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Lifestyle Changes and Remission in Patients With New-Onset Type 2 Diabetes: A Nationwide Cohort Study

Jinyoung Kim [1], **Bongseong Kim** [2], **Mee Kyoung Kim** [1], **Ki-Hyun Baek** [1], **Ki-Ho Song** [1], **Kyungdo Han** [3], and **Hyuk-Sang Kwon** [1]

[1]Division of Endocrinology and Metabolism, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea
[2]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea
[3]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea

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Address for Correspondence:
Kyungdo Han, PhD
Department of Statistics and Actuarial Science, Soongsil University, 369 Sangdo-ro, Dongjak-gu, Seoul 06978, Korea.
Email: hkd917@naver.com

Hyuk-Sang Kwon, MD, PhD
Division of Endocrinology and Metabolism, Department of Internal Medicine, Yeouido St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 10, 63-ro, Yeongdeungpo-gu, Seoul 07345, Korea.
Email: drkwon@catholic.ac.kr

ORCID iDs
Jinyoung Kim
https://orcid.org/0000-0003-4581-9493
Bongseong Kim
https://orcid.org/0000-0002-1022-3553
Mee Kyoung Kim
https://orcid.org/0000-0003-3205-9114

ABSTRACT

Background: Lifestyle-related factors have been studied as a fundamental aspect in the onset and progression of type 2 diabetes mellitus. However, behavioral factors are easily overlooked in clinical practice. This study investigated whether lifestyle changes were associated with diabetes remission in newly diagnosed type 2 diabetes patients.
Methods: We enrolled patients with new-onset type 2 diabetes from 2009 to 2012 using a health examination cohort from the Korean National Health Insurance Service (KNHIS). Remission was defined as a fasting glucose level less than 126 mg/dL at least once during a health examination after stopping medication. A self-administered questionnaire was used to investigate patients' lifestyles. We investigated smoking, alcohol consumption, and regular exercise before and after starting diabetes medication and the odds ratios (ORs) of logistic regression on remission to evaluate the associations.
Results: A total of 138,211 patients diagnosed with type 2 diabetes from 2009 to 2012 were analyzed, and 8,192 (6.3%) reported remission during the follow-up period to 2017. Baseline fasting blood glucose level measured before starting diabetes medication was significantly higher in the non-remission group (180 mg/dL vs. 159 mg/dL, $P < 0.001$). In addition, the use rate of combined oral hypoglycemic agent treatment was higher in the non-remission group (15% vs. 8%, $P < 0.001$). Consistent smoking and drinking showed negative associations with remission (OR, 0.72; 95% confidence interval [CI], 0.67–0.77 and OR, 0.90; 95% CI, 0.84–0.95, respectively), and initiation of regular exercise presented a positive association with remission (OR, 1.54; 95% CI, 0.46–1.63). Abstinence from alcohol increased the likelihood of remission in the male population (OR, 1.20; 95% CI, 1.10–1.32). The association with smoking history or smoking cessation was not clear, but new smoking behavior interfered with remission in women (OR, 0.48; 95% CI, 0.28–0.81).
Conclusion: We confirmed associations between a healthy lifestyle and diabetic remission in new-onset type 2 diabetes patients. The results of this study suggest that improving lifestyle after diabetes diagnosis may contribute to disease remission.

Keywords: Diabetes Mellitus, Type 2; Prevention and Control; Smoking; Alcohol Drinking; Exercise; Lifestyle Changes

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Ki-Hyun Baek
https://orcid.org/0000-0002-4097-1077
Ki-Ho Song
https://orcid.org/0000-0003-1883-7039
Kyungdo Han
https://orcid.org/0000-0002-6096-1263
Hyuk-Sang Kwon
https://orcid.org/0000-0003-4026-4572

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Disclosure
The authors have no potential conflicts of interest to disclose.

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INTRODUCTION

Lifestyle-related factors have been studied as a fundamental aspect in the onset and progression of type 2 diabetes mellitus (T2DM).[1-3] As risk factors that can be modified by lifestyle management, alcohol use, smoking, and sedentary behaviors are crucial considerations in diabetes care. Experts recommend that diabetic patients quit smoking, not drink excessively, and engage in a certain amount of physical activity on a regular basis.[4] However, these behavioral factors are easily overlooked in clinical practice because their impact is difficult to quantify.

Additionally, there are conflicting opinions regarding lifestyle changes, which can lead to confusion among patients. It is often reported that moderate alcohol consumption may have a beneficial effect on cardiovascular health.[5,6] There are also studies that concluded smoking cessation may increase the risk of diabetes in the early period after quitting.[7] Physical activity is generally thought to be beneficial,[8] but it is difficult to recommend given the diverse types of physical activity and differences in individual exercise abilities.[9]

Accordingly, we aimed to confirm the associations between lifestyle modification after diagnosis of T2DM and diabetes remission through a comprehensive analysis of a lifestyle questionnaire among new-onset T2DM patients included in the national health examination cohort.

METHODS

Data sources

The data of this study were from a cohort of the general population who underwent health examinations provided by the Korean National Health Insurance Service (KNHIS).[10] The contents of the health check-up vary depending on the age of individuals, but examination for adults typically includes physical measurements (height, weight, and waist circumference), basic blood tests, and questionnaires. Through a self-administered questionnaire, prescribed medications for high blood pressure, diabetes, dyslipidemia, smoking history, drinking status, and physical activity level are evaluated. Health check-ups are provided every other year, and cohort data were provided anonymously after official review and approval by the KNHIS.

Data analysis

Health examination data were combined with claims data to select new-onset T2DM patients. Adult diabetic patients aged 20 years or older who participated in the health examination program from 2009 to 2012 were screened using the International Statistical Classification of Diseases, 10th Revision (ICD-10) codes for T2DM (category E11). Patients younger than 20 years who had the code for type 1 diabetes mellitus (category E10) or gestational diabetes (category O24) were excluded, as were those who had been medically treated for diabetes before the examination. Patients were also excluded if they experienced transient hyperglycemia, defined as a baseline fasting blood glucose (FBG) level less than 126 mg/dL, after the health check-up but before starting diabetes treatment or if they had received diabetes medication prescriptions less than twice in a year. Patients whose health status was confirmed by at least one health examination up to 2017 were eligible for the study, and those whose FBG level was less than 126 mg/dL at least once during the follow-up period were further investigated. We reviewed claims for diabetes medication up to two years prior to the examination when FBG was measured in the normal range. Finally, remission was defined

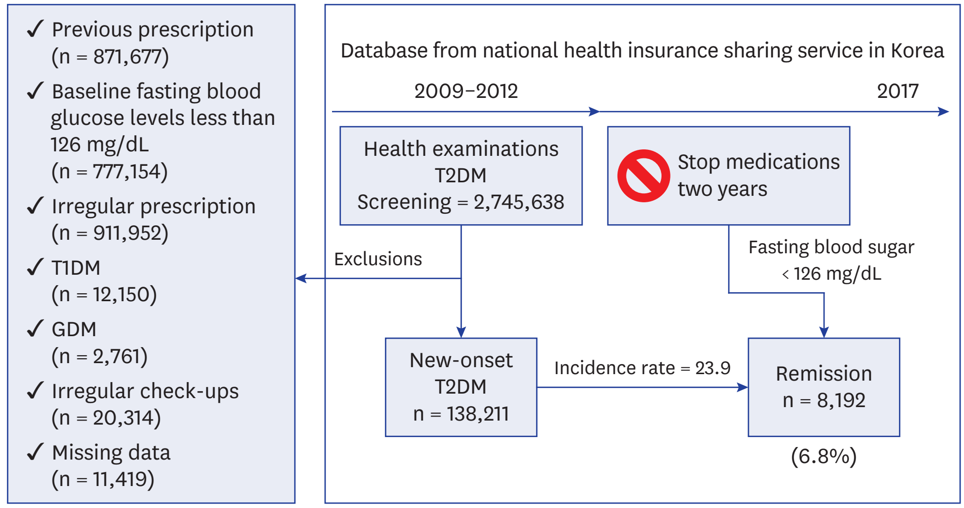

Fig. 1. Study flowchart.
T1DM = type 1 diabetes mellitus, GDM = gestational diabetes mellitus, T2DM = type 2 diabetes mellitus.

as FBG less than 126 mg/dL after more than two years since discontinuation of diabetes medication (**Fig. 1**).

The categorization definitions of lifestyle factors were defined as follows based on the results of the questionnaire. A current smoker was a person who had smoked on the day of the examination, and an ex-smoker was a person who had smoked more than 100 cigarettes in their lifetime. Average weekly alcohol consumption less than 30 g per day was classified as mild, otherwise it was classified as heavy consumption. Regular exercise was defined as brisk walking-intensity exercise more than 5 times a week or running-intensity exercise more than 3 times a week.

To describe baseline characteristics, continuous variables are presented as mean and standard deviation, and categorical variables are expressed as number and percentage. For comparison between remission and non-remission groups, *t*-tests were performed for continuous variables and χ^2 tests for categorical variables. According to the results of questionnaires from health examinations before and after the start of diabetes treatment, a group that had no exposure to smoking, alcohol, or exercise was set as the reference. When interpreting the remission results between groups, univariate and multivariate logistic regression analyses were performed. In the subgroup analysis for men and women, an additional interaction analysis for sex was performed.

In all statistical results, a two-sided *P* value less than 0.05 was considered significant. We used SAS analytics software, version 9.4. (SAS Institute, Cary, NC, USA) for the analyses.

Ethics statement

The Institutional Review Board of Yeouido St. Mary's Hospital approved this study with a waiver of informed consent (SC23ZISI0132).

RESULTS

Remission of new-onset T2DM

A total of 138,211 patients diagnosed with T2DM from 2009 to 2012 were analyzed, and 8,192 (6.3%) patients reported remission during the follow-up period to 2017. Baseline FBG level measured before starting diabetes medication was significantly higher in the non-remission group (180 mg/dL vs. 159 mg/dL, $P < 0.001$). In addition, the use rate of combined oral hypoglycemic agent treatment was higher in the non-remission group (15% vs. 8%, $P < 0.001$). The proportion of people with hypertension or dyslipidemia was also higher in the non-remission group (**Table 1**).

Lifestyle changes in patients with new-onset T2DM

Lifestyle changes were grouped before and after starting diabetes treatment, and univariate and multivariate logistic regression analyses were performed to assess the associations of lifestyle changes with remission (**Table 2**). When non-smokers were used as the reference group, the odds ratio (OR) for remission in the persistent smoker group was 0.72, with 95% confidence interval (CI) was 0.67–0.77. Cessation of smoking showed no significant association. When the group that did not drink alcohol was used as a reference, the OR for remission in the drinking group was 0.90, with 95% CI was 0.84–0.95. Abstinence from alcohol showed a positive association with remission (OR, 1.14; 95% CI, 1.05–1.26). When using the sedentary group as a reference, both the consistent exercise and the starting exercise groups showed a significant correlation with remission (OR, 1.22; 95% CI, 1.12–1.32 and OR, 1.54; 95% CI, 1.46–1.63, respectively).

Table 1. Baseline characteristics of the study population (N = 138,211)

Characteristics	Non-remission (n = 130,019)	Remission (n = 8,192)	*P* value
Age, yr	54.9 ± 10.6	55.4 ± 10.8	< 0.001
Sex (male)	76,562 (58.9)	5,243 (64.0)	< 0.001
Income (75th percentile)	26,460 (20.4)	1,653 (20.2)	0.707
Weight, kg	68.3 ± 11.8	68.5 ± 12.2	0.237
Waist circumference, cm	86.5 ± 8.5	86.3 ± 8.6	0.019
Body-mass index, kg/m^2	25.7 ± 3.4	25.5 ± 3.5	< 0.001
SBP, mmHg	130 ± 16	129 ± 16	< 0.001
DBP, mmHg	81 ± 11	80 ± 10	< 0.001
FBG, mg/dL	180 ± 59	159 ± 48	< 0.001
AST, IU/L	28.5 (28.4–28.5)	29.6 (29.3–29.9)	< 0.001
ALT, IU/L	32.2 (32.0–32.3)	32.7 (32.2–33.1)	0.022
Creatinine, mg/dL	0.97 ± 1.03	1.03 ± 1.28	< 0.001
Total cholesterol, mg/dL	217 ± 44	213 ± 45	< 0.001
Triglyceride, mg/dL[a]	172 (171–172)	162 (160–164)	< 0.001
HTN	68,627 (52.8)	4,089 (49.9)	< 0.001
Hyperlipidemia	62,868 (48.4)	3,702 (45.2)	< 0.001
More than three oral hypoglycemic agents	19,573 (15.1)	652 (8.0)	< 0.001
Alcohol consumption			0.193
None	68,996 (53.1)	4,320 (52.7)	
Mild	45,949 (35.3)	1,892 (23.1)	
Heavy	15,074 (11.6)	1,980 (24.2)	
Smoking			< 0.001
None	70,124 (53.9)	4,320 (52.7)	
Ex-smoker	24,755 (19.0)	1,892 (23.1)	
Current smoker	35,140 (27.0)	1,980 (24.2)	
Regular exercise (yes)	22,241 (17.1)	1,451 (17.7)	0.158

Values are presented as mean ± standard deviation, number (%), or median (interquartile range).
SBP = systolic blood pressure, DBP = diastolic blood pressure, FBG = fasting blood glucose, AST = aspartate aminotransferase, ALT = alanine aminotransferase, HTN = hypertension.
[a]Serum triglycerides level did not follow a normal distribution, so we described it as median and interquartile range.

Table 2. Logistic regression analysis to evaluate the association between life style changes and remission of type 2 diabetes

Lifestyle change	Remission	Model 1	*P* value	Model 2	*P* value	Model 3	*P* value
	No. (%)	OR (95% CI)		OR (95% CI)		OR (95% CI)	
Smoking			< 0.001		< 0.001		< 0.001
None/Ex > None/Ex	5,892 (6.13)	1 (ref.)		1 (ref.)		1 (ref.)	
Current > None/Ex	558 (6.59)	1.08 (0.988–1.182)		0.95 (0.87–1.05)		0.96 (0.87–1.05)	
None/Ex > Current	320 (6.44)	1.05 (0.938–1.183)		0.93 (0.83–1.05)		0.96 (0.85–1.08)	
Current > Current	1,422 (4.96)	0.80 (0.753–0.849)		0.70 (0.66–0.75)		0.72 (0.67–0.77)	
Alcohol			< 0.001		< 0.001		< 0.001
None > None	3,716 (5.75)	1 (ref.)		1 (ref.)		1 (ref.)	
Mild/Heavy > None	1,024 (6.89)	1.21 (1.129–1.303)		1.15 (1.06–1.24)		1.14 (1.05–1.26)	
None > Mild/Heavy	578 (6.66)	1.17 (1.068–1.28)		1.08 (0.98–1.18)		1.05 (0.96–1.15)	
Mild/Heavy > Mild/Heavy	2,874 (5.74)	0.99 (0.95–1.05)		0.93 (0.88–0.99)		0.90 (0.84–0.95)	
Exercise			< 0.001		< 0.001		< 0.001
No > No	5,013 (5.37)	1 (ref.)		1 (ref.)		1 (ref.)	
Yes > No	768 (5.49)	1.02 (0.95–1.11)		0.99 (0.92–1.08)		0.97 (0.90–1.05)	
No > Yes	1,728 (8.13)	1.56 (1.47–1.65)		1.53 (1.47–1.62)		1.54 (1.46–1.63)	
Yes > Yes	683 (7.05)	1.34 (1.23–1.45)		1.27 (1.17–1.38)		1.22 (1.12–1.32)	

Model 1: unadjusted; Model 2: adjusted by age, sex, income, hypertension, dyslipidemia, chronic kidney disease, smoking, alcohol consumption, and regular exercise; Model 3: adjusted by age, sex, income, hypertension, dyslipidemia, chronic kidney disease, smoking, alcohol consumption, regular exercise, fasting glucose levels, more than three oral hypoglycemic agents, insulin use, and baseline body weight.

Sex differences in the associations between lifestyle habit changes and remission in new-onset T2DM

The associations of lifestyle changes with remission were analyzed separately for men and women (**Fig. 2**), and the adverse effects of smoking were more pronounced in women. Starting smoking after initiation of diabetes treatment was negatively associated with remission in women. In those performing regular exercise, interaction analysis reported a significantly higher correlation in men compared to that in women (*P* for interaction < 0.001).

DISCUSSION

This study was a nationwide population-based study to investigate the associations between lifestyle changes and remission of newly diagnosed type 2 diabetes. A total of 138,211 patients diagnosed with T2DM from 2009 to 2012 were analyzed, and 8,192 (6.3%) reported remission during the follow-up period up to 2017. We investigated the drinking, smoking, and regular exercise statuses of patients before and after they started taking diabetes medication, and odds ratios of remission in logistic regression on remission were used to evaluate the associations. Consistent smoking and drinking showed negative associations with remission (OR, 0.72; 95% CI, 0.67–0.77 and OR, 0.90; 95% CI, 0.84–0.95, respectively), and initiation of regular exercise presented a positive association with remission (OR, 1.54; 95% CI, 0.46–1.63). Abstinence from alcohol increased the likelihood of remission in the male population (OR, 1.20; 95% CI, 1.10–1.32). The association with smoking history or smoking cessation was not clear, but new smoking behavior interfered with remission in women (OR, 0.48; 95% CI, 0.28–0.81).

The incidence rate of remission was 23.9 per 1,000 person-years in the new-onset T2DM group of this study, which was observed for approximately five years of follow-up after start of the initial treatment. This is similar to a Japanese study that found the incidence rate of remission in patients with early type 2 diabetes less than one year after onset to be approximately 20 per 1,000 person-years.[11] However, the incidence of remission differed significantly depending on the study population and definition.[12,13] The incidence of

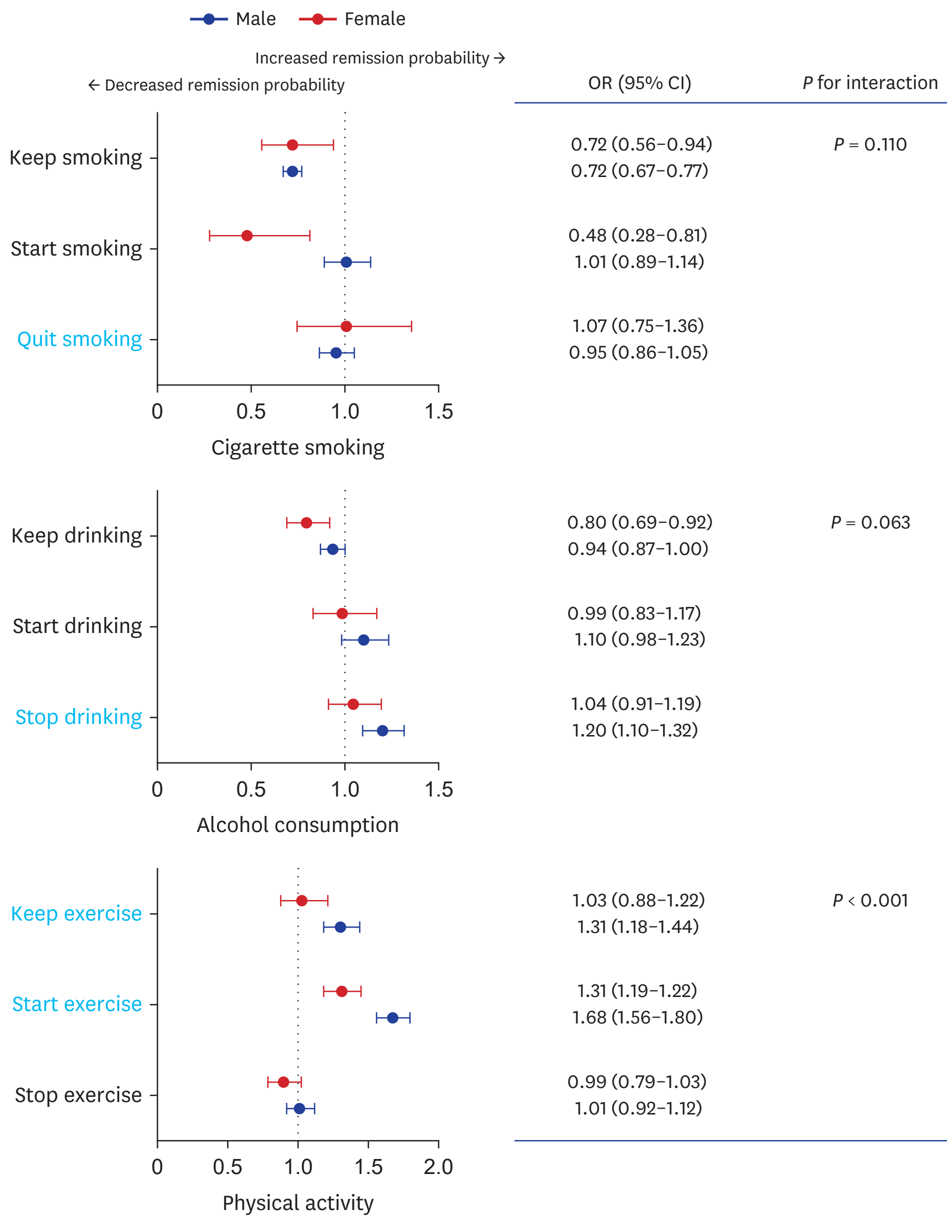

Fig. 2. Sex differences in the association between life style changes and remission in new-onset type 2 diabetes. References in each multivariate logistic regression analysis were the groups not consistently exposed to lifestyle factors before and after starting diabetes treatment. The results of the female subgroup are displayed in red, and the results of the male subgroup are displayed in blue. The described *P* values were calculated by interaction analyses according to sex.
OR = odds ratio, CI = confidence interval.

remission in this study needs to be interpreted considering that the study population consisted of new-onset diabetes patients. In addition, baseline characteristics of remission and non-remission groups were analyzed through health check-up data before starting diabetes treatment. No obvious differences were observed in the rates of smoking, drinking, and regular exercise in the remission and non-remission groups. However, the FBG level and the rate of use of combined oral hypoglycemic agents were higher in the remission group than in the non-remission group. Therefore, remission is thought to be related to diabetes severity at the time of diagnosis.

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Smoking can cause a wide range of disabilities across all organs and systems in the human body. Continued smoking may increase insulin resistance that worsens glycemic control in patients with diabetes.[14] However, conflicting results have been reported regarding smoking cessation.[15] Smoking cessation may increase risk of diabetes, and could negatively impact glycemic control in patients with diabetes.[16,17] Smoking cessation can generally cause weight gain, with an average gain of 4–5 kg at one year after quitting.[18] Therefore, the results of previous studies showing that smoking cessation worsens glycemic control in the short term are thought to be primarily mediated by weight gain. In a study stratifying weight change, no increased risk of diabetes was identified in short-term smokers or those without weight gain.[7] Although the association with remission was reported to be neutral in the population that quit smoking after diabetes diagnosis in this study, a significant inverse association between continued smoking and remission was confirmed (**Table 2**). In particular, if a person starts smoking after being diagnosed with diabetes, the chance of remission decreases significantly to less than half in the female population (OR, 0.48; 95% CI, 0.28–0.81) (**Fig. 2**). Women are generally at greater risk from smoking, which has been reported as causing cardiovascular disease, lung dysfunction, and cancer.[19] Based on the results of this study, smoking can contribute to the worsening of diabetes, and it is assumed that women are more vulnerable than men to this worsening of glycemic control. In general, women are reported to be more influenced by psychosocial factors for smoking behavior,[20] so emotional factors can have a negative impact on glycemic control. In addition, epigenetic changes that are biologically induced by smoking are reported to be more profound in women.[21]

Alcohol is commonly associated with weight gain and hyperglycemia, but individual susceptibility to alcohol can vary greatly.[22] Therefore, even small amounts of alcohol consumption were categorized as drinking in this study. Our findings showed that abstinence from alcohol may generally help alleviate diabetes. On the other hand, continuous drinking was confirmed to lower the likelihood of remission (**Table 2**). Drinking habits may be commonly associated with weight gain.[23] However, a previous cross-sectional study in Koreans reported that drinking behavior may actually lower serum glucose levels.[24] Additionally, studies have shown that moderate alcohol consumption lowers the risk of diabetes.[25] Drinking behavior is generally associated with social gathering and can be accompanied by physical activity and emotional support. However, the protective effect of alcohol consumption does not apply to heavy drinkers.[26] In the subgroup analysis, drinking cessation showed a significant association with diabetes remission only in the male population (**Fig. 2**). We believe this could be explained by the larger proportion of heavy drinkers in men.

Maintaining physical activity was significantly associated with remission, as was starting exercise after being diagnosed with diabetes (**Table 2**). Among new-onset T2DM patients, it has been reported that cardiovascular mortality could be reduced by 30% in those who continue to exercise, and it is reduced by about 20% in those starting regular exercise.[27] Exercise can lower glycated hemoglobin by 0.7% in diabetic patients, unrelated to body weight change.[8] In our study, starting exercise increased the likelihood of remission by nearly 50%, which was higher than the 20% effect of continued exercise. In terms of remission, it is possible that people who started exercise experienced weight loss compared to the continuing exercisers, producing a higher remission rate.[28] The association between exercise and remission was significantly higher in men (P for interaction < 0.001; **Fig. 2**). This supports the idea that sensitivity to exercise is higher in men than in women.[29] Additionally, men have a higher muscle mass than women.[30,31] Skeletal muscle is insulin-sensitive and responsible for glucose uptake, and low muscle mass is likely associated with lower glucose processing capacity.[32] In terms of exercise type preferences, men tend to choose muscle-strength training rather than flexibility exercises compared to women, which is beneficial for body composition.[33]

Considering that only a few previous studies set remission as a primary outcome, our study is valuable as rare evidence that remission of diabetes can be promoted by lifestyle change. In addition, it is very unlikely that researcher bias was involved, because the data used were not collected for research purposes. However, this study had several limitations. First, it did not examine nutritional aspects and weight changes, which are thought to be highly related to remission of diabetes.[34,35] Second, the retrospective design of this study makes it difficult to confirm causal relationships compared to studies that set lifestyle change as an intervention. Last, this study was conducted only with Koreans, and other races and/or ethnicities were not considered.

In summary, this study investigated the relationships of smoking, drinking, and regular exercise (representative lifestyle factors) with remission of early diabetes. In clinical practice, improvements in general lifestyle habits can be easily overlooked due to other significant confounders such as difficulty in assessing an individual's mixed existing lifestyle, choice to use multiple medications, and weight changes. Through this study, we illustrate the impact of lifestyle management on remission in patients with new-onset T2DM.

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