performed to detect abnormal heart rate (e.g., arrhythmia).

Outcomes

Deaths were identified through follow-up linkage to Taiwan's National Death File registry until May 31, 2020. We used the International Classification of Diseases, 9th Revision (ICD-9), and International Classification of Diseases, 10th Revision (ICD-10) codes to classify the underlying causes of death. The primary health outcomes for the present study were all-cause and CVD mortality (ICD-9, 390-405, 410-414, and 420-440; ICD-10, I01-I02, I05-I15, I20-I25, I27, and I30-I70), since these are the most critical mortality outcomes prioritized by the WHO PA guidelines advisory group (1,4).

Statistical analysis

We calculated the follow-up person years from the date of the first examination and the date of death or the end of follow-up (May 31, 2020), whichever came first. A time-varying covariate Cox proportional hazards regression model, with age as the underlying time scale, were used to calculate adjusted hazard ratios (HRs) and 95% CIs for long-term leisure-time PA and each study outcome. To examine the dose-response relationship between long-term leisure-time PA and all-cause and CVD mortality, we modelled curves from restricted cubic spline Cox regressions, with 4 knots (5^{th}, 35^{th}, 65^{th}, 95^{th}) distributed across the range of MET-h/week values. HRs and 95% CIs for all-cause and CVD mortality associated with long-term leisure-time PA categories (with none as the reference category) were calculated for the total sample and by subgroups according to age, gender, obesity (≥25 kg/m^2 for this Asian population) and cardiometabolic chronic conditions (hypertension, dyslipidemia, and diabetes); the likelihood ratio test was used to compare the model with and without the interaction term. To examine the extent to which the dose-response associations differed using the baseline leisure-time PA measurement compared with the repeated measures, long-term modelling, we also calculated the HRs and 95%CIs of leisure-time PA at baseline with all-cause and CVD mortality.

All analyses were adjusted for the following covariates at baseline and updated at each medical examination; sex (male, female), educational attainment (middle school or below, high school, junior school, college or above), marital status (married or living with partner, single or widowed), smoking (never, former, current), alcohol consumption (never, former, current), regular meal patterns (suboptimal, optimal), occupational PA (sedentary, sedentary with occasional standing/walking, standing or walking, heavy labor), body mass index (<18.5, 18.5-22.9, 23.0-24.9, 25.0-26.9, 27.0-29.9, >30.0 kg/m^2), cancer (yes, no), cardiovascular disease (yes, no), hypertension (yes, no), dyslipidemia (yes, no), diabetes (yes, no), electrocardiogram (abnormal, normal). If necessary, we included an indicator for missing data in the regression models at baseline, although the most missing information for any covariate was 5%. To minimize missing values on covariates during follow-up, missing variables were replaced with the last value carried forward.

To minimize reverse causation and rule out preexisting subclinical disease, we repeated the analysis after excluding (i) former/current smoker participants, (ii) incident physician-diagnosed cancer or CVD reported in subsequent medical examinations, and (iii) those who died in the first 4 years of follow-up since the last medical examination. Finally, in sensitivity analyses, we examined the main associations by calculating the cumulative average by 1) weighting more the first measure obtained before the outcome (i.e., the baseline examination) 2) weighting more the most recent medical examination before the outcome (i.e. the last examination), or; 3) using the last measure obtained (also called simple update) (17,24). We tested the proportional-hazards assumption by modeling the interaction of follow-up time with leisure-time PA and observed no significant deviations. Analyses were conducted with the use of STATA software, version 14.1. Statistical tests were two-sided with alpha set at 0.05.

Patient and public involvement

No patients were directly involved in designing the research question or in conducting the research. No patients were asked for advice on interpretation or writing up of the results. There were no plans to involve patients or the relevant patient community in the dissemination of study findings currently.

RESULTS

We included 210,327 participants (50.6% female), aged 18 to 97 years (mean age; 38.6 years; SD, 12.1) (table S3), providing 867,968 data points (98.5% from 881,340 repeated measures included in the present analysis) between 1997 and 2016 (median, IQR: 4.8 years, 2.3-9.0) for estimating long-term leisure-time PA (table S4). The median of long-term leisure-time PA was 3.8 (IQR, 1.3-9.0) MET-h/week, and the prevalence of participants with none, insufficient, recommended, and additional amounts of leisure-time PA was 6.7%, 62.7%, 19.0% and 11.6%, respectively. Overall, participants with more medical examinations had similar characteristics at baseline than participants with more examinations during the follow-up (table S5). Table 1 shows the characteristics of the total sample, by long-term leisure-time PA categories.

During up to 23 years of follow-up (total person-years, 3,655,734) 10,539 participants died, 1,919 from CVD. We observed an inverse, nonlinear dose-response association between long-term leisure-time PA and all-cause and CVD mortality (figure 1). The shape of the dose-response association curves for all-cause and CVD mortality showed a pronounced risk reduction at about 5-10 MET-h/week, with a risk reduction greater in magnitude for CVD deaths. At higher levels of leisure-time PA, a linear lower risk was observed, being slightly more decrescent for all-cause mortality.

Compared with the referent (i.e., no leisure-time PA), insufficient, recommended, and additional amounts of leisure-time PA were associated with lower all-cause and CVD mortality risk (figure 2, table S6). The risk reductions were 26%, 36% and 41% for all-cause mortality by increasing categories of leisure-time PA, as compared with no leisure-time PA; the corresponding risk reductions for CVD mortality were 32%, 44% and 44% for insufficient, recommended, and additional amounts of leisure-time PA, respectively. Doing additional leisure-time PA appeared associated with a somewhat further reduced risk for all-cause mortality but not for CVD mortality. The risk reductions of doing insufficient amounts of leisure-time PA were substantial, and even doing about half of the recommended amount was associated with a markedly reduced risk compared with doing no leisure-time PA (table

S7). Without exceptions, the associations between long-term leisure-time PA with all-cause and CVD mortality were consistent (P for interactions> 0.1 for all) when stratified by age and sex, and among participants with obesity and cardiometabolic health conditions (table 2).

Leisure-time PA at baseline (first examination) showed a similar shape of distribution to long-term data, but with an important difference in frequency density (figure 3). The association between leisure-time PA and risk of death was greater in magnitude (19-32% and 34-43% lower risk for any cause and CVD deaths, respectively) when using repeated measures of PA compared with the associations between baseline PA (single point) and risk of death (figure 4, table S8).

Sensitivity analyses suggested that our results were attenuated by only a small amount after accounting for reverse causation when excluding smokers, those with underlying diseases, and early deaths within 4 years (table S9). Also, we found similar associations using different methods of calculating the cumulative average. However, when modelling a single measure of PA in the last examination, the associations with mortality outcomes were greater in magnitude than those previously observed when modeling PA at baseline as the single measure exposure (table S10).

DISCUSSION

Findings into context

In this large Taiwanese cohort of more than 210 000 participants, long-term leisure-time PA calculated from up to 20 repeated measures showed a clear nonlinear dose-response association with long-term all-cause and CVD mortality. Participating in leisure-time PA less than the recommended levels (i.e., <7.5 MET-h/week) reduced total and CVD mortality risk by around 30% compared with the inactive referent. Recommended amounts of leisure-time PA were associated with reductions in all-cause and CVD mortality risks of 36% and 44%, respectively. Engagement in additional amounts of leisure-time PA than those recommended was also associated with a lower risk of 41% and 44% for deaths from all causes and CVD mortality, respectively, and almost similar in magnitude when compared with the mortality risk reductions observed in those doing the recommended amounts.

Conceivably, to date, the most comprehensive work exploring the dose-response association between PA and mortality was the pooled analysis conducted by Arem et al. (8) including 661,137 participants (median age 62 years) from 6 population-based prospective cohorts, and they found that compared to no leisure-time PA (0 MET-h/week), the HR (95%CI) was 20%, 31%, 37%, 39%, 39% and 31% for amounts of 0.1 to <7.5, 7.5 to <15.0, 15.0 to <22.5, 22.5 to <40.0, 40.0 to <75.0, and ≥75.0 MET-h/week, respectively. Other large cohort studies and pooled analyses have also examined dose-response associations between PA and mortality, but the differences in reference and comparison groups have made comparisons difficult. For example, Lear et al. (9) in the Prospective Urban Rural Epidemiologic study examined whether total PA (including leisure-time and other domains), was associated with lower risk of mortality in 130,843 participants (mean age 50 years) from 17 high-, middle-, and low-income countries, and compared to not meeting the recommended amount of PA, those doing between 1 to 5 times the recommended amount, and more than 5 times the recommended amount, the HR (95%CI) mortality risk reduction was 20% and 35%, respectively. In a pooled analysis of 467,729 East Asian adults (mean age 55 years) (10), compared with those who reported no or almost no leisure-time PA, there was a 14-15% reducing risk of all-cause mortality among those with higher amounts of leisure-time PA. Wen et al. (11) including 416,175 individuals (mean age 42 years) from this Taiwan MJ cohort showed that compared with those doing <3.75 MET-h/week, the HR (95%CI) was 0.86 for 3.75-7.49 MET-h/week, 0.80 for 7.50-16.49 MET-h/week, 0.71 for 16.50-25.49 MET-h/week and 0.65 for ≥25.50 MET-h/week.

All these previous studies, however, examined associations with mortality risk using a single data point of PA assessed at baseline, whereas we used repeated measures of the exposure which likely provides more robust estimates and consider changes in PA behavior over time. The Nurses' Health Study I and II and the Health Professionals Follow-up Study included updated information on leisure-time PA every 2 years, allowing for modelling long-term PA, and some work with these cohorts has shown the associations of long-term PA on mortality outcomes (17,25-29). Among women from the Nurses' Health Study I, the all-cause relative risks (RR) (95%CI) were 0.82 (0.76-0.89), 0.75 (0.69-0.81), 0.74 (0.68-0.81), and 0.71 (0.61-0.82) for amounts of <1 h/week, 1-1.9 h/week, 2-3.9 h/week, 4-6.9 h/week and ≥7 h/week in leisure-time PA, respectively; corresponding estimates for cardiovascular mortality were 0.80 (0.68-0.96) 0.74 (0.62-0.88) 0.62 (0.50-0.77) 0.69 (0.49-0.97). Among diabetic men from the Health Professionals Follow-up Study the RR risks for all-cause mortality across fifths of leisure-time PA were 1.0, 0.80, 0.57, 0.58, and 0.58. Overall, these studies found strong inverse dose-response associations, but comparisons with the present study should be interpreted with caution owing to differences in cohort designs, and the specific characteristics in these cohorts (e.g., selected populations, high socioeconomic status, Caucasian) (17,25-29). However, these previous studies and our present work that have included repeated measures suggest that the association between PA and mortality are bigger than most of the evidence has shown to date using on a single self-reported measure of PA (16).

Possible explanations of our results

PA promotes acute physiological responses by activating a number of molecular pathways in whole organ systems and thereby reducing the risk of developing chronic diseases such as CVD, cancer, and others aging-related diseases that poorer survival outcomes

(29-32). PA assessed with repeated measures likely better captures the effect of exercise adaptations on health since we found stronger associations between PA and from repeated measures of PA compared with one single measure assessed at baseline. This might explain the large effect size observed for the association between long-term PA and CVD mortality and other CVD-related mortality outcomes because the benefits of regular PA for the cardiovascular system seems to be more pronounced than for other organ systems (29,30). The stronger association observed compared with studies using a single measure of PA may also be a result of the reduction in random measurement errors, which bias associations towards the null.

Public health and research implications

Our results provide additional support for PA guidelines suggesting that any PA is better than none (i.e., 'every move counts'), and are in agreement with previous observations suggesting a marked risk reduction even if not meeting the current recommendations compared with those doing no PA (1,2). We also found that doing additional amounts of leisure-time PA beyond the recommended levels provides small but significant additional reductions in mortality risks; this supports the recommendation that doing more than 300 min at moderate-intensity or 150 min at vigorous intensity has small but additional health benefits (i.e., reduces mortality risk), and consequently is considered a conditional recommendation (i.e., the balance of benefits to harms is small).

Although randomized controlled trials are the 'gold standard' research design to provide the highest levels of certainty in evidence, trials are most feasibly conducted in ideal and often unrealistic conditions with highly-motivated and homogenous participants, which provide results with high internal validity but limited external validity. In addition, trials that aim to examine mortality as the primary outcome require inclusion of at least 3 arms to explore a dose-response and an unrealistic effort to maintain compliance in a supervised weekly training over many years (34). Consequently, large scale observational studies including repeated measures, such as the present study, are important for confirming current PA guidelines and providing new data to inform future guidelines.

Strengths and limitations

Limitations of this work should be considered. First, we relied on self-reported PA measures. Although repeated measures minimize measurement error and within-individual variability over time, the PA questionnaire was slightly modified over time and some issues that usually reduce the validity of self-report (e.g., misclassifications, social desirability, and recall bias, etc.) remain. Second, selection bias might be also introduced since according our study design participants had a different number of medical examinations (e.g., the healthy participant effect); however, our analyses showed that participants with fewer medical examinations had similar patterns of leisure-time PA over time and comparable socio-demographic characteristics, lifestyle behaviors and health risk factors at baseline as those participants with more medical examinations. These potential reporting and selection biases would likely have led to an underestimation of the observed dose-response effect sizes of PA on mortality outcomes in the present study. Third, although the analyses were adjusted for key confounders, the potential for residual confounding remains due to unmeasured confounders and the very low-resolution measurement of some confounders (e.g., diet and alcohol). Fourth, this was an observational study that neither can demonstrate causality, nor rule out effects of unmeasured or residual confounding; however, our sensitivity analyses confirmed our main findings.

On the other hand, we only examined leisure-time PA, therefore, we could not evaluate associations with total PA and/or other domain-specific PA (i.e., transportation, work, household). Also, information on sedentary behaviors was not collected in this cohort and therefore potential moderating effects on these results could not be investigated (5,35). Future research using repeated objective measures, such as accelerometers, might be critical to providing evidence on dose-response association of PA on health outcomes (36). Finally, despite that the MJ cohort may be the most representative of the general population of Taiwan to date, the final analytic sample may not be representative since our sample comprised of participants with additional medical examinations, who tend to be from higher socioeconomic background.

CONCLUSIONS

Based on a large Taiwanese cohort of relatively young adults, we found non-linear, inverse dose-response associations between repeated measures of leisure-time PA and all-cause and CVD mortality, and the magnitude of risk reductions, mainly for CVD deaths, were larger than when considering only one measure of PA at baseline. Doing some PA, even less than the currently recommended levels, was associated with substantially lower mortality risk compared with the inactive referent. Doing the recommended and additional amounts of leisure-time PA over a long-term was associated with even further risk reductions. Hence, these findings provide more certain evidence for most of the recommendations and good practice statements included in the recent WHO PA guidelines.

ACKNOWLEDGMENTS

The authors thank MJ Health Research Foundation for the authorization of using MJ health data.

CONTRIBUTORS

Dr Martinez-Gomez conceived and designed the study. Drs Martinez-Gomez, Rodriguez-Artalejo and Yu acquired the data. Drs Martinez-Gomez and Cabanas-Sanchez analyzed and interpreted the data. Drs Martinez-Gomez and Rodriguez-Artalejo obtained the funding. Dr Martinez-Gomez drafted the first version of this article. All authors critically revised and edited the article. Drs Ding, Lee, and Ekelund supervised this work.

FUNDING

This work was supported by FIS grants (State Secretary of R+D+I and FEDER/FSE; 16/609, 16/1512, 18/287, 19/319, 20/00657). DMG is supported by a 'Ramon y Cajal' contract (RYC-2016-20546) and DD by a Heart Foundation Australia Future Leader Fellowship (no. 101234) while contributing to this work. A preliminary version of this work was awarded the 2020 National Sports Medicine Award (University of Oviedo, Oviedo, Spain).

DISCLAMER

The funders had no role in study design, data collection, data analysis, data interpretation or writing of the report. Any interpretation or conclusion related to this article does not represent the views of MJ Health Research Foundation.

COMPETING INTEREST

There are no conflicts of interest associated with this manuscript.

ETHICS APPROVAL

This study was approved by the institutional review boards of the MJ Health Management Institution, the National Health Research Institutes and at National Cheng Kung University (A-ER-108–081).

DATA AVAILABILITY STATEMENT

The data of this study can be requested from the MJ Health Research Foundation (http://www.mjhrf.org).

REFERENCES

1. World Health Organization. WHO guidelines on physical activity and sedentary behaviour. Geneva: World Health Organization; 2020.
2. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, Dempsey PC, DiPietro L, Ekelund U, Firth J, Friedenreich CM, Garcia L, Gichu M, Jago R, Katzmarzyk PT, Lambert E, Leitzmann M, Milton K, Ortega FB, Ranasinghe C, Stamatakis E, Tiedemann A, Troiano RP, van der Ploeg HP, Wari V, Willumsen JF. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020 Dec;54(24):1451-1462.
3. Ding D, Mutrie N, Bauman A, Pratt M, Hallal PRC, Powell KE. Physical activity guidelines 2020: comprehensive and inclusive recommendations to activate populations. Lancet. 2020 Dec 5;396(10265):1780-1782.
4. DiPietro L, Al-Ansari SS, Biddle SJH, Borodulin K, Bull FC, Buman MP, Cardon G, Carty C, Chaput JP, Chastin S, Chou R, Dempsey PC, Ekelund U, Firth J, Friedenreich CM, Garcia L, Gichu M, Jago R, Katzmarzyk PT, Lambert E, Leitzmann M, Milton K, Ortega FB, Ranasinghe C, Stamatakis E, Tiedemann A, Troiano RP, van der Ploeg HP, Willumsen JF. Advancing the global physical activity agenda: recommendations for future research by the 2020 WHO physical activity and sedentary behavior guidelines development group. Int J Behav Nutr Phys Act. 2020 Nov 26;17(1):143.
5. Warburton DE, Charlesworth S, Ivey A, Nettlefold L, Bredin SS. A systematic review of the evidence for Canada's Physical Activity Guidelines for Adults. Int J Behav Nutr Phys Act. 2010 May 11;7:39.

6. 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.
7. Arem H, Moore SC, Patel A, Hartge P, Berrington de Gonzalez A, Visvanathan K, Campbell PT, Freedman M, Weiderpass E, Adami HO, Linet MS, Lee IM, Matthews CE. Leisure-time physical activity and mortality: a detailed pooled analysis of the dose-response relationship. JAMA Intern Med. 2015 Jun;175(6):959-67.
8. Lear SA, Hu W, Rangarajan S, Gasevic D, Leong D, Iqbal R, Casanova A, Swaminathan S, Anjana RM, Kumar R, Rosengren A, Wei L, Yang W, Chuangshi W, Huaxing L, Nair S, Diaz R, Swidon H, Gupta R, Mohammadifard N, Lopez-Jaramillo P, Oguz A, Zatonska K, Seron P, Avezum A, Poirier P, Teo K, Yusuf S. The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. Lancet. 2017 Dec 16;390(10113):2643-2654. doi: 10.1016/S0140-6736(17)31634-3. Epub 2017 Sep 21. Erratum in: Lancet. 2017 Dec 16;390(10113):2626. PMID: 28943267.
9. Liu Y, Shu XO, Wen W, Saito E, Rahman MS, Tsugane S, Tamakoshi A, Xiang YB, Yuan JM, Gao YT, Tsuji I, Kanemura S, Nagata C, Shin MH, Pan WH, Koh WP, Sawada N, Cai H, Li HL, Tomata Y, Sugawara Y, Wada K, Ahn YO, Yoo KY, Ashan H, Chia KS, Boffetta P, Inoue M, Kang D, Potter JD, Zheng W. Association of leisure-time physical activity with total and cause-specific mortality: a pooled analysis of nearly a half million adults in the Asia Cohort Consortium. Int J Epidemiol. 2018;47(3):771-779.
10. Wen CP, Wai JP, Tsai MK, Yang YC, Cheng TY, Lee MC, Chan HT, Tsao CK, Tsai SP, Wu X. Minimum amount of physical activity for reduced mortality and extended life expectancy: a prospective cohort study. Lancet. 2011 Oct 1;378(9798):1244-53.

11. Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJ, Martin BW; Lancet Physical Activity Series Working Group. Correlates of physical activity: why are some people physically active and others not? Lancet. 2012 Jul 21;380(9838):258-71.
12. Mok A, Khaw KT, Luben R, Wareham N, Brage S. Physical activity trajectories and mortality: population based cohort study. BMJ. 2019 Jun 26;365:l2323.
13. Saint-Maurice PF, Coughlan D, Kelly SP, Keadle SK, Cook MB, Carlson SA, Fulton JE, Matthews CE. Association of Leisure-Time Physical Activity Across the Adult Life Course With All-Cause and Cause-Specific Mortality. JAMA Netw Open. 2019 Mar 1;2(3):e190355.
14. Gregg EW, Cauley JA, Stone K, Thompson TJ, Bauer DC, Cummings SR, Ensrud KE; Study of Osteoporotic Fractures Research Group. Relationship of changes in physical activity and mortality among older women. JAMA. 2003 May 14;289(18):2379-86.
15. Huang Y, Jiang C, Xu L, Zhang W, Zhu F, Jin Y, Cheng KK, Lam TH. Mortality in relation to changes in physical activity in middle-aged to older Chinese: An 8-year follow-up of the Guangzhou Biobank Cohort Study. J Sport Health Sci. 2020 Aug 20:S2095-2546(20)30105-8.
16. Ekelund U, Dalene KE, Tarp J, Lee IM. Physical activity and mortality: what is the dose response and how big is the effect? Br J Sports Med. 2020 Oct;54(19):1125-1126.
17. Lee DH, Rezende LFM, Ferrari G, Aune D, Keum N, Tabung FK, Giovannucci EL. Physical activity and all-cause and cause-specific mortality: assessing the impact of reverse causation and measurement error in two large prospective cohorts. Eur J Epidemiol. 2021 Jan 11. doi: 10.1007/s10654-020-00707-3. Epub ahead of print. PMID: 33428024.

18. Wu X, Tsai SP, Tsao CK, Chiu ML, Tsai MK, Lu PJ, Lee JH, Chen CH, Wen C, Chang SS, Hsu CY, Wen CP. Cohort Profile: The Taiwan MJ Cohort: half a million Chinese with repeated health surveillance data. Int J Epidemiol. 2017 Dec 1;46(6):1744-1744g.
19. MJ Health Research Foundation. The introduction of MJ Health Database. Taipei, Taiwan: MJ Health Research Foundation, Technical Report MJHRF-TR-01, 2016.
20. Martinez-Gomez D, Esteban-Cornejo I, Lopez-Garcia E, García-Esquinas E, Sadarangani KP, Veiga OL, Rodriguez-Artalejo F. Physical activity less than the recommended amount may prevent the onset of major biological risk factors for cardiovascular disease: a cohort study of 198 919 adults. Br J Sports Med. 2020 Feb;54(4):238-244.
21. St-Onge MP, Ard J, Baskin ML, Chiuve SE, Johnson HM, Kris-Etherton P, Varady K; American Heart Association Obesity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Clinical Cardiology; and Stroke Council. Meal Timing and Frequency: Implications for Cardiovascular Disease Prevention: A Scientific Statement From the American Heart Association. Circulation. 2017 Feb 28;135(9):e96-e121.
22. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-3104.
23. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA.2001;285:2486–2497.

24. Hu FB, Stampfer MJ, Rimm E, Ascherio A, Rosner BA, Spiegelman D, Willett WC. Dietary fat and coronary heart disease: a comparison of approaches for adjusting for total energy intake and modeling repeated dietary measurements. Am J Epidemiol. 1999 Mar 15;149(6):531-40.
25. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation. 2003 May 20;107(19):2435-9.
26. Hu FB, Willett WC, Li T, Stampfer MJ, Colditz GA, Manson JE. Adiposity as compared with physical activity in predicting mortality among women. N Engl J Med. 2004 Dec 23;351(26):2694-703.
27. Baer HJ, Glynn RJ, Hu FB, Hankinson SE, Willett WC, Colditz GA, Stampfer M, Rosner B. Risk factors for mortality in the nurses' health study: a competing risks analysis. Am J Epidemiol. 2011 Feb 1;173(3):319-29.
28. Al-Shaar L, Li Y, Rimm EB, Manson JE, Rosner B, Hu FB, Stampfer MJ, Willett WC. Physical Activity and Mortality among Male Survivors of Myocardial Infarction. Med Sci Sports Exerc. 2020 Aug;52(8):1729-1736.
29. Rockhill B, Willett WC, Manson JE, et al. Physical activity and mortality: a prospective study among women. Am J Public Health. 2001;91(4):578-583.
30. Hawley JA, Hargreaves M, Joyner MJ, Zierath JR. Integrative biology of exercise. Cell. 2014 Nov 6;159(4):738-49.
31. Moreira JBN, Wohlwend M, Wisløff U. Exercise and cardiac health: physiological and molecular insights. Nat Metab. 2020 Sep;2(9):829-839.
32. Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. Cell Metab. 2018 Jan 9;27(1):10-21.

33. Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, Santos-Lozano A, Fiuza-Luces C, Morán M, Emanuele E, Joyner MJ, Lucia A. Exercise attenuates the major hallmarks of aging. Rejuvenation Res. 2015 Feb;18(1):57-89.
34. Stensvold D, Viken H, Steinshamn SL, Dalen H, Støylen A, Loennechen JP, Reitlo LS, Zisko N, Bækkerud FH, Tari AR, Sandbakk SB, Carlsen T, Ingebrigtsen JE, Lydersen S, Mattsson E, Anderssen SA, Fiatarone Singh MA, Coombes JS, Skogvoll E, Vatten LJ, Helbostad JL, Rognmo Ø, Wisløff U. Effect of exercise training for five years on all cause mortality in older adults-the Generation 100 study: randomised controlled trial. BMJ. 2020 Oct 7;371:m3485.
35. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, Bauman A, Lee IM; Lancet Physical Activity Series 2 Executive Committe; Lancet Sedentary Behaviour Working Group. 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 Sep 24;388(10051):1302-10.
36. Ekelund U, Tarp J, Steene-Johannessen J, Hansen BH, Jefferis B, Fagerland MW, Whincup P, Diaz KM, Hooker SP, Chernofsky A, Larson MG, Spartano N, Vasan RS, Dohrn IM, Hagströmer M, Edwardson C, Yates T, Shiroma E, Anderssen SA, Lee IM. Dose-response associations between accelerometry measured physical activity and sedentary time and all cause mortality: systematic review and harmonised meta-analysis. BMJ. 2019 Aug 21;366:l4570.

FIGURE LEGENDS

Figure 1. Dose-response associations between long-term leisure-time physical activity with total and cardiovascular mortality in 210,327 adults. Long-term leisure-time physical activity was calculated as the cumulative average with between 2 and 20 repeated measures from 1997 to 2016 and truncated to 40.00 MET-h/week. A total of 10539 participants died, 1919 from cardiovascular disease. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, cancer, cardiovascular diseases, diabetes, hypertension, dyslipidemia, and electrocardiogram.

Figure 2. Associations between long-term leisure-time physical activity categories with total and cardiovascular mortality in 210,327 adults. Long-term leisure-time physical activity was calculated as the cumulative average (see methods section) with between 2 and 20 repeated measures from 1997 to 2016. Insufficient: 0.01-7.49 MET-h/week. Recommended: 7.50-15.00 MET-h/week. Additional: >15.00 MET-h/week. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, diabetes, hypertension, dyslipidemia, and electrocardiogram. n for each increasing category is 14042, 131838, 40065, and 24382. Deaths for all/cardiovascular cases for each increasing category are 930/178, 5148/896, 2617/476, and 1844/369.

Figure 3. Descriptive data on leisure-time physical activity at baseline (first examination, blue) and long-term (cumulative average, red) in the present study. IQR: interquartile range, 25th-75th. Baseline leisure-time physical activity was also truncated to 40.00 MET-h/week (99th percentile of distribution) for this analysis.

Figure 4. Dose-response associations between long-term (red) and baseline (blue) leisure-time physical activity with total and cardiovascular mortality in 210,327 adults. Long-term leisure-time physical activity was calculated as the cumulative average (see methods section) with between 2 and 20 repeated measures from 1997 to 2016 and truncated to 40.00 MET-h/week. A total of 10539 participants died, 1919 from cardiovascular disease. Values are hazard ratios and 95% confidence interval lines were removed for simplicity purposes. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, cancer, cardiovascular diseases, diabetes, hypertension, dyslipidemia, and electrocardiogram.

Table 1. Study population characteristics at baseline by categories of long-term leisure-time physical activity

	None	Insufficient	Recommended	Additional
n	14042	131838	40065	24382
Sex				
Male	6373 (45.4)	59119 (44.8)	22405 (55.9)	15956 (65.4)
Female	7669 (54.6)	72719 (55.2)	17660 (44.1)	8426 (34.6)
Age groups				
18-39 years	9546 (68.0)	90518 (68.7)	19636 (49.0)	9411 (38.6)
40-64 years	4097 (29.2)	38363 (29.1)	18062 (45.1)	13030 (53.4)
65 years and above	399 (2.8)	2957 (2.2)	2367 (5.9)	1941 (8.0)
Educational attainment				
Middle school or below	2008 (14.3)	12901 (9.8)	5989 (15.0)	4192 (17.2)
High school	873 (6.2)	5721 (4.3)	2470 (6.2)	1903 (7.8)
Junior school	6853 (48.8)	61335 (46.5)	16506 (41.2)	96745 (40.0)
College or above	4164 (29.7)	50717 (38.5)	14714 (36.7)	8241 (33.8)
Marital status				
Married or living with partner	8830 (62.9)	81184 (61.6)	27018 (67.4)	17169 (70.4)
Single or widowed	4853 (34.5)	47192 (35.8)	12056 (30.1)	6581 (27.0)
Smoking status				
Never	9355 (66.6)	95120 (72.2)	28274 (70.6)	16516 (67.7)
Former	701 (5.0)	6560 (5.0)	2614 (6.5)	2163 (8.9)
Current	3401 (24.2)	25993 (19.7)	7632(19.1)	4856 (19.9)
Alcohol consumption				
Never	10973 (78.1)	106222 (80.6)	30232 (75.5)	17185 (70.5)
Former	336 (2.4)	2573 (2.0)	950 (2.4)	769 (3.2)
Current	1911 (13.6)	16880 (12.8)	6608 (16.5)	5062 (20.8)
Regular meal patterns				
Suboptimal	6760 (48.1)	54417 (41.3)	12487 (31.2)	6936 (28.5)
Optimal	6724 (47.9)	73815 (56.0)	26216 (65.4)	16670 (68.4)
Occupational physical activity				
Sedentary	7378 (52.5)	80257 (60.7)	24021 (60.2)	13383 (54.9)
Sedentary with occasional walking	3950 (28.1)	35981 (27.3)	10943 (27.3)	6626 (27.2)
Standing or walking	1780 (12.7)	10846 (8.2)	3249 (8.1)	2681 (11.0)
Heavy labor	572 (4.1)	2444 (1.8)	700 (1.8)	748 (3.1)
Body mass index				
< 25 kg/m^2	10576 (75.3)	101927 (77.3)	28981 (72.3)	17103 (70.2)
≥ 25 kg/m^2	3462 (24.7)	29877 (22.7)	11075 (27.6)	7277 (29.9)
Hypertension				
No	12279 (87.4)	116971 (88.7)	32561 (81.3)	18986 (77.9)
Yes	1763 (12.6)	14867 (11.3)	7504 (18.7)	5396 (22.1)
Dyslipidemia				
No	7876 (56.1)	79801 (60.5)	22536 (56.3)	14072 (57.7)
Yes	6166 (43.9)	52037 (39.5)	17529 (43.8)	10310 (42.3)
Diabetes				
No	13601 (96.9)	128066 (97.1)	38222 (95.4)	23016 (94.4)
Yes	441 (3.1)	3772 (2.9)	1843 (4.6)	1366 (5.6)
Electrocardiogram				
Normal	11471 (81.7)	108530 (82.3)	32178 (80.3)	18870 (77.4)
Abnormal	2562 (18.2)	23124 (17.5)	7844 (19.6)	5487 (22.5)

Values are n (%). Insufficient: 0.01-7.49 MET-h/week. Recommended: 7.50-15.00 MET-h/week. Additional: >15.00 MET-h/week. Long-term leisure-time physical activity was calculated as the cumulative average (see methods section) using 2 to 20 repeated measures from 1997 to 2016.

Table 2. Associations between long-term leisure-time physical activity categories with all-cause and cardiovascular mortality by age, gender, obesity and cardiometabolic chronic conditions at baseline

	None	Insufficient	Recommended	Additional
All-cause mortality				
18-64 years, n/deaths	13643/684	1128881/3706	37698/1516	22441/1087
HR (95%CI)	1 (Reference)	0.72 (0.66-0.78)	0.61 (0.56-0.67)	0.58 (0.53-0.64)
65 years and above, n/deaths	399/246	2957/1442	2367/1101	1941/757
HR (95%CI)	1 (Reference)	0.81 (0.71-0.93)	0.72 (0.62-0.83)	0.62 (0.53-0.72)
Men, n/deaths	6373/563	59119/2779	22405/1524	15956/1316
HR (95%CI)	1 (Reference)	0.74 (0.67-0.81)	0.65 (0.59-0.72)	0.58 (0.52-0.64)
Women, n/deaths	7669/367	72719/2369	17660/1093	8426/528
HR (95%CI)	1 (Reference)	0.75 (0.67-0.84)	0.64 (0.56-0.72)	0.61 (0.53-0.69)
With obesity, n/deaths	3462/316	29877/1877	11075/921	7277/671
HR (95%CI)	1 (Reference)	0.77 (0.69-0.87)	0.64 (0.56-0.73)	0.63 (0.55-0.72)
With hypertension, n/deaths	1763/369	14867/2048	7504/1235	5396/861
HR (95%CI)	1 (Reference)	0.77 (0.69-0.86)	0.66 (0.59-0.75)	0.60 (0.53-0.68)
With diabetes, n/deaths	441/137	3772/728	1843/445	1365/299
HR (95%CI)	1 (Reference)	0.68 (0.57-0.82)	0.63 (0.52-0.77)	0.58 (0.47-0.72)
With dyslipidemia, n/deaths	6166/574	52037/3072	17529/1548	10310/1020
HR (95%CI)	1 (Reference)	0.74 (0.68-0.81)	0.64 (0.58-0.71)	0.58 (0.52-0.65)
Cardiovascular mortality				
18-64 years, n/deaths	13643/111	128881/556	37698/225	22441/188
HR (95%CI)	1 (Reference)	0.68 (0.55-0.84)	0.54 (0.43-0.69)	0.59 (0.46-0.75)
65 years and above, n/deaths	399/67	2957/340	2367/251	1941/181
HR (95%CI)	1 (Reference)	0.69 (0.53-0.91)	0.59 (0.45-0.78)	0.55 (0.41-0.73)
Men, n/deaths	6373/104	59119/493	22405/273	15956/278
HR (95%CI)	1 (Reference)	0.69 (0.55-0.85)	0.57 (0.45-0.72)	0.61 (0.48-0.77)
Women, n/deaths	7669/74	72719/403	17660/203	8426/91
HR (95%CI)	1 (Reference)	0.70 (0.54-0.90)	0.57 (0.44-0.75)	0.51 (0.38-0.70)
With obesity, n/deaths	3462/81	39877/370	11075/177	7277/135
HR (95%CI)	1 (Reference)	0.60 (0.47-0.76)	0.46 (0.35-0.60)	0.48 (0.36-0.64)
With hypertension, n/deaths	1763/100	14867/495	7504/309	5396/209
HR (95%CI)	1 (Reference)	0.68 (0.55-0.85)	0.60 (0.47-0.75)	0.53 (0.42-0.68)
With diabetes, n/deaths	441/29	3772/149	1843/88	1365/58
HR (95%CI)	1 (Reference)	0.68 (0.45-1.03)	0.58 (0.38-0.90)	0.55 (0.34-0.88)
With dyslipidemia, n/deaths	6166/124	52037/581	17529/315	10310/208
HR (95%CI)	1 (Reference)	0.66 (0.54-0.80)	0.56 (0.45-0.70)	0.51 (0.40-0.64)

HR, Hazard ratios. CI, confidence interval. All analyses showed nonsignificant interactions (p for interaction >0.1). Obesity is ≥25 kg/m^2 for this Asian population. Long-term leisure-time physical activity was calculated (cumulative average) with between 2 and 20 repeated measures from 1997 to 2016. Insufficient: 0.01-7.49 MET-h/week. Recommended: 7.50-15.00 MET-h/week. Additional: >15.00 MET-h/week. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, cancer, cardiovascular disease, diabetes, hypertension, dyslipidemia, and electrocardiogram.

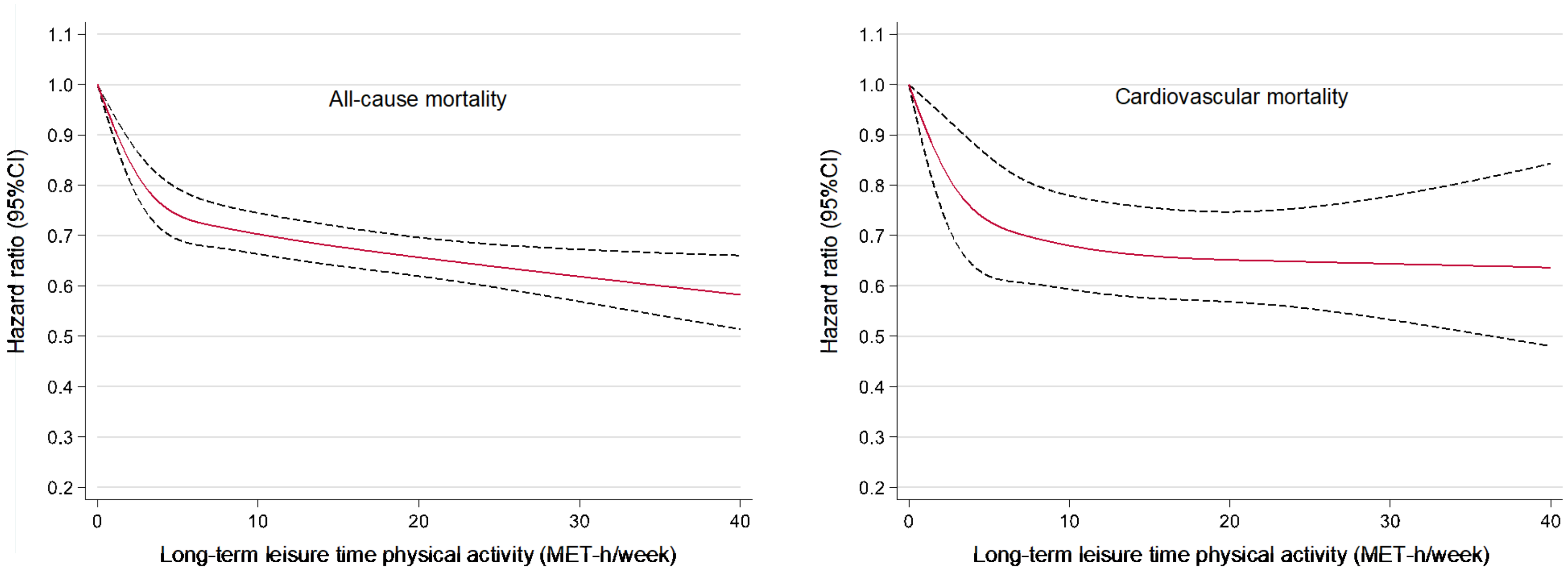

Figure 1. Dose-response associations between long-term leisure-time physical activity with total and cardiovascular mortality in 210,327 adults. Long-term leisure-time physical activity was calculated as the cumulative average with between 2 and 20 repeated measures from 1997 to 2016 and truncated to 40.00 MET-h/week. A total of 10539 participants died, 1919 from cardiovascular disease. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, cancer, cardiovascular diseases, diabetes, hypertension, dyslipidemia, and electrocardiogram.

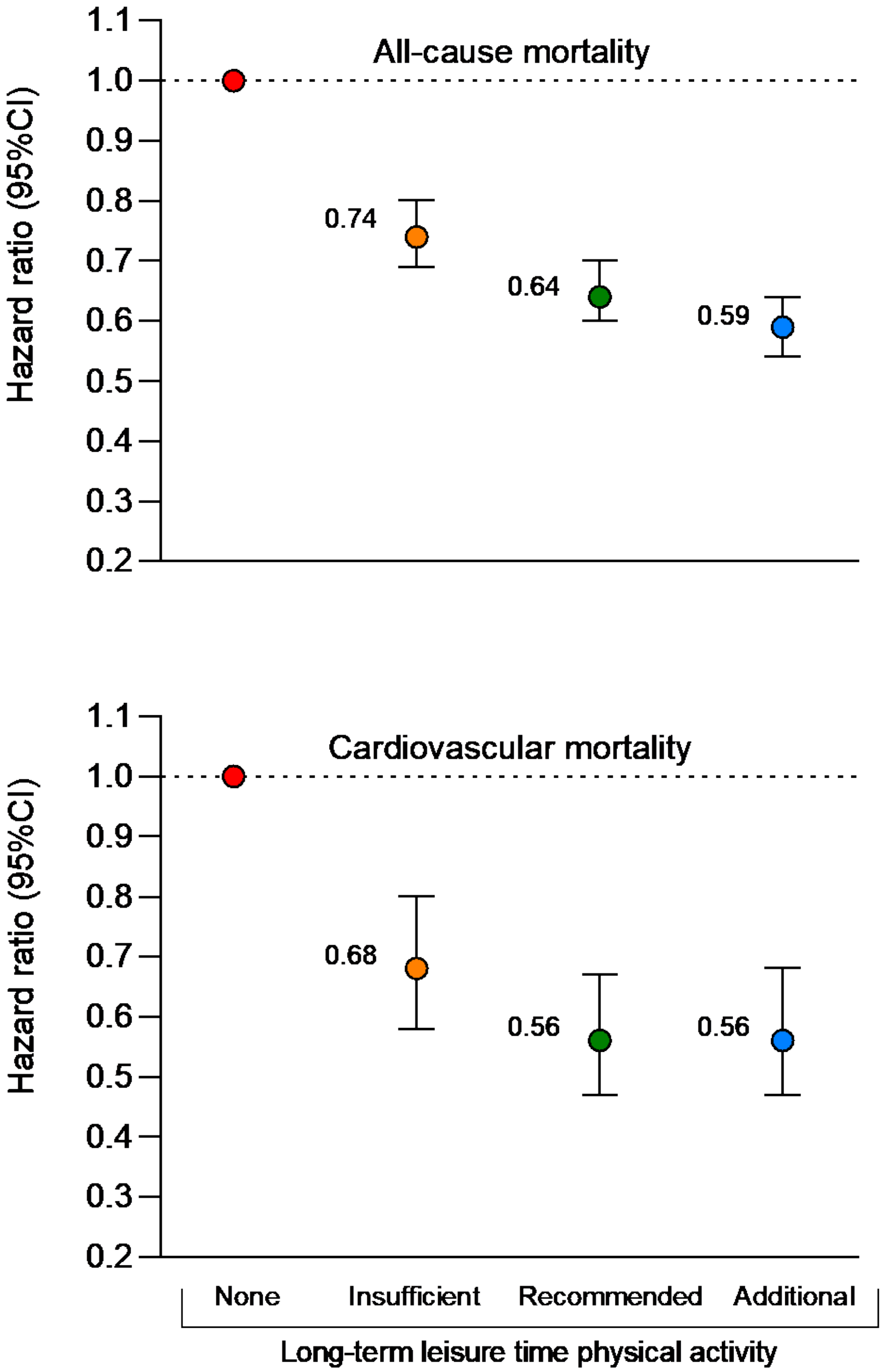

Figure 2. Associations between long-term leisure-time physical activity categories with total and cardiovascular mortality in 210,327 adults. Long-term leisure-time physical activity was calculated as the cumulative average (see methods section) with between 2 and 20 repeated measures from 1997 to 2016. Insufficient: 0.01-7.49 MET-h/week. Recommended: 7.50-15.00 MET-h/week. Additional: >15.00 MET-h/week. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, diabetes, hypertension, dyslipidemia, and electrocardiogram. n for each increasing category is 14042, 131838, 40065, and 24382. Deaths for all/cardiovascular cases for each increasing category are 930/178, 5148/896, 2617/476, and 1844/369.

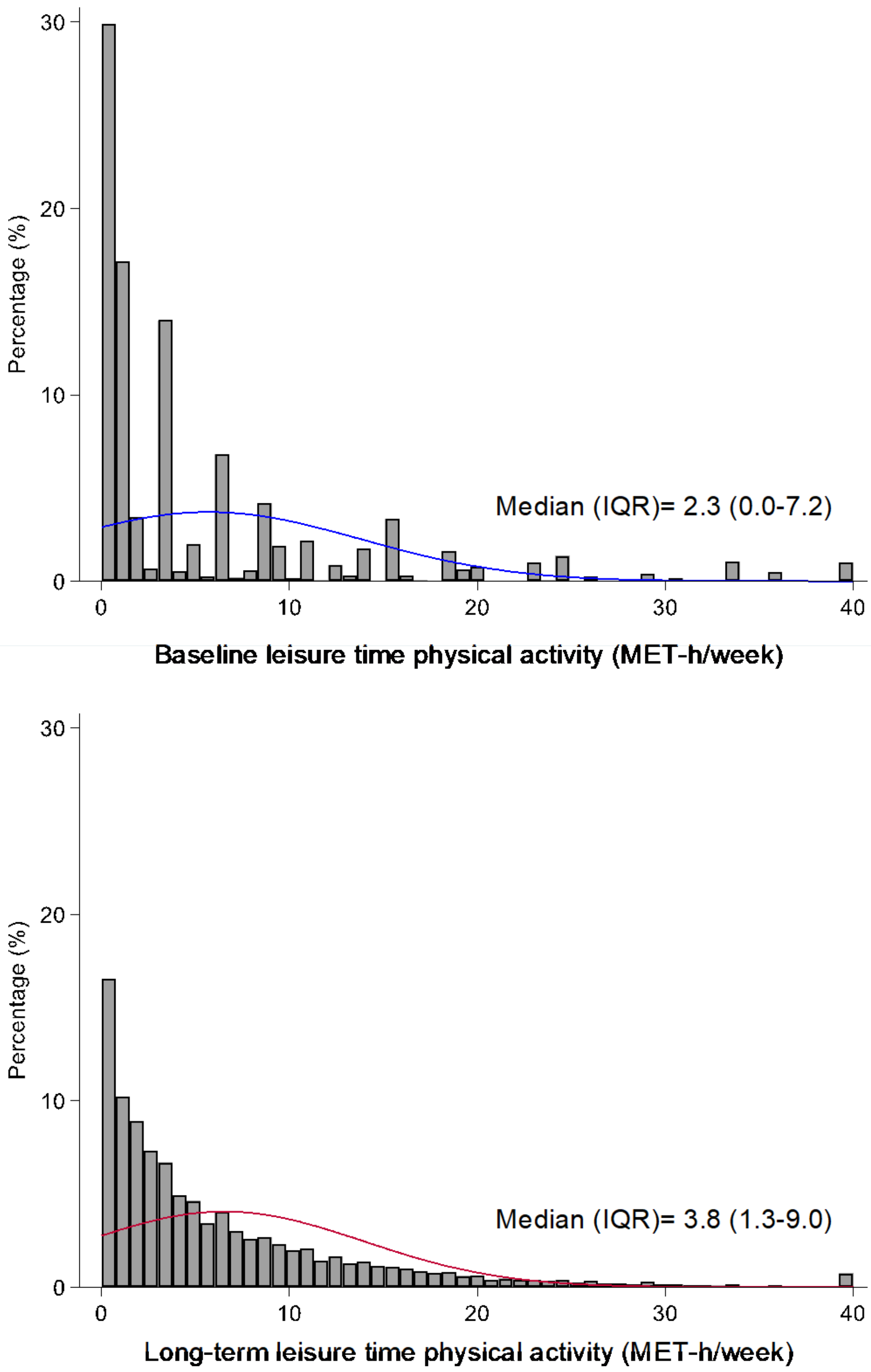

Figure 3. Descriptive data on leisure-time physical activity at baseline (first examination, blue) and long-term (cumulative average, red) in the present study. IQR: interquartile range, 25th-75th. Baseline leisure-time physical activity was also truncated to 40.00 MET-h/week (99th percentile of distribution) for this analysis.

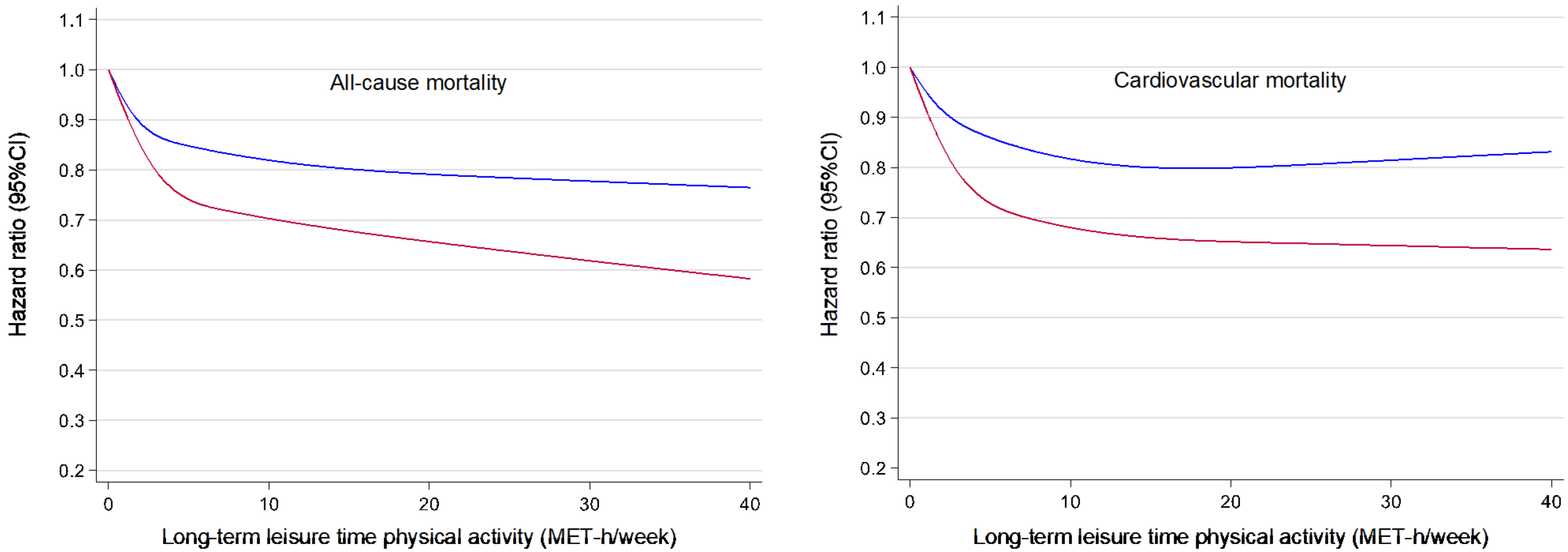

Figure 4. Dose-response associations between long-term (red) and baseline (blue) leisure-time physical activity with total and cardiovascular mortality in 210,327 adults. Long-term leisure-time physical activity was calculated as the cumulative average (see methods section) with between 2 and 20 repeated measures from 1997 to 2016 and truncated to 40.00 MET-h/week. A total of 10539 participants died, 1919 from cardiovascular disease. Values are hazard ratios, and 95% confidence interval lines were removed for simplicity purposes. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, cancer, cardiovascular diseases, diabetes, hypertension, dyslipidemia, and electrocardiogram.

SUPPLEMENTAL MATERIAL

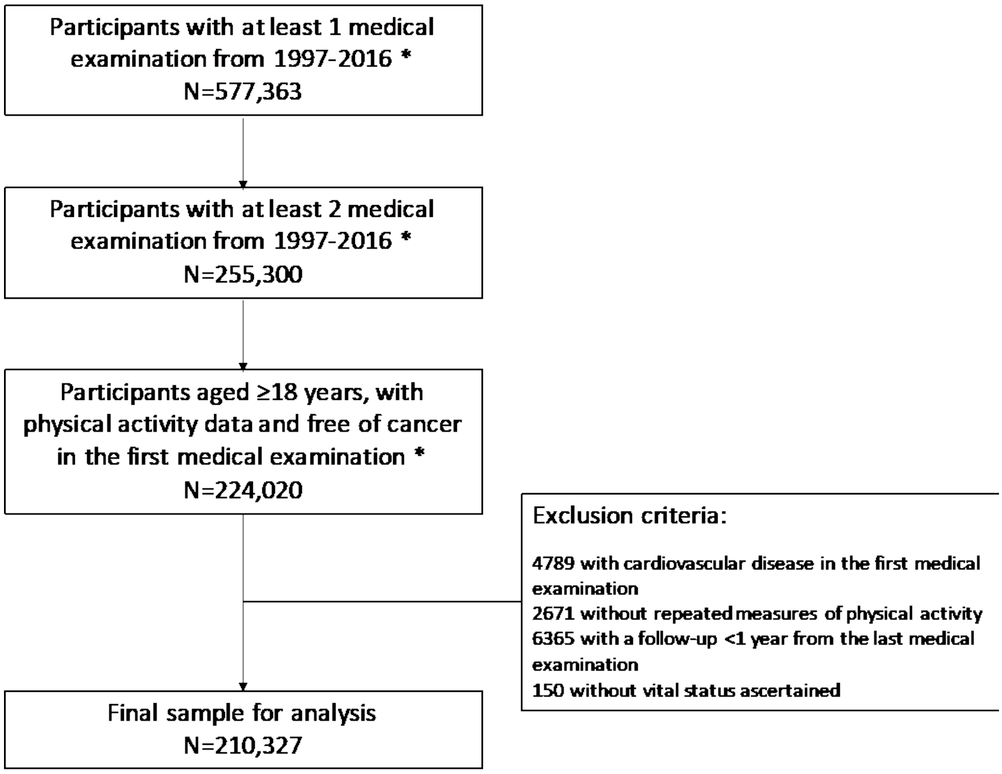

Figure S1. Flowchart of participants in the present study from the Taiwan MJ cohort. * Conducted by the MJ Health Research Foundation.

Table S1. The MJ physical activity questionnaire over the years

Questions	Options	Years
What kind of exercise do you usually do? (multiple choice) -Light exercise: gardening, sweeping the floor, mopping the floor, golf, baseball, light aerobics, dancing (regular), biking (slow speed) -Medium exercise: basketball, volleyball, table tennis, badminton, dancing (intensive), swimming (as wished), brisk walking -Heavy exercise: jogging (8 kilometers per hour), mountain climbing, climbing the stairs, swimming (freestyle and breaststroke) -Intensive exercise: running (12 kilometers per hour), jump rope, rowing, swimming (butterfly), speed skating	 No/yes No/yes No/yes No/yes	1997-2008
How much time do you devote to regular exercise? (one choice)	(1) None or less than 1 h/week (2) 1-2 h/week (3) 2-3 h/week (4) over 4 h/week	1997
How much time do you devote to regular exercise? (one choice)	(1) None or less than 1 h/week (2) 1-2 h/week (3) 3-4 h/week (4) 5-6 h/week (5) over 7 h/week	1998-2008
What is your regular exercise? (one choice)	1) Light exercise: gardening, sweeping the floor, mopping the floor, golf, Tai Chi, light aerobics, dancing (regular), and biking (slow speed). (2) Medium exercise: basketball, volleyball, table tennis, badminton, dancing (intensive), swimming (breaststroke) and brisk walking. (3) Heavy exercise: jogging (8 km/h), mountain climbing, climbing the stairs, and swimming (freestyle and back stroke). (4) Intensive exercise: running (12 km/h), rope-jumping, rowing, swimming (butterfly), and speed skating.	2009-2016
How often do you exercise during the last two weeks? (one choice)	(1) 2-3 times a day (2) once a day (3) once every 2-3 days (4) once a week (5) none or rarely	2009-2016
How many hours do you spend on exercise during the last two weeks? (one choice)	(1) <0.5 h (2) 0.5-1 h (3) 1-2 h (4) over 2 h	2009-2016
What is the second choice of exercise that you do regularly? (one choice) – optional	(1) Light exercise: gardening, sweeping the floor, mopping the floor, golf, Tai Chi, light aerobics, dancing (regular), and biking (slow speed). (2) Medium exercise: basketball, volleyball, table tennis, badminton, dancing (intensive), swimming (breaststroke) and brisk walking. (3) Heavy exercise: jogging (8 km/h), mountain climbing, climbing the stairs, and swimming (freestyle and back stroke). (4) Intensive exercise: running (12 km/h), rope-jumping, rowing, swimming (butterfly), and speed skating.	2009-2016
How often do you exercise during the last two weeks in this second choice? (one choice)	(1) 2-3 times a day (2) once a day (3) once every 2-3 days (4) once a week (5) none or rarely	2009-2016
How many hours do you spend on exercise during the last two weeks in this second choice? (one choice)	(1) <0.5 h (2) 0.5-1 h (3) 1-2 h (4) over 2 h	2009-2016

Table S2. Levels of physical activity in the total sample and by number of repeated measures in each medical examination over time

	Medical examination																			
Number of repeated measures (n)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
2 (78559)	2 (0-7)	3 (0-9)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
3 (43977)	2 (0-7)	3 (0-9)	3 (0-9)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
4 (26125)	2 (0-7)	3 (0-9)	4 (1-9)	4 (1-9)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5 (17222)	2 (0-8)	4 (1-9)	4 (1-9)	4 (1-9)	4 (1-9)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
6 (11546)	2 (0-8)	4 (0-9)	4 (1-9)	4 (1-9)	4 (1-9)	4 (1-10)	—	—	—	—	—	—	—	—	—	—	—	—	—	—
7 (8387)	3 (0-8)	4 (0-9)	4 (1-9)	4 (1-9)	4 (1-9)	4 (1-10)	4 (1-12)	—	—	—	—	—	—	—	—	—	—	—	—	—
8 (6256)	3 (0-9)	4 (0-9)	4 (1-9)	4 (1-9)	4 (1-10)	4 (1-11)	4 (1-12)	5 (1-13)	—	—	—	—	—	—	—	—	—	—	—	—
9 (4599)	2 (0-8)	4 (0-9)	4 (1-9)	4 (1-9)	4 (1-10)	4 (1-10)	4 (1-11)	5 (1-12)	5 (1-13)	—	—	—	—	—	—	—	—	—	—	—
10 (3560)	4 (0-9)	4 (0-9	4 (1-9)	4 (1-10)	4 (1-11)	4 (1-12)	4 (1-12)	4 (1-13)	5 (1-13)	5 (1-13)	—	—	—	—	—	—	—	—	—	—
11 (2705)	4 (0-9)	4 (0-9)	4 (1-10)	4 (1-10)	4 (1-12)	4 (1-12)	4 (1-12)	4 (1-12)	5 (1-13)	5 (1-13)	5 (1-13)	—	—	—	—	—	—	—	—	—
12 (2016)	4 (0-9)	4 (0-9)	4 (1-10)	4 (1-12)	4 (1-14)	4 (1-13)	4 (1-13)	5 (1-13)	5 (1-13)	5 (2-13)	5 (2-13)	5 (2-13)	—	—	—	—	—	—	—	—
13 (1617)	4 (0-9)	4 (0-9)	4 (0-9)	4 (1-12)	4 (1-12)	4 (1-14)	4 (1-14)	4 (1-14)	5 (1-14)	5 (2-13)	5 (2-13)	5 (2-13)	5 (2-13)	—	—	—	—	—	—	—
14 (1249)	4 (0-9)	4 (0-10)	4 (0-10)	4 (1-12)	4 (1-13)	4 (1-14)	4 (1-14)	4 (1-14)	5 (1-14)	5 (1-14)	5 (2-13)	5 (2-13)	5 (2-13)	6 (2-13)	—	—	—	—	—	—
15 (954)	4 (0-9)	4 (0-9)	4 (0-12)	4 (1-12)	4 (1-14)	4 (1-14)	4 (1-14)	5 (1-14)	5 (1-14)	6 (2-14)	6 (2-14)	5 (2-13)	5 (2-13)	5 (2-13)	6 (2-13)	—	—	—	—	—
16 (651)	4 (0-10)	4 (0-10)	4 (0-14)	4 (1-12)	4 (1-14)	4 (1-14)	5 (1-14)	4 (1-14)	5 (1-14)	7 (2-14)	6 (2-14)	6 (2-13)	7 (2-13)	6 (2-13)	6 (2-13)	8 (3-14)	—	—	—	—
17 (422)	4 (0-10)	4 (0-14)	4 (0-10)	4 (1-14)	4 (1-16)	4 (1-14)	5 (1-14)	4 (1-16)	5 (1-14)	7 (1-16)	5 (2-14)	7 (2-14)	7 (2-13)	7 (2-14)	7 (2-13)	8 (2-16)	8 (2-13)	—	—	—
18 (281)	4 (0-11)	4 (0-12)	4 (0-14)	4 (0-10)	4 (1-16)	4 (1-16)	7 (1-14)	4 (1-14)	4 (1-14)	6 (1-14)	8 (3-16)	7 (3-13)	7 (3-13)	7 (2-13)	7 (2-13)	8 (2-13)	8 (2-13)	8 (2-16)	—	—
19 (147)	4 (0-11)	4 (1-10)	4 (0-14)	4 (0-16)	4 (1-16)	9 (1-16)	7 (1-16)	7 (1-16)	9 (4-14)	8 (4-16)	9 (4-16)	9 (4-16)	10 (4-23)	10 (4-17)	12 (4-18)	10 (1-19)	13 (5-16)	13 (4-17)	13 (4-24)	—
20 (54)	1 (0-4)	4 (0-9)	4 (0-12)	4 (0-10)	5 (0-14)	4 (1-14)	4 (1-16)	4 (1-14)	5 (1-16)	7 (1-14)	4 (4-19)	7 (1-19)	6 (3-13)	5 (2-13)	8 (2-14)	6 (2-13)	7 (3-13)	11 (1-13)	7 (4-16)	13 (2-26)
All (210327)*	2 (0-7)	3 (0-9)	4 (1-9)	4 (1-9)	4 (1-10)	4 (1-11)	4 (1-12)	5 (1-13)	5 (1-13)	5 (2-13)	5 (2-13)	6 (2-13)	6 (2-13)	6 (1-13)	7 (2-13)	8 (2-15)	9 (3-13)	10 (2-16)	12 (4-24)	13 (2-26)

Values are median (25^{th}-75^{th}) in MET-h/week and presented without decimals for simplicity purposes. * Participants with between 2 and 20 medical examinations and data available in each medical examination.

Table S3. Descriptive characteristics in the total sample at baseline

n	210327
Sex	
Men	103853 (49.4)
Women	106474 (50.6)
Age groups	
18-39 years	129638 (61.6)
40-64 years	73108 (34.8)
65 years and above	7581 (3.6)
Educational attainment	
Middle school or below	25090 (11.9)
High school	10967 (5.2)
Junior school	94439 (44.9)
College or above	77836 (37.0)
Marital status	
Married or living with partner	134201 (63.8)
Single or widowed	70682 (33.6)
Smoking status	
Never	149265 (71.0)
Former	12038 (5.7)
Current	41882 (19.9)
Alcohol consumption	
Never	164612 (78.3)
Former	4628 (2.2)
Current	30461 (14.5)
Regular meal patterns	
Suboptimal	80600 (38.3)
Optimal	123425 (58.7)
Occupational physical activity	
Sedentary	125039 (59.5)
Sedentary with occasional walking	57500 (27.3)
Standing or walking	18556 (8.8)
Heavy labor	4464 (2.1)
Body mass index	
< 25 kg/m^2	158587 (75.4)
≥ 25 kg/m^2	51691 (24.6)
Hypertension	
No	180797 (86.0)
Yes	29530 (14.0)
Dyslipidemia	
No	124285 (59.1)
Yes	86042 (40.9)
Diabetes	
No	202906 (96.5)
Yes	7421 (3.5)
Electrocardiogram	
Normal	171049 (81.3)
Abnormal	39017 (18.6)

Values are n (%).

Table S4. Number of data points of repeated measures in the present study and long-term leisure-time physical activity

Nº of repeated measures	Nº of potential measures	Participants	Person-time at risk*	Deaths	Period of following physical activity	Data points of physical activity	Long-term leisure-time physical activity (MET-h/week)
2	14 (10-18)	78559	1343.4 (997.7-1649.7)	4755	2.1 (1.3-3.6)	157118	3.2 (0.8-8.3)
3	15 (10-18)	43977	760.8 (576.1-923.5)	2373	4.0 (2.7-6.2)	131931	3.6 (1.3-8.6)
4	15 (11-19)	26125	462.4 (363.1-561.7)	1196	5.9 (4.0-8.4)	104500	4.0 (1.6-8.9)
5	16 (12-19)	17222	313.4 (249.7-372.0)	722	7.3 (5.1-10.1)	86110	4.3 (1.8-9.3)
6	16 (13-19)	11546	213.6 (177.5-252.9)	454	8.8 (6.5-11.7)	69276	4.6 (2.0-9.5)
7	17 (13-19)	8387	165.2 (135.0-185.4)	307	9.9 (7.7-12.7)	58709	4.9 (2.1-9.8)
8	17 (14-19)	6256	124.8 (103.8-139.4)	213	10.8 (8.7-13.5)	50048	5.2 (2.3-10.3)
9	18 (15-19)	4599	95.2 (66.7-103.2)	135	11.9 (9.8-14.4)	41391	5.2 (2.4-10.6)
10	18 (15-20)	3560	74.9 (63.4-80.1)	108	12.7 (10.7-14.8)	35600	5.9 (2.8-11.3)
11	19 (16-20)	2705	58.2 (50.8-61.2)	87	13.5 (11.6-15.6)	29755	5.8 (2.8-11.2)
12	19 (17-20)	2016	43.9 (39.5-45.9)	68	14.3 (12.7-16.1)	24192	6.6 (3.0-12.2)
13	19 (17-20)	1617	35.6 (32.3-36.9)	47	15.0 (13.5-16.7)	21021	6.6 (3.1-12.2)
14	19 (18-20)	1249	27.7 (25.7-28.6)	34	15.6 (14.4-17.0)	17486	6.5 (3.3-12.1)
15	20 (18-20)	954	21.5 (20.1-21.9)	11	16.0 (15.1-18.0)	14310	7.1 (3.3-13.1)
16	20 (19-20)	651	14.7 (14.2-14.9)	14	17.0 (15.8-18.3)	10416	7.6 (3.9-12.8)
17	20 (19-20)	422	9.5 (9.2-9.7)	9	17.9 (16.8-18.7)	7174	7.7 (3.6-14.4)
18	20 (19-20)	281	6.4 (6.2-6.5)	5	18.4 (17.8-18.9)	5058	7.8 (4.0-14.0)
19	20 (20-20)	147	3.4 (3.3-3.4)	1	18.8 (18.3-19.2)	2793	9.3 (4.8-15.1)
20	20 (20-20)	54	1.2 (1.2-1.2)	0	19.0 (18.9-19.2)	1080	7.7 (4.8-13.5)
All	15 (11-19)	210327	3806.9 (2923.5-4543.1)	10539	4.8 (2.3-9.0)	867968	3.8 (1.3-9.0)

Values are median (25^{th}-75^{th}). *Per 1000.

Table S5. Study population characteristics at baseline by number of examinations

	Number of medical examinations			
	2	3	4	5 or more
n	76318	44093	26582	63334
Sex				
Male	36541 (47.9)	21737 (49.3)	13331 (50.2)	32244 (50.9)
Female	39777 (52.1)	22356 (50.7)	13251 (49.9)	31090 (49.1)
Age groups				
18-39 years	46806 (61.3)	27350 (62.0)	16719 (62.9)	38236 (60.4)
40-64 years	26094 (34.2)	15086 (34.2)	9000 (33.9)	23372 (36.9)
65 years and above	3418 (4.5)	1657 (3.8)	863 (3.3)	1726 (2.7)
Educational attainment				
Middle school or below	10238 (13.4)	5243 (11.9)	3010 (11.3)	6599 (10.4)
High school	4120 (5.4)	2312 (5.2)	1300 (4.9)	3235 (5.1)
Junior school	32822 (43.0)	19184 (43.5)	11846 (44.6)	30587 (48.3)
College or above	28374 (37.2)	16921 (38.4)	10201 (38.4)	22340 (35.3)
Marital status				
Married or living with partner	46345 (60.7)	27148 (61.6)	16656 (62.7)	44052 (69.6)
Single or widowed	27771 (36.4)	15721 (35.7)	9234 (34.7)	17956 (28.4)
Smoking status				
Never	53879 (70.6)	31334 (71.1)	18994 (71.5)	45058 (71.1)
Former	4307 (5.6)	2496 (5.7)	1506 (5.7)	3729 (5.9)
Current	15699 (20.6)	8893 (20.2)	5242 (19.7)	12048 (19.0)
Alcohol consumption				
Never	59666 (78.2)	34653 (78.6)	21088 (79.3)	49205 (77.7)
Former	1824 (2.4)	993 (2.3)	531 (2.0)	1280 (2.0)
Current	11056 (14.5)	6315 (14.3)	3712 (14.0)	9378 (14.8)
Regular meal patterns				
Suboptimal	30569 (40.1)	17282 (39.2)	10337 (38.9)	22412 (35.4)
Optimal	43594 (57.1)	25554 (58.0)	15507 (58.3)	38770 (61.2)
Occupational physical activity				
Sedentary	44875 (58.8)	26279 (59.6)	15797 (59.4)	38088 (60.1)
Sedentary with occasional walking	20740 (27.2)	11956 (27.1)	7320 (27.5)	17484 (27.6)
Standing or walking	7058 (9.3)	3943 (8.9)	2318 (8.7)	5237 (8.3)
Heavy labor	1834 (2.4)	900 (2.0)	578 (2.2)	1152 (1.8)
Body mass index				
< 25 kg/m^2	56760 (74.4)	33020 (74.9)	20020 (75.3)	48787 (77.0)
≥ 25 kg/m^2	19539 (25.6)	11065 (25.1)	6555 (24.7)	14532 (23.0)
Hypertension				
No	64942 (85.1)	37734 (85.6)	22932 (86.3)	55189 (87.1)
Yes	11376 (14.9)	6359 (14.4)	3650 (13.7)	8145 (12.9)
Dyslipidemia				
No	45972 (60.2)	26593 (60.3)	15903 (59.8)	35817 (56.6)
Yes	30346 (39.8)	17500 (39.7)	10679 (40.2)	27517 (43.5)
Diabetes				
No	73138 (95.8)	42495 (96.4)	25655 (96.5)	61617 (97.3)
Yes	3180 (4.2)	1598 (3.6)	927 (3.5)	1717 (2.7)
Electrocardiogram				
Normal	61193 (80.2)	35679 (80.9)	21693 (81.6)	52484 (82.9)
Abnormal	15023 (19.7)	8345 (18.9)	4861 (18.3)	10788 (17.0)

Values are n (%).

Table S6. Associations between long-term leisure-time physical activity categories with all-cause and cardiovascular mortality in sequentially adjusted models

	None	Insufficient	Recommended	Additional
n	14042	131838	40065	24382
All-cause mortality				
deaths	930	5148	2617	1844
Age-adjusted HR (95%CI)	1 (Reference)	0.70 (0.65-0.75)	0.58 (0.54-0.63)	0.55 (0.50-0.59)
Multivariable-adjusted 1 HR (95%CI)	1 (Reference)	0.75 (0.70-0.80)	0.62 (0.58-0.67)	0.55 (0.51-0.60)
Multivariable-adjusted 2 HR (95%CI)	1 (Reference)	0.77 (0.72-0.83)	0.66 (0.61-0.71)	0.60 (0.55-0.65)
Multivariable-adjusted 3 HR (95%CI)	1 (Reference)	0.75 (0.70-0.81)	0.65 (0.60-0.70)	0.58 (0.53-0.63)
Multivariable-adjusted 4 HR (95%CI)	1 (Reference)	0.74 (0.69-0.80)	0.64 (0.60-0.70)	0.59 (0.54-0.64)
Cardiovascular mortality				
deaths	178	896	476	369
Age-adjusted HR (95%CI)	1 (Reference)	0.66 (0.56-0.77)	0.52 (0.44-0.62)	0.53 (0.44-0.63)
Multivariable-adjusted 1 HR (95%CI)	1 (Reference)	0.70 (0.60-0.82)	0.56 (0.47-0.66)	0.53 (0.44-0.64)
Multivariable-adjusted 2 HR (95%CI)	1 (Reference)	0.72 (0.62-0.85)	0.59 (0.50-0.70)	0.58 (0.48-0.70)
Multivariable-adjusted 3 HR (95%CI)	1 (Reference)	0.70 (0.60-0.83)	0.57 (0.48-0.68)	0.56 (0.47-0.68)
Multivariable-adjusted 4 HR (95%CI)	1 (Reference)	0.68 (0.58-0.80)	0.56 (0.47-0.67)	0.56 (0.47-0.68)

Long-term leisure-time physical activity was calculated (cumulative average) with between 2 and 20 repeated measures from 1997 to 2016. Insufficient: 0.01-7.49 MET-h/week. Recommended: 7.50-15.00 MET-h/week. Additional: >15.00 MET-h/week. Multivariable-adjusted 1 includes age (time scale), sex, educational level, and marital status. Multivariable-adjusted 2 includes covariates from Multivariable-adjusted 1 plus smoking, alcohol consumption, occupational physical activity and regular meal patterns. Multivariable-adjusted 3 includes covariates form Multivariable-adjusted 2 plus cancer and cardiovascular disease. Multivariable-adjusted 4 includes covariates form Multivariable-adjusted 3 plus body mass index groups, diabetes, hypertension, dyslipidemia, and electrocardiogram.

Table S7. Associations between long-term leisure-time physical activity with all-cause and cardiovascular mortality among groups with insufficient physical activity

	MET-h/week		
	0	0.01-3.74	3.75-7.49
n	14042	90536	41302
All-cause mortality			
deaths	930	3413	1735
HR (95%CI)	1 (Reference)	0.78 (0.72-0.83)	0.68 (0.63-0.74)
Cardiovascular mortality			
deaths	178	577	319
HR (95%CI)	1 (Reference)	0.70 (0.59-0.83)	0.65 (0.54-0.78)

HR, Hazard ratios. CI, confidence interval. Long-term leisure-time physical activity was calculated (cumulative average) with between 2 and 20 repeated measures from 1997 to 2016. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, cancer, cardiovascular disease, diabetes, hypertension, dyslipidemia, and electrocardiogram.

Table S8. Associations of leisure-time physical activity at baseline (first examination) with all-cause and cardiovascular mortality

	None	Insufficient	Recommended	Additional
n	61965	95846	25425	27091
All-cause mortality				
deaths	3077	3631	2044	1787
HR (95%CI)	1 (Reference)	0.88 (0.84-0.93)	0.83 (0.78-0.88)	0.78 (0.73-0.83)
Cardiovascular mortality				
deaths	535	651	382	351
HR (95%CI)	1 (Reference)	0.91 (0.81-1.02)	0.78 (0.68-0.89)	0.80 (0.70-0.92)

HR, Hazard ratios. CI, confidence interval. Insufficient: 0.01-7.49 MET-h/week. Recommended: 7.50-15.00 MET-h/week. Additional: >15.00 MET-h/week. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, cancer, cardiovascular diseases, diabetes, hypertension, dyslipidemia, and electrocardiogram.

Table S9. Associations of long-term leisure-time physical activity categories with all-cause and cardiovascular mortality excluding selected participants

	None	Insufficient	Recommended	Additional
Excluding 61062 current/former smoker participants				
n	9355	95120	28274	16516
All-cause mortality				
deaths	446	2950	1581	1107
HR (95%CI)	1 (Reference)	0.74 (0.67-0.82)	0.64 (0.58-0.71)	0.62 (0.55-0.70)
Cardiovascular mortality				
deaths	88	504	288	223
HR (95%CI)	1 (Reference)	0.67 (0.53-0.84)	0.54 (0.42-0.68)	0.56 (0.44-0.72)
Excluding 9009 participants with incident cancer/CVD *				
n	13703	127036	37728	22851
All-cause mortality				
deaths	836	4444	2191	1557
HR (95%CI)	1 (Reference)	0.78 (0.72-0.84)	0.67 (0.62-0.73)	0.63 (0.57-0.68)
Cardiovascular mortality				
deaths	160	737	392	299
HR (95%CI)	1 (Reference)	0.70 (0.59-0.83)	0.59 (0.49-0.71)	0.59 (0.49-0.72)
Excluding 2360 participants who died the first 4 years of follow-up				
n	13885	130644	39478	23960
All-cause mortality				
deaths	773	3954	2030	1422
HR (95%CI)	1 (Reference)	0.72 (0.66-0.77)	0.59 (0.54-0.65)	0.54 (0.49-0.59)
Cardiovascular mortality				
deaths	147	721	376	309
HR (95%CI)	1 (Reference)	0.68 (0.57-0.82)	0.55 (0.46-0.67)	0.58 (0.47-0.71)

CVD, cardiovascular disease. HR, Hazard ratios. CI, confidence interval. *Physician-diagnosed cancer or cardiovascular disease reported in subsequent medical examinations. Long-term leisure-time physical activity was calculated (cumulative average) with between 2 and 20 repeated measures from 1997 to 2016. Insufficient: 0.01-7.49 MET-h/week. Recommended: 7.50-15.00 MET-h/week. Additional: >15.00 MET-h/week. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, meal patterns, cancer, CVD, diabetes, hypertension, dyslipidemia, and electrocardiogram.

Table S10. Associations between long-term leisure-time physical activity categories modeled with two different methods and in the last examination and with all-cause and cardiovascular mortality

		All-cause mortality		Cardiovascular mortality	
	n	deaths	HR (95%CI)	deaths	HR (95%CI)
Cumulative average given more weight to the first (baseline) examination before the outcome*					
None	14042	930	1 (Reference)	178	1 (Reference)
Insufficient	136329	5287	0.72 (0.67-0.77)	917	0.66 (0.56-0.78)
Recommended	36866	2603	0.67 (0.62-0.72)	481	0.58 (0.49-0.69)
Additional	23090	1719	0.61 (0.56-0.66)	343	0.58 (0.48-0.71)
Cumulative average given more weight to the most recent (last) examination before the outcome*					
None	14042	930	1 (Reference)	178	1 (Reference)
Insufficient	130090	5128	0.74 (0.69-0.80)	890	0.68 (0.58-0.80)
Recommended	39407	2581	0.66 (0.61-0.71)	483	0.59 (0.50-0.71)
Additional	26788	1900	0.57 (0.53-0.62)	368	0.54 (0.45-0.65)
Last examination (simple update) before the outcome					
None	50054	2532	1 (Reference)	482	1 (Reference)
Insufficient	95805	3629	0.87 (0.82-0.91)	607	0.76 (0.67-0.85)
Recommended	33357	2207	0.79 (0.74-0.83)	415	0.71 (0.63-0.82)
Additional	31111	2171	0.73 (0.69-0.78)	415	0.70 (0.61-0.80)

*Long-term leisure-time physical activity was calculated (cumulative average) with between 2 and 20 repeated measures from 1997 to 2016. Analyses were adjusted for age (time scale), sex, educational level, marital status, smoking, alcohol consumption, body mass index groups, occupational physical activity, regular meal patterns, cancer, cardiovascular disease, diabetes, hypertension, dyslipidemia, and electrocardiogram.