



Risk of Diabetes in Subjects with Positive Fecal Immunochemical Test: A Nationwide Population-Based Study

Kwang Woo Kim¹, Hyun Jung Lee¹, Kyungdo Han², Jung Min Moon³, Seung Wook Hong⁴, Eun Ae Kang⁵, Jooyoung Lee⁶, Hosim Soh¹, Seong-Joon Koh¹, Jong Pil Im¹, Joo Sung Kim¹

¹Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine; ²Department of Statistics and Actuarial Science, Soongsil University; ³Department of Internal Medicine, Chung-Ang University College of Medicine; ⁴Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine; ⁵Department of Internal Medicine and Institute of Gastroenterology, Yonsei University College of Medicine; ⁶Department of Internal Medicine, Healthcare Research Institute, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Korea

Background: Positive fecal immunochemical test (FIT) results have been recently suggested as a risk factor for systemic inflammation. Diabetes induces inflammation in the gastrointestinal tract via several ways. We investigated the association between FIT results and the incidence of diabetes.

Methods: A total of 7,946,393 individuals aged ≥ 50 years from the National Cancer Screening Program database who underwent FIT for colorectal cancer (CRC) screening from 2009 to 2012 were enrolled. The primary outcome was newly diagnosed diabetes based on the International Classification of Disease 10th revision codes and administration of anti-diabetic medication during the follow-up period.

Results: During a mean follow-up of 6.5 years, the incidence rates of diabetes were 11.97, 13.60, 14.53, and 16.82 per 1,000 person-years in the FIT negative, one-positive, two-positive, and three-positive groups, respectively. The hazard ratios (HRs) for the incidence of diabetes were 1.14 (95% confidence interval [CI], 1.12 to 1.16; HR, 1.21; 95% CI, 1.16 to 1.27; and HR, 1.40; 95% CI, 1.28 to 1.55) in the one-positive, two-positive, and three-positive FIT groups compared with the FIT negative group, respectively. The effect was consistent in individuals with normal fasting blood glucose (adjusted HR 1.55 vs. 1.14, P for interaction < 0.001).

Conclusion: Positive FIT results were associated with a significantly higher risk of diabetes, suggesting that the FIT can play a role not only as a CRC screening tool, but also as a surrogate marker of systemic inflammation; thus, increasing the diabetes risk.

Keywords: Occult blood; Diabetes mellitus; Inflammation; Surrogate marker; Population; Cohort studies

Received: 23 May 2021, Revised: 4 August 2021, Accepted: 19 August 2021

Corresponding authors: Joo Sung Kim

Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-740-8112, Fax: +82-2-743-6701, E-mail: jooskim@snu.ac.kr

Kyungdo Han

Department of Statistics and Actuarial Science, Soongsil University, 369 Sangdo-ro, Dongjak-gu, Seoul 06978, Korea

Tel: +82-2-820-7025, Fax: +82-2-823-1746, E-mail: hkd917@naver.com

Copyright © 2021 Korean Endocrine Society

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

A positive result of blood in feces implies a risk of developing colorectal cancer (CRC) or a precancerous lesion such as an adenoma [1]. The fecal immunochemical test (FIT) applies antibodies against human hemoglobin (Hb) and provides evidence for occult blood in feces [2]. It is widely used for CRC screening because of its convenience of the number of tests required for verification and preparation for the test [3]. It is well known that CRC screening with FIT reduces the incidence and mortality of CRC [4]. The National Cancer Screening Program (NCSP) was developed in 2002 in Korea, and has offered an annual FIT for CRC screening to all Korean men and women aged 50 years old or more since 2004 [5]. As FIT has been used for many years worldwide, positive FIT results have been recently reported to be associated with cardiovascular diseases and all-cause mortality, even excluding death from CRC beyond the presence of colorectal neoplasia [6,7], implicating a possible link with systemic inflammation.

Diabetes is a serious long-term disease and one of the 10 most common causes of death in adults. The prevalence of diabetes has increased, and 475 million people worldwide had diabetes in 2017 [8]. The many risk factors for diabetes include a family history, presence of an abnormal immune system, age, obesity, physical inactivity, hypertension, and dyslipidemia. Diabetes also induces an inflammation, including in the gastrointestinal tract via oxidative stress, increased levels of inflammatory cytokines, and dysbiosis [9,10]. By linking the previous studies suggesting clinical role of the FIT applying to systemic inflammation and the inflammatory condition in diabetes, we speculated

the association between diabetes and FIT results. However, a few research have assessed the relationship between a positive FIT result and the incidence of diabetes. Therefore, we investigated the association between FIT results and diabetes risk in the general Korean population.

METHODS

Data sources and the study population

The National Health Insurance Service (NHIS) is a public health insurance system that support most of the general Korean population (approximately 97%). The NHIS database includes demographics, disease diagnoses, medical treatments, and laboratory data.

We conducted a retrospective, nationwide population-based cohort study using the NCSP data in the NHIS database. In total, 7,946,393 individuals aged ≥ 50 years who underwent the FIT for CRC screening between January 2009 and December 2012 were enrolled. Participants who did not undergo consecutive CRC screenings at least every 2 years, those with missing data, those with fasting blood glucose (FBG) ≥ 126 mg/dL in the health check-up database, and those diagnosed with diabetes prior to enrollment were excluded. A total of 1,193,149 participants were finally included as the study population and were followed up until diabetes was diagnosed or until December 2017 (Fig. 1). This study was approved by the Institutional Review Board of Seoul National University Hospital (IRB number, E-1906-008-1036) and informed consent was waived by the board.

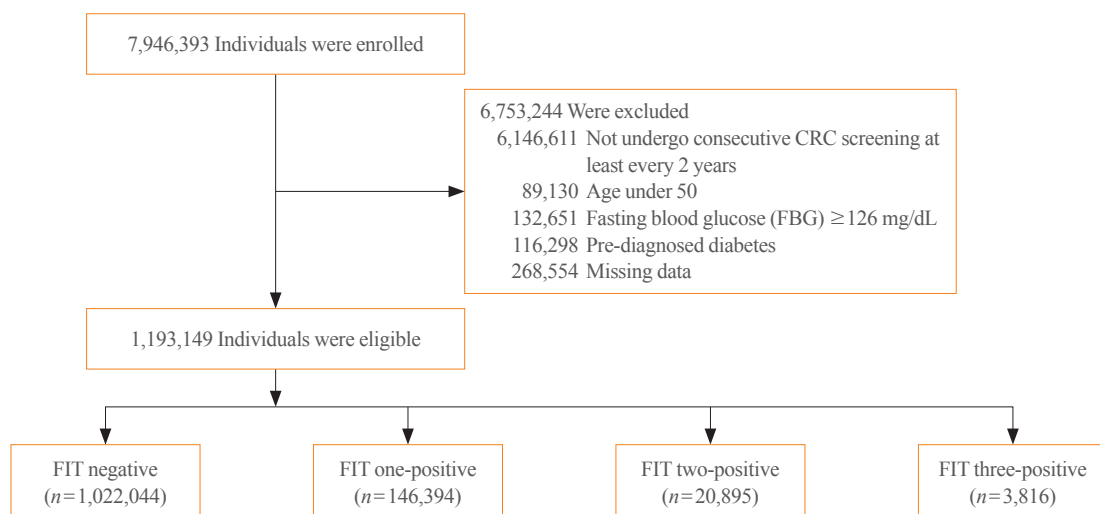


Fig. 1. Study flow of population enrollment. CRC, colorectal cancer; FIT, fecal immunochemical test.

Data collection

The data investigated included age, sex, smoking status, alcohol consumption, income level, physical activity, presence of diabetes, hypertension, hypercholesterolemia, metabolic syndrome, lipid level, glucose level, body mass index (BMI), waist circumference, estimated glomerular filtration rate, and history of malignancy including CRC.

Detailed information regarding smoking status, alcohol consumption and physical activity of the study participants was assessed via standardized self-reported questionnaires. Smoking status was classified as current, ex-, and non-smoker. The classification was defined as follows: non-smoker, those with less than five packs of smoking history; ex-smoker, those with five or more packs of smoking history but had quit smoking; current smoker, those with five or more packs of smoking history and currently smoking. Heavy drinkers were defined if the amount of alcohol consumed exceeded 30 g/day. Exercise was defined as 'yes' in the case of moderate intensity for 30 min/day, at least 5 day/week or vigorous exercise for 20 min/day, at least 3 day/week. The history of malignancy and CRC were defined according to the International Classification of Diseases, 10th Revision (ICD-10) codes (V193 & ICD-10 C code; V193 & ICD-10 codes C18-20, respectively).

The normal range of waist circumference was defined as <90 cm in men and <85 cm in woman. Obesity was defined as BMI >25 kg/m² according to the Asia-Pacific BMI criteria established by the Western Pacific Region of the World Health Organization [11]. Hypertension or hypercholesterolemia was diagnosed using laboratory data (systolic blood pressure \geq 140 mm Hg or diastolic blood pressure \geq 90 mm Hg; total cholesterol level \geq 240 mg/dL, respectively) or by ICD code (ICD-10 codes I10–I15; E78, respectively) with the list of prescribed medicines. The definitions with ICD-10 codes were validated in the previous study [12]. Metabolic syndrome was defined as a combination of the following; hyperglycemia, central obesity, atherogenic dyslipidemia, and hypertension according to the National Cholesterol Education Program Expert Panel and Adult Treatment Panel III criteria.

FIT measurements

Subjects who underwent CRC screening sampled their stool using either a qualitative or a quantitative 1-day sampling method. They were educated to avoid contact with urine or water before sampling the stool. After sampling, the subjects submitted the stool immediately or stored it in a refrigerator shortly before submission if they could not submit the samples immediately.

There were various data from the hospitals and the details of the kits were different. The OC-Hemocatch Light kit (Eiken Chemical Co., Tokyo, Japan) with a cut-off value of 50 ng Hb per milliliter of buffer (ng Hb/mL); the FOB test kit (Humasis Co., Seoul, Korea) with a cut-off value of 50 ng Hb/mL; ASAN Easy Test FOB kit (Asan Pharm Co., Seoul, Korea) with a cut-off value of 50 ng Hb/mL; and the SD Bioline FOB kit (SD Co., Seoul, Korea) with a cut-off value of 30 ng Hb/mL were used for the qualitative method. The OC-Sensor DIANA kit (Eiken Chemical Co.) with a cut-off value of 100 ng Hb/mL; the Hemo Tech NS-1000 kit (Alfresa Pharma Co., Osaka, Japan) with a cut-off value of 40 ng Hb/mL; and the Medex HM-JACK kit (Kyowa Chemical Industry Co., Kagawa, Japan) with a cut-off value of 30 ng Hb/mL, were used for the quantitative method. The positivity of the FIT results was defined by the cut-off value of each test kit, as positive above the point and negative below the point [13].

Study endpoints

The primary outcome was newly diagnosed diabetes, which was identified based on the ICD-10 codes E11, E12, E13, or E14 and administration of anti-diabetic medication during the follow-up. This operational definition of diabetes was validated in a previous study [14]. Subjects who were diagnosed with diabetes within 1 year from the index date were excluded because of the possibility of not being causally related to a positive FIT result.

Statistical analysis

Data were analyzed using Student's *t* test for normally distributed continuous variables and the chi-square test for categorical variables. Incidence rate was calculated as the number of newly diagnosed diabetes cases per 1,000 person-years. The hazard ratio (HR) for the risk of diabetes in the positive FIT group was calculated after adjusting for age, sex, smoking status, alcohol consumption, regular exercise, BMI, FBG, and use of statin using the Cox-proportional hazard model. The incidence rate of diabetes in each group was estimated by a Kaplan-Meier analysis and the log-rank test. A *P*<0.05 was considered significant. The SAS version 9.3 (SAS Institute, Cary, NC, USA) and SPSS version 25.0 (IBM Co., Armonk, NY, USA) software packages were used for statistical analyses.

RESULTS

Baseline characteristics of the study population

Of the 1,193,149 individuals, 171,105 patients (14.3%) had

Table 1. Baseline Characteristics of the Study Population

Characteristic	FIT negative (n=1,022,044)	FIT one-positive (n=146,394)	FIT two-positive (n=20,895)	FIT three-positive (n=3,816)	P value
Age, yr	62.38±6.85	62.98±7.06	63.35±7.14	63.03±7.15	<0.0001
Male sex	436,025 (42.66)	72,789 (49.72)	12,153 (58.16)	2,551 (66.85)	<0.0001
Height, cm	159.27±8.2	159.94±8.3	160.94±8.28	162.3±8.17	<0.0001
Body weight, kg	61±9.35	61.71±9.54	62.72±9.68	64.04±9.95	<0.0001
BMI, kg/m ²	24±2.86	24.08±2.88	24.16±2.88	24.25±2.93	<0.0001
Waist circumference, cm	81.49±8.06	82.24±8.09	83.08±8.1	83.72±8.12	<0.0001
Smoking					<0.0001
Non-smoker	736,885 (72.10)	98,992 (67.62)	13,063 (62.52)	2,322 (60.85)	
Ex-smoker	178,528 (17.47)	28,163 (19.24)	4,524 (21.65)	817 (21.41)	
Current smoker	106,631 (10.43)	19,239 (13.14)	3,308 (15.83)	677 (17.74)	
Alcohol consumption, heavy	36,054 (3.53)	7,058 (4.82)	1,360 (6.51)	290 (7.6)	<0.0001
Exercise, regular	517,273 (50.61)	71,508 (48.85)	10,197 (48.8)	2,025 (53.07)	<0.0001
Hypertension	426,864 (41.77)	66,144 (45.18)	10,060 (48.15)	1,833 (48.03)	<0.0001
Hypercholesterolemia	309,576 (30.29)	44,993 (30.73)	6,468 (30.95)	1,220 (31.97)	0.0002
Metabolic syndrome	389,838 (38.14)	58,647 (40.06)	8,760 (41.92)	1,583 (41.48)	<0.0001
Laboratory findings					
FBG, mg/dL	94.99±10.9	95.23±11.24	95.42±11.56	94.62±12.47	<0.0001
GFR, mL/min/1.73 m ²	84.97±31.82	84.45±29.61	84.22±26.67	84.76±36.28	<0.0001
HDL, mg/dL	54.83±14.81	54.51±14.97	54.29±14.86	55.03±15.5	<0.0001
LDL, mg/dL	120.66±33.74	119.51±34.35	118.03±34.9	117.73±34.55	<0.0001
TG, mg/dL	113.13±0.11	116.03±0.30	118.47±0.83	118.03±1.98	<0.0001

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

FIT, fecal immunochemical test; BMI, body mass index; FBG, fasting blood glucose; GFR, glomerular filtration rate; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride.

positive FIT results and were divided into four groups according to the number of positive FIT results: negative ($n=1,022,044$), one-positive ($n=146,394$), two-positive ($n=20,895$), and three-positive results ($n=3,816$). The baseline characteristics are shown in Table 1. Participants with more positive FIT results were more likely to be older, male, current smokers, and heavy alcohol drinkers, have a higher BMI, weight, height, and waist circumference, and have lower rates of low income (all $P<0.001$). In addition, they tended to have more comorbidities, such as hypertension, hypercholesterolemia and metabolic syndrome (all $P<0.001$). However, subjects who exercised regularly had significantly fewer positive FIT results ($P<0.001$).

The incidence of diabetes according to the number of positive FIT results

During a mean follow-up of 6.5 years, 94,635 incident cases of diabetes (7.9% of the total study population) were identified.

The incidence rates of diabetes were 11.97, 13.60, 14.53, and 16.82 per 1,000 person-years in the FIT negative, one-positive, two-positive, and three-positive results groups, respectively (Table 2). The cumulative risk of diabetes increased gradually as the number of positive FIT results increased, and a significantly different risk was observed according to the frequency of FIT positivity (Fig. 2).

The HRs for diabetes incidence were 1.14 (95% confidence interval [CI], 1.12 to 1.16), 1.21 (95% CI, 1.16 to 1.27), and 1.40 (95% CI, 1.28 to 1.55) in the one-positive, two-positive, and three-positive FIT groups compared with those in the FIT negative group, respectively (log-rank $P<0.001$) (Table 2). A higher number of FIT-positive results was significantly associated with the incidence of diabetes. Moreover, similar significant associations were observed between the number of FIT-positive results and the incidence of diabetes after adjusting for age, sex, smoking, alcohol consumption, regular exercise, BMI,

Table 2. Incidence of Diabetes Associated with Fecal Immunochemical Test Results

No. of positive FIT results	Number	Diabetes	IR	HR (95% CI)			
				Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 4 ^d
0	1,022,044	79,399	11.97	1 ^e	1 ^e	1 ^e	1 ^e
1	146,394	12,876	13.60	1.14 (1.12–1.16)	1.11 (1.09–1.13)	1.08 (1.06–1.10)	1.07 (1.05–1.09)
2	20,895	1,946	14.53	1.21 (1.16–1.27)	1.17 (1.11–1.22)	1.10 (1.05–1.15)	1.08 (1.03–1.13)
3	3,816	414	16.82	1.40 (1.28–1.55)	1.35 (1.23–1.49)	1.35 (1.23–1.49)	1.31 (1.19–1.45)

FIT, fecal immunochemical test; IR, incidence rate (per 1,000 person-years); HR, hazard ratio; CI, confidence interval.

^aNot adjusted; ^bAdjusted with age, sex; ^cAdjusted with age, sex, smoking status, alcohol consumption, regular exercise, body mass index, fasting blood glucose; ^dAdjusted with age, sex, smoking status, alcohol consumption, regular exercise, body mass index, fasting blood glucose, use of statin; ^eAs reference value.

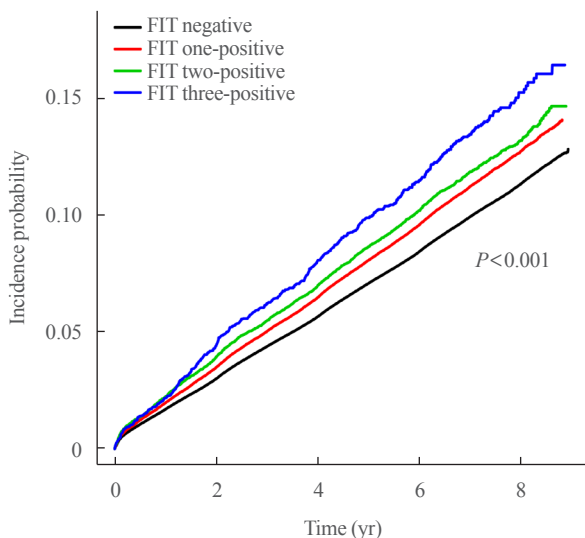


Fig. 2. Cumulative risk of diabetes associated with the number of fecal immunochemical test results. FIT, fecal immunochemical test.

FBG, and use of statin.

Subgroup analysis of the incidence of diabetes

The trend for an increased incidence of diabetes with the increase in the number of FIT-positive results was consistently observed in all subgroups. Among the subgroups, the effect of positive FIT results on the development of diabetes was more prominent in individuals with a normal FBG (<math>< 100\text{ mg/dL}</math>) (adjusted HR 1.55 vs. 1.14, P for interaction <math>< 0.001</math>) (Table 3).

As the FIT results and diabetes are both associated with malignancies, such as CRC, we further stratified the total population according to the presence of all cancers including CRC, and analyzed the association between positive FIT results and the incidence of diabetes (Table 4). However, no significant effects of all cancers and CRC on the incidence of diabetes were de-

tected as the number of positive FIT results increased (P for interaction 0.5375 and 0.3124, respectively).

DISCUSSION

In this population-based study, a positive FIT result was associated with a significantly increased risk of diabetes and a linear relationship was found between the number of FIT-positive cases and the incidence of diabetes. These results were consistent even after adjusting for well-known diabetes risk factors, including age, sex, and obesity. Our study also demonstrated a greater effect of positive FIT results on the incidence of diabetes in individuals with a normal FBG.

The prevalence of diabetes is rapidly increasing in the Asia-Pacific region, which has been mainly attributed to a global increase in obesity [15]. The increase in the incidence of diabetes has become a medical concern due to long-term complications and the economic burden. The FIT, generally used as a CRC screening tool, has been demonstrated to reflect colonic mucosal inflammation in inflammatory bowel disease, as well as systemic inflammation related to all-cause mortality [7,16]. Diabetes is also related to a chronically inflamed environment; however, only a few studies have found positive FIT results that are correlated with diabetes risk but the results were inconsistent. A Japanese cross-sectional study reported that a positive fecal occult blood test (FOBT) group has a significantly higher glycated hemoglobin (HbA1c) level than that of a negative FOBT group even in subjects not receiving anti-diabetic medications [17]. A Taiwanese cross-sectional study showed an increased tendency for FIT positivity in a diabetic group compared to a nondiabetic group [18]. Our study is the first to clarify the association with a positive FIT result and the development of diabetes in a general population.

Table 3. Subgroup Analysis of the Incidence of Diabetes

Subgroup	No. of positive FIT results	IR	HR (95% CI) Model 4 ^a	P for interaction
Age, yr				0.0557
<65	0	10.24	1 ^b	
	1	11.64	1.08 (1.05–1.11)	
	2	11.80	1.03 (0.96–1.09)	
	3	14.32	1.23 (1.07–1.40)	
≥65	0	15.29	1 ^b	
	1	16.86	1.06 (1.04–1.09)	
	2	18.75	1.15 (1.08–1.22)	
	3	21.04	1.41 (1.22–1.62)	
Sex				0.2698
Male	0	12.97	1 ^b	
	1	14.58	1.08 (1.05–1.10)	
	2	15.65	1.12 (1.06–1.19)	
	3	17.02	1.30 (1.16–1.47)	
Female	0	11.24	1 ^b	
	1	12.65	1.06 (1.04–1.09)	
	2	13.01	1.02 (0.95–1.10)	
	3	16.43	1.34 (1.13–1.59)	
Obesity				0.0024
No	0	8.87	1 ^b	
	1	10.22	1.08 (1.05–1.11)	
	2	11.51	1.15 (1.08–1.23)	
	3	12.48	1.30 (1.13–1.50)	
Yes	0	18.10	1 ^b	
	1	19.91	1.06 (1.03–1.09)	
	2	19.80	1.02 (0.96–1.09)	
	3	23.79	1.32 (1.15–1.50)	
Hypertension				0.9871
No	0	8.72	1 ^b	
	1	9.72	1.05 (1.02–1.09)	
	2	10.31	1.06 (0.99–1.14)	
	3	12.55	1.31 (1.12–1.53)	
Yes	0	16.63	1 ^b	
	1	18.46	1.08 (1.05–1.10)	
	2	19.25	1.09 (1.03–1.15)	
	3	21.66	1.30 (1.14–1.47)	
Hypercholesterolemia				<0.0001
No	0	9.87	1 ^b	
	1	11.40	1.07 (1.05–1.09)	
	2	11.79	1.08 (1.03–1.13)	
	3	15.69	1.33 (1.20–1.46)	
Yes	0	16.93	1 ^b	
	1	18.67	0.96 (0.89–1.05)	
	2	20.80	1.15 (0.94–1.39)	
	3	19.27	1.08 (0.67–1.74)	
FBG, mg/dL				<0.0001
<100	0	6.24	1 ^b	
	1	7.36	1.12 (1.09–1.15)	
	2	8.59	1.26 (1.18–1.36)	
	3	10.52	1.55 (1.34–1.80)	

(Continued to the next)

Table 3. Continued

Subgroup	No. of positive FIT results	IR	HR (95% CI) Model 4 ^a	P for interaction
≥100	0	25.85	1 ^b	
	1	27.62	1.04 (1.01–1.06)	
	2	27.07	0.98 (0.93–1.04)	
	3	30.69	1.14 (1.00–1.29)	
Metabolic syndrome				<0.0001
No	0	6.53	1 ^b	
	1	7.67	1.11 (1.08–1.15)	
	2	8.08	1.13 (1.04–1.22)	
	3	10.56	1.48 (1.26–1.73)	
Yes	0	21.15	1 ^b	
	1	22.81	1.04 (1.02–1.07)	
	2	23.77	1.05 (0.99–1.11)	
	3	25.83	1.22 (1.08–1.38)	
Smoking				0.0439
Non-smoker	0	11.21	1 ^b	
	1	12.69	1.07 (1.04–1.09)	
	2	13.50	1.09 (1.03–1.15)	
	3	16.33	1.34 (1.19–1.52)	
Ex-smoker	0	12.92	1 ^b	
	1	13.92	1.03 (0.99–1.08)	
	2	15.81	1.16 (1.06–1.27)	
	3	16.40	1.31 (1.06–1.62)	
Current smoker	0	15.56	1 ^b	
	1	17.74	1.12 (1.07–1.17)	
	2	16.50	0.99 (0.89–1.10)	
	3	18.27	1.22 (0.97–1.52)	
Heavy drinker				0.7031
No	0	11.89	1 ^b	
	1	13.46	1.07 (1.05–1.09)	
	2	14.38	1.08 (1.03–1.13)	
	3	16.70	1.33 (1.20–1.47)	
Yes	0	14.08	1 ^b	
	1	16.41	1.12 (1.03–1.21)	
	2	16.56	1.09 (0.92–1.29)	
	3	18.35	1.20 (0.86–1.69)	
Regular exercise				0.2150
No	0	12.81	1 ^b	
	1	14.31	1.05 (1.03–1.08)	
	2	15.29	1.06 (1.00–1.13)	
	3	19.18	1.37 (1.20–1.56)	
Yes	0	11.15	1 ^b	
	1	12.86	1.09 (1.06–1.12)	
	2	13.74	1.11 (1.04–1.19)	
	3	14.77	1.26 (1.09–1.45)	

FIT, fecal immunochemical test; IR, incidence rate (per 1,000 person-years); HR, hazard ratio; CI, confidence intervals; FBG, fasting blood glucose.

^aAdjusted with age, sex, smoking status, alcohol consumption, regular exercise, body mass index, fasting blood glucose, use of statin; ^bAs reference value.

Table 4. Stratification According to History of Malignancy and Colorectal Cancer

Subgroup	No. of positive FIT results	IR	HR (95% CI) Model 4 ^a	<i>P</i> for interaction
History of malignancy				0.5375
No	0	11.89	1 ^b	
	1	13.47	1.07 (1.05–1.09)	
	2	14.25	1.07 (1.02–1.12)	
	3	16.93	1.33 (1.20–1.46)	
Yes	0	14.23	1 ^b	
	1	16.52	1.07 (0.98–1.16)	
	2	20.47	1.19 (0.99–1.43)	
	3	14.45	0.99 (0.59–1.64)	
History of colorectal cancer				0.3124
No	0	11.96	1 ^b	
	1	13.57	1.07 (1.05–1.09)	
	2	14.46	1.08 (1.03–1.13)	
	3	16.77	1.32 (1.20–1.45)	
Yes	0	15.64	1 ^b	
	1	15.92	0.91 (0.71–1.17)	
	2	17.02	0.95 (0.63–1.41)	
	3	8.50	0.56 (0.14–2.28)	

FIT, fecal immunochemical test; IR, incidence rate (per 1,000 person-years); HR, hazard ratio; CI, confidence interval.

^aAdjusted with age, sex, smoking status, alcohol consumption, regular exercise, body mass index, fasting blood glucose, use of statin; ^bAs reference value.

Several possible mechanisms might be involved in the association between FIT positivity and the incidence of diabetes. First, hyperglycemia and advanced glycation end-products, which are a by-product of hyperglycemia, cause predisposing micro-/macroangiopathy. These end-products inhibit the synthesis of nitric oxide and induce oxidative stress [9]. Increased levels of tumor necrosis factor- α , a key factor of angiogenesis, as well as other cytokines, including interleukin (IL)-1 and IL-6, and C-reactive protein are detected in patients with diabetes [19]. These series of changes in the gastrointestinal tract consequently elicit microhemorrhages that produce a positive FIT result [20,21]. These findings suggest that diabetes itself can be a systemic inflammation factor, particularly in the gut, by inducing generalized colonic inflammation [22]. A positive FIT result may be a marker reflecting systemic inflammation.

The gut microbiome may provide another potential link between a positive FIT result and diabetes. Some studies show that diabetes has a significant effect on the gut microbiome and gut barrier integrity [23,24]. The gut microbiota is significantly different between diabetic patients and healthy individuals as the proportions of *Firmicutes* and *Clostridium* are reduced and

the levels of *Bacteroides* and *Escherichia coli* increase in diabetic groups [10]. The dysbiosis observed in type 2 diabetes patients activates low-grade chronic inflammation of islets, which can cause damage and dysfunction of islet β -cells [25]. In addition, metabolites from the gut microbes contribute to gut barrier integrity. A compromised barrier leads to leakage of inflammatory mediators into the systemic circulation and, therefore, increases insulin resistance [24].

Many epidemiological studies have reported an increased risk of cancer, including stomach, colorectal, liver, pancreatic, and kidney cancer in patients with diabetes [26]. Hyperinsulinemia, hyperglycemia, and chronic inflammation have been implicated in increasing the cancer risk through their effects on the neoplastic process [27]. In particular, type 2 diabetes significantly increases the risk for CRC [28], and a higher HbA1c level is associated with a higher prevalence of colorectal neoplasia [18]. However, when we conducted subgroup analyses according to the presence of cancer, the increased risk for the development of diabetes was consistent regardless of the presence of any cancer and CRC. We postulate that FIT positivity itself could be an independent predictor of diabetes.

The most intriguing finding in this study was that the effect of prediabetes and obesity on the incidence of diabetes in FIT-positive populations was different. Prediabetes and obesity are two predominant risk factors for the development of diabetes [29]. The association between FIT positivity and the development of diabetes was more prominent in those with a normal FBG, which could be explained that the effect of high FBG is dominant in subjects who already have prediabetes, compared to the effect of FIT positivity. In other words, baseline FBG has a stronger influence than a positive FIT result on the development of diabetes. Positive FIT results were consistently associated with a diabetes risk in the obese and non-obese subgroups. Further studies are required to reveal the different effects of FIT positivity on the relationship between well-known risk factors and diabetes.

This study had some limitations. First, as the diagnosis of diabetes was defined only by ICD-10 codes and administration of anti-diabetic medications [14], subjects who satisfied postprandial diagnostic criteria for diabetes or did not visit a hospital during the study period could have been missed from our data. In addition, less-severe or untreated diabetic patients could be a risk of misclassification. Therefore, further studies regarding appropriate operational definitions are required to minimize the inaccurate results. Second, we could not evaluate the correlation between positive FIT results and the HbA1c levels of the diabetic population, and the NHIS database did not provide HbA1c levels. Third, the NCSP has provided an annual FIT to all Korean adults above 50 years of age, however, still only one-third of the general population received CRC screening [30]. Though we included all the individuals who underwent the FIT during the study period and the trend of CRC screening rates increased annually, further studies to identify factors that influence screening rates and enhance the compliance are needed. Fourth, the data about antithrombotic drugs were not available which could lead to false-positive FIT results. In addition, we could not obtain data regarding endoscopic or pathological findings. Instead, subgroup analyses with subjects without all cancer and CRC revealed robust results. Finally, it was not possible to determine an accurate causal relationship due to the nature of a retrospective epidemiological study.

In conclusion, participants with a positive FIT result had a significantly higher risk of diabetes compared with those with a negative FIT result, after adjusting for conventional risk factors. In addition, a dose-relationship was observed between FIT positivity and the incidence of diabetes. These results suggest that FIT can play a role not only as a CRC screening tool, but also as

a surrogate marker of systemic inflammation and thus in increasing the diabetes risk.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conception or design: K.W.K., K.H., J.S.K. Acquisition, analysis, or interpretation of data: K.W.K., H.J.L., K.H., J.M.M., S.W.H., E.A.K., J.L., H.S., S.J.K., J.P.I., J.S.K. Drafting the work or revising: K.W.K., H.J.L., K.H., J.S.K. Final approval of the manuscript: K.W.K., K.H., J.S.K.

ORCID

Kwang Woo Kim <https://orcid.org/0000-0002-5379-1016>

Joo Sung Kim <https://orcid.org/0000-0001-6835-4735>

Kyungdo Han <https://orcid.org/0000-0002-6096-1263>

REFERENCES

1. Carroll MR, Seaman HE, Halloran SP. Tests and investigations for colorectal cancer screening. *Clin Biochem* 2014; 47:921-39.
2. Chen LS, Yen AM, Fraser CG, Chiu SY, Fann JC, Wang PE, et al. Impact of faecal haemoglobin concentration on colorectal cancer mortality and all-cause death. *BMJ Open* 2013;3:e003740.
3. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut* 2015;64:1637-49.
4. Ladabaum U, Dominitz JA, Kahi C, Schoen RE. Strategies for colorectal cancer screening. *Gastroenterology* 2020;158: 418-32.
5. Sohn DK, Kim MJ, Park Y, Suh M, Shin A, Lee HY, et al. The Korean guideline for colorectal cancer screening. *J Korean Med Assoc* 2015;58:420-32.
6. Moon JM, Lee HJ, Han K, Kim DH, Hong SW, Soh H, et al. Occult blood in feces is associated with an increased risk of ischemic stroke and myocardial infarction: a nationwide population study. *J Am Heart Assoc* 2021;10:e017783.
7. Libby G, Fraser CG, Carey FA, Brewster DH, Steele RJ. Occult blood in faeces is associated with all-cause and non-

- colorectal cancer mortality. *Gut* 2018;67:2116-23.
8. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;392:1789-858.
 9. Bassi R, Trevisani A, Tezza S, Ben Nasr M, Gatti F, Vergani A, et al. Regenerative therapies for diabetic microangiopathy. *Exp Diabetes Res* 2012;2012:916560.
 10. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. *PLoS One* 2010;5:e9085.
 11. Seo MH, Lee WY, Kim SS, Kang JH, Kang JH, Kim KK, et al. 2018 Korean Society for the Study of Obesity guideline for the management of obesity in Korea. *J Obes Metab Syndr* 2019;28:40-5.
 12. Kim MK, Han K, Park YM, Kwon HS, Kang G, Yoon KH, et al. Associations of variability in blood pressure, glucose and cholesterol concentrations, and body mass index with mortality and cardiovascular outcomes in the general population. *Circulation* 2018;138:2627-37.
 13. Cha JM, Suh M, Kwak MS, Sung NY, Choi KS, Park B, et al. Risk of interval cancer in fecal immunochemical test screening significantly higher during the summer months: results from the National Cancer Screening Program in Korea. *Am J Gastroenterol* 2018;113:611-21.
 14. Lee YH, Han K, Ko SH, Ko KS, Lee KU; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Data analytic process of a nationwide population-based study using National Health Information Database established by National Health Insurance Service. *Diabetes Metab J* 2016;40:79-82.
 15. Rhee EJ. Diabetes in Asians. *Endocrinol Metab (Seoul)* 2015;30:263-9.
 16. Dai C, Jiang M, Sun MJ, Cao Q. Fecal immunochemical test for predicting mucosal healing in ulcerative colitis patients: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2018;33:990-7.
 17. Nakajima K, Suwa K. Association between positive fecal occult blood test and diabetes in a population undergoing health screening. *Clin Biochem* 2017;50:97-100.
 18. Tseng PH, Lee YC, Chiu HM, Chen CC, Liao WC, Tu CH, et al. Association of diabetes and HbA1c levels with gastrointestinal manifestations. *Diabetes Care* 2012;35:1053-60.
 19. Lainampetch J, Panprathip P, Phosat C, Chumpathat N, Prangthip P, Soonthornworasiri N, et al. Association of tumor necrosis factor alpha, interleukin 6, and C-reactive protein with the risk of developing type 2 diabetes: a retrospective cohort study of rural Thais. *J Diabetes Res* 2019;2019:9051929.
 20. De Las Casas LE, Finley JL. Diabetic microangiopathy in the small bowel. *Histopathology* 1999;35:267-70.
 21. Sasor A, Ohlsson B. Microangiopathy is common in submucosal vessels of the colon in patients with diabetes mellitus. *Rev Diabet Stud* 2014;11:175-80.
 22. Mine S, Takeshima F, Akazawa Y, Matsushima K, Minami H, Yamaguchi N, et al. Correlation of fecal markers with magnifying endoscopic stratification in patients with ulcerative colitis who are in clinical remission. *Digestion* 2018;97:82-9.
 23. Sharma S, Tripathi P. Gut microbiome and type 2 diabetes: where we are and where to go? *J Nutr Biochem* 2019;63:101-8.
 24. Upadhyaya S, Banerjee G. Type 2 diabetes and gut microbiome: at the intersection of known and unknown. *Gut Microbes* 2015;6:85-92.
 25. Wang H, Lu Y, Yan Y, Tian S, Zheng D, Leng D, et al. Promising treatment for type 2 diabetes: fecal microbiota transplantation reverses insulin resistance and impaired islets. *Front Cell Infect Microbiol* 2020;9:455.
 26. Kim SK, Jang JY, Kim DL, Rhyu YA, Lee SE, Ko SH, et al. Site-specific cancer risk in patients with type 2 diabetes: a nationwide population-based cohort study in Korea. *Korean J Intern Med* 2020;35:641-51.
 27. Garg SK, Maurer H, Reed K, Selagamsetty R. Diabetes and cancer: two diseases with obesity as a common risk factor. *Diabetes Obes Metab* 2014;16:97-110.
 28. Jee SH, Ohrr H, Sull JW, Yun JE, Ji M, Samet JM. Fasting serum glucose level and cancer risk in Korean men and women. *JAMA* 2005;293:194-202.
 29. Rhee EJ, Cho JH, Kwon H, Park SE, Jung JH, Han KD, et al. Relation between baseline height and new diabetes development: a nationwide population-based study. *Diabetes Metab J* 2019;43:794-803.
 30. Ministry of Health and Welfare. National cancer screening program [Internet]. Wonju: NHIS; 2021 [cited 2021 Sep 13]. Available from: https://www.index.go.kr/potal/main/EachDtlPageDetail.do?idx_cd=1440.