ORIGINAL RESEARCH

Occult Blood in Feces Is Associated With an Increased Risk of Ischemic Stroke and Myocardial Infarction: A Nationwide Population Study

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BACKGROUND: Although occult hemoglobin in feces is universally valued as a screening tool for colorectal cancer (CRC), only few studies investigated the clinical meaning of fecal immunochemical test (FIT) in other diseases. We evaluated the clinical utility of FIT in patients with cardiovascular diseases (namely, ischemic stroke and myocardial infarction [MI]).

METHODS AND RESULTS: Using the National Health Insurance database, participants (aged >50 years) with CRC screening records from 2009 to 2012 were screened and followed up. Subjects with a history of cardiovascular diseases and CRC were excluded. Ischemic stroke, MI, and other comorbidities were defined by *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes. Age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, and body mass index were adjusted in a multivariate analysis. A total of 6 277 446 subjects were eligible for analysis. During the mean 6.79 years of follow-up, 168 570 participants developed ischemic stroke, 105 983 developed MI, and 11 253 deaths were observed. A multivariate-adjusted model revealed that the risk of ischemic stroke was higher in the FIT-positive population (adjusted hazard ratio [HR], 1.09; 95% CI, 1.07–1.11). Similarly, FIT-positive subjects were at an increased risk of MI (adjusted HR, 1.09; 95% CI, 1.06–1.12). Moreover, increased all-cause mortality was observed in the FIT-positive population (adjusted HR, 1.15; 95% CI, 1.07–1.23). The increased risk remained consistent in the stratified analysis on anemia and CRC status.

CONCLUSIONS: Positive FIT findings were associated with ischemic stroke, MI, and mortality. Occult blood in feces may offer more clinical information than its well-known conventional role in CRC screening.

Key Words: cardiovascular diseases ■ cohort ■ fecal immunochemical test ■ myocardial infarction ■ stroke

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide.[1] A stool test for occult blood is a commonly used method in average-risk subjects with CRC, as it is easily repeatable with a single sample and is less invasive, user friendly, and cost-effective.[2] Fecal immunochemical tests (FITs) have improved sensitivity compared with guaiac-based fecal occult blood tests for detecting CRC.[3] The clinical effectiveness of these stool-based tests has been well demonstrated in previous studies; their efficacy has resulted in reductions in the incidence of CRC and/or CRC-specific mortality.[4–6]

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CLINICAL PERSPECTIVE

What Is New?

- Positive fecal immunochemical test was associated with an increased risk of ischemic stroke, myocardial infarction, and all-cause mortality.
- The association was verified in the multivariate analysis of known cardiovascular risk factors, such as age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, and body mass index.
- In particular, we found that result remained consistent in the stratified analysis on anemia and colorectal cancer status.

What Are the Clinical Implications?

- Importance of positive fecal immunochemical test result should be further examined as it may offer more clinical significance as well as its original role in colorectal cancer screening.

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Nonstandard Abbreviations and Acronyms

FIT   fecal immunochemical test
NHIS   National Health Insurance Service

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Only a few studies have been performed to evaluate the utility of FIT in other medical fields. As a significant portion of positive FIT results does not correlate with a corresponding lesion on colonoscopy, previous studies investigated the clinical significance of FIT positivity in detecting other gastrointestinal cancers, such as gastric cancer.[7–9] Further studies discussed the possible interaction between FIT results and diabetes mellitus, as patients with diabetes mellitus are prone to gut microangiopathy.[10,11] FIT is useful in predicting flare-up[12] and mucosal disease activity in patients with inflammatory bowel disease.[13,14]

Cardiovascular diseases and CRCs share several risk factors, including old age, smoking, and physical inactivity,[15,16] suggesting that particular underlying pathogenesis of CRC could also be applied to cardiovascular diseases. Many of these listed factors are reported to be associated with chronic systemic inflammatory reactions.[17,18] Furthermore, anemia related to occult blood in feces is an independent risk factor for cardiovascular diseases[19]; and iron deficiency anemia, in particular, has a detrimental effect on cardiovascular outcomes.[20] However, no previous study has investigated the impact of FIT results on the development of cardiovascular diseases.

Therefore, we evaluated whether positive FIT results are associated with an increased risk of cardiovascular diseases (ischemic stroke and myocardial infarction [MI]) and all-cause mortality, using a nationwide population-based cohort. We also identified any mediating factors, such as anemia and CRC, on the clinical outcomes.

METHODS

The Korean national health insurance service offers a publicly available, deidentified data set that can be accessed by qualified researchers via national health insurance sharing service (https://nhiss.nhis.or.kr). The study protocol was approved by the Seoul National University Hospital Institutional Review Board (H-1906-008-1036).

Study Population

South Korean residents undergo a routine national health examination that is covered by the National Health Insurance Service (NHIS) for >97% of the population. The NHIS database has records of all reimbursements for outpatient and inpatient visits. This includes *International Classification of Diseases, Tenth Revision* (*ICD-10*), information of the diagnosis; physical and laboratory findings; medical procedures; medication prescriptions; and medical costs. Moreover, the NHIS supports funds for a biennial national medical inspection program for all beneficiaries aged >50 years. Thus, we used the NHIS data set for subjects aged >50 years undergoing CRC screening from 2009 to 2012. Patients with a history of cardiovascular disease before the index date were excluded to detect new-onset clinical events and to ensure the accuracy of the outcome assessment. Those already diagnosed with cancer were excluded. A detailed study profile is illustrated in Figure 1. *ICD-10* codes were used to exclude patients. Finally, 6 277 446 subjects were included for analysis. The study population was followed up until 2017.

FIT Measurements

FITs were processed using a 1-day qualitative or quantitative sampling method. Study participants were instructed to return the fecal samples immediately or to store them shortly in a home refrigerator before returning. The fecal samples were to be collected before making contact with urine or water. OC-Hemocatch Light kits (Eiken Chemical, Co, Tokyo, Japan), with a cutoff of 50 ng/mL; FOB test kits (Humasis, Co, Seoul, Korea), with a cutoff of 50 ng/mL; ASAN Easy Test FOB kits (Asan Pharm, Co, Seoul, Korea), with a cutoff of 50 ng/mL; and SD Bioline FOB kits (SD, Co, Seoul, Korea), with a cutoff of 30 ng/mL, were used for the qualitative method.
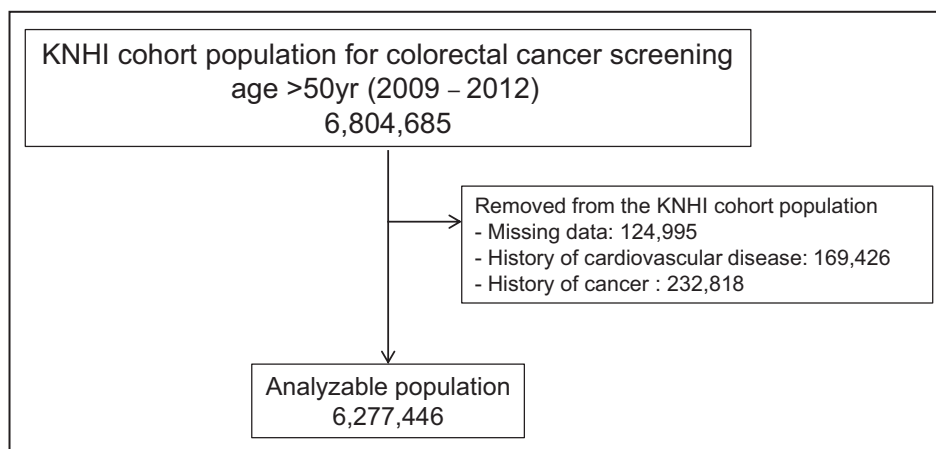
Figure 1. **Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the study population.**
KNHI indicates Korean national health insurance.

OC-Sensor DIANA kits (Eiken Chemical, Co), with a cutoff of 100 ng/mL; Hemo Tech NS-1000 kits (Alfresa Pharma, Co, Osaka, Japan), with a cutoff of 40 ng/mL; and Medex HM-JACK kits (Kyowa Chemical Industry, Co, Kagawa, Japan), with a cutoff of 30 ng/mL, were used for the quantitative method.[21] The results were categorized into negative and positive according to the cutoff points of each test kit.

Covariates

Other physical measurements, such as weight, height, and body mass index, as well as laboratory measurements, such as hemoglobin, estimated glomerular filtration rate, and the lipid profile, were all collected from the NHIS database on the index date. Anemia was defined as a serum hemoglobin level <12 mg/dL for men and 13 mg/dL for women, according to the World Health Organization criteria. Other clinical information, such as smoking, alcohol, and physical activity, was collected as self-answered questionnaires. Smoking status was categorized into 3 groups: nonsmoker, defined as those with <5 packs of smoking history; ex-smoker, defined as those with >5 packs but had quit smoking; and current smoker, defined as those with >5 packs and still smoking. Alcohol status was also subdivided according to consumption level per week: 0, 0 to 30, and >30 g/wk. The regular exercise group performed high-intensity exercise >3 days per week for at least 30 minutes or moderate-intensity exercise of >5 days per week for at least 20 minutes. Information on patient comorbidities was identified by *ICD-10* codes: hypertension (*ICD-10* codes I10-I11 and antihypertensive medication or systolic/diastolic blood pressure ≥140/90 mm Hg); diabetes mellitus (*ICD-10* codes E11-E14 and antidiabetic medication or fasting glucose level ≥126 mg/dL); and dyslipidemia (*ICD-10* code E78 and lipid-lowering agents or total cholesterol ≥240 mg/dL). These definitions using these *ICD-10* codes were validated in previous studies.[22]

Study End Point

The primary outcome was newly diagnosed ischemic stroke or MI. The secondary outcome was all-cause mortality during the follow-up period. *ICD-10* codes were used to define these diseases: ischemic stroke was defined as *ICD-10* code I63 or I64 during hospitalization with brain computed tomography or magnetic resonance imaging claim data; and MI was defined as hospitalization with *ICD-10* code of I21 or I22.[22] Patients who died of any cause were included as all-cause mortality. Up until the follow-up period of December 2017, deaths before MI or stroke event were censored according to the date of death.

All personal information was encrypted, and all data were anonymous; thus, informed consent of the study subjects was waived. The study was exempted by the Institutional Review Board of the Seoul National University Hospital (Institutional Review Board No. E-1906-008-1036).

Statistical Analysis

Student *t* test and the χ^2 test were used to compare the differences in continuous and categorical variables, respectively. The incidence rate was the number of events per 10 000 person-years. Univariate and multivariate-adjusted Cox regression models were used to estimate adjusted hazard ratios (aHRs) for the incidence of outcomes with the 95% CI. Multivariate models were adjusted for various factors known to be a risk for cardiovascular diseases, such as age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, and

body mass index.[23] Subgroup analyses were performed to demonstrate the trends of the relationship within the subgroups. With clinical significance of anemia and CRC having an association with FIT, further stratified analyses for patients with anemia and CRC were conducted to determine the association between the FIT results and outcomes, using multivariate-adjusted Cox regression. A sensitivity analysis using the internal validation group of those with >2 FIT results was also performed. We analyzed the data with SAS version 9.4 software (SAS Institute, Cary, NC) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered significant for all tests.

RESULTS

Characteristics of the Study Population

Among the 6 804 685 subjects screened, 6 277 446 were analyzed after excluding missing data, previously diagnosed cardiovascular diseases, and cancer. A total of 370 140 (5.9%) participants had positive FIT results, and baseline characteristics of the FIT-positive population are listed in Table 1. Subjects with positive FIT results were older, more likely to be men, current smokers, and heavy drinkers. Other comorbidities, such as diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome, and chronic kidney disease, were also more commonly observed in the FIT-positive population.

Incidence and Risk of Ischemic Stroke and MI

During the median follow-up period of 6.79 years, the incidence rates of ischemic stroke per 1000 person-years were 3.90 and 4.88 in the FIT-negative and FIT-positive groups, respectively. Incidence rates per 1000 person-years for MI were 2.44 and 2.99 in the FIT-negative and FIT-positive groups, respectively.

Compared with the FIT-negative group, the FIT-positive group showed an increased risk of ischemic stroke (aHR, 1.25 [95% CI, 1.23–1.27]), which was also significant after adjusting for age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, and body mass index (aHR, 1.09 [95% CI, 1.07–1.11]) (Table 2).

Similarly, the crude data and the multivariate analysis demonstrated elevated risk for MI in the FIT-positive group (aHR, 1.22 [95% CI, 1.19–1.25]; and aHR, 1.09 [95% CI, 1.06–1.12], respectively) (Table 2). Cumulative incidence was similar to an increased probability of stroke and MI in the FIT-positive population, as shown in Figure 2. The disparity became more apparent during the follow-up.

Table 1. Baseline Characteristics of the Study Population

Characteristic	FIT (−)	FIT (+)	P Value
No.	5 907 306	370 140	
Age, y	60.42±8.16	61.2±8.53	<0.0001
Men, n (%)	2 563 831 (43.4)	193 208 (52.2)	<0.0001
Smoking, n (%)			<0.0001
Never smoker	4 068 423 (68.87)	234 334 (63.31)	
Ex-smoker	939 307 (15.9)	63 837 (17.25)	
Current smoker	899 576 (15.23)	71 969 (19.44)	
Alcohol, n (%)			<0.0001
None (0 g)	3 914 102 (66.26)	226 852 (61.29)	
Mild (0–30 g)	1 634 052 (27.66)	110 160 (29.76)	
Heavy (>30 g)	359 152 (6.08)	33 128 (8.95)	
Low income, n (%)*	1 307 320 (22.13)	83 898 (22.67)	<0.0001
Regular exercise, n (%)	1 287 194 (21.79)	77 225 (20.86)	<0.0001
Diabetes mellitus, n (%)	885 881 (15)	62 990 (17.02)	<0.0001
Hypertension, n (%)	2 520 411 (42.67)	175 043 (47.29)	<0.0001
Dyslipidemia, n (%)	1 820 217 (30.81)	117 221 (31.67)	<0.0001
Metabolic syndrome, n (%)	2 436 215 (41.24)	160 889 (43.47)	<0.0001
CKD, n (%)	456 155 (7.72)	33 948 (9.17)	<0.0001
Height, cm	159.7±8.47	160.59±8.62	<0.0001
Weight, kg	61.75±9.97	62.56±10.27	<0.0001
Body mass index, kg/m²	24.16±3.01	24.2±3.05	<0.0001
Waist circumference, cm	81.91±8.44	82.82±8.49	<0.0001
Systolic blood pressure, mm Hg	126±15.6	127.04±15.81	<0.0001
Diastolic blood pressure, mm Hg	77.37±10.05	78.01±10.23	<0.0001
eGFR, mL/min	85.43±31.7	84.67±30.04	<0.0001
Fasting glucose, mg/dL	101.69±24.53	103.01±26.39	<0.0001
Total cholesterol, mg/dL	201.22±37.97	200.43±38.92	<0.0001
HDL cholesterol, mg/dL	54.45±15.47	54.07±14.99	<0.0001
LDL cholesterol, mg/dL	119.87±34.91	118.67±35.97	<0.0001
Triglyceride, mg/dL	119.09 (119.04–119.14)	121.93 (121.72–122.14)	<0.0001

Values are presented in number (percentage) or mean±SD. CKD indicates chronic kidney disease; eGFR, estimated glomerular filtration rate; FIT, fecal immunochemical test; HDL, high-density lipoprotein; and LDL, low-density lipoprotein.

*Low income was defined as lowest 20% of the entire National Health Insurance Service population.

The positive FIT population had a higher risk of ischemic stroke and MI regardless of age, sex, and other comorbidities compared with the FIT-negative population (Figure 3). The trend toward an increased risk for cardiovascular diseases remained consistent, even with statistically significant heterogeneity of P for the interaction values, with a minor exception for heavy drinkers and current smokers.

We performed stratified analyses according to anemia and CRC, which are known as independent predictors for FIT results and cardiovascular diseases.[3,20]

Table 2. Risk of Ischemic Stroke, MI, and All-Cause Mortality in the FIT-Positive Population

Variable	FIT	No.	Outcome	Duration*	IR†	HR (95% CI)		
						Model 1	Model 2	Model 3
Ischemic stroke	No	5 907 306	156 193	40 094 101	3.90	1 (Reference)	1 (Reference)	1 (Reference)
	Yes	370 140	12 377	2 536 712	4.88	1.25 (1.23–1.27)	1.12 (1.10–1.15)	1.09 (1.07–1.11)
Myocardial infarction	No	5 907 306	98 355	40 311 977	2.44	1 (Reference)	1 (Reference)	1 (Reference)
	Yes	370 140	7628	2 554 674	2.99	1.22 (1.19–1.25)	1.12 (1.09–1.14)	1.09 (1.06–1.12)
All-cause mortality	No	5 907 306	10 333	40 602 874	0.25	1 (Reference)	1 (Reference)	1 (Reference)
	Yes	370 140	920	2 578 067	0.36	1.40 (1.31–1.49)	1.18 (1.10–1.26)	1.15 (1.07–1.23)

Model 1: crude data. Model 2: age and sex adjusted. Model 3: age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, and body mass index adjusted. FIT indicates fecal immunochemical test; HR, hazard ratio; IR, incidence rate; and MI, myocardial infarction.

*Follow-up duration in person-years.

†IR per 1000 person-years.

In terms of anemia, the risk of ischemic stroke and MI increased in the FIT-positive group regardless of anemia status, and there was no significant interaction between the FIT results and anemia, as depicted in Figure 4. In contrast, a significant interaction was detected between FIT and CRC incidence. A positive FIT result in those without CRC was associated with an increased risk of stroke (aHR, 1.10 [95% CI, 1.08–1.12]; $P<0.01$) and MI (aHR, 1.10 [95% CI, 1.07–1.12]; $P<0.01$).

Incidence and Risk of All-Cause Mortality

The cumulative incidence of mortality according to the FIT results is illustrated in Figure 2. The FIT-positive group was at a higher risk for all-cause mortality in the crude Cox regression analysis after adjusting for other factors (aHR, 1.40 [95% CI, 1.31–1.49]; and aHR, 1.15 [95% CI, 1.07–1.23], respectively) (Table 2). A subgroup analysis revealed an increased risk for all-cause mortality in FIT-positive participants regardless of age, sex, smoking status, alcohol consumption, regular activity, diabetes mellitus, hypertension, dyslipidemia, body mass index, or metabolic syndrome (Table S1).

Mortality was increased significantly by 15% in the FIT-positive compared with the FIT-negative group, even after excluding those with CRCs, as depicted in Figure 4.

Sensitivity Analysis

We collected a subset of data for participants with 3 consecutive FIT-positive results for the sensitivity analysis. In this subset, main results were redemonstrated; the FIT-positive population was at a higher risk of developing ischemic stroke, MI, and all-cause mortality (aHR, 1.10 [95% CI, 1.07–1.14]; aHR, 1.12 [95% CI, 1.08–1.16]; and aHR, 1.12 [95% CI, 1.07–1.35], respectively) (Table S2).

DISCUSSION

To our knowledge, this is the first observational study to evaluate the association between FIT results and cardiovascular diseases using a nationwide population cohort. The positive FIT results were associated with
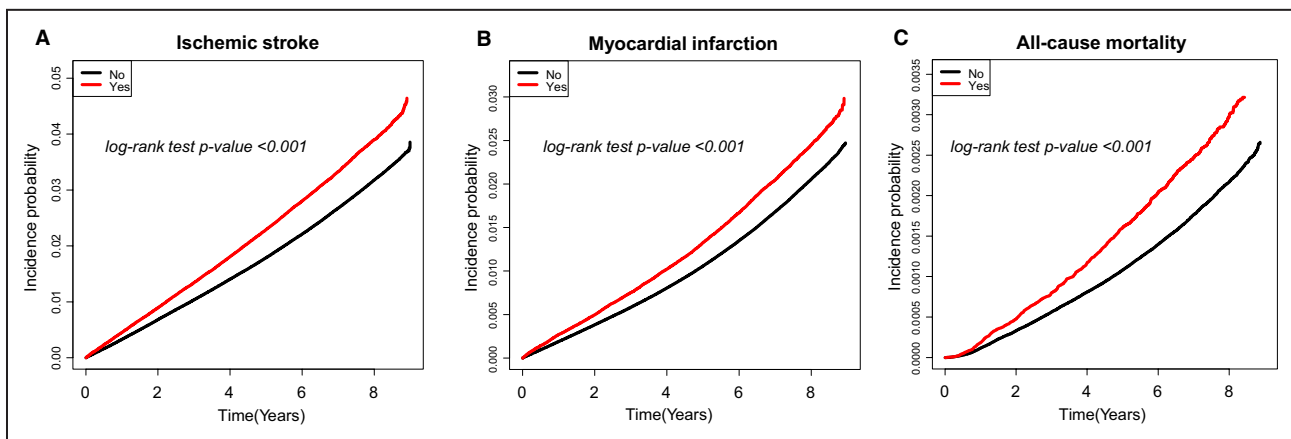

Figure 2. Kaplan-Meier curves for the incidence of ischemic stroke and myocardial infarction.
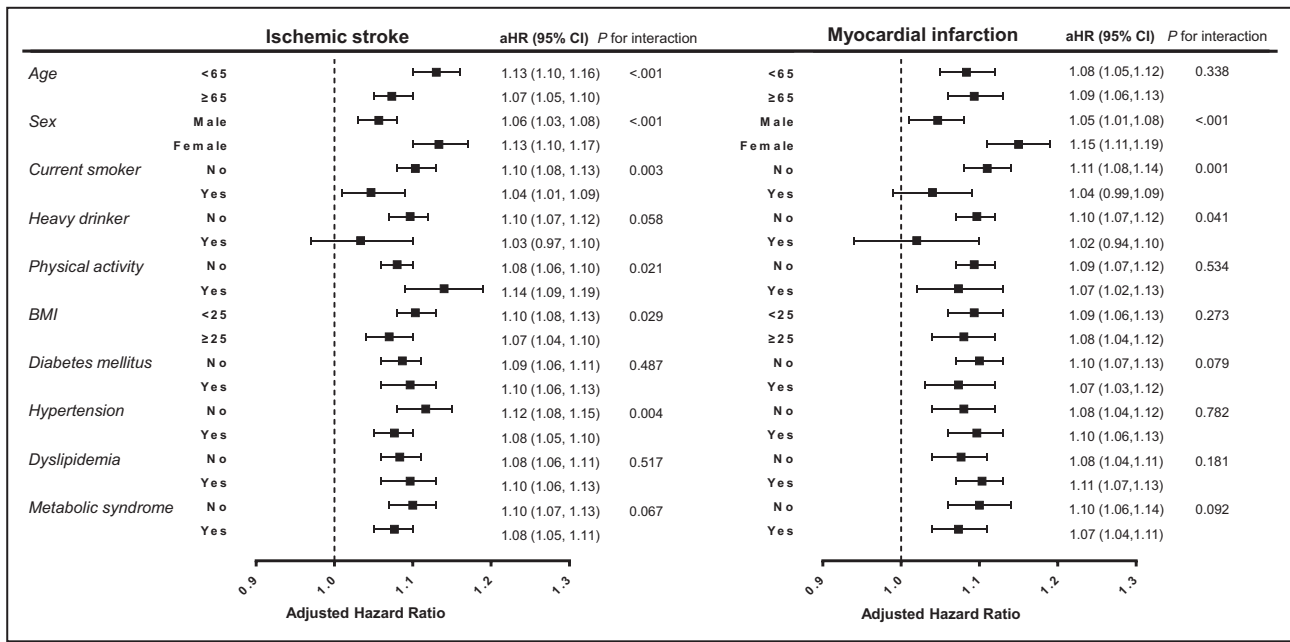**A**, Ischemic stroke. **B**, Myocardial infarction. **C**, All-cause mortality.

Figure 3. Hazard ratios for ischemic stroke and myocardial infarction of the fecal immunochemical test–positive population in different subgroups.
A, Ischemic stroke. **B**, Myocardial infarction. Hazard ratios (HRs) presented are with adjustment to age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, and body mass index (BMI). aHR indicates adjusted HR.

an increased risk of ischemic stroke, MI, and all-cause mortality. The development of cardiovascular diseases and mortality was independent of established risk factors.[23] Moreover, the association between positive FIT results and all-cause mortality remained positive, even in the non-CRC group.

The FIT-positive population and the studied outcomes (stroke and MI) share common risk factors, such as old age, smoking, heavy alcohol consumption, physical inactivity, and obesity.[15,16] Although the underlying mechanisms are not completely understood, the association between FIT positivity and cardiovascular diseases may be explained by systemic inflammation. Chronic systemic inflammation is known to be associated with numerous cancers, including CRCs,[24] by inducing gene mutations, promoting carcinogenesis, angiogenesis,

and cell proliferation, as well as inhibiting apoptosis.[17] Therefore, positive FIT results can be interpreted as generalized gut inflammation along with occult bleeding. Furthermore, a similar potential mechanism of the systemic inflammation sequence underlies ischemic stroke, MI, and their outcomes. One of the most common causative factors in stroke and MI is thromboembolism resulting from the rupture of an atherosclerotic plaque.[25] The initiation and progression of atherosclerotic plaques consist of a series of inflammatory pathways in the vascular wall involving molecular and cellular inflammatory mediators. An inflammatory condition that can trigger instability of atherosclerosis can alter susceptibility to stroke and MI.[18] Muir et al suggested that patients with an increased CRP (C-reactive protein) level have an increased risk of stroke.[26] Consequently, positive
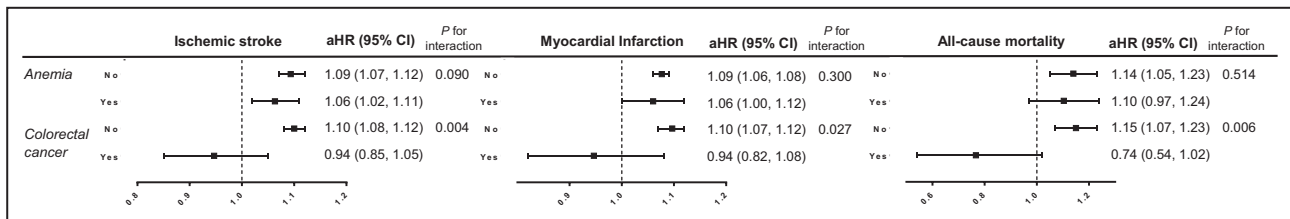

Figure 4. Stratified analysis by anemia status and colorectal cancer diagnosis in the fecal immunochemical test–positive population.
Hazard ratios (HRs) presented are with adjustment to age, sex, smoking, alcohol consumption, regular exercise, diabetes mellitus, hypertension, dyslipidemia, and body mass index. aHR indicates adjusted HR.

FIT results as a marker of the inflammatory reaction can be associated with cardiovascular disease and mortality.

The relationship between gut microbiota and cardiovascular diseases is controversial, and studies are ongoing to investigate the possible mechanism.[27] The levels of gut microbial-derived trimethylamine-N-oxide and dietary phosphatidylcholine metabolite via gut microbes are related to an increased risk of cardiovascular disease and atherosclerosis.[28] This finding supports the idea that the gut microbiota has relevance beyond the gastrointestinal tract. Disruption of intestinal barrier function (ie, "leaky gut") may lead to occult hemoglobin in the stool. FIT positivity may indicate dysregulation of the intestinal epithelial barrier, resulting in bacterial translocation and release of cytokines promoting atherosclerosis.[29] A change in the gut microbiota can also be associated with myocardial dysfunction, leading to disruption of the gut.[30] In this manner, recent studies have highlighted the brain-gut axis by discovering a proof-of-concept relationship between gut-microbiota–derived metabolites and stroke.[31,32]

Previous studies have shown that anemia is a strong predictor of cardiovascular diseases and outcomes.[19,20,33] Therefore, we determined whether the association between FIT positivity and cardiovascular disease is influenced by baseline anemia. However, our stratified analysis did not show a significant difference according to anemia status, suggesting that FIT positivity may be directly linked to cardiovascular disease independent of anemia status. Mechanisms other than anemia, such as systemic inflammation and gut microbiota, may play a greater role in the interaction between the FIT results and cardiovascular diseases.

The prognostic value of FIT results in CRC screening has been well established.[2,4,5] Acknowledging the interaction between FIT and CRC, we performed an interaction analysis to assess the value of FIT in the non-CRC population. The results revealed a 15% increased risk of mortality even for those without CRCs, which was consistent with our main outcome. This observation further supports the biological mechanisms of systemic inflammation and changes in gut microbiota.

A major limitation of this study is that it evaluated the association between the FIT results and the main outcomes, not the causal relationships. In addition, the long lag time from the FIT-positive results to the occurrence of stroke and MI may have hindered interpreting the relationship. However, we confirmed the consistency of our results by performing subgroup, interaction, and internal validation analyses. This trend was maintained by adjusting for other factors as well, providing more concrete evidence for our results. Second, no medication information, such as aspirin, other nonsteroidal anti-inflammatory drugs, and antiplatelet agents, was collected and adjusted for in the analysis. Antithrombotic agents are essential in cardiovascular disease and are also one of the main reasons for false-positive FIT results. Although not all of the medications were adjusted at baseline, we minimized bias by excluding all subjects with any history of cardiovascular disease and identified only those with first-time stroke and MI. Moreover, the subgroup analysis by anemia revealed no significant interaction between anemia and FIT, indicating consistency in the main outcome. Third, we could not distinguish between the first time ever MI/stroke and recurrent events because of the innate limitation in using *ICD-10* codes of the claims data. Further study is needed for future application in real-world practice. Last, some of the clinical information, such as smoking, alcohol consumption, and physical exercise, was collected via self-answered questionnaire, indicating a careful approach in interpretation.

In conclusion, we demonstrated that FIT positivity predicted an increased association with cardiovascular diseases and mortality. Subjects with a positive FIT result are not only at risk of colorectal neoplasia but may also be at risk of developing stroke and MI. Further study is needed to confirm the causal relationship, but this study postulated the novel concept of the clinical significance of FIT in fields other than CRC screening, which may pave the way for possible expansion of its use in the future.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Hazard ratios for all-cause mortality of the fecal immunochemical test (FIT)-positive population in various subgroups.

		Death	P for interaction
Age	<65	1.19 (1.04, 1.37)	0.325
	≥65	1.14 (1.05, 1.23)	
Sex	Male	1.15 (1.06, 1.25)	0.864
	Female	1.14 (1.02, 1.28)	
Current smoker	No	1.16 (1.07, 1.25)	0.446
	Yes	1.11 (0.97, 1.27)	
Heavy drinker	No	1.15 (1.07, 1.23)	0.960
	Yes	1.16 (0.92, 1.46)	
Physical activity	No	1.13 (1.05, 1.22)	0.364
	Yes	1.23 (1.051, 1.44)	
Diabetes	No	1.14 (1.05, 1.24)	0.781
	Yes	1.16 (1.03, 1.30)	
Hypertension	No	1.21 (1.08, 1.37)	0.144
	Yes	1.12 (1.03, 1.22)	
Dyslipidemia	No	1.18 (1.09, 1.28)	0.213
	Yes	1.08 (0.96, 1.22)	
BMI	<25	1.17 (1.08, 1.27)	0.240
	≥25	1.09 (0.96, 1.23)	
Metabolic syndrome	No	1.17 (1.07, 1.28)	0.352
	Yes	1.11 (1.00, 1.23)	
CKD	No	1.18 (1.09, 1.27)	0.038
	Yes	1.02 (0.88, 1.17)	

Table S2. Sensitivity analysis to evaluate the risk of ischemic stroke, myocardial infarction, and all-cause mortality in the fecal immunochemical test (FIT)-positive population of the validation cohort.

	FIT	Number	Outcome	Duration[a]	IR[b]	HR(95% C.I)		
						Model1	Model2	Model3
Ischemic Stroke	No	1,157,997	29,854	7812370	3.82	1(ref.)	1(ref.)	1(ref.)
	Yes	167,226	5,269	1133287	4.65	1.22(1.18,1.25)	1.13(1.10,1.16)	1.10(1.07,1.14)
Myocardial Infarction	No	1,157,997	18,579	7852167	2.37	1(ref.)	1(ref.)	1(ref.)
	Yes	167,226	3,278	1140634	2.87	1.21(1.17,1.26)	1.14(1.10,1.18)	1.12(1.08,1.16)
All-cause mortality	No	1,157,997	1,659	7906360	0.21	1(ref.)	1(ref.)	1(ref.)
	Yes	167,226	331	1150188	0.29	1.37(1.21,1.54)	1.22(1.08,1.37)	1.12(1.07,1.35)