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Effect of physical activity on risk reduction of infective endocarditis among patients with diabetes: a nationwide cohort study

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Patients with diabetes mellitus (DM) are at a higher risk of infectious diseases, and exercise is an important treatment modality for DM. Despite their susceptibility to infection in diabetic patients, the association between the amount of physical activity and the incidence of infective endocarditis (IE) is unclear. We attempted to demonstrate risk reduction by physical activity in diabetic patients with IE. From the National Health Insurance database, patients with DM were verified, and the incidence of IE was investigated. The level of physical activity was categorized into < 500, 500–999, 1,000–1,499, and ≥ 1,500 metabolic equivalent task (METs) minutes/week. Cox proportional hazard models were used to analyze the relationship between incident IE and physical activity. A total of 2,603,012 patients were included in this study. The incidence rate of IE was 10.06, 9.45, 7.78, and 8.84 in < 500, 500–999, 1,000–1,499, and ≥ 1,500 METs-minutes/week groups, respectively (100,000 person/year). A significant risk reduction of incident IE was observed in the 1,000–1499 and ≥ 1,500 METs-min/week groups compared to the < 500 METs-min/week group (Hazard ratio = 0.82, 95% confidence interval [0.690–0.976], HR = 0.831, 95% CI [0.704–0.981]). An analysis of a large national cohort database demonstrated that physical exercise reduced the risk of IE in patients with DM.

Keywords Diabetes mellitus, Exercise, Infective endocarditis, Physical activity, Prevalence, Prevention

Infective endocarditis (IE) is a highly lethal disease with an overall mortality rate of approximately 25%[1]. Generally, IE is not a prevalent disease, with an annual incidence of 3–10 per 100,000 people-years[1]. However, a recent study reported that the endocarditis is increasing worldwide[2]. The risk factors for IE include hemodialysis, intravenous drug use, and structural valvular disease[3]. In addition, patients with diabetes, a representative non-communicable disease, might have a higher risk of IE than patients without diabetes[4]. Patients with diabetes are considered susceptible to IE because they have an impaired immune response[5,6]. Additionally, poor glycemic control is associated with increased susceptibility to various infections[5,7]. Moreover, it is also known that the incidence of endocarditis increases with the duration of diabetes mellitus (DM)[6]. Diabetes is also a poor prognostic factor in patients with IE[8].

Exercise improves glycemic control in patients with diabetes[9]. Exercise is recommended for all people, and the World Health Organization has recommended at least 150–300 min of moderate-intensity aerobic physical activity, at least 75–150 min of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate-intensity and vigorous-intensity activity throughout the week for adults 18–64 years of age in 2020[10].

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Physical activity is beneficial against all-cause mortality and is known to prevent several diseases[10,11]. Several studies also suggest that this risk reduction increases in proportion to the intensity of physical activity[10,11].

Exercise is an important treatment modality for DM, and the American Diabetes Association specifies the least amount of physical activity for patients with DM[9]. However, little is known about the risk reduction by physical activity in the development of infectious diseases in patients with diabetes. Since diabetes is a poor prognostic factor for IE and the burden and prevalence of diabetes are increasing worldwide, results obtained by investigating the reduction in the incidence of infectious diseases through physical activity would facilitate the management of patients with diabetes[12,13].

In this study, we attempted to demonstrate risk reduction by physical activity in diabetic patients with IE by analyzing a nationwide database in South Korea.

Results

Participants

A total of 2,603,012 individuals with DM were identified in the National Health Insurance Service (NHIS) database (Supplementary Fig. S1). The median follow-up duration were 7.14 (6.01–8.08) years. The mean age was 57.44 ± 12.34 years old. The percentage of females was 39.97%. Metabolic equivalent task (MET)-min/week < 500 was observed in 54% of the total cohort, MET-min/week < 1,000 in 25.1%, MET-min/week < 1,500 in 10.5%, and MET-min/week ≥ 1,500 in 10.4%. Among the cohort participants, 1,703 patients with IE were identified.

The lowest MET-min/week group (< 500) was likely to be obese females, with a higher proportion of low-income, lesser proportion of heavy drinkers, and shorter duration of DM (Table 1). Comorbidities, such as dyslipidemia and chronic kidney disease (CKD), tended to be more prevalent in the lowest MET-min/week group.

Those with IE were less likely to exercise regularly (18.44% and 20.6%; $P = 0.0276$) and perform vigorous grade exercise (13.27% and 16.85%; $P < 0.0001$) (Table 2). The IE group had a higher proportion of participants aged ≥ 65 years and a smaller proportion of current smokers and heavy drinkers. In terms of diabetes, the number of oral hypoglycemic agents, proportion of insulin users, and duration of diabetes were greater in those with IE than in those without IE ($P < 0.0001$). Hypertension (72.34% and 56.79%, respectively), dyslipidemia (46.92% and 41.93%, respectively), and CKD (25.37% and 11.56%, respectively) were significantly more prevalent in the IE group ($P < 0.0001$).

Risk of incident infective endocarditis according to MET – min/week classification

The incidence rates of IE were 10.064 per 100,000 person-years in the MET-min/week < 500 group, 9.452 in the 500 ≤ MET-min/week < 1,000 group, 7.784 in the 1000 ≤ MET-min/week < 1,500 group, and 8.837 in the MET-min/week ≥ 1,500 group (Table 3). In the multivariable analysis, 1,000 ≤ MET-min/week < 1,500 and MET-min/

	Metabolic equivalent task, min/week				
	< 500	**< 1,000**	**< 1,500**	**≥ 1,500**	
Number	**1,405,950**	**652,842**	**274,491**	**269,729**	***P*-value**
Age, years	57.62 ± 12.73	56.94 ± 12.32	56.4 ± 11.42	58.81 ± 10.95	< 0.001
BMI, kg/m^2	25.12 ± 3.51	25.04 ± 3.36	25.04 ± 3.25	24.85 ± 3.12	< 0.001
Female, *n* (%)	615,924 (43.81)	245,550 (37.61)	90,269 (32.89)	88,597 (32.85)	< 0.001
Income, Lowest Q1, *n* (%)	305,649 (21.74)	133,471 (20.44)	54,180 (19.74)	53,295 (19.76)	< 0.001
Smoking, *n* (%)					< 0.001
Non	827,800 (58.88)	341,540 (52.32)	137,147 (49.96)	141,947 (52.63)	
Ex-smoker	211,214 (15.02)	134,911 (20.67)	67,345 (24.53)	67,673 (25.09)	
Current smoker	366,936 (26.1)	176,391 (27.02)	69,999 (25.5)	60,109 (22.28)	
Drinking, *n* (%)					< 0.001
Non drink	858,025 (61.03)	349,924 (53.6)	136,929 (49.88)	146,900 (54.46)	
Mild drink	412,919 (29.37)	236,447 (36.22)	108,695 (39.6)	94,153 (34.91)	
Heavy drink	135,006 (9.6)	66,471 (10.18)	28,867 (10.52)	28,676 (10.63)	
Comorbidity, *n* (%)					
Hypertension	800,150 (56.91)	366,848 (56.19)	152,792 (55.66)	158,630 (58.81)	< 0.001
Dyslipidemia	593,191 (42.19)	272,220 (41.7)	113,445 (41.33)	112,781 (41.81)	< 0.001
CKD	171,260 (12.18)	71,812 (11)	27,656 (10.08)	30,506 (11.31)	< 0.001
DM Duration, ≥ 5 years	421,567 (29.98)	202,713 (31.05)	86,505 (31.51)	98,992 (36.7)	< 0.001
Combined OHA ≥ 3	205,212 (14.6)	92,352 (14.15)	38,116 (13.89)	41,716 (15.47)	< 0.001
Insulin	126,768 (9.02)	54,780 (8.39)	21,975 (8.01)	24,580 (9.11)	< 0.001

Table 1. Baseline characteristics according to physical activity classification in patients with diabetes mellitus. *BMI* body mass index, *Q1* quartile 1, *CKD* chronic kidney disease, *DM* diabetes mellitus, *OHA* oral hypoglycemic agent.

	Total	No IE	IE	*P*-value
Number	**2,603,012**	**2,601,309**	**1,703**	
Age, *n* (%)				< 0.0001
< 40	196,648 (7.55)	196,605 (7.56)	43 (2.52)	
40–64	1,620,755 (62.26)	1,619,947 (62.27)	808 (47.45)	
≥ 65	785,609 (30.18)	784,757 (30.17)	852 (50.03)	
Female, *n* (%)	1,040,340 (39.97)	1,039,639 (39.97)	701 (41.16)	0.3135
Smoking, *n* (%)				< 0.0001
Non	1,448,434 (55.64)	1,447,410 (55.64)	1,024 (60.13)	
Ex-smoker	481,143 (18.48)	480,806 (18.48)	337 (19.79)	
Current smoker	673,435 (25.87)	673,093 (25.88)	342 (20.08)	
Drinking, *n* (%)				< 0.0001
Non drink	1,491,778 (57.31)	1,490,617 (57.3)	1,161 (68.17)	
Mild drink	852,214 (32.74)	851,814 (32.75)	400 (23.49)	
Heavy drink	259,020 (9.95)	258,878 (9.95)	142 (8.34)	
Exercise, *n* (%)				
Regular exercise	536,116 (20.6)	535,802 (20.6)	314 (18.44)	0.0276
PA : Vigorous	438,589 (16.85)	438,363 (16.85)	226 (13.27)	< 0.0001
PA : Moderate	248,006 (9.53)	247,830 (9.53)	176 (10.33)	0.2565
PA : Walking	747,330 (28.71)	746,809 (28.71)	521 (30.59)	0.0858
Comorbidity, *n* (%)				
Hypertension	1,478,420 (56.8)	1,477,188 (56.79)	1,232 (72.34)	< 0.0001
Dyslipidemia	1,091,637 (41.94)	1,090,838 (41.93)	799 (46.92)	< 0.0001
CKD	301,234 (11.57)	300,802 (11.56)	432 (25.37)	< 0.0001
DM Duration, ≥ 5 years	809,777 (31.11)	809,008 (31.1)	769 (45.16)	< 0.0001
OHA ≥ 3	377,396 (14.5)	377,082 (14.5)	314 (18.44)	< 0.0001
Insulin	228,103 (8.76)	227,732 (8.75)	371 (21.79)	< 0.0001

Table 2. Baseline characteristics of patients with and without infective endocarditis. *IE* infective endocarditis, *PA* physical activity, *CKD* chronic kidney disease, *DM* diabetes mellitus, *OHA* orally administered hypoglycemic agent.

week ≥ 1,500 groups were associated with a lower risk of incident IE. (Model 3: hazard ratio (HR) = 0.820, 95% confidence interval (CI) (0.690–0.976) in 1000 ≤ MET-min/week < 1,500; HR = 0.831, 95%CI (0.704–0.981) in MET-min/week ≥ 1500. This finding was observed for all three models (Models 1, 2, and 3). Kaplan-Meier analysis also showed a significantly lower incidence of IE in the groups with higher physical activity ($P < 0.001$, log-rank test) (Fig. 1).

Subgroup analyses

Subgroup analyses stratified by age (< 40, 40–65, and ≥ 60 years), smoking, obesity (body mass index [BMI] ≥ 25), hypertension, and duration of diabetes are shown in Fig. 2. No significant interaction was observed in the subgroup analyses. Subgroup analyses including additional variables are shown in Supplementary Tables S2, S3, and S4.

Discussion

By analyzing a nationwide cohort, this study demonstrated that physical activity in patients with diabetes may be linked to a reduced risk of incident IE. Physical activity is one of the components of daily life and is a highly accessible element of lifestyle modification. Therefore, the results of this study have important clinical implications for the management of patients with diabetes.

Extended sedentary behavior is associated with poorer glycemic control in individuals with type 2 diabetes[14]. In contrast, even light walking or simple resistance activities would benefit glycemic control in patients with diabetes[15,16]. Moreover, aerobic exercise clearly improves glycemic control in people with type 2 diabetes, mainly when executed for at least 150 min per week[17]. Several studies have reported an association between poor glycemic control and increased risk of infection[7]. Reduced neutrophil degranulation, decreased functioning of immune cells, and inhibition of complement-mediated reactions have been suggested as the underlying mechanisms for the increased risk of infection in diabetic patients[18–20]. Considering the above, improving glycemic control through physical activity is the end result of this study: risk reduction by physical activity on IE.

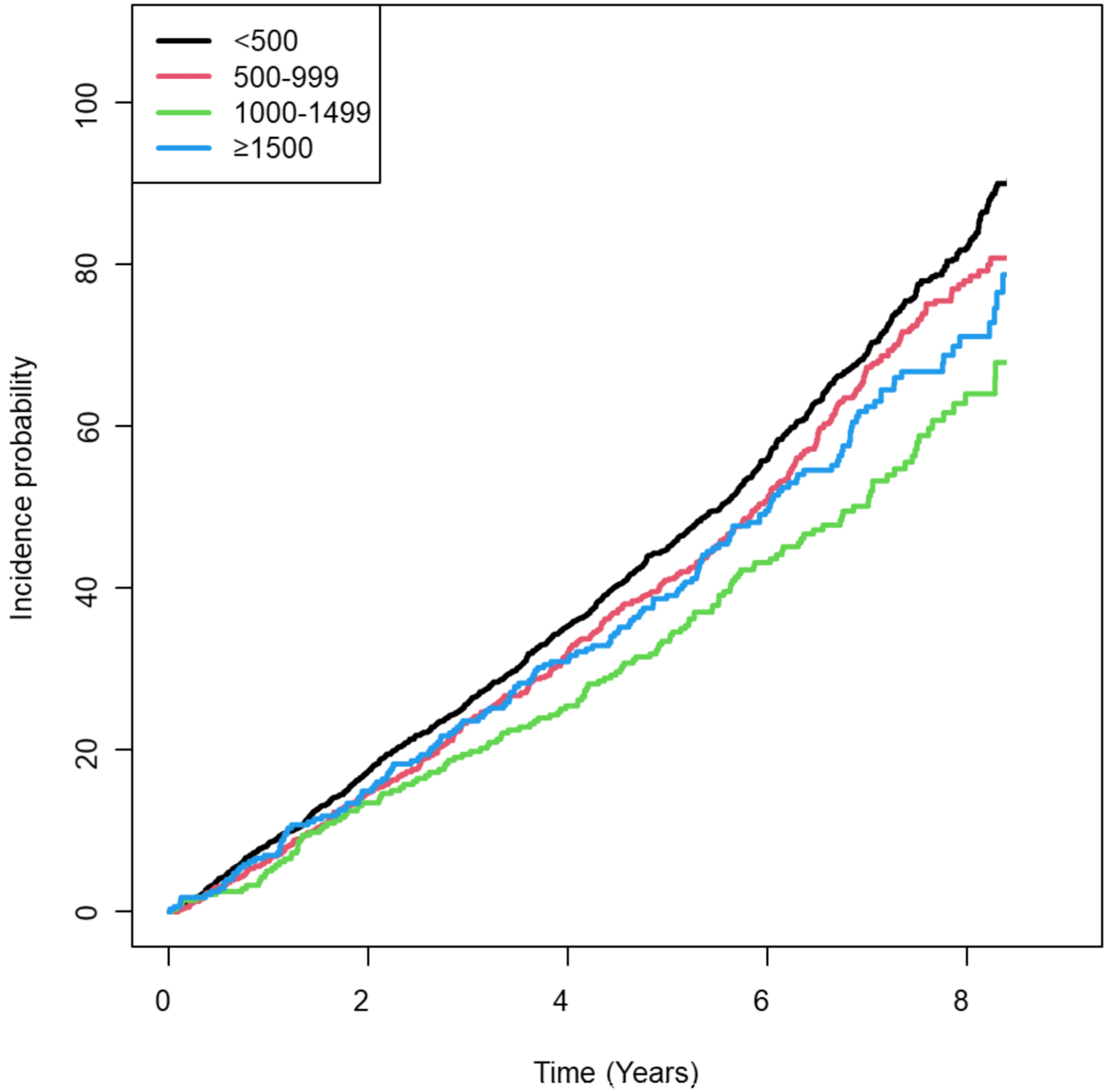
In addition to glycemic control, physical activity is thought to benefit the immune response through various pathways. In a systematic review by Chastin et al., physical activity was associated with higher concentrations of CD4 + helper T cells and salivary immunoglobulin IgA[21]. In addition, several studies have reported an association between regular exercise and enhanced neutrophil and monocyte phagocytosis, increased natural killer cell function, lower numbers of exhausted T cells, and lower levels of circulating inflammatory cytokines[22]. However, several studies have suggested that exhaustive exercise may decrease immune function[23,24].

Several studies have supported the protective effects of physical activity against chronic diseases. These studies showed a negative dose-response association between physical activity and the risk of breast cancer, colon cancer, diabetes, ischemic heart disease, ischemic stroke, and hypertension[11,25]. However, a J-shaped dose-response association between exercise and the immune system might be present, as intense physical activity could alter immune protection and increase the risk of infection[24,26]. Accordingly, the same pattern may be observed in the risk reduction of IE by the intensity of physical activity. In this study, the incidence of IE was significantly reduced in the group with 1,000–1,499 MET-min/week and 1,500 or higher MET-min/week, but there was no significant difference in the incidence of IE between these two groups. We could not classify the participant groups further according to MET-min/week, as items of the questionnaire used in the health check-up program in South Korea could not be applied to the cut-off value of MET-min/week higher than 1,500. Through a further study that classifies MET-min/week in more detail, more precise recommendations for exercise in patients with diabetes would be possible.

The World Health Organization 2020 guidelines on physical activity and sedentary behavior have recommended that all adults should undertake regular physical activity and should aim to achieve at least 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate-intensity and vigorous-intensity aerobic physical activity and reduce sedentary behavior[27]. The American Diabetes Association also stated that most adults with diabetes should engage in 150 min or more moderate-to-vigorous intensity activity weekly, spread over at least three days/week, with no more than two consecutive days without activity[9]. Approximately 150 min/week of brisk walking (moderate activity) or 75 min/

	N	Event	Incidence rate[a]	Hazard ratio (95% confidential interval)		
MET/week				Model 1[b]	Model 2[c]	Model 3[d]
MET < 500	1,405,950	963	10.06	1 (Ref.)	1 (Ref.)	1 (Ref.)
MET < 1,000	652,842	425	9.45	0.948 (0.846, 1.063)	0.964 (0.859, 1.081)	0.968 (0.863, 1.086)
MET < 1,500	274,491	149	7.78	*0.795 (0.669, 0.945)	*0.814 (0.684, 0.968)	*0.820 (0.690, 0.976)
MET ≥ 1,500	269,729	166	8.84	*0.819 (0.694, 0.967)	*0.831 (0.704, 0.981)	*0.831 (0.704, 0.981)

Table 3. Incidence and hazard ratios for incident infective endocarditis according to metabolic equivalent task classification. *MET* metabolic equivalent task. [a] Incidence rate: 100,000 person-years. [b] Model 1. Adjusted for age and sex. [c] Model 2. Adjusted for Model 1 + body mass index, low income, smoking, drinking, hypertension, dyslipidemia, and chronic kidney disease. [d] Model 3. Adjusted for model 2 + glucose, orally administered hyperglycemia agent, insulin usage, and diabetes duration (> 5 years). * indicates that the *P*-value was less than 0.05.



	0	2	4	6	8
	1,405,950	1,369,162	1,328,679	1,046,423	410,138
	652,842	640,395	625,326	498,677	193,960
	274,491	270,194	265,134	214,398	86,840
	269,729	264,840	258,740	209,741	85,609

Fig. 1. Cumulative incidence of infective endocarditis according to metabolic equivalent task classification (log-rank < 0.001), (incidence probability: 100,000 person/year, metabolic equivalent task: min/week).

week of running (vigorous activity) would be 600 MET-min/week[12]. In this study, we observed that the incidence rate of IE was lower in the groups with more physical activity than that recommended in the current guidelines.

A key strength of this study was the large number of study subjects obtained by analyzing a nationwide claims database. As a result, it was possible to draw a conclusion that could be applied to patients with diabetes without biasing the characteristics of the study subjects. Another strength of this study was its robust methodology using nationwide data to overcome the low incidence of IE.

		METs-min/week	Incidence rate	HR (95% CI)
Age	<40	<500	26.11	1 (Ref.)
		500-999	39.74	1.526 (0.781, 2.981)
		1,000-1,499	35.79	1.354 (0.508, 3.607)
		≥1,500	33.91	1.254 (0.373, 4.221)
	<65	<500	79.16	1 (Ref.)
		500-999	67.27	0.854 (0.722, 1.010)
		1,000-1,499	49.85	0.626 (0.483, 0.812)
		≥1,500	65.78	0.781 (0.615, 0.992)
	≥65	<500	165.82	1 (Ref.)
		500-999	172.38	1.059 (0.902, 1.245)
		1,000-1,499	167.88	1.047 (0.824, 1.330)
		≥1,500	142.61	0.867 (0.686, 1.095)
Smoking	Non,Ex	<500	108.71	1 (Ref.)
		500-999	100.75	0.953 (0.838, 1.085)
		1,000-1,499	83.73	0.826 (0.681, 1.003)
		≥1,500	94.07	0.840 (0.700, 1.009)
	Current	<500	77.53	1 (Ref.)
		500-999	77.44	1.025 (0.800, 1.313)
		1,000-1,499	60.28	0.797 (0.540, 1.178)
		≥1,500	68.04	0.788 (0.530, 1.172)
Obesity	Yes	<500	99.19	1 (Ref.)
		500-999	91.03	0.957 (0.810, 1.129)
		1,000-1,499	76.55	0.820 (0.639, 1.054)
		≥1,500	88.39	0.845 (0.663, 1.076)
	No	<500	102.1	1 (Ref.)
		500-999	97.83	0.978 (0.835, 1.146)
		1,000-1,499	79.05	0.821 (0.646, 1.043)
		≥1,500	88.35	0.820 (0.654, 1.029)
Hypertension	Yes	<500	129.71	1 (Ref.)
		500-999	118.69	0.947 (0.827, 1.085)
		1,000-1,499	106.38	0.881 (0.721, 1.076)
		≥1,500	110.06	0.832 (0.685, 1.011)
	No	<500	63.04	1 (Ref.)
		500-999	63.96	1.020 (0.825, 1.261)
		1,000-1,499	42.26	0.675 (0.476, 0.957)
		≥1,500	57.76	0.828 (0.604, 1.137)
DM duration	< 5 years	<500	79.27	1 (Ref.)
		500-999	74.56	0.974 (0.834, 1.137)
		1,000-1,499	60.5	0.805 (0.635, 1.020)
		≥1,500	76.78	0.921 (0.737, 1.151)
	≥ 5 years	<500	151.16	1 (Ref.)
		500-999	138.77	0.960 (0.810, 1.138)
		1,000-1,499	115.05	0.838 (0.650, 1.079)
		≥1,500	108.19	0.741 (0.579, 0.948)

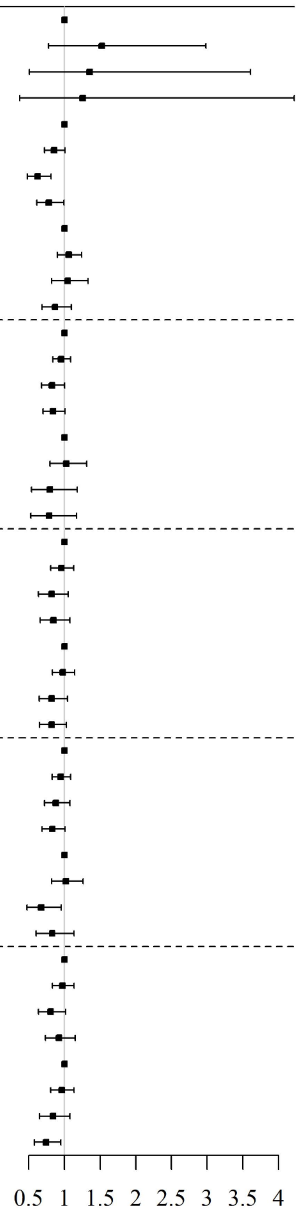


Fig. 2. Subgroup analyses by Cox proportional hazards model according to age, smoking, obesity (BMI ≥ 25), hypertension, and duration of diabetes. *BMI* body mass index, *MET* metabolic equivalent task, *HR* hazard ratio, *CI* confidence interval, *DM* diabetes mellitus. Incidence rate: 100,000 person-years.

This study had several limitations. First, this study was conducted using a nationwide claims database. Consequently, variables not included in the NHIS health check-up program, such as HbA1c levels, could not be adjusted. Second, data on physical activity for the participants were assessed via a self-reported questionnaire, which might have been subject to recall bias, and the degree of physical activity could have been overstated. However, a previous study showed the usefulness of self-reported questionnaires for identifying physical activity[28]. Third, we could not adjust for the participants' physical activity changes during the study period. Fourth, the participants' types of physical activity, such as resistance and aerobic exercise, could not be assessed. Therefore, this study could not demonstrate differences in benefits according to exercise type. Fifth, the extent to which patients with physical disabilities could not undergo health examination could not be assessed in this study. Finally, due to the nature of the observational study, causality and the direct mechanistic link between exercise and infectious disease outcomes could not be determined.

Conclusion

In conclusion, we observed a reduced risk of IE with physical activity of more than 1,000 MET-min/week in diabetic patients by analyzing a nationwide DM cohort. Further studies with a detailed classification of exercise type and amount will enable detailed recommendations on physical activity for risk reduction of infectious diseases in patients with diabetes.

Methods

Study design

This retrospective study analyzed the incidence of IE in South Korea using nationwide population data, mainly focusing on the incidence of IE with respect to exercise behavior, especially in those with DM. The present study utilized general health checkup data from the NHIS, and no additional participants were enrolled. The analyses strictly obeyed the operating regulations of the NHIS. This study was approved by the institutional review board of Soongsil University (approval no. SSU-202003-HR-201–01), and permission to use the NHIS health check-up data was granted. De-identified and anonymized data were used for analyses, and the requirement for informed consent was waived. The study was performed in accordance with the standards of ethics outlined in the Declaration of Helsinki.

Data source

This study utilized health screening data from 2009 to 2012 based on the NHIS. South Korea operates a centralized universal health insurance program, and insured citizens ≥ 40 years of age are required to participate biannually in the health check-up program of NHIS; conversely, employed individuals ≥ 20 years of age participate in annual check-ups. It is estimated that almost 97.0% of Koreans participate in this mandatory universal health checkup. The NHIS manages the NHI program, which includes approximately 50 million Korean people.

The claimed data, composed of the NHIS health check-up program, include information such as age, sex, insurer payment coverage, area of residence, medical utilization/transaction information, deductions, and claims data. During the check-up, a trained examiner took note of anthropometric measurements, including height (cm), weight (kg), waist circumference (WC) (cm), systolic blood pressure (SBP) (mmHg), and diastolic blood pressure (DBP) (mmHg). Laboratory test results included fasting blood glucose (mg/dL), total cholesterol (mg/dL), low-density lipoprotein cholesterol (LDL-C) (mg/dL), high-density lipoprotein cholesterol (HDL-C) (mg/dL), and triglycerides (mg/dL). General health behaviors were investigated using self-completed questionnaires that included questions about alcohol consumption, smoking, and exercise.

Participants

We retrieved the health checkup data of participants with diabetes during 2009–2012 from the NHIS database (n = 2,746,079) and excluded participants younger than 20 years (n = 390) and those with missing data (n = 117,449). Subjects diagnosed with IE (n = 659) before receiving health screening were excluded. A total of 24,569 patients were excluded due to 1 year lag period (death or occurrence of IE within 1 year of enrollment). In total, 2,603,012 participants were included in the main analysis. Last followed-up date was December 31, 2018 (mean follow-up duration of 6.86 ± 1.59 years) for the occurrence of IE.

Definition of study variables

Participants with diabetes were defined as follows: (1) at least one claim data for antidiabetic medications with International Classification of Disease 10th Revision (ICD-10) codes E11 to E14 or (2) fasting glucose level ≥ 126 mg/dL during health check-ups without a prescription of antidiabetic medications. IE was defined as patients who were admitted to hospitals with ICD-10 codes (I33.x, I38.x, and I39.8). Of the patients with ICD-10 codes for IE, only those who were hospitalized for > 14 days or died within 14 days were included in the analyses, and anyone with ≤ 14 days without death during hospitalization was censored (Supplementary Table S1). Comorbidities included hypertension, dyslipidemia, and chronic kidney disease. The prescriptions of antidiabetic medications such as sulfonylureas, metformin, dipeptidyl peptidase 4 inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, and insulins were analyzed. Heavy alcohol drinkers were defined as participants with alcohol consumption > 30 g/day. Low income was defined as the lowest quadrant (25%) income level.

Exercise evaluation and classification: MET-min/week

Physical activity-related energy expenditure (MET-min/week) was calculated by summing the products of frequency, intensity, and duration. The level of physical activity per week was categorized as < 500, 500–999, 1,000–1,499, and ≥ 1,500 MET-min/week[15]. Data on physical activity were collected using self-report structured questionnaires using a 7-day recall method during a health check-up, using the Korean version of the international physical activity questionnaire (K-IPAQ) short form. The questionnaire section on exercise was composed of three questions about the frequency (days per week) of light, moderate, and vigorous exercise during a recent week, that is, the frequency of (i) light intensity exercise (e.g., walking slowly or light physical activity) for more than 30 min, (ii) moderate-intensity exercise (e.g., brisk-pace walking, tennis doubles, or bicycling leisurely, scrubbing) for more than 30 min, and (iii) vigorous intensity exercise (e.g., running, climbing, fast cycling, or aerobics) for more than 20 min[29].

Statistical analysis

Categorical variables are presented as frequencies and percentages and were compared using the chi-square test. Continuous variables are presented as mean and standard deviation or median with range and were compared using the Student's *t*-test. For clinical outcome analysis, incidence rates were estimated using the total number of clinical outcomes during the follow-up period divided by 100,000 person-years at risk. The risk of incident IE according to the MET-min/week classification was analyzed using the Kaplan-Meier method and log-rank test. Cox proportional hazard models were used to analyze the relationship between incident IE and physical activity classification using univariate and multivariate analyses. Covariates were incorporated in the multivariable analysis to obtain adjusted hazard ratios and 95% confidential intervals, including age, sex (model 1), model 1 + BMI, income, smoking, drinking, hypertension, dyslipidemia, chronic kidney disease (model 2), model 2 + glucose, oral administration of antihyperglycemic agents, insulin use, and DM duration (model 3). Subgroup analyses were conducted using multivariable Cox proportional hazard models according to the following variables: age (< 40, 40–65, and ≥ 65 years), sex, smoking, drinking, BMI, abdominal obesity, hypertension, insulin use, and duration of diabetes (< 5 or ≥ 5 years). The model was adjusted for age, sex, BMI, low income, smoking, drinking, hypertension, dyslipidemia, CKD, fasting glucose level, insulin use, DM duration, and the number of oral hypoglycemic agents.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA), and all two-tailed $P < 0.05$ were considered statistically significant.

Data availability

The data are available from the Korean National Health Insurance Sharing Service which is open to researchers on request with approval by the institutional review board. If someone wants to request the data from this study, please contact the corresponding author of this study.

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Author contributions
S.J.L. and H.K. drafted the manuscript. S.J.L., H.K., K.H., N.S.K., and S.H.L. contributed to the conception, design, analysis, and interpretation of the data. K.H. contributed to the acquisition of data. J.K., J.H.K., W.K.P., J.Y.A., S.J.J., J.Y.C., J.Y., K.H., N.S.K., and S.H.L. contributed to the discussion and critically revised the manuscript. All the authors have read and approved the final manuscript and have agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Declarations

Competing interests
The authors declare no competing interests.

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