Glycative Stress Research

Online edition : ISSN 2188-3610
Print edition : ISSN 2188-3602
Received : October 15, 2019
Accepted : November 4, 2019
Published online : December 31, 2019
doi:10.24659/gsr.6.4_241

Review article

Physical activity and cancer: evidence from epidemiological studies

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Abstract

Scientific evaluation on health impacts of physical activity can be verified by an epidemiological study on humans. The ideal method is to perform a randomized controlled trial with a random allocation of physical activity levels and to examine relationships with health outcomes. Practically, the total amount of physical activity is obtained from a specific large-scale group. Subsequently, evidence is required from prospective cohort studies to verify associations with health outcomes. Other than that, cause-effect relations are examined along with scientific grounds such as animal experiments and mechanism investigations. Physical activity has preventive effectiveness for some cancer sites. Its effect on colon cancer is "convincing" grade criteria according to global consensus, and it is also evaluated as "probable" on post-menopausal breast cancer and endometrium cancer. The same evidence was also obtained in Japan. As one of the mechanisms of cancer prevention, physical activity is effective in the improvement of insulin resistance. Although there is not enough evidence to determine how much physical activity is effective, it has been suggested that physical activities, even if small, could lead to a decreased risk of cancers. Increased total physical activity level would be beneficial to extend healthy life expectancy, preventing not only cancers but also diabetes mellitus and circulatory diseases.

***KEY WORDS*:** physical activity, cancer, cohort study, diabetes, insulin resistance

1. Physical activity and cancer: confounder, bias, and chance against causal relationships

To provide epidemiological verifications of the hypothesis that people with a large amount of physical activity tend not to develop cancer, the following is required: to perform a survey with a target of a specific group who has no cancer, examining a total amount of physical activities in their daily life, work and leisure time and then to compare the incidence rate of cancers. The knowledge and findings of the prospective cohorts are necessary evidence.

There is, however, a limitation of these observational studies. Even if they suggest an association that people with a large amount of physical activity tend not to develop cancer, this relation cannot be recognized as sufficient proof for a cause and effect relation. First, spurious correlation can be generated due to common components and confounding factors. For example, smoking, which is related to both physical activity and cancer, can affect exercise conditions and, at the same time, it is a causal factor in developing various types of cancer. Therefore, the association that people who do healthy exercise tend not to get a cancer may not be related to physical activity, but to smoking. Verifications are required to control confounding effects using multi-variate analysis or stratification analysis. The second possibility is a latent cancer, which leads to a reverse causality. People with cancer tend to have physical deconditioning so that their physical activity levels are low. Thus, a reverse causality, which is an apparent association that people with a small amount of physical activity would tend to develop a cancer, can be shown where the onset of a cancer is observed soon after the survey of physical activity level. These factors, which systematically induce a spurious causation, are referred to as bias. Cautious analysis is required, such as exclusion of patients who develop a cancer within several years after the commencement of the follow-up study. Lastly, there is the possibility of chance, which results from a small number of research participants. To avoid coincidental effects, various measures are required such as a large-scale

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Glycative Stress Research 2019; 6 (4): 241-247
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research, integration of multiple studies by meta-analysis and/or pooled analysis, increasing accurate estimation and statistical power.

In research involving humans, randomization is the best and only method to eliminate effects of confounding and bias. Thus, evidence based on integrated analysis on randomized control trials is the most reliable, as is observed. However, it is extremely difficult to conduct a trial where the amount of physical activity is randomly assigned, and differences in cancer incident rates are verified with sufficient statistical power. As a matter of fact, a large-scale cohort study provides evidence with relatively high quality. Avoiding spurious correlations due to confounding, bias and chance, a causality must be cautiously interpreted referring to scientific grounds based on animal experiments and mechanism investigations.

2. Global situation of evaluation on a cause-effect relationship

Increased amounts of physical activity in daily life play a role of the prevention of cancers, as is confirmed. World Cancer Research Fund International conducted a project for analysis of correlation between physical activities and cancer risks until 2018. This global research [1], as interpretations of epidemiological evidence, provides judging criteria for preventive effectiveness on cancers. Effectivness of increasing the amout of physical activity is evaluated as having a “convincing” grade for colon cancer, and a “probable” grade for post-menopausal breast and endometrium cancer. The possibility of preventive effectiveness, “limited-suggestive” is judged regarding esophagus, lung, liver, and pre-menopausal breast cancer. Furthermore, they evaluate that vigorous-intensity physical activity has a “probable” effect to prevent breast cancer both pre-menopausal and post-menopausal. Contrarily, no cancer sites are shown as having higher cancer risk due to larger amount of physical activity (*Table 1*).

Among these assessments, a “convincing” grade must meet rigid criteria. That is, two types or more of epidemiologic studies provide evidence, or at least two independent cohort studies provide evidence. There are no contradictory research results. Support is gained by high-quality studies denying possibilities of chance, bias, and confounding. Additionally, dose-response relationships can be biologically confirmed. Supportive data is required for prevention of human cancers using animal experiments and/or biomarkers. Judgement of a “probable” grade in preventive effectness requires evidence from five or more case-control studies in the place of evidence from cohort studies, which has slightly looser criteria than that of the “convincing” level.

Colon cancer, which is categorized into “convincing” grade criteria regarding the preventive effects by physical activities, was estimated through meta-analysis of 52 studies [2]. Relative risk for the group with the highest physical activity level, compared with the group with the lowest physical activity level, was 0.76 in men (95% confidence interval: 0.71–0.82) and 0.79 in women (0.71–0.88). By types of research analysis, relative risk was 0.69 (0.65–0.74) in case-control studies and 0.83(0.78–0.88) in cohort studies; cohort studies had a slightly weaker relation. By stratified analysis of the type of physical acitivities and exercise, the same level risk decrease was shown in both occupation and leasure time. From the findings mentioned above, convincing evidence has been obtained for the effectiveness of physcal activities to prevent colon cancer.

3. Evidence in Japanese population

Many people in Japan currently seem not to have sufficient physical activity due to changes in social structures. This is considered to affect trends in cancers. For example, a smaller amount of physical activities has been considered to be a possible cause of the increase in age-adjusted death rate of colon cancer since the postwar period. Epidemiological research in Japan has had difficulty developing due to varied circumstances, where much evidence from Europe and America has been relied on. However, prior to, and even after 1990, multiple cohort studies have been initiated with a target scale ranging from several tens of thousands to over a hundred thousand. A large volume of evidence has been reported in Japan as their research findings.

Table 1. Physical activity and the risk of cancer: Global judging the evidence

	Increases risk	Decreases risk
Convincing	None	Colon
Probable	None	Brest (postmenopause) Endometrium Breast (post- & pre-menopause)* *Vigorous intensity physical activity
Limited - suggestive	None	Esophagus Lung Liver Breast (premenopause)

Data are quoted from the site of CUP (Continuous Update Project): Physical activity and the risk of cancer.
https://www.wcrf.org/dietandcancer/exposures/physical-activity

Under these circumstances, we started a project in 2003, and our project is ongoing with the support of Research Grants from the Ministry of Health, Labour and Welfare, and the National Cancer Center Research and Development Fund. We collect and organize information regarding Japanese evidence and examine stepwise the presence or the absence of a causality relation between lifestyle factors and cancer incidence. These evaluations are also based on scientific grounds such as animal data and mechanisms, as well present global assessments. We perform periodic evaluations and report the research results through our website (http://epi.ncc.go.jp/can_prev/).

We have finished the criteria judgments on cancer at all sites, and specific sites such as the colorectal, breast, uterus, lung, ovary, and prostate. Colorectal (colon) was judged as "probable" and breast "limited-suggestive." These levels are similar to those of global judgments, although they are slightly lower in Japan, as evidence in Japan is still insufficient to some extent. Other sites have been assessed as having "insufficient data," as there has not been enough evidence.

Two cohort studies and six case-control studies had been reported regarding colon cancer at the time of assessment. Relations between physical activity and cancer prevention of the colon or/and rectum were observed, according to all of the five case-control studies that represented odds ratios separately by colon and rectum. In particular, relationships with colon cancer were frequently reported in the studies. Both of the two cohort studies indicated a strong relation of men with colon cancer [3, 4]. Examining this evidence, it was judged that physical activity prevented colorectal cancers in the "probable" grade criteria [5].

4. Evidence from the JPHC Study

i. Relationships between total physical activity level and incident risk of cancers

We have been conducting the Japan Public Health Center-based Prospective Study (JPHC Study). The research, which examined relations between the level of physical activities and cancer incident rates of cancer at all sites, and by major specific sites, followed up approximately eighty thousand male and female research participants (45–74 years of age) until 2004 who had responded to five-year follow-up questionnaire surveys conducted from 1995 to 1998 [6].

The participants were asked in questionnaire surveys regarding the duration of average physical activities, whose items included durations of muscle labor and vigorous sports, sitting, standing, walking, and sleeping. Individual average amounts of physical activity per day was obtained as a calculated score as follows: Met (metabolic equivalent) of these physical activity levels were multiplied by activity duration. "METs-time" scores of each activity were added up. Validity and reproducibility were examined for 110 subjects among all subjects. METs/day, estimated values obtained in the questionnaire surveys, showed 0.68 (95% confidence interval: 0.56–0.77) for rank correlation coefficient in two different periods. Furthermore, rank correlation coefficients of estimated values, which were obtained from four-day physical activity records, showed 0.55 (0.40–0.67) and 0.49 (0.33–0.60) in two periods. It was observed that validity was verified to some extent when a large number of subjects were classified into four groups by their level of physical activities.

During approximately eight years of follow-up surveys, a total number of 4,334 subjects (men: 2,704 and women: 1,630) developed one cancer or more. Groups with a higher level of total physical activity indicated lower risks of cancer incidence in both men and women (***Fig. 1***). Compared with the group of the lowest level, the group of the highest level showed reduced risk of developing cancer by 0.87 times in men and 0.84 times in women, which were statistically significant reductions. Specifically, women tended to show a more marked tendency that physical activity reduced cancer incidence risk. The aged group and the high frequency physical activity group in their leisure time demonstrated clear risk reductions. By cancer sites in the analysis, the group with the highest level of physical activity had statistically significant reduction in cancer risks for colon and liver in men and gastric cancer in women. There was a trend toward significance in pancreatic cancer of men. To eliminate the possibility of a reverse causality, analysis was performed after excluding subjects who developed a cancer within three years after the commencement of the study. Consequently, the analysis results were almost the same of those of previous analysis.

Considering that validity of estimated physical activity level based on the questionnaire survey was approximately 0.5, actual effectiveness on prevention due to the increased level of physical activities was likely to be larger, if misclassification did not have either direction of bias; a certain misclassification may occur for physical activity estimation.

ii. Relationships between physical activity and mortality risk

In the JPHC Study, analysis was also performed using death as an endpoint. For a baseline of all cohort studies, it is 15 years of follow up when the oldest subject (69 years of age) reaches the average life span in Japan. Therefore, a death before that point is caused by some reason prior to reaching the average life span, as is recognized. We had examined relations between daily total physical activity level and premature death risk until 2005, conducting follow-up studies with approximately 83,000 male and female subjects, ranging from 45–74 years of age, who had responded to the five-year follow-up questionnaire surveys from 1995 to 1998 [7]. During approximately nine years of follow-up studies, the deaths of 3,098 men and 1,466 women were confirmed.

Death risk in both men and women decreased to a greater extent in the group of higher total physical activity level (***Fig. 2***). Compared with the lowest level group, the highest-level group showed a reduced risk of death by 0.73 times in men and 0.61 times in women, which were statistically significant reductions. Dividing subjects based on age and frequency of exercise in leisure time, similar results were observed in both cases. Dividing subjects based on degree of obesity as expressed by body mass index (BMI), the group with a level higher than 27 had a small reduction of death risk due to physical activity.

Observing causes of death in men, the risk of cancer

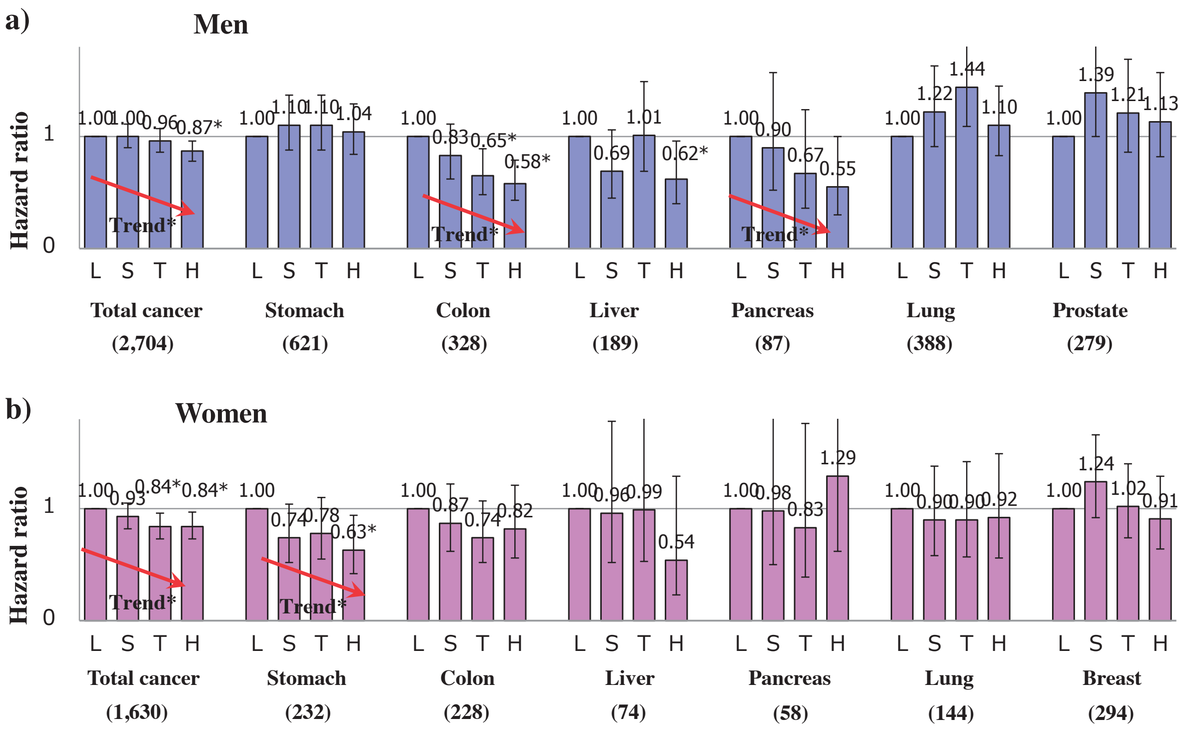

Fig. 1. **Hazard ratios for cancer, total and at specific sites, incidence according to daily total physical activity level: JPHC Study.**

Mutlivariate-adjusted hazard ratios were calculated with a Cox proportional hazards model. Hazard ratios were expressed with ± 95% CI (vertical bar), * for $p < 0.05$ (see arrows for trend test). Quartile of physical activity level: L, lowest; S, second; T, third; H, highest. Quartile median value (METs/day): L, 25.45; S,31.85; T, 34.25; H, 42.65 in men (n = 37,898); L, 26.10; S, 31.85; T, 34.25; H, 42.65 in women (n = 41,873). Parentheses indicate the number of cases. JPHC Study, the Japan Public Health Center-based Prospective Study; 95% CI, 95% confidence interval; METs, metabolic equivalents. The figures are made based on the data in Reference 6).

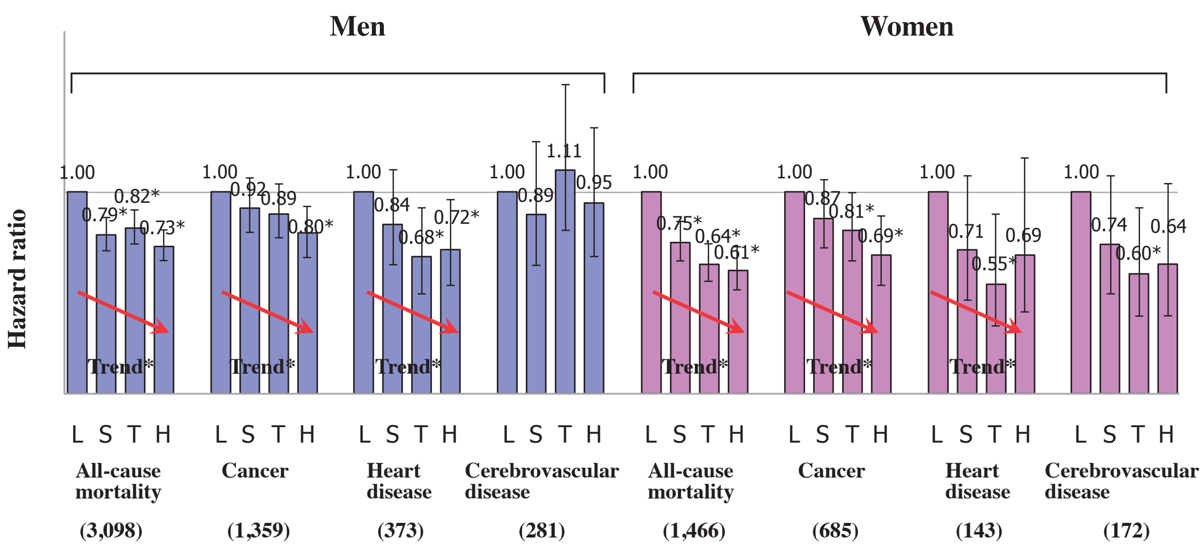

Fig. 2. **Hazard ratios for all-cause and major specific-cause mortality according to daily total physical activity level: JPHC Study.**

Mutlivariate-adjusted hazard ratios were calculated with a Cox proportional hazards model. Hazard ratios were expressed with ± 95% CI (vertical bar),* for $p < 0.05$ (see arrows for trend test). Quartile of physical activity level: L, lowest; S, second; T, third; H, highest. Quartile median value (METs/day): L, 25.45; S, 31.85; T, 34.25; H, 42.65 in men (n = 39,183); L, 26.10; S, 31.85; T, 34.25; H, 42.65 in women (n = 43,851). JPHC Study, the Japan Public Health Center-based Prospective Study; CI, confidence interval; METs, metabolic equivalents. The figures are made based on the data in Reference 7).

mortality was notably reduced by 0.80 times in the group with the highest level of physical activity, and the death risk of heart disease was notably reduced by 0.72 times. Contrarily, reduction in death risk was not observed in cerebrovascular diseases. The group of women with the highest level of physical activity showed a decline in cancer mortality risk by 0.69 times. However, mortality risks of women due to heart diseases and stroke did not show statistical significance, although a tendency of reduction in mortality risk was recognized. Excluding subjects who died within three years of the commencement of the study, analysis indicated a significant decline in men, although the degree of decline was slightly weakened. Analysis in women showed similar results.

5. Physical activity and cancer: mechanism, paticularily relationship with inslin resistance

To name influential mechanisms of cancer prevention and health promotion due to physical activities, the obesity solution, the enhanced immune function, the shorter intestinal tansit time of excrement, and the influences on bile acid metabolism are recognized. A relation with insulin resistance has also been gaining increased attention in recent years [8].

We examined the relationship between diabetes and cancer in the JPHC Study; subjects were approximately one hundred thousand men and women (40–69 years of age) who had responded to the baseline questionnarie surveys conducted from 1990 to 1994. Relations were analysed between the history of physician diagnosed-diabetes and cancer incidence based on cancer at all sites as well as major specific sites [9]. During approxiately eleven years of follow-up investigations, 3,907 men and 2,555 women had one cancer or more. Comparing with subjects with no diabetes anamnesis, subjects with diabetes anamnesis (7% of men and 3% of women) had a higher risk by 1.27 times in men and 1.21 times in women. Observing by cancer sites, male subjects with diabetes were likely to have cancers of the liver, kidney, pancreas, colon, and stomach. Cancer sites of female subjects with diabetes were stomach, liver, and ovary. That is, there were similarities to cancer sites whose risks decreased due to high total physical activity level mentioned above; liver, pancreas, and colon in men. Women had similarity in stomach cancer.

In the JPHC Study regarding colorectal cancer, a nested case-control study within the cohort was conducted for C-peptide values, which were measured using collected and preserved blood plasma in baseline surverys. This investigation were performed with 375 cases who had colorectal cancer (196 men and 179 women) and 750 control group cases who were randmonly chosen from subjects with no colorectal cancer, considering matching factors such as age, sex, residential area, and condition on blood sampling [10]. Consequently, male subjests showed that the group with the highest value of C-peptide had a higher risk for colorectal cancer by 3.2 times in comparison with the group with the lowest value. There was a tendency, in the group with high values, that risk gradually increased along with the rise in C-peptide value. This correlation was espesially strong in colon cancer. Contrarily, there was no relation in female subjects.

C-peptide is formed as a byproduct in insulin biosynthesis. Measurment of C-peptide in blood is an index of insulin secretion. Insulin resistence increases the risk for colon cancer. For the improvement of insulin resistance, physical activity is expected to be effective. Accordingly, the mechanism that physical activity decreases the risk for colon cancer is supported by the above mentioned data. It is inferred that the deficienct function of insulin secreted from the pancreas promotes the secretion to induce hyperinsulinism, and the increase of insulin-like growth factor-I (IGF-I). Subsequently, this promotes the proliferation of tumor cells in the colon, the liver, and pancreas and, in addition, inhibits apoptosis. Consequently, this mechanism would be involved in carcinogenesis. It is also suggested that in the state of insulin resistance, the secretion of sex hormone-binding globulin (SHBG) by the liver was reduced, which induces the increase of free estrogen. This suggests a possibility of increasing the cancer risks of the breast and the endometrium.

Physical activity protects against obesity-related cancers. Judging by these mechanisms, however, physical activity would be effective to prevent cancer not merely because of the obesity solution. Daily physical activites, regardless of body shape, could have promising effects on Japanese people, even though the rate of obesity is relatively low in Japan.

6. Physical activity and its benefits

There is not sufficient evidence for a dose-response relationship; more physical activities, healthier. However, it was suggested in a meta-analysis of 32 cohort studies examining the relationship between the level of physical activity and the risk of cancer death, that approximately 10 METs-hours per week is related to 7% reduction in risks of cancer death due (METs: Metabolic equivalents). That is, evidence suggests that it is desirable to be as physically active as possible. However, evidence also suggests that in more than 10–20 METs × length of time (in hour), risk reduction tended to be moderated [11]. Furthermore, dose-response relationships with circulatory diseases have been examined in a wide range by the JPHC Study. Risks for both stroke and coronary artery diseases decreased when the amount of physical activity per day increased, excluding length of time sitting and standing. The maximal risk reduction was gained in 5–10 METs-hours/day. Effects, however, were not observed in longer amounts of time. There was a risk of increasing cerebral stroke, as was suggested (***Fig. 3***) [12]. Thorough meta-analyses for diverse diseases of dose-response relationships have commonly confirmed that the appropriate physical activity largely lowered risks in colon cancer, diabetes, ischemic heart disease, and ischemic stroke and then, risk reductions were moderated when the amount of activity reached a certain level [13].

A World Cancer Research Fund report showed physical activity affects the risk of developing cancer and recommends “Walk more and sit less. Be physically active as part of everyday life.” According to “Physical Activity Reference 2013” by the Ministry of Health, Labour

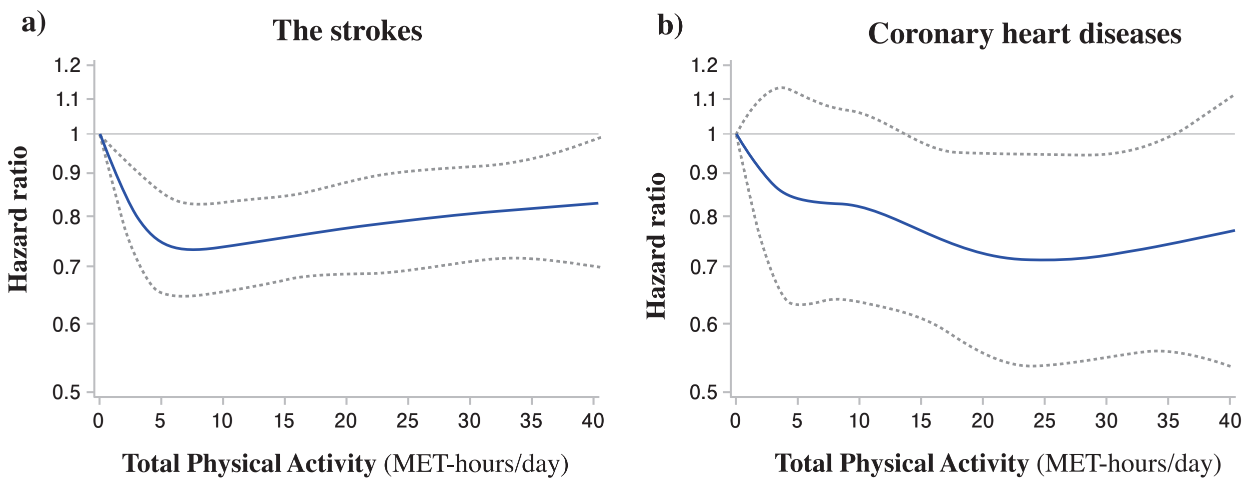

Fig. 3. **Multivariable-adjusted associations of daily total physical activity level with cardiovascular outcomes in men and women: JPHC Study.**

During the 12-years of follow-up for the 74,913 participants, 3,345 incident cases of CVD are documented, including **a)** the strokes (n = 2,738) and **b)** coronary heart diseases (n = 607).Solid lines, hazard ratios; dashed lines, 95% CI. Hazard ratios were calculated with a Cox proportional hazards model and were mutlivariate-adjusted by age, sex, smoking status, ethanol intake, parental history of CVD, sedentary time, and public health area. JPHC, the Japan Public Health Center-based Prospective; CVD, cardiovascular disease; CI, confidence interval; METs, metabolic equivalents. The figures are quoted from Reference 12).

and Welfare, Japan, people of 18 – 64 years of age are recommended to engage in "physical activity of 3 METs or higher for 60 minutes every day (example: 60-minute walking)" and "exercise of 3 METs or higher for 60 minutes per week (example: 30-minute light jogging twice a week)." People over 65 years of age are recommended "physical activity for 40 minutes every day, regardless of strength (example: 40-minute walking)." In other words, "Be as active as possible without putting significant strain on yourself."

To enhance total physical activity level is to have preventive effects on not only cancers, including colon cancer, but also diabetes and circulatory diseases. This is a significant health promotion method for the extension of a healthy life span.

Conflict of interest statement

The authors claim no conflict of interest in this study.

Acknowledgement

The summary of this research was presented at ifia/HFE Japan 2019 on May 24, 2019, Tokyo (ifia, International Food Ingredients &Additives Exhibition & Conference; HFE, Health Food Exposition & Conference).

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