Dose-Dependent Effect of Smoking on Risk of Diabetes Remains after Smoking Cessation: A Nationwide Population-Based Cohort Study in Korea

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Background: This study aimed to evaluate the dose-dependent effects of smoking on risk of diabetes among those quitting smoking.

Methods: We analyzed clinical data from a total of 5,198,792 individuals age 20 years or older who received health care check-up arranged by the national insurance program of Korea between 2009 and 2016 using the Korean National Health Insurance Service database. Cumulative smoking was estimated by pack-years. Smokers were classified into four categories according to the amount of smoking: light smokers (0.025 to 5 smoking pack-years), medium smokers (5 to 14 smoking pack-years), heavy smokers (14 to 26 smoking pack-years), and extreme smokers (more than 26 smoking pack-years).

Results: During the study period, 164,335 individuals (3.2% of the total population) developed diabetes. Compared to sustained smokers, the risk of diabetes was significantly reduced in both quitters (hazard ratio [HR], 0.858; 95% confidence interval [CI], 0.838 to 0.878) and nonsmokers (HR, 0.616; 95% CI, 0.606 to 0.625) after adjustment for multiple risk factors. The risk of diabetes gradually increased with amount of smoking in both quitters and current smokers. The risk of diabetes in heavy (HR, 1.119; 95% CI, 1.057 to 1.185) and extreme smokers (HR, 1.348; 95% CI, 1.275 to 1.425) among quitters was much higher compared to light smokers among current smokers.

Conclusion: Smoking cessation was effective in reducing the risk of diabetes regardless of weight change. However, there was a potential dose-dependent association between smoking amount and the development of diabetes. Diabetes risk still remained in heavy and extreme smokers even after smoking cessation.

Keywords: Diabetes; Risk factors; Smoking; Smoking cessation; Weight
INTRODUCTION

Smoking is well established as a causal risk factor for major chronic diseases and lower life expectancy [1]. Although many environmental and genetic factors are known to be the cause of diabetes [2], active smoking has also been recognized as a risk factor for type 2 diabetes mellitus (T2DM) [3]. The hypothesis that smoking increases the risk for incident T2DM is plausible due to the general inflammation caused by smoking, along with increased insulin resistance and greater abdominal obesity in smokers [4]. Although smoking cessation is known to significantly reduce the risk of chronic disease in both Asian and Western populations, subsequent weight gain has been recognized as one of the minor disadvantages and concerns among smokers who may attempt to quit smoking. T2DM is strongly related to weight gain in adult life and accumulation of excess fat within major organs [5,6].

Recent studies suggest that weight gain after smoking cessation might cause a temporary increase in the risk of T2DM. However, it is not clear whether the severity of weight gain after quitting smoking is similar between Asians and non-Asians [7], and only a few studies have addressed the issue of weight gain following smoking cessation in an Asian population [8,9]. Furthermore, there is not enough evidence to evaluate correlations between the amount of smoking and risk of diabetes after smoking cessation. With longitudinal, repeated assessments of smoking status and body weight in a large cohort study of men and women, the current investigation aimed to evaluate the risk trajectories of diabetes among those who reported quitting smoking, according to body weight changes after smoking cessation. We also evaluated the association between risk of diabetes and cumulative smoking in pack-years as measures of smoking exposure after quitting smoking.

METHODS

Study population and source of data

We evaluated data from the records of 5,198,792 Korean residents aged 20 years or older who had undergone one biennial medical evaluation provided by the National Health Insurance Service (NHIS) between January 1, 2005 and December 31, 2016. Enrollees in the National Health Insurance Corporation are recommended to undergo standardized medical examination every 2 years, so we used 2-year windows to define screening program participation. The Health Insurance Review and Assessment database includes data on approximately 7.0% of the Korean population’s health insurance claims; details of the NHIS database have been described elsewhere [10]. The database is open to any researchers whose study protocols are approved by the official review committee.

The median follow-up period was 4.87 years. Medical examinations in 2009–2010 and 2015–2016 included measurements of height, weight, blood pressure, and laboratory tests such as fasting glucose and cholesterol, serum creatinine, liver enzymes, and urinalysis (Supplementary Fig. 1). Past medical history and health-related behaviors such as lifestyle factors and smoking, alcohol intake, and physical activity were collected using standardized self-reporting questionnaires.

Quality control procedures for laboratory tests were performed in accordance with the Korean Association of Laboratory Quality Control. These databases and the aforementioned nationwide medical records were combined and analyzed to construct a cohort for investigating health problems, after the NHIS approved the use of its database for the research (research number NHIS-2019-1-151). Our study protocol was approved by the official review committee and the Institutional Review Board of the Korea National Institute for Bioethics Policy (P01-201603-21-005) and informed consent was waived because of the anonymous nature of the data. This study was carried out according to the ethical principles of the Declaration of Helsinki.

Definition

The primary outcome was development of diabetes between 1 January 2009 and 31 December 2016 in each participant. We excluded people previously diagnosed diabetes. For diagnosis of diabetes, we additionally used anti-diabetic drug descriptions with codes for insulins, sulfonylureas, metformin, meglitindases, thiazolidinediones, dipeptidyl peptidase-4 inhibitors, and α-glucosidase inhibitors along with the 10th International Statistical Classification of Diseases (ICD-10) codes E11–14 [11]. Dyslipidemia was defined as total cholesterol level ≥240 mg/dL (≥6.21 mmol/L) or presence of one or more claims per year for anti-hyperlipidemic medications with ICD-10 code E78. The diagnosis of hypertension was confirmed using laboratory data (systolic blood pressure ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg) or ICD-10 code (I10–15) with a claim for anti-hypertensive medication.

Data on socioeconomic characteristics such as income level, and lifestyle factors, including smoking, alcohol drinking, and
exercise, were obtained using standardized questionnaires. Low income level was defined as being in the lower one-fifth of the whole population. Heavy alcohol drinking was defined as drinking equal to or more than 30 g/day. Exercise (regular) was defined as mid-term exercise ≥5 days or vigorous exercise ≥3 days in a week. At each health check-up period, the participants responded to a self-reported health survey questionnaire and participated in a physical examination.

Assessment of changes in smoking behavior and weight
Participants in the NHIS biennial health check-up were grouped into current smokers, quitters, and nonsmokers based on responses to the self-reported survey between baseline at 2005–2006 and health check-up from 2009–2010. We identified participants who had reported that they were smokers in 2005–2006 but were not smokers in 2009–2010 as quitters. Current smokers and quitters were further classified by smoking amount. Cumulative smoking was measured using pack-years, where 1 pack-year equaled smoking 20 cigarettes smoked per day during 1 year. Smokers were classified according to current smoking habits into four categories: light smokers (0.025 to 5 smoking pack-years); medium smokers (5 to 14 smoking pack-years); heavy smokers (14 to 26 smoking pack-years); and extreme smokers (more than 26 smoking pack-years) [12].

Weight change was calculated as the difference in body weight between 2009–2010 and 2015–2016, corresponding to the period between the first and last health check-up. Based on the study performed by Corrada et al. [13], we defined the weight stable group as weight change within 5%, and we categorized weight change into three groups by 5% increase or decrease as follows: weight loss ≥5%; weight change <5%; weight gain ≥5%.

Statistical analysis
The general characteristics of subjects are expressed as mean±standard deviation for continuous variables and number (percentage) for categorical variables, according to smoking status. Continuous variables were evaluated using analysis of variance (ANOVA), and categorical variables were evaluated using chi-square tests.

The hazard ratios (HRs) using the Cox proportional hazards model with a 95% confidence interval (CI) for risk of diabetes according to smoking status and smoking amount in packs per day were analyzed by multivariable Cox proportional hazard models, after adjusting for age and sex in model 1; age, sex, alcohol drinking, income, exercise, body mass index (BMI), hypertension, and dyslipidemia in model 2; and age, sex, alcohol drinking, income, exercise, BMI, hypertension, dyslipidemia, and weight change in model 3. Subgroup analyses were performed by sex, age group, hypertension, dyslipidemia, regular exercise, weight change according to smoking status and amount. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA), and P<0.05 for two tailed tests was considered statistically significant.

RESULTS
Baseline characteristics
Participant baseline characteristics are shown in Table 1. The participants were divided based on smoking status as follows: nonsmokers, 3,734,732 (71.8%); quitters, 252,661 (4.9%); and current smokers, 1,211,399 (23.3%). The proportion of men was higher among current smokers and quitters compared with nonsmokers. The risk of diabetes was slightly increased in quitters and current smokers compared with nonsmokers. Quitters and current smokers had a lower risk of hypertension and dyslipidemia, higher waist circumference, higher fasting glucose level, and higher systolic blood pressure compared with nonsmokers. The prevalence of hypertension and dyslipidemia, BMI, waist circumference, and fasting glucose level were all higher among quitters than among current smokers.

Risk of diabetes according to baseline smoking status and intensity of smoking
After a median follow-up period of 4.87 years, 164,335 individuals (3.2% of the total population) developed diabetes. Diabetes incidence over time according to smoking status is shown in Table 2. Current smokers served as the reference, and the age, sex-adjusted HR (95% CI) showed that the risk of diabetes was lower in quitters and nonsmokers (HR, 0.922; 95% CI, 0.901 to 0.943) (HR, 0.619; 95% CI, 0.61 to 0.628). The multivariate models that considered age, sex, alcohol, income, exercise, BMI, hypertension, dyslipidemia, and weight change also showed a similarly lower risk of diabetes for quitters and nonsmokers (HR, 0.858; 95% CI, 0.838 to 0.878) (HR, 0.616; 95% CI, 0.606 to 0.625). Nonsmokers had the lowest risk of diabetes according to smoking status among all group (Table 2).

Fig. 1 presents the risk of diabetes based on cumulative smoking by packs per year (Supplementary Table 1). The risk
Table 1. Participant baseline characteristics according to smoking status

| Characteristic                                      | Nonsmokers (n=3,734,732) | Quitters (n=252,661) | Current smoker (n=1,211,399) | P value |
|-----------------------------------------------------|---------------------------|----------------------|-----------------------------|---------|
| **Sex**                                             |                           |                      |                             | <0.0001|
| Male                                                | 971,103 (26)              | 245,020 (96.98)      | 1,179,838 (97.39)           |         |
| Female                                              | 2,763,629 (74)            | 7,641 (3.02)         | 31,561 (2.61)               |         |
| **Amount of smoking**                               |                           |                      |                             | <0.0001|
| Mean±SD                                             | -                         | 17.07±14.72          | 17.19±12.49                 |         |
| Light smoker (0.025–5 smoking pack-years)           | -                         | 35.31±14.98          | 100.46±8.29                 |         |
| Medium smoker (5–14 smoking pack-years)             | -                         | 90.036 (35.64)       | 455.872 (37.63)             |         |
| Heavy smokers (14–26 smoking pack-years)            | -                         | 76.669 (30.34)       | 427.226 (35.27)             |         |
| Extreme smokers (more than 26 smoking pack-years)   | -                         | 50.642 (20.04)       | 227.838 (18.81)             |         |
| **Age group, yr**                                   |                           |                      |                             | <0.0001|
| 20–39                                               | 856,729 (22.94)           | 85,642 (33.9)        | 505.637 (41.74)             |         |
| 40–64                                               | 2,261,763 (60.56)         | 144,964 (57.37)      | 626.837 (51.74)             |         |
| ≥65                                                 | 616,240 (16.5)            | 22,055 (8.73)        | 78.925 (6.52)               |         |
| **Alcohol drinking (heavy)**                        | 70,792 (1.9)              | 35,165 (13.92)       | 205.777 (16.99)             | <0.0001|
| **Income (low)**                                    | 632,423 (16.93)           | 27,696 (10.96)       | 139,403 (11.51)             | <0.0001|
| **Exercise (regular)**                              | 695,790 (18.63)           | 63,060 (24.96)       | 212,562 (17.55)             | <0.0001|
| **Hypertension prevalence**                         | 939,834 (25.16)           | 64,417 (25.5)        | 246,788 (20.37)             | <0.0001|
| **Dyslipidemia prevalence**                         | 723,005 (19.36)           | 49,047 (19.41)       | 183,332 (15.13)             | <0.0001|
| **Weight, kg**                                      | 59.72±10.06               | 70.86±10.29          | 69.6±10.91                  | <0.0001|
| **BMI, kg/m²**                                      | 23.39±3.08                | 24.44±2.9            | 23.93±3.1                   | <0.0001|
| **Waist circumference, cm**                         | 78.02±8.75                | 84.18±7.48           | 82.9±7.77                   | <0.0001|
| **Fasting glucose level, mg/dL**                    | 92.24±10.88               | 94.46±11.51          | 93.27±11.72                 | <0.0001|
| **Systolic blood pressure, mm Hg**                  | 120.91±15.07              | 124.26±13.47         | 123.32±13.44                | <0.0001|
| **Diastolic blood pressure, mm Hg**                 | 75.16±9.88                | 78.08±9.47           | 77.62±9.44                  | <0.0001|
| **Total cholesterol level, mg/dL**                  | 197±36.25                 | 199.19±35.92         | 196.8±35.41                 | <0.0001|

Values are presented as number (%) or mean±standard deviation.

SD, standard deviation; BMI, body mass index.

Table 2. Risk of diabetes according to baseline smoking status by sex and age group

| Smoking status          | No. of subjects | Diabetes | HR (95% CI) | Model | Model 2 | Model 3 |
|-------------------------|-----------------|----------|-------------|-------|---------|---------|
| Nonsmokers              | 3,734,732       | 114,250  | 0.619 (0.61–0.628) | 0.616 (0.606–0.625) | 0.616 (0.606–0.625) |
| Quitters                | 252,661         | 8,826    | 0.922 (0.901–0.943) | 0.828 (0.809–0.847) | 0.858 (0.838–0.878) |
| Current smokers         | 1,211,399       | 41,259   | 1 (reference) | 1 (reference) | 1 (reference) |

Model 1: adjusted for age and sex; Model 2: adjusted for age, sex, alcohol drinking (heavy), income (low), exercise (regular), body mass index, hypertension, and dyslipidemia; Model 3: adjusted for age, sex, alcohol drinking (heavy), income (low), exercise (regular), body mass index, hypertension, dyslipidemia, and weight change.

HR, hazard ratio; CI, confidence interval.
Smoking cessation and diabetes

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In subgroup analyses, the result of smoking with respect to the risk of diabetes tended to be similar across subgroups. Weight gain did not modify the associations between smoking status and risk of T2DM (Fig. 2, Supplementary Table 2). The overall effects of cumulative smoking on risk estimates for diabetes were also consistent across the categories for subgroup analyses (Supplementary Table 3).

DISCUSSION

We found that smoking cessation was associated with a reduced risk of diabetes regardless of post-cessation weight changes, based on a nationally representative database linked to clinical records of more than 5,000,000 Koreans. Further, we identified dose-dependent associations between cumulative smoking by pack-years and the risk of diabetes.

An association between smoking cessation and the risk of T2DM has been controversial. Previous studies showed increased risk of diabetes after smoking cessation, suggesting that weight gain after quitting smoking might affect the development of diabetes. Considerable weight gain may occur in quitters after smoking cessation, probably due to increased appetite and reduced energy expenditure [14]. It was reported that adults who quit smoking experienced relatively more adverse changes in their metabolic profile and an increased risk for incident diabetes, peaking within 3 years of quitting, but still observable 6 years after quitting [15]. Another study also observed that the peak of risk of T2DM was observed among quitters with the most weight gain at 5 to 7 years of cessation [16]. However, our study showed that those who sustained smoking cessation over 6 years did not increase the risk of diabetes. Although weight gain is a well-known risk factor for diabetes, our data also showed that subsequent weight gain did not attenuate the apparent benefits of smoking cessation on diabetes within 6 years. Consistent with our data, Jee et al. [17] also found that the risks for diabetes were higher in current smokers than in quitters in Koreans. We observed a beneficial role for smoking cessation in potentially reducing the disease burden of diabetes despite the subsequent weight change. The discrepancies resulting from such studies may be due to different participant characteristics and ethnicities, sample size, or measurement methods.

When smoking exposure was measured in pack-years, both current smokers and quitters carried an increased risk of diabetes based on the amount smoked after adjustment for other risk factors, including weight change. Although quitters still had a lower risk compared to current smokers, the risk of diabetes in heavy and extreme smokers among quitters was much higher compared to light smokers among current smokers. It is of note that the harmful effect of smoking on the development of diabetes seems to be dependent on the amount of smoking and remained in quitters with >14 pack-years even after smoking cessation. Only a few studies have examined the effect of cumulative smoking on the risk of diabetes [15-17]. Previous studies usually focused on a dose-response relationship between smoking amount in current smokers and diabetes risk. Our study expanded on previous findings by showing

| Subgroup       | Smoking status | No. of events/No. of participants | HR for diabetes (95% CI) |
|----------------|----------------|----------------------------------|-------------------------|
| Nonsmokers     | Light smoker   | 705/35314                        | 0.807 (0.772,0.844)     |
|                | Medium smoker  | 2091/90036                       | 0.913 (0.838,0.994)     |
|                | Heavy smoker   | 2821/76669                       | 0.958 (0.901,1.018)     |
|                | Extreme smoker | 3209/50642                       | 1.119 (1.057,1.185)     |
| Quitters       | Light smoker   | 2050/100463                      | 1.348 (1.275,1.425)     |
|                | Medium smoker  | 9718/455872                      | 1.059 (1.01,1.111)      |
|                | Heavy smoker   | 15445/427226                     | 1.333 (1.273,1.396)     |
|                | Extreme smoker | 14046/227838                     | 1.6 (1.527,1.677)       |

Fig. 1. Risk of diabetes according to intensity of smoking in packs per day. HR, hazard ratio; CI, confidence interval.
a dose-dependent effect of smoking on diabetes risk even after smoking cessation.

The exact mechanism by which smoking increases the risk of diabetes and deteriorates glucose homeostasis has not been fully elucidated, but a few biological mechanisms associated with post-cessation changes in health status and diabetes may explain our study findings. Cigarette smoking can lead to insulin resistance [18]. Smoking reduces insulin-mediated glucose uptake by 10% to 40% in men who smoke compared with non-smoking men [19]. Additionally, several studies have shown that current cigarette smokers have lower β-cell function than never smokers, suggesting that smoking may impair measures of β-cell function [20,21].

This study had some limitations. First, we only analyzed one

| Subgroup | Smoking status | No. of events/No. of participants | HR (95% CI) | P-Interaction |
|----------|----------------|----------------------------------|-------------|---------------|
| Sex      |                |                                  |             |               |
| Male     | Nonsmokers     | 27806/971103                     | 0.593 (0.584, 0.603) | 0.4831 |
|          | Quitters       | 8578/245020                      | 0.849 (0.829, 0.869) |          |
|          | Current smokers| 39831/1179838                     | 1 (Ref.)     |          |
| Female   | Nonsmokers     | 86444/2763629                     | 0.599 (0.569, 0.632) |          |
|          | Quitters       | 24876/41                          | 0.839 (0.733, 0.96) |          |
|          | Current smokers| 1428/3156                         | 1 (Ref.)     |          |
| Age group |                |                                  |             |               |
| Age 20-39| Nonsmokers     | 5401/856729                      | 0.724 (0.694, 0.756) | < 0.0001 |
|          | Quitters       | 1071/85642                        | 0.806 (0.756, 0.86) |          |
|          | Current smokers| 7596/505637                       | 1 (Ref.)     |          |
| Age 40-64| Nonsmokers     | 6869/12261763                     | 0.582 (0.571, 0.594) |          |
|          | Quitters       | 6112/144964                       | 0.832 (0.81, 0.856) |          |
|          | Current smokers| 27717/626837                      | 1 (Ref.)     |          |
| Age 65-  | Nonsmokers     | 40158/616240                      | 0.671 (0.65, 0.693) |          |
|          | Quitters       | 1643/22055                        | 0.902 (0.854, 0.952) |          |
|          | Current smokers| 5946/78925                        | 1 (Ref.)     |          |
| Hypertension |              |                                  |             |               |
| No       | Nonsmokers     | 54736/2794898                     | 0.607 (0.595, 0.62) | < 0.0001 |
|          | Quitters       | 4709/18244                        | 0.862 (0.835, 0.889) |          |
|          | Current smokers| 24465/96461                       | 1 (Ref.)     |          |
| Yes      | Nonsmokers     | 59514/939834                      | 0.646 (0.632, 0.661) |          |
|          | Quitters       | 4117/64417                        | 0.851 (0.823, 0.881) |          |
|          | Current smokers| 16794/246788                      | 1 (Ref.)     |          |
| Dyslipidemia |              |                                  |             |               |
| No       | Nonsmokers     | 69689/3011727                     | 0.606 (0.595, 0.617) | 0.007    |
|          | Quitters       | 5750/203614                       | 0.856 (0.832, 0.881) |          |
|          | Current smokers| 29178/1028067                     | 1 (Ref.)     |          |
| Yes      | Nonsmokers     | 44561/723005                      | 0.638 (0.621, 0.657) |          |
|          | Quitters       | 3076/49047                        | 0.866 (0.832, 0.901) |          |
|          | Current smokers| 12081/183332                      | 1 (Ref.)     |          |
| Regular exercise |             |                                  |             |               |
| No       | Nonsmokers     | 91887/3038942                     | 0.621 (0.61, 0.632) | 0.003    |
|          | Quitters       | 6604/189601                       | 0.873 (0.85, 0.897) |          |
|          | Current smokers| 33448/999837                      | 1 (Ref.)     |          |
| Yes      | Nonsmokers     | 22363/695790                      | 0.598 (0.578, 0.618) |          |
|          | Quitters       | 2222/63060                        | 0.816 (0.778, 0.856) |          |
|          | Current smokers| 7811/212562                       | 1 (Ref.)     |          |
| Weight change |              |                                  |             |               |
| < -5%    | Nonsmokers     | 16298/516553                      | 0.603 (0.578, 0.629) | < 0.0001 |
|          | Quitters       | 692/19045                         | 0.843 (0.779, 0.913) |          |
|          | Current smokers| 5140/132657                       | 1 (Ref.)     |          |
| -5 ~ 5%  | Nonsmokers     | 78385/2499048                     | 0.608 (0.597, 0.619) |          |
|          | Quitters       | 5338/147147                       | 0.832 (0.808, 0.857) |          |
|          | Current smokers| 28673/810016                      | 1 (Ref.)     |          |
| ≥ 5%     | Nonsmokers     | 19567/719131                      | 0.661 (0.638, 0.686) |          |
|          | Quitters       | 2796/86469                        | 0.912 (0.873, 0.953) |          |
|          | Current smokers| 7446/268726                       | 1 (Ref.)     |          |

Fig. 2. Smoking status and risk of diabetes by subgroup. HR, hazard ratio; CI, confidence interval.
time smoking cessation and could not confirm the exact starting point and duration of smoking cessation. Quitters are likely to relapse [18], and their subsequent disease risk may vary according to the duration of cessation and cumulative smoking. Second, there was a possibility of bias in the confirmation of characteristics through self-questionnaires and diagnosis of outcome through claim of insurance. Also, the smoking amount assessed by self questionnaries, and some smoking amount could have been missed depend on memory. Third, we were not able to examine the exact reason for smoking cessation among quitters. There is a possibility that those who decided to quit smoking had already experienced worsening health conditions due to smoking, which may have affected study outcomes. Fourth, we also recognized the heterogeneity of sex ratio. However, according to other studies, the portion of smoker was higher in men [22]. Thus, our study also reflects this trend. Last, our study only included Asians (Korean) and results may not be generalizable to other countries or races.

Despite limitations, our results provide important evidence of the beneficial role of smoking cessation in potentially reducing the disease burden of diabetes, despite subsequent weight change. Our findings also suggest that there was a dose-dependent effect of smoking on diabetes risk, and this risk remained even after smoking cessation. Smoking should be recognized as a modifiable risk factor in diabetes prevention or screening strategies.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0061.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: S.E.P, M.H.S., E.J.R., W.Y.L.
Acquisition, analysis, or interpretation of data: K.D.H., J.H.J.
Drafting the work or revising: S.E.P, M.H.S., J.H.C., H.K., Y.H.K., Y.G.P., E.J.R., W.Y.L.
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