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ORIGINAL RESEARCH

Low Risk of Dementia in Patients With Newly Diagnosed Atrial Fibrillation and a Clustering of Healthy Lifestyle Behaviors: A Nationwide Population-Based Cohort Study

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BACKGROUND: Limited data are available on the clinical impact of healthy lifestyle behaviors on the risk of dementia in patients with new-onset atrial fibrillation (AF). Here, we aimed to evaluate the association between a combination of healthy lifestyle behaviors and the risk of incident dementia in patients with AF.

METHODS AND RESULTS: Using the Korean National Health Insurance database between 2009 and 2016, we identified 199 952 adult patients who were newly diagnosed as AF without dementia. Patients were categorized into 4 groups by healthy lifestyle behavior score (HLS) with 1 point each being assigned for no current smoking, alcohol abstinence, and regular exercise. The HLS 0, 1, 2, and 3 groups included 4.4%, 17.4%, 53.4%, and 24.8% of the patients, respectively. We performed an inverse probability of treatment weighting to balance covariates between HLS groups. The HLS 1, 2, and 3 groups were associated with a lower risk of dementia compared with the HLS 0 group (hazard ratio [HR], 0.769; 95% CI, 0.704–0.842 for HLS 1; HR, 0.770; 95% CI, 0.709–0.836 for HLS 2; and HR, 0.622; 95% CI, 0.569–0.679 for HLS 3). The risk of dementia showed a tendency to decrease with an increase in HLS (*P*-for-trend <0.001).

CONCLUSIONS: A clustering of healthy lifestyle behaviors was associated with a significantly lower risk of dementia in patients with new-onset AF. These findings support the promotion of a healthy lifestyle within an integrated care approach to AF patient management.

Key Words: atrial fibrillation ■ dementia ■ healthy lifestyle behaviors

Dementia is emerging as one of the greatest health problems of an aging society.[1] Given that dementia causes patients to lose multiple abilities such as memory, language, problem-solving, and cognitive skills that are essential for independent living, its development makes caring for such patients difficult.[2,3]

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia, increases the risk of stroke, congestive heart failure, and hospitalization causing an increase in mortality and morbidity.[4–6] Moreover, AF is an independent risk factor for all forms of dementia.[7–10] Although the pathophysiological mechanisms of AF-induced dementia are not fully established, there are some explanations for this association, including stroke, silent stroke, cerebral hypoperfusion attributable to beat-to-beat heart rate variability, and vascular inflammation.[11,12]

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CLINICAL PERSPECTIVE

What Is New?

- A clustering of healthy lifestyle behaviors (including not smoking, alcohol abstinence, and regular physical activity) was associated with a significantly lower risk of all dementia, Alzheimer dementia, and vascular dementia in patients with new-onset atrial fibrillation.
- There was a trend for lower risk of dementia as the number of healthy lifestyle behaviors increased.
- The beneficial effect of a healthy lifestyle behavior cluster on the risk of dementia was consistently and more prominently observed in the low-risk subgroups.

What Are the Clinical Implications?

- This study has an implication to extend the previous findings, which lifestyle behavior prevents incident dementia, to patients with new-onset atrial fibrillation.
- The results of our study support the promotion of a healthy lifestyle within an integrated care approach to atrial fibrillation patient management.

Nonstandard Abbreviations and Acronyms

HLS	healthy lifestyle behavior score
IPTW	inverse probability of treatment weighting
NHIS	National Health Insurance Service
OAC	oral anticoagulant

As dementia and AF are both age-related diseases, they have common risk factors. In patients with AF, oral anticoagulant (OAC) therapy is associated with a low risk of dementia.[10,13–15] Although previous reports have described an association between individual components of healthy lifestyle behaviors[16–29] or the combination of such lifestyle factors and the risk of dementia in the general population,[30,31] data remain limited on the relationship between the risk of dementia and combination of healthy lifestyle behaviors amongst patients with new-onset AF.

In this study, using a Korean nationwide population-based cohort, we examined the association between the combination of healthy lifestyle behaviors (including not smoking, alcohol abstinence, and regular physical activity) and risk of incident dementia in patients with new-onset AF.

METHODS

All data and materials have been made publicly available at the National Health Insurance Sharing Service and can be assessed at https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do.

Data Source and Study Population

For this analysis, we used data from the Korean National Health Insurance Service (NHIS) database.[32,33] The Korean NHIS is a mandatory health insurance program administered by the Korean government, and it covers almost the entire Korean population (≈50 million people). The Korean NHIS established the comprehensive claims database on enrollees' medical usage to review and reimburse the medical expense. This database contains enrollees' sociodemographic information, and all the medical services uses both at outpatient clinics and at admissions, including diagnostic codes using the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes, examinations, prescription records, procedures, and surgeries. Except for deaths or rare loss of qualifications, data on medical use are considered to have no missing values in the NHIS system. We also used the national health screening examination data that linked with the NHIS database. All Korean adults are recommended to receive a national health examination every 1 or 2 years provided by the Korean National Insurance Cooperation. Physical examinations, regular blood tests, and self-reported questionnaires on their lifestyle behaviors are administered. The participation rate of the national health screening examinations was 74.8% in 2014.[32]

We screened patients newly diagnosed with nonvalvular AF between January 1, 2009 and December 31, 2016 (n=576 077) and included patients who underwent a national health screening examination within 2 years after receiving the AF diagnosis (n=209 880) (Figure 1). We excluded patients aged <20 years (n=29), those for whom values were missing from the health screening examinations (n=1189), and those with dementia (n=8713). A total of 199 952 patients were included in this study. This study was exempted from review by the Seoul National University Hospital Institutional Review Board (E-2105-173-1221).

Definition of Healthy Lifestyle Behavior Score

During each national health screening period, the participants of the NHIS cohort respond to a series of self-reported questionnaires on lifestyle behaviors. We investigated 3 lifestyle behaviors, including smoking status, alcohol consumption, and physical activity, based on this questionnaire. Smoking status was classified as non-smoker, ex-smoker, or current smoker. Alcohol consumption was classified as non-drinker and current drinker. Finally, physical activity intensity and frequency were recorded. Light physical activity

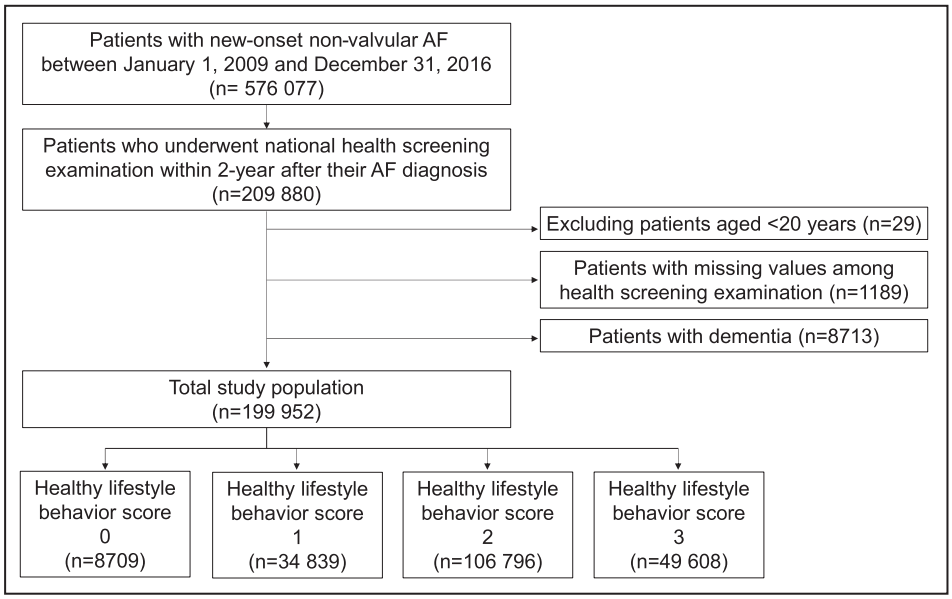

Figure 1. Flowchart of the study population and follow-up.
Healthy lifestyle behavior score was calculated by assigning 1 point each for no current smoking, abstaining from alcohol, and performing regular exercise. AF indicates atrial fibrillation.

was defined as walking slowly or sweeping carpets for >30 minutes per day, moderate physical activity was defined as brisk walking, dancing, or gardening for >30 minutes per day, and vigorous physical activity was defined as running fast, cycling, or aerobics >20 minutes per day.[34–36] Physical activity was divided into regular exercise, which was defined as moderate physical activity performed ≥5 times per week or vigorous physical activity performed ≥3 times per week, or a lack of regular exercise.[35,36]

The healthy lifestyle behavior score (HLS), ranging from 0 to 3, was calculated by assigning 1 point each to no current smoking, alcohol abstinence, and regular exercise. Patients were categorized into 4 groups according to HLS.

Covariates

We investigated age, sex, and comorbidities (hypertension, diabetes, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, and chronic kidney disease) which were based on the diagnoses defined in the medical claim and health screening examination databases. Table S1 shows the detailed definitions of these comorbidities.

The CHA_2DS_2-VASc score was calculated based on the patients' demographic information and comorbidities.[5] Body mass index was calculated as body weight in kilograms divided by the square of height in meters (kg/m^2). The status of medication, including OACs (warfarin or non-vitamin K antagonist OACs), antiplatelet agents, and statins, was obtained. Low income was defined as having a lower 25% of income of the entire Korean population.

Study Outcomes

The primary outcome was the first occurrence of dementia, including Alzheimer dementia, vascular dementia, and other forms. Dementia was defined using the diagnostic codes (F00, F01, F02, F03, G30, or G31) and prescription of medication for dementia such as rivastigmine, galantamine, memantine, or donepezil.[10,37–39] Secondary outcomes were defined as individual components of dementia (Alzheimer dementia [F00 or G30] and vascular dementia [F01]). When both codes for 2 types of dementia were claimed, we followed the primary diagnosis, and if both were claimed as additional diagnoses up to the secondary diagnoses, the patient was classified as other forms of dementia. Patients were followed up starting from the index date (at the health screening examination) until the occurrence of the study outcomes, death, or December 31, 2017, whichever came first.

Statistical Analysis

The baseline characteristics are presented as mean±SD for continuous variables and number (percentage) for categorical variables. The incidence rate of dementia was calculated by dividing the total number of dementia diagnoses by the total person-years during the follow-up period (per 1000 person-years).

Before comparing the risk of dementia among HLS groups, since the baseline characteristics of each group stratified by HLS were significantly different, we performed an inverse probability of treatment weighting (IPTW) to balance covariates between HLS groups.[40] The propensity score used in the IPTW was calculated using age, sex, hypertension, diabetes, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of OAC, antiplatelet agents, and statins, body mass index, and low income. An imbalance in a covariate after IPTW was noted when the maximum absolute standardized difference of the covariates exceeded 0.1 (10%).[41]

The association between the risk of dementia and HLS was analyzed using a weighted Cox proportional hazards regression model with IPTW and presented as the hazard ratio (HR) and 95% CIs for the primary and secondary outcomes. Each HLS group was analyzed using the HLS 0 group as the reference group. *P*-for-trend were calculated including the ordinal HLS variable as a continuous variable in the Cox proportional hazards regression model to show trend for lower risk of dementia according to increase in HLS. Weighted incidence rates were calculated as the weighted number of clinical events per 1000 person-years at risk. Kaplan–Meier method was used to present weighted cumulative incidence curves and outcomes were evaluated using a log rank test.

As a sensitivity analysis, a Cox proportional hazards regression model was used to compare the HLS groups for the risk of clinical outcomes. The Cox models were as follows: model 1 was unadjusted; model 2 was adjusted for age and sex; and model 3 was further adjusted for all variables used in the propensity score calculation.

As dementia does not occur immediately after exposure to unhealthy lifestyle or risk factors, we additionally analyzed the incidence of dementia among patients who had at least 1-year follow-up duration. Namely, we excluded patients with <1 year from the index period to the occurrence of dementia or end of follow-up. As dementia is a cognitive disorder that is affected by incident stroke, we further performed analyses after censoring patients with incident stroke during follow-up.

Since smoking is a well-known risk factor for stroke in patients with AF and cognitive dysfunction/dementia in the general population,[42–44] we conducted a sensitivity analysis using modified HLS score excluding smoking factor and including exercise and alcohol consumption. We evaluated the association between these modified HLS scores and the risk of dementia both in non-current smokers and current smokers.

According to a recent study, early rhythm control could affect the risk of stroke in patients with newly diagnosed AF.[45] Thus, we conducted a sensitivity analysis to adjust rhythm control treatment on the final multivariable Cox regression model.

Subgroup analyses were performed for age (<65, 65–75, and ≥75 years), sex, CHA_2DS_2-VASc score ([men <2 and women <3], [men ≥2 and women ≥3]), presence of prior history of ischemic stroke, and use of OACs. We performed a multivariable Cox proportional hazards regression model for subgroup analyses. For the multivariable adjustment, variables including propensity score calculation were included in the model.

In the main analysis, the reference group was HLS 0 group. However, there is a possibility that HLS 0 group tended to care less about their health and have more other unhealthy lifestyle behaviors compared with other HLS groups. The association of dementia between the HLS 0 group and HLS 1, 2, or 3 groups could be mainly attributed to these characteristics of HLS 0. To address the impact of the clustering HLS on the risk of dementia, we additionally performed exploratory analyses to provide the HRs for dementia of the group pooled HLS 2 and 3 groups compared with HLS 1 group. Also, we added the HRs for dementia of HLS 2 and 3 groups compared with HLS 1 group.

To evaluate the association between exercise dose or intensity and the risk of dementia, we conducted an exploratory analysis. Exercise doses or intensity were defined as follow: (1) moderate-intensity physical activity for 3 to 7 days per week and vigorous-intensity physical activity for 3 to 7 days per week, (2) moderate-intensity physical activity for 5 to 7 days per week and vigorous-intensity physical activity for 5 to 7 days per week, (3) moderate to vigorous physical activity for 1 to 2 days per week, 3 to 4 days per week, 5 to 6 days per week, and ≥7 days per week,[46] and (4) calculating metabolic equivalent of task (MET)-min per week, and categorized into 0 to <500 MET-min per week, 500 to 999 MET-min per week, 1000 to 1499 MET-min per week, and ≥1500 MET-min per week.[47] The non-regular exercise group was the reference group.

All analyses were 2-tailed, and statistical significance was defined as values of $P<0.05$. Statistical analyses were conducted using SAS (version 9.4; ASA Institute Inc., Cary, NC, USA).

Patient and Public Involvement

As the study was conducted using deidentified nationwide data, the authors had no direct contact information of the individual study participants. No patients were involved in establishing the research question or the outcome measures, nor were they involved in developing plans for recruitment, design, or implementation of the study. No patients were asked to advise on interpretation or writing of the results. There is no plan for dissemination of the study results to participants and linked communities.

RESULTS

A total of 199 952 patients (mean age, 63.2 [SD, 12.6] years; 60.2% men) were included in this analysis (Figure 1). The study population was distributed by HLS as follows: 8709 (4.4%) patients in the HLS 0 group; 34 839 (17.4%) in HLS 1 group; 106 796 (53.4%) in HLS 2 group; and 49 608 (24.8%) in HLS 3 group. The median duration between the AF diagnosis and national health screening examination was 318 (interquartile range, 164–496) days. The baseline characteristics by the HLS group are presented in Table 1.

Patients in the HLS 0 group who had a cluster of 3 unhealthy lifestyle behaviors (current smoking, current drinking, and lack of regular exercise) were younger, were more likely to be men, had lower CHA_2DS_2-VASc scores, and had a lower prevalence of comorbidities compared with those in the HLS 3 group with 3 healthy lifestyle behaviors. The HLS 0 group showed a lower body mass index and higher prevalence of low income than did the HLS 3 group. The proportion of patients receiving OACs and statins was higher in the HLS 3 group than in the HLS 0 group.

Risk of Dementia by HLS

During a median 3.4 (IQR, 1.7–5.5) years of follow-up, dementia occurred in 327 (9.99/1000 person-years), 1425 (11.01/1000 person-years), 7625 (19.80/1000 person-years), and 2444 (13.52 per 1000 person-years) patients in the HLS 0, 1, 2, and 3 groups, respectively. Table 1 shows that baseline characteristics were well balanced among the different HLS groups after IPTW. The weighted incidence rates of dementia were 21.8, 16.8, 16.8, and 13.6/1000 person-years in the HLS 0, 1, 2, and 3 groups, respectively.

The weighted cumulative incidence curves for the HLS groups are shown in Figure 2. After IPTW, the HLS 1, 2, and 3 groups were associated with a lower risk of dementia compared with the HLS 0 group (HR, 0.769 [95% CI, 0.704–0.842] for HLS 1; HR, 0.770 [95% CI, 0.709–0.836] for HLS 2; and HR, 0.622 [95% CI, 0.569–0.679] for HLS 3). The beneficial effect of the combination of healthy lifestyle behaviors was consistently observed for the risk of both Alzheimer dementia and vascular dementia (Figure 3). *P*-for-trends for risk of dementia, Alzheimer dementia, and vascular dementia according to HLS were <0.001 (Figure 3).

Sensitivity Analyses

After multivariable adjustment using model 3, the results of the competing risk analysis of the HLS 1, 2, and 3 groups compared with the HLS 0 group were in line with those of the main analysis (HR, 0.753 [95% CI, 0.667–0.849] for HLS 1; HR, 0.728 [95% CI, 0.650–0.815] for HLS 2; and HR, 0.622 [95% CI, 0.553–0.699] for HLS 3). Consistent results were observed for the risk of Alzheimer dementia and vascular dementia. Table S2 shows the unadjusted and adjusted HR values for the primary and secondary outcomes by HLS group.

In the sensitivity analyses including patients who had at least 1-year follow-up duration from index period, and censoring patients with incident stroke during the follow-up, the results were largely consistent with those of the main analysis (Table 2).

The results of sensitivity analyses that evaluated the association between HLS scores and the risk of dementia in non-current smokers and current smokers using modified HLS scores, including exercise and alcohol consumption, are presented in Table S3. In non-current smokers, although the risk reduction was attenuated in higher HLS scores compared with main results, the trends of lower risk of dementia in the higher modified HLS compared with modified HLS 0 group was shown. Since smoking cessation has a strong preventive effect on dementia, the beneficial effects of alcohol abstinence or regular physical exercise were attenuated in non-smokers. However, an increased number of healthy lifestyles above HLS 2 was still associated with a lower risk of dementia. Among current smokers, higher HLS scores were consistently associated with a lower risk of dementia compared with HLS score 0 group (*P*=0.007). From these sensitivity analyses, although the amplitude of risk reduction in higher HLS scores composed of exercise and alcohol consumption was slightly different according to smoking status, HLS scores excluding smoking also showed an inverse correlation with the risk of dementia.

Table S4 showed the proportion of patients receiving rhythm control from AF diagnosis to index health examination. In the total study population, 25.1% of patients received rhythm control treatment for a median of 318 days (interquartile range, 164–496 days) after AF diagnosis. There was a higher proportion of patients receiving rhythm control in the HLS 3 group than other HLS groups. After adjusting rhythm control treatment, the HRs of HLS 1, 2, and 3 compared with HLS 0 for dementia, Alzheimer dementia, and vascular dementia were consistent with the main results (Table S5).

Subgroup Analyses

There was consistency in the results of the subgroup analyses stratified by age, sex, CHA_2DS_2-VASc score, prior stroke history, and OAC use. The trends of lower risk of dementia in the HLS 1, 2, and 3 groups compared with the risk of dementia in the HLS 0 group were not significantly different among the different subgroups (Table 3). The beneficial effect of higher HLS was more prominent in younger patients (age <65 years), lower CHA_2DS_2-VASc scores (men <2

Table 1. Baseline Characteristics of the Study Population

	Pre-IPTW					Post-IPTW				
	Healthy lifestyle behavior score					Healthy lifestyle behavior score				
	0 (n=8709)	1 (n=34 839)	2 (n=106 796)	3 (n=49 608)	Maximum ASD	0 (n=8136)	1 (n=34 109)	2 (n=107 374)	3 (n=49 324)	Maximum ASD
Age, y										
Mean±SD	56.2±12.4	59.3±13.0	64.9±12.4	63.5±11.7	0.70	61.7±12.1	62.5±12.7	63.0±13.0	63.4±12.0	0.08
<65	74.8	63.3	45.2	49.5		58.0	53.8	51.5	48.7	
65 to <75	19.0	25.4	32.7	34.6		25.5	28.8	30.2	34.4	
≥75	6.15	11.3	22.1	15.9		16.5	17.4	18.4	16.9	
Sex (men)	94.7	86.1	53.6	50.4	1.14	64.3	62.2	60.6	60.2	0.08
Low income	19.8	18.5	17.8	16.7	0.08	19.2	18.4	17.7	17.9	0.04
CHA_2DS_2-VASc										
Mean±SD	2.31±1.57	2.65±1.71	3.55±1.97	3.35±1.82	0.69	3.09±1.74	3.2±1.84	3.26±1.96	3.32±1.83	0.07
0	8.6	6.3	3.0	2.6	0.26	3.9	3.6	4.2	3.0	0.06
1	27.4	23.4	13.6	13.6		17.4	16.7	16.8	14.2	
2	25.3	23.2	17.8	20.0		21.6	20.5	19.4	19.7	
≥3	38.7	47.0	65.7	63.8		57.1	59.2	59.6	63.1	
Comorbidities										
Hypertension	82.8	83.6	85.7	83.1	0.08	83.0	83.8	84.4	84.7	0.05
Diabetes	24.4	22.9	23.9	22.2	0.05	20.9	22.4	23.2	23.6	0.06
Dyslipidemia	38.8	40.9	46.4	47.1	0.17	43.5	44.7	45.1	45.4	0.04
Heart failure	26.1	28.1	34.7	31.4	0.19	30.7	32.3	32.1	32.8	0.05
Prior ischemic stroke	15.5	18.6	25.9	24.8	0.26	22.3	23.3	23.6	24.2	0.04
Prior MI	9.7	10.6	11.8	11.6	0.07	10.9	11.4	11.3	11.6	0.02
PAD	18.1	19.5	22.7	20.7	0.11	20.1	21.2	21.3	21.7	0.04
COPD	16.1	17.6	20.8	19.5	0.12	19.7	19.5	19.6	19.8	0.01
Cancer	2.2	3.5	5.8	8.0	0.27	6.1	6.1	5.7	5.9	0.01
CKD	7.8	11.2	18.4	16.5	0.32	15.3	16.0	16.1	16.6	0.04
Health examination										
BMI (kg/m^2)										
Mean±SD	22.2±3.5	24.6±3.4	24.5±3.4	24.4±3.2	0.10	24.4±3.5	24.5±3.4	24.5±3.4	24.5±3.2	0.04
≥25	39.8	43.7	42.9	40.6	0.07	41.1	42.6	42.6	41.5	0.03
Antithrombotic treatment										
Oral anticoagulants	20.4	22.9	27.1	27.8	0.17	25.2	26.4	26.1	26.7	0.03

(*Continued*)

Table 1. Continued

	Pre-IPTW					Post-IPTW				
	Healthy lifestyle behavior score					Healthy lifestyle behavior score				
	0 (n=8709)	1 (n=34 839)	2 (n=106 796)	3 (n=49 608)	Maximum ASD	0 (n=8136)	1 (n=34 109)	2 (n=107 374)	3 (n=49 324)	Maximum ASD
Warfarin	15.2	16.5	18.6	18.9	0.11	17.9	18.0	18.2	18.3	0.01
NOAC	5.2	6.4	8.6	8.9	0.14	7.3	8.4	7.9	8.4	0.04
Antiplatelet agent	24.6	26.3	26.9	24.3	0.06	24.2	25.8	26.0	26.2	0.05
Aspirin	21.7	22.8	22.9	20.5	0.06	20.4	22.0	22.2	22.2	0.05
P2Y12 inhibitor	5.9	6.5	7.5	6.9	0.06	7.0	6.7	7.1	7.5	0.03
Statin	14.1	15.4	18.7	18.6	0.12	15.8	17.7	17.8	18.0	0.06

Categorical variables were presented as a percentage and continuous variables were presented as mean and SD.

Healthy lifestyle behavior score was calculated by assigning 1 point each for no current smoking, abstaining from alcohol, and performing regular exercise. ASD indicates absolute standardized difference; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IPTW, inverse probability of treatment weighting; MI, myocardial infarction; NOAC, non-vitamin K antagonist oral anticoagulant; PAD, peripheral artery disease; and SBP, systolic blood pressure.

and women <3), and those without a prior history of ischemic stroke (Table 3). There were no significant interactions between subgroups and the impact of HLS score on the risks of Alzheimer dementia and vascular dementia (Tables S6 and S7).

Exploratory Analyses

The results of exploratory analyses to compare the risk of dementia for patients having HLS 1 to those having HLS 2 or 3 are presented in Tables S8 and S9. Among patients with at least 1 healthy lifestyle behavior, HLS 2 or 3 groups were associated with a lower risk of all dementia compared with HLS 1 group (P=0.010). When the risk of dementia for HLS 2 and 3 was compared with HLS 1, respectively, HLS 3 was significantly associated with a lower risk of all dementia (HR, 0.826 [95% CI, 0.773–0.884]), whereas HLS 2 tends to show a lower risk (HR, 0.968 [95% CI, 0.912–1.027]). The risk of dementia showed a tendency to decrease with an increase in HLS (P-for-trend <0.001). From these exploratory analyses, clustering of healthy lifestyle behaviors was associated with a lower risk of dementia compared with single healthy lifestyle behavior.

The association between exercise dose or intensity and the risk of dementia are presented in Table S10. First, the vigorous-intensity exercise showed lower HRs than moderate-intensity exercise when performing those exercises for the same ranges of days per week. When the exercise dose was defined using the frequency of moderate to vigorous exercise per week, 5 to 6 per week moderate to vigorous exercise showed the lowest HRs compared with non-regular exercise group. When calculating the exercise dose as metabolic equivalent of task (MET)-min per week, there was an inverse dose-response relationship between MET-min per week and the risk of dementia. Patients with 1000 to 1499 MET-min per week and ≥1500 MET-min per week showed a significantly lower risk of dementia compared with non-regular exercise group, those with <500 MET-min per week and those with 500 to 999 MET-min per week.

DISCUSSION

In this analysis, based on a large-scale nationwide population-based cohort, we investigated whether a combination of healthy lifestyle behaviors was associated with a low risk of dementia in patients with new-onset AF. Our principal findings are as follows: (1) a substantial number and proportion of patients continued to engage in some of their unhealthy lifestyle behaviors after their diagnosis of AF; (2) patients with clustering of healthy lifestyle behaviors had a significantly lower risk of all dementia, Alzheimer dementia, and vascular dementia than those of patients with

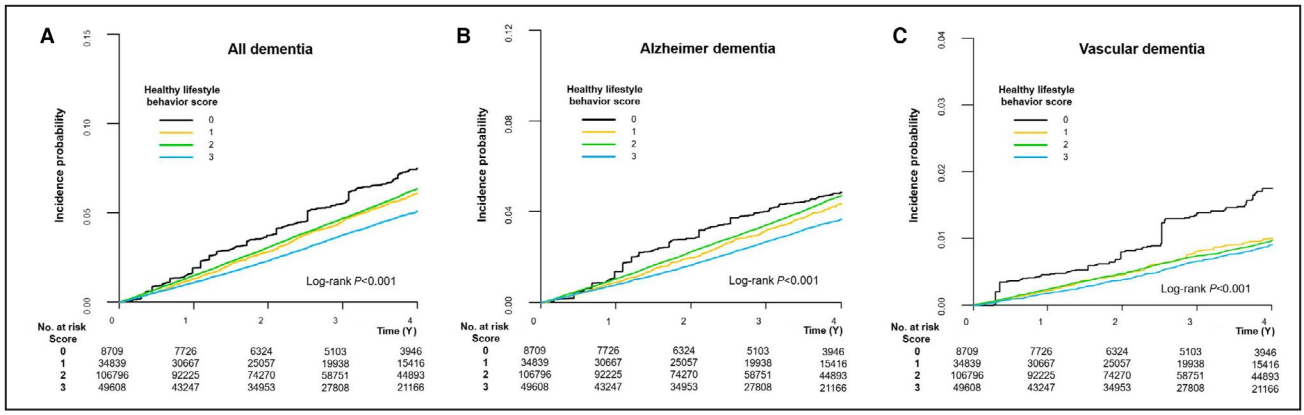

Figure 2. Weighted Kaplan–Meier curves for incident dementia by healthy lifestyle behavior score.
The healthy lifestyle behavior score groups 1, 2, and 3 showed a lower incidence rate of dementia than the healthy lifestyle behavior score 0 group. (**A**) All dementia. (**B**) Alzheimer dementia. (**C**) Vascular dementia. HLS indicates healthy lifestyle behavior score.

a combination of unhealthy lifestyle behaviors; and (3) the beneficial effect of a healthy lifestyle behavior cluster on the risk of dementia was consistently and more prominently observed in the low-risk subgroups, including patients with younger age (age <65 years), lower CHA_2DS_2-VASc score (men <2 and women <3), and those without a prior history of ischemic stroke, than in high-risk subgroups.

As the prevalence of dementia is increasing in our increasingly aging population, dementia is gaining attention as a major clinical outcome of patients with AF. OAC treatment according to patient stroke risk profile was associated with a low risk of dementia in patients with AF.[10,13–15] Catheter ablation as a rhythm control strategy was also associated with a low risk of dementia in patients with AF.[48,49]

The recent European Society of Cardiology AF management guidelines highlighted the Atrial Fibrillation Better Care Pathway for the integrated care management of AF: "A" Anticoagulation/Avoid stroke; "B"

	Healthy lifestyle behavior score	Weighted IR (per 1000 PY)	IPTW HR (95% CI)		*P*-value	*P*-for-trend
All dementia	0	21.75	1 (reference)		<0.001	<0.001
	1	16.80	0.769 (0.704-0.842)			
	2	16.83	0.770 (0.709-0.836)			
	3	13.58	0.622 (0.569-0.679)			
Alzheimer dementia	0	14.77	1 (reference)		<0.001	<0.001
	1	12.29	0.823 (0.739-0.917)			
	2	12.47	0.839 (0.760-0.927)			
	3	9.80	0.660 (0.594-0.734)			
Vascular dementia	0	4.97	1 (reference)		<0.001	<0.001
	1	2.65	0.532 (0.437-0.648)			
	2	2.51	0.503 (0.422-0.600)			
	3	2.27	0.458 (0.378-0.554)			

Figure 3. Risk of primary and secondary outcomes by healthy lifestyle behavior score: an inverse probability of treatment weighting analysis.
Healthy lifestyle behavior score was calculated by assigning 1 point each for no current smoking, abstaining from alcohol, and performing regular exercise. Lines indicate 95% confidential interval; bars, indication of hazard ratio 1.0; and dots, hazard ratio. HR indicates hazard ratio; IPTW, inverse probability of treatment weighting; IR, incidence rate; and PY, person-years.

Table 2. Sensitivity Analyses

Healthy lifestyle behavior score	No.	Event	IR per 1000 person-years	Adjusted HR (95% CI)	*P* value
Sensitivity analysis I: excluding patients with <1 y follow-up duration from index period to the occurrence of dementia or end of follow-up					
All dementia					
0	7718	263	10.72	1 (reference)	<0.001
1	30 647	1146	11.86	0.758 (0.662–0.867)	
2	92 171	5847	20.50	0.714 (0.629–0.811)	
3	43 221	1924	14.33	0.618 (0.542–0.705)	
Alzheimer dementia					
0	7718	162	6.66	1 (reference)	<0.001
1	30 647	829	8.58	0.869 (0.734–1.029)	
2	92 171	4426	15.52	0.833 (0.709–0.978)	
3	43 221	1396	10.40	0.702 (0.595–0.828)	
Vascular dementia					
0	7718	75	3.06	1 (reference)	<0.001
1	30 647	187	1.94	0.468 (0.358–0.613)	
2	92 171	834	2.92	0.425 (0.332–0.544)	
3	43 221	325	2.42	0.410 (0.317–0.532)	
Sensitivity analysis II: censoring incident stroke during follow-up					
All dementia					
0	8709	255	7.98	1 (reference)	<0.001
1	34 839	1185	9.38	0.796 (0.695–0.912)	
2	106 796	6741	17.88	0.794 (0.699–0.902)	
3	49 608	2147	12.10	0.682 (0.598–0.778)	
Alzheimer dementia					
0	8709	177	5.54	1 (reference)	<0.001
1	34 839	903	7.14	0.854 (0.727–1.004)	
2	106 796	5155	13.67	0.834 (0.715–0.971)	
3	49 608	1618	9.12	0.717 (0.612–0.839)	
Vascular dementia					
0	8709	52	1.63	1 (reference)	<0.001
1	34 839	148	1.17	0.535 (0.390–0.735)	
2	106 796	843	2.24	0.594 (0.445–0.793)	
3	49 608	289	1.63	0.514 (0.380–0.695)	

Adjusted for age, sex, hypertension, diabetes, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of oral anticoagulant, antiplatelet agent, and statin, body mass index (BMI), and low income. Healthy lifestyle behavior score was calculated by assigning 1 point each for no current smoking, abstaining from alcohol, and performing regular exercise. HR indicates hazard ratio; and IR, incidence rate.

Better symptom management with a patient-centered symptom-directed rate or rhythm control; and "C" Cardiovascular risk factor and comorbidity optimization.[5] There is sporadic evidence of "A" and "B" preventing dementia as shown above, and compliance with the "ABC" pathway is associated with a low risk of dementia.[50]

Although many studies have elucidated that healthy lifestyle behaviors are associated with reducing the AF burden and risks of adverse clinical outcomes in observational studies[51–55] and well-designed randomized controlled trials,[56] there are limited data on whether healthy lifestyle behaviors could decrease the risk of dementia in patients with AF. Indeed, healthy lifestyle behaviors could effectively prevent dementia in patients with AF since they can simultaneously help maintain one's cognitive reserve and reduce neuropathological damage by decreasing the AF burden. From this perspective, our study supports the importance of the "C" criterion in the "ABC" pathway for the prevention of dementia in patients with AF.

Lifestyle modification has been traditionally emphasized for the prevention of dementia, and the effect of healthy lifestyle behaviors has been well established.[3] The association between smoking status and dementia

Table 3. Subgroup Analyses

Subgroup	HLS	No.	Events	IR per 1000 person-years	Adjusted HR (95% CI)	*P* value	*P*-for-interaction
Age (y)							
<65	0	6515	88	3.50	1 (reference)	<0.001	0.215
	1	22 040	233	2.72	0.705 (0.552–0.902)		
	2	48 275	621	3.26	0.623 (0.494–0.785)		
	3	24 539	250	2.59	0.479 (0.372–0.616)		
65 to <75	0	1658	142	23.51	1 (reference)	<0.001	
	1	8860	597	18.58	0.750 (0.625–0.901)		
	2	34 956	2852	22.36	0.727 (0.612–0.864)		
	3	17 180	1085	17.56	0.609 (0.509–0.728)		
≥75	0	536	97	61.94	1 (reference)	<0.001	
	1	3939	595	50.77	0.791 (0.638–0.981)		
	2	23 565	4152	62.11	0.789 (0.643–0.968)		
	3	7889	1109	48.93	0.684 (0.555–0.843)		
Sex							
Men	0	8249	304	9.77	1 (reference)	<0.001	0.280
	1	29 994	1166	10.47	0.755 (0.665–0.857)		
	2	57 185	2963	14.51	0.745 (0.661–0.839)		
	3	24 989	1048	11.85	0.639 (0.562–0.727)		
Women	0	460	23	14.38	1 (reference)	<0.001	
	1	4845	259	14.32	0.632 (0.413–0.969)		
	2	49 611	4662	25.77	0.565 (0.374–0.851)		
	3	24 619	1396	15.12	0.408 (0.318–0.725)		
CHA_2DS_2-VASc score							
Men <2 and women <3	0	3268	28	2.09	1 (reference)	0.006	0.531
	1	11 581	75	1.58	0.612 (0.396–0.946)		
	2	24 679	230	2.25	0.633 (0.422–0.951)		
	3	12 749	94	1.80	0.475 (0.306–0.737)		
Men ≥2 and women ≥3	0	5441	299	15.47	1 (reference)	<0.001	
	1	23 258	1350	16.49	0.767 (0.677–0.87)		
	2	82 117	7395	26.15	0.740 (0.657–0.833)		
	3	36 859	2350	18.29	0.632 (0.559–0.715)		
Prior ischemic stroke							
No	0	7361	197	7.02	1 (reference)	<0.001	0.085
	1	28 359	849	7.9	0.727 (0.622–0.849)		
	2	79 163	4108	13.95	0.674 (0.582–0.782)		
	3	37 320	1323	9.5	0.570 (0.489–0.664)		
Yes	0	1348	130	27.83	1 (reference)	<0.001	
	1	6480	576	26.25	0.769 (0.635–0.930)		
	2	27 633	3517	38.80	0.783 (0.655–0.936)		
	3	12 288	1121	26.97	0.671 (0.559–0.807)		
OAC							
No	0	6932	260	9.65	1 (reference)	<0.001	0.609
	1	26 877	1073	10.29	0.733 (0.639–0.839)		
	2	77 822	5528	18.57	0.691 (0.608–0.786)		
	3	35 812	1754	12.68	0.595 (0.521–0.680)		
Yes	0	1777	67	11.60	1 (reference)	<0.001	
	1	7962	352	14.00	0.840 (0.646–1.091)		
	2	28 974	2097	23.98	0.867 (0.677–1.110)		
	3	13 796	690	16.25	0.724 (0.562–0.933)		

Adjusted for age, sex, hypertension, diabetes, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of oral anticoagulant, antiplatelet agent, and statin, body mass index, and low income. HLS indicates healthy lifestyle behavior score; HR, hazard ratio; IR, incidence rate; and OAC, oral anticoagulant.

was also examined.[16–18] Although a smoker may die of another cause before developing dementia, the risk of smoking on incident dementia is evident.[19] Studies examining the long-term effects of alcohol consumption on dementia have produced conflicting results according to alcohol intake amount.[20–23] Even though the association between heavy alcohol use and an increased risk of dementia was consistent in numerous observational studies, light to moderate alcohol use was associated with a decreased risk.[21,23] Nevertheless, a French hospital cohort study[24] revealed that alcohol use disorders were the strongest modifiable risk factor for dementia onset as reflected in the 2020 report of the Lancet Commission.[3]

Regular exercise is also associated with a reduced risk of dementia.[25–27] Although randomized controlled trials did not show that exercise prevents cognitive decline or dementia,[28,29] this was perhaps because of small sample sizes, short intervention periods, limited follow-up durations, and differences in cohorts and protocols. As many long-term follow-up observational studies reported an inverse relationship between exercise and the risk of dementia, the association has been well established.[25–27] In addition, physical exercise prevents dementia in older people by improving balance, reducing falls, improving mood and function.[57]

The studies mentioned above focused on an isolated component of lifestyle behaviors and the prevention of dementia. However, lifestyle factors are not isolated; rather, they often occur in clusters with other healthy lifestyle factors.[35,58,59] In this context, 1 study showed that the increased number of the American Heart Association's Life's Simple 7 metrics (non-smoking; body mass index <25; regular physical activity; eating fish, fruits, and vegetables; untreated cholesterol <200 mg/dL; untreated fasting glucose <100 mg/dL; and untreated blood pressure <120/80 mm Hg) was associated with a reduced risk of dementia.[30] Another study also showed that healthy lifestyle factors (no current smoking, regular physical activity, healthy diet, and moderate alcohol consumption) were statistically independent of genetic risk factors for dementia and the association between the combination of healthy lifestyle behaviors and the risk of dementia, consistent with our study findings.[31]

Although some studies reported that a combination of healthy lifestyle behaviors was associated with a decreased risk of dementia in the general population,[30,60,61] we are unaware of any previous study in patients with AF. In this large study, the HLS 1, 2, and 3 groups were associated with a substantially lower risk of dementia, Alzheimer dementia, and vascular dementia compared with the HLS 0 group. According to our results, the risk reduction of vascular dementia was more prominent than that of Alzheimer dementia in patients with a healthier lifestyle. In recent studies from our group, adoption of healthy lifestyle changes after AF diagnosis, such as alcohol abstinence, quitting smoking, and performing regular exercise, were associated with a lower risk of stroke.[10,43,47,62] Since vascular dementia could be regarded as a manifestation of subclinical stroke, the close association of a healthy lifestyle with stroke risk reduction could be a plausible mechanism of the risk reduction of vascular dementia through clustering healthy lifestyles. In patients with AF, vascular dementia, and Alzheimer dementia risks are known to increase.[10] Although the mechanism of Alzheimer dementia has not been fully elucidated, several studies have reported that cerebrovascular disease, including cerebral infarct, affects the onset and progression of Alzheimer dementia.[63–65] Healthy lifestyle behavior might lower the risk of Alzheimer dementia by lowering the general risk burden of cardiovascular disease.

Interestingly, the IPTW HR for all dementia types was similar between HLS 1 and 2 groups, whereas the HLS 3 group showed lower IPTW HR for all dementia types than HLS 1 and 2 groups. This trend was shown in the weighted cumulative incidence curves and was consistent with IPTW HR for Alzheimer dementia. On the other hand, if patients had at least 1 healthy lifestyle behavior, there was no significant difference in reducing vascular dementia according to the number of healthy lifestyle behaviors. Based on these results, at least 1 healthy lifestyle behavior is associated with as low a risk of dementia as 2 healthy lifestyle behaviors in patients with AF. Thus, health care professionals should motivate patients to correct their unhealthy lifestyle behaviors.

Although we did not directly compare the impact of each factor on the risk of dementia in the main analysis, according to the results of complementary analysis (Table S11), current smoking was associated with a higher risk of dementia by 24% compared with non-smokers. Regular physical activity was associated with a lower risk of dementia by 20% compared with non-regular exercise group. Thus, among lifestyle factors, both smoking and exercise were significantly associated with the risk of dementia. Moderate to heavy alcohol consumption tended to be associated with a higher risk of dementia. Alcohol consumption per se, as a single factor, did not show a significant increase in dementia risk. More importantly, our study results suggested that there was a trend for a lower risk of dementia as the number of healthy lifestyle behaviors increased. The impact of bad or good lifestyle habit combinations might reflect the synergistic effect and affect the dose or intensity of each component. In our model, oral anticoagulation did not show a significant association with the risk of dementia.

In subgroup analysis, the beneficial effect of a healthy lifestyle behavior cluster on the risk of dementia

was consistently and more prominently observed in patients with younger age (age <65 years), lower CHA_2DS_2-VASc score (men <2 and women <3), and those without a prior history of ischemic stroke, which were considered to be the low-risk subgroups for incident dementia, than in high-risk subgroups. In addition, the benefits of a healthy lifestyle behavior cluster were consistently observed regardless of whether the patients were treated with OAC. Of note, patients with unhealthy lifestyle behaviors in this population tended to have relatively low-risk baseline characteristics. Therefore, it would be beneficial to encourage that even low-risk patients modify their unhealthy lifestyle behaviors to prevent dementia.

Limitations

This study had several limitations. First, because of the inherent limitations of the study design, the associations between the combination of healthy lifestyle behaviors and the risk of dementia could not be directly interpreted as a causal relationship. Second, we collected information on the healthy lifestyle behaviors of patients using self-reported questionnaires, which could have resulted in recall bias. Third, although we balanced the baseline characteristics of the different groups using IPTW and performed a multivariate adjustment, we could not exclude the possibility of unmeasured confounding factors. Fourth, changes in baseline variables or lifestyle behaviors during follow-up, including lifestyle factors and medication use, were not considered in this analysis. Fifth, HLS could be associated with the individual's interest in their health and the actual treatment adherence (or compliance). Although we assessed the prescription records and balanced the medications used, including oral anticoagulation therapy among different HLS groups, we could not fully elucidate the difference and impact of the implementation of guideline adherent therapy and the actual treatment adherence in different HLS score groups in this data set. Sixth, we included patients with new-onset AF from the entire Korean population. To evaluate the impact of healthy lifestyle behaviors, we only included patients who received a national health examination within 2-year after AF diagnosis. Patients whose lifestyle behaviors information indicated patients who received the national health checkup provided by the government and there might be the possibility of a selection bias. Patients without lifestyle behavior information were older, more likely to be women and had more prevalent comorbidities than those with lifestyle behavior information (Table S12). These results should be evaluated and applied to the general population with caution. Finally, as we used diagnostic codes to define comorbidities and clinical outcomes in the claims database, errors may have arisen from coding inaccuracies.

CONCLUSIONS

A clustering of healthy lifestyle behaviors was associated with a significantly lower risk of dementia in patients with new-onset AF. These findings support the promotion of a healthy lifestyle within an integrated care approach to AF patient management.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S12

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SUPPLEMENTAL MATERIAL

Table S1. Definition of covariates and outcomes

Diagnosis	ICD-10-CM code and definition	Diagnostic definition
Inclusion/exclusion criteria		
Atrial fibrillation	I48.0-48.4, I48.9	Admission or outpatient department≥1
Valvular atrial fibrillation	I05.0, I05.2, I05.9, Z95.2-Z95.4	Admission or outpatient department≥1
Comorbidities		
Hypertension	I10-I13, I15; and minimum 1 prescription of anti-hypertensive drug (thiazide, loop diuretics, aldosterone antagonist, alpha-/beta-blocker, calcium-channel blocker, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker).	Admission≥1 or outpatient department≥1
	Or systolic/diastolic blood pressure ≥ 140/90 mmHg	Index health examination
Diabetes mellitus	E11-E14; and minimum 1 prescription of anti-diabetic drugs (sulfonylureas, metformin, meglitinides, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, α-glucosidase inhibitors, and insulin).	Admission≥1 or outpatient department≥1
	Or fasting glucose level ≥ 126 mg/dL	Index health examination
Dyslipidemia	E78	Admission or outpatient department≥1
	Or Total cholesterol ≥ 240 mg/dL	Index health examination
Heart failure	I50	Admission or outpatient department≥1
Prior stroke	I63, I64	Admission or outpatient department≥1
Vascular disease		
Prior myocardial infarction	I21, I22	Admission or outpatient department≥1
Peripheral artery disease	I70, I73	Admission or outpatient department≥1
Chronic kidney disease	Estimated glomerular filtration rate <60 ml/min/1.73m^2	Index health examination
Chronic obstructive pulmonary disease	J41-44	Admission or outpatient department≥1
Cancer	C00-97 and RID code (V193)	Admission or outpatient department≥1
Scores		

CHA_2DS_2-VASc score	Heart failure (1 point), hypertension (1 point), age ≥75 years (2 points), diabetes (1 point), previous stroke/systemic embolism/transient ischemic attack (2 points), vascular disease (prior MI or PAD, 1 point) and female sex (1 point)

ICD, international classification of disease; CM, clinical modification.

Table S2. Cox analyses: hazard ratios for all dementia, Alzheimer's dementia, and vascular dementia according to the combination of healthy lifestyle behavior

Healthy lifestyle behavior score	Number	Event	IR (per 1,000 PY)	Unadjusted HR (95% CI)	Age- and sex-adjusted HR (95% CI)	Multivariable adjusted HR (95% CI)
All dementia						
0	8,709	327	9.99	1 (reference)	1 (reference)	1 (reference)
1	34,839	1,425	11.01	1.103 (0.978-1.244)	0.729 (0.646-0.822)	0.753 (0.667-0.849)
2	106,796	7,625	19.80	1.988 (1.779-2.220)	0.728 (0.650-0.816)	0.728 (0.650-0.815)
3	49,608	2,444	13.52	1.356 (1.208-1.522)	0.611 (0.543-0.687)	0.622 (0.553-0.699)
p-value				<0.001	<0.001	<0.001
Alzheimer's dementia						
0	8,709	207	6.33	1 (reference)	1 (reference)	1 (reference)
1	34,839	1,020	7.88	1.247 (1.074-1.448)	0.802 (0.69-0.931)	0.83 (0.714-0.964)
2	106,796	5,687	14.77	2.344 (2.041-2.693)	0.804 (0.698-0.926)	0.808 (0.701-0.931)
3	49,608	1,767	9.77	1.550 (1.342-1.709)	0.665 (0.574-0.769)	0.681 (0.588-0.788)
p-value				<0.001	<0.001	<0.001
Vascular dementia						
0	8,709	88	2.69	1 (reference)	1 (reference)	1 (reference)
1	34,839	238	1.84	0.685 (0.536-0.874)	0.499 (0.391-0.638)	0.510 (0.399-0.651)
2	106,796	1,105	2.87	1.069 (0.861-1.328)	0.497 (0.396-0.622)	0.480 (0.383-0.601)
3	49,608	410	2.27	0.845 (0.671-1.063)	0.454 (0.359-0.575)	0.446 (0.352-0.565)
p-value				<0.001	<0.001	<0.001

Multivariable adjusted model included age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of oral anticoagulant, antiplatelet agent, and statin, BMI, and low income.

CI, confidence interval; HR, hazard ratio; IR, incidence rate; PY, person-years.

Table S3. Sensitivity analyses: the association between HLS score and the risk of dementia according to smoking status (non-current smokers and current smokers)

Outcome	HLS	Number	Events	IR	Adjusted HR (95% CI)	p-value
Excluding current smokers						
Dementia	0	18,811	847	12.27	1 (reference)	<0.001
	1	102,509	7,475	20.25	1.030 (0.957-1.109)	
	2	49,608	2,444	13.52	0.880 (0.812-0.953)	
Among current smokers						
Dementia	0	8,709	3,27	9.99	1 (reference)	0.007
	1	16,028	5,78	9.58	0.826 (0.719-0.947)	
	2	4,287	1,50	9.35	0.769 (0.633-0.935)	

IR, per 1,000 person-years

CI, confidence interval; HLS, healthy lifestyle behavior score; HR, hazard ratio; IR, incidence rate.

Table S4. Rhythm control treatment in different HLS score groups

	Total (n=199,952)	HLS 0 (n=8709)	HLS 1 (n=34839)	HLS 2 (n=106796)	HLS 3 (n=49608)	p-value
Rhythm control	50,293 (25.1%)	1,916 (22%)	8,251 (23.7%)	26,421 (24.7%)	13,705 (27.6%)	<0.001
AAD	49,473 (24.7%)	1,866 (21.4%)	8,073 (23.2%)	26,028 (24.4%)	13,506 (27.2%)	<0.001
DCC	6,067 (3.0%)	267 (3.1%)	1,073 (3.1%)	3,011 (2.8%)	1,716 (3.5%)	<0.001
RFCA	1,917 (1.0%)	44 (0.5%)	256 (0.7%)	925 (0.9%)	692 (1.4%)	<0.001

AAD, antiarrhythmic drug; DCC, direct current cardioversion; HLS, healthy lifestyle score; RFCA, radiofrequency catheter ablation.

Table S5. Sensitivity analysis: additionally adjusted rhythm control treatment

	Final model HR (95% CI)	Additionally adjusted rhythm control treatment HR (95% CI)
Dementia		
HLS 0	1 (reference)	1 (reference)
HLS 1	0.753 (0.667-0.849)	0.756 (0.67-0.853)
HLS 2	0.728 (0.65-0.815)	0.733 (0.655-0.822)
HLS 3	0.622 (0.553-0.699)	0.629 (0.559-0.707)
p-value	<0.001	<0.001
Alzheimer's dementia		
HLS 0	1 (reference)	1 (reference)
HLS 1	0.830 (0.714-0.964)	0.832 (0.716-0.967)
HLS 2	0.808 (0.701-0.931)	0.813 (0.705-0.937)
HLS 3	0.681 (0.588-0.788)	0.686 (0.593-0.795)
p-value	<0.001	<0.001
Vascular dementia		
HLS 0	1 (reference)	1 (reference)
HLS 1	0.510 (0.399-0.651)	0.512 (0.401-0.655)
HLS 2	0.480 (0.383-0.601)	0.485 (0.387-0.608)
HLS 3	0.446 (0.352-0.565)	0.453 (0.358-0.575)
p-value	<0.001	<0.001

CI, confidence interval; HLS, healthy lifestyle behavior score; HR, hazard ratio.

Table S6. Subgroup analyses for Alzheimer's dementia

Subgroup	HLS	Number	Events	IR	Adjusted HR (95% CI)	p-value	p-for-interaction
Age (years)							
<65	**0**	6,515	48	1.91	1 (reference)	<0.001	0.751
	1	22,040	128	1.50	0.697 (0.500-0.972)		
	2	48,275	400	2.10	0.675 (0.495-0.920)		
	3	24,539	162	1.68	0.519 (0.371-0.726)		
65 to <75	**0**	1,658	91	15.07	1 (reference)	<0.001	
	1	8,860	428	13.32	0.835 (0.666-1.048)		
	2	34,956	2,051	16.08	0.799 (0.645-0.990)		
	3	17,180	765	12.38	0.660 (0.529-0.824)		
≥75	**0**	536	68	43.42	1 (reference)	<0.001	
	1	3,939	464	39.59	0.874 (0.677-1.128)		
	2	23,565	3,236	48.40	0.867 (0.680-1.106)		
	3	7,889	840	37.06	0.732 (0.570-0.939)		
Sex							
Men	**0**	8,249	191	6.14	1 (reference)	<0.001	0.380
	1	29,994	830	7.46	0.835 (0.713-0.977)		
	2	57,185	2,149	10.52	0.826 (0.711-0.959)		
	3	24,989	736	8.32	0.695 (0.592-0.816)		
Women	**0**	460	16	10.01	1 (reference)	<0.001	
	1	4,845	190	10.51	0.656 (0.393-1.093)		
	2	49,611	3,538	19.56	0.598 (0.366-0.978)		
	3	24,619	1,031	11.16	0.501 (0.305-0.821)		
CHA_2DS_2-VASc score							
Men<2 and women <3	**0**	3,268	15	1.12	1 (reference)	0.093	0.484
	1	11,581	38	0.80	0.558 (0.306-1.016)		
	2	24,679	145	1.42	0.676 (0.390-1.172)		
	3	12,749	62	1.18	0.525 (0.292-0.944)		

Men≥2 and women ≥3	**0**	5,441	192	9.94	1 (reference)	<0.001	
	1	23,258	982	12.00	0.850 (0.728-0.992)		
	2	82,117	5,542	19.60	0.821 (0.708-0.951)		
	3	36,859	1,705	13.27	0.689 (0.592-0.802)		
Prior ischemic stroke							
No	**0**	7,361	129	4.60	1 (reference)	<0.001	0.664
	1	28,359	626	5.82	0.792 (0.654-0.957)		
	2	79,163	3,122	10.60	0.727 (0.606-0.871)		
	3	37,320	992	7.12	0.617 (0.511-0.744)		
Yes	**0**	1,348	78	16.7	1 (reference)	<0.001	
	1	6,480	394	17.96	0.860 (0.674-1.097)		
	2	27,633	2,565	28.3	0.908 (0.722-1.142)		
	3	12,288	775	18.64	0.751 (0.593-0.951)		
OAC							
No	**0**	6,932	166	6.16	1 (reference)	<0.001	0.652
	1	26,877	775	7.43	0.810 (0.685-0.959)		
	2	77,822	4,155	13.96	0.772 (0.659-0.906)		
	3	35,812	1,279	9.24	0.654 (0.555-0.772)		
Yes	**0**	1,777	41	7.10	1 (reference)	0.004	
	1	7,962	245	9.74	0.919 (0.660-1.280)		
	2	28,974	1,532	17.52	0.953 (0.696-1.306)		
	3	13,796	488	11.49	0.791 (0.573-1.092)		

IR, per 1,000 person-years.

Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of oral anticoagulant, antiplatelet agent, and statin, BMI, and low income.

CI, confidence interval; HLS, healthy lifestyle behavior score; HR, hazard ratio; IR, incidence rate; OAC, oral anticoagulant.

Table S7. Subgroup analyses for Vascular dementia

Subgroup	HLS	Number	Events	IR	Adjusted HR (95% CI)	p-value	p-for-interaction
Age (years)							
<65	**0**	6,515	35	1.39	1 (reference)	<0.001	0.528
	1	22,040	68	0.79	0.526 (0.350-0.792)		
	2	48,275	152	0.80	0.431 (0.294-0.631)		
	3	24,539	65	0.67	0.354 (0.231-0.544)		
65 to <75	**0**	1,658	34	5.63	1 (reference)	0.002	
	1	8,860	104	3.24	0.552 (0.374-0.813)		
	2	34,956	458	3.59	0.517 (0.361-0.740)		
	3	17,180	202	3.27	0.496 (0.342-0.721)		
≥75	**0**	536	19	12.13	1 (reference)	0.015	
	1	3,939	66	5.63	0.464 (0.278-0.773)		
	2	23,565	495	7.40	0.494 (0.309-0.790)		
	3	7,889	143	6.31	0.456 (0.281-0.742)		
Sex							
Men	**0**	8,249	83	2.67	1 (reference)	<0.001	0.665
	1	29,994	197	1.77	0.508 (0.392-0.657)		
	2	57,185	469	2.30	0.491 (0.387-0.623)		
	3	24,989	194	2.19	0.474 (0.365-0.615)		
Women	**0**	460	5	3.13	1 (reference)	0.046	
	1	4,845	41	2.27	0.473 (0.187-1.198)		
	2	49,611	636	3.52	0.384 (0.159-0.929)		
	3	24,619	216	2.34	0.351 (0.144-0.854)		
CHA_2DS_2-VASc score							
Men<2 and women <3	**0**	3,268	11	0.82	1 (reference)	0.063	0.722
	1	11,581	21	0.44	0.479 (0.230-0.995)		
	2	24,679	54	0.53	0.474 (0.242-0.931)		
	3	12,749	21	0.40	0.352 (0.164-0.756)		

Men≥2 and women ≥3	**0**	5,441	77	3.99	1 (reference)	<0.001	
	1	23,258	217	2.65	0.519 (0.400-0.673)		
	2	82,117	1,051	3.72	0.487 (0.383-0.619)		
	3	36,859	389	3.03	0.457 (0.356-0.588)		
Prior ischemic stroke							
No	**0**	7,361	47	1.68	1 (reference)	<0.001	0.340
	1	28,359	123	1.14	0.495 (0.353-0.694)		
	2	79,163	532	1.81	0.475 (0.348-0.649)		
	3	37,320	194	1.39	0.425 (0.305-0.591)		
Yes	**0**	1,348	41	8.78	1 (reference)	<0.001	
	1	6,480	115	5.24	0.519 (0.363-0.742)		
	2	27,633	573	6.32	0.476 (0.343-0.661)		
	3	12,288	216	5.2	0.453 (0.322-0.638)		
OAC							
No	**0**	6,932	70	2.60	1 (reference)	<0.001	0.460
	1	26,877	174	1.67	0.480 (0.363-0.634)		
	2	77,822	749	2.52	0.422 (0.327-0.546)		
	3	35,812	274	1.98	0.398 (0.303-0.522)		
Yes	**0**	1,777	18	3.12	1 (reference)	0.263	
	1	7,962	64	2.54	0.637 (0.377-1.076)		
	2	28,974	356	4.07	0.691 (0.426-1.122)		
	3	13,796	136	3.20	0.625 (0.379-1.029)		

IR, per 1,000 person-years.

Adjusted for age, sex, hypertension, diabetes mellitus, dyslipidemia, heart failure, prior ischemic stroke, prior myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer, chronic kidney disease, CHA_2DS_2-VASc score, use of oral anticoagulant, antiplatelet agent, and statin, BMI, and low income.

CI, confidence interval; HLS, healthy lifestyle behavior score; HR, hazard ratio; IR, incidence rate; OAC, oral anticoagulant.

Table S8. Exploratory analyses: the risk of dementia between HLS 1 and HLS 2 or 3

Outcomes	HLS	Number	Events	IR	Adjusted HR (95% CI)	p-value
All dementia	1	34,839	1,425	11.01	1 (reference)	0.010
	2,3	156,404	10,069	17.79	0.926 (0.874-0.982)	

IR, per 1,000 person-years

CI, confidence interval; HLS, healthy lifestyle behavior score; HR, hazard ratio; IR, incidence rate.

Table S9. Exploratory analyses: the risk of dementia between HLS 1, 2 and 3

Outcomes	HLS	Number	Events	IR	Adjusted HR (95% CI)	p-value	p-for-trend
All dementia	1	34,839	1,425	11.01	1 (reference)	<0.001	<0.001
	2	106,796	7,625	19.80	0.968 (0.912-1.027)		
	3	49,608	2,444	13.52	0.826 (0.773-0.884)		

IR, per 1,000 person-years

CI, confidence interval; HLS, healthy lifestyle behavior score; HR, hazard ratio; IR, incidence rate.

Table S10. The association between exercise amount/intensity and the risk of dementia

Exercise intensity/dose	Number	Events	IR	Adjusted HR (95% CI)
[MPA or VPA per 3-7 d/week]				
Non-exerciser	147,417	9,845	18.42	1 (reference)
MPA, 3-7 d/week	19,039	796	11.54	0.810 (0.754-0.871)
VPA, 3-7 d/week	33,496	1,180	9.47	0.781 (0.735-0.831)
p-value				<0.001
[MPA or VPA per 5-7 d/week]				
Non-exerciser	175,382	10,780	16.90	1 (reference)
Moderate intensity exercise, 5-7 d/week	9,688	443	12.69	0.848 (0.771-0.933)
Vigorous intensity exercise, 5-7 d/week	14,882	598	10.80	0.796 (0.733-0.865)
p-value				<0.001
[Exercise doses stratified by the frequency of MVPA]				
Non-exerciser	108,380	8,416	21.65	1 (reference)
MVPA 1-2/week	39,037	1,429	9.80	0.832 (0.786-0.880
MVPA 3-4/week	27,965	935	9.05	0.763 (0.713-0.818)
MVPA 5-6/week	14,764	533	9.86	0.754 (0.691-0.824)
MVPA ≥7/week	9,806	508	14.04	0.785 (0.717-0.859)
p-value				<0.001
[Exercise doses stratified by MET-min/week]				
Non-exerciser	53,173	4,643	24.05	1 (reference)
0 to <500 MET-min/week	55,144	3,055	15.13	0.869 (0.830-0.910)

500-999 MET-min/week	55,494	2,784	13.85	0.840 (0.801-0.881)
1000-1499 MET-min/week	22,651	819	9.91	0.739 (0.686-0.797)
≥1500 MET-min/week	13,490	520	10.55	0.720 (0.656-0.789)
p-value				<0.001

IR, per 1,000 person-years

CI, confidence interval; d, day; HR, hazard ratio; IR, incidence rate; MPA, moderate-intensity physical activity; MVPA, moderate to vigorous physical activity; MET, metabolic equivalent task; VPA, vigorous-intensity physical activity.

Table S11. Univariable and multivariable HRs for the risk of dementia

Variable	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (years)	1.128 (1.125-1.130)	<0.001	1.106 (1.103-1.110)	<0.001
Male	1.714 (1.654-1.778)	<0.001	1.199 (1.132-1.269)	<0.001
BMI (kg/m^2)	0.928 (0.923-0.934)	<0.001	0.968 (0.963-0.974)	<0.001
CHA_2DS_2-VASc	1.621 (1.606-1.635)	<0.001	1.077 (1.041-1.114)	<0.001
SBP (mmHg)		<0.001		0.671
<120	1 (reference)		1 (reference)	
120 to <130	1.102 (1.047-1.161)		0.974 (0.925-1.026)	
130 to <140	1.256 (1.195-1.319)		0.975 (0.927-1.025)	
≥140	1.605 (1.526-1.689)		0.973 (0.923-1.025)	
Diabetes	1.545 (1.485-1.607)	<0.001	1.152 (1.093-1.215)	<0.001
Dyslipidemia	1.204 (1.161-1.248)	<0.001	0.982 (0.942-1.024)	0.399
Heart failure	2.027 (1.954-2.103)	<0.001	1.061 (1.007-1.117)	0.026
Prior MI	1.479 (1.406-1.556)	<0.001	1.034 (0.977-1.094)	0.243
Prior stroke	2.998 (2.892-3.109)	<0.001	1.509 (1.401-1.627)	<0.001
PAD	1.703 (1.637-1.771)	<0.001	1.064 (1.012-1.119)	0.015
COPD	1.767 (1.699-1.839)	<0.001	1.113 (1.069-1.159)	<0.001
Cancer	0.932 (0.860-1.011)	0.091	0.918 (0.846-0.997)	0.041
CKD	2.470 (2.376-2.568)	<0.001	1.140 (1.095-1.186)	<0.001
Low income	1.088 (1.038-1.139)	0.004	1.135 (1.084-1.190)	<0.001
OAC	1.339 (1.286-1.395)	<0.001	1.029 (0.987-1.074)	0.181
Antiplatelet	1.353 (1.303-1.406)	<0.001	1.028 (0.987-1.072)	0.183
Statin	1.240 (1.185-1.298)	<0.001	0.973 (0.921-1.027)	0.313
Smoking		<0.001		<0.001
non	1 (reference)		1 (reference)	
ex-smoker	0.603 (0.575-0.632)		0.969 (0.916-1.024)	
current smoker	0.489 (0.459-0.521)		1.237 (1.153-1.329)	
Alcohol		<0.001		<0.001
non	1 (reference)		1 (reference)	

mild	0.396 (0.378-0.416)		0.876 (0.830-0.925)	
moderate	0.566 (0.393-0.815)		1.196 (0.829-1.724)	
heavy	0.745 (0.240-2.309)		1.760 (0.567-5.462)	
Exercise		<0.001		<0.001
non	1 (reference)		1 (reference)	
regular PA	0.573 (0.543-0.604)		0.805 (0.763-0.849)	

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; MI, myocardial infarction; OAC, oral anticoagulant; PA, physical activity; PAD, peripheral artery disease; SBP, systolic blood pressure.

Table S12. Baseline characteristics of patients with and without the national health examinations within 2-year

	Total (n=576,077)	Patients receiving health examinations within 2-year after AF diagnosis (n=209,880)	Patients not receiving health examinations within 2-year after AF diagnosis (n=366,197)	p-value
Age, years	66.82±15.6	63.73±12.7	68.6±16.7	<0.001
Male	309,043 (53.7)	124,614 (59.4)	184,429 (50.4)	<0.001
Low income	131,093 (22.8)	37,359 (17.8)	93,734 (25.6)	<0.001
Heart failure	171,455 (29.8)	51,053 (24.3)	120,402 (32.9)	<0.001
Prior stroke	124,644 (21.6)	31,039 (14.8)	93,605 (25.6)	<0.001
Prior MI	43,699 (7.6)	11,622 (5.5)	32,077 (8.8)	<0.001
PAD	121,433 (21.1)	45,694 (21.8)	75,739 (20.7)	<0.001
COPD	146,235 (25.4)	42,303 (20.2)	103,932 (28.4)	<0.001
Cancer	59,348 (10.3)	12,035 (5.7)	47,313 (12.9)	<0.001

COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; PAD, peripheral artery disease.