JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Adherence to healthy lifestyle behaviors as a preventable risk factor for severe hypoglycemia in people with type 2 diabetes: A longitudinal nationwide cohort study

Jae-Seung Yun[1†], Kyungdo Han[2†], Yong-Moon Park[3], Eugene Han[4], Yong-ho Lee[5], Seung-Hyun Ko[1]*

[1]Department of Internal Medicine, College of Medicine, St. Vincent's Hospital, The Catholic University of Korea, Seoul, Korea, [2]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea, [3]Department of Epidemiology, Fay W. Boozman College of Public Health, University of Arkansas for Medical Sciences, Little Rock, AZ, USA, [4]Department of Internal Medicine, Daegu Dongsan Hospital, Keimyung University, Daegu, Korea, and [5]Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Keywords
Diabetes, type 2, Lifestyle behavior, Severe hypoglycemia

***Correspondence**
Seung-Hyun Ko
Tel.: +82-31-881-8900
Fax: 82-31253-8898
E-mail address:
kosh@catholic.ac.kr

J Diabetes Investig 2022; 13: 1533–-1542

doi: 10.1111/jdi.13818

ABSTRACT

Aims/Introduction: We investigated the associations between a combination of lifestyle factors and changes to these factors and the subsequent risk of severe hypoglycemia (SH) in type 2 diabetes patients.

Materials and Methods: Individuals with adult type 2 diabetes who underwent consecutive 2-year interval health screening programs from 2009 to 2012 from the Korean National Health Insurance Service database were included and followed up until 2018. Information on history of smoking status, alcohol consumption and physical activity, as well as changes to these factors, was obtained. The primary outcome was incident SH.

Results: Of the 1,490,233 type 2 diabetes patients, 30,539 (2.1%) patients developed SH. Current smokers and heavy drinkers had increased risk of SH, compared with non-smokers and non-drinkers, respectively (hazard ratio 1.28, 95% confidence interval 1.23–1.34; hazard ratio 1.22, 95% confidence interval 1.15–1.30). However, regular physical activity was associated with reduced SH risk (hazard ratio 0.79, 95% confidence interval 0.77–0.82). A combination of unhealthy lifestyle habits was associated with increased SH risk in a dose-dependent fashion (*P* for trend <0.001). Compared with participants without changes in their unhealthy lifestyles, participants who improved lifestyles had decreased risk of SH.

Conclusions: Greater adherence to healthy lifestyle factors and any improvement in unhealthy lifestyle habits were associated with a substantially lower risk of SH in individuals with type 2 diabetes.

INTRODUCTION

Hypoglycemia in people with diabetes is troublesome and an important obstacle in diabetes care, especially for implementing intensification of glycemic control. According to the revised classification by the International Hypoglycemia Study Group, severe hypoglycemia (SH) is defined as severe events characterized by altered mental and/or physical status requiring assistance for recovery[1]. SH is an advanced and life-threatening form of hypoglycemia that can cause seizures, loss of consciousness, dementia, cardiovascular disease (CVD) and even death[2]. The incidence of SH in randomized controlled trials has been shown to be at least a two- to threefold higher in groups undergoing intensive glucose control than in conventional controls[3,4].

An increase in hypoglycemia severity has a negative impact on health-related quality of life and overall healthcare resource use, including costs[5,6]. More importantly, the clinical significance of SH is that it is closely associated with an increased risk for subsequent cardiovascular (CV) outcomes and mortality in people with type 2 diabetes[7–10]. Analyses of several large-scale,

†These authors contributed equally as co-first authors.

Received 31 January 2022; revised 3 April 2022; accepted 25 April 2022

long-term randomized CV outcome trials evaluating glucose-lowering agents or intensive treatment strategies have identified an approximately 1.5–3.5-fold increased risk of CV events, CV mortality or all-cause mortality among participants with type 2 diabetes who had SH than among those who did not have SH[8,9]. Therefore, it is important to establish strategies for preventing and identifying predictors, especially for patients with type 2 diabetes at high risk of SH.

Nevertheless, regarding the risk factors for SH among type 2 diabetes patients, most high-risk patients with SH generally are very old, are fragile, have long-standing diabetes, are treated with insulin and have multiple underlying advanced comorbidities[11]. For these reasons, it is not easy to find preventable and modifiable risk factors for intervention. If practicable strategies, such as adherence to a healthy lifestyle, could be used to help prevent SH, many vulnerable patients with type 2 diabetes could avoid this harmful and dangerous situation.

Lifestyle management is essential and foundational to achieving proper care for type 2 diabetes[12,13]. Unhealthy lifestyles, such as heavy alcohol consumption, sedentary behavior, smoking and unhealthy diet, have been associated with an increased risk of complications in diabetes[14–17]. However, evidence is very limited regarding the impact of lifestyle habits on incident SH in type 2 diabetes.

Therefore, in the present study, we aimed to investigate the associations between clusters of unhealthy lifestyle factors, defined by combinations of smoking, heavy alcohol consumption and a lack of regular exercise, and the risk of SH in individuals with type 2 diabetes using a longitudinal Korean nationwide population-based cohort.

MATERIALS AND METHODS

Study population

We used the Korean National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) database, which includes qualified claims data based on International Classification of Diseases (ICD)-10 codes, health checkups, prescription dispensing records and death information[18,19]. The NHIS provides a regular national health examination program for the public, and all Korean adults are recommended to undergo general health screening at least once every 2 years, including the collection of demographic information, laboratory tests and self-administered questionnaires on lifestyle behaviors[20]. The present study was carried out in accordance with the Declaration of Helsinki. Because the NHIS-HEALS database has been made publicly available with anonymous and deidentified information, the requirement of consent from individual participants was waived. This study was approved by both the NHIS and the institutional review board of the Catholic University of Korea (VC21ZISI0094), and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines[21].

In this analysis, we screened 2,745,637 individuals with type 2 diabetes who were aged ≥20 years and underwent health examination from 1 January 2009 to 31 December 2012. To investigate the association of any lifestyle changes with SH development, we included participants who received an additional consecutive health examination within 2 years from baseline (n = 1,947,440) and followed them up until 31 December 2018. Exclusion of those with missing information on lifestyle factors, cancer, liver cirrhosis, end-stage renal disease or alcoholic liver disease resulted in a total of 1,490,233 participants for the main analysis (Figure S1).

Lifestyle factors

Information on history of smoking status, alcohol consumption and physical activity was obtained from a health checkup self-report questionnaire. Smoking status was classified as non-smoker, ex-smoker or current smoker. The frequency of alcohol consumption per week and an average amount of alcohol consumption per drinking session were collected. Then alcohol consumption was categorized as none, mild-to-moderate alcohol consumption (<30 g/day) or heavy alcohol consumption (≥30 g/day) based on the assumptions for calculating the amount of alcohol consumption[18–20]. The structured questionnaire was based on the International Physical Activity Questionnaire, and both the reliability and validity of the Korean version of the International Physical Activity Questionnaire short form have been proven[22,23]. Regular exercise was defined as carrying out moderate-intensity physical activity for at least 30 min/day at least five times/week or strenuous-intensity physical activity for at least 20 min/day at least three times/week[20–23]. The same questionnaire form was used in the biennial health examinations during 2009–2012. The primary exposures of interest were lifestyle factors and changes in lifestyle factors between the two separate biennial health examinations.

To assess the impact of clusters of unhealthy lifestyle factors, we assigned 0 points for a healthy level and 1 point for an unhealthy level in each lifestyle factor. Then, we divided the participants into four groups based on the combinations of each unhealthy lifestyle habit as follows: (i) participants without any unhealthy lifestyle factors (score 0); (ii) those with a single unhealthy lifestyle factor (score of 1); (iii) those with different combinations of two unhealthy lifestyle factors (score of 2); and (iv) participants with all three unhealthy lifestyle factors (score of 3). Thus, the higher score represents more unhealthier lifestyle.

We also further investigated the changes in each lifestyle habit between the two consecutive health examinations. We classified changes in the smoking and alcohol consumption factors as follows according to the response on questionnaires at the first and second examination: healthy habit maintained, no–no; starting or restarting of unhealthy habits, no–yes; unhealthy habits discontinued, yes–no; and unhealthy habit maintained, yes–yes. As regular exercise is a healthy habit, for this factor, we expressed "healthy habit maintained" as "yes–yes", and "unhealthy habit maintained" as "no–no".

Primary outcome and assessment of covariates

We collected all episodes reporting SH as the primary outcome, which was defined as the diagnostic clinical codes for hypoglycemia (ICD-10 codes of E 160–162, E1165, E1465) from the emergency room claims dataset[24]. We also extracted information on a prior SH history within 3 years before the second health screening examination.

Type 2 diabetes was defined based on: (i) ICD-10 codes (E11–E14) and the claims for antidiabetic medications; or (ii) a fasting glucose level test (≥126 mg/dL) during a health screening program. The criteria for socioeconomic status were based on the average monthly insurance payments imposed by the Korean NHI Corporation. Hypertension was defined based on diagnostic ICD-10 codes (I10-13 or I15) and at least one claim/year for antihypertensive medication or systolic/diastolic blood pressure ≥140/90 mmHg[25]. Dyslipidemia was defined based on diagnostic codes (E78) and at least one claim/year for a lipid-lowering agent or total cholesterol ≥240 mg/dL[25,26]. CVD was defined as diagnostic codes of I21-22 or I63-64[25,26]. All types of cancer, liver cirrhosis and end-stage renal disease were also identified using the ICD-10 codes, and then excluded[25,26]. The estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the Modification of Diet in Renal Disease Study Group equation[27].

Statistical analysis

Baseline characteristics are presented as numbers and percentages for categorical variables, and the mean ± standard deviation for continuous variables. The annual incidence rate of the primary outcome is presented as the number of events per 1,000 person-years. After the index date of the second health checkup, participants were followed up for incident SH until death or until the end of the study period, 31 December 2018, whichever came first. Cox proportional hazard regression was used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations of each lifestyle habit and the overall healthy lifestyle score (score 0, 1, 2 or 3) with risk of SH in type 2 diabetes patients. Next, we analyzed the association between unhealthy lifestyle habit changes and the subsequent risk of SH in type 2 diabetes patients. We classified participants into four groups based on the change in each unhealthy lifestyle factor from the first to the second health examination: constantly unhealthy, starting or restarting unhealthy, starting or restarting healthy and constantly healthy. We further checked whether the changes in unhealthy lifestyle habits could influence the risk of SH during the follow-up period. In multivariate models, we adjusted for age, sex, smoking status, heavy alcohol consumption, regular exercise habit, socioeconomic status (lower 25%), duration of treatment with antihyperglycemic agents (≥5 vs <5 years), prior history of SH within the past 3 years, body mass index, eGFR, oral hypoglycemic agents (≥3 classes), fasting glucose level, insulin use and the presence of comorbidities (hypertension, dyslipidemia, CVD). We assessed potential effect modification through stratified analysis and interaction testing using a likelihood ratio test. Analyses were further stratified by age (<65 or ≥65 years), sex, treatment duration of diabetes (<5 or ≥5 years), income status (lower 25% or ≥25%), insulin or sulfonylurea use, presence of chronic kidney disease (CKD) or CVD and prior history of SH. Sensitivity analyses that calculated the risk of SH at 1 year from the index date as the outcome were carried out to show the robustness of our results. Schoenfeld residuals were used to assess the proportional hazard assumption. A two-sided P-value of <0.05 was considered significant. All statistical analyses were carried out using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Baseline characteristics

The baseline clinical characteristics of the study population according to SH development are presented in Table 1. Among 1,490,233 participants with type 2 diabetes, 30,539 patients (2.1%) experienced incident SH during a median follow-up period of 6.4 years. Participants' mean age was 58.1 ± 12.4 years, and 57.6% were men. The proportion of participants who had diabetes treatment for > 5 years was 36.0%. The prevalence of current smokers was 23.2%, that of heavy alcohol drinkers was 7.4% and that of participants engaging in regular exercise was 22.4%. Compared with patients without SH events, patients with SH events were older; were more likely to be female; had lower body mass index; had a higher level of fasting glucose; had a lower level of eGFR; had a higher prevalence of hypertension and CVD; were more likely to have a previous history of an SH event; had a longer duration of diabetic medication, insulin or sulfonylurea use; and were more likely to be taking multiple classes of oral hypoglycemic agents. Current smoking and heavy alcohol drinking were more common in patients without incident SH; however, the proportion of participants who carried out regular exercise was lower in patients with incident SH (all P-values <0.001; Table 1). Clinical baseline characteristics according to the number of severe hypoglycemia events are also shown in Table S1. We further classified into five subgroups according to eGFR category to identify SH risk factors. As shown in Table S2, participants with a lower eGFR category were more prone to SH events. Furthermore, repeated SH events occurred more frequently in patients with reduced renal function (Table S2).

Risk of severe hypoglycemia according to baseline unhealthy lifestyle habits

In the multivariable Cox proportional hazard model, after multiple demographic, laboratory and comorbidity confounders were adjusted for, the risk of SH was significantly increased in the group with current smokers or heavy alcohol drinkers compared with that in the group with non-smokers or non-alcohol drinkers (Table 2). However, the regular exercise group significantly reduced the subsequent SH risk by 21% compared with those who did not exercise regularly among those with type 2

Table 1 | Baseline clinical characteristics of the study population according to incident severe hypoglycemia

	Total	Severe hypoglycemia		
	n = 1,490,233	No (*n* = 1,459,694)	Yes (*n* = 30,539)	*P*-value
Age (years)	58.1 ± 12.4	57.9 ± 12.4	68.0 ± 10.3	<0.001
Male sex	857,561 (57.6)	843,661 (57.8)	13,900 (45.5)	<0.001
Weight (kg)	65.7 ± 11.8	65.8 ± 11.8	60.6 ± 10.5	<0.001
BMI (kg/m^2)	24.9 ± 3.3	24.9 ± 3.3	24.3 ± 3.4	<0.001
SBP (mmHg)	127.9 ± 15.2	127.8 ± 15.2	130.7 ± 16.9	<0.001
DBP (mmHg)	78.1 ± 10.0	78.2 ± 9.9	77.2 ± 10.5	<0.001
Income status (lower 25%)	347,032 (23.3)	339,326 (23.3)	7,706 (25.3)	<0.001
Hypertension (yes)	824,802 (55.4)	801,260 (54.9)	23,542 (77.1)	<0.001
Dyslipidemia (yes)	644,992 (43.3)	629,207 (43.1)	15,785 (51.7)	<0.001
CVD history (yes)	80,103 (5.4)	76,106 (5.2)	3,997 (13.1)	<0.001
SH history within 3 years (yes)	6,606 (0.4)	5,145 (0.4)	1,461 (4.8)	<0.001
No. SH events				
No SH	1,482,994 (99.5)	1,454,190 (99.6)	28,804 (94.3)	<0.001
SH, 1 time	6,242 (0.42)	4,907 (0.34)	1,335 (4.37)	
SH, ≥2 times	997 (0.07)	597 (0.04)	400 (1.31)	
Duration of diabetic medication ≥5 years	537,114 (36.0)	514,062 (35.2)	23,052 (75.5)	<0.001
SU use (yes)	572,185 (38.4)	550,229 (37.7)	21,956 (71.9)	<0.001
Meglitinide (yes)	16,963 (1.14)	15,841 (1.09)	1,122 (3.67)	<0.001
Insulin use (yes)	120,638 (8.1)	111,093 (7.61)	9,545 (31.3)	<0.001
Oral hypoglycemic agents (≥3 classes)	233,139 (15.6)	222,919 (15.3)	10,220 (33.5)	<0.001
Glucose (mg/dL)	131.8 ± 45.5	131.7 ± 45.1	138.1 ± 59.9	<0.001
eGFR (mL/min/1.73 m^2)	86.7 ± 38.5	87.0 ± 38.6	72.6 ± 31.1	<0.001
Current smoker (yes)	345,474 (23.2)	340,922 (23.4)	4,552 (14.9)	<0.001
Heavy alcohol consumption (yes)	109,600 (7.4)	108,265 (7.4)	1,335 (4.4)	<0.001
Regular exercise (yes)	333,749 (22.4)	328,344 (22.5)	5,405 (17.7)	<0.001

Data are mean ± SD or *n* (%). BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; SH, severe hypoglycemia; SU, sulfonylurea.

diabetes (Table 2). In the subgroup analysis, consistent results were observed when further stratified by age, low income, treatment duration of diabetes, presence of CKD, sulfonylurea use and multiple classes of oral hypoglycemic agents (Figure 1). However, no significant association between unhealthy lifestyle factors and incident SH was found in the following subgroups for each lifestyle factor: female participants and participants with a prior history of SH for smoking factors (Figure 1a); female participants, insulin users and participants with a prior history of SH or CVD for alcohol consumption factors (Figure 1b); and participants with a prior history of SH for regular exercise factors (Figure 1c). Remarkably, for patients with previous SH experience, no significant associations between all three unhealthy lifestyle factors and the risk of incident SH were detected (Figure 1).

In the categorization of participants based on their unhealthy lifestyle factors, 16.8% of participants did not have any unhealthy lifestyle factors (score of 0), 61.4% had only one unhealthy factor (score of 1), and 18.7% and 3.1% had two (score 2) and three (score 3) unhealthy lifestyle factors, respectively. A total of 83.2% of the total study population had at least one unhealthy lifestyle factor. An increased score was significantly associated with a higher risk of incident SH in a dose-dependent fashion. Compared with participants with a score of 0, the participants with a score of 1 had an HR of 1.29 (95% CI 1.25–1.34), those with a score of 2 had an HR of 1.46 (95% CI 1.35–1.58) and those with a score of 3 had an HR of 1.81 (95% CI 1.51–2.12) for incident SH risk in type 2 diabetes (*P* for trend <0.0001, Figure 2). The participants with all three unhealthy lifestyle factors showed an 81% higher risk of SH compared with those without any unhealthy lifestyle factor.

Risk of severe hypoglycemia according to unhealthy lifestyle behavior changes

Next, the participants were divided into four categories according to the change in each lifestyle behavior over 2 years: healthy-healthy, healthy-unhealthy, unhealthy-healthy and unhealthy-unhealthy. Compared with no change to an unhealthy lifestyle, any improvement in each lifestyle factor was significantly associated with a lower risk for SH incidence (Table 3). In the case of smoking habits, compared with constant non-smokers, those who newly started smoking, those who stopped smoking and constant smokers had HRs of 1.32, 1.17 and 1.30, respectively (*P* for trend <0.001). A similar trend

Table 2 | Lifestyle factors and risk of severe hypoglycemia in type 2 diabetes patients

	n	SH	IR	Model 1	*P*-value	Model 2	*P*-value
Current smoker							
No	1,144,759	25,987	3.57	Reference	<0.001	Reference	<0.001
Yes	345,474	4,552	2.03	1.23 (1.18–1.28)		1.28 (1.23–1.34)	
Heavy alcohol consumption							
No	1,380,633	29,204	3.31	Reference	<0.001	Reference	<0.001
Yes	109,600	1,335	1.88	1.14 (1.07–1.21)		1.22 (1.15–1.30)	
Regular exercise							
No	1,156,484	25,134	3.41	Reference	<0.001	Reference	<0.001
Yes	333,749	5,405	2.50	0.80 (0.78–0.83)		0.79 (0.77–0.82)	

Data are hazard ratios (95% confidence interval). Model 1: age, sex, smoking, drinking, regular exercise and income (lower 25%). Model 2: model 1 plus hypertension, dyslipidemia, presence of cardiovascular diseases, body mass index, estimated glomerular filtration rate level, fasting glucose level, previous severe hypoglycemia (SH(events, insulin use, multiple classes of oral hypoglycemic agents (≥3 classes) and duration of diabetes treatment ≥5 years. IR, incidence rate (per 1,000 person-years).

was observed in type 2 diabetes patients with heavy alcohol consumption (*P* for trend <0.001). Compared with constant non-drinkers, constant heavy drinkers and alcohol abstainers had increased risk of SH by 28% and 13%, respectively. The SH risk significantly increased in the group starting or restarting heavy alcohol consumption over 2 years compared with that in the constant non-drinker group (HR 1.20, 95% CI 1.11–1.31). In addition, the risk of subsequent SH was significantly reduced by 27% in participants who constantly exercised regularly in both periods compared with the participants who did not. In particular, in the case of regular exercise, starting regular exercise could lower the risk of SH by 20% (Table 3). We further carried out multivariate sensitivity analysis, which investigated the relationship between changes in unhealthy lifestyle factors and the risk of SH at 1 year from the index date as the outcome. We also found consistent results that patients who maintained constant unhealthy lifestyle factors had an increased subsequent SH risk for all three exposure factors compared with those who had constant healthy lifestyles (Table S3).

In the subgroup analysis, we investigated the interaction of lifestyle changes and multiple main variables in the context of SH risk, and found that the association of SH risk with lifestyle changes varied by age, sex, sulfonylurea or insulin use, presence of CKD and previous history of SH (Table S4).

DISCUSSION

In the present large prospective nationwide cohort study, we found that unhealthy lifestyle factors, defined as current smoking, heavy alcohol consumption and lack of regular exercise, were significantly associated with increased risk of SH in individuals with type 2 diabetes. A combination of unhealthy lifestyle factors was significantly associated with higher SH risk in people with type 2 diabetes in a dose-dependent manner. Notably, compared with those who were adherent to unhealthy lifestyles, individuals with any improvements in these unhealthy lifestyle factors had a lower risk of subsequent SH events. These beneficial effects appeared even at the 1-year follow up after a behavior change within 2 years. To the best of our knowledge, this is the first long-term nationwide study on the association of lifestyle habits and its interval changes with the risk of SH in type 2 diabetes patients.

Lifestyle modification is an essential component of diabetes self-care, optimal glycemic control and CV health outcomes among individuals with type 2 diabetes[12–14]. The Nurses' Health Study and the Health Professionals Follow-Up Study found that an overall healthy lifestyle after diabetes diagnosis, defined as eating a high-quality diet, not smoking, engaging in moderate-to-vigorous intensity physical activity and drinking alcohol in moderation, was significantly associated with a lower risk of CVD incidence and CVD mortality[28]. In addition to type 2 diabetes, adherence to a healthy lifestyle among adults with mild-to-moderate CKD was associated with a reduced risk for adverse outcomes, including progression of CKD, atherosclerotic events and all-cause mortality[29], even in adults receiving maintenance hemodialysis[30,31]. However, the beneficial effect of lifestyle modification on the prevention of SH in type 2 diabetes patients has not been fully evaluated.

Studies reporting the relationship between SH and lifestyle behavior in people with diabetes are very limited. In young people with type 1 diabetes, patients who reported SH events were more likely to be physically active and to have lower glycated hemoglobin levels, and being physically active was associated with an 87% higher likelihood of SH events[32]. Smoking habit was not associated with SH. For type 2 diabetes patients, the independent predictors of incident SH among lifestyle factors in the longitudinal observational Fremantle Diabetes Study were alcohol consumption (≥10 g/day) and current smoking[33]. In contrast, current alcohol consumption was not associated with SH in Japanese insulin-treated patients with type 1 diabetes and type 2 diabetes[34]. For patients with type 2 diabetes treated with insulin from the Dutch Diabetes Pearl cohort

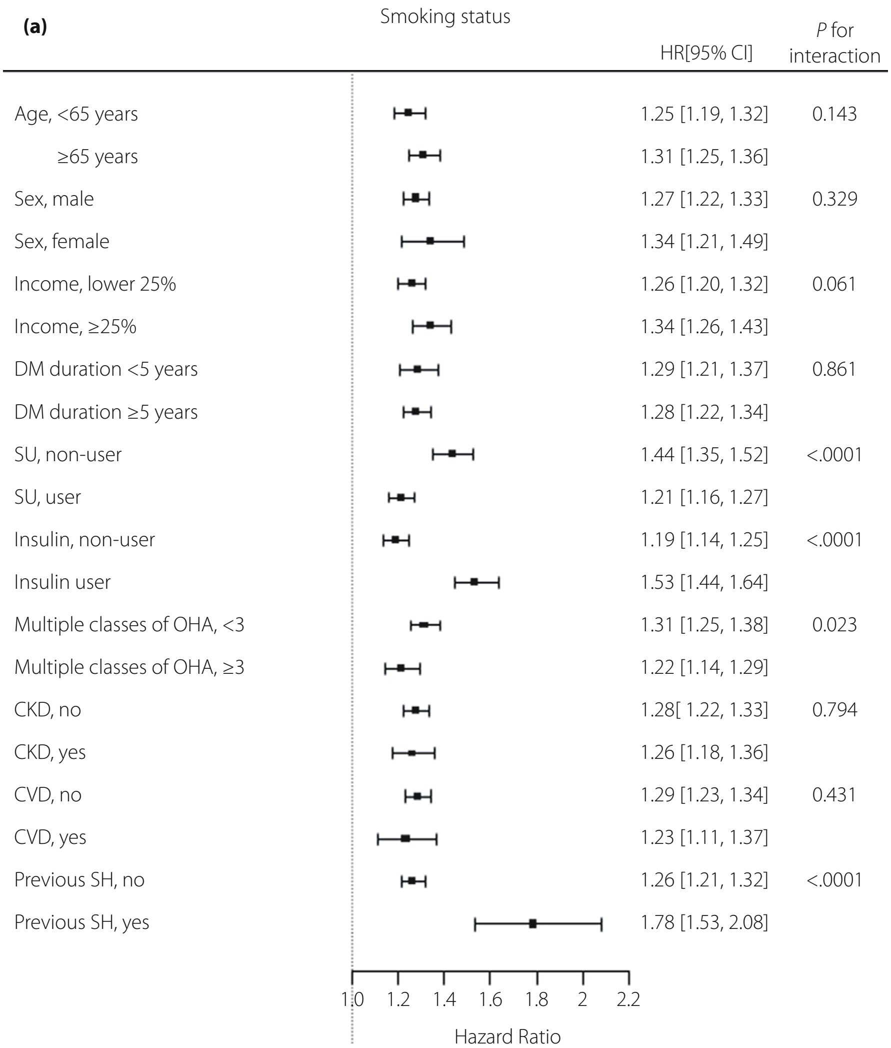

Figure 1 | Stratified analysis of the association of lifestyle factors with severe hypoglycemia in type 2 diabetes patients. (a) Smoking status, (b) heavy alcohol consumption and (c) regular exercise. CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes mellitus; HR, hazard ratio; OHA, oral hypoglycemic agent; SH, severe hypoglycemia; SU, sulfonylurea.

study, there were no significant differences between the group with and without impaired hypoglycemia unawareness regarding smoking and alcohol consumption (≥14 glasses/week)[35]. In the post-hoc epidemiological analysis of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, alcohol habits did not interact with glycemic treatment and SH[36].

In the current study, current smoking, heavy alcohol consumption and lack of regular exercise were associated with 28%, 22% and 21% higher risks for new-onset SH in type 2 diabetes patients, respectively. The results of the present study further provided evidence of the effect of current smoking and heavy alcohol consumption on the risk of SH in individuals who were aged <65 years, had a relatively short-term diabetes duration (<5 years), had underlying CVD or CKD, or were non-insulin users, although these groups are known to have a low risk of hypoglycemia. Therefore, the detrimental effect of unhealthy lifestyle on the risk of SH should be emphasized from the early stage of type 2 diabetes, especially for individuals at high risk for SH. At the same time, patients with a high risk of SH, especially those with previous experience with SH, might require more special strategies other than lifestyle modification. Therefore, we suggest that for these high-risk populations, more specific strategies than lifestyle management, including specialized intensive education about hypoglycemia and close glucose monitoring using technological approaches, are required[37].

More meaningful findings of the present study show that, compared with participants without changes in lifestyle, those who improved their lifestyles had decreased risk of incident SH. Starting unhealthy lifestyle habits was as detrimental as

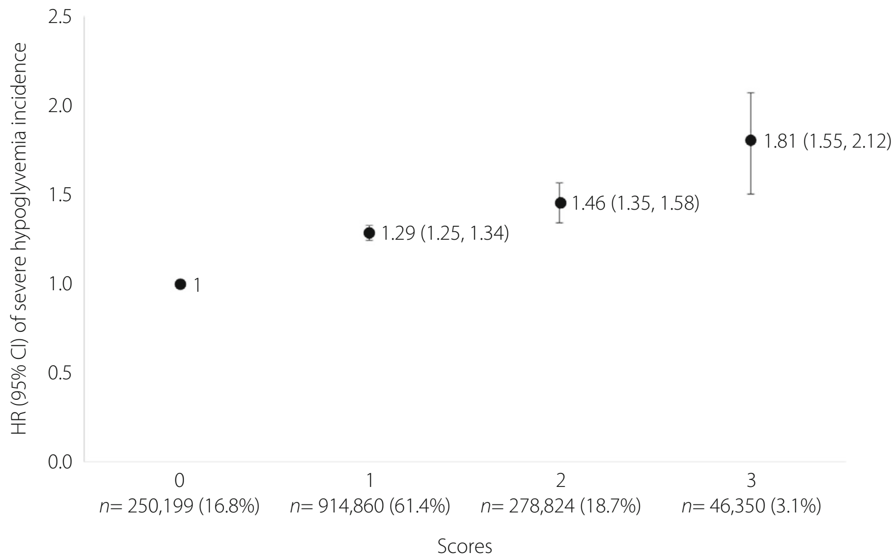

Figure 2 | Multivariable-adjusted hazard ratios (HRs; 95% confidence intervals [CIs]) of severe hypoglycemia incidence according to the lifestyle factor score among people with type 2 diabetes. We assigned 0 points for a healthy level and 1 point for an unhealthy level (including current smoking, heavy alcohol consumption and lack of regular exercise) for each lifestyle factor, and divided the cohort into four groups based on the combinations of each unhealthy lifestyle habit as follows: (i) participants without any unhealthy lifestyle factors (score 0); (ii) those with a single unhealthy lifestyle factor (score of 1); (iii) those with different combinations of 2 unhealthy lifestyle factors (score of 2); and (iv) participants with all three unhealthy lifestyle factors (score of 3).

Table 3 | Risk of severe hypoglycemia according to the changes in unhealthy lifestyle factors between the two health examinations during the study period

1st/2nd health exam (change)	Model 1	*P*-value	Model 2	*P*-value	Model 3	*P*-value
Current smoking						
No–no	1 (Ref.)	<0.001	1 (Ref.)	<0.001	1 (Ref.)	<0.001
No–yes	1.25 (1.17–1.35)		1.31 (1.21–1.41)		1.32 (1.23–1.43)	
Yes–no	1.23 (1.16–1.31)		1.23 (1.15–1.31)		1.17 (1.10–1.24)	
Yes–yes	1.21 (1.16–1.25)		1.25 (1.19–1.30)		1.30 (1.25–1.36)	
Heavy alcohol consumption						
No–no	1 (Ref.)	0.717	1 (Ref.)	<0.001	1 (Ref.)	<0.001
No–yes	1.01 (0.93–1.09)		1.13 (1.04–1.23)		1.20 (1.11–1.31)	
Yes–no	1.004 (0.94–1.08)		1.07 (0.995–1.15)		1.13 (1.05–1.21)	
Yes–yes	1.05 (0.97–1.13)		1.16 (1.07–1.26)		1.28 (1.18–1.39)	
Regular exercise						
No–no	1 (Ref.)	<0.001	1 (Ref.)	<0.001	1 (Ref.)	<0.001
No–yes	0.80 (0.77–0.83)		0.81 (0.78–0.84)		0.80 (0.77–0.83)	
Yes–no	0.90 (0.87–0.93)		0.90 (0.87–0.94)		0.86 (0.83–0.89)	
Yes–yes	0.73 (0.70–0.76)		0.75 (0.72–0.78)		0.73 (0.70–0.76)	

Data are hazard ratios (95% confidence interval). Model 1: age and sex. Model 2: model 1 plus smoking, drinking, regular exercise and income (lower 25%). Model 3: model 2 plus hypertension, dyslipidemia, presence of cardiovascular diseases, body mass index, estimated glomerular filtration rate level, fasting glucose level, previous severe hypoglycemia (SH) events, sulfonylurea or insulin use, multiple classes of oral hypoglycemic agents (≥3 classes) and duration of diabetes treatment ≥5 years. IR, incidence rate (per 1,000 person-year).

maintaining them. In particular, prior experience with regular exercise could prevent SH events, even after discontinuation, similar to the "legacy effect" of early intensive glycemic control for the prevention of diabetic complications. Therefore, more attention should be directed at modifiable unhealthy lifestyles for the prevention of incident SH in type 2 diabetes.

Several mechanisms for unhealthy lifestyle-induced SH might be proposed. Smoking is known to reduce insulin clearance[38]. Nicotine exposure might paradoxically increase the incidence of SH in insulin-treated patients, possibly through reduced clearance of subcutaneous insulin and enhancement of insulin action[39]. The increased risk after alcohol consumption in diabetes patients was mainly explained by a reduction in endogenous hepatic gluconeogenesis and/or glycogenolysis[40]. Despite the controversial results, an increase in insulin secretion and a reduction in growth hormone secretion after drinking can be possible mechanisms that worsen with the combination of defects in the glucose counterregulatory response in people with SH[41]. Alcohol can cause hypoglycemia unawareness and cognitive impairment, despite exaggerated physiological changes against hypoglycemia[42]. In addition, a healthy lifestyle including sustained regular exercise might reflect usual good self-management. Glycemic control and glucose monitoring are likely to be better in individuals with healthy lifestyles.

The strengths of the present study were that it was a large-scale nationwide study with long-term follow up, measured outcomes within a heavily subsidized healthcare system with a high retention rate and carried out repeated measurements of lifestyle factors of the same qualified items from biennial health checkups.

There were also several limitations. Lifestyle habits were obtained by a self-report questionnaire. Second, the present study lacked important variables for glycemic control status, such as HbA1c or blood glucose level, medication dosage and detailed information about disease duration. Third, the participants who were enrolled were relatively healthy and could receive national health screening programs regularly, therefore, selection bias might have occurred. Fourth, among lifestyle factors, dietary quality was not evaluated. Finally, only individuals of Asian ethnicity were included. For generalization, further study in a more diverse ethnic population is required.

Nevertheless, the present study has provided novel evidence to suggest that adopting a healthy lifestyle could be a feasible, cost-effective and practical prevention strategy for people with type 2 diabetes to reduce the risk of developing SH. Furthermore, behavioral modification from an unhealthy to a healthier lifestyle was also associated with lower SH in adults with type 2 diabetes. However, populations with a very high risk of SH, such as very old, vulnerable patients with a previous history of SH, require more specific intervention strategies beyond lifestyle modification. Therefore, a more intensive, individualized and patient-centered detailed approach for the prevention of SH should also be developed in this high-risk population for type 2 diabetes.

ACKNOWLEDGMENTS

This research was supported by a grant of the Korea Health Industry Development Institute (KHIDI), Korea (HI19C0784). The authors thank the participants of the Korean National Health Insurance Service-Health Screening program.

DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: This study was approved by both the NHIS and the institutional review board of the Catholic University of Korea (VC21ZISI0094).

Informed consent: N/A.

Registry and the registration no. of the study/trial: N/A.

Animal Studies: N/A.

REFERENCES

1. IHSG International Hypoglycemia Study Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2017; 40: 155–157.
2. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol* 2014; 10: 711–722.
3. Bonds DE, Miller ME, Bergenstal RM, *et al*. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010; 340: b4909.
4. Hemmingsen B, Lund SS, Gluud C, *et al*. Intensive glycaemic control for patients with type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. *BMJ* 2011; 343: d6898.
5. Pawaskar M, Witt EA, Engel SS, *et al*. Severity of hypoglycaemia and health-related quality of life, work productivity and healthcare costs in patients with type 2 diabetes in Europe. *Endocrinol Diabetes Metab* 2018; 1: e00011.
6. Lee J, Kim TM, Kim H, *et al*. Differences in clinical outcomes between patients with and without hypoglycemia during hospitalization: a retrospective study using real-world evidence. *Diabetes Metab J* 2020; 44: 555–565.
7. Choi SY, Ko SH. Severe hypoglycemia as a preventable risk factor for cardiovascular disease in patients with type 2 diabetes mellitus. *Korean J Intern Med* 2021; 36: 263–270.
8. Yun JS, Ko SH. Current trends in epidemiology of cardiovascular disease and cardiovascular risk management in type 2 diabetes. *Metabolism* 2021; 123: 154838.
9. Davis SN, Duckworth W, Emanuele N, *et al*. Investigators of the veterans affairs diabetes trial. Effects of severe hypoglycemia on cardiovascular outcomes and death in the veterans affairs diabetes trial. *Diabetes Care* 2019; 42: 157–163.
10. Yun JS, Park YM, Han K, *et al*. Severe hypoglycemia and the risk of cardiovascular disease and mortality in type 2 diabetes: a nationwide population-based cohort study. *Cardiovasc Diabetol* 2019; 18: 103.
11. Misra-Hebert AD, Pantalone KM, Ji X, *et al*. Patient characteristics associated with severe hypoglycemia in a

type 2 diabetes cohort in a large, integrated health care system from 2006 to 2015. *Diabetes Care* 2018; 41: 1164–1171.
12. Hur KY, Moon MK, Park JS, *et al*. 2021 Clinical practice guidelines for diabetes mellitus of the Korean Diabetes Association. *Diabetes Metab J* 2021; 2021: 461–481.
13. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. *Diabetes Care* 2021; 44(Suppl 1): S111–S124.
14. Liu G, Li Y, Hu Y, *et al*. Influence of lifestyle on incident cardiovascular disease and mortality in patients with diabetes mellitus. *J Am Coll Cardiol* 2018; 71: 2867–2876.
15. Yang R, Xu H, Pedersen NL, *et al*. A healthy lifestyle mitigates the risk of heart disease related to type 2 diabetes: a prospective nested case-control study in a nationwide Swedish twin cohort. *Diabetologia* 2021; 64: 530–539.
16. American Diabetes Association. Facilitating behavior change and well-being to improve health outcomes: standards of medical care in diabetes-2021. *Diabetes Care* 2021; 44(Suppl 1): S53–S72.
17. Arnett DK, Blumenthal RS, Albert MA, *et al*. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol* 2019; 74: e177–e232.
18. Kim HK, Song SO, Noh J, *et al*. Data configuration and publication trends for the Korean National Health Insurance and Health Insurance Review & Assessment Database. *Diabetes Metab J* 2020; 44: 671–678.
19. Park JH, Ha KH, Kim BY, *et al*. Trends in cardiovascular complications and mortality among patients with diabetes in South Korea. *Diabetes Metab J* 2021; 45: 120–124.
20. Lee SR, Choi EK, Ahn HJ, *et al*. Association between clustering of unhealthy lifestyle factors and risk of new-onset atrial fibrillation: a nationwide population-based study. *Sci Rep* 2020; 10: 19224.
21. von Elm E, Altman DG, Egger M, *et al*. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370: 1453–1457.
22. World Health Organization. WHO Guidelines on Physical Activity and Sedentary Behaviour. Geneva: World Health Organization, 2020; 104.
23. Chun MY. Validity and reliability of Korean version of international physical activity questionnaire short form in the elderly. *Korean J Fam Med* 2012; 33: 144–151.
24. Yun JS, Han K, Ko SH. Trends of severe hypoglycemia in patients with type 2 diabetes in Korea: a longitudinal nationwide cohort study. *J Diabetes Investig* 2022. https://doi.org/10.1111/jdi.13786.
25. Kim YS, Park YM, Han KD, *et al*. Fasting glucose level and all-cause or cause-specific mortality in Korean adults: a nationwide cohort study. *Korean J Intern Med* 2021; 36: 647–658.
26. Koh ES, Han K, Kim MK, *et al*. Weight change and microvascular outcomes in patients with new-onset diabetes: a nationwide cohort study. *Korean J Intern Med* 2021; 36: 932–941.
27. Levey AS, Stevens LA, Schmid CH, *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612.
28. Shan Z, Li Y, Baden MY, *et al*. Association between healthy eating patterns and risk of cardiovascular disease. *JAMA Intern Med* 2020; 180: 1090–1100.
29. Ricardo AC, Anderson CA, Yang W, *et al*. Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the chronic renal insufficiency cohort (CRIC) study. *Am J Kidney Dis* 2015; 65: 412–424.
30. Su G, Saglimbene V, Wong G, et al. Healthy lifestyle and mortality among adults receiving hemodialysis: the DIET-HD study. *Am J Kidney Dis* 2022; 79: 688–698.
31. Long GH, Cooper AJ, Wareham NJ, *et al*. Healthy behavior change and cardiovascular outcomes in newly diagnosed type 2 diabetic patients: a cohort analysis of the ADDITION-Cambridge study. *Diabetes Care* 2014; 37: 1712–1720.
32. Saydah S, Imperatore G, Divers J, *et al*. Occurrence of severe hypoglycaemic events among US youth and young adults with type 1 or type 2 diabetes. *Endocrinol Diabetes Metab* 2019; 2: e00057.
33. Davis TME, Bruce DG, Finn J, *et al*. Temporal changes in the incidence and predictors of severe hypoglycaemia in type 2 diabetes: The Fremantle Diabetes Study. *Diabetes Obes Metab* 2019; 21: 648–657.
34. Sonoda N, Morimoto A, Ugi S, *et al*. Predictors for mild and severe hypoglycemia in insulin-treated Japanese diabetic patients. *PLoS One* 2015; 10: e0130584.
35. van Meijel LA, de Vegt F, Abbink EJ, *et al*. High prevalence of impaired awareness of hypoglycemia and severe hypoglycemia among people with insulin-treated type 2 diabetes: the Dutch diabetes pearl cohort. *BMJ Open Diabetes Res Care* 2020; 8: e000935.
36. Miller ME, Bonds DE, Gerstein HC, *et al*. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* 2010; 340: b5444.
37. International Hypoglycaemia Study Group. Minimizing hypoglycemia in diabetes. *Diabetes Care* 2015; 38: 1583–1591.
38. Bott S, Shafagoj YA, Sawicki PT, *et al*. Impact of smoking on the metabolic action of subcutaneous regular insulin in type 2 diabetic patients. *Horm Metab Res* 2005; 37: 445–449.
39. Tweed JO, Hsia SH, Lutfy K, *et al*. The endocrine effects of nicotine and cigarette smoke. *Trends Endocrinol Metab* 2012; 23: 334–342.

40. Avogaro A, Beltramello P, Gnudi L, *et al*. Alcohol intake impairs glucose counterregulation during acute insulin-induced hypoglycemia in IDDM patients. Evidence for a critical role of free fatty acids. *Diabetes* 1993; 42: 1626–1634.
41. Kerr D, Cheyne E, Thomas P, *et al*. Influence of acute alcohol ingestion on the hormonal responses to modest hypoglycaemia in patients with type 1 diabetes. *Diabet Med* 2007; 24: 312–326.
42. Kerr D, Macdonald IA, Heller SR, *et al*. Alcohol causes hypoglycaemic unawareness in healthy volunteers and patients with type 1 (insulin-dependent) diabetes. *Diabetologia* 1990; 33: 216–221.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Study design and enrollment flow.

Table S1 | Clinical baseline characteristics according to the number of severe hypoglycemia events

Table S2 | Baseline clinical characteristics of the study population according to the incidence of severe hypoglycemia.

Table S3 | The risk of severe hypoglycemia according to the changes in unhealthy lifestyle factors between the two health examinations at the 1-year follow up

Table S4 | Stratified analysis of the association of the changes in lifestyle factors with severe hypoglycemia in type 2 diabetes patients.