Changes in Physical Activity and the Risk of Dementia in Patients With New-Onset Type 2 Diabetes: A Nationwide Cohort Study

Jung Eun Yoo,[1] Kyungdo Han,[2] Bongseong Kim,[2] Sang-Hyun Park,[3] Seon Mee Kim,[4] Hye Soon Park,[5] and Ga Eun Nam[4]

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OBJECTIVE

We investigated the association between interval changes in physical activity (PA) and dementia risk among patients with new-onset type 2 diabetes.

RESEARCH DESIGN AND METHODS

We identified 133,751 participants newly diagnosed with type 2 diabetes in a health screening (2009–2012), with a follow-up health screening within 2 years (2010–2015). PA level changes were categorized into continuous lack of PA, decreaser, increaser, and continuous PA groups. Dementia was determined using dementia diagnosis codes and antidementia drug prescriptions.

RESULTS

During the median follow-up of 4.8 years, 3,240 new cases of all-cause dementia developed. Regular PA was associated with lower risks of all-cause dementia (adjusted hazard ratio [aHR] 0.82; 95% CI 0.75–0.90), Alzheimer disease (AD) (aHR 0.85; 95% CI 0.77–0.95), and vascular dementia (VaD) (aHR 0.78; 95% CI 0.61–0.99). Increasers who started to engage in regular PA had a lower risk of all-cause dementia (aHR 0.86; 95% CI 0.77–0.96). Moreover, the risk was further reduced among those with continuous regular PA: all-cause dementia (aHR 0.73; 95% CI 0.62–0.85), AD (aHR 0.74; 95% CI 0.62–0.88), and VaD (aHR 0.62; 95% CI 0.40–0.94). Consistent results were noted in various subgroup analyses.

CONCLUSIONS

Regular PA was independently associated with lower risks of all-cause dementia, AD, and VaD among individuals with new-onset type 2 diabetes. Those with continuous regular PA and, to a lesser extent, those who started to engage in regular PA had a lower risk of dementia. Regular PA should be encouraged to prevent dementia in high-risk populations and those with new-onset type 2 diabetes.

Worldwide, nearly 35 million people live with dementia, and this number is expected to increase by more than threefold by 2050, representing a public health priority (1). Because of the growing importance of dementia, more research on modifiable risk factors for dementia is warranted (2). Some dementia cases are

[1]Department of Family Medicine, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, Republic of Korea
[2]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea
[3]Department of Medical Statistics, College of Medicine, Catholic University of Korea, Seoul, Republic of Korea
[4]Department of Family Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea
[5]Department of Family Medicine, Asan Medical Center, Ulsan University College of Medicine, Seoul, Republic of Korea

Corresponding author: Ga Eun Nam, namgaaa@daum.net

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preventable or may have a delayed onset through managing risk factors or by improving and increasing the educational attainment of patients (3).

Type 2 diabetes is a robust predictor of dementia, including Alzheimer disease (AD) and vascular dementia (VaD), mild cognitive impairment, and cognitive decline (4). Previous studies have reported an association between type 2 diabetes and cognitive impairment (5,6), and individuals with type 2 diabetes experienced global cognitive decline at a twofold rate compared with those without type 2 diabetes over a 5-year period (7). Furthermore, individuals with type 2 diabetes represent an important risk group for dementia. For example, a meta-analysis found that type 2 diabetes was associated with a 73% increase in risk of all-cause dementia (8), and a population-based longitudinal study found a 16% increased risk of dementia, even among those with recent-onset type 2 diabetes (9).

Physical activity (PA) has a clear beneficial effect for those with type 2 diabetes (10). Regular PA has potential therapeutic effects on glucose regulation and cardiovascular health, both of which may threaten cognitive integrity when compromised (11,12). Recently, it was shown that PA can also enhance cognitive function and reduce dementia risk (13–16). Given the increased risk of dementia posed by type 2 diabetes, it is important to define the utility of PA with regard to dementia in a type 2 diabetes cohort. However, only a few studies have examined the applicability of these findings to individuals with type 2 diabetes at high risk of cognitive decline or dementia (17–22). Indeed, these studies did not distinguish between patients with type 2 diabetes and those with impaired glucose tolerance (17,18,20,22). In cohort studies, PA was measured only once; however, the level of PA can change over time (18,19). In particular, a disease diagnosis, such as type 2 diabetes, may motivate health behavior changes (23). In addition, they only investigated cognitive function as an outcome, not for the development of dementia (17–22). Other limitations of previous studies include a small study population ($N < 1,550$) (19) and limitation to specific populations, such as women (19) or the elderly (19–21).

We designed a retrospective cohort study using a large population-based database to investigate the association between regular PA and the incidence of dementia. We also assessed the influence of changes in PA in patients newly diagnosed with type 2 diabetes on dementia development.

RESEARCH DESIGN AND METHODS

Data Source and Study Setting

The National Health Insurance Service (NHIS) is the single insurer in Korea and provides mandatory universal comprehensive medical care to the entire Korean population, except for Medicaid beneficiaries in the lowest income bracket (3% of the population). The NHIS provides a free biennial cardiovascular health screening and an annual screening for workers in jobs requiring physical labor. Therefore, the NHIS database contains a complete set of health information pertaining to 50 million Koreans, which includes a qualification database (e.g., age, sex, place of residence, and income level), a claims database (e.g., general information on specifications, consultation statements, diagnosis statements defined by the ICD-10, and prescription statements), and a health screening database (results of general health examinations) (24). The NHIS database has been used to establish cohort data for various epidemiologic studies (25).

Study Population

To identify patients with new-onset type 2 diabetes, of 17,314,795 participants (age ≥40 years) who underwent a health screening between 2009 and 2012, we excluded those with fasting plasma glucose <126 mg/dL at the health screening (n = 15,399,771) and those with a history of type 2 diabetes (n = 1,620,496), which was defined as an ICD-10 code (E11–E14) diagnosis with at least one claim for prescription of an antidiabetic agent before the health screening. This definition was based on the consensus of relevant findings widely used in previous studies (26,27). As a result, 294,528 participants newly diagnosed with type 2 diabetes were identified. Among them, 139,733 participants underwent follow-up health screening after 2 years (2010–2015). We also excluded those who had missing information (n = 5,052) and had a history of dementia (n = 930). Finally, 133,751 eligible participants were followed up from the last health screening date to the date of any incident of dementia, death, or end of the study period (31 December 2017), whichever came first (Supplementary Figs. 1 and 2).

This study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Korea University Anam Hospital (no. 2019AN0201). The requirement for written informed consent was waived, because anonymous and deidentified information was used for the analysis.

Exposure: Regular PA

During the NHIS health screening, PA was measured using the International Physical Activity Questionnaire (IPAQ)–Short Form, which has been recommended as a cost-effective method to assess PA. In the questionnaire, moderate and vigorous PA was assessed with the following questions, respectively: "During the last 7 days, how many days did you perform moderate physical activities such as carrying light loads, bicycling at a regular place, or double tennis?" and "During the last 7 days, how many days did you do vigorous activities like heavy lifting, digging, aerobics, or fast bicycling?" Regular PA was defined as ≥30 min of moderate PA at least five times per week or ≥20 min of vigorous PA at least three times per week (Supplementary Material 1) (28).

The interval change in regular PA was defined by using two consecutive 2-year interval health screenings, baseline (2009–2012) and follow-up (2010–2015), among participants who were newly diagnosed with type 2 diabetes at baseline. Participants were divided into the following categories: *1*) continuous lack of PA (those who did not exercise regularly), *2*) decreaser (those who stopped regular PA), *3*) increaser (those who started regular PA), and *4*) continuous PA (those who maintained regular PA) (29).

Study Outcome: Dementia

The end point of the study was newly diagnosed dementia, which was further classified as AD and VaD. The outcomes were defined if an acetylcholinesterase inhibitor (donepezil hydrochloride, rivastigmine, or galantamine) or an N-methyl-D-aspartate receptor antagonist (memantine) was prescribed at least twice, with the relevant ICD-10 code (F00 or G30 for AD; F01 for VaD; and F02, F03, G23.1, or G31 for other dementia). To file expense claims for acetylcholinesterase inhibitor or

N-methyl-D-aspartate receptor antagonist (memantine) prescriptions for dementia treatment, Korean physicians need to document evidence of cognitive dysfunction according to the National Health Insurance Reimbursement criteria: a Mini-Mental State Examination score ≤26 and either a Clinical Dementia Rating ≥1 or a Global Deterioration Scale stage ≥3 (30,31).

Covariates

Covariates were assessed at the follow-up examination (2010–2015). We considered socioeconomic status, including income level, a potential covariate. Information on current smoking and alcohol consumption was obtained using a questionnaire. Alcohol consumption was classified as none, mild (<15 g alcohol per day), moderate (15–30 g alcohol per day), or heavy (≥30 g alcohol per day). BMI was calculated as participant weight (kg) divided by the square of participant height (m^2).

Comorbidities such as hypertension, dyslipidemia, chronic kidney disease, cancer, and depression were based on claims data before the screening date and health screening results. Hypertension was defined according to *1*) the presence of at least one claim under ICD-10 codes I10–I13 or I15 and at least one claim for the prescription of an antihypertensive agent or *2*) systolic blood pressure/diastolic blood pressure ≥140/90 mmHg. Dyslipidemia was defined according to *1*) the presence of at least one claim under ICD-10 code E78 and at least one claim for the prescription of a lipid-lowering agent or *2*) total cholesterol ≥240 mg/dL. Chronic kidney disease was defined as a glomerular filtration rate of <60 mL/min/1.73 m^2 as estimated by the Modification of Diet in Renal Disease equation. Cancer was defined using the ICD-10 C codes. Depression was defined using ICD-10 code F22 or F33.

Statistical Analyses

Continuous variables are presented as means ± SDs, and categorical variables are presented as numbers and percentages. The results were compared using one-way ANOVA or Pearson χ^2 test. The incidence rate of dementia was calculated as the number of cases per 1,000 person-years. Hazard ratios (HRs) and 95% CIs for dementia were analyzed using the multivariate-adjusted Cox proportional hazards models according to baseline regular PA and interval change in regular PA. Model 1 accounted for age and sex, and model 2 was adjusted for age, sex, smoking status, alcohol consumption, income level, BMI, and comorbidities (hypertension, dyslipidemia, chronic kidney disease, cancer, and depression). Model 3 was adjusted for variables in model 2 and the use of antidiabetic drugs (number of oral hypoglycemic agents and insulin). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC), and a *P* value <0.05 was considered statistically significant.

Data and Resource Availability

This study was performed using the Korean National Health Insurance System database. Restrictions apply to the availability of these data, which were used under license for this study.

RESULTS

Baseline Characteristics of the Study Population

The characteristics of the study participants are described in Table 1. During the 2 years before initiation of the study, 62.8% had a lack of regular PA, 10.8% became decreasers, 15.8% became increasers, and the remaining 8.6% maintained regular PA, according to the study definition. Compared with participants continuously without regular PA, those who adhered to regular PA were older, more likely to be male and heavy alcohol drinkers, and less likely to be current smokers; had a lower prevalence of comorbid conditions such as dyslipidemia, chronic kidney disease, and depression; and used a lower number of oral antidiabetic drugs and insulin.

Regular PA and Dementia

During the median follow-up period of 4.8 years (interquartile range, 3.8–5.8 years), there were 3,240 new cases of all-cause dementia, 74.7% (2,420 cases) of which were AD and 14.5% (469 cases) of which were VaD. After adjusting for all potential confounding variables, regular PA was associated with a lower risk of all-cause dementia (adjusted HR [aHR] 0.82; 95% CI 0.75–0.90), AD (aHR 0.85; 95% CI 0.77–0.95), and VaD (aHR 0.78; 95% CI 0.61–0.99) (Table 2).

Increasers who started to engage in regular PA during the 2-year interval among participants with new-onset type 2 diabetes showed a lower risk of all-cause dementia (aHR 0.86; 95% CI 0.77–0.96) (Table 3). In addition, the risk was further reduced among those with continuous regular PA during the 2-year interval among participants with new-onset type 2 diabetes: all-cause dementia (aHR 0.73; 95% CI 0.62–0.85), AD (aHR 0.74; 95% CI 0.62–0.88), and VaD (aHR 0.62; 95% CI 0.40–0.94). These associations persisted in sensitivity analyses adopting the definition of regular PA as ≥1,000 metabolic equivalent task min per week (Supplementary Table 1). Consistent results were observed with changes in PA during the 4-year study period (Supplementary Table 2). Consistent results were also observed even after adjusting for confounders both at initial and follow-up assessment (Supplementary Table 3). We also considered the relative degrees of change in PA and additionally analyzed the risk of dementia according to PA level at the follow-up assessment in each PA change group (Supplementary Table 4). In this analysis, the risks of all-cause dementia and AD were reduced in the continuous regular PA group with ≥1,000 metabolic equivalent task min per week at the follow-up assessment. The analysis performed after additionally adjusting for the changes in the frequency of PA between two consecutive examinations is shown in Supplementary Table 5. In this analysis, consistent findings showed that continuous regular PA was associated with lower risks of all-cause dementia, AD, and VaD.

Subgroup Analyses

Stratified analyses by age, sex, stroke, and depression were conducted. The associations between change in PA and dementia showed similar patterns in all subgroups. Compared with the continuous lack of PA group, the continuous regular PA group remained predictive of lower incidences of all-cause dementia and AD in the older age group, both sexes, and those without stroke or depression (Table 4). There was a significant interaction with stroke in the association between change in PA and risk of VaD. Lower VaD risk was observed

Table 1—Baseline characteristics of study participants according to PA change

Variable	Interval change in regular PA*				*P*
	Continuous lack of PA	Decreaser	Increaser	Continuous PA	
n	86,643	14,396	21,159	11,553	
Age, years	57.6 ± 9.8	59.1 ± 9.3	57.2 ± 9.1	58.2 ± 9.0	<0.001
Sex (male)	52,971 (61.1)	9,353 (65.0)	14,241 (67.3)	8,557 (74.1)	<0.001
Current smoker	22,492 (26.0)	3,168 (22.0)	4,692 (22.2)	2,333 (20.2)	<0.001
Heavy alcohol drinker	8,221 (9.5)	1,263 (8.8)	1,884 (8.9)	1,219 (10.6)	<0.001
Income (lowest quartile)	22,106 (25.5)	3,683 (25.6)	5,093 (24.1)	2,552 (22.1)	<0.001
Height, cm	162.8 ± 9.0	163.3 ± 8.6	164.0 ± 8.5	165.1 ± 8.1	<0.001
Weight, kg	67.5 ± 11.5	67.5 ± 11.1	67.8 ± 10.9	68.4 ± 10.6	<0.001
BMI, kg/m^2	25.4 ± 3.3	25.2 ± 3.1	25.1 ± 3.1	25.0 ± 3.0	<0.001
WC, cm	86.0 ± 8.4	85.7 ± 8.3	85.2 ± 8.1	85.1 ± 7.8	<0.001
Systolic BP, mmHg	127.2 ± 14.5	127.7 ± 14.4	126.8 ± 14.3	127.6 ± 14.0	<0.001
Diastolic BP, mmHg	78.6 ± 9.6	78.6 ± 9.5	78.3 ± 9.4	78.6 ± 9.2	<0.001
Glucose, mg/mL	134.6 ± 37.0	133.7 ± 36.0	129.8 ± 32.9	131.6 ± 32.3	<0.001
TC, mg/mL	187.8 ± 39.8	186.3 ± 39.1	185.0 ± 38.5	185.2 ± 38.4	<0.001
Comorbidities					
Hypertension	48,830 (56.4)	8,469 (58.8)	11,457 (54.2)	6,564 (56.8)	<0.001
Dyslipidemia	45,193 (52.2)	7,387 (51.3)	10,578 (50.0)	5,673 (49.1)	<0.001
Chronic kidney disease	5,388 (6.2)	979 (6.8)	1,170 (5.5)	694 (6.0)	<0.001
Stroke	894 (1.0)	165 (1.2)	248 (1.2)	127 (1.1)	0.246
Cancer	2828 (3.3)	558 (3.9)	822 (3.9)	428 (3.7)	<0.001
Depression	4732 (5.5)	817 (5.7)	1026 (4.9)	493 (4.3)	<0.001
Antidiabetic drugs					
≥3 oral drugs†	13,183 (15.2)	2,049 (14.2)	3,052 (14.4)	1,393 (12.1)	<0.001
Insulin	6951 (8.0)	1,170 (8.1)	1,719 (8.1)	822 (7.1)	0.005

Data are expressed as mean ± SD or *n* (%). BP, blood pressure; TC, total cholesterol; WC, waist circumference. *Regular PA was defined as ≥30 min of moderate PA at least five times per week or ≥20 min of vigorous PA at least three times per week. †Oral antidiabetic drugs included metformin, sulfonylurea, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and α-glucosidase inhibitors.

in the continuous regular PA group without stroke (aHR 0.63; 95% CI 0.41–0.97).

CONCLUSIONS

With repeated measurements of PA, we confirmed that regular PA was independently associated with lower risks of all-cause dementia, AD, and VaD among participants with new-onset type 2 diabetes. The risks were further reduced by continuous regular PA. In addition, for those who increased their PA level from no PA to regular PA over 2 years, the incidence of all-cause dementia was also significantly reduced. Our stratified analyses also demonstrated that regular PA was consistently associated with a lower dementia risk among individuals with various characteristics.

It has been shown that PA can also enhance cognitive function and reduce dementia risk (13–16). PA may lead to an increase in brain tissues, including the hippocampus, and result in an increased level of brain-derived neurotrophic factor in association with increased hippocampal volume and slowed cognitive decline (15). Consistently, we showed that regular PA also had a protective effect on dementia among those with recent-onset type 2 diabetes. Glucose intolerance, a characteristic of type 2 diabetes, has been associated with an increased risk of cognitive impairment and dementia compared with that in healthy peers (32–34). Type 2 diabetes often contributes to numerous harmful consequences for peripheral systems and neurophysiologic and structural changes in the brain that adversely affect cognition and ultimately increase the risk of dementia (35). Although these cerebral neuropathologic changes are believed to begin in the early stages of type 2 diabetes (36), the current study highlights that the patients with newly diagnosed type 2 diabetes who have not engaged in regular PA can prevent dementia by starting regular PA.

Insulin has been suggested to play a role in AD. Insulin can cross the blood-brain barrier and compete with amyloid-β peptide (Aβ) in the brain, including the hippocampus (36). Insulin is also produced in the brain and may have an alternatively beneficial effect on amyloid clearance (36). Peripheral hyperinsulinemia may inhibit brain insulin production, which in turn results in impaired amyloid clearance and a higher risk of AD (36,37). In addition, hyperglycemia can cause glucose toxicity, leading to advanced protein glycosylation, mitochondrial dysfunction, and oxidative stress, giving rise to AD pathology (36,37). For example, glycation of Aβ enhances its aggregation in vitro,

Table 2—HRs and 95% CIs for incidence of dementia according to regular PA

Regular PA	*n*	Event	PYs	Incidence rate per 1,000 PYs	HR (95% CI) Model 1*	Model 2†	Model 3‡
All-cause dementia							
No	101,039	2,677	484,045	5.53	1 (reference)	1 (reference)	1 (reference)
Yes	32,712	563	158,234	3.56	0.81 (0.74–0.88)	0.82 (0.75–0.90)	0.82 (0.75–0.90)
P					<0.001	<0.001	<0.001
AD							
No	101,039	1,996	484,045	4.12	1 (reference)	1 (reference)	1 (reference)
Yes	32,712	424	158,234	2.68	0.84 (0.75–0.93)	0.85 (0.76–0.94)	0.85 (0.77–0.95)
P					0.001	0.002	0.003
VaD							
No	101,039	387	484,045	0.80	1 (reference)	1 (reference)	1 (reference)
Yes	32,712	82	158,234	0.52	0.75 (0.59–0.95)	0.78 (0.61–0.99)	0.78 (0.61–0.99)
P					0.017	0.039	0.043

PY, person-year. *Model 1 was adjusted for age and sex. †Model 2 was adjusted for age, sex, smoking status, alcohol consumption, income level, BMI, and comorbidities (hypertension, dyslipidemia, chronic kidney disease, cancer, and depression). ‡Model 3 was adjusted for age, sex, smoking status, alcohol consumption, income level, BMI, comorbidities (hypertension, dyslipidemia, chronic kidney disease, cancer, and depression), and antidiabetic drugs.

and receptors for advanced glycosylation products have been found to be specific cell-surface receptors for Aβ, thus potentially causing neuronal damage (36). Therefore, it is possible that regular PA, which can induce decreasing peripheral hyperinsulinemia and increasing brain insulin levels, has a beneficial effect on AD among individuals with type 2 diabetes.

PA is also associated with the incidence of VaD, which is caused by an altered supply of blood to the brain, typically by a series of strokes. This is not surprising, because VaD is generally considered a manifestation of cardiovascular disease, and PA not only improves blood glucose control in type 2 diabetes but also reduces cardiovascular risk factors and contributes to weight loss. The mechanism of cardiovascular disease in patients with type 2 diabetes has been demonstrated. Type 2 diabetes and its comorbid conditions, such as obesity, hypertension, or dyslipidemia, are associated with macro- and microvascular changes, leading to vascular pathology in the brain (37,38). Insulin resistance can cause complex changes in cerebral energy metabolism, induce inflammation, and substantially affect the vasculature (37,38). Regular PA also causes favorable changes in insulin sensitivity; thus, it can contribute to preventing VaD in new-onset type 2 diabetes.

In the current study, regular PA consistently decreased the risk of dementia, even after various stratifications. These findings highlight the causal inverse relationship between regular PA and the development of dementia. Interestingly,

Table 3—HRs and 95% CIs for incidence of dementia according to change in regular PA

Change in regular PA	*n*	Event	PYs	Incidence rate per 1,000 PYs	HR (95% CI) Model 1*	Model 2†	Model 3‡
All-cause dementia							
Continuous lack of PA	86,643	2,322	414,451	5.60	1 (reference)	1 (reference)	1 (reference)
Decreaser	14,396	355	69,594	5.10	0.89 (0.80–1.00)	0.90 (0.80–1.00)	0.90 (0.80–1.01)
Increaser	21,159	385	102,371	3.76	0.85 (0.76–0.95)	0.85 (0.77–0.95)	0.86 (0.77–0.96)
Continuous PA	11,553	178	55,863	3.19	0.69 (0.59–0.81)	0.72 (0.62–0.84)	0.73 (0.62–0.85)
AD							
Continuous lack of PA	86,643	1,744	414,451	4.21	1 (reference)	1 (reference)	1 (reference)
Decreaser	14,396	252	69,594	3.62	0.86 (0.75–0.98)	0.86 (0.75–0.98)	0.86 (0.75–0.98)
Increaser	21,159	292	102,371	2.85	0.88 (0.78–1.00)	0.88 (0.78–1.00)	0.88 (0.78–1.00)
Continuous PA	11,553	132	55,863	2.36	0.71 (0.59–0.84)	0.73 (0.61–0.87)	0.74 (0.62–0.88)
VaD							
Continuous lack of PA	86,643	328	414,451	0.79	1 (reference)	1 (reference)	1 (reference)
Decreaser	14,396	59	69,594	0.85	1.01 (0.76–1.33)	1.02 (0.77–1.35)	1.02 (0.78–1.35)
Increaser	21,159	59	102,371	0.58	0.85 (0.64–1.12)	0.87 (0.66–1.15)	0.87 (0.66–1.15)
Continuous PA	11,553	23	55,863	0.41	0.57 (0.37–0.87)	0.61 (0.40–0.93)	0.62 (0.40–0.94)

PY, person-year. *Model 1 was adjusted for age and sex. †Model 2 was adjusted for age, sex, smoking status, alcohol consumption, income level, BMI, and comorbidities (hypertension, dyslipidemia, chronic kidney disease, cancer, and depression). ‡Model 3 was adjusted for age, sex, smoking status, alcohol consumption, income level, BMI, comorbidities (hypertension, dyslipidemia, chronic kidney disease, cancer, and depression), and antidiabetic drugs.

Table 4—HRs and 95% CIs for incidence of dementia according to regular PA change by subgroup

Subgroup	Continuous lack of PA	Decreaser	Increaser	Continuous PA	*P* for interaction
All-cause dementia					
Age, years					0.402
<65	1 (reference)	1.02 (0.79–1.32)	0.98 (0.78–1.23)	0.75 (0.54–1.05)	
≥65	1 (reference)	0.85 (0.75–0.96)	0.81 (0.72–0.92)	0.69 (0.58–0.83)	
Sex					0.925
Male	1 (reference)	0.93 (0.80–1.08)	0.87 (0.75–1.00)	0.73 (0.60–0.88)	
Female	1 (reference)	0.87 (0.74–1.02)	0.85 (0.72–1.00)	0.72 (0.56–0.94)	
Stroke					0.096
No	1 (reference)	0.88 (0.78–0.98)	0.87 (0.78–0.97)	0.73 (0.62–0.85)	
Yes	1 (reference)	1.46 (0.92–2.33)	0.72 (0.41–1.26)	0.56 (0.24–1.48)	
Depression					0.941
No	1 (reference)	0.91 (0.81–1.03)	0.87 (0.78–0.98)	0.74 (0.62–0.87)	
Yes	1 (reference)	0.83 (0.61–1.11)	0.77 (0.57–1.04)	0.65 (0.41–1.04)	
AD					
Age, years					0.582
<65	1 (reference)	0.94 (0.68–1.31)	1.03 (0.78–1.36)	0.75 (0.50–1.14)	
≥65	1 (reference)	0.82 (0.71–0.95)	0.84 (0.73–0.96)	0.70 (0.58–0.86)	
Sex					0.382
Male	1 (reference)	0.94 (0.79–1.13)	0.86 (0.73–1.03)	0.78 (0.62–0.97)	
Female	1 (reference)	0.78 (0.64–0.94)	0.91 (0.76–1.09)	0.67 (0.49–0.92)	
Stroke					0.816
No	1 (reference)	0.86 (0.75–0.98)	0.89 (0.79–1.02)	0.73 (0.61–0.88)	
Yes	1 (reference)	0.84 (0.43–1.64)	0.77 (0.41–1.44)	0.79 (0.31–2.00)	
Depression					0.959
No	1 (reference)	0.87 (0.75–1.00)	0.90 (0.79–1.03)	0.76 (0.63–0.91)	
Yes	1 (reference)	0.85 (0.60–1.19)	0.80 (0.57–1.12)	0.59 (0.34–1.04)	
VaD					
Age, years					0.785
<65	1 (reference)	1.18 (0.70–1.99)	0.77 (0.45–1.32)	0.56 (0.24–1.28)	
≥65	1 (reference)	0.94 (0.68–1.31)	0.90 (0.65–1.25)	0.62 (0.38–1.02)	
Sex					0.063
Male	1 (reference)	0.89 (0.60–1.32)	1.10 (0.79–1.53)	0.65 (0.40–1.08)	
Female	1 (reference)	1.24 (0.84–1.84)	0.54 (0.31–0.94)	0.56 (0.25–1.26)	
Stroke					0.001
No	1 (reference)	0.88 (0.65–1.19)	0.88 (0.66–1.17)	0.63 (0.41–0.97)	
Yes	1 (reference)	5.55 (2.30–13.40)	0.83 (0.18–3.81)	—	
Depression					0.715
No	1 (reference)	1.08 (0.81–1.45)	0.92 (0.68–1.23)	0.64 (0.41–1.00)	
Yes	1 (reference)	0.68 (0.29–1.59)	0.60 (0.26–1.41)	0.48 (0.12–2.00)	

HRs were adjusted for age, sex, smoking status, alcohol consumption, income level, BMI, comorbidities (hypertension, dyslipidemia, chronic kidney disease, cancer, and depression), and antidiabetic drugs.

the beneficial effect of regular physical exercise on dementia was more prominent in patients with new-onset type 2 diabetes without a history of stroke. On the other hand, the risk of VaD increased when those with a history of stroke decreased their level of PA. Therefore, encouraging regular PA to prevent dementia should be reinforced, regardless of stroke history.

In the current guidelines, such as those from the American Diabetes Association, PA is recommended for all individuals with type 2 diabetes as part of the management of glycemic control and overall health (10). A type 2 diabetes diagnosis may motivate patients to maintain or increase PA. One study reported that a shorter time since diagnosis of type 2 diabetes was associated with a greater increase in PA for 6 months (39). Our study also provides evidence that patients with new-onset type 2 diabetes who sustained regular PA or started regular PA may have a decreased risk of developing dementia. Therefore, health care professionals should consider how best to capitalize on this opportunity to encourage increased PA and maintenance.

Our study has several limitations. First, we obtained information on PA based on a self-administered questionnaire, the IPAQ, which may not accurately reflect the actual levels of PA among participants. However, self-administered questionnaires approximate PA at the population level, and the effectiveness of the IPAQ-based self-administered questionnaire has been confirmed in several studies (29). Second, considering the long preclinical period of dementia, long-term date of PA would be informative (40). Unfortunately, because of a lack of data availability, our data were limited to a short span, preventing trajectory analyses. Third, the etiologic diagnosis of dementia was not based on AD biomarkers because of the design of the current study, which was based on epidemiologic data. Discrepancies between

the diagnoses made by individuals in medical practice and those recorded in claims data may have led to inaccurate analyses. However, under the Korean NHIS, the specificity of the data is usually high because of the requirements to fulfill strict insurance criteria. The sensitivity of the data is also considered high, because dementia can be detected with only clinically meaningful symptoms as a result of accessibility to the health care system. Fourth, because this study was based on data that were not originally collected to study dementia, we did not have all the pertinent information relevant to the condition, such as apolipoprotein E4 carrier status and education level, which might affect cognitive function. However, it is unlikely that apolipoprotein E acts as a hidden confounder causing the association between PA and dementia. Additionally, education level is the most important determinant of income; the effect of education on dementia could therefore be minimized by controlling for income. Lastly, the selection of study participants based on repeated participation in health examinations might be a source of bias, because individuals with healthier behaviors and better health care access are more likely to participate in regular health checkups.

In conclusion, in this nationwide population-based cohort study, we demonstrated that regular PA was independently associated with lower risks of all-cause dementia, AD, and VaD among patients with new-onset type 2 diabetes. Of these patients, those with continuous regular PA and, to a lesser extent, those who started regular PA had a lower risk of dementia. These findings suggest that regular PA should be encouraged to prevent dementia in high-risk populations and those with recent-onset type 2 diabetes.

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