



Research Article

Association between Light-Intensity and Moderate-to-Vigorous-Intensity Physical Activity Habits and Kidney Dysfunction: A General Population Cohort Study

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Few studies have considered physical activity (PA) intensity and frequency in relation to kidney dysfunction. This study aimed to investigate the association of regular light intensity, occasional moderate-to-vigorous physical activities, and their combination with kidney function in the general population. This community-based historical cohort study included Japanese people aged ≥ 40 years. Participants were divided into four groups according to their PA habits: inactive group (neither regular light-intensity physical activity (LPA) nor occasional moderate-to-vigorous physical activity (MVPA)), LPA group (1.5–3.0 metabolic equivalents (METs) for at least 60 min a day), MVPA group (> 3.0 METs for at least 30 min twice a week), and LPA + MVPA group (combination of LPA and MVPA). The primary outcome was a 40% decrease in the estimated glomerular filtration rate from the baseline. The Cox proportional hazards model was used to examine the association between PA habits and kidney function. In total, 72,999 participants were included in this study. During the mean follow-up period of 5.9 years, 2,989 (4.1%) participants achieved the outcome. Compared to participants with neither LPA nor MVPA, the adjusted hazard ratios were 0.94 (95% confidence interval (CI), 0.85–1.03; $p = 0.182$) for LPA alone, 0.97 (95% CI, 0.85–1.10; $p = 0.618$) for MVPA alone, and 0.83 (95% CI, 0.76–0.91; $p < 0.001$) for a combination of LPA and MVPA. There was a significant interaction between sex and PA habit ($p = 0.015$). Generally, combined LPA and MVPA were associated with a lower risk of kidney dysfunction than was the lack of PA. Future studies are required to determine the PA intensity and duration required to protect kidney function.

1. Introduction

For health benefits and mitigation of health risks, a physical activity (PA) guideline of the World Health Organization (WHO) recommends at least 150 min of moderate-intensity, 75 min of vigorous-intensity PA, or some equivalent combination of moderate-intensity and vigorous-intensity PA weekly for adults [1]. Despite such recommendations, a nationwide cohort study in the United States found that 55.0% of the general population did not meet the PA

guidelines and 34.3% did not engage in any moderate-intensity PA [2]. Similarly, in Japan [3] and Canada [4], 71% and 84% of the general population, respectively, did not meet the guidelines.

Chronic kidney disease (CKD) is a global financial and resource burden on healthcare systems [5, 6]. Lifestyle modification is important for the prevention of CKD progression [7–10], and PA has been attracting attention recently. In patients with CKD not undergoing dialysis, moderate-to-vigorous PA (MVPA) for more than 150 min

a week was shown to be associated with a lower risk of end-stage kidney disease [11]. A meta-analysis showed that the daily PA level was significantly correlated with a reduced risk of CKD and end-stage kidney disease (ESKD) and a decreased estimated glomerular filtration rate (eGFR) [7].

Light-intensity PA (LPA) and MVPA are commonly implemented PA habits. Walking, a representative LPA, is associated with a reduced risk of all-cause mortality and ESKD in patients with CKD [12, 13], while MVPA (such as brisk walking, jogging, and leisure-time sports) is associated with a lower risk of CKD [14, 15]. However, previous studies have only evaluated the association between kidney function and either LPA or MVPA or the total amount of PA [8, 11, 14–19]. The effect of a combination of different PA habits of different intensities has not been clearly highlighted. The aim of this study was to investigate the association between regular LPA and occasional MVPA and their combination on kidney function in general population.

2. Methods

In this study, we analyzed the association between PA habits and kidney dysfunction in a general population cohort. Two types of PA habits and their combinations were assessed. Each PA habit was assessed based on intensity and frequency.

2.1. Data Source. This study used data from a community-based historical cohort of adults who underwent annual medical examinations in Kanazawa City, Ishikawa, Japan. All adults aged ≥ 40 years who were covered by the national health insurance were eligible to undergo medical examinations.

2.2. Study Participants and Inclusion/Exclusion Criteria. This study included participants who underwent medical examinations at least two times between 1999 and 2018 in Kanazawa City, Ishikawa Prefecture, Japan. All adults aged ≥ 40 years were eligible to undergo these medical examinations. All the data were collected and deidentified. Participants who wanted to opt out or with missing baseline information regarding covariates, including PA habits, age, sex, body mass index (BMI), systolic blood pressure, diastolic blood pressure, current smoking status, diabetes, history of coronary artery disease, history of stroke, treatment for hypertension, eGFR, proteinuria, hemoglobin, glycated hemoglobin (HbA1c), or total cholesterol levels, were excluded. Participants without follow-up measurements of eGFR or a follow-up period of < 1 year were also excluded.

2.3. Clinical Outcomes. The outcome of this study was eGFR loss, defined as a 40% decrease in eGFR [20] from baseline. The eGFR was calculated from serum creatinine levels using the equation for Japanese individuals [21]. Serum creatinine was measured at each annual medical examination. Between 1999 and 2001, creatinine levels had been measured using

Jaffe's reaction; however, from 2002 onwards, it was measured by enzymatic methods. Serum creatinine levels measured by Jaffe's reaction were adjusted by subtracting 0.2 mg/dL [22].

2.4. Physical Activity Habits. Data on PA habits were collected at each annual medical examination using a questionnaire of the national health program aimed at preventing metabolic syndrome in Japan [23]. The questionnaire aims to estimate PA and has been validated in a previous study [24]. The PA habits were determined based on participants' responses to the following questionnaire items (Supplementary Table 1): (1) PA equivalent to walking for at least 1 hour per day (yes or no) and (2) habitual moderate PA for ≥ 30 min per session ≥ 2 times per week (yes or no). According to the questionnaire, we defined PA intensity and frequency. Regular LPA was defined by 1.5–3.0 metabolic equivalents (METs) for at least 1 hour/day, while occasional MVPA was defined by > 3.0 METs for at least 30 min twice a week for more than a year. Each definition was based on the WHO 2020 guidelines [1]. The participants were divided into four groups according to their PA habits as follows: inactive (neither LPA nor MVPA), LPA (only LPA), MVPA (only MVPA), and LPA + MVPA (both LPA and MVPA) groups (Supplementary Table 1).

2.5. Covariates. Several covariates were included in our study for the analyses of the association between PA and kidney dysfunction outcomes. Participants rested before the blood pressure measurements. Urine collected at random spots was evaluated using a urinary dipstick test strip, and the results were classified as negative/trace or $\geq 1+$ ($1+$ corresponded to a urinary protein level of approximately 30 mg/dL). Diabetes mellitus was defined according to the following criteria: glycated hemoglobin $\geq 6.5\%$, fasting blood glucose ≥ 126 mg/dL (≥ 7.0 mmol/L), or undergoing treatment for diabetes [25]. The following information was obtained from the questionnaire: PA habits, current smoking status, history of coronary artery disease (angina pectoris or myocardial infarction), history of stroke (hemorrhagic or ischemic), and treatment for hypertension.

2.6. Statistical Analyses. Continuous variables with a normal distribution are expressed as mean and standard deviation, whereas skewed variables are expressed as median and interquartile range. Categorical variables are presented as number and percentage. We calculated the incidence rate of a 40% decrease in eGFR from baseline per 1000 person-years for each PA group. A Cox proportional hazards model was used to estimate the outcome risk for each group. The inactive group was used as a reference. In the multivariate analysis, each model was adjusted for potential confounders based on the previous studies [26]. The following models were used: model 1, unadjusted; model 2, adjusted for age at baseline and sex; and model 3, adjusted for age, sex, BMI, systolic blood pressure, diastolic blood pressure, current smoking status, diabetes, history of coronary artery disease,

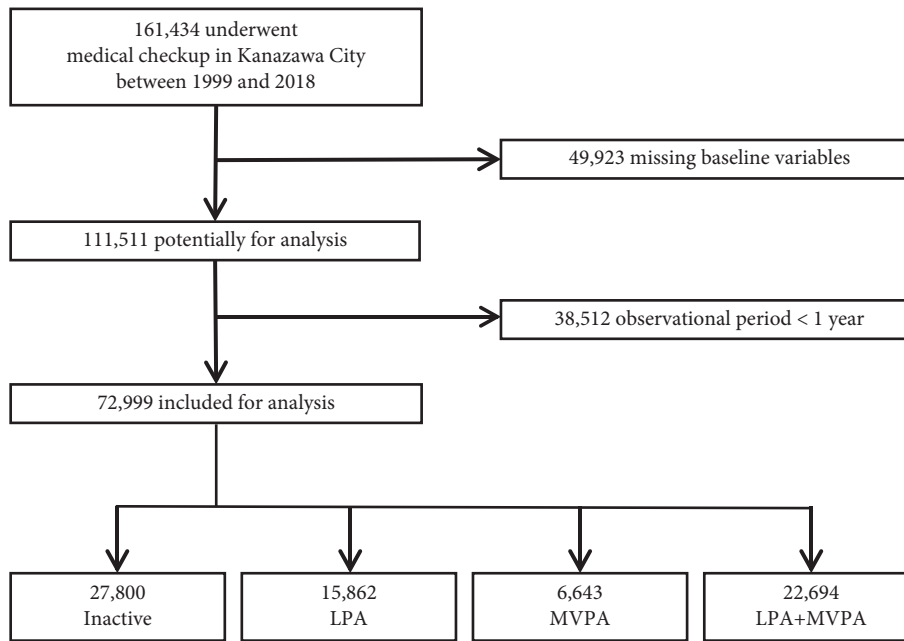


FIGURE 1: Flow diagram of this study.

history of stroke, treatment of hypertension, eGFR, proteinuria, and hemoglobin and total cholesterol levels at baseline.

We performed a subgroup analysis to evaluate the interaction between PA habits and baseline variables, including age (<65, 65–74, and ≥ 75 years), sex (men and women), obesity (BMI <25, 25–30, and ≥ 30 kg/m²), diabetes, and eGFR (<60 and ≥ 60 mL/min/1.73 m²).

The two-sided significance level was set at $p < 0.05$. All analyses were performed using Stata/SE statistical software (version 16.1; StataCorp LP, College Station, TX, USA).

2.7. Institutional Review Board Approval. The study protocol was approved by the Ethics Committee of the Kanazawa University Hospital (approval number: 2287-1) and was conducted in accordance with the principles of the Declaration of Helsinki. Participants were provided with the opportunity to opt out of this study. If participants did not want to be included in this study, they provided written consent to be excluded.

3. Results

3.1. Population-Specific Characteristics. Of the 161,434 participants, 72,999 (45.2%) met the eligibility criteria (Figure 1), and the mean follow-up period was 5.9 years. The median number of creatinine measurements was 6 (minimum 2 and maximum 10). Table 1 shows the baseline characteristics of participants according to their PA habits. The overall mean age was 69.5 years, 39% of the participants were men, and the mean eGFR was 72 mL/min/1.73 m². The inactive group had the highest number of participants, followed by the LPA + MVPA group. The proportion of men

was higher in the LPA + MVPA group (47%) than that in the other groups. All groups showed similar characteristics in terms of age, BMI, blood pressure, current smoking status, diabetes, history of coronary disease, history of stroke, treatment of hypertension, and laboratory data.

3.2. Physical Activity Habits and Outcomes. During the follow-up period, 2,989 (4.1%) participants achieved the outcome, with an incidence rate of 7.0 per 1000 person-years (Table 2). The highest incidence rate was found in the inactive group (7.7 per 1,000 person-years), whereas the lowest incidence rate was found in the LPA + MVPA group (6.1 per 1,000 person-years).

Figure 2 shows the cumulative incidence of the outcome using Kaplan–Meier curves for each group. At 6-year follow-up, 3.3% of the inactive group and 2.1% of the LPA + MVPA group achieved the outcome. Table 3 shows the unadjusted and adjusted hazard ratios (HRs) for each group for the outcome. In Model 3, compared to the inactive group, the HRs were 0.94 (95% confidence interval (CI), 0.85–1.03; $p = 0.182$) for the LPA group, 0.97 (95% CI, 0.85–1.10; $p = 0.618$) for the MVPA group, and 0.83 (95% CI, 0.76–0.91; $p < 0.001$) for the LPA + MVPA group.

3.3. Subgroup Analysis by Baseline Status. Figure 3 shows the subgroup analysis by baseline status of risk factors, including age, sex, BMI, diabetes, and eGFR. A significant interaction was observed between sex and PA habits (p for interaction = 0.015). No significant interactions were observed among the other subgroups ($p > 0.05$). Similar to individuals without diabetes, the LPA + MVPA group was associated with a lower risk of eGFR loss in individuals with diabetes (HR, 0.78; 95% CI, 0.65–0.94).

TABLE 1: Baseline characteristics of the study participants by physical activity habits ($N=72,999$).

| Variables | Inactive ($n=27,800$) | LPA ($n=15,862$) | MVPA ($n=6,643$) | LPA + MVPA ($n=22,694$) | Overall ($n=72,999$) |
|--------------------------------------|----------------------------|-----------------------|-----------------------|------------------------------|---------------------------|
| Age (years) | 69.7 ± 12 | 69.0 ± 10 | 69.2 ± 9 | 69.6 ± 8 | 69.5 ± 10 |
| Sex (men) | 9,772 ± 35 | 5,270 ± 33 | 2,727 ± 41 | 10,544 ± 47 | 28,313 ± 39 |
| Body mass index (kg/m ²) | 23.0 ± 3.5 | 22.8 ± 3.4 | 23.1 ± 3.2 | 22.9 ± 3.1 | 22.9 ± 3.3 |
| Systolic blood pressure (mmHg) | 129 ± 17 | 129 ± 17 | 129 ± 17 | 129 ± 16 | 129 ± 17 |
| Diastolic blood pressure (mmHg) | 75 ± 11 | 75 ± 10 | 75 ± 10 | 75 ± 10 | 75 ± 11 |
| Current smoking (yes) | 3,646 ± 13 | 2,115 ± 13 | 771 ± 12 | 2,701 ± 12 | 9,233 ± 13 |
| Diabetes mellitus (yes) | 3,561 ± 13 | 1,835 ± 12 | 958 ± 14 | 3,164 ± 14 | 9,518 ± 13 |
| History of coronary disease (yes) | 3,659 ± 13 | 1,882 ± 12 | 796 ± 12 | 2,564 ± 11 | 8,901 ± 12 |
| History of stroke (yes) | 2,341 ± 8 | 946 ± 6 | 430 ± 7 | 1,328 ± 6 | 5,045 ± 7 |
| Treatment of hypertension (yes) | 11,730 ± 42 | 6,634 ± 42 | 2,706 ± 41 | 9,441 ± 42 | 30,511 ± 42 |
| eGFR (mL/min/1.73 m ²) | 72 ± 18 | 73 ± 16 | 71 ± 15 | 72 ± 15 | 72 ± 16 |
| Proteinuria (≥1+) | 2,140 ± 8 | 1,130 ± 7 | 473 ± 7 | 1,466 ± 7 | 5,209 ± 7 |
| Hemoglobin (g/dL) | 13.3 ± 1.5 | 13.3 ± 1.4 | 13.5 ± 1.4 | 13.5 ± 1.4 | 13.4 ± 1.5 |
| HbA1c (%) | 5.7 (5.4, 5.9) | 5.7 (5.4, 5.9) | 5.8 (5.4, 5.9) | 5.7 (5.4, 5.9) | 5.7 (5.4, 5.9) |
| Total cholesterol (mg/dL) | 204 ± 35 | 205 ± 35 | 205 ± 34 | 204 ± 34 | 204 ± 35 |
| Follow-up period (years) | 5.6 ± 3 | 5.9 ± 3 | 6.1 ± 3 | 6.3 ± 3 | 5.9 ± 3 |

Note: Data are presented in numbers (%), mean ± standard deviation, or median (25th and 75th percentiles). LPA, regular light-intensity physical activity; MVPA, occasional moderate-to-vigorous physical activity; eGFR, estimated glomerular filtration rate.

TABLE 2: Incidence rates of a 40% decrease in eGFR by physical activity habits ($N=72,999$).

| | Inactive ($n=27,800$) | LPA ($n=15,862$) | MVPA ($n=6,643$) | LPA + MVPA ($n=22,694$) | Overall ($n=72,999$) |
|-------------------------------|----------------------------|-----------------------|-----------------------|------------------------------|---------------------------|
| Number of events | 1,187 (4.3%) | 653 (4.1%) | 286 (4.3%) | 863 (3.8%) | 2,989 (4.1%) |
| Person-years | 154,095 | 94,424 | 40,190 | 140,822 | 427,532 |
| Events per 1,000 person-years | 7.7 | 7.1 | 7.1 | 6.1 | 7.0 |

Note: eGFR, estimated glomerular filtration rate; LPA, regular light-intensity physical activity; MVPA, occasional moderate-to-vigorous physical activity.

4. Discussion

4.1. Clinical Significance and Study Implications. In this observational study of the Japanese general population, we observed that a combination of regular light-intensity PA habit and occasional moderate-to-vigorous-intensity PA habits was significantly associated with a lower risk of eGFR loss than no PA habit. This result remained significant, even after adjusting for potential confounders. In contrast, regular light-intensity or occasional moderate-to-vigorous-intensity PA habits alone were not associated with reduced risk of eGFR loss. To the best of our knowledge, this is the first observational study to report an association between a combination of PA habits and eGFR loss.

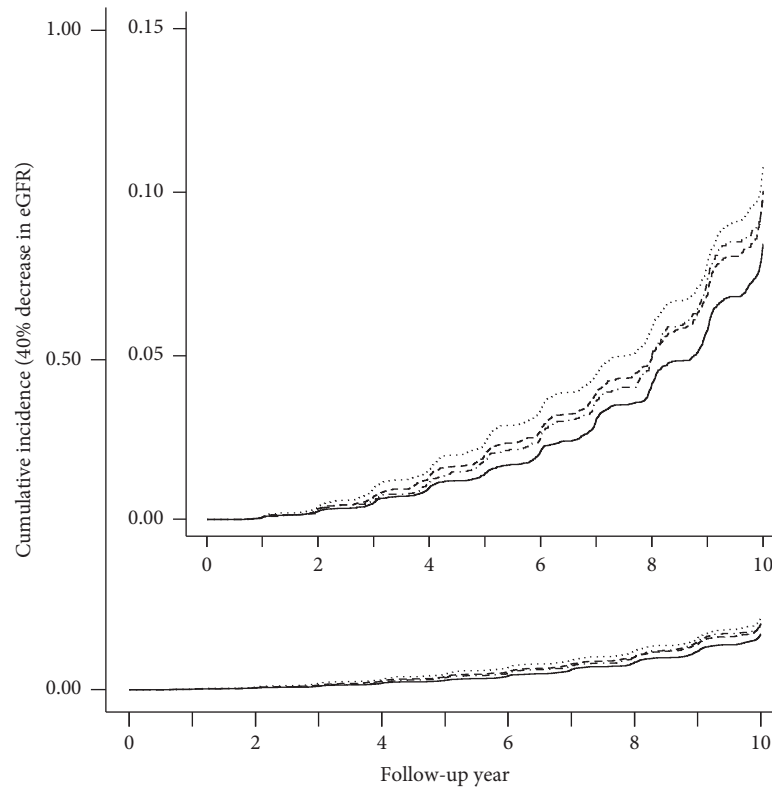
We used the questionnaire used in the national health program in Japan [23]. In the validation study of the questionnaire, the total amount of PA was significantly higher for participants with LPA + MVPA habits than for those with only LPA or MVPA habits [24]. The total PA comprises the PA duration and intensity, which are possible factors for slower eGFR loss. Because of the format of the questionnaire, it was not possible to perform more detailed analysis of PA, including differentiation of moderate and vigorous PA.

The duration of PA is associated with a reduced risk of CKD progression in a time-dependent manner [8, 12, 27, 28]. For example, each 60 min longer weekly PA is associated with a 0.5% slower eGFR decline per year in the

CKD population [28]. Considering these definitions, the LPA + MVPA group participated in PA for at least 60 min daily, in addition to 30 min twice a week, which might have been a sufficient time for slowing down the eGFR loss, thus leading to lower risks of CKD. In contrast, because of the limited duration of PA, the MVPA group might not have had sufficient time for the development of an association with slower eGFR decline [29]. However, it is unclear why the LPA group did not show a reduced risk of CKD. A study reported that longer MVPA was associated with a reduced risk of low eGFR, whereas longer LPA was not associated [17]. Therefore, light PA alone may not impart sufficient protective effects on kidney functions.

The intensity of PA is also an important factor for slower eGFR decline [18, 27]. Moderate or vigorous PA has been associated with a lower risk of eGFR decline [15–18, 27, 30]. MVPA is hypothesized to have a protective effect against oxidative stress in the kidney [31]. In our study, although the MVPA group performed PA at an intensity expected to be related to a lower risk of eGFR decline, this association was not found. A possible reason is that the MVPA group, who did not have a habit of LPA, had a sedentary lifestyle, which is associated with kidney dysfunction [14, 15, 17].

A significant interaction between PA habits and sex was found for eGFR loss. Our study showed that PA habits were more related to a reduced risk of kidney dysfunction in men than in women. This is consistent with a previous study reporting that PA is associated with a lower risk of kidney



| Number at risk | | | | | | |
|--------------------------|----------|-------|-------|------------|------|------|
| Inactive | 27800 | 22952 | 17272 | 12362 | 8219 | 1888 |
| LPA | 15862 | 13412 | 10392 | 7639 | 5239 | 1282 |
| MVPA | 6643 | 5734 | 4486 | 3384 | 2397 | 597 |
| LPA + MVPA | 22694 | 19676 | 15854 | 12072 | 8705 | 2202 |
| Physical activity habits | | | | | | |
| | Inactive | | ---- | MVPA | | |
| --- | LPA | | — | LPA + MVPA | | |

FIGURE 2: Kalpan-Meier curves for the 40% decrease of eGFR in each exercise habit.

TABLE 3: The Cox proportional hazards model for the risk of a 40% decrease in eGFR.

| Variables | Model 1 | <i>p</i> | Model 2 | <i>p</i> | Model 3 | <i>p</i> |
|---|------------------|----------|------------------|----------|------------------|----------|
| Inactive | 1.0 (reference) | | 1.0 (reference) | | 1.0 (reference) | |
| LPA | 0.88 (0.80–0.97) | 0.012 | 0.89 (0.81–0.98) | 0.017 | 0.94 (0.85–1.03) | 0.182 |
| MVPA | 0.86 (0.76–0.98) | 0.028 | 0.91 (0.80–1.03) | 0.137 | 0.97 (0.85–1.10) | 0.618 |
| LPA + MVPA | 0.73 (0.67–0.80) | <0.001 | 0.75 (0.69–0.82) | <0.001 | 0.83 (0.76–0.91) | <0.001 |
| Age (+1 year) | | | 1.10 (1.09–1.10) | <0.001 | 1.07 (1.06–1.07) | <0.001 |
| Men (vs. women) | | | 1.16 (1.07–1.25) | <0.001 | 1.21 (1.10–1.32) | <0.001 |
| Body mass index (+1 kg/m ²) | | | | | 1.04 (1.03–1.05) | <0.001 |
| Systolic blood pressure (+10 mmHg) | | | | | 1.15 (1.12–1.17) | <0.001 |
| Diastolic blood pressure (+5 mmHg) | | | | | 0.97 (0.95–0.99) | 0.003 |
| Current smoking (vs. no) | | | | | 1.92 (1.72–2.15) | <0.001 |
| Diabetes (vs. no) | | | | | 1.53 (1.40–1.68) | <0.001 |
| History of coronary disease (vs. no) | | | | | 1.18 (1.08–1.29) | <0.001 |
| History of stroke (vs. no) | | | | | 1.24 (1.11–1.40) | <0.001 |
| Treatment of hypertension (vs. no) | | | | | 1.77 (1.63–1.92) | <0.001 |
| eGFR (+10 mL/min/1.73 m ²) | | | | | 0.99 (0.97–1.01) | 0.418 |
| Proteinuria ≥1+ (vs. negative/trace) | | | | | 2.91 (2.65–3.20) | <0.001 |
| Hemoglobin (+1 g/dL) | | | | | 0.78 (0.75–0.80) | <0.001 |
| Total cholesterol (+10 mg/dL) | | | | | 0.99 (0.98–1.00) | 0.206 |

Note: Model 1, unadjusted; model 2, adjusted for age and sex; model 3, adjusted for the variables in model 2 plus body mass index, systolic blood pressure, diastolic blood pressure, current smoking, diabetes, history of coronary artery disease, history of stroke, treatment of hypertension, eGFR, proteinuria, and hemoglobin and total cholesterol levels.

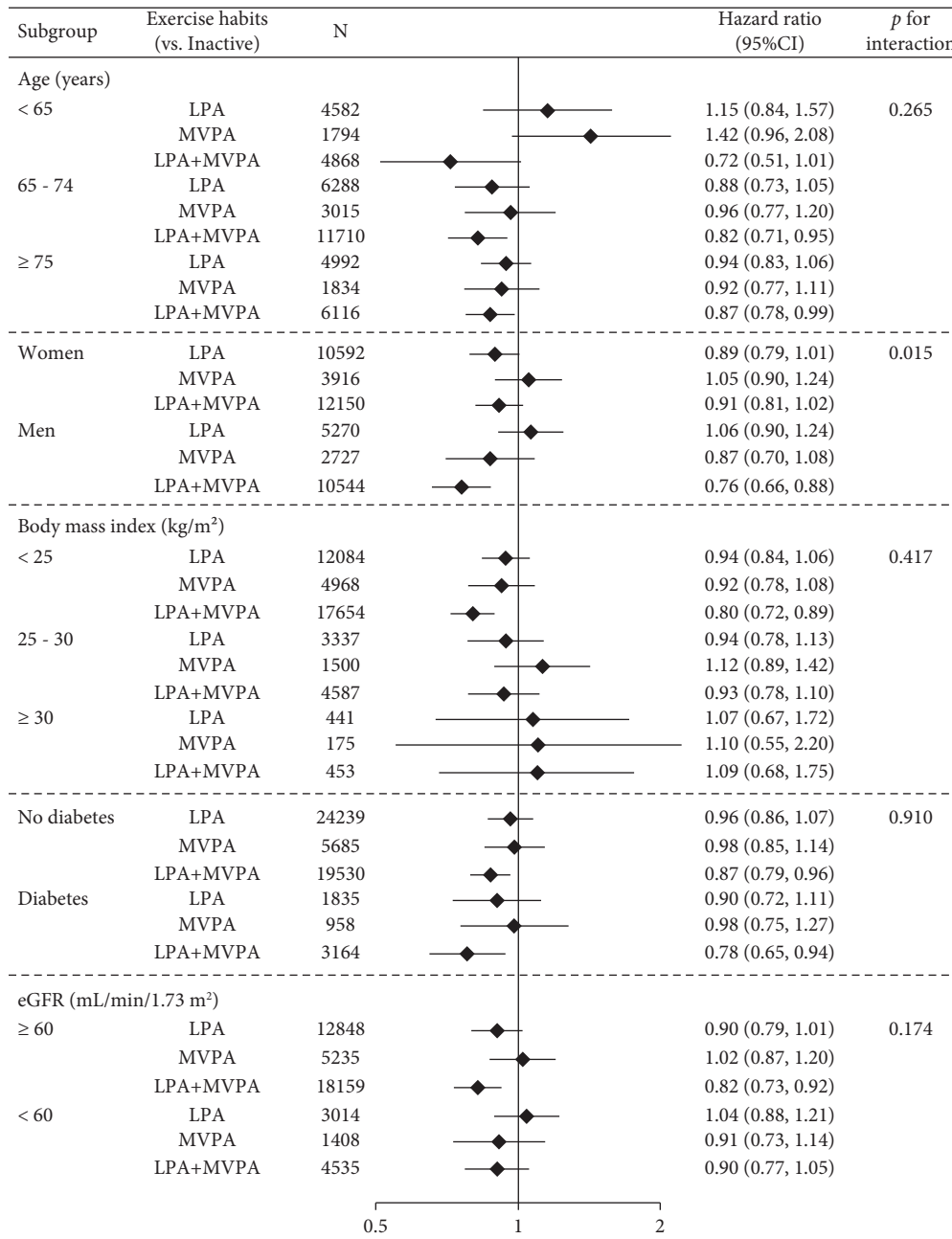


FIGURE 3: Subgroup analysis by baseline kidney risk factors. The differences in risk of 40% decrease of eGFR according to age, sex, body mass index, diabetes, and baseline eGFR. The inactive group was used as a reference. Adjusted for age, sex, body mass index, systolic blood pressure, diastolic blood pressure, current smoking, diabetes, history of coronary artery disease, history of stroke, treatment of hypertension, eGFR, proteinuria, hemoglobin, and total cholesterol.

dysfunction in men than in women [15, 32]. We speculate that there are sex differences in the association of risk factors such as high BMI [33] or that women may be less affected by exercise because of the protective effects of sex hormones on the kidneys [34]. However, these aspects were not investigated in this study.

LPA + MVPA were associated with a lower risk of eGFR loss in participants with and without diabetes. This result is consistent with a previous study that assessed moderate PA and kidney dysfunction [30]. Improvement in the common

risk factors for diabetes and nondiabetes based on PA habits may be one of the mechanisms for stable eGFR. For example, a longitudinal study showed that weight loss was associated with an increase in eGFR in both diabetic and nondiabetic individuals [35].

In light of the findings of Sasaki et al. [17], a delayed decline in eGFR was observed when resting time was replaced by exercise time. Consequently, it can be suggested that replacement of inactivity with LPA + MVPA may contribute to a slower decline in eGFR. One possible

mechanism by which PA benefits the kidneys is the upregulation of Klotho expression due to exercise [36]. Klotho, a multifunctional protein, contributes to a decrease in renal damage by attenuating immune responses and inhibiting fibrotic processes [37].

4.2. Strengths and Limitations. This study has several strengths. First, it included a large sample size and a long-term follow-up period, which facilitated the observation of several outcomes. Second, the inclusion of many individuals with diabetes allowed us to identify associations in subgroups with diabetes.

Nevertheless, this study had some limitations. First, because it was based on responses to a self-reported questionnaire on PA habits, it did not confirm the actual amount of PA. Second, the participants were stratified based on PA habits at baseline, and alterations in PA habits during the follow-up period were not considered. Third, eGFR was calculated using creatinine, which is affected by muscle mass. Finally, most participants were elderly, and the proportion of women was higher than that of men, as more women underwent medical examinations, which was an eligibility criterion for this study.

5. Conclusions

In the general population, regular LPA and occasional MVPA habits were associated with a lower risk of eGFR loss than that in no PA habit. This association was consistent among subgroups based on baseline characteristics, including the presence of diabetes. Further interventional studies are required to clarify the underlying causal association.

Data Availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Additional Points

What is known about this topic and what this article adds? (i) The health benefits of physical activity (PA) are well known, and the WHO recommends that all adults should undertake 150–300 min of moderate-intensity, 75–150 min of vigorous-intensity PA, or some equivalent combination of moderate-intensity and vigorous-intensity PA weekly. (ii) In previous studies, an adequate amount of moderate-to-vigorous PA was associated with a lower risk of end-stage kidney disease. (iii) We showed that regular light-intensity PA and occasional moderate-to-vigorous-intensity PA habits are associated with a lower risk of decrease in the estimated glomerular filtration rate.

Disclosure

The funder had no role in the study design, data collection, analysis, interpretation of data, or preparation of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

GS and TT conceived the idea of the study. TT developed the statistical analysis plan and conducted statistical analyses. GS drafted the original manuscript. TW and YI supervised the conduct of this study. All authors reviewed the manuscript and revised it critically on intellectual content. All authors approved the final version of the manuscript to be published.

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Supplementary Materials

Supplementary Table 1: questionnaire items and group classification. (*Supplementary Materials*)

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