



BMJ Open Association between faecal haemoglobin concentration and the risk of cardiovascular diseases among Taiwanese adults in a community-based screening cohort

Kuo-Liong Chien ¹, Ting-Yu Lin,¹ Chen-Yang Hsu,¹ Chang-Chuan Chan,² Tony Hsiu-Hsi Chen ¹, Li-Sheng Chen^{3,4}

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For numbered affiliations see end of article.

Correspondence to
Dr Li-Sheng Chen;
samchen@tmu.edu.tw

ABSTRACT

Objectives The role of faecal haemoglobin as a colorectal cancer screening tool has been demonstrated. However, the association between the faecal haemoglobin concentration and the risk of cardiovascular disease events and deaths is still unclear.

Design Cohort study design.

Setting Population-based organised integrated service screening in Keelung City, Taiwan

Participants A total of 33 355 healthy individuals aged over 40 years who were free of cardiovascular disease at study entry were followed up.

Main outcomes and measures Newly diagnosed cardiovascular disease events and deaths.

Results After a median follow-up of 2.39 years, a total of 2768 participants developed cardiovascular events, and after a median follow-up of 8.43 years, 317 cases of cardiovascular deaths occurred. The risk of cardiovascular disease increased with baseline faecal haemoglobin in a dose–response manner, yielding a significant elevated risk of cardiovascular disease in parallel with the incremental concentration of faecal haemoglobin (adjusted HRs=1.04, 1.10, 1.40 and 1.23 for faecal haemoglobin concentrations of 1–19, 20–49, 50–99 and ≥100 ng/mL, trend test, $p<0.0001$, as compared with the reference group with undetectable faecal haemoglobin concentrations). A similar pattern was observed for the risk of cardiovascular disease deaths. In addition, the faecal haemoglobin improved the prediction performance of the model for the risk of cardiovascular diseases; the integrated discrimination improvement was 0.3% ($p<0.001$) for cardiovascular events and 0.1% ($p=0.020$) for cardiovascular deaths.

Conclusions Our data support that faecal haemoglobin concentrations may be associated with the risk of cardiovascular diseases. The biological mechanisms underlying the role of faecal haemoglobin as health outcomes should be investigated.

INTRODUCTION

Cardiovascular disease is a great burden for non-communicable diseases globally. Lifestyle-related risk factors and metabolic

Strengths and limitations of this study

- This prospective cohort study, with substantial sample sizes and follow-up periods, showed that the faecal immunochemical test was associated with the cardiovascular risk and may be used as the primary prevention strategy.
- Comprehensive statistical approaches, including competing risks, cubic spline modelling and net reclassification improvement statistics, were applied.
- Only one-time measurement was performed.

status are considered important risk factors for cardiovascular diseases. Current evidence supports that the faecal immunological test improves colorectal cancer prognosis, and the test is recommended for screening in adult populations.^{1–3} The faecal haemoglobin concentration derived from faecal immunological test results is considered a novel biomarker of non-communicable diseases such as metabolic syndrome and chronic periodontitis.^{4,5} Previous studies have shown the association of faecal haemoglobin with various outcomes, especially all-cause deaths,⁶ and our recent study clearly demonstrated that metabolic syndrome status and some components, including waist circumference, fasting glucose and low high-density lipoprotein (HDL) cholesterol level, are associated with a high faecal haemoglobin level.⁵

Evidence has been provided for the role of faecal haemoglobin in colorectal cancer screening; however, the role of faecal haemoglobin in cardiovascular disease risk is unknown. Therefore, we examined the following in this study in participants who had undertaken the Keelung community colorectal cancer screening programme: first, we tested the association between

faecal haemoglobin levels and the risk of cardiovascular diseases, including coronary events and stroke subtypes; second, we investigated the potential dose–response relationship. We attempted to elucidate possible biological mechanisms underlying the association.

METHODS

Study design and population

We conducted this community-based cohort study in participants who had undertaken the Keelung Community Integrated Screening (KCIS) Program.^{7–9} In brief, the cohort was composed of 39 384 adult participants from Keelung City, which is the northernmost city in Taiwan, and the participants were invited to take part in a screening programme. For cancers and cardiovascular diseases, screening strategies with various items were designed accordingly,⁹ and for the KCIS programme, annual recruitment was conducted between 1999 and 2004. Data on demographic characteristics and lifestyle habits were collected using structured questionnaires, and blood samples and faecal samples were collected using standard procedures. Data on lifestyle risk factors, including smoking, alcohol drinking, exercise, and dietary habits, were obtained using the structured questionnaire. Personal and family histories of diabetes mellitus, hypertension and cardiovascular diseases were collected.

Written informed consent of each participant was obtained at recruitment into the programme.

Measurements of faecal haemoglobin concentration

Measurements of faecal haemoglobin concentrations have been described previously.^{4 6} In brief, trained public health nurses or volunteer health workers were provided standard instructions on how to collect faecal samples, using the faecal immunochemical test collecting kits (OC-SENSOR, Eiken, Japan) as a part of the on-site screening activity. Our results of 100 ng of haemoglobin/mL of buffer equals 20 µg of haemoglobin per gramme of faeces.¹⁰ One sample from a bowel movement was collected from each participant. The attendees were asked to return the samples to the nearest health centre within 3–5 days. The collected samples were then stored in a 4°C refrigerator and sent to the central laboratory for analysis at no more than 7 days after the screening activity. The reading of the faecal haemoglobin concentration was reported using an interval scale. No reading of the faecal haemoglobin concentration was recorded as undetected, and the participants with a faecal haemoglobin concentration of ≥ 100 ng/mL were referred to undergo colonoscopy to confirm whether they had adenoma or invasive carcinoma of the colon and rectum. The participants with faecal haemoglobin levels less than the cut-off were invited for the next round of screening.

Case ascertainment and matched control selection

We defined cardiovascular events and cardiovascular deaths (International Classification of Diseases codes:

410–414 and 430–438 for cardiovascular events and 410–414, 430–438, I20–I25 and I60–I69 for cardiovascular deaths) from the linkage data of the national death certificate as the following criteria. First, cardiovascular events, including coronary heart disease and stroke, were identified. Incident coronary heart disease cases were defined based on the following criteria: fatal coronary heart disease and hospitalisation due to non-fatal myocardial infarction or percutaneous coronary intervention and coronary bypass surgery. These criteria were ascertained based on the combined information from patients and medical record review. Incident stroke cases were ascertained based on the following criteria: a sudden neurological deficit of vascular origin that lasted longer than 24 hours, with supporting evidence from image studies and medical records. Second, cardiovascular deaths were identified as deaths from coronary heart disease and stroke based on information from the official certificate documents, which was further verified by house-to-house visits. Based on the follow-up strategy, we examined cardiovascular events up to 2004 and cardiovascular deaths up to 2010 (online supplementary figure 1).

Statistical analysis

The participants were categorised based on faecal haemoglobin concentrations; analysis of variance and χ^2 tests were used to compare means and proportions among various faecal haemoglobin groups. In addition, age-adjusted and sex-adjusted partial Spearman correlation coefficients were estimated to determine the association between haemoglobin and various metabolic risk factors.

The incidence rates of cardiovascular events and deaths were calculated by dividing the number of cases by the number of person years of the follow-up for each quartile. We plotted the Kaplan-Meier survival curves for all-cause deaths and cardiovascular events stratified by the faecal haemoglobin status, and the log-rank test was conducted to determine the difference across survival functions. The multiple Cox proportional hazards regression model was used to calculate the HR and 95% CI of faecal haemoglobin levels, with the undetectable group used as the reference. Model 1 included age and gender; model 2 additionally included body mass index, smoking (yes/no or abstinence), current alcohol drinking status (current/quit or none) and regular exercise (yes/no, defined as ≥ 30 min moderate-intensity physical activity, such as walking or cycling, per day). Model 3 additionally included clinical variables, including systolic and diastolic blood pressure, fasting glucose, total cholesterol, triglycerides, HDL cholesterol and white blood cell counts. Model 4 additionally included drug usages for hypertension, diabetes and hyperlipidaemia. The test for trend was estimated by the significance value from the regression model with the median value of each category of the dummy faecal haemoglobin.

We additionally used two competing risk models including colorectal cancer events ($n=73$). We used two approaches: cause-specific hazard risk and Fine and

Gary competing risk model.¹¹ Moreover, we performed subgroup analyses of baseline covariates, including age, sex, body mass index, smoking, hypertension and diabetes mellitus status. In addition, we tested the proportional hazard model assumption by plotting the log(-log(survival time)) versus the log of survival time and including time-dependent covariates, and the results were acceptable.

To further investigate the role of faecal haemoglobin concentrations in predicting cardiovascular risk, we compared the model including traditional risk factors and the model additionally including faecal haemoglobin concentrations and tested the prediction performance of models based on calibration and discrimination ability. First, we assessed the goodness of fit for all models based on the Hosmer–Lemeshow test,¹² which is a calibration measure used to calculate how close predicted risks are to actual observed risks, and the results showed favourable calibration. Second, we compared the discrimination ability by using the area under receiver operative characteristic curve (AUC). An AUC curve is a graph of sensitivity versus 1—specificity (or false-positive rate) for various cut-off definitions of a positive diagnostic test result.¹³ Statistical differences in AUCs were compared using the method of DeLong *et al.*¹⁴ The AUC is a global summary measure for discrimination between individuals developing outcomes and those who did not.¹⁵ Third, we compared the models by using the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) statistics.¹⁶ The NRI statistic was based on reclassification tables and was calculated from a sum of differences between the ‘upward’ movement in categories for event participants and the ‘downward’ movement in those for nonevent participants. We presented the NRI according to the a priori risk categories. IDI can be interpreted as the difference between improvement in average sensitivity and any potential increase in average 1—specificity, and the statistic showed a difference in Yates discrimination slopes with and without faecal haemoglobin concentration information.

We used the natural cubic spline semiparametric regression models to examine the relationship between the faecal haemoglobin concentration and the risk of cardiovascular events and deaths. Natural cubic splines are smooth polynomial functions that can be used to fit data and accommodate potential changes in the direction of the association between the exposure variable and the outcome of interest, and they are constructed of piecewise third-order polynomials that pass through a set of control points and its linear in this tail beyond the boundary knots.^{17 18} An SAS macro named ‘lgtphcurv9’ written by Harvard scholars¹⁹ was used, and it implements the natural cubic spline methodology to fit potential nonlinear dose–response curves in proportional hazards models. Likelihood ratio tests were performed to test nonlinear and linear relationships.

All statistical analyses were performed using SAS (V.9.4; SAS Institute), and $p < 0.05$ was considered statistically significant.

Patient and public involvement

Patient and public involvement in this study was achieved by the inclusion of personnel from the local public health sector and Public Health Bureau in Keelung City, who are responsible for the monitoring health indicators. The results of the study will be disseminated to the public through the personnel of the Public Health Bureau of Keelung City.

RESULTS

After excluding those with prevalent cardiovascular diseases ($n=6029$), a total of 33 355 participants were recruited into this study. Table 1 presents the distributions of basic demographic and clinical characteristics of the study participants according to faecal haemoglobin concentrations. Compared with those with undetectable or lower faecal haemoglobin levels, the participants with higher faecal haemoglobin levels were older; more likely to be men; more likely to have the habit of current smoking; less likely to perform regular exercise; had higher systolic and diastolic blood pressure, fasting glucose, and total and HDL cholesterol; and lower haemoglobin level. We found that the distribution of faecal haemoglobin levels was skewed to the right (online supplementary figure 2).

The correlation coefficients for the association between faecal haemoglobin and various clinical variables were small, ranging from -0.153 for haemoglobin to 0.114 for HDL cholesterol concentration (online supplementary table 1), implying that the faecal haemoglobin level was not associated with other atherosclerotic risk factors.

After a median follow-up of 2.39 years (IQR 1.26–3.35 years), a total of 2768 participants developed cardiovascular events, and after a median follow-up of 8.43 years, 2299 cases of deaths occurred; among them, 317 cases were due to cardiovascular deaths. The Kaplan–Meier curves for the event-free rates for both cardiovascular events and deaths for various faecal haemoglobin groups were significantly different (the log-rank test, $p < 0.001$, figure 1).

Table 2 shows the incidence rates and adjusted HRs and 95% CIs of faecal haemoglobin concentrations for the risk of cardiovascular events and deaths in the study participants. Regarding cardiovascular events, as faecal haemoglobin concentrations increased, the adjusted HRs increased progressively (1.04 for 1–19 ng/mL, 1.10 for 20–49 ng/mL, 1.40 for 50–99 ng/mL and 1.23 for ≥ 100 ng/mL, p for trend < 0.0001). The similar pattern was observed for cardiovascular deaths (1.26 for 1–19 ng/mL, 1.13 for 20–49 ng/mL, 1.31 for 50–99 ng/mL and 1.73 for ≥ 100 ng/mL, p for trend < 0.0001).

Using the faecal haemoglobin as a screening tool for colorectal cancer risk, we used the competing risk model, in which colorectal cancer ($n=73$) was considered as the competing risk. The results showed a significant association between faecal haemoglobin and the risk of cardiovascular events and deaths, and for faecal haemoglobin ≥ 100 ng/mL, adjusted HRs were 1.24 (95% CI 1.04 to

Table 1 Basic characteristics of the study participants according to the faecal haemoglobin concentration status

Characteristics	Total	Faecal Hb concentration (ng/mL)					P value
		Undetected	1–19 ng/mL 0.1–3.9 µg/g	20–49 ng/mL 4–9.9 µg/g	50–99 ng/mL 10–19.9 µg/g	≥100 ng/mL ≥20 µg/g	
Age, year, mean±SD	55.0±11.2	53.5±10.5	54.8±11.1	56.1±11.5	57.5±12.1	58.5±12.1	<0.0001
Age group, n (%)							<0.0001
40–49	13 157	4924 (43.2)	4662 (39.9)	2403 (36.3)	694 (33.1)	474 (29.8)	
50–59	8933	3301 (29.0)	3118 (26.7)	1674 (25.3)	480 (22.9)	360 (22.6)	
60–69	6959	2102 (18.5)	2430 (20.8)	1510 (22.8)	517 (24.7)	400 (25.2)	
70+	4306	1059 (9.3)	1464 (12.5)	1024 (15.5)	403 (19.2)	356 (22.4)	
Gender, n (%)							<0.0001
Men	12 867	4431 (38.9)	4381 (37.5)	2501 (37.8)	852 (40.7)	702 (44.2)	
Women	20 488	6955 (61.1)	7293 (62.5)	4110 (62.2)	1242 (59.3)	888 (55.8)	
Smoking, n (%)							<0.0001
No	24 434	8380 (74.7)	8618 (74.8)	4890 (74.9)	1463 (70.7)	1083 (69.1)	
Quit	2074	688 (6.1)	720 (6.3)	395 (6.0)	160 (7.7)	111 (7.1)	
Current	6389	2145 (19.1)	2177 (18.9)	1248 (19.1)	445 (21.5)	374 (23.9)	
Alcohol intake, n (%)							0.006
No	25 054	8536 (76.8)	8785 (76.7)	5008 (76.9)	1568 (76.0)	1157 (74.1)	
Quit	1237	392 (3.5)	407 (3.6)	260 (4.0)	103 (5.0)	75 (4.8)	
Current	6408	2182 (19.6)	2265 (19.8)	1241 (19.1)	391 (19.0)	329 (21.1)	
Regular exercise, n (%)							<0.0001
No	21 527	7103 (64.3)	7600 (66.6)	4425 (68.0)	1386 (67.3)	1013 (65.3)	
Yes	11 060	3952 (35.7)	3817 (33.4)	2079 (32.0)	674 (32.7)	538 (34.7)	
Systolic BP (mm Hg)	128.8±20.6	129.5±20.4	128.5±20.4	127.6±20.8	129.5±21.8	130.8±21.4	<0.0001
Diastolic BP (mm Hg)	79.9±12.3	79.1±12.6	80.3±12.1	80.1±11.7	81±12.3	80.8±12.5	<0.0001
Fasting sugar (mg/dL)	98.0±32.0	98.7±31.5	96.9±30.7	97.3±33	99.9±36	100.7±35.4	<0.0001
Total cholesterol (mg/dL)	201.2±38.5	202.2±38	200.5±38.5	200.1±38.8	201.3±39.4	202.9±38.9	0.0004
Triglyceride (mg/dL)	133.5±115.8	135.2±116.0	132.8±117.5	130.3±116.5	132.6±100.9	140.1±116.5	0.009
HDL cholesterol (mg/dL)	57.7±14.6	55.8±14.4	58.0±14.4	60.1±14.4	58.9±14.5	56.4±15.1	<0.0001
Haemoglobin (g/dL)	13.8±1.7	14.1±1.7	13.8±1.7	13.5±1.7	13.6±1.7	13.7±1.8	<0.0001
WBC (10 ⁹ /L)	6.3±1.7	6.3±1.6	6.2±1.6	6.2±1.6	6.3±1.7	6.5±2.0	<0.0001
Treatment of DM, n (%)							0.0003
No	32 197	11 047 (97.0)	11 276 (96.6)	6349 (96.0)	2001 (95.6)	1524 (95.8)	
Yes	1158	339 (3.0)	398 (3.4)	262 (4.0)	93 (4.4)	66 (4.2)	
Treatment of HTN, n (%)							<0.0001
No	30 684	10 587 (93.0)	10 748 (92.1)	6024 (91.1)	1888 (90.2)	1437 (90.4)	
Yes	2671	799 (7.0)	926 (7.9)	587 (8.9)	206 (9.8)	153 (9.6)	
Treatment of HLD							0.25
No	32 871	11 225 (98.6)	11 509 (98.6)	6508 (98.4)	2055 (98.1)	1574 (99.0)	
Yes	484	161 (1.4)	165 (1.4)	103 (1.6)	39 (1.9)	16 (1.0)	
Colorectal death							
Cases		11	18	16	7	21	
Person year		89 122.8	95 131.3	56 474.7	17 324.8	12 240.9	
Rates/1000 person year		0.123	0.189	0.283	0.404	1.716	<0.0001

BP, blood pressure; HDL, high-density lipoprotein; WBC, white blood cell; DM, diabetes mellitus; HTN, hypertension; HLD, hyperlipidaemia.

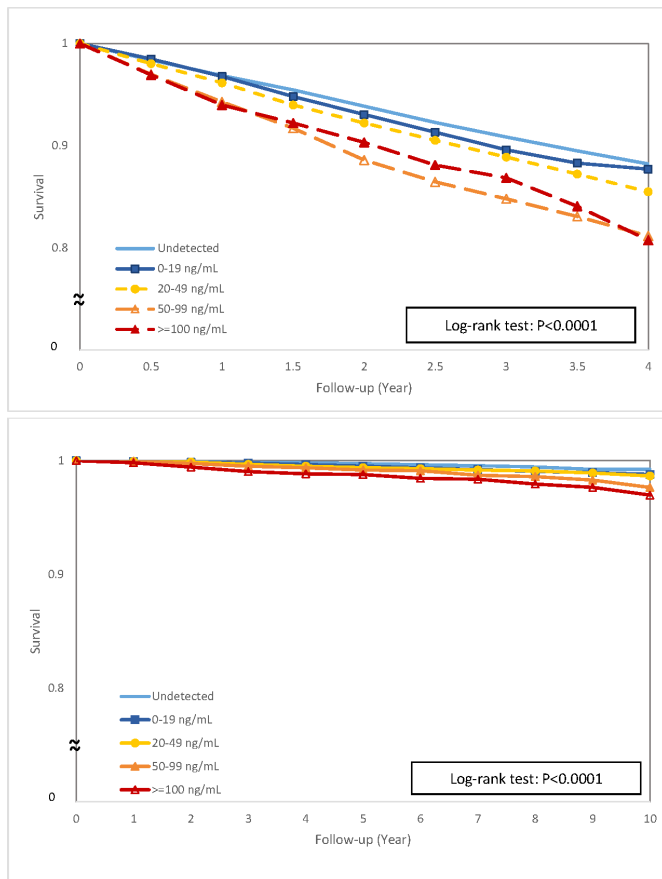


Figure 1 Survival curves for the risk of cardiovascular events (upper) and deaths (lower) in the study participants (the log-rank test, $p < 0.001$ for both figures).

1.48) for cardiovascular events and 1.80 (95% CI 1.17 to 2.76) for cardiovascular deaths (online supplementary table 2).

We estimated the prediction ability of the faecal haemoglobin concentration for cardiovascular risk. We found that the areas under the receiver operating characteristic (ROC) curves were not significant between the models without and with faecal haemoglobin (0.708 vs 0.713 for cardiovascular events and 0.877 vs 0.879 for deaths, online supplementary table 3), and the ROC curves overlapped for the models without and with faecal haemoglobin (online supplementary figure 3). However, we found that after adding faecal haemoglobin, IDI values increased by 0.3% ($p < 0.001$) for cardiovascular events and 0.1% for cardiovascular deaths ($p = 0.020$) (online supplementary table 3).

Using the natural cubic spline semiparametric regression models, we found that the relationship between faecal haemoglobin and cardiovascular events and deaths was linear across faecal haemoglobin levels less than 100 ng/mL (figure 2).

We performed subgroup analyses and checked the modification of the potential effect by various confounding factors, including age, gender, body mass index, blood pressure, fasting glucose, total cholesterol, triglycerides, HDL cholesterol and haemoglobin, and

the results showed that the relationships between faecal haemoglobin and cardiovascular risk were consistent across various variables, without significant interaction effects of these variables (online supplementary table 4).

DISCUSSION

Main findings

This is the first large-scale community-based cohort study to investigate the role of faecal haemoglobin in the risk of cardiovascular disease. The results clearly demonstrated a dose-response and consistent relationship across various clinical statuses. In addition, the prediction ability of the model additionally including faecal haemoglobin for the risk of cardiovascular diseases was higher than that of the model including traditional atherosclerotic risk factors.

Comparison of the current study with previous studies

Our previous studies based on faecal haemoglobin concentrations for various health statuses have provided evidence for the role of faecal haemoglobin in non-communicable disease prevention. Chiang *et al* studied 956 005 Taiwanese adults aged 50–69 years in a nationwide colorectal cancer screening programme to compare two methods, namely OC-Sensor versus HM-Jack, for determining the validity of the faecal haemoglobin level.²⁰ Yen *et al* investigated the same community-based integrated screening programme for colorectal cancer prevention ($n = 54\,921$ patients 40 years or older) and demonstrated a strong linear dose-response relationship for the risk of colorectal cancer among men, rather than women.⁴ Moreover, Lee *et al* found a dose-response relationship between faecal haemoglobin and colorectal cancer risk when they examined 59 389 individuals (4.0%) among 1 489 937 Taiwanese adults aged 50–69 years with faecal haemoglobin ≥ 20 $\mu\text{g/g}$ haemoglobin during 2004 and 2009.²¹ Moreover, Chiu *et al* obtained data during 2004–2009 from 29 969 patients who underwent colonoscopy after positive faecal haemoglobin in the Taiwanese Nationwide Colorectal Screening Program and investigated the interval colorectal cancer incidence.²² Regarding other chronic diseases, Yen *et al* demonstrated an association between faecal haemoglobin and the periodontal index among 6214 attendees in the community.⁴ Our research group also demonstrated that faecal haemoglobin was associated with the metabolic syndrome status in the community-based screening cohort,⁵ implying faecal haemoglobin as a risk factor for atherosclerotic diseases.

Libby *et al* conducted a screening programme of 134 192 adults aged 54–74 years in Scotland based on the faecal haemoglobin status (positive (2.03%) vs negative status) over 16-year follow-up,²³ and they found that compared with those with negative faecal haemoglobin, the participants with positive faecal haemoglobin had a higher risk of death from both colorectal cancer (adjusted HR 7.79 (95% CI 6.13 to 9.98)) and all causes excluding colorectal cancer (adjusted HR 1.58 (1.45 to 1.73)). The death rates for colorectal cancer in the Scotland cohort were much

Table 2 Incidence rates, follow-up person years and rates of cardiovascular disease events and cardiovascular deaths as well as HRs and 95% CIs of faecal haemoglobin concentrations in the participants according to undetected, 1–19, 20–49, 50–99 and ≥100 ng/mL

	Undetected		1–19 ng/mL		20–49 ng/mL		50–99 ng/mL		≥100 ng/mL		
Median, nmol/L	0	9	28	64	229						
CVD events											
Cases	696	932	694	277	169						
Person year (py)	21 826.6	26 317.0	17 517.4	5061.3	3244.9						
Rates/1000 py	31.9	35.4	39.6	54.7	52.1						
	HR	HR	HR	HR	HR	95% CI	95% CI	95% CI	HR	95% CI	Trend test
Model 1	1	1.03	1.09	1.38	1.21	0.98 to 1.21	1.20 to 1.59	1.02 to 1.43	1.21	1.02 to 1.43	<0.0001
Model 2	1	1.02	1.10	1.4	1.23	0.98 to 1.22	1.21 to 1.61	1.03 to 1.45	1.23	1.03 to 1.45	<0.0001
Model 3	1	1.04	1.12	1.41	1.24	1.00 to 1.25	1.22 to 1.63	1.04 to 1.48	1.24	1.04 to 1.48	<0.0001
Model 4	1	1.04	1.10	1.40	1.23	0.99 to 1.24	1.21 to 1.63	1.04 to 1.47	1.23	1.04 to 1.47	0.002
CVD death											
Cases	66	112	71	35	33						
Py	89 122.8	95 131.3	56 474.7	17 324.8	12 240.9						
Rates/1000 py	0.7	1.2	1.3	2.0	2.7						
	HR	HR	HR	HR	HR	95% CI	95% CI	95% CI	HR	95% CI	Trend test
Model 1	1	1.27	1.14	1.45	1.88	0.81 to 1.60	0.96 to 2.19	1.24 to 2.86	1.88	1.24 to 2.86	0.009
Model 2	1	1.23	1.10	1.35	1.76	0.78 to 1.55	0.89 to 2.06	1.15 to 2.70	1.76	1.15 to 2.70	0.026
Model 3	1	1.30	1.18	1.33	1.79	0.83 to 1.67	0.86 to 2.06	1.17 to 2.76	1.79	1.17 to 2.76	0.026
Model 4	1	1.26	1.13	1.31	1.73	0.8 to 1.6	0.85 to 2.02	1.13 to 2.66	1.73	1.13 to 2.66	0.025

Model 1: adjusted for age and gender.

Model 2: model 1 variables and additionally adjusted for body mass index, smoking, alcohol drinking and regular exercise.

Model 3: model 2 variables and additionally adjusted for systolic blood pressure, diastolic blood pressure, fasting glucose, total cholesterol, triglycerides and HDL cholesterol, and white blood cell.

Model 4: model 3 variables and additionally adjusted for drug usages for hypertension, diabetes and hyperlipidaemia.

CVD, cardiovascular disease.

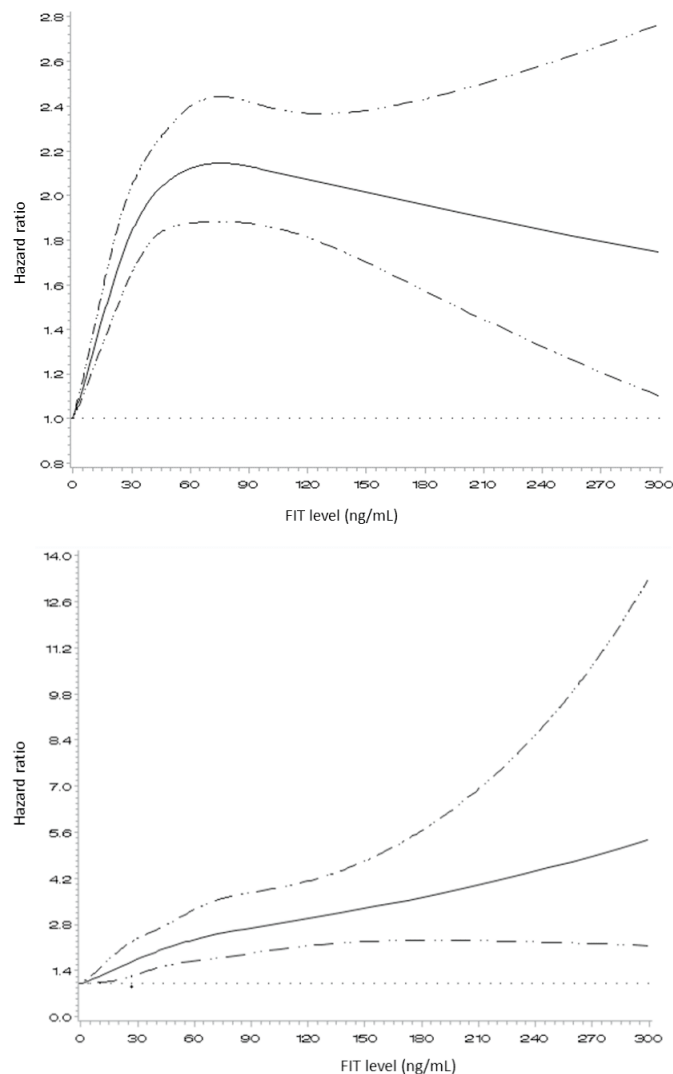


Figure 2 The cubic spline relationship between faecal haemoglobin concentration (FIT level) and the risk of cardiovascular events (upper) and deaths (lower), test for linearity, $p < 0.0001$; test for overall significance of the curves $p < 0.0001$.

higher (0.35/1000 person years in the negative group and 3.42/1000 person years in the positive group) than our data (0.12/1000 person years in the undetected group). The discrepancy between the two cohorts may be attributed to young age (including 40 years and older) and low colorectal cancer risk in Taiwan. However, our data provided a consistent relationship between faecal haemoglobin and health outcomes, including colorectal cancer and cardiovascular risk.

The proposed biological mechanism for the role of faecal haemoglobin

The biological mechanisms for the effect of faecal haemoglobin on the risk of atherosclerotic diseases remain unknown. The mechanisms may be as follows: first, faecal haemoglobin may be considered a biomarker of atherosclerosis and inflammation and may be related to the nutritional status for health. Intestinal microbiota,

an atherosclerotic predisposition, may be related to inflammation and dysbiosis in intestines.²⁴ Second, our previous studies have demonstrated that faecal haemoglobin concentrations are associated with colorectal benign lesions, such as adenoma and polyps,²⁵ and nutrition-related factors may be associated with the risk of colorectal cancer and cardiovascular diseases. Third, faecal haemoglobin may be a surrogate endpoint related to atherosclerosis, including chronic periodontitis and metabolic syndrome,⁴ implying coexisting health status contributed to the association between faecal haemoglobin and cardiovascular risk.

Immunological pathways for insulin resistance and atherosclerosis as well as elevated faecal haemoglobin concentrations have been postulated to explain colorectal cancer risk.^{26–28} Moreover, inflammatory processes underlie metabolic syndrome and atherosclerosis and the platelet activation of thrombosis contribute to inflammation and colorectal cancer.²⁹

Laboratory data showed that the adiponectin-adenosine monophosphate-activated protein kinase alpha signalling pathway is related to colorectal carcinogenesis activation, and the underlying hyperinsulinaemia of metabolic syndrome and atherosclerosis is strongly related to inflammatory pathways, including activating insulin receptor, insulin growth factor-1, tumour necrosis factor-alpha and interleukins.^{30 31} Additional studies on inflammation, tumour genesis and atherosclerosis, which are related to intestinal microbiota and platelet functions, may provide insights into the biological mechanism for faecal haemoglobin and cardiovascular diseases.

Public health implications

Based on the finding of a strong and dose–response association between faecal haemoglobin and health outcomes, including colorectal cancer, all-cause deaths and cardiovascular diseases, we propose the implementation of a screening programme with faecal haemoglobin measurements for health promotion. Vigilant awareness for high faecal haemoglobin levels and further health consultation for high-risk individuals may aid in the early prevention of the aforementioned chronic diseases.

Study strength and weakness

The strengths of the present study included a large sample size and a long follow-up time, and the standardisation of outcome ascertainment from the national health insurance database enabled the comparability and validity of endpoints. In addition, detailed lifestyle and clinical variables were incorporated into the model to evaluate the effect of faecal haemoglobin as the primary prevention strategy. Moreover, we considered colorectal cancer as the competing risk in the model and evaluated the prediction performance of faecal haemoglobin levels as the additional measure. However, several limitations should be mentioned. First, we did not include extensive dietary and nutrient information in our study, which may confound the association between faecal

haemoglobin and cardiovascular risk. Second, one-time faecal haemoglobin measurement was conducted, and no trend patterns or repeated measures were available. Third, medications and changes in comorbidities were not considered due to the primary prevention strategy, although the prevalence of preventive treatments such as aspirin was relatively low. Finally, the use of non-steroidal anti-inflammatory drugs and warfarin was not quantified in this study.

In conclusion, our study provides compelling evidence for faecal haemoglobin as a biomarker of the risk of cardiovascular disease; faecal haemoglobin showed a dose–response association that was consistent across various clinical statuses. In addition, faecal haemoglobin had a higher prediction power for cardiovascular diseases risk than traditional risk factors. Additional studies of the biological mechanism of faecal haemoglobin for cardiovascular diseases are warranted.

Author affiliations

¹Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei, Taiwan

²Institute of Occupational Medicine and Industrial Hygiene, College of Public Health, National Taiwan University, Taipei, Taiwan

³School of Oral Hygiene, College of Oral Medicine, Taipei Medical University, Taipei, Taiwan

⁴TMU Research Center of Cancer Translational Medicine, Taipei Medical University, Taipei, Taiwan

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ORCID iDs

Kuo-Liong Chien <http://orcid.org/0000-0003-4979-8351>

Tony Hsiu-Hsi Chen <http://orcid.org/0000-0002-5799-6705>

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