Repeatedly Measured Smoking Status and Eight-year Risk of Diabetes Mellitus in Korean Men: Korea Medical Insurance Corporation Study

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ABSTRACT

Objective: To investigate the relationship between smoking status and the risk for developing impaired fasting glucose and diabetes mellitus; and to assess the effect of smoking cessation on the risk of developing impaired fasting glucose and diabetes mellitus.

Design: An eight-year prospective study with baseline examinations in 1990 and 1992, and follow-up examinations in 1998 and 2000.

Setting: Government and private school employees in Korea

Participants: 27,635 men aged 35 to 44 years with normal fasting serum glucose and no diseases at baseline were selected. Baseline levels of fasting serum glucose index were the mean of the 1990 and 1992 measurements, and the final levels were the mean of the 1998 and 2000 measurements. The participants were classified as 5,701 never smokers, 7,477 ex-smokers and 14,457 sustained smokers, using repeatedly measured smoking status.

Main results: After an eight-year period, 21.6% and 4.2% men developed impaired fasting glucose and diabetes of never smokers, 20.4% and 3.6% of ex-smokers, and 22.8% and 4.9% of sustained smokers, respectively. Compared with never smokers, the fully adjusted relative risk of ex-smokers and sustained smokers for impaired fasting glucose was 1.09 (95% CI, 0.98 to 1.21) and 1.22 (1.11 to 1.34). The corresponding risk ratio for diabetes was 1.22 (0.96 to 1.55) and 1.60 (1.29 to 1.97), respectively. Dose-response relationships were observed between smoking duration and the risk of developing impaired fasting glucose and diabetes. For ex-smokers who quit smoking

prior to 1992, a slight risk comparison to never smokers was discovered; both subjects sustained impaired fasting glucose (RR 1.02) and diabetes mellitus (RR 0.95). Subjects who quit smoking between 1992 and 1993 showed little higher risk compared with never smokers (1.09 and 1.44, respectively). However, subjects who quit smoking between 1994 and 1995 showed a significantly higher risk for impaired fasting glucose (1.35) and diabetes mellitus (2.13)

Conclusion: This study indicates that smoking is associated with increased risk for development impaired fasting glucose and diabetes mellitus. Thus, the recommendation that the prevention of cigarette smoking may aid in the prevention of diabetes mellitus is supported.

Keywords: Smoking cessation, impaired fasting glucose, diabetes mellitus

1. INTRODUCTION

Diabetes mellitus, long considered a disease of minor significance to world health, is now becoming one of the main threats to human health in the 21st century (*Zimmet, 2000*). This condition is escalating in epidemic proportions in both developed and developing nations, with the global population predicted to rise from 118 million in 1995 to 220 million in 2010 (*Younis et al, 2004; Zimmet et al, 2001; King et al, 1998; Amos et al, 1997*).

Diabetes mellitus undermines health, shortens life expectancy, and causes enormous suffering, disability, and economic costs. Especially, individuals with type II diabetes mellitus are at a significantly higher risk for coronary heart disease, peripheral vascular disease and stroke, as well as microvascular complications affecting various organs such as the eyes, kidneys and nerves (*Nakanishi et al, 2000; Manson et al, 1991; Humphrey et al, 1989; Nathan et al, 1986*). The economic impact of diabetes is substantial in developed countries, the treatment of diabetes and its associated complications accounts for 10% or more of the total health care budget (*Younis et al, 2004; American Diabetes Association, 1998*).

However, much of the burden caused by diabetes could be avoided and controlled if there existed a systematic application of lifestyle modification. Epidemiologic studies show an inverse relationship between development of diabetes mellitus and moderate exercise. Interventions leading to weight loss or prevention of weight gain, reduction in dietary fat, increase in complex carbohydrates, and increased exercise are

lifestyle changes that reduce insulin resistance and have the potential to prevent type II diabetes mellitus (*LeRoith et al, 2000*). Two recent trials have shown consistent results with previous studies that a >50% reduction in progression of impaired glucose tolerance to type II diabetes mellitus can be achieved by lifestyle measures with moderate exercise and diet (*Tuomilehto et al, 2001; Younis et al, 2004; Diabetes Prevention Program Research Group, 2002*). Counseling by medical caregivers can profoundly increase a smokers' motivation to stop using tobacco.

Diabetes mellitus is a chronic illness that can occur at any age throughout one's lifespan. The mortality rates of diabetes mellitus are increasing among middle-aged individuals.

Cigarette smoking is well established as a causal factor in coronary heart disease and stroke. However, it was not a well-documented risk factor for type II diabetes, although diabetes and cardiovascular disease have many causal factors in common.

Recent cohort studies suggest that smoking also may be an independent and modifiable risk factor for the development of type II diabetes or impaired fasting glucose in the general populations. Among participants in the American Cancer Society Cancer Prevention Study cohort, men and women who smoked ≥ 2 packs per day at baseline had a 45% and 74% higher incidence rate of diabetes mellitus respectively, than that of men and women who had never smoked. A similar association between smoking and type II diabetes was observed among US male physicians, other health professionals, and middle-aged men in Britain and Japan. (*Nakanishi et al, 2000; Will et al, 2001; Wannamethee et al, 2001; Sairenchi et al,*

2004; Uchimoto et al, 1999; Ko et al, 2001; Rimm et al, 1999, Manson et al, 2000). This may be mediated via direct metabolic effects solely, or in combination with a metabolically unfavorable lifestyle (*Bjorn, 2003*).

But these studies did not consider the change of smoking status nor show consistent results for the effects of smoking cessation in ex-smokers. Some studies have been conducted during the follow-up after a smoking status change, including long-term observational studies and intervention studies (*Wilsgaard and Arnesen, 2004; Aveyard et al, 2001; Pederson and Lefcoe, 1986; Prochaska et al, 1985*). Uchimoto and colleagues (1999) suggested that repeated measurements of smoking status were needed in future studies, to manifest the relationship between smoking status and glucose level change. In regards to smoking cessation, the studies are shown two contrary results. Some of them reported that quitting smoking reduced the incidence of diabetes as compared to nonsmokers. Others reported that quit smoking substantially lower risk for diabetes mellitus than current smokers. However, this study did not consider the repeated measurement of smoking status finally. Will et al (2001) suggested further studies to show evidence of a dose-respondent association between cigarette smoking and diabetes as well as evidence that removal of the exposure diminishes the risk of developing diabetes.

It is important to explore the relationship between smoking status change, which was measured repeatedly during the follow-up period, and the risk of impaired fasting glucose and diabetes mellitus in middle-aged men.

2. OBJECTIVE

The purpose of this study is to explore the relationship between smoking status and the risk for developing impaired fasting glucose (IFG) and diabetes mellitus (DM), according to the smoking status which was measured repeatedly during the follow-up period.

Specifically,

1) to investigate the relationship between smoking and the risk for developing IFG and DM and

2) to assess the effect of smoking cessation on the risk for developing IFG and DM.

3. METHODS

Study Population

The study population was selected from the Korea Medical Insurance Corporation study (KMIC) cohort. The KMIC provided health insurance to government and private school employees and their dependents. In 1990, the corporation insured 118,213,594 workers and 3,389,767 dependents, equaling approximately 11% of the total Korean population. All insured workers are required to take a bi-annual health examination. The KMIC study cohort consists of 115,200 men and 67,932 women aged 35-59 who underwent health examinations in 1990 (95% participant rate) and 1992 (94% participant rate). The cohort was composed of a 25% systematic random sample of male workers and all of female workers, drawn from insured members ordered by national identification numbers (Kim et al, 2004). Of the 115,200 men, 108,464 had completed examination at the first two examinations (1990 and 1992). In this study, the subjects were confined to men, because the smoking rate was too low among the women.

For the analyses of this study, subjects based on the inclusion criteria outlined in Figure 1 were included.

Those have data on fasting serum glucose levels in baseline (1990 and 1992) and follow-up (1998 and 2000). Subjects were confined to male cohort members aged 35-44 years (54,237 men), because of the follow-up rate was not fully sufficient for those

over 45 years of age due to the age-limit system of the government employees and private school teachers and staff. The subjects in 1992 had no previously diagnosed disease, and the mean value of the fasting serum glucose level was not over 126 mg/dl or more in baseline. Subjects with no information regarding smoking status at the baseline and follow-up periods were excluded in the study, as well as subjects with a difference in fasting serum glucose levels in 1992 and 1990 of 3±standard deviation of the mean.

Eventually, 27,635 men were enrolled for the study.

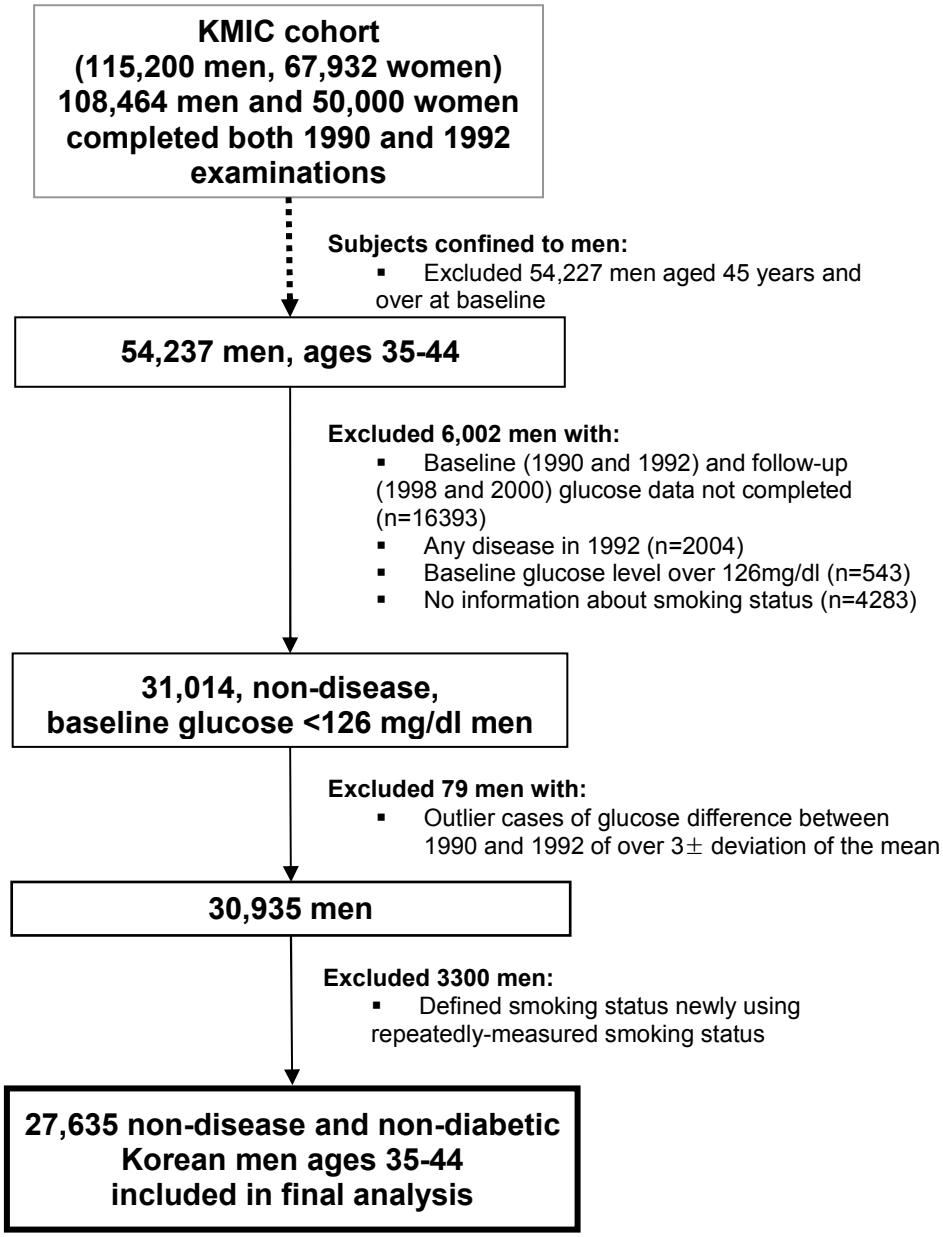

Figure1. Participant Selection Flow

Data Collection

For each examination, weight, height, and blood pressure were measured. Blood pressure was measured in a seated position by a registered nurse or blood pressure technician using a standard mercury sphygmomanometer or automatic manometer. Fasting blood samples were taken and analyzed for fasting serum glucose levels, serum cholesterol and aminotransferase levels. Each hospital participating in the assessment followed internal and external quality control procedures as stipulated by the Korean Society of Quality Control in Clinical Pathology (*Chung et al, 1991; Kim et al, 1993; Min et al, 1999; Min et al, 2001*). Body mass index was calculated by dividing weight (kg) by the square of height (m).

Data on health-related lifestyles in each examination (including cigarette smoking, alcohol consumption and exercise) and disease history of the participants was obtained from self-administered questionnaires.

Baseline data from the 1990 and 1992 health examinations, as well as follow-up data from the 1998 and 2000 health examinations, was obtained. Mean values for blood pressure, total cholesterol, serum glucose and body mass index at the baseline data (1990 and 1992) and follow-up data (1998 and 2000) were also used**.**

Definition of Repeatedly Measured Smoking Status

At the baseline, subjects (n=44931) were classified as 10,094 non smokers (22.5), 9,195 ex-smokers (20.5%) and 25,642 current smokers (57.1%).

Subjects were newly defined using repeatedly measured smoking status. To explore the effect of smoking cessation, ex-smokers were defined as subjects who had quit smoking during the follow-up period, as determined by repeated measurements of smoking status. Furthermore, subjects were classified as those who never smoked, ex-smokers, and sustained smokers by smoking status in 1992, 1994, and 1996. 27,635 men were included in the analysis.

(1) Never smokers were defined as subjects who reported non-smoking consistently in 1992, 1994 and 1996 examinations (n=5,701, 20.6%).

(2) Ex-smokers were defined as follows (including recent quitters n=7,477, 27.1%):

- Subjects who quit smoking before 1992
- Subjects who quit smoking between 1992 and 1993
- Subjects who quit smoking between 1994 and 1995

(3) Sustained smokers were defined as those who answered affirmatively to smoking consistently in all three health examinations from 1992 to 1996 (n=14,457, 52.3%).

Table 1 displays newly defined smoking status criteria using repeated measurements of smoking status for each of the three examinations.

Smoking duration and amounts were categorized in the administered questionnaire in 1996. Smoking duration was categorized into five categories: 1. never smokers 2. ex-smokers who smoked less than 5 years 3. ex-smokers who smoked more than 5 years but less than 10, and 4. ex-smokers who smoked 10 years or more. For sustained smokers, smoking amounts were categorized into 1. less than 10 cigarettes 2. over 10 and less than 20 cigarettes and 3. 20 cigarettes or more per day as compared to newly defined never smokers and ex-smokers.

Table1. Definition of Smoking Status

Criteria	Total no.	Health examination			Quit period among ex-smokers
		1992 (baseline)	1994	1996	
Never-smokers	5701	N	N	N	
Ex-smokers	7477	E	E	E	Quit smoking before 1992 (N=4744)
		C	E	E	Quit smoking 1992 - 1993 (N=1396)
		C	C	E	Quit smoking 1994 - 1995 (N=1337)
Sustained smokers	14457	C	C	C	
Total	27635				

Abbreviations : N, non-smokers; E, ex-smokers; C, current smokers

Definition of IFG and DM

Mean values of 1990 and 1992 measurements for baseline levels and 1998 and 2000 measurements for follow-up levels were used. IFG was defined as a follow-up fasting serum glucose level of 100 mg/dl or more, and DM was defined as a follow-up fasting serum glucose level of 126 mg/dl or more in accordance with the new

classification of DM by the American Diabetes Association (*American Diabetes Association, 2004)*.

Statistical analysis

General characteristics of study subjects were displayed. Analysis of variance and chi-square tests were performed to show the difference in the distribution of each variable. Logistic regression models were used to investigate the relationship between smoking and the risk of developing IFG and DM. Data was unadjusted for any covariates and adjusted for age, baseline serum glucose levels and body mass index, weight change, family history of DM and cardiovascular disease, and baseline drinking and exercise status.

Stratified analysis was performed according to whether or not the fasting serum glucose level was 100 to 125 mg/dl at the baseline. Fully adjusted logistic regression analysis was used to investigate the relationship between smoking status and the risk for developing DM only.

Other stratified analyses were performed according to the baseline body mass index, alcohol consumption and disease occurrence during follow-up examinations. The results of the stratified analyses were presented using fully adjusted logistic regression analysis. The criteria variables were excluded in each stratified analysis.

4. RESULTS

Characteristics of the Study Population at Baseline and Follow-up

Table 2 shows the baseline characteristics of the study populations by smoking status.

Sustained smokers were comparatively slightly younger with a lower systolic blood pressure level and higher total cholesterol level than never smokers or ex-smokers. The rate of regular exercise was lowest for this group, but the rate of drinking was the highest in sustained smokers. Smoking status, family history of DM and CVD had no effect on baseline fasting serum glucose levels. Body mass index levels at the baseline were slightly varied according to smoking status. The proportion of subjects with baseline fasting glucose levels of 100-125 mg/dl was not significantly different according to smoking status.

Table 3 displays follow-up characteristics of the study population. During the eight-year period (1993 to 2000), changes in fasting serum glucose levels and average fasting serum glucose levels were higher in sustained smokers. After eight years of follow up, 5,960 subjects (21.6%) had IFG and 1,170 (4.1%) had a diabetic range of fasting serum glucose levels. The incidents of IFG and DM were higher in sustained smokers than in never smokers or ex-smokers.

Table 2. Baseline Characteristics of 27,635 Men According to Repeatedly Measured Smoking Status

Mean±SD, Number (%)

Variables	Never smokers (n=5701)	Ex-smokers (n=7477)	Sustained smokers (n=14457)	P value
Age, years	39.2 ± 2.9	39.3 ± 2.9	39.0 ± 2.9	<0.0001
Fasting serum glucose, mg/dl	88.6 ± 10.0	88.4 ± 10.0	88.4 ± 10.4	0.2428
Body mass index, kg/m^2	23.4 ± 2.3	23.4 ± 2.3	23.3 ± 2.4	<0.0001
Systolic blood pressure, mmHg	122.5 ± 11.8	122.2 ± 11.8	121.7 ± 11.4	<0.0001
Total cholesterol, mg/dl	188.6 ± 30.7	189.8 ± 31.3	191.1 ± 31.6	<0.0001
Family history of diabetes mellitus				
No	4302 (95.0)	5508 (94.2)	10780 (94.4)	0.2052
Yes	229 (5.0)	341 (5.8)	645 (5.6)	
Family history of cardiovascular disease				
No	4009 (83.8)	5169 (83.3)	10182 (84.4)	0.1894
Yes	777 (16.2)	1034 (16.7)	1889 (15.6)	
Alcohol consumption				
No	1954 (34.4)	1671 (22.4)	2196 (15.2)	<0.0001
Yes	3730 (65.6)	5792 (77.6)	12243 (84.8)	
Exercise status				
No	3907 (69.1)	5227 (70.1)	11351 (78.9)	<0.0001
Yes	1748 (30.9)	2230 (29.9)	3042 (21.1)	
Baseline fasting serum glucose category				
Normal (<100 mg/dl)	4954 (86.9)	6535 (87.4)	12517 (86.6)	0.2330
Impaired (100-125 mg/dl)	747 (13.1)	942 (12.6)	1940 (13.4)	

Table 3. Follow-up Characteristics of 27,635 men According to Repeatedly Measured Smoking Status

Mean±SD, Number (%)

Variables	Never smokers (n=5701)	Ex-smokers (n=7477)	Sustained smokers (n=14457)	P value
Fasting serum glucose, mg/dl				
Follow-up level	92.4 ± 18.2	93.1 ± 18.9	93.9 ± 20.4	<0.0001
Eight-year change	3.8 ± 17.8	4.6 ± 18.8	5.6 ± 19.8	<0.0001
Body mass index, kg/m^2				
Follow-up level	24.2 ± 2.5	24.3 ± 2.5	24.0 ± 2.6	<0.0001
Eight-year change	0.7 ± 1.2	0.9 ± 1.3	0.7 ± 1.2	<0.0001
Final fasting serum glucose category				
Normal (< 100 mg/dl)	4570 (80.2)	5949 (79.6)	11156 (77.2)	<0.0001
Impaired (≥ 100 - <125 mg/dl)	943 (16.5)	1256 (16.8)	2591 (17.9)	
Diabetes (≥ 126 mg/dl)	188 (3.3)	272 (3.6)	710 (4.9)	

Risk for Development of IFG and DM

Table 4 presents the risk ratio of IFG and DM according to repeatedly measured smoking status. Compared with never smokers, sustained smokers had a significantly higher risk for IFG and DM. Ex-smokers showed a slightly higher risk, but this difference was not statistically significant.

The fully adjusted risk ratios of ex-smokers and sustained smokers for IFG were 1.09 (95% CI, 0.98 to 1.21) and 1.22 (1.11 to 1.34). For DM, the fully adjusted risk ratios of ex-smokers and sustained smokers were 1.22 (0.96 to 1.55) and 1.60 (1.29 to 1.97), respectively. The risk to sustained smokers was slightly higher than that of ex-smokers, but the difference was not statistically significant.

Dose-response relationships were shown between smoking and the risk of developing IFG and DM, as indicated by the results of smoking duration and amounts (Table 5-6). In relation to smoking duration, the risk of IFG and DM was elevated for subjects who smoked over 5 years. The fully adjusted risk ratios of subjects who smoked ≥ 5- <10 years and 10 years more were 1.17 (95% CI, 1.05 to 1.31) and 1.22 (95% CI, 1.10 to 1.34) for developing IFG, respectively. The risks were 1.44 (95% CI, 1.13 to 1.83) and 1.59 (95% CI, 1.29 to 1.97) for developing DM (Table 5).

The results showed similar relationships according to smoking levels. Risk of IFG was elevated for subjects who smoked over 10 cigarettes per day. The fully adjusted risk ratio of subjects who smoked over 10 but less than 20 cigarettes per day and 20

cigarettes or more per day was 1.23 (95% CI, 1.11 to 1.36) and 1.26 (95% CI, 1.11-1.43). DM results revealed a similar trend; the risks elevated serial, only for those who smoked over 10 cigarettes per day for IFG, the fully adjusted risk ratio of those who smoked under 10 was 1.23 (95% CI, 0.86 to 1.77); subjects who smoked over 10 but under 20 cigarettes per day was 1.60 (95% CI, 1.28- 2.00) and subjects who smoked over 20 cigarettes per day was 1.75 (95% CI, 1.35 to 2.27) (Table 6).

To evaluate the effects of smoking cessation, ex-smokers were stratified according to the quit smoking period. In relation to IFG, the risk ratios were shown to be increased in serial according to the quit smoking period, but the risk for subjects who quit smoking during 1994 and 1995 was statistically significant (RR 1.35, 95% CI 1.13 to 1.60). The risk was not statistically significant for subjects who quit smoking before 1992 (RR 1.02, 95% CI 0.91 to 1.15) and during 1992 and 1993 (RR 1.09, 95% CI 0.91 to 1.30), although the risk was slightly higher than that of never smokers.

The fully adjusted risk for DM was slightly lower for those who quit smoking before 1992 (RR 0.95, 95% CI 0.72 to 1.25), but was not statistically significant. Subjects who quit smoking during 1992 and 1993 presented a slightly higher risk (RR 1.44, 95% CI 0.96 to 2.15) compared to never smokers, but this was also not statistically significant. However, subjects who quit smoking during 1994-1995 showed a significantly higher risk for DM (RR 2.13, 95% CI 1.51 to 3.00). The risk for both IFG and DM presented a higher ratio than sustained smokers (RR 1.25, 95% CI

1.11 to 1.34; RR 1.61, 95% CI 1.30 to 1.98, respectively) but the differences of the risks were not statistically significant (Table 7).

Table 4. Risk Ratio of Impaired Fasting Glucose and Diabetes Mellitus in Relation to Smoking Status

Smoking status	Total no.	No. of events (%)	Impaired fasting glucose		No. of events (%)	Diabetes mellitus	
			Unadjusted RR (95% CI)	Fully adjusted* RR (95% CI)		Unadjusted RR (95% CI)	Fully adjusted* RR (95% CI)
Never smokers	5701	1131 (19.8)	1.00	1.00	188 (3.3)	1.00	1.00
Ex-smokers	7477	1528 (20.4)	1.04 (0.95-1.13)	1.09 (0.98-1.21)	272 (3.6)	1.11 (0.92-1.34)	1.22 (0.96-1.55)
Sustained smokers	14457	3301 (22.8)	1.20 (1.11-1.29)	1.22 (1.11-1.34)	710 (4.9)	1.51 (1.29-1.78)	1.60 (1.29-1.97)

RR : Risk ratio

*Adjusted for age, baseline fasting serum glucose level, weight change, baseline body mass index , family history of diabetes, alcohol consumption and exercise status

Table 5. Risk Ratio of Impaired Fasting Glucose and Diabetes Mellitus According to Smoking Duration

Smoking status	Total no.	No. of events (%)	Impaired fasting glucose		No. of events (%)	Diabetes mellitus	
			Unadjusted RR (95% CI)	Fully adjusted* RR (95% CI)		Unadjusted RR (95% CI)	Fully adjusted* RR (95% CI)
Never smokers	5701	1131 (19.8)	1.00	1.00	188 (3.3)	1.00	1.00
Ex-smokers	1374	273 (19.9)	1.00 (0.86-1.16)	1.08 (0.90-1.29)	43 (3.1)	0.95 (0.68-1.33)	1.10 (0.74-1.65)
Sustained smokers							
< 5 years	1723	340 (19.7)	0.99 (0.87-1.14)	0.94 (0.79-1.11)	57 (3.3)	1.00 (0.74-1.36)	0.95 (0.65-1.41)
≥ 5- < 10 years	6422	1380 (21.5)	1.11 (1.01-1.21)	1.17 (1.05-1.31)	276 (4.3)	1.32 (1.09-1.59)	1.44 (1.13-1.83)
≥ 10 years	10384	2408 (23.2)	1.20 (1.11-1.29)	1.22 (1.10-1.34)	532 (5.1)	1.51 (1.27-1.78)	1.59 (1.29-1.97)

RR : Risk ratio

*Adjusted for age, baseline fasting serum glucose level, weight change, baseline body mass index , family history of diabetes, alcohol consumption and exercise status

Table 6. Risk ratio of impaired fasting glucose and diabetes mellitus according to the smoking amount

Smoking status	Total no.	Impaired fasting glucose			Diabetes mellitus		
		No. of Events (%)	Unadjusted RR (95% CI)	Fully adjusted* RR (95% CI)	No. of Events (%)	Unadjusted RR (95% CI)	Fully adjusted* RR (95% CI)
Never smokers	5701	1131 (19.8)	1.00	1.00	188 (3.3)	1.00	1.00
Ex-smokers	7477	1528 (20.4)	1.04 (0.95-1.13)	1.09 (0.98-1.21)	272 (3.6)	1.11 (0.92-1.34)	1.22 (0.96-1.55)
Sustained smokers							
< 10 cigarettes/day	1752	358 (20.4)	1.04 (0.91-1.19)	1.07 (0.91-1.26)	70 (4.0)	1.22 (0.92-1.61)	1.23 (0.86-1.77)
≥ 10 – <20 cigarettes/day	9284	2096 (22.6)	1.18 (1.09-1.28)	1.23 (1.11-1.36)	435 (4.7)	1.44 (1.21-1.72)	1.60 (1.28-2.00)
≥ 20 cigarettes/day	3421	847 (24.8)	1.33 (1.20-1.47)	1.26 (1.11-1.43)	205 (6.0)	1.87 (1.53-2.29)	1.75 (1.35-2.27)

RR : Risk ratio

*Adjusted for age, baseline fasting serum glucose level, weight change, baseline body mass index , family history of diabetes, alcohol consumption and exercise status

Table 7. Risk Ratio of Impaired Fasting Glucose and Diabetes Mellitus According to Quit Smoking Period

Smoking status	Total no.	No. of events (%)	Impaired fasting glucose		No. of events (%)	Diabetes mellitus	
			Unadjusted RR (95% CI)	Fully adjusted* RR (95% CI)		Unadjusted RR (95% CI)	Fully adjusted* RR (95% CI)
Never smokers	5701	1131 (19.8)	1.00	1.00	188 (3.3)	1.00	1.00
Ex-smokers							
Quit before 1992	4744	933 (19.7)	0.99 (0.90-1.09)	1.02 (0.91-1.15)	150 (3.2)	0.96 (0.77-1.19)	0.95 (0.72-1.25)
Quit 1992-1993	1396	274 (19.6)	0.99 (0.85-1.14)	1.09 (0.91-1.30)	49 (3.5)	1.07 (0.78-1.47)	1.44 (0.96-2.15)
Quit 1994-1995	1337	321 (24.0)	1.28 (1.11-1.47)	1.35 (1.13-1.60)	73 (5.5)	1.69 (1.28-2.23)	2.13 (1.51-3.00)
Sustained smokers	14457	3301 (22.8)	1.20 (1.11-1.29)	1.22 (1.11-1.34)	710 (4.9)	1.52 (1.29-1.78)	1.61 (1.30-1.98)

RR : Risk ratio

*Adjusted for age, baseline fasting serum glucose level, weight change, baseline body mass index , family history of diabetes, alcohol consumption and exercise status

Stratified Analysis by Baseline Glucose Level, Body Mass Index, Alcohol Consumption and Disease

Table 8 shows stratified analysis according to both baseline glucose levels under 100 mg/dl and 100-125 mg/dl. For the under 100 mg/dl group, the result of baseline glucose levels revealed a similar trend to the relationship between smoking status and the risk for developing DM. Ex-smokers who quit before 1994 did not show a significant elevated risk ratio for developing DM, but the risk was significant for both subjects who quit after 1994 and sustained smokers. For the baseline glucose level group of 100-125 mg/dl, the risks were increased according to the quit smoking period, but was not significant in ex-smokers. However, for sustained smokers, the risk for developing DM was higher (RR 1.59, 95% CI, 1.13 to 2.23) and proved to be statistically significant.

Risks for developing DM according to smoking status by baseline glucose levels showed similar trends as outlined in the table in Figure 2.

Additional stratified analyses were performed based upon baseline body mass index, alcohol consumption and disease occurrence during the follow-up. The risk ratios were higher when baseline glucose levels were 100-125 mg/dl, baseline body mass index was over 23 kg/m^2, and disease was present during follow up. However, risks were not significantly higher in the drinker group compared to the non-drinker group. Also, stratified analyses showed increasing risks of sustained smokers for

developing DM as compared to never smokers. Similar trends were shown in all the stratified analyses, with the exception of the disease occurrence group.

Table 8. Risk Ratio of Diabetes Mellitus Stratified Baseline Glucose Levels

Smoking status	Baseline glucose level lower then 100 mg/dl			Baseline glucose level 100 – 125 mg/dl		
	Total No.	No. of events (%)	Diabetes mellitus RR (95% CI)	Total No.	No. of events (%)	Diabetes mellitus RR (95% CI)
Smoking duration						
Never smokers	4954	96 (1.9)	1.00	747	92 (12.3)	1.00
Ex-smokers	1191	22 (1.9)	1.20 (0.71-2.02)	183	21 (11.5)	0.97 (0.52-1.83)
Sustained smokers						
< 5 years	1498	32 (2.1)	1.05 (0.65-1.70)	225	25 (11.1)	0.80 (0.42-1.51)
≥ 5- < 10 years	5595	143 (2.6)	1.48 (1.09-2.02)	827	133 (16.1)	1.39 (0.96-2.01)
≥ 10 years	10768	352 (3.3)	1.68 (1.30-2.22)	1647	254 (15.4)	1.40 (1.01-1.96)
Smoking amount						
Never smokers	4954	96 (1.9)	1.00	747	92 (12.3)	1.00
Ex-smokers	6535	155 (2.4)	1.35 (0.99-1.83)	942	117 (12.4)	1.03 (0.71-1.50)
Sustained smokers						
< 10 cigarettes/day	1522	34 (2.2)	1.06 (0.65-1.73)	230	36 (15.7)	1.52 (0.90-2.59)
≥ 10 – <20 cigarettes/day	8054	247 (3.1)	1.71 (1.29-2.27)	1230	188 (15.3)	1.41 (1.00-2.00)
≥ 20 cigarettes/day	2941	113 (3.8)	1.74 (1.25-2.42)	480	92 (19.2)	1.63 (1.09-2.46)
Quit smoking period						
Never smokers	4954	96 (1.9)	1.00	747	92 (12.3)	1.00
Ex-smokers						
Quit before 1992	4128	74 (1.8)	0.96 (0.67-1.38)	616	76 (12.3)	0.99 (0.64-1.53)
Quit 1992-1993	1240	31 (2.5)	1.46 (0.88-2.41)	156	18 (11.5)	1.43 (0.72-2.84)
Quit 1994-1995	1167	50 (4.3)	2.63 (1.74-3.96)	170	23 (13.5)	1.40 (0.74-2.65)
Sustained smokers	12517	394 (3.2)	1.66 (1.27-2.18)	1940	316 (16.3)	1.59 (1.13-2.23)

RR : Risk ratio, *Adjusted for age, baseline fasting serum glucose level, weight change, baseline body mass index , family history of diabetes, alcohol consumption and exercise status

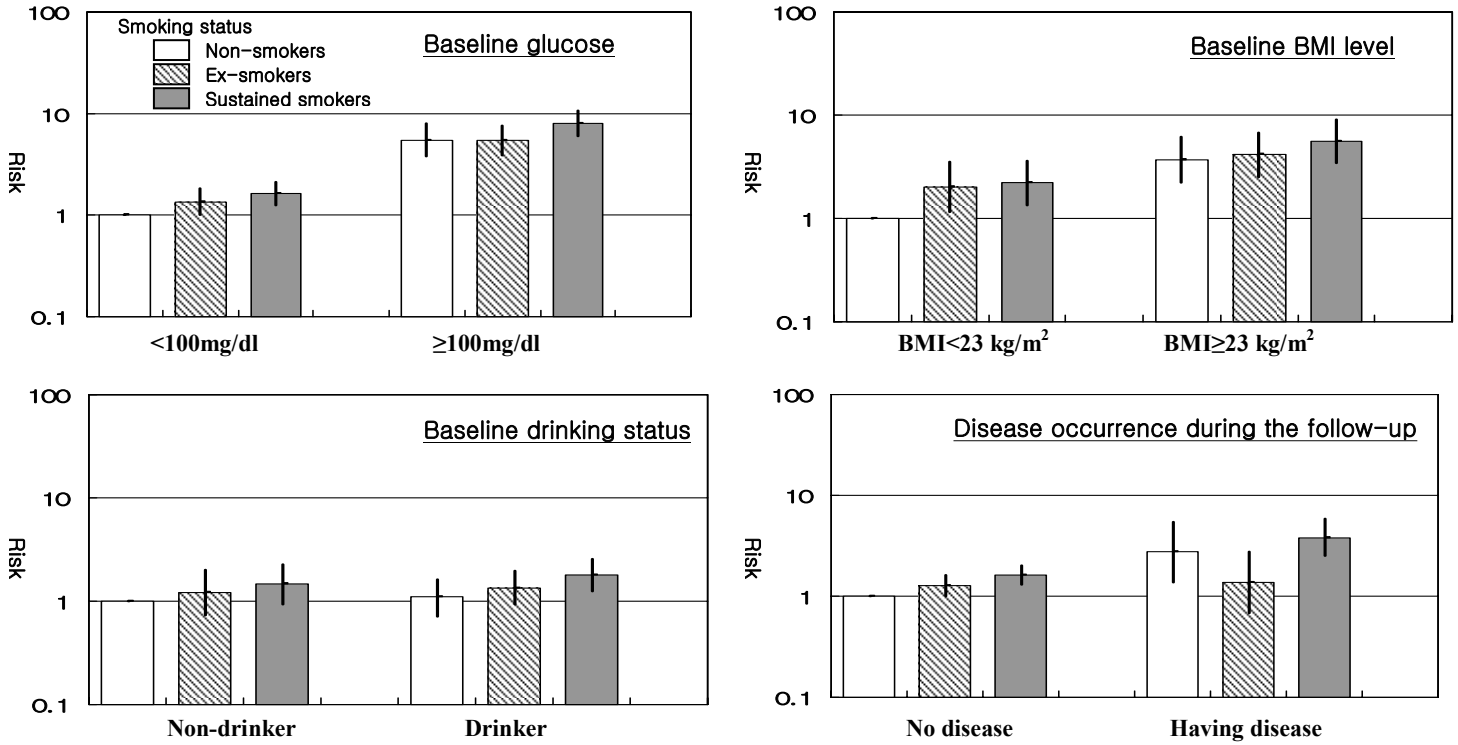

Figure 2. Risk or Diabetes Mellitus Stratified Baseline Glucose Level, Body Mass Index, Alcohol Consumption and Disease

5. DISCUSSION

The relationship between smoking status and risks for developing IFG and DM in middle-aged Korean men, using repeatedly measured eight-year follow-up data was examined. The risk of IFG and DM was significantly increased in sustained smokers compared to never smokers. The dose-response relationship between smoking and the risk for developing IFG and DM was observed by smoking duration and amount.

Subjects who quit smoking before 1992 showed a lower risk for development of IFG and DM than never smokers. Subjects who quit smoking between 1992 and 1993 showed slightly higher risks compared to never smokers, but the difference was not statistically significant. Those who quit smoking between 1994 and 1995 showed similar risks to sustained smokers for IFG, and higher risks than sustained smokers for DM.

Repeatedly Measured Smoking Status and the Effect of Smoking Cessation

Increasing evidence exists to support the association between cigarette smoking and impaired glucose tolerance and DM *(Nakanishi et al, 2000; Will et al, 2001; Wannamethee et al, 2001; Sairenchi et al, 2004; Uchimoto et al, 1999; Ko et al, 2001; Manson et al, 2000; Beziaud et al, 2004*). Previous studies showed increased risk of impaired glucose tolerance in both current smokers and ex-smokers. In addition, recent prospective studies in current smokers and ex-smokers in Asian populations showed a

higher risk for developing diabetes than never smokers *(Nakanishi et al, 2000; Will et al, 2001, Sairenchi et al, 2004; Uchimoto et al, 1999; Hu et al, 2001)*. However, except in four studies, the increased risks of ex-smokers were not statistically significant. One study reported a significantly increased risk for DM among those who quit smoking within a five-year period before screening, but there was no trend following the quitting years (*Wannamethee et al, 2001). Sairenchi and Colleagues (2004)* reported significantly increased risks for developing DM in smokers and ex-smokers, as compared with never smokers. Similar results were shown in one cross-sectional study in French populations; however, no association was found with the duration of smoking cessation (*Beziaud et al, 2004*). There is a report which used a large cohort study *(Hu et al, 2001)*, that shows a significant relationship between ex-smokers and developing DM in women. However, other previous studies showed that age or multivariate-adjusted relative risks were not statistically significant for ex-smokers. Thus, it is proposed that repeated measurement of smoking status is needed in future studies to manifest the relationship between smoking status and fasting glucose level changes *(Uchimoto et al, 1999).*

Differences in the definition of ex-smokers may be a reason for the inconsistent findings. In this study, smoking status was measured repeatedly, at baseline and the end of the study period. Thus, the effects of changes in smoking status during the follow-up period could be reduced and the measurement error in smoking status could be weakened. The risk ratio was 0.98(95% CI, 0.81 – 1.17) for ex-smokers and 1.62(95% CI, 1.40 – 1.88) for current smokers, when the subjects were categorized

based on baseline smoking status only (Data not shown). Therefore, it is possible that finding significant relationships between smoking status and fasting serum glucose level changes and development to IFG and DM, exists not only in sustained smokers, but also in ex-smokers who quit smoking within 5 years of follow-up. It is consistent with the result of the preceding study (*Wannamethee et al, 200; Ilno et al, 2004).* However, the disease occurrence group during follow-up showed a different trend in relation to smoking and the risk for developing IFG or DM (Figure 2). The relationship between smoking and the risk for developing IFG or DM was not observed in the disease occurrence group during follow-up. In general, smokers quit smoking either when they feel unhealthy or are worried about their health. However, the proportions of the disease-occurrence group is small (only 3.4% of all participants), and the non-disease occurrence group showed the relationship between smoking and risk for developing IFG or DM, so that the risk of developing IFG of DM from smoking is possible.

Other Risk Factors for Developing DM

Diabetes is associated with several other factors, e.g. obesity, alcohol consumption, family history of DM, and physical activity. These and some other covariates were controlled in statistical models. In particular, stratified analyses were performed according to baseline body mass index, alcohol consumption and glucose levels. In addition, another stratified analysis relating to disease occurrence during the

follow-up was conducted because overall health status change may have occurred and thus influenced the result, although excluded subjects who had any disease at baseline.

Obesity is an important risk factor for development of diabetes (*Watkins, 1998*) and smoking cessation could be a factor in substantial weight gain (*Carney et al, 1984*). The result of this study indicated that ex-smokers showed the highest body mass index levels and changes at the eight-year follow-up. But the risks for developing IFG and DM were higher in sustained smokers than ex-smokers. The result of the stratified the subjects according to the baseline body mass index level showed similar trends for the relationship between smoking and developing IFG and DM. Thus, it could be argued that the effect of smoking on developing IFG and DM is independent of the effect of bodyweight.

Similar results were shown in the stratified analysis for alcohol consumption. The risk for developing DM was increased in sustained smokers for both drinkers and non-drinkers (Appendix 1). However, the risks were not much higher in drinkers as compared to non-drinkers.

Pre-elevated fasting serum glucose levels could be leading to the development of DM. As shown in Table 8 and Figure 2, the risk for developing DM was higher in subjects with fasting serum glucose of 100 to 125 mg/dl at the baseline than subjects in the normal group. Nevertheless, the trend relating to the relationship between smoking and DM was consistent in the normal group and similar in the other group. The risk ratio for developing DM was significant only in the sustained smokers group with

fasting serum glucose of 100 to 125 mg/dl, while an increased risk ratio was significant in both subjects who quit within 5 years and sustained smokers in the normal group.

Biological Plausibility

The existence of a causal association between cigarette smoking and type 2 DM is biologically plausible for several reasons. It has been suggested that cigarette smoking has a direct effect on body fat distribution, although smokers have different lifestyles than nonsmokers which, in turn, can influence body composition. And although smokers tend to be thinner, cigarette smoking has also been linked to increased abdominal fat distribution and greater waist-to-hip ratio, which may affect glucose tolerance (*Rimm et al, 1993; Wannamethee et al, 2001; Reaven and Laws, 1999; Eliasson, 2003*).

Smoking increases blood glucose levels after an oral glucose challenge and may impair insulin sensitivity. Smokers are more resistant than never smokers to insulin-mediated glucose uptake and are more hyperinsulinemic in response to an oral glucose load (*Manson et al, 2000*). In addition, smokers are characterized by several abnormalities in lipoprotein levels and activity of enzymes regulating lipoprotein metabolism, which by elevating post-absorptive levels of triglyceride-rich lipoproteins, lower hyper density lipoprotein cholesterol, as well as an increase the prevalence of small dense low density lipoprotein particles, which are readily oxidized and considered particularly atherogenic. This insulin resistance associated with smoking

may account, in part, for the dyslipidemia and increased risk of coronary heart disease among smokers. Finally, nicotine, carbon monoxide, and other chemical components of tobacco may have direct toxic effects on the pancreas, beta-cell function, and insulin receptor sensitivity (*Manson et al, 2000; Reaven and Laws, 1999*).

Limitations and Strengths

Several potential limitations of this study should be considered. First, there is no objective information about anti-diabetic medication, and the definition of DM was based upon fasting serum glucose levels of 126 mg/dl or more, It is therefore possible that the incidence of DM could underestimated. However, the misclassification bias, if any, is likely to be non-differential, and the results are unlikely to have been distorted by measurement errors. Second, bi-annual health examinations were conducted at hundreds of hospitals throughout the country and the laboratory technique was not standardized. All hospitals, however, followed the internal and external quality control procedures stipulated by the Korean Society of Quality Control in Clinical Pathology. The variation index scores for serum glucose measurements were 72, 60, 38 and 45 in 1990, 1992, 1998 and 2000, respectively. This index of quality control is widely used and a value less than 100 indicates high quality *(Chung et al, 1991; Kim et al, 1993; Min et al, 1999; Min et al, 2001*). Third, non-fasting serum glucose concentrations could be enrolled for the analyses, because blood samples were collected from mass screening tests. This may lead to underestimation of IFG or diabetes at both baseline

and follow-up examinations. Finally, the different characteristics of excluded participants whose smoking status was not completed with the other participants of this study could be a factor. There are no differences in characteristics between the excluded subjects and included subjects except in regard to body mass index (Appendix 2). However, body mass index did not affect the results mentioned above.

Despite these limitations, this study has several strong points. First, the smoking status of the participants was defined using repeated questionnaires over a six-year interval. Therefore, the unexpected effects of change in smoking habits during the follow-up period could be minimized. Second, for continuous variables, mean values of 1990 and 1992 measurements for baseline levels were used, as well as 1998 and 2000 measurements for follow-up levels. This could have decreased the possibility of measurement error in fasting serum glucose and major covariates. Finally, this study has considerable strength in its generalizeability, because it was performed with a relatively large general population of 27,635 men.

Smoking cessation is one of the few interventions that can safely and cost effectively be recommended for all patients. It has been recommended that smoking cessation is of utmost importance to facilitate glycemic control and limit the development of diabetic complication for diabetes care *(Eliasson, 2003; Madsbad et al, 1980; American Diabetes Association, 2004)*. However, recent studies report that diabetes could be another possible consequence of cigarette smoking in normal populations, and the results of this study corresponds with such studies.

6. CONCLUSION

In this study, a statistically significant and positive relationship was shown between smoking and developing IFG and DM in middle-aged Korean men. Also, a dose-response relationship was shown when observing smoking duration and amounts. In addition, the effect of smoking cessation was observed after quitting 5 years to reduce the risk of developing IFG and DM. This association was independent from baseline body mass index, alcohol consumption and glucose level, and disease occurence during the follow-up. Smoking status was repeatedly measured over a six-year period in order to minimize the change of smoking status during the follow-up.

These results suggest that smoking is an independent and modifiable risk factor for IFG and DM. Smoking cessation could decrease the risk for developing IFG and DM in the long term. Therefore, it should be recommended that individuals either stop smoking or never start to prevent DM.

Appendix table 1. Risk ratio of impaired fasting glucose and diabetes mellitus stratified to baseline body mass index, alcohol consumption and disease

	Smoking status	Total no.	No. of events (%)	Impaired fasting glucose Risk ratio (95% CI)	No. of events (%)	Diabetes mellitus Risk ratio (95% CI)
Baseline body mass index						
< 23 kg/m^2	Never smokers	2548	343 (13.5)	1.00	28 (1.1)	1.00
	Ex-smokers	3376	536 (15.9)	1.20 (1.00 - 1.43)	63 (1.9)	2.00 (1.14 - 3.51)
	Sustained smokers	6959	1203 (17.3)	1.31 (1.12 - 1.54)	183 (2.6)	2.31 (1.38 - 3.86)
≥ 23 kg/m^2	Never smokers	3153	788 (25.0)	1.00	160 (5.1)	1.00
	Ex-smokers	4101	992 (24.2)	1.03 (0.91 - 1.18)	209 (5.1)	1.12 (0.86 - 1.46)
	Sustained smokers	7498	2098 (28.0)	1.17 (1.04 - 1.32)	527 (7.0)	1.50 (1.19 - 1.89)
Alcohol consumption						
Non-drinker	Never smokers	1954	344 (17.6)	1.00	786 (21.1)	1.00
	Ex-smokers	1671	264 (15.8)	1.01 (0.81 - 1.24)	1261 (21.8)	1.13 (1.00 - 1.28)
	Sustained smokers	2196	361 (16.4)	0.97 (0.80 - 1.18)	2935 (24.0)	1.29 (1.16 - 1.44)
Drinker	Never smokers	1954	56 (2.9)	1.00	132 (3.5)	1.00
	Ex-smokers	1671	44 (2.6)	1.21 (0.72 - 2.01)	228 (3.9)	1.23 (0.94 - 1.62)
	Sustained smokers	2196	78 (3.6)	1.42 (0.91 - 2.23)	632 (5.2)	1.64 (1.29 - 2.09)
Having disease during follow-up						
No	Never smokers	5508	1076 (19.5)	1.00	170 (3.1)	1.00
	Ex-smokers	7172	1468 (20.5)	1.11 (0.99 - 1.24)	258 (3.6)	1.28 (1.00 - 1.64)
	Sustained smokers	13999	3170 (22.6)	1.23 (1.12 - 1.36)	652 (4.7)	1.62 (1.30 - 2.01)
Yes	Never smokers	193	55 (28.5)	1.00	18 (9.3)	1.00
	Ex-smokers	305	60 (19.7)	0.62 (0.36 - 1.08)	14 (4.6)	0.46 (0.17 - 1.28)
	Sustained smokers	458	131 (28.6)	0.81 (0.49 - 1.35)	58 (12.7)	1.45 (0.61 - 3.42)

* Adjusted for age, baseline fasting serum glucose level, weight change, baseline body mass index, family history of diabetes, alcohol consumption, and exercise status

Appendix table 2. Comparison of general characteristics of the final subjects and excluded subjects

Mean±SD, Number (%)

Variables	Final subjects (n=27635)	Excluded subjects (n=3300)	P value
Age, years	39.1 ± 2.9	39.1 ± 2.9	0.6431
Fasting serum glucose level, mg/dl	88.4 ± 10.2	88.5 ± 10.2	0.6534
Body mass index, kg/m^2	23.3 ± 2.3	23.4 ± 2.3	0.0072
Systolic blood pressure, mmHg	122.0 ± 11.6	122.0 ± 11.1	0.9730
Total cholesterol, mg/dl	190.2 ± 31.4	189.6 ± 31.4	0.2577
Family history of diabetes			
No	20590 (94.4)	2444 (94.3)	0.7492
Yes	1215 (5.6)	149 (5.7)	
Family history of cardiovascular disease			
No	19360 (84.0)	2308 (85.0)	0.1919
Yes	3700 (16.0)	409 (15.1)	
Alcohol consumption			
No	5821 (21.1)	654 (19.9)	0.1237
Yes	21765 (78.9)	2628 (80.1)	
Exercise status			
No	20485 (74.5)	2330 (71.5)	0.0003
Yes	7020 (25.5)	927 (28.5)	
Baseline fasting serum glucose category			
Normal (<100 mg/dl)	24006 (86.9)	2856 (86.6)	0.6235
Impaired (100-125 mg/dl)	3629 (13.1)	444 (13.4)	

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Abstract in Korean

반복 측정한 흡연상태와 당뇨 발생과의 관련성

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세계적으로 당뇨병 유병인구는 지속적으로 증가하고 있으며 생활양식의 변화로 인하여 우리 나라에서도 당뇨병 발생 증가가 꾸준하다. 당뇨병은 그 자체라기 보다는 여러 가지 합병증으로 인하여 개인적으로나 사회적으로 질병부담이 큰 질병인 반면 생활습관의 개선을 통해 충분히 예방하고 조절할 수 있다는 것이 그 특징이다. 최근 흡연이 당뇨병의 독립적인 위험요인이라는 연구보고들이 많이 있다. 기존 연구들에서는 흡연과 당뇨병 발생에 대해서는 일관적인 결과를 제시하였으나 흡연 기간과 흡연량, 특히 금연한 사람들에 대해서는 아직 결론적이지 않다. 따라서 장기간 추적 연구를 통해 반복적으로 측정한 흡연상태를 이용하여 흡연과 내당능장애, 당뇨병 발생과의 관련성을 알아보고 또한 금연이 해당 질병 발생 위험의 예방효과가 있는지를 알아보고자 한다.

본 연구는 Korea Medical Insurance Corporation (KMIC) 코호트 자료를 이용하였다. 연구 대상은 1990년과 1992년 두 차례의 건강검진에 모두 참여한 사람 중 35-44세 남성으로 1998년과 2000년의 검진자료가 모두 있는 사람이다. 1992년 당시에 이미 질병을 가지고 있다고 응답한 사람과 혈당농도가 126 mg/dl 이상인 사람, 흡연상태가 정

의한 기준에 부합하지 않은 사람은 대상에서 제외되었다. 내당능장애는 1998년과 2000년의 혈당농도평균이 100 mg/dl 이상인 경우로, 당뇨병 발생은 126 mg/dl 이상인 경우로 정의하였다. 독립변수인 흡연 (흡연상태, 흡연기간, 흡연량, 금연기간에 따른 흡연상태)과 종속변수인 내당능장애와 당뇨 발생 각각의 관계는 다중 로지스틱 회귀분석을 통하여 분석하였으며 연령, 연구 시작시점에서의 혈당농도, 체질량지수 (body mass index)와 추적기간 동안의 체중변화, 당뇨병 가족력, 음주 상태, 운동 여부 등의 변수는 통계적 방법으로 보정하였다.

연구 대상자 27, 635명 가운데 추적기간 동안 3620명이 내당능장애, 1170명이 당뇨병 발생을 보였다. 비흡연자와 비교하여 내당능장애 발생 위험은 금연자와 흡연자에서 각각 1.09 (95% 신뢰구간 0.98 – 1.21)와 1.22 (1.11 –1 .34)였고 당뇨병 발생 위험은 각각 1.22와 1.60이었으며 이는 통계적으로 유의하였다. 흡연기간과 흡연량과 관련 질병 발생에 있어서도 용량–반응 관계를 보였다. 금연기간과 내당능장애, 당뇨병 발생 위험과의 관련성은 1994년과 1995년 사이에 금연한 사람들의 경우 각각 1.35배, 2.13배 위험이 증가하였고 1994년 이전에 금연하여 금연을 지속한 경우(5년 이상)는 비흡연자에 비해 발생 위험이 약간 높았으나 통계적으로 유의하지 않았다.

요약하면, 이 연구결과는 흡연이 당뇨병 발생에 위험요인일 수 있다는 기존 연구결과들을 지지하며 흡연 예방과 금연을 통해 당뇨병 발생 위험을 줄일 수 있음을 보여주었다.

핵심되는 말: 흡연, 금연, 내당능장애, 당뇨