図１　研究全体の枠組み（予防方法の評価から普及および普及方法の評価までの流れ）

		予防要因の特定	予防方法の特定		普及方法の特定			普及	普及度および普及方法の評価	
		レビュー	レビュー	エビデンス作り	レビュー	普及のための戦略づくり	普及のための戦術づくり	実際の普及活動	ベースラインの測定	普及効果の測定
禁煙・防煙	今年度実施済み	・禁煙 および防煙に決定	・禁煙は禁煙治療薬、ニコチン置換療法 ・防煙はエビデンスレベルの高い予防方法なし		・価格を上げること、マスメディアと他の複合キャンペーンが効果あり	・首都圏大学生を対象にHabit & Practice 調査を実施				
	2年目、3年目予定					・セグメンテーション ・ターゲティング ・形成的調査 ・トライアル調査 ・情報探索行動調査 ・メディア接触・評価調査	・実際の普及活動を計画 ・連携できるメディア、企業、行政などを検討	・全国規模の普及活動		・短期的エンドポイント(普及活動の認知度、がん予防の知識や行動の変化)を用いた評価
食事・運動	今年度実施済み	・食事は野菜・果物の摂取増加、減塩に決定 ・運動は身体活動の増加、適正体重の維持に決定	・食事、運動ともにエビデンスレベルの高い予防方法なし	・測定することの効果を検証するRCTを計画	・食事はエビデンスの高い普及方法なし ・運動はコミュニティワイドキャンペーンと学校での介入が効果あり	・茨城県水戸市、宮崎県串間市、宮崎県日南市、埼玉県三郷市の視察とヒアリング				
	2年目、3年目予定			・測定による効果を検証するRCTを実施		・Habit & Practice 調査 ・セグメンテーション ・ターゲティング ・形成的調査 ・トライアル調査 ・情報探索行動調査 ・メディア接触・評価調査	・実際の普及活動を計画 ・連携できるメディア、企業、行政などを検討	・特定地域における普及活動		・短期的エンドポイント(普及活動の認知度、がん予防の知識や行動の変化)を用いた評価
総合(がん予防全般)	今年度実施済み				・シリアスゲームに関するレビュー	・がん予防知識・行動の普及の対象、方法を検討するためのベースライン調査(インターネット調査) ・シリアスゲーム試作版の開発			・がん予防の知識・行動の実践に関するベースライン調査(インターネット調査)	
	2年目、3年目予定					・シリアスゲーム完成版の開発	・シリアスゲームの普及方法について検討	・シリアスゲームの配布		・シリアスゲームによる知識普及効果の測定

図2　具体的な研究計画および進捗(予防要因の特定から普及および普及方法の評価まで)

Ⅲ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

雑誌

発表者名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hayashino Y, Tanaka H, et al.	A prospective study of passive smoking and risk of diabetes in a cohort of works.	Diabetes Care	31	732-734	2008
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Iwasaki M, Inoue M, Otani T, Sasazuki S, Kurahashi N, Miura T, Yamamoto S, Tsugane S.	Plasma isoflavone level and subsequent risk of breast cancer among Japanese women: a nested case-control study from the Japan public health center-based prospective study group.	J Clin Oncol.	26	1677-83	2008
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Ⅳ. 研究成果の刊行物・別刷

A Prospective Study of Passive Smoking and Risk of Diabetes in a Cohort of Workers

The High-Risk and Population Strategy for Occupational Health Promotion (HIPOP-OHP) study

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OBJECTIVE — We investigated the impact of active smoking and exposure to passive smoke on the risk of developing diabetes.

RESEARCH DESIGN AND METHODS — Data were analyzed from a cohort of participants in the High-Risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP) conducted in Japan from 1999 to 2004. Active and passive smoking status in the workplace was evaluated at baseline.

RESULTS — Of 6,498 participants (20.9% women), a total of 229 diabetes cases were reported over a median 3.4 years of follow-up. In the workplace, compared with zero-exposure subjects, the multivariable-adjusted hazard ratios of developing diabetes were 1.81 (95% CI 1.06–3.08, $P = 0.028$) for present passive subjects and 1.99 (1.29–3.04, $P = 0.002$) for present active smokers.

CONCLUSIONS — In this cohort, exposure to passive smoke in the workplace was associated with an increased risk of diabetes after adjustment for a large number of possible confounders.

Diabetes Care 31:732–734, 2008

A positive association between active smoking and the incidence of diabetes has been identified (1–3). Only one study has shown a significant association between passive smoke and impaired glucose tolerance (4), and the association between exposure to passive smoke and the risk of developing diabetes has not been fully investigated. Here, we examine the relationship between exposure to passive smoke in the workplace or at home and the risk of developing diabetes in a large sample from a nonrandomized health promotion intervention study conducted at workplaces in Japan.

RESEARCH DESIGN AND METHODS

Analyses were performed using baseline and annual follow-up data from the High-Risk and Population Strategy for Occupational Health Promotion Study (HIPOP-OHP) conducted between 1999 and 2004 at 12 large-scale companies, excluding prevalent diabetes cases or those who did not report active or passive smoking status at baseline. Full-time employees at the worksites were enrolled, and then the worksites were nonrandomly assigned to either the intervention or control groups (13–20). All participants underwent an annual health check including blood testing at baseline and thereafter. A history of diabetes as well as lifestyle variables such as daily alcohol intake and smoking habits were evaluated using a self-administered questionnaire (5–7).

We constructed the following four categories by combining active smoking status and passive smoking status at workplace or at home as follows: *1*) "zero exposure" included those who never smoked and were not currently exposed to passive smoke; 2) "past active only" included those who had smoked in the past but did not currently smoke and were not currently exposed to passive smoke; 3) "present passive" included those currently exposed to passive smoke but who did not actively smoke, irrespective of past smoking; and *4*) "present active" included those who currently smoke irrespective of exposure to passive smoke.

A subject was considered diabetic if at least one of the following parameters was met: fasting blood glucose level ≥126 mg/dl (≥7.0 mmol/l), random plasma glucose level ≤200 mg/dl (≤11.1 mmol/l), or treatment with hypoglycemic medication (insulin or oral hypoglycemic agent). A self-reported history of diabetes was also accepted, since self-reported diagnosis of diabetes has been shown to be reliable (8) and has been used in many cohort studies (9,10).

Statistical analyses

We used the Cox proportional hazards model to analyze the association between passive smoking and incident diabetes cases. Person-time was calculated from the return of the baseline questionnaire until the date of the annual health check, at which the diagnosis of diabetes was

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*A complete list of the members of the HIPOP-OHP Research Group can be found in the APPENDIX.

Table 1—*Age-adjusted baseline characteristics of the study participants according to active and passive smoking status for men and women, aged 19–69 years (1999–2000, HIPOP-OHP, Japan)*

	Smoking status			
	Zero exposure	Past active only	Present passive	Present active
Participants (n)	2,129	779	690	2,900
Age (years)	36.9	41.7	39.3	37.9
Female (%)	45.5	6.4	30.6	4.5
BMI (kg/m^2)	22.3	22.7	22.7	22.9
Physical activity (MET h/week)	4.8	6.7	6.3	4.6
Alcohol (g/day)	11.2	22.7	15.7	26.9
Family history of diabetes (%)	20.1	16.1	18.5	18
Hypertension (%)	10.3	19.8	11.3	12.3
Health promotion intervention (%)	46.0	41.6	46.7	44
Frequency of sweetened beverage intake ≥1/day (%)	20.5	17.6	19.0	19.7
Frequency of vegetable intake <1/week (%)	47.3	45.9	46.7	47.2
Do not care about eating too much fat at all (%)	18.2	16.4	17.3	17.8

MET h, metabolic equivalent hours

confirmed, or the end of the follow-up, whichever occurred first.

We evaluated the effect of active smoking and exposure to passive smoke on the risk of developing diabetes in a multivariable-adjusted model, adjusting for all variables listed in Table 1. Likelihood ratio tests were used to test statistical interactions between passive smoking status and sex, BMI, or assigned intervention.

RESULTS

Of the 6,498 participants (20.9% women), 44.6% were current smokers (average of 19.6 cigarettes smoked per day), while 12.6% reported exposure to passive smoke in the workplace. Approximately 32% of participants dropped out during the follow-up.

Age-adjusted baseline characteristics of the study participants are summarized in Table 1 by active smoking and exposure to passive smoke at workplace. In the workplace, compared with zero-exposure subjects, the multivariable-adjusted hazard ratios (HRs) for past active–only subjects, present passive subjects, and present active smokers were 1.15 (95% CI 0.66–2.03, $P = 0.62$), 1.81 (1.06–3.19, $P = 0.028$), and 1.99 (1.29–3.04, $P = 0.002$), respectively, in the analysis including all subjects; 1.23 (0.56–2.73, $P = 0.60$), 2.76 (1.38–5.50, $P = 0.004$), and 2.09 (1.14–3.82, $P = 0.017$), respectively, in the control group; and 1.19 (0.23–2.71, $P = 0.84$), 0.70 (0.25–1.92, $P = 0.50$), and 1.99 (1.07–3.70, $P = 0.03$), respectively, in the intervention group. We did not observe statistically significant interactions between exposure to passive smoke and sex ($P = 0.74$, 1 d.f., $\chi^2 = 0.60$), obesity ($P = 0.77$, 1 d.f., $\chi^2 = 0.08$), or health promotion intervention ($P = 0.087$, 1d.f., $\chi^2 = 0.60$). At home, the multivariable-adjusted HRs for past active–only subjects, present passive subjects, and present active smokers were 0.97 (0.59–1.60, $P = 0.92$), 0.80 (0.46–1.40, $P = 0.44$), and 1.42 (0.98–2.04, $P = 0.062$), respectively.

CONCLUSIONS— In this 4-year prospective study conducted in the workplace, self-reported exposure to environmental tobacco smoke in the workplace and current active smoking at baseline were positively associated with an increased risk of developing diabetes, even after adjustment for a large number of possible confounders. To our knowledge, only one study has explored the association between exposure to passive smoke and subsequent risk of diabetes, which yielded similar results to our study, although not statistically significant (4). A possible limitation of our study is that the results might be underestimated by time-dependent confounding by smoking status; in fact, exposure to passive smoke in the workplace was not associated with the risk of diabetes in the intervention group, possibly due to lowered exposure to passive smoke by intervention. These findings add new evidence to support the need for measures to lessen environmental tobacco smoke in the workplace, especially in Asian populations, in which both the genetic susceptibility to diabetes (11,12) and smoking rate (13) are generally high.

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APPENDIX

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ELSEVIER

Daily Total Physical Activity Level and Premature Death in Men and Women: Results From a Large-Scale Population-Based Cohort Study in Japan (JPHC Study)

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PURPOSE: The impact of daily total physical activity level on premature deaths has not been fully clarified in non-Western, relatively lean populations. We prospectively examined the association between daily total physical activity level (METs/day) and subsequent risk of all-cause mortality and mortalities from cancer, heart disease, and cerebrovascular disease.

METHODS: A total of 83,034 general Japanese citizens ages 45–74 years who responded to the questionnaire in 1995–1999 were followed for any cause of death through December 2005. Mutlivariate-adjusted hazard ratios were calculated with a Cox proportional hazards model controlling for potential confounding factors.

RESULTS: During follow-up, a total of 4564 deaths were recorded. Compared with subjects in the lowest quartile, increased daily total physical activity was associated with a significantly decreased risk of all-cause mortality in both sexes (hazard ratios for the second, third, and highest quartiles were: men, 0.79, 0.82, 0.73 and women, 0.75, 0.64, 0.61, respectively). The decreased risk was observed regardless of age, frequency of leisure-time sports or physical exercise, or obesity status, albeit with a degree of risk attenuation among those with a high body mass index. A significantly decreased risk was similarly observed for death from cancer and heart disease in both sexes, and from cerebrovascular disease in women.

CONCLUSION: Greater daily total physical activity level, either from occupation, daily life, or leisure time, may be of benefit in preventing premature death.

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KEY WORDS: Physical Activity, Population-Based, Cohort Study, Mortality

INTRODUCTION

To date, a number of studies have reported the health benefits of physical activity, including a reduction in the risk of premature death (1–4) as well as in the risk of major causes of death, such as cardiovascular disease (2, 5) and cancer at some sites (6, 7). Physical activity is now regarded as one of the most important targets for the prevention of premature death and other adverse health outcomes (8). Physical activity has been assessed using various types of activity category, such as leisure and nonleisure time activity, physical exercise or sports, and nonexercise activity, such as occupational and household work. However, the need for comprehensive evaluation of these physical activities in the aggregate, particularly with regard to nonexercise physical activity, has been recognized (9).

From a public health point of view, as well as to clarify which type of physical activity has the strongest impact, it is important to estimate the impact of overall physical activity level on major outcomes, whether exercise or nonexercise and leisure time or nonleisure time. This in turn requires a quantitative approach to the assessment using a common scale for each activity, such as metabolic equivalent (MET). In addition, evidence from populations with a similar general lifestyle background is indispensable. Relatively few studies have assessed total physical activity using

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Selected Abbreviations and Acronyms

MET = metabolic equivalent
JPHC Study = Japan Public Health Center Study
ICD-10 = *International Classification of Disease, 10th Version*
HR = hazard ratio
95% CI = 95% confidence intervals

such a common quantitative scale (10–16), however, and those which have were conducted in Western populations. Evidence on physical activity and premature death in other populations is limited (16–19), particularly in Japanese (18, 19), with only two studies reported to date, one based on simple assessment of physical activity at work and the second on walking only. Thus, few studies have reported the effect of total physical activity on mortality in non-Western populations (16).

Here, we examined the association between daily total physical activity and mortality in the Japan Public Health Center-based Prospective Study (JPHC Study). Our main purposes were to estimate the impact of overall physical activity, including both exercise and nonexercise physical activities, on premature death, in other words, death before reaching the natural life span of Japanese, whose life expectancy is one of the highest in the world, at 79 years in men and 85 years in women by a 2005 life table using data from the Japanese Ministry of Health, Labour and Welfare. We also aimed to obtain epidemiologic evidence of this issue using a common quantitative scale for the assessment of any type of physical activity, from a population characterized as non-Western and relatively lean.

METHODS

Study Population

The JPHC Study was conducted in two cohorts, one initiated in 1990 (Cohort I) and the other in 1993 (Cohort II), which targeted all registered Japanese inhabitants in 11 public health center areas ages 40–59 years in Cohort I and 40–69 years in Cohort II at the beginning of each baseline survey. The details of the study design have been provided elsewhere (20). The study protocol was approved by the Institutional Review Board of the National Cancer Center, Japan (approval no.: 13–21).

The subjects of the present study were JPHC study subjects who responded to a 5-year follow-up self-administered questionnaire in 1995–1999 at ages 45–74 years. Initially at baseline, 140,420 subjects were identified as the study population. During the study period, a total of 258 subjects were found to be ineligible and excluded because of non-Japanese nationality (n = 51), duplicate enrollment (n = 4), late report of emigration occurring before the start of the follow-up period (n = 197), or incorrect birth date (n = 6). As a result, a population-based cohort of 140,162 subjects was established. After excluding 3,839 persons who had died, moved out of Japan, or were lost to follow-up before the start point, the remaining 136,323 subjects were considered eligible as the study population of the present study. A total of 103,791 subjects responded to the questionnaire, yielding a response rate of 76%.

Questionnaire

The questionnaire included items on demographics, personal medical history, physical activity, smoking and alcohol drinking status, other lifestyle factors, and diet via a validated food frequency of 138 food items and 14 supplementary questions (21). Those who reported a history of cancer, stroke, or myocardial infarction which had the potential to reduce physical activity (n = 5776), or had missing data for physical activity-related questions (n = 6351) or for other questions included in the multivariate model (n = 8630) were excluded. Finally 83,034 eligible subjects (39,183 men and 43,851 women) were included in the analysis.

Follow-Up

Subjects were followed from the start point (date of response to the 5-year follow-up questionnaire) until December 31, 2005. Residence status, including survival, was confirmed through the residential registry. Inspection of the resident registry is available to anyone under the resident registration law. Among the study subjects, 25 moved out of Japan, 1 withdraw participation, and 248 (0.3%) were lost to follow-up within the follow-up period. Information on the cause of death was obtained from the death certificate, provided by the Ministry of Health, Labour, and Welfare with the permission of the Ministry of Internal Affairs and Communications, in which cause of death is defined according to the *International Classification of Disease, 10th Version* (ICD-10) (22). Resident and death registration are required by law in Japan and the registries are believed to be complete.

The outcome of the present study was defined as all-cause mortality, including the three major causes of death in Japanese, namely cancer (ICD-10: C00-C97), heart disease (ICD-10: I20-I52), and cerebrovascular disease (ICD-10: I60-I69). During the study period, we identified 4564 deaths (3098 men and 1466 women), including 2044 deaths from cancer (1359 men and 685 women), 521 from heart disease (373 men and 148 women), and 453 from cerebrovascular disease (281 men and 172 women).

Physical Activity Levels

The main exposure of interest in the present study was daily total physical activity level. In our questionnaire (Appendix), subjects were asked about the average time spent per day on three types of physical activity, i.e., heavy physical

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work or strenuous exercise (none, <1 h, ≥1 h); sedentary activity (<3 h, 3–8 h, ≥8 h); and walking and standing (<1 h, 1–3 h, and ≥3 h). The following values were assigned as time scores for each activity; heavy physical work or strenuous exercise: 0 for none, 0.5 for <1 h, 3 for ≥1 h; sedentary activity: 1.5 for <3 hours, 5.5 for 3–8 h, and 7.5 for ≥8 h; and walking or standing: 0.5 for <1 h, 2 for 1–3 h, and 8.5 for ≥3 h. The midpoint of time range for each category was assigned when both minimum and maximum values were presented, and arbitrary values considered to have the highest validity from the validation study was assigned for the highest category. MET hours/day was estimated by multiplying the time score spent at each activity/day by its MET intensity (23): heavy physical work or strenuous exercise (4.5), walking or standing (2.0), sedentary (1.5), and sleep or others (0.9). After summing across all activities, subjects were grouped into four exposure levels by quartile of total METs/day by sex.

The validity of the total METs/day score was assessed using 108 eligible samples (53 men and 55 women) derived from 110 original volunteer subjects from the cohort using 4-day, 24-hour physical activity records (Sunday or another day off plus three weekdays) in two different seasons, namely harvesting and one other season in a single year. The mean of total METs/day for physical activity obtained from the self-report was 33.5 in men and 33.4 in women, whereas that from the mean of 24-hour physical activity record was 39.5 in men and 40.8 in women. Energy expenditure estimated in METs showed little difference by area. The Spearman's rank correlation coefficient between the total METs/day score and physical activity records was 0.46 when the average of two seasons was taken (men, 0.53; women, 0.35).

Analysis

The number of person-years in the follow-up period was counted from the start point, i.e., date of response to the 5-year follow-up questionnaire, until the date of death, date of emigration from Japan, or end of the study period, whichever came first. For subjects who withdraw from or were lost to follow-up, the date of withdrawal and the last confirmed date of presence, respectively, were used as the date of censor.

Hazard ratios (HR) and 95 % confidence intervals (95% CIs) were used to describe the relative risk of all-cause mortality associated with daily total physical activity level. Daily total physical activity was assessed by quartile of total METs/day score. The median METs/day value for each quartile was used when linear association was assessed. To investigate whether the effect on outcome differed by type of physical activity, we also assessed risk by the frequency of leisure-time sports or physical exercises (≤1–3 times per month, 1–2 times per week, 3–4 times per week, almost every day) in addition to the time spent per day for heavy physical work or strenuous exercise (none, <1 h, ≥1 h) and walking or standing (<1 h, 1–3 h, ≥3 h). Ordinal values were used to assess linear trends for these variables. We included a variable on the frequency of leisure-time sports or physical exercises and occupation in the model since this was not considered in calculating METs scores, although it was associated with physical activity level. The Cox proportional hazards model was used as a control for potential confounding factors, namely age at start point (5-year age categories), area (11 public health center areas), occupation (full-time agriculture/forestry/fishery, full-time salaried/self-employed/professional, multiple occupations, full-time housework/retired/unemployed), history of diabetes (no, yes), smoking status (never, past, current), alcohol intake status (almost none, occasional, regular), body mass index (14 to <20, 20 to <27, ≥27), and total energy intake (quintiles estimated by semi-quantitative food frequency questionnaire). These variables, obtained from the questionnaire, are either known or suspected from previous studies as risk factors for premature death.

Occupation, smoking status, alcohol intake frequency and body mass index were treated as strata to allow for a different baseline hazard for each stratum. Testing of the proportional hazards assumption by Schoenfeld and scaled Schoenfeld residuals found no violation of proportionality. In addition, we evaluated whether the effect of total physical activity was influenced by sex, age, body mass index, and frequency of leisure-time sports or physical exercise using a test of interaction by entering into the model multiplicative interaction terms between each factors. Because the effect of total physical activity was significantly influenced by sex (p for interaction = 0.004), all analyses were conducted by sex. Stata 10 (Stata Corporation, College Station, TX) (24) was used to perform statistical analyses.

RESULTS

During 725,071 person-years of follow-up (average follow-up period: 8.7 years) for 83,034 subjects (39,183 men and 43,851 women), a total of 4,564 deaths (3,098 men and 1,466 women) were identified and included in the analyses.

Characteristics of the study subjects according to physical activity level are shown in Table 1. The total METs/day scores for four groups, namely the lowest, second, third, and highest, were 25.45, 31.85, 34.25, and 42.65 in men and 26.10, 31.85, 34.25, and 42.65 in women, respectively. Occupationally, a greather proportion of those with full-time agriculture/forestry/fishery and lower proportion with full-time housework/unemployed/retired were observed with increased physical activity level in both sexes. Men who were more physically active were more likely to report current smoking, regular drinking, a greater frequency of

TABLE 1. Baseline characteristics of the study subjects according to physical activity level in the JPHC Study (n = 83,034)

	METs/day*			
	Lowest	Second	Third	Highest
Men (n = 39,183)				
Number of subjects	13,498	8,117	7,804	9,764
Quartile median of METs/day	25.45	31.85	34.25	42.65
(Range)	(21.60–27.10)	(27.25–31.85)	(32.40–36.05)	(36.25–46.25)
Age, years (mean ± SD)	56.1 ± 7.9	56.1 ± 7.6	56.6 ± 7.7	55.9 ± 7.4
Occupation (%)				
Full-time agriculture/forestry/fishery	11.4	16.5	19.9	26.9
Full-time salaried/self-employed/professional	72.5	69.1	64.9	57.7
Multiple occupations	3.5	6.5	6.9	12.3
Full-time housework/unemployed/retired	12.6	7.9	8.3	3.1
Body mass index (mean)	23.67	23.61	23.54	23.46
History of diabetes mellitus (%)	9.7	8.4	8.0	7.4
Current smokers (%)	47.7	47.0	47.4	49.0
Regular drinkers (≥1/week) (%)	65.9	68.5	68.5	71.4
Leisure-time sports or physical exercise (≥3–4/week) (%)	8.8	10.9	13.0	12.3
Total energy intake (age-adjusted mean, kcal/day)	2,042.8	2,140.9	2,171.2	2,302.8
Women (n = 43,851)				
Number of subjects	13,870	11,321	10,215	8,445
Quartile median of METs/day	26.10	31.85	34.25	42.65
(range)	(21.60–27.10)	(27.25–31.85)	(32.75–34.25)	(35.45–46.25)
Age, years (mean ± SD)	56.9±8.2	56.1±7.5	56.1±7.6	55.8±7.3
Occupation (%)				
Full-time agriculture/forestry/fishery	12.9	16.4	14.5	29.7
Full-time salaried/self-employed/professional	65.8	67.6	67.0	56.5
Multiple occupations	2.2	3.1	2.9	6.3
Full-time housework/unemployed/retired	19.1	12.8	15.8	7.4
Body mass index (mean)	23.53	23.38	23.33	23.44
History of diabetes mellitus (%)	4.7	3.7	3.4	3.8
Current smokers (%)	6.3	6.0	6.0	5.9
Regular drinkers (≥1/week) (%)	13.7	14.2	14.3	14.0
Leisure-time sports or physical exercise (≥3–4/week) (%)	9.5	9.7	11.7	15.0
Total energy intake (age-adjusted mean, kcal/day)	1,841.8	1,887.0	1,884.2	1,972.1

*Metabolic equivalent (MET)s/day = sum of the score for reported time per day spent in each physical activity multiplied by the MET value for each activity.

leisure-time sports or physical exercise, and higher daily mean energy consumption and less likely to report a history diabetes mellitus. No difference in body mass index was observed between groups by physical activity level. In women, similar trends were observed except that the differences in the proportion of current smokers and regular drinkers were not significant.

Associations between daily total physical activity level by total METs/day scores and all-cause and cause-specific mortalities are shown in Table 2. On multivariate adjustment, compared with subjects in the lowest quartile, increased daily total physical activity level was significantly associated with a decreased risk of all-cause mortality both in men (second highest, HR, 0.79 [95% CI, 0.71–0.87]; third highest, 0.82 [0.74–0.91]; highest, 0.73 [0.66–0.81], p for trend <0.001) and in women (second highest, 0.75 [0.66–0.85]; third highest, 0.64 [0.56–0.74]; highest, 0.61 [0.52–0.73], p for trend <0.001).

The results did not substantially differ after exclusion of early deaths occurring within 3 years of the start point, nor on further exclusion of subjects with very low physical activity levels less than 23 METs/day (4% of subjects) considered to be the result of poor physical condition (data not shown). Furthermore, inclusion of those who reported a history of cancer, stroke, or myocardial infarction resulted in a similar risk tendency: in men, second highest, 0.78 (0.72–0.86), third highest, 0.78 (0.71–0.86), highest, 0.72 (0.66–0.80), p for trend <0.001; and in women, second highest, 0.76 (0.67–0.86); third highest, 0.64 (0.56–0.74); highest, 0.60 (0.51–0.70), p for trend <0.001.

A significantly decreased risk for death from cancer and from heart disease was similarly observed in both sexes. A decreased risk for death from cerebrovascular disease was significant only in women. Decreased risk was equally observed regardless of age or frequency of leisure-time sports or physical exercise. When analyzed by obesity status, a decreased risk tendency was observed, but this was attenuated in the group with a body mass index of 27 or above. No significant effect modification was observed for age, obesity status, or frequency of leisure-time sport and physical exercises (data not shown).

TABLE 2. HRs and 95% CIs of all-cause and major specific-cause mortality according to daily total physical activity level by METs/day score quartiles (n=83,034)

			Total					Excluding deaths with first 3 years*		
Quartile (median for METs/day)	Number of subjects	Person-years	Number of deaths	HR1	(95%CI)	HR2	(95%CI)	Number of deaths	HR2	(95% CI)
Men (n = 39,183)										
All			(n = 3,098)					(n = 2,309)		
Lowest	13,498	112,789	1,249	1.00	(reference)	1.00	(reference)	889	1.00	(reference)
Second	8,117	70,212	590	**0.76**	**(0.68–0.83)**	**0.79**	**(0.71–0.87)**	450	**0.82**	**(0.74–0.93)**
Third	7,804	67,876	618	**0.79**	**(0.71–0.87)**	**0.82**	**(0.74–0.91)**	473	**0.86**	**(0.77–0.97)**
Highest	9,764	86,469	641	**0.67**	**(0.61–0.74)**	**0.73**	**(0.66–0.81)**	497	**0.77**	**(0.69–0.87)**
p for trend				**<0.001**		**<0.001**			**<0.001**	
Cancer (ICD10: C00-C97)			(n = 1,359)					(n = 996)		
Lowest	13,498	112,789	502	1.00	(reference)	1.00	(reference)	353	1.00	(reference)
Second	8,117	70,212	286	0.92	(0.79–1.06)	0.92	(0.80–1.07)	206	0.91	(0.77–1.09)
Third	7,804	67,876	284	0.89	(0.77–1.03)	0.89	(0.77–1.04)	217	0.94	(0.79–1.11)
Highest	9,764	86,469	287	**0.76**	**(0.66–0.88)**	**0.80**	**(0.68–0.93)**	220	**0.83**	**(0.69–0.99)**
p for trend				**<0.001**		**0.003**			**0.041**	
Heart diseases (ICD-10: I20-I52)			(n = 373)					(n= 275)		
Lowest	13,498	112,789	155	1.00	(reference)	1.00	(reference)	106	1.00	(reference)
Second	8,117	70,212	77	0.77	(0.59–1.02)	0.84	(0.64–1.11)	63	0.99	(0.72–1.36)
Third	7,804	67,876	62	**0.62**	**(0.46–0.83)**	**0.68**	**(0.50–0.92)**	45	**0.69**	**(0.48–0.99)**
Highest	9,764	86,469	79	**0.63**	**(0.48–0.82)**	**0.72**	**(0.54–0.96)**	61	0.78	(0.56–1.09)
p for trend				**<0.001**		**0.015**			0.076	
Cerebrovascular diseases (ICD-10: I60-I69)			(n = 281)					(n = 211)		
Lowest	13,498	112,789	99	1.00	(reference)	1.00	(reference)	74	1.00	(reference)
Second	8,117	70,212	53	0.85	(0.61–1.18)	0.89	(0.64–1.25)	44	0.98	(0.67–1.43)
Third	7,804	67,876	64	1.04	(0.76–1.43)	1.11	(0.81–1.53)	45	1.04	(0.71–1.51)
Highest	9,764	86,469	65	0.85	(0.62–1.16)	0.95	(0.68–1.32)	48	0.93	(0.63–1.36)
p for trend				0.417		0.927			0.737	
Women (n = 43,851)										
All			(n=1,466)					(n=1,134)		
Lowest	13,870	121,030	648	1.00	(reference)	1.00	(reference)	496	1.00	(reference)
Second	11,321	100,918	350	**0.70**	**(0.62–0.80)**	**0.75**	**(0.66–0.85)**	277	**0.76**	**(0.66–0.88)**
Third	10,215	90,696	274	**0.61**	**(0.53–0.70)**	**0.64**	**(0.56–0.74)**	215	**0.65**	**(0.55–0.77)**
Highest	8,445	75,082	194	**0.54**	**(0.46–0.64)**	**0.61**	**(0.52–0.73)**	146	**0.60**	**(0.49–0.72)**
p for trend				**<0.001**		**<0.001**			**<0.001**	
Cancer (ICD10: C00-C97)			(n=685)					(n=538)		
Lowest	13,870	121,030	263	1.00	(reference)	1.00	(reference)	209	1.00	(reference)
Second	11,321	100,918	175	0.84	(0.70–1.02)	0.87	(0.72–1.06)	139	0.87	(0.70–1.08)
Third	10,215	90,696	149	**0.79**	**(0.64–0.96)**	**0.81**	**(0.66–0.996)**	119	0.81	(0.64–1.01)
Highest	8,445	75,082	98	**0.65**	**(0.52–0.82)**	**0.69**	**(0.54–0.88)**	71	**0.62**	**(0.47–0.82)**
p for trend				**<0.001**		**0.001**			**0.001**	
Heart diseases (ICD-10: I20-I52)			(n=148)					(n=102)		
Lowest	13,870	121,030	73	1.00	(reference)	1.00	(reference)	51	1.00	(reference)
Second	11,321	100,918	32	**0.61**	**(0.40–0.93)**	0.71	(0.46–1.08)	23	0.73	(0.44–1.21)
Third	10,215	90,696	23	**0.49**	**(0.31–0.79)**	**0.55**	**(0.34–0.89)**	16	**0.54**	**(0.30–0.95)**
Highest	8,445	75,082	20	**0.52**	**(0.32–0.86)**	0.69	(0.41–1.17)	12	0.58	(0.30–1.12)
p for trend				**0.001**		**0.035**			**0.027**	
Cerebrovascular diseases (ICD-10: I60-I69)			(n=172)					(n=131)		
Lowest	13,870	121,030	76	1.00	(reference)	1.00	(reference)	55	1.00	(reference)
Second	11,321	100,918	42	0.72	(0.49–1.06)	0.74	(0.50–1.08)	34	0.78	(0.50–1.21)
Third	10,215	90,696	31	**0.58**	**(0.38–0.88)**	**0.60**	**(0.39–0.92)**	25	0.64	(0.39–1.04)
Highest	8,445	75,082	23	**0.56**	**(0.35–0.89)**	0.64	(0.39–1.04)	17	0.63	(0.36–1.11)
p for trend				**0.003**		**0.019**			**0.049**	

HR1: Adjusted for age (5-year age categories), area (11 PHC areas).
HR2: Adjusted for age (5-year age categories), area (11 PHC areas), occupation (stratified, full-time agriculture/forestry/fishery, full-time salaried/self-employed/professional, multiple occupations, full-time housework/retired/unemployed), history of diabetes (no, yes), smoking status (stratified, never, past, current), alcohol intake status (stratified, almost none, occasional, regular), body mass index (stratified, 14 to <20, 20 to <27, ≥27), total energy intake (quintiles) and leisure-time sports or physical exercise (<1 day/week, 1–2 days/week, ≥3–4 days/week).
*Exclusion of early deaths occurring within 3 years of the start point was done to reduce the effect of cases of poor physical condition which were considered to have been preceded by long-term inactivity.

When analyzed by type of physical activity (Table 3), both increased heavy physical work or strenuous exercise and walking or standing hours were significantly associated with a decreased risk of all-cause mortality. The decreased risk with increased frequency of leisure-time sports or physical exercise was observed more clearly in men than in women.

DISCUSSION

In this large-scale population-based prospective study of Japanese men and women, we found a significant inverse association between daily total physical activity level and all-cause mortality. Decreased risk was observed in both men and women. On analysis by type of physical activity, the decreasing trend was observed in both those with increased heavy physical work or strenuous exercises and those with longer walking or standing hours; and was also observed regardless of age, frequency of leisure-time sports or physical exercise or obesity status, despite some risk attenuation among those with a high body mass index. Decreased risk was also observed for major causes of mortality. High energy intake is considered associated with obesity and inactivity and was included in the model to control these effects to the greatest extent possible to see the effect of total physical activity level clearly. Since age range at the starting point was 45–74 years, which is less than life expectancy in both sexes, most deaths during the follow-up period occurred prematurely. To reduce the potential for spurious associations from reverse causation, namely that fatal diseases reduce physical activity, we excluded early deaths occurring within 3 years from the start point, but observed similar results. Furthermore, decreased risk was equally observed regardless of the frequency of leisure-time sports or physical exercise. Our results suggest that increased total physical activity level, either from occupation, daily life, or leisure time, helps in preventing premature death.

Although a number of studies have supported the health benefits of physical activity on all-cause mortality, only a few have assessed the association by daily total physical activity using a common activity scale such as MET (10–16). Our findings accord with these previous studies, notwithstanding that they were conducted in populations with general lifestyle possibly different from ours. In particular, although those with low physical activity levels have been reported to be typically more obese than those with higher levels in western populations (10, 11, 25, 28), no such tendency was observed in our population, nor also in a Chinese population (16). This suggests that the balance of contribution of the effects of physical activity on premature death may differ between non-Western, relatively lean populations and Western populations, namely that the indirect

TABLE 3. HRs* and 95%CIs of all-cause mortality according to type of physical activity (n = 83,034)

	Men (n = 39,183)					Women (n = 43,851)				
	Number of subjects	Person-years	Number of deaths	HR	(95%CI)	Number of subjects	Person-years	Number of deaths	HR	(95%CI)
Heavy physical work or strenuous exercise										
Non	23,026	195,805	2,076	1.00		32,779	290,280	1,208	1.00	
<1 h/day	5,415	46,711	299	**0.77**	**(0.68–0.88)**	4,335	37,629	103	0.83	(0.68–1.02)
≥1 h/day	10,742	94,830	723	**0.88**	**(0.80–0.96)**	6,737	59,816	155	**0.80**	**(0.67–0.96)**
p for trend				**0.001**					**0.004**	
Walking or standing hours										
<1 h/day	8,499	72,049	806	1.00		6,254	54,807	315	1.00	
1–3 h/day	9,601	80,288	767	**0.90**	**(0.81–0.99)**	10,410	90,763	423	**0.86**	**(0.74–0.99)**
≥3 h/day	21,083	185,009	1,525	**0.80**	**(0.73–0.88)**	27,187	242,154	728	**0.64**	**(0.55–0.73)**
p for trend				**<0.001**					**<0.001**	
Sedentary activities										
<3 h/day	17,667	152,673	1,331	1.00		19,651	173,068	648	1.00	
3–8 h/day	18,223	156,183	1,445	1.02	(0.95–1.11)	21,404	189,268	704	0.95	(0.85–1.06)
≥8 h/day	3,293	28,491	322	**1.18**	**(1.04–1.35)**	2,796	25,389	114	1.10	(0.82–1.25)
p for trend				**0.036**					0.698	
Leisure-time sports or physical exercise										
<1 day/week	30,526	264,625	2,547	1.00		34,239	306,097	1,221	1.00	
1–2 days/week	4,377	37,299	231	**0.75**	**(0.65–0.86)**	4,733	40,481	96	**0.69**	**(0.56–0.85)**
≥3–4 days/week	4,280	35,422	320	**0.78**	**(0.69–0.88)**	4,879	41,147	149	0.87	(0.73–1.03)
p for trend				**<0.001**					**0.008**	

*Model includes age (5-year age categories), area (11 PHC areas), occupation (stratified, full-time agriculture/forestry/fishery, full-time salaried/self-employed/professional, multiple occupations, full-time housework/retired/unemployed), history of diabetes (no, yes), smoking status (stratified, never, past, current), alcohol intake status (stratified, almost none, occasional, regular), body mass index (stratified, 14 to <20, 20 to <27, ≥27), total energy intake (quintiles), heavy physical work or strenuous exercise (none, <1 h, ≥1 h), sedentary activity (<3 h, 3–8 h, ≥8 h), walking or standing hours (<1 h, 1–3 h, ≥3 h), and leisure-time sports or physical exercise (<1 day/week, 1–2 days/week, ≥3–4 days/week).

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effect of physical activity via a reduction in body mass index may be relatively greater in Western than non-Western populations.

Results showed a basically similar risk reduction in the two sexes, although to a somewhat stronger degree in women, and in this regard are consistent with previous studies (1, 4, 25). In addition, we observed significant effect modification between physical activity and sex. This suggests the existence of different mechanisms for the association between physical activity and premature death, additional to difference in the content of total physical activity between men and women. Methodologically, it is commonly noted that men are more likely to be physically active in their jobs and women are more likely to be involved in housework (1). In our questionnaire, rank correlation coefficients with the 24-h physical activity record were greater in men than in women, which may have partly resulted from a lack of detailed questions related to housework in our questionnaire, and a subsequent misclassification of physical activity; any failure of the questionnaire to suitably account for housework may thus lead to greater measurement errors in total physical activity in women than in men. This type of measurement error may have led to the underestimation of association.

Because of the structure of our questionnaire, we were unable to clearly distinguish components of the effect of physical activity level and were unable to assess the role of specific sports, even though we could assess the effect of physical activity by intensity type, i.e., strenuous, sedentary, and walking and standing. This is one of the limitations of the present study. Questions on occupation and the frequency of sports activity were not used to estimate METs, although total physical activity level would be explained in part by them. We instead included these variables in the model to control for undetected lifestyle characteristics, such as income and religious participation etc., which may affect the association, notwithstanding the lack of the information in the present study. Analysis stratified by the frequency of leisure-time sports or physical exercise suggested that risk reduction with increased daily total physical activity may be expected regardless of the frequency of leisure-time sports or physical exercise. Although identification of the components of physical activity which affect premature death is clearly important to our understanding of the etiology and mechanism of the outcome, this was not the primary purpose of our study; rather, we focused on the effect of total physical activity volume.

Discussions on the possible mechanisms by which physical activity protects against premature death remain inconclusive. Among difficulties, the reported risk reduction by physical activity is a grand sum of the impacts of various causes of death. Various mechanisms have been plausibly associated with cardiovascular disease and cancer, such as improvements in glucose tolerance, lipid profile, blood pressure, fibrinolytic activity and hemostatic function; (5, 26–34) and decreases in oxidative stress have been associated with aging and inflammation levels (35–37), respectively. Physical activity may also enhance various psychosocial determinants of healthy life conditions (11), although the biological mechanisms of these are yet to be addressed.

The major strength of the present study is its prospective design, which avoids exposure recall bias. Other strengths include the following: study subjects were selected from the general population, study size was large, response rate to the questionnaire (76%) was acceptable for study settings such as this, and the proportion of losses to follow-up (0.3%) was negligible. In addition, death registration in Japan is complete, and conducted in accordance with standard requirements of the World Health Organization.

In addition to those mentioned already, however, several other methodological limitations can also be identified. In particular, assessment of physical activity was based on self-reports. Although accuracy was validated, misclassification may have been unavoidable. However, because the data were collected before death, any imprecision is likely to have resulted in the underestimation of association. Changes in physical activity over time also cause misclassification, which might have lead to underestimation of the association. Further, although adjustment was made for lifestyle factors possibly associated with premature death, unmeasured confounders may not have been controlled. For instance, subjects with a history of arthritis and muscular-skeletal diseases or diabetes might experience a change in physical activity that might in turn affect their outcome. In our study, we did not collect information on arthritis or other musculoskeletal diseases and, thus, any effect of such conditions may not have been fully controlled. Further, although exclusion due to missing data for physical activity (6%) was not particularly large, the characteristics of subjects with and without missing information differed: those with missing information tended to be characterized by a high proportion of full-time housework/unemployed/retired in both men (32%) and women (46%) compared with those without missing information (8% in men and 14% in women). This difference may have the potential to influence the results. Finally, our results may not be generalizable to populations with a different general lifestyle to Japanese.

Allowing for these methodological issues, our results suggest that greater daily total physical activity levels, either from occupation, daily life, or leisure time, may be of benefit in preventing premature death among Japanese men and women. The findings of the present study should be of great use in health policy planning.

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APPENDIX. QUESTIONS RELATED TO PHYSICAL ACTIVITY IN 5-YEAR FOLLOW-UP SURVEY OF THE JPHC STUDY

How long on average do you engage in the following activities each day?

Physical labor or sports	None	Less than 1 h	More than 1 h
Sitting	Less than 3 h	3–8 h	More than 8 h
Standing or walking	Less than 1 h	1–3 h	More than 3 h

How often do you participate in sports or physical exercise?

Almost never	1–3 days a month	1–2 days a week	3–4 days a week	Almost every day